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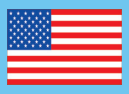

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REVIEW

Identity and schizophrenia: Who do I want to be?

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Abstract

Many individuals with schizophrenia have occasional difficulty defining both to themselves and to others who they truly are. Perhaps for this reason they make attempts to change core aspects of themselves. These attempts may be delusional, but are too often unjustly dismissed as delusional before the potential value of the change is considered. Instead of facilitation, obstacles are placed in the way of hoped-for body modifications or changes of name or of religious faith. This paper discusses the various changes of identity sometimes undertaken by individuals with schizophrenia who may or may not be deluded. Ethical and clinical ramifications are discussed. The recommendation is made that, when clinicians respond to requests for help with identity change, safety needs to be the main consideration.

Key words: Schizophrenia; Identity; Body modification; Religious conversion; Name change

Core tip: Everyone tries at times to change aspects of their identity. When people with schizophrenia do it, it should not necessarily be interpreted as delusional, but safety issues need always to be kept in the foreground.

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INTRODUCTION

Schizophrenia has been referred to as an "I am" illness[1], meaning that this disorder affects an individual's core identity, the qualities, characteristics and continuities that distinguish one person from another. Identity, however, is never static and, particularly in the context of schizophrenia, it has been associated with fluidity and characterized by inconsistent autobiographical recall and changes in self-representation over time[2-4]. The appreciation of a sense of self has been reported as deficient in this illness[5-8]. This is illustrated in a study by Scharfetter[9]. Persons with schizophrenia, when administered a standardized questionnaire about identity, endorsed items such as: "I didn't know who I was", "My ancestry changed", "I often had to look in the mirror", "I thought I had children", "I had to say

repeatedly "I am who I am", "My body or parts of it changed", "My sex changed". They showed an imprecise awareness of the continuity over time of their body, personal history, and social function.

Given a hypothesized fluidity of self-perceived identity, it is perhaps to be expected that some patients with schizophrenia, once over the acute stage of illness, might want to change their external appearance to conform to a changed self-image[10]. They might also want to re-invent other aspects of who they perceive themselves to be: Their origins, their name, their faith. Reported examples of identity transformations in the schizophrenia literature include: Becoming a vegetarian[11], changing religion[12,13], acquiring identity-changing tattoos and body piercings[14], seeking rhinoplasty[15], changing names[16], and changing genders[17-19]. The question with which clinicians are faced is whether such seemingly abrupt identity changers are signs of psychotic exacerbation, decisions made on delusional grounds, or whether individuals with psychosis, like everyone else and for identical half-rational, half-irrational reasons, occasionally change diets and appearance, convert from one religion to another, and, at times, change genders. The clinician has to determine whether a sudden transformation of self-representation in a person with pre-existing psychosis calls for hospitalization or, instead, whether the person should be referred, as appropriate, to nutritionists, plastic surgeons, chaplains, or gender identity clinics? Because clinicians are often uncertain as to how best to respond to requests for assistance with proposed changes of this nature, I undertook a review of the literature on identity changes in the context of schizophrenia.

METHOD

My search strategy was to pair words representing aspects of identity (name, body, religion, dress, food, gender, ethnicity) with schizophrenia or psychosis in the multidisciplinary Google Scholar database. This yielded 200 abstracts, of which 60 appeared relevant to my purpose. Searching the references of these 60 papers, I found 15 further relevant papers. I will first discuss the various changes of identity reportedly undertaken by individuals with schizophrenia and subsequently I will address ethical and clinical ramifications.

NAME CHANGE

Ethnicity, religion, ancestry, gender, social class, birth order, physical appearance, time and place of birth all contribute to what is called identity, and most of these contributions can be reflected in a person's name[20-22]. A name change is therefore a powerful way to assume a new identity. Changes of name can act as connections[23], a way for instance, of blending in with a new environment, of marking a valued affiliation or being reborn into a new religion. Sometimes, however, changing one's name can serve as a separation. It can be a way to hide one's former identity, to repudiate one's ancestry. These different motivations apply to persons with schizophrenia as to anyone else with the added possibility that the wish to hide a previous identity in this population stems from paranoia and originates in delusional thinking. In a 12-year retrospective study of patients attending a psychiatric unit (31% of whom suffered from schizophrenia), it has been reported that 0.7% had at some time in life adopted an alias[24]. In another study, Völlm *et al*[25] found that up to one fifth of psychiatric offender patients had changed their names at least once, motivated by the wish to either consolidate or break family ties, make a fresh start in life, or simply to discard a disliked name. Persons with psychosis, more than other patients, gave idiosyncratic reasons for changing their name, and the names they selected were characterized by being relatively famous names or names that carried symbolic significance. Völlm *et al*[25] note that the reasons given for name changes by patients in their sample with a diagnosis of schizophrenia sounded as if they might be delusional "It was something mysterious, sinister. Sinister, mysterious name" (25; p. 46).

PHYSICAL APPEARANCE

It is generally acknowledged that facial features (eyes, nose, lips, ears, skin, hair) are fundamental indices of identity and human beings throughout history have attempted to enhance or camouflage these features by cosmetics, depilation, piercing, ornamentation, wigs, head coverings, veils, tanning, bleaching, dreadlocks, crew cuts, and plastic surgery.

With respect to tattoos, a higher than average prevalence of skin markings has been found among young adults who use mental health services[26,27]. In an early study of visible tattoos on a psychiatric ward, Birmingham *et al*[28] reported a 30% rate of schizophrenia. The percentage would be much lower today because, in many parts of the world, tattoos have become quite commonplace. An example of a tattoo motivated by a delusion is provided in Campo *et al*[29] where a man with a tattoo states, "I thought I lived with Satan and therefore I needed his sign on my back" (29; p. 166). For the most part, however, the literature considers tattoos as non-delusional attempts to declare a new identity or to rebel against an old one. Like names, they can be marks of affiliation or differentiation or they can merely be efforts to stay in vogue with current fashion[30]. Because they are considered to represent "toughness", tattoos often increase self-confidence and feelings of empowerment, especially when they are strategically situated so that their visibility is under the control of the wearer[31,32]. This can serve important morale-boosting purposes in persons with schizophrenia. Whether people with schizophrenia choose specific configurations or themes for their tattoos has not been investigated.

The treatment of schizophrenia can sometimes

transform a person's appearance, weight gain being a prime example[33] and the illness itself can significantly change a person's voice, accent, and language use, markedly affecting the responses of others[34-37] and, therefore, secondarily, influencing one's self-evaluation.

Drastic changes in appearances have been reported in schizophrenia[29], often precipitated by major life events[38] and sometimes achieved through plastic surgery. Cosmetic surgery for nose or breast is widespread in the general population, but actively seeking it is particularly common in those with body dysmorphic disorder[39-41], a condition that shows some overlap with schizophrenia[42-44]. While some common changes, such as hairstyles[45], are frequent and ubiquitous and harmless, the drive to change appearance can sometimes have dangerous results[46]. Major self-mutilation, defined as individuals amputating their limb or their genitals or removing an eye, has been strongly associated in the literature with the presence of psychosis[47,48].

Body modifications include taking hormones or undergoing sex-reassignment surgery. A recognizable minority of individuals with gender identity disorder are said to suffer from a psychotic illness[17-19,49-51]. Gender identity disorder patients who are psychotic are often denied gender surgery in the same way that people with psychosis were once denied bariatric surgery for morbid obesity[52,53]. Decisions on what is right under these circumstances can be very difficult for clinicians.

CONSUMMATORY BEHAVIORS

Humans use belongings and personal effects to create and recreate an identity and to show themselves to others in a selective fashion[54]. Personal identity is often expressed in what one owns, how one dresses, where one lives, and even what one eats. The decision to become a vegetarian, for example, is taken by a large percentage of the population. It is usually seen as the mark of an animal rights devotee or a fitness enthusiast, but obsessive attention to diet can, at times, represent a form of psychotic eating disorder[55-58].

Dress, a well-recognized symbol of identity[59,60], is often described as idiosyncratic in individuals with schizophrenia[61-63]. A way of dressing that strikes others as odd may be deliberate (as a form of identification with a particular subculture or a renunciation of a previous identification) or it may simply be the result of economic constraints and needing to make do with second hand clothing[64]. Dishevelment can also result from apathy and negative symptoms and cognitive deficits. In addition, problems with thermal regulation leading to redundant clothing have been postulated in schizophrenia[65]. In other words, it cannot be assumed that dressing in an "odd" way is intentional or indicative of wanting to assume an "odd man out" identity. On the other hand, the symbolic self-completion theory[66] proposes that, when people feel incomplete in an identity - persons who are newly homeless for instance - they may deliberately adorn themselves with symbols associated with that identity (rags, layers of clothes, unwashed clothes) in order to more fully embrace the new role and achieve a sense of completeness. This may apply even when the new identity is unwanted.

IDENTITY BY ANCESTRY

Many people nurture a fantasy about being adopted, about having a long lost twin, about their "true" hidden parentage; many renounce their national or ethnic identity and adopt a new one, usually for safety or economic reasons. Many do so for delusional reasons as did John Nash when he renounced his United States citizenship upon developing psychosis[67]. Motives can include a desire to individuate or a desire to assimilate. Identification with an idealized other may be responsible[68]. There is at least one report in the literature of distorted ethnic identity in the context of psychosis[69]. An attempt to change ethnicity is more dangerous than the other changes discussed in this paper because it may arouse political suspicion and potential retaliation.

RELIGIOUS IDENTITY

In the Western world, many contemporary men and women choose, at some point in their lives, to leave the religion of their parents and establish a different religious identity for themselves[70]. They do so for a number of different reasons, rational, emotional, and spiritual[71]. Conversion to a new religion is often experienced as a transformational change, and has been described with vocabulary that is similar to that used to describe an episode of psychosis. Conversion is said, for instance, to give people a new sense of life's meaning and a new relationship to God[72-77]. Individuals with psychotic illness use very similar terms when they talk about their beliefs, making it difficult to distinguish religious conversion from delusional thinking. In fact, conversion experiences in the context of schizophrenia are not rare[13,78]; individuals with psychosis appear to be attracted, more than others are, to new religious movements[12], perhaps because such movements offer explanation of and salvation from the distress of psychotic symptoms. They have been described as capable of fulfilling emotional needs and stimulating spiritual growth[79]. New religious movements are also, as social communities, more welcoming than traditional religions to relatively isolated persons. Religious delusions have been reported to trigger conversion[80]. Interestingly, in a study of 14 forensic psychiatric patients who had changed faiths[81], one person with a diagnosis of schizophrenia gave as his reason for converting the conviction that his former religion was responsible for fueling his delusions.

LIMITATIONS OF THE REVIEW

This review of the literature skips over many difficulties

(such as definitions of identity) and does not mention political, professional, and social class identities. Nor does it discuss personality and behavior changes that can seemingly transform a person, especially in the context of psychotic illness. This paper should be viewed as exploratory, with much important territory left uncovered.

DISCUSSION

The literature suggests that individuals with schizophrenia sometimes make fundamental changes to their identity and sometimes ask clinicians for assistance. It is acknowledged that change decisions can, at times, be grounded in delusional thinking, leaving clinicians in a quandary as to how to respond. Sanati *et al*[82] argue, however, that not taking a person's statements at face value constitutes an act of testimonial injustice[83], an unjustified devaluation of a person's word. Individuals with a diagnosis of psychosis are often exposed to this form of injustice because the term, schizophrenia, is linked in many people's minds with personal attributes such as irrationality and untrustworthiness. It is well known, however, that decisions and acts can at times, in everyone, be made on irrational grounds; to discredit them a priori, based on a person's diagnosis, is manifestly unjust. The assumption that a person's thinking in a given circumstance is affected by having once been deluded about a different matter, may be correct, but may not be. Once a person has been diagnosed with delusions, to subsequently dismiss all their stated beliefs is an example of unfair bias[84,85].

Clinicians, of course, form their opinions about a patient's credibility on more than the diagnosis and the psychiatric history. They have their own prior opinions about what is believable and what is not. The credibility of patients with schizophrenia who declare, "I've decided from now on to take my medication as prescribed" will go unquestioned. This decision will be deemed wise. "I've decided to become a vegetarian" may also be met with approval, given that vegetarianism is likely to lead to weight loss, often necessary in individuals with schizophrenia who have gained weight as a result of treatment. But the vegetarian decision may be appraised differently if the clinician does not believe in it[86].

Clinicians' responses also depend on what they perceive to be the logic behind the intended change. For instance, wanting to change one's name because the original name is hard to pronounce[87] makes sense to a clinician, but wanting to be renamed Clark Kent "Because I am able to unleash supernatural powers", will arouse alarm. Psychiatrist and philosopher, Karl Jaspers (1883-1969) wrote, "the mentally ill person surely has as much right to be illogical as the healthy one"[88], and this is worth keeping in mind, but what is more important than logic is safety.

Most clinicians would agree that individuals with schizophrenia should be as free as anyone else to engage in acts of self-redefinition[89], but the line is drawn where safety is called into question. One important aspect of safety is reversibility. Shaving off one's hair to look like a favorite movie actor makes for a decisive change in one's appearance, but hair grows back. Another matter altogether is identifying with and wanting to emulate a film star who has undergone a mastectomy. Such a body modification would be, for all intents and purposes, permanent, a form of self-mutilation that leaves an irreversible mark[90].

How then, should clinicians react to requests for help in changing identity? There are no hard and fast rules; the following are suggestions based on the limited literature: (1) the clinician should not assume that the request is delusional and signals illness deterioration; (2) the clinician should not discredit or dismiss the request out of hand; (3) asking about the reasons behind the request is always in order. Staying actively interested encourages the patient to discuss motivations at length; (4) risk assessment should be carried out after considering the person's track record, the person's demonstrated knowledge about the choice she or he is making, and the coherence of the argument presented; (5) self-reflection is important. The clinician should try to be consciously aware of personal biases with respect to the person, to the nature of his/her illness, and to the choice being made; (6) the clinician must be able to recognize the effects of age and culture on choices and decisions. In the end, safety has to be the prime consideration; (7) safety issues need to be discussed with the patient; (8) the clinician is advised to inquire about and become familiar with published outcome studies of all proposed body modifications, and to share these results with the patient; (9) a family meeting to expand the discussion and learn about ramifications for family and for community is always useful; (10) recommendations for specialist referral are usually needed; (11) if distance travel is involved in the proposed change, travel precautions need to be ensured[91]; (12) the issue of the patient's competence to make significant decisions must be assessed; and (13) should there be imminent danger of injury to the patient or to others, hospital treatment must be arranged, against the patient's will if necessary.

CONCLUSION

When individuals with schizophrenia ask their care providers to assist them in changing their identity through body modification or religious conversion or name change for instance, clinicians have difficulty deciding how to react. This review suggests that whether the request is delusional or not, it should always be taken seriously and the motivation for it thoroughly investigated. There may be risks, however, when acceding to such requests. Safety considerations should always be borne in mind.

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EVIDENCE-BASED MEDICINE

Differences between British and Japanese perspectives on forensic mental health systems: A preliminary study

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Abstract

AIM

To clarify the differences in views on forensic mental health (FMH) systems between the United Kingdom and Japan.

METHODS

We conducted a series of semi-structured interviews with six leading forensic psychiatrists. Based on a discussion by the research team, we created an interview form. After we finished conducting all the interviews, we qualitatively analyzed their content.

RESULTS

In the United Kingdom the core domain of FMH was risk assessment and management; however, in Japan, the core domain of FMH was psychiatric testimony. In the United Kingdom, forensic psychiatrists were responsible for ensuring public safety, and psychopathy was identified as a disease but deemed as not suitable for medical treatment. On the other hand, in Japan, psychopathy was not considered a mental illness.

CONCLUSION

In conclusion, there are considerable differences between the United Kingdom and Japan with regard

to the concepts of FMH. Some ideas taken from both cultures for better FMH practice were suggested.

Key words: Forensic mental health; Medical treatment and supervision act; Psychopathy; International comparison; Qualitative research

Core tip: Several differences regarding the policy and perspective in forensic mental health have found between British and Japanese forensic psychiatrists; psychopathy is deemed as a mental illness in the United Kingdom, but not in Japan; British forensic psychiatrists considered to be responsible for ensuring public safety, whereas Japanese do not think so.

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INTRODUCTION

Forensic psychiatry is a sub-branch of psychiatry that deals with patients and problems at the interface of the legal and psychiatric systems[1]. Therefore, it follows that forensic psychiatric practice will vary from country to country. Many countries have established how to deal with mentally disordered offenders (MDOs), and this involves different disciplines[2].

Japan established the Forensic Mental Health (FMH) scheme, which coincided with the enforcement of the Medical Treatment and Supervision Act (MTSA; the Act on Medical Care and Treatment for the Persons Who Had Caused Serious Cases under the Condition of Insanity) in 2005[3]. For the establishment of the forensic psychiatric care scheme in Japan, the government referred to their English counterpart to a considerable extent. On the other hand, there are many differences between countries with regard to the cultural background and history of FMH and with regard to the criminal justice system.

Considering these facts, it is hypothesized that there are differences between the United Kingdom and Japan in basic perspectives on and the level of awareness with regard to forensic psychiatry. The aim of the present study was to clarify these differences by conducting a series of semi-structured interviews.

MATERIALS AND METHODS

We created an interview form, using which we conducted the semi-structured interviews. The items on the interview form were formulated by means of a discussion (among the authors) that was based on a relevant literature search. The interview included questions concerning people's opinions on various issues pertaining to the current systems of and context surrounding FMH in the United Kingdom and Japan.

The interviewees were forensic psychiatrists who were engaged in FMH practice or research in either Japan or the United Kingdom. For our preliminary study, we used convenience sampling to select three participants from each country.

All participants provided written informed consent for participation in the study. The first author conducted the semi-structured interview with each participant. Each interview lasted for approximately forty-five minutes. We digitally recorded the interviews and examined their content after they had been conducted. We transcribed and qualitatively analyzed each comment made by the participants.

The study protocol was approved as an international comparison study of forensic psychiatry by the ethics committee of the Graduate School of Medicine of Chiba University on June 19, 2015.

RESULTS

All six participants answered all the questions that they were asked during the interview, and no questions were omitted.

The participants comprised the following individuals: One British and one Japanese professor of a department of FMH, one British and one Japanese clinical psychiatrist, each of whom was working in a forensic ward, and one British and one Japanese postgraduate student who had each worked in a forensic ward. The length of time for which the participants had worked as a medical doctor (mean, 27.7 years; 12-43) and for which they had worked in the area of FMH (mean, 16.2 years; 5-40) differed.

All three British participants identified psychopathy as a mental disorder, whereas the participants from Japan were neutral to or skeptical of this view. Notwithstanding this, almost all participants were opposed to treating psychopathic patients in a psychiatric ward. The British participants emphasized that there was a lack of evidence suggesting that treatment outcomes for psychopaths were desirable.

In the United Kingdom, seclusion and restraint were rarely implemented, except in the case of psychiatric emergency wards. In Japan, inpatients in general psychiatric wards were occasionally secluded and/or restrained, whereas those in MTSA inpatient facilities were seldom secluded and/or restrained. The British participants felt that seclusion and restraint should be a last resort for managing patients' aggressive acts. In contrast, the Japanese participants felt that secluded circumstances could be beneficial for patients, for example, those who were bothered by auditory hallucinations, as it would help them become more aware of their psychotic symptoms.

Only one Japanese participant had been involved in masked medication. The Japanese participants were rather accepting of masked medication and considered it a necessary evil, except for one participant, who was absolutely against it; furthermore, all the British participants were against masked medication.

All three British participants stated that forensic psychiatrists should be responsible not just for patients' treatment but also for public safety to some extent, whereas only one Japanese participant supported this view.

The British participants believed that the core competencies of forensic psychiatrists should be risk assessment and the management and understanding of the psychiatric basis of violent behaviors. In contrast, the Japanese participants felt that the core specialties of forensic psychiatrists should be the understanding of criminal responsibility and psychiatric testimony skills.

In the United Kingdom, the term of hospitalization is six months to two years in medium secure units (MSU), and five to seven years in high secure units (HSU), and in Japan, the MTSA usually requires MDOs to be hospitalized for two to three years in inpatient facilities.

All participants supported the policy that forensic psychiatric care should be funded by the government. Furthermore, the British participants supported the idea that forensic psychiatric services should be covered by the private sector as well; however, the Japanese participants' opinion regarding this matter was divided.

DISCUSSION

We conducted a series of semi-structured interviews with forensic psychiatrists from the United Kingdom and Japan. The results revealed some significant differences between the opinions of psychiatrists from the two nations.

The British specialists seemed to consider risk assessment, while focusing on MDOs' aggressive behaviors, as the key areas that should be addressed by FMH. This would imply that psychopaths and substance abusers are at the center of forensic psychiatric treatment, because they are highly relevant to violence and crimes[4]. This view also places a sense of obligation on forensic psychiatrists to maintain public safety through the risk management of MDOs.

However, the British psychiatrists seemed to be ambivalent with regard to the paradox that psychopathy as a form of mental impairment is unsuitable for the psychiatric treatment setting. Since 2001, England has been prepared for the treatment of the so-called "dangerous and severe personality disorders"[5]. However, there continues to be considerable skepticism about the efficacy and cost-effectiveness of this treatment for such disorders[6,7].

On the contrary, the Japanese psychiatrists believed that forensic psychiatric practice should involve engaging in tasks related to people who have to give psychiatric testimony and who are involved with FMH legislation. In other words, they believed that forensic practice should involve dealing only with people whose criminal responsibility is questionable[8]. Consequently, in Japan, offenders with schizophrenia are inevitably dominant in the FMH setting[9]. Since forensic psychiatrists in Japan devote most of their expertise and energy to the treatment of schizophrenic patients, they hardly deal with psychopathic patients who may be incarcerated in prison[10]. Additionally, Japanese forensic psychiatrists do not have a very strong sense of responsibility with regard to contributing to public safety.

This, however, does not imply that risk assessment is ignored in forensic practice in Japan. Considering the fact that approximately three percent of the inpatients of general psychiatric wards are secluded or physically restrained[11], psychiatrists in Japan frequently have to evaluate the risk of violent behaviors in psychiatric patients. However, it is doubtful that these assessments are based on structured professional judgment. In addition, masked medication may still be accepted in some contexts in Japan. By and large, it appears that Japanese psychiatrists tend to behave in a paternalistic manner with psychiatric patients.

In the United Kingdom, private hospitals are rapidly growing in the FMH sector[12]. Some private facilities deal with specialized or niche needs such as developmental disorders. In contrast, in Japan, the private sector has been dominant in providing psychiatric beds[11]. At present, the MTSA inpatient facilities are limited to the public sector. Nonetheless, further discussion is required to clarify the future role of the private sector in relation to FMH.

Forensic specialists from both countries paid attention to the prolongation of the term of hospitalization of MDOs. Similar to MSUs in the United Kingdom in terms of their capacity and human resources, Japanese inpatient facilities, in accordance with the MTSA in Japan[13], have more long-stay patients. However, this fact should be interpreted cautiously because some patients discharged from an MSU are transferred to a low secure unit, HSU, or prison. In contrast, Japanese legislation has no provision for discharged patients to be recalled to prison[10]; moreover, there are no facilities equivalent to HSUs in Japan.

In conclusion, this preliminary study revealed some substantial differences between the United Kingdom and Japan with regard to FMH systems as well as significant differences between the views of British and Japanese specialists in this academic area. Therefore, great caution should be exercised when analyzing evidence in different countries.

Additionally, to improve the management of MDOs, there are points that should be taken from both Japan and the United Kingdom. In Japan, the task of making structured clinical judgments for risk assessment and management should be shared broadly among psychiatric practitioners. In the United Kingdom, a consensus needs to be reached with regard to the dispute surrounding the treatability of personality disorders and

psychopathy. Furthermore, in both countries, a more detailed dialogue between general psychiatrists and forensic psychiatrists is required in order to shed light on what exactly FMH practice should entail.

COMMENTS

Background

Forensic mental health is one of the focused regions in psychiatry. Japan has established a newly forensic mental health system since a decade ago. However, there are potentially several differences in the perspective of forensic mental health among countries, considering the various histories of each country.

Research frontiers

Treatment of psychopaths is a hot topic in forensic psychiatry. In many countries, several attempts have done to reduce the future risk of recidivism of psychopathic persons. But most of them were in failure. From the medical economic point of view, some countries are going to abandon the treatment of psychopaths.

Innovations and breakthroughs

This mini-study revealed the difference of ideas and perspectives toward forensic mental health in the United Kingdom and Japan. Several international comparisons are conducted previously. But there are no other examples to investigate the basic thoughts regarding this region, such as the treatment of psychopaths, social responsibility of forensic psychiatrists, and medical economics of forensic mental health.

Applications

The reader will deeply understand the difference between two countries on forensic mental health. It will provide readers a widened view and sensibility about the interpretation of the contents when readers read papers mentioning the situation in other countries.

Terminology

The Medical Treatment and Supervision Act was a legislation established in Japan in 2003, enforced in 2005, for improved care and treatment for offenders with mental disorders.

Peer-review

This is an interesting paper, with an important contribution to understanding neurobiology.

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SYSTEMATIC REVIEWS

Functional neuroanatomy in panic disorder: Status quo of the research

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Abstract

AIM

To provide an overview of the current research in the functional neuroanatomy of panic disorder.

METHODS

Panic disorder (PD) is a frequent psychiatric disease. Gorman *et al* (1989; 2000) proposed a comprehensive neuroanatomical model of PD, which suggested that fear- and anxiety-related responses are mediated by a so-called "fear network" which is centered in the amygdala and includes the hippocampus, thalamus, hypothalamus, periaqueductal gray region, locus coeruleus and other brainstem sites. We performed a systematic search by the electronic database PubMed. Thereby, the main focus was laid on recent neurofunctional, neurostructural, and neurochemical studies (from the period between January 2012 and April 2016). Within this frame, special attention was given to the emerging field of imaging genetics.

RESULTS

We noted that many neuroimaging studies have reinforced the role of the "fear network" regions in the pathophysiology of panic disorder. However, recent functional studies suggest abnormal activation mainly in an extended fear network comprising brainstem, anterior and midcingulate cortex (ACC and MCC), insula, and lateral as well as medial parts of the prefrontal cortex. Interestingly, differences in the amygdala activation were not as consistently reported as one would predict from the hypothesis of Gorman *et al* (2000). Indeed, amygdala hyperactivation seems to strongly depend on stimuli and experimental paradigms, sample heterogeneity and size, as well as on limitations of neuroimaging techniques. Advanced neurochemical studies have substantiated the

major role of serotonergic, noradrenergic and glutamatergic neurotransmission in the pathophysiology of PD. However, alterations of GABAergic function in PD are still a matter of debate and also their specificity remains questionable. A promising new research approach is "imaging genetics". Imaging genetic studies are designed to evaluate the impact of genetic variations (polymorphisms) on cerebral function in regions critical for PD. Most recently, imaging genetic studies have not only confirmed the importance of serotonergic and noradrenergic transmission in the etiology of PD but also indicated the significance of neuropeptide S receptor, CRH receptor, human TransMEMbrane protein (TMEM123D), and amiloride-sensitive cation channel 2 (*ACCN2*) genes.

CONCLUSION

In light of these findings it is conceivable that in the near future this research will lead to the development of clinically useful tools like predictive biomarkers or novel treatment options.

Key words: Panic disorder; Anterior cingulate cortex; Amygdala; Insula; Functional magnetic resonance imaging; Diffusion tensor imaging; Voxel-based morphometry; Imaging genetics; Serotonin; Noradrenaline

Core tip: This systematic review is focused on the most current research in the functional neuroanatomy of panic disorder. Recent neurofunctional studies suggest that the "fear network", as proposed by Gorman *et al*, may need to be amended by additional regions (ACC, insula). Most recently, imaging genetic studies have not only confirmed the importance of serotonergic and noradrenergic transmission in the etiology of panic disorder (PD) but also indicated the significance of neuropeptide S receptor and corticotropin releasing hormone receptor gene variants. Imaging genetics studies are of major importance for the refining of the neuroanatomical model, because genetic risk variants may significantly influence fear network activity in PD.

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INTRODUCTION

Panic disorder (PD) is a considerably common psychiatric disease. According to epidemiological studies, six-month prevalence rates have been estimated roughly 1%[1] while lifetime prevalence amounts to 2%-5%[2,3]. PD is characterized by the occurrence of recurrent panic attacks, which are not explained by another psychiatric or medical condition. According to the Diagnostic and Statistical Manual of Mental Disorders (5th edition) panic attacks are sudden episodes of intense fear or discomfort that may be accompanied by palpitations, accelerated heart rate, sweating, trembling, chest pain, nausea or abdominal distress, dizziness, paresthesias, derealization, depersonalization, fear of "going crazy" or even fear of dying[4]. Besides panic attacks, many patients with PD suffer from anticipatory anxiety and maladaptive changes in cognition and behavior resulting in phobic avoidance[5]. PD therefore is often accompanied by agoraphobia and other mental disorders[6].

With regard to the pathogenesis of PD, several cognitive, behavioral and neurobiological theories have been developed[7-9]. Gorman *et al*[10] introduced a neuroanatomical model that was aimed at integrating the different views of PD as either a biological or a psychological disease. The authors suggested experiments to test their theories. Later, they provided a revised version of their model[11]. Since its inception, this neuroanatomical model has stimulated and greatly influenced research in PD - primarily in the field of neuroimaging studies.

According to Gorman *et al*[10] three components of PD: (1) acute panic attacks, (2) anticipatory anxiety; and (3) phobic avoidance are located in three specific sites of the CNS: The brainstem, limbic system, and prefrontal cortex. These three neural systems were suggested to be structurally and functionally closely connected, reflecting manifold interactions of the three mentioned clinical features. Hence, according to Gorman *et al*[10] different treatments for PD and agoraphobia not only affect different symptoms of the illness but also different parts of the brain. Thus, according to the authors, antipanic drugs like tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs) block brainstem-provoked panic attacks; benzodiazepines and relaxation training reduce anticipatory anxiety *via* the limbic system, and desensitization and cognitive therapies relieve phobic avoidance by influencing functions of the prefrontal cortex. In our opinion it is notable that both psychopharmacological and psychotherapeutic treatments are put on the same level by being conceptualized to act directly on specific neural networks. Therefore the neuroanatomical model proposed by Gorman *et al*[10] successfully integrates biological and psychological facets of PD.

In the revised version of their hypothesis, Gorman *et al*[11] suggest that the behavioral symptoms of PD are mediated by a "fear network" in the brain, which is centered in the amygdala and includes the hippocampus, thalamus, hypothalamus, the periaqueductal gray (PAG) region, locus coeruleus (LC), and other brainstem sites. This theory states that patients with PD have a decreased threshold for the activation of the fear network. Excessive activity in this network leads to autonomic and neuroendocrine activation through

projections from the amygdala to the brainstem and hypothalamus, resulting in typical PD symptoms. The lateral nucleus of the amygdala receives afferents from cortical regions involved in processing and evaluating sensory information. According to Gorman *et al*[11] abnormal functioning in these cortical areas could potentially result in the misinterpretation of sensory information (bodily cues), leading to an inappropriate activation of the fear network *via* misguided excitatory input to the amygdala. The authors propose that activation of the fear network as a result of cognitive misinterpretations could lead to the release of certain neurotransmitters that can cause autonomic behavioral responses related to PD. These responses include an increase in respiratory rate, increases in blood pressure, heart rate, defensive behaviors and postural freezing. Thus, processes at the biological level can directly lead to behavioral symptoms[11]. With regards to drug therapy in PD, Gorman *et al*[11] not only stated that antidepressants exhibit their antipanic effects *via* the brainstem, as proposed in their original model[10], but also that therapy with SSRIs might act directly on the limbic system (in particular on the central and lateral nuclei of the amygdala; please see section "The role of serotonin")[11]. In light of the above, it is intriguing that recent antidepressant medications seem to be able to enhance neuroplasticity mechanisms and adult neurogenesis in the hippocampus and even in the prefrontal cortex[12]. Therefore, due to its unique characteristics, the novel antidepressant agomelatine might also be effective in PD. Preliminary studies have provided encouraging results regarding effectiveness and tolerability of this substance, although it has to be noted that agomelatine is not yet approved for the treatment of PD[13,14].

One of the most important techniques of the neuroanatomical approach to PD is to perform neuroimaging studies on the brain regions that are supposedly active during panic attacks. Today, there are numerous neurofunctional, neurostructural, and neurochemical studies that have demonstrated the significant role of certain structures in the fear network[15-18].

A promising new research method is "imaging genetics". In this approach genetic information and functional magnetic resonance imaging (fMRI) data are combined in the same subject to define neuromechanisms linked to genetic variation[19]. Imaging genetics studies are of major importance for the adjustment and refining of the neuroanatomical model, because genetic risk variants may partly drive fear network activity in PD[15]. The aim of this review is to provide a comprehensive overview of the most significant findings in the field of the functional and structural neuroanatomy of PD. Because of the wide range of this topic, we will focus on recent studies. With regards to prior studies (published before January 2012), we refer to previously published review articles, *e.g.*[15-18]. However, a complete and exhaustive presentation of all relevant studies is infeasible and certainly beyond the scope of this work.

MATERIALS AND METHODS

We searched the electronic database PubMed for neurostructural, neurofunctional, and neurochemical studies on PD that were published in the period between January 2012 and April 2016. The search was conducted using the following search terminology: "(Panic disorder) and [functional magnetic resonance imaging (fMRI) or diffusion tensor imaging (DTI) or positron emission tomography (PET) or single-photon emission computed tomography (SPECT) or magnetic resonance spectroscopy (MRS) or near-infrared spectroscopy (NIRS) or imaging genetics or serotonin or norepinephrine or noradrenaline or locus coeruleus or dopamine or hypothalamic-pituitary-adrenal (HPA) axis or insula]". The total number of publications found by the PubMed research was 457 (fMRI: 94; DTI: 2; PET: 5; SPECT: 5; MRS: 11; NIRS: 2; imaging genetics: 21; serotonin: 137; norepinephrine: 19; noradrenaline: 28; locus coeruleus: 3; dopamine: 8; HPA axis: 23; insula: 99). The total number of publications after screening for topic was reduced to 281 (fMRI: 88; DTI: 2; PET: 3; SPECT: 1; MRS: 8; NIRS: 1; imaging genetics: 17; serotonin: 106; norepinephrine: 11; noradrenaline: 4; locus coeruleus: 2; dopamine: 2; HPA axis: 16; insula: 20). The remaining 281 studies were screened for duplicates and finally evaluated for eligibility. Subsequently, a secondary search was conducted that involved a broad review of potential neuroimaging studies by carefully perusing through the citation lists of the retrieved articles. Thereafter, a final screening of the retrieved articles was performed to ensure that the focus of the articles was within the scope of the present review. The literature search was conducted both jointly and independently by the authors (TS, GW). Finally, 76 studies published between January 2012 and April 2016 were included in this review.

RESULTS

Functional neuroimaging studies

Resting state studies: Only a few studies investigated neural functional connectivity pattern using resting state functional magnetic resonance imaging (rs-fMRI) in patients with PD. In one of these studies, Pannekoek *et al*[20] examined differences in the resting-state functional connectivity (RSFC) of the amygdala, dorsal anterior cingulate cortex (dACC) as well as posterior cingulate cortex (PCC) among 11 patients with PD and 11 healthy controls. They mainly found an increased RSFC between the amygdala and the bilateral precuneus as well as altered RSFC between dACC and frontal, parietal and occipital areas. Lai *et al*[21-23] reported abnormalities in 30 first-episode medication-naive patients with PD compared to 21 matched controls using different rs-fMRI parameters. They observed right-lateralized altered local

fractional amplitude of low frequency fluctuations (fALFF) signal in the occipital cortex, putamen and thalamus in PD patients[21]. ALFF represents the strength or intensity of low frequency oscillations in the BOLD (*i.e.*, blood-oxygen-level dependent) signal. The fractional ALFF represents the ratio of the amplitude in a low frequency band to the amplitude in the total frequency band. The authors also observed abnormal regional homogeneity in the occipital cortex of PD patients compared to controls[22] and decreased inter-hemispheric functional coordination (based on the voxel-mirrored homotopic connectivity) in PD patients in the PCC and precuneus.

Shin *et al*[24] combined rs-fMRI and magnetic resonance spectroscopy (MRS) techniques to investigate the functional connectivity of the perigenual ACC in 11 patients with PD and whether or not it is mediated by the local gamma-aminobutyric acid (GABA) concentration. Patients showed increased RSFC between ACC and precuneus. This functional connectivity negatively was correlated with the GABA concentration of the ACC.

Provocation studies: As extensively described in a recent review by Dresler *et al*[15], the most consistent differences between patients with PD and healthy controls yielded by provocation studies were found in the cingular, insular, frontal and brainstem areas. An electronic search of PD provocation studies between 2012 and 2016 returned only one additional investigation. Goossens *et al*[25] studied the effects of hypercapnia on the brainstem BOLD signal in 15 patients with PD using fMRI. Three brainstem regions were defined as regions of interest (ROI) due to their putative involvement in panic and chemosensitivity: The PAG, the raphe nuclei and the LC. The authors demonstrated increased brainstem activation, *i.e.*, located in the rostral raphe ROI in response to hypercapnia compared to 12 healthy controls and 15 healthy divers. However, a limitation of this study is a rather low voxel resolution, which limits the ability to differentiate between closely situated brainstem nuclei.

Nevertheless, this study provides further support for the significant role of specific brainstem nuclei in triggering panic attacks.

Motor, sensory and cognitive tasks

Investigating auditory habituation by means of fMRI, Pfleiderer *et al*[26] reported an increased activity of superior temporal and frontopolar cortex in 20 PD patients during the third block of auditory stimulation when compared to 20 healthy controls, as well as a positive correlation of these regions with anxiety measures.

Using fMRI, Wintermann *et al*[27] studied a sample of 13 patients with PD both with and without agoraphobia, and 13 healthy controls while olfactorily stimulating their senses with stress-related sweat odors as well as artificial odors and non-fearful non-body odors. Although PD patients did not differ from HC regarding their olfactory identification ability, patients showed an increased activation in the superior temporal gyrus, the supramarginal gyrus, and the cingulate cortex for sweat odor caused by ergometric exercise. Presenting sweat odor from the anxiety condition, PD patients showed an increased activation in the inferior frontal gyrus (IFG), which was positively correlated with the severity of the psychopathology. By means of a pH-sensitive MRI strategy Magnotta *et al*[28] investigated brain pH in 13 PD patients, which has been suggested to play a critical role in PD. Greater activity-evoked (visual flashing checkerboard) T1 rho changes, indicating pH changes in the visual cortex and ACC in patients compared to 13 HC, were detected.

Emotional processing

In order to understand the neurobiological underpinnings of PD, functional neuroimaging studies have often investigated the neurobiological bases of anxiety using paradigms focusing on activation correlates of stimuli with direct diagnostic relevance to PD. For example, panic-related pictures are presented to people suffering from PD to study the neural underpinnings of threat processing in this group[29].

In the present review, studies will be presented divided in paragraphs for the modality of stimulation (*i.e.*, pictorial stimuli, word stimuli, conditioned stimuli).

Emotional processing - pictorial stimuli

By means of fMRI, Gorka *et al*[30] investigated insular response to unpredictable aversiveness using negative or neutral images selected from the International Affective Picture System in 13 PD patients with comorbid major depressive disorder (MDD). Patients with PD exhibited greater bilateral insula activation to unpredictable aversiveness compared with 19 healthy controls and 9 control patients with MDD only. This study highlights the specific role of the insula in the pathophysiology of anxiety disorders. Wittman *et al*[31] investigated the neural correlates of the anticipation of agoraphobic situations in 72 PD patients with agoraphobia using agoraphobia-specific and neutral pictures presented with and without anticipatory stimulus. Stronger activations were observed in the bilateral ventral striatum and left insula in patients compared to 72 controls during the anticipation of agoraphobia-specific pictures.

Engel *et al*[32] used pictures showing characteristic panic/agoraphobia situations to investigate activation differences in 19 PD patients in the predefined ROIs, *i.e.*, prefrontal, cingulate, and insular cortex, and the amygdalo-hippocampal complex. Greater activation in PD patients than in 21 controls was detected in the insula, left IFG, dorsomedial prefrontal cortex (DMPFC), the left hippocampal formation, and left caudatum, when panic-related and neutral scenes were compared.

In a very recent fMRI study, Feldker *et al*[29] presented panic-related and neutral visual scenes to

26 PD patients to study the neural underpinnings of threat processing. Similarly to the results found by Engel *et al*[32], patients showed hyperactivation in an extended fear network comprising the brainstem, insula, thalamus, ACC, midcingulate cortex and DMPFC for disorder-related *vs* neutral scenes, compared to 26 healthy controls. No significant amygdala differences between groups could be found. Subjective levels of anxiety significantly correlated with brainstem activation in PD patients.

Interestingly, Liebscher *et al*[33] very recently showed that successful cognitive-behavioral therapy (CBT) led to a greater decrease in anxiety symptoms and associated reduction in bilateral amygdala activation during processing of agoraphobia-related pictures compared to the patients receiving antidepressants and a wait-list control group.

Four recent studies investigated the neural activation in patients with PD during processing of emotionally neutral and disorder-specific faces. Ottaviani *et al*[34] studied amygdala response to masked fearful faces as well as only to faces containing low range of spatial frequencies (LSF) in PD in 13 PD patients. In contrast to 15 healthy controls, patients failed to show bilateral amygdala activation to fearful masked faces *vs* neutral faces. LSF faces did not elicit an amygdala response in patients or controls. Demenescu *et al*[35] examined amygdala fMRI activation and its connectivity with the medial prefrontal cortex during emotional face perception in 14 patients with PD and 17 patients with social phobia. Patients with PD, but not those with social phobia showed hypoactivation in the amygdala and lingual gyrus during perception of angry, fearful, happy and neutral faces, compared to 16 healthy participants. The authors also found a positive correlation between degree of anxiety symptoms and functional connectivity of the amygdala to dACC and to DMPFC during perception of fearful faces.

Petrowski *et al*[36] investigated the neural activation of emotionally neutral faces and places in 15 PD patients with agoraphobia. Patients showed decreased neural activation in the occipital cortex and the cerebellum, and increased activation in the precuneus compared with 15 healthy controls.

Poletti *et al*[37] applied in their fMRI study a face-matching paradigm to 18 outpatients with PD to study the neural correlates of implicit emotional processing of fearful or angry affective facial expressions. The authors performed a correlational analysis and showed a positive relationship between anxiety sensitivity and fMRI activation during emotional processing in the a-priori defined ROIs, *i.e.*, the DMPFC, ACC and insula, but not in the amygdala.

Emotional processing - word stimuli

Only two recently published studies (from 2012 till 2016) used word stimuli to investigate altered functional activation in PD patients.

In an fMRI study with 20 PD patients, Dresler *et al*[38] applied an emotional Stroop task with panic-related and neutral words. On the behavioral level, PD patients showed a significant emotional Stroop effect (panic-related compared to neutral words), which, on the neural level, was accompanied by increased BOLD signal in the left IFG compared to 23 healthy controls. van Tol *et al*[39] used fMRI to examine neural activation during the performance of an emotional word encoding and recognition paradigm in 51 patients with MDD, 59 patients with comorbid MDD and anxiety, and 56 patients with PD and/or social anxiety disorder without comorbid MDD. Both groups of patients, *i.e.*, with MDD and PD showed a common hyporesponse in the right hippocampus during positive word encoding compared with 49 control subjects. During negative encoding, altered insular, amygdala and ACC activation was observed in depressed patients only. During positive word recognition, only PD patients showed increased IFG activation.

Emotional processing - conditioned stimuli

In an fMRI study by Tuescher *et al*[40], 8 PD patients, 8 posttraumatic stress disorder patients and 8 healthy controls learned to associate specific neutral stimuli with either a safe or threat context indicating the possibility of an electrical shock. In comparison to the other two groups, PD patients demonstrated significantly less activation in response to the "threat" condition and increased activation in response to the "safe" condition in the subgenual cingulate cortex, ventral striatum, amygdala, and in the PAG.

Lueken *et al*[41] investigated neural activation patterns in 60 patients with PD and agoraphobia during a fear conditioning task. Differential conditioning was associated with enhanced activation of the bilateral IFG, whereas simple conditioning and safety signal processing were related to increased midbrain activation in patients with PD and agoraphobia *vs* 60 healthy controls. Anxiety sensitivity was positively associated with the magnitude of midbrain activation.

In a randomized, controlled, multicenter clinical trial Kircher *et al*[42] investigated the effects of cognitive behavioral therapy (CBT) and brain activation during fear conditioning in 42 medication-free patients with PD and agoraphobia. After CBT, patients revealed reduced activation for the conditioned response ($CS^+ > CS^-$) in the left IFG compared to control subjects, which was correlated with reduction in agoraphobic symptoms. Patients also demonstrated increased functional connectivity between the IFG and amygdala, insula, as well as ACC after CBT.

Emotional processing - internal triggers of fear

The hypothesis of an increased attentional focus in PD towards bodily symptoms and their neural correlates was tested in a study by Pfleiderer *et al*[43] in a group at risk for PD, *i.e.*, 24 healthy female students with high

levels of anxiety sensitivity. In contrast to 24 females with normal levels of anxiety sensitivity, the highly anxiety-sensitive group reported higher arousal scores and higher activation during interoception (attention on the heartbeats) in a network of cortical, *i.e.*, frontal, motor regions and subcortical brain regions, *i.e.*, claustrum, thalamus, amygdala, parahippocampus that overlaps with known fear circuitry structures.

Brief summary: Even if not always consistent, functional studies suggest abnormal activation mainly in an extended fear network comprising brainstem, insula, anterior and midcingulate cortex and lateral as well as medial parts of the prefrontal cortex. Interestingly, differences in amygdala activation were not as consistently reported as one would predict from the hypothesis of Gorman *et al*[11].

Structural neuroimaging studies

Previous structural neuroimaging data in PD using a manual tracing of ROI as well as using an automated voxel-based morphometry (VBM) technique showed changes in total and in gray matter (GM) volume in limbic structures, *e.g.*, in the amygdala, hippocampus, in frontal, cingulate and temporal cortical areas, in the basal ganglia, and in the brainstem structures, such as midbrain and rostral pons (comprehensive review of structural findings in PD until 2012 by *e.g.*[15,44]). Regarding the latter finding, Fujiwara *et al*[45] also showed increased midbrain volume in 38 PD patients compared to the control group of 38 matched healthy subjects.

With regard to subcortical structures, Kartalci *et al*[46] reported that 27 patients with PD had significantly smaller pituitary volumes compared to 27 healthy subjects. In particular, patients with agoraphobia had a significantly smaller pituitary volume than patients without agoraphobia. In addition, Terlevic *et al*[47] observed decreased hypothalamic volumes in 12 patients with generalized anxiety disorder, but not in those with PD (11 patients) compared to 21 healthy controls.

A cortical area often studied in PD and known for its reciprocal connections with the amygdala is the orbitofrontal cortex (OFC). Atmaca *et al*[48] detected significantly smaller left OFC volumes in 20 PD patients compared with 20 healthy controls. Lai *et al*[49] showed in 30 first-episode, drug-naive and late-onset PD patients lower GM volumes in left OFC, as well as in the left IFG, left superior temporal gyrus and in the right insula compared to 21 healthy controls. Na *et al*[50] showed decreased GM volume in the left medial OFC in only 12 patients with both PD and agoraphobia compared to 22 healthy control subjects, but not in the 10 patients with PD and without agoraphobia nor in in the total sample.

Considering the white matter (WM) abnormalities in PD, the first study to investigate the WM integrity by applying the DTI technique revealed higher structural integrity in terms of greater fractional anisotropy (FA) values in the cingulum bundle[51]. In a recent study with 30 first-episode, medication-naive and late-onset PD patients, Lai *et al*[52] showed reduced integrity in WM tracts of the right inferior fronto-occipital fasciculus (IFOF), left body of corpus callosum and left superior longitudinal fasciculus (SLF) when compared to 21 controls. Kim *et al*[53] reported no significant difference in WM integrity between 26 PD patients and 26 healthy controls. However, the authors showed increased right-lateralized FA in posterior thalamic radiation, posterior and superior corona radiata, SLF, and sagittal stratum in catechol-O-methyltransferase (COMT) AA/AG genotype group compared to GG genotype in PD.

Kim *et al*[54] reported decreased FA in frontal WM and the genu of the corpus callosum in 36 short-term medicated patients with PD compared to 27 healthy controls.

Furthermore, increased structural integrity in the internal capsule, corpus callosum, superior and posterior corona radiata, thalamic radiations, sagittal stratum, and SLF were detected in 12 PD patients with a suicide attempt compared to 24 PD patients without suicidal attempt[55]. However, due the lack of a healthy control group, this result is difficult to interpret.

Very recently, Lai *et al*[56] compared 53 medication-naive patients with 1st-episode PD, 53 medication-naive patients with 1st-episode MDD and 54 healthy controls with regard to the WM integrity. The PD group had lower integrity in bilateral superior longitudinal fasciculi and left IFOF when compared to controls, whereas MDD patients revealed reductions in the WM integrity when compared to controls in the bilateral superior longitudinal fasciculi, inferior longitudinal fasciculi, inferior fronto-occipital fasciculi, and corpus callosum. The MDD group had lower WM integrity than the PD group in the left anterior thalamic radiation, left uncinate fasciculus, left IFOF, and bilateral corpus callosum.

Using VBM, Konishi *et al*[57] demonstrated in 40 PD patients significant volumetric reductions in widespread WM regions including fronto-limbic, thalamo-cortical and cerebellar pathways compared to 40 healthy controls.

One structural imaging study investigated cortical gyrification in PD and detected significant reduction in gyrification in 23 patients with PD in the lateral brain, extending from the fronto-parietal to the temporal areas compared with 33 healthy individuals[58].

Schwartz *et al*[59] demonstrated a significant relationship between behavioral inhibition and hippocampal structure. Behavioral inhibition in childhood predicted reduced hippocampal volumes in adolescents who were offspring of parents with PD or PD with comorbid major depression, suggesting a role of the hippocampus in anxiety disorder. Trzesniak *et al*[60] was one of the first to use proton magnetic resonance spectroscopy imaging [(1)H-MRSI] to examine possible neurochemical abnormalities in the hippocampus in PD. Compared with 18

controls, twenty-five PD patients demonstrated significantly lower NAA/Cr in the left hippocampus.

Interestingly, Shinoura *et al*[61] reported in a case report study that damages to the dorsal part of the ACC led to repeated panic attacks, indicating that this structure might play an important pathophysiologic role in PD.

Brief summary of structural findings: Previous and recent neurostructural findings indicate the presences of structural neuroanatomical alterations in PD in multiple cortical, subcortical and brainstem areas. Studies on WM also revealed significant abnormalities in the structural connectivity between these regions.

Neurochemical alterations in PD

The role of serotonin: It is well established that PD responds to drugs that increase serotonergic function, such as certain TCAs, inhibitors of monoamine oxidase (classical MAOIs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors SNRIs[62]. The SSRIs are now generally accepted as the first-line pharmacological treatment for PD[63]. Therefore, there is clear evidence for an important role of serotonin in the pathophysiology of PD that has led to extensive research - predominantly in neuroimaging and animal studies. According to Gorman *et al*[11] the anxiolytic effect of SSRIs is mediated by at least three mechanisms: (1) inhibitory serotonergic projections from the raphe nuclei downregulate the activity of noradrenergic neurons in the LC[64]. The authors concluded that SSRIs, by increasing serotonergic activity in the brain, have a secondary effect of decreasing noradrenergic activity. This would lead to an amelioration of the somatic symptoms of panic attacks; (2) the projection of the dorsal raphe (DRN) neurons to the PAG is thought to modify defense/escape behaviors. As derived from animal studies, stimulation of the DRN markedly increases serotonin release in the dorsal PAG region, resulting in diminished activity in this brain area[65] associated with reduced defense/escape responses, *i.e.*, reduced propensity for panic-like reactions; and (3) as a third point, Gorman *et al*[11] state that long-term treatment with an SSRI may reduce hypothalamic release of corticotropin-releasing factor CRF[66]. CRF, which leads to adrenal cortical production of cortisol, is also a neurotransmitter in the CNS and has been shown to increase fear in preclinical models[67]. CRF enhances activity of the LC, when administered directly into the brain[68]. Furthermore, as stated by Gorman *et al*[11] SSRIs seem to have an effect on the central nucleus of the amygdala itself. Serotonergic neurons originating in the dorsal and medial raphe nuclei project directly to the amygdala *via* the medial forebrain bundle[69]. Moreover, serotonergic neurons modulate sensory input at the lateral nucleus of the amygdala, inhibiting excitatory inputs from glutamatergic thalamic and cortical pathways[70]. According to Gorman *et al*[11] this might be one of the major mechanisms for the anxiolytic action of the SSRIs.

Neumeister *et al*[71] used PET to study serotonin type 1A (5-HT1A) receptor binding in 16 patients with PD and 15 matched healthy controls. PD patients showed lower values in the anterior and posterior cingulate cortex (PCC) as well as in the raphe nuclei. For the first time, this study provided *in vivo* evidence for the involvement of serotonin type 1A receptors in the pathophysiology of PD. Nash *et al*[72] performed a 5-HT1A receptor binding study in PD patients at different stages of therapy. Nine drug-naive patients with PD, 7 patients who had recovered on SSRI medication and 19 healthy volunteers underwent a single PET scan. In untreated patients, both presynaptic and postsynaptic 5-HT1A receptor binding was reduced predominantly in the raphe nuclei, OFC, temporal cortex and amygdala. In recovered patients, presynaptic binding was also reduced, but there was no significant reduction in postsynaptic binding. Maron *et al*[73] investigated the binding of the serotonin transporter (SERT) in patients with PD by SPECT. The authors reported a significant decrease in SERT binding in the midbrain, in the temporal lobes and in the thalamus in 8 acute PD patients, but not in 8 remitted patients in comparison to matched controls. Regional SERT binding was negatively correlated with the severity of panic symptoms. In a further SERT binding study of PD, Maron *et al*[74] reported increased binding potential of the serotonin transporter in the raphe nuclei and several cortical areas. These findings were observed in male patients, but not in females. The authors concluded that distinctive functioning of the serotonin system in male and female PD patients might underlie the gender-dependent expression of the disease.

Given the fact that several neurochemical studies revealed altered 5-HT function in the raphe nuclei, it is noteworthy that structural abnormalities of this area have also been very recently reported. Šilhán *et al*[75] detected reduced brainstem raphe echogenicity in 26 patients with PD by transcranial sonography (TCS). TCS of the raphe nuclei indicated the diagnosis of PD with a sensitivity of 64% and a specificity of 73%. These findings are suggestive of structural disintegration of the brainstem raphe in PD, an anatomical region, that has also been assumed to be a biological focus in the pathogenesis of depression[76].

Deakin *et al*[77] proposed a hypothesis suggesting that different subpopulations of serotonergic neurons in the dorsal and median raphe nucleus through topographically organized projections to different brain regions are involved in the pathophysiology of anxiety and affective disorders. These different subpopulations of serotonergic neurons included: (1) serotonergic neurons within the DNR projecting to the dorsal PAG that inhibit innate panic-/escape-like physiological and behavioral responses; (2) serotonergic neurons within the dorsal raphe nucleus projecting to the amygdala, that facilitate conditioned fear and conflict anxiety-like responses; and (3) serotonergic neurons within the

median raphe nucleus that increase stress resilience and mediate antidepressant-like effects. This concept partly overlaps with the model developed by Gorman *et al*[11]. The Deakin/Graeff hypothesis still is a cornerstone that stimulates most recent research in PD.

Spiacci *et al*[78] investigated whether or not the enhancement of 5-HT-mediated neurotransmission within the dorsal PAG affects panic-like defensive reactions in rats submitted to a hypoxia challenge. Intra-dorsal-PAG injection of serotonin, a 5-HT1A receptor agonist or a 5-HT2A agonist reduced the number of upward jumps during hypoxia, interpreted as escape attempts. These effects were similar to those caused by chronic, but not acute, intraperitoneal administration of the antidepressant fluoxetine, or acute systemic administration of the benzodiazepine receptor agonist alprazolam. These observations confirm that the dorsal PAG is a key region involved in panic-like defensive behaviors. In a subsequent study, the authors demonstrated that serotonergic neurons of the lateral wings of the DRN (one of the five subnuclei of the DRN) are primarily involved in the mediation of PD-associated responses[79].

While the function of the DRN in the regulation of panic-like defense behaviors is well understood, the median raphe nucleus has received less attention. Generally, evidence derived from animal studies points to a relevant role of this raphe nucleus in the regulation of anxiety, but not of panic. This can be achieved through the serotonergic pathway that rises from the MRN to the dorsal hippocampus[80]. Alternatively, the DRN seems to participate in both anxiety and panic. Interestingly, the regulation of anxiety by the dorsal and median raphe serotonergic pathway is carried out through different target structures - the amygdala, dorsal PAG and ventral hippocampus in the case of the DRN, and the dorsal hippocampus in the case of the median raphe nucleus. Because these structures have different functional profiles, it is conceivable that different aspects of anxiety are underpinned by each of them. In this regard, Gray *et al*[81] have argued that the amygdala may underpin the neurovegetative arousal and affective components of anxiety, whereas the dorsal hippocampus may regulate cognitive manifestations, such as worry. This suggestion is supported by the reported interaction between the dorsal hippocampus and the prefrontal cortex underpinning fear learning and memory[80,82]. According to a recent study by Ohmura *et al*[83] the ventral (anterior part in humans) hippocampus may be involved in inappropriate retrieval of fear memory in PD. By microinjection of a 5-HT7 receptor antagonist into a rat's ventral hippocampus, the expression of freezing behavior - an index of fear memory retrieval - was significantly suppressed. The authors argue that the 5-HT7 receptor might be a target of drug development for the treatment of PD.

Brief summary: A major role of serotonin in the pathophysiology of PD has been deduced from the therapeutic effects of serotonergic drugs. In accordance with this hypothesis, studies on 5-HT1AR and SERT binding have revealed altered and mostly reduced serotonergic activity in the raphe nuclei, orbitofrontal cortex, temporal lobes, ACC and PCC, amygdala, and hypothalamus in patients with PD. In the course of therapy with SSRIs, postsynaptic alterations seem to decline, while the presynaptic changes persist. In addition to these functional alterations structural abnormalities, *e.g.*, disintegration of the raphe nuclei in the brainstem have also been described. Serotonin is synthesized primarily in the dorsal and median raphe nuclei. There is evidence from preclinical studies, that efferent inputs of dorsal raphe neurons may moderate panic-like defensive behaviors by controlling the activity of the dorsal PAG.

Alterations of the noradrenergic system

Much research into the neurochemistry of PD has explored the function of the monoamine transmitter noradrenaline. The noradrenergic system plays an important role by regulating the attentional alerting system that prepares and sustains alertness to process high priority signals[84]. Noradrenergic transmission is closely linked to the serotonergic system and to the HPA axis, and therefore mediates between central arousal and the peripheral physical reactions. According to Gorman *et al*[11] the response to sensory input for the conditioned stimuli is carried out by amygdalar projections. Efferents of the central nucleus of the amygdala are directed to the LC, resulting in an increase in noradrenaline release and contributing to increases in blood pressure, heart rate, and the behavioral fear response[85]. Recent studies in anxiety disorders and particularly in PD revealed higher baseline noradrenaline secretion and increased reactivity to challenges of the noradrenergic system[86-88]. It has furthermore been suggested that the noradrenergically mediated attentional alerting system is particularly active in states of anxiety[89,90]. The assumption of an important role of noradrenergic transmission in the pathophysiology of PD has recently been confirmed by genetic studies that revealed an association between PD and variation in genes modulating the noradrenergic system, such as the *COMT*[91], the monoamine oxidase A (*MAOA*)[92] and the norepinephrine transporter (*NET*)[93-95] genes.

Brief summary: The noradrenergic system plays an important role by regulating the attentional alerting system, which exhibits increased activity during states of anxiety. Noradrenergic transmission is closely linked to the serotonergic system and to the HPA axis, and therefore mediates between central arousal and peripheral physical reactions. Neurochemical studies have revealed higher baseline noradrenaline secretion and increased reactivity to challenges of the noradrenergic system in patients suffering from PD. Recently, genetic studies have demonstrated that there is an association between PD and variations in

COMT, *MAOA*, and *NET* genes, thus underlining the high importance of noradrenergic transmission in the pathophysiology of PD.

The role of GABAergic neurotransmission

Benzodiazepines are among the most potent and powerful anxiolytic agents[96]. These drugs act through an enhancement of gamma-aminobutyric acidergic (GABAergic) inhibition targeting the GABA receptor[97]. This fact, along with the results of several neurochemical studies, point towards a major role of the GABA system in the pathophysiology of PD. Thus, anticipatory anxiety and panic attacks might be triggered by a decreased GABAergic inhibition in distinct brain regions. In this light, decreased GABA receptor binding or reduced GABA activity (MRS studies) has been reported mostly in frontal, limbic, temporal and respectively insular regions. However, results are inconsistent, as some authors observed reciprocal effects like increased GABA receptor binding in patients with PD (cf. comprehensive review articles by, *e.g.*[15,98]). In a recent study, Long *et al*[99] investigated GABA levels in different cerebral regions by MRS. Eleven PD patients, including five with PD family history, six without PD family history and eight healthy controls participated in the study. The authors observed decreased GABA activity in the ACC/medial prefrontal cortex in PD patients, which tended to be more pronounced in patients with PD family history.

However, some methodological limitations of the abovementioned studies have to be taken in account. Firstly, spectroscopic studies still lack a sufficient image and spectral resolution as well as discriminatory power of ROIs. Secondly, it has not yet been proven that the results are specific for PD. In our opinion it would be advisable to include psychiatric comparison groups. Schür *et al*[100] pointed out that the inhibitory GABA system is thought to be involved in the etiology of several psychiatric disorders. The authors therefore performed a meta-analysis including a total of 40 MRS studies in seven different psychiatric disorders (n = 1.591). Brain GABA levels were lower in autism spectrum disorders and in depressed - but not in remitted - patients compared with healthy controls. No significant differences in GABA levels were found in PD (n = 81). In conclusion, alterations of GABAergic function in PD are still a matter of debate and also their specificity remains questionable.

Brief summary: The results of several neurochemical studies point towards an involvement of the GABAergic system in the etiology of PD. Decreased GABAergic inhibition was reported in limbic, frontal, temporal, and respectively insular regions. Unfortunately, the findings regarding the GABAergic system are partly inconsistent and may not be specific for PD.

Alterations of glutamatergic neurotransmission

There is some evidence derived from animal studies that an excitatory-inhibitory imbalance might play a role in the pathophysiology of PD[101]. Glutamate is the main excitatory neurotransmitter in the mammalian cortex while GABA is the main inhibitory neurotransmitter. Glutamate is the metabolic precursor of GABA, which can be recycled through the tricarboxylic acid cycle to synthesize glutamate[102]. As has already been stressed in the previous section, some studies point towards decreased activity of the inhibitory GABA system in patients with PD, although results of the available studies are inconclusive. Glutamate deploys its excitatory action *via* binding with N-methyl-D-aspartate and alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors, which are predominantly located in the cortical and limbic structures[103]. According to animal studies, glutamatergic neurotransmission in the lateral nucleus of the amygdala (LA) is involved in fear-conditioning and extinction[104]. Until now, only a few studies have investigated the possible role of glutamate in PD.

Zwanzger *et al*[101] studied the effects of cholecystokinin-tetrapeptide (CCK-4)-induced panic on brain glutamate plus glutamine (Glx) levels in eighteen healthy subjects by MRS. The authors reported an increase of Glx/creatine levels in the bilateral ACC peaking at 2-10 min after administration of a challenging task. Moreover, HPA axis stimulation was monitored while a significant increase in plasma cortisol was observed throughout the challenge. Maddock *et al*[105] investigated changes in glutamate plus glutamine in twenty-one PD patients (thirteen remitted, eight symptomatic) and twelve healthy control subjects. MRS was used to measure Glx changes in the visual cortex induced by visual stimulation. PD patients had smaller Glx responses than healthy control subjects, regardless of whether they were acutely ill or remitted. The authors conclude that their results contradict the assumption of a general upregulation of brain metabolic responses in PD.

Preclinical data have suggested that GABA and glutamate neurotransmission are modulated by the neuropeptide S (NPS) system. NPS receptors are widely distributed in the central nervous system with highest expressions in the cortex, thalamus, hypothalamus and the amygdala[106]. Polymorphisms of the NPS receptor gene might genetically drive altered fear circuit function and therefore increase the risk of PD in humans. Ruland *et al*[107] performed a study of CCK-4-induced panic on brain Glx levels and enrolled thirty-five healthy volunteers with functional neuropeptide S receptor gene (NPSR1) rs324981 A/T variants. MRS during the challenge revealed significantly lower increases of Glx/Cr levels in T risk allele carriers as compared to AA homozygotes in bilateral ACC. These results of a blunted and possibly maladaptive ACC glutamatergic reactivity in T allele carriers are in accordance with the assumption that the NPS system conceivably plays an important role in the pathophysiology of PD.

Brief summary: Glutamate is the main excitatory

neurotransmitter in the mammalian cortex. Preclinical studies have suggested that an excitatory-inhibitory imbalance of the glutamatergic and GABAergic systems might play a role in the etiology of PD. Glutamatergic neurotransmission in the amygdala is thought to be involved in fear-conditioning and extinction. The results of animal studies have further suggested that glutamatergic and GABAergic transmissions are modulated by the NPS system. NPS receptors are widely distributed in the central nervous system with highest expressions in the cortex, thalamus, hypothalamus and the amygdala. In a recent imaging genetic study, blunted glutamatergic ACC response due to CCK-4-induced panic was reported in NPSR1 risk allele carriers.

Imaging genetics

During the past decade, studies on the genetic basis of PD have focused on genes related to classical neurotransmitters, mainly monoamines. More recently, other groups of molecules have been identified, including genes involved in neurodevelopment and synaptic plasticity. More than twenty different genes were reported to confer susceptibility to - or modulate the pathological mechanisms of - PD[108]. Identified genes belong to different biological pathways and implicate inter alia the serotonergic, noradrenergic, neuropeptidergic (*e.g.*, NPS) or glucocorticoid system. Imaging genetic studies, as specified below, are designed to evaluate the impact of genetic variations (polymorphisms) on cerebral function in regions critical for PD. Most of the imaging genetic studies used functional magnetic resonance imaging. Some other studies assessed structural connectivity and structural alterations by DTI and VBM.

Genetic variations of serotonin receptor 1A, SERT, and MAOA

Evidence from preclinical and clinical research, including genetic studies, pharmacological trials and neuroimaging, reveals a substantial impact of the serotonin system and particularly the serotonin receptor 1A (5-HT1AR) on the neurobiology of PD[109,110]. Yu *et al*[111] performed an imaging genetic study by investigating the impact of 5-HTR1A polymorphism on WM connectivity within the cingulum bundle in PD. For this purpose, 32 patients were examined by DTI. The patients were divided into a CC genotype group and a non CC genotype group (GG/CG genotype group) with regard to the 5-HTR1A rs6295 polymorphism. Tractography revealed significantly increased FA values in the left cingulum bundle in the 5-HTR1A CC genotype group compared to the GG/CG genotype. The extent of this alteration was positively correlated with the severity of symptoms that was assessed by several rating scales. Another target of research is the serotonin transporter (*SERT*) gene, which is also hypothesized to be involved in the pathophysiology of PD due to its identified polymorphisms[112]. According to Bijlsma *et al*[113] disturbance of SERT functioning leads to fear learning deficits. In a preclinical study, the authors reported disrupted fear acquisition and a concomitant increase in contextual conditioned startle fear in SERT knockout rats. Kang *et al*[114] demonstrated that SERT polymorphisms can predict health-related quality of life assessments in patients with PD. They used the 36-Item Short Form Health Survey (SF-36), which is a set of generic and coherent quality of life measures. The sample consisted of 179 patients with PD and 110 healthy controls. Patients with PD showed lowered quality of life in all sub-domains of the SF-36 compared to healthy controls. SERT polymorphisms independently and additively accounted for 2.2% of variation (6.7% of inherited variance). Despite its conceivably significant role in the pathophysiology of PD, no imaging genetic study on the SERT polymorphisms in PD has yet been carried out. Reif *et al*[115] investigated the impact of a promoter polymorphism in the monoamine oxidase A gene (MAOA-uVNTR) on CBT response and brain activity in fear conditioning in a large controlled multicenter study on 369 patients with PD and agoraphobia. This promoter polymorphism is associated with PD and agoraphobia[116] and also has been demonstrated to influence gene expression and monoamine levels[117]. Carriers of the risk allele (causing higher activity of MAOA) had significantly worse clinical outcome. This was accompanied by elevated heart rate and increased fear during an anxiety exposition task. Moreover, risk allele carriers did not habituate due to repetitive exposure. FMRI with a classical fear conditioning paradigm revealed that the protective allele is associated with increased activation of the ACC upon presentation of the CS^+ during acquisition of fear. After treatment, further differentiation between high- and low-risk subjects was observed in the inferior parietal lobes, implying differential brain activation patterns upon CBT. This complex multicenter study has demonstrated that a genetic risk factor for PD and agoraphobia may be associated with poor response to CBT and specific underlying neural mechanisms. The authors emphasize that, in the future, genetic information might help to develop individualized treatment methods.

Brief summary: According to recent studies, SERT polymorphisms are associated with fear learning deficits and lowered quality of life measures in healthy subjects. Imaging genetic studies in PD have demonstrated that there is a significant impact of genetic variations on severity of symptoms (5-HTR1A) and response to CBT (MAOA). DTI revealed higher structural integrity within the left cingulum in patients carrying the 5-HTR1A risk allele. In an fMRI study, PD patients with a MAOA risk allele (causing higher activity of MAOA) exhibited a blunted anterior cingulate response during a classical fear conditioning paradigm. After cognitive behavioral treatment, differential brain activation patterns, primarily in the inferior parietal lobes, were described in high- and low-risk subjects.

Genetic variations of COMT and NET

With regard to the noradrenergic system, the COMT and *NET* gene polymorphisms are hypothesized to be involved in the pathophysiology of PD. Kim *et al*[53] studied the effects of the COMT gene polymorphism on WM connectivity in PD by DTI. Twenty-six patients with PD and 26 matched healthy controls were enrolled and underwent genotype analysis for COMT rs4680. No differences in WM connectivity were found between patients and healthy control subjects. However, comparison of COMT AA/AG genotype and GG genotype groups in PD patients revealed increased FA in posterior thalamic radiation, posterior and superior corona radiata, superior longitudinal fasciculus (SLF), and sagittal stratum, all located in the right hemisphere. Symptom severity scores in the COMT AA/AG genotype group were positively correlated with the FA in WM tracts. Inoue *et al*[118] investigated possible associations of COMT, human TransMEMbrane protein 132D (TMEM132D), and GABA receptor alpha 6 subunit (GABRA6) genotypes in PD patients and healthy controls. The polymorphisms rs4680 in COMT and rs3219151 in GABRA6 showed positive associations with PD. In a second step, the authors examined neurophysiological correlates of emotional function in the following areas: ACC and frontal cortex. In PD patients, fMRI responses in the bilateral ACC were stronger in carriers of the AA genotype *vs* AC + CC genotype in TMEM132D, and stronger in CT + TT genotype *vs* CC genotype in GABRA6. A response observed in the medial OFC was stronger in carriers of the CT + TT genotype in GABRA6. These results suggest that TMEM132D, GABRA6, and COMT variants may increase vulnerability to panic. Other genetic variants that have attracted growing interest are the polymorphism of the *NET* gene. The NET is responsible for the reuptake of norepinephrine into presynaptic nerve terminals. Buttenschøn *et al*[94] studied different variants located within the *NET* gene with regard to possible associations with PD. The case-control sample consisted of 449 patients with PD and 279 matched controls. Genotyping revealed 29 single nucleotide polymorphisms. Seven polymorphisms were significantly associated with PD, and the *NET* gene showed overall evidence for association with the disease. These results indicate that *NET* gene polymorphisms could be involved in the pathophysiology of PD.

Brief summary: Specific polymorphisms of *COMT* and *NET* genes have been demonstrated to be associated with a diagnosis of PD. COMT risk allele carriers suffering from PD seem to exhibit increased symptom severity, accompanied by disturbed WM connectivity in wide-spread areas of the right hemisphere (*e.g.*, posterior thalamic radiation, posterior and superior corona radiata, SLF, and sagittal stratum).

Polymorphism of neuropeptide S receptor 1 gene

As already mentioned in the paragraph "alterations of glutamatergic neurotransmission", NPS is thought to modulate GABAergic and glutamatergic neurotransmission and therefore might be involved in the pathophysiology of PD by affecting fear circuit function. Domschke *et al*[119] applied a multilevel approach to explore the role of a NPS receptor (*NPSR1*) gene variant (A/T) in the etiology of PD. The T allele leads to a 10-fold increase in NPSR expression and NPS efficacy[120]. Domschke *et al*[119] reported that the T allele was associated with PD in female patients. The T risk allele was also related to elevated anxiety sensitivity, increased heart rate and higher symptom reports during a behavioral avoidance test. During an emotional activation task, T allele carriers showed decreased activity in the dorsolateral prefrontal, lateral orbitofrontal and anterior cingulate cortices. Dannlowski *et al*[121] studied the effects of the T risk allele on amygdala and PFC function by means of fMRI. Seventy-nine healthy subjects were enrolled and genotyped for (*NPSR1*) gene variants. The authors reported increased amygdala and PFC responses to anxiety related emotional stimuli in risk allele carriers. Guhn *et al*[122] measured neural correlates of cognitive emotion regulation in 66 volunteers genotyped for the NPSR1 A/T variant (AA homozygotes *vs* T allele carriers) by means of an emotional n-back task presented during functional near-infrared spectroscopy scanning. T allele carriers showed a signal increase to negative pictures in the dorsolateral and medial prefrontal cortex (DLPFC and mPFC). The authors considered this activation to be part of an adaptive mechanism to compensate for presumably increased subcortical activity driven by an overactive NPS system. Neufang *et al*[123] investigated the impact of *NPSR1* gene variations in 47 healthy subjects on cerebral activation patterns during a task probing alerting functions (Attention Network Task) using fMRI. In the alerting condition, homozygote TT allele carriers showed higher activation in the right PFC and the LC as compared to the AA/AT group. In a recent study, Domschke *et al*[124] explored the influence of NPSR1 genotypes on fronto-limbic connectivity within the developing brain. Sixty healthy subjects (8-21 years) were examined by fMRI during presentation of a go/no-go task. In A allele carriers, connectivity between the right DLPFC and the right amygdala was higher in older ($\geqslant$ 14 years) than in younger ($<$ 14 years) subjects. TT homozygotes ($\geqslant$ 14 years) showed a reduction of fronto-limbic connectivity between the DLPFC and both the amygdala and the insula. These results suggest a risk-increasing effect of the NPSR1T allele for possible anxiety-related traits *via* impaired top-down control of limbic structures during adolescence.

Brief summary: The T risk allele of the *NPSR1* gene is associated with PD in female patients. This genetic variation is also related to elevated anxiety sensitivity. Moreover, fMRI studies revealed decreased activity in the dorsolateral prefrontal, lateral orbitofrontal and anterior cingulate cortices. Healthy subjects carrying

the risk allele exhibit increased amygdala and PFC responses to anxiety related emotional stimuli. During a probe of alerting function, higher activations in the right PFC and the LC region have been observed in healthy risk allele carriers. The results of a very recent study suggest that the NPSR1T allele might be responsible for impaired top-down control of limbic structures during adolescence, therefore increasing the risk for possible anxiety-related traits.

Polymorphisms of corticotropin releasing hormone receptor 1 gene

Another neuropeptide that has attracted attention is the neurotransmitter corticotropin-releasing hormone (CRH), also known as corticotropin-releasing factor (CRF) or corticoliberin. CRH plays a central role in the regulation of the HPA axis. The CRH receptor 1 (CRHR1) triggers the release of the stress response regulating hormone cortisol. Preclinical and clinical studies have indicated that CRHR1 is a possible candidate gene for mood and anxiety disorders[79,125,126]. Weber *et al*[127] studied different variants located within the CRHR1 gene with regard to possible associations with PD. Genotyping in 531 matched case/control pairs (PD patients and healthy control subjects) revealed 9 single nucleotide polymorphisms (SNPs). Four SNPs were associated with PD. One risk allele (the minor allele of rs17689918) was found to significantly increase risk for PD in females. Subsequently, fMRI was used in 48 PD patients. The risk allele carriers showed aberrant fear conditioning predominantly in the bilateral prefrontal cortex and altered safety signal processing in the amygdala, suggesting existing fear sensitization and sustained fear. Furthermore, in this multilevel study, Weber *et al*[127] performed an expression analysis of *CRHR1* gene. For this purpose, postmortem tissue of 76 deceased individuals obtained from the MRC Sudden Death Brain and Tissue Bank, Edinburgh, United Kingdom, was analyzed. In *CRHR1* risk allele carriers, the authors found decreased *CRHR1* mRNA expression in forebrains and amygdalae. These results indicate that *CRHR1* polymorphisms may play a significant role in the pathophysiology of PD and elucidate the mechanisms by which genetic variation in *CRHR1* is linked to this disorder. Aberrant fear conditioning due to *CRHR1* variation has been investigated in an earlier study by Heitland *et al*[128]. One-hundred and fifty healthy volunteers were genotyped for *CRHR1* gene polymorphism rs878886. Risk allele carriers showed no acquisition of fear conditioned responses (FPS) to a threat cue in the uninstructed phase. Moreover, these participants exhibited increased FPS. In a recent study, the authors were able to replicate their results in a larger sample (n = 224)[129].

Brief summary: Preclinical and clinical studies have indicated that *CRHR1* is a possible candidate gene for PD. In a multi-level study, one allele was found to increase risk for PD in females. Aberrant fear conditioning due to *CRHR1* variation was demonstrated in PD as well as in healthy subjects. MRI scans in PD patients revealed that risk allele carriers exhibited aberrant fear conditioning with blunted activations in the bilateral prefrontal cortex. Moreover, during processing of safety cues, patients of this group showed elevated responses in the amygdalae compared to patients without the risk allele. Behavioral and neurofunctional findings of this study indicated an increased fear sensitization and sustained fear in this group. Postmortem analyses in risk allele carriers revealed decreased *CRHR1* mRNA expression in the PFC and amygdala.

Polymorphisms of human TransMEMbrane protein TMEM123D and amiloride-sensitive cation channel 2 genes

The human TransMEMbrane protein TMEM123D is expressed in neurons and colocalized with actin filaments that putatively function as a cell-surface marker for oligodendrocyte differentiation[130]. Recent case-control genome-wide association studies have linked variants of the TMEM132D gene with PD, anxiety comorbidity with depression, and anxiety symptom severity in healthy and diseased subjects[131,132]. Haaker *et al*[133] investigated an independent sample of 315 healthy normal subjects (99 female) of Caucasian descent, of which 132 (22 female) underwent structural MRI assessment. Carriers of a specific risk allele (rs11060369 A homozygotes) showed higher GM volumetric estimates in the left amygdala. Moreover, participants of this group had higher ratings for trait anxiety, behavioral inhibition, and negative affect. Variants of the *TMEM123D* gene therefore may play an important role in the etiology of PD.

Animal studies have shown that carbon dioxide-mediated fear behavior depends on chemosensing of acidosis in the amygdala through the acid-sensing ion channel[134]. In humans, the amygdala also acts as a chemosensor that detects hypercarbia and acidosis *via* the amiloride-sensitive cation channel 2 (ACCN2)[135]. Patients with PD exhibit a hypersensitivity to inhaled carbon dioxide, possibly reflecting a lowered threshold for sensing signals of suffocation[136]. Smoller *et al*[135] examined whether genetic variation of ACCN2 is associated with PD, as well as with amygdala structure and function. The authors conducted a case-control analysis (n = 414 PD cases and 846 healthy control subjects) of ACCN2 SNPs. Two SNPs at the ACCN2 locus showed evidence of association with PD (rs685012; rs10875995). The association appeared to be stronger when PD cases with early-onset (age $\leqslant$ 20 years) and with prominent respiratory symptoms were compared with controls. One of the detected PD risk alleles (rs10875995) was associated with increased amygdala volume and heightened task-evoked amygdala reactivity to fearful and angry faces as assessed by fMRI. These results suggest that altered chemosensing of acidosis in the amygdala triggered by *ACCN2* gene

variants may be involved in the pathophysiology of PD.

Brief summary: Recent association studies have linked variants of the *TMEM132D* gene with PD. Morphometric analyses in healthy volunteers revealed that carriers of a specific risk allele show increased GM volume in the left amygdala. Moreover, these subjects had higher ratings for trait anxiety, behavioral inhibition, and negative affect. Thus, the results of population genetic studies are confirmed by imaging genetic studies.

Patients with PD exhibit increased sensitivity to inhaled carbon dioxide. The amygdala acts as a chemosensor that detects hypercarbia and acidosis *via* the *ACCN2*. In a recent study, it was demonstrated that genetic variation of *ACCN2* is associated with PD as well as with amygdala structure and function. Two polymorphisms of the *ACCN2* gene showed association with PD. One of the detected PD risk alleles was associated with increased amygdala volume and elevated amygdala reactivity to fearful and angry faces. These results suggest that genetic variation of *ACCN2* may be involved in the pathophysiology of PD.

DISCUSSION

Functional neuroimaging studies

The "fear network" proposed by Gorman *et al*[11] includes the amygdala, the hippocampus, thalamus, hypothalamus, the PAG region, LC, and other brainstem sites. Prior neuroimaging studies have reinforced the role of these regions in the pathophysiology of PD. Additionally, functional alterations in the ACC, orbitofrontal cortex, and insula have been reported (for comprehensive literature overviews, see *e.g.*[15,16,137]). Recent functional studies suggest abnormal activation mainly in an extended fear network comprising brainstem, anterior and midcingulate cortex, insula, and lateral as well as medial parts of the prefrontal cortex. Interestingly, differences in the amygdala activation were not as consistently reported as one would predict from the hypothesis of Gorman *et al*[11]. Feldker *et al*[29] stated that, given the role of the amygdala proposed for the pathophysiology of PD, it seems surprising that amygdala hyperactivation only reached marginal significance. In the same tenor, Etkin *et al*[138] concluded that "in PD, amygdala hyperactivity appears to be the exception, rather than the rule". At present, it remains unclear whether aberrant amygdala activation is simply not as characteristic of PD as proposed earlier, whether it is too weak to be detected with common thresholds, or whether specific methodological limitations make it difficult to detect. Indeed, amygdala hyperactivation seems to strongly depend on stimuli and experimental paradigms, sample heterogeneity and size, as well as on limitations of neuroimaging techniques[16,139,140]. However, in our view, it is notable that the amygdala is strongly involved in salience and significance detection in the information stream[141]. Since paradigms with specific fear-evoking stimuli are more difficult to develop for PD patients in contrast to patients with specific phobias, we can speculate that the often observed lack of amygdala hyperactivation in PD might be based on such methodological issues, *e.g.*, using appropriate stimuli and experimental paradigms.

In summary, the alterations of neural activation in patients with PD as reported in past and present studies are somewhat inconsistent. Interestingly, two very recent studies using clear panic-related pictorial stimuli and relatively large sample sizes have put strong emphasis on a specific role of the insula and dACC in the pathophysiology of PD[29,32]. There is growing evidence that the insula, the dACC as well as subcortical structures, such as the amygdala, play a crucial role in salience processing across multiple sensory and cognitive domains by integrating external sensory information with internal emotional and bodily state signals[142]. The latter can be paraphrased with the term interoception, which refers to conscious awareness, emotional processes and behavior related to physiological information arising from the body. This includes processing of proprioceptive and viscerceptive processes such as heart rate, respiration, and blood pressure. Abnormal interoception has been suggested to play a key role in the etiology and maintenance of anxiety disorders[143] in terms of oversensitive perception of somatic sensations and subsequent catastrophizing interpretations. There is evidence to assume that ascending inputs providing information about interoceptive and visceromotor signals related to the current bodily state converge in the insular cortices[144]. In close cooperation with the amygdala, insular activity seems to represent a specific subjective emotional state and the emotive value of external stimuli in terms of salience[145]. Thus, this observation may explain differences between studies on PD patients regarding the amygdala or insula activation, which might be attributed to different subjective emotive values of presented stimuli. Another source of variability that induces potentially different insula/amygdala activation in patients with PD, as well as in control subjects, is the subject-specific state of physiological arousal. Thus, simultaneous acquisition of physiological signals, *e.g.*, heart or respiratory rate in the MR scanner, may potentially explain some part of activation variance in these brain structures.

In addition, the ACC is another brain structure considered to be a key node within the salience network[142] and which has often been observed to show abnormal functioning in PD. It is involved in automatic attentional control as well as in response selection and conflict monitoring[146], thus enabling rapid access to the motor system.

Moreover, the salience network recruits the ventral fronto-parietal network, mainly consisting of the temporo-parietal junction and inferior frontal gyrus (IFG)[147], which is typically activated by infrequent or unexpected behaviorally relevant (salient) events. This recruits additional executive resources to ensure focused attention on task-relevant goals, *e.g.*, to cope with panic-

relevant stimuli[148]. This may explain the often observed abnormal activation of the IFG in patients in PD.

In summary, besides the brainstem/midbrain, amygdala and prefrontal cortex, further brain areas such as the insula and the ACC are emerging from recent imaging studies in PD and seem to be of greater importance than originally proposed.

Interestingly, recent studies applying the DTI to investigate the WM connectivity in PD reported abnormal WM integrity in the cingulum bundle as well as in the major fiber tracts, which connect frontal with temporal, parietal and occipital brain regions: The inferior and superior longitudinal fasciculi[149]. This finding is in accordance with the observation of abnormal functional activation in regions of the salience network and of the ventral fronto-parietal network. However, to date only few studies have investigated the integrity of specific WM tracts in patients with PD. Therefore, more studies are required to elucidate the abnormal structural connectivity in PD.

Structural neuroimaging studies

With regard to structural brain imaging studies of GM, volumetric and morphometric changes in limbic structures in frontal and temporal cortical areas, in the basal ganglia, in the pituitary gland and hypothalamus as well as in the midbrain/brainstem structures were reported in recent studies. Similar findings have been described in prior neurostructural studies in PD[15,44,150-152]. The relatively large heterogeneity between studies makes it difficult to relate abnormal GM structure in a specific brain region or a network to PD. The reasons for this inconsistency are manifold. Many of the reviewed studies had the disadvantages of relatively small sample sizes and of comorbid depression or other psychiatric disorders among patients, which may also have an impact on the GM volume estimation.

Neurochemical studies

A major role of serotonin in the pathophysiology of PD has been deduced from the therapeutic effects of serotonergic drugs[62,63]. In accordance with this hypothesis, studies on 5-HT1AR and SERT binding have revealed altered and mostly reduced serotonergic activity in the raphe nuclei, orbitofrontal cortex, temporal lobes, ACC and PCC, amygdala, and hypothalamus in patients with PD[71-74]. In the course of therapy with SSRIs postsynaptic alterations seem to decline, while the presynaptic changes persist[72]. In addition to these functional alterations structural abnormalities, *e.g.*, disintegration of the raphe nuclei in the brainstem, have also been described[75]. Ascending serotonergic projections to cortical and subcortical brain regions have their origin mainly in the dorsal and median raphe nuclei. There is evidence from current animal studies, that efferent inputs of dorsal raphe neurons may moderate panic-like defensive behaviors by controlling the activity of the dorsal PAG[78,79], thus confirming the earlier hypotheses of Deakin and Graeff[77] as well as of Gorman *et al*[11] on this point. Very recently, serotonergic transmission has been proposed as a possible new drug target for PD, as suggested by the results of a preclinical study, which demonstrated that a 5-HT7 receptor antagonist reduced fear memory retrieval[83].

The noradrenergic system is centrally involved in the regulation of the attentional alerting system[84], which exhibits increased activity during states of anxiety[89,90]. Noradrenergic transmission is closely linked to the serotonergic system and to the HPA axis, and therefore mediates between central arousal and peripheral physical reactions[11]. Neurochemical studies have revealed higher baseline noradrenaline secretion and increased reactivity to challenges of the noradrenergic system in patients suffering from PD[86-88]. Recently, genetic studies have demonstrated that there is an association between PD and variations in *COMT*[91], *MAOA*[92], and *NET*[93-95] genes, thus underlining the important role of noradrenergic transmission in the pathophysiology of PD.

Benzodiazepines are among the most potent and powerful anxiolytic agents[96]. These drugs act through an enhancement of gamma-aminobutyric acidergic (GABAergic) inhibition, targeting the GABA receptor[97]. This fact, along with the results of several neurochemical studies points towards an involvement of the GABA system in the pathophysiology of PD. Decreased GABAergic inhibition was reported in limbic, frontal, temporal, and respectively insular regions[15,98,99]. Unfortunately, the findings regarding the GABAergic system are partly inconsistent and may not be specific for PD[100].

Glutamate is the main excitatory neurotransmitter in the mammalian cortex. It is the metabolic precursor of GABA, which can be recycled through the tricarboxylic acid cycle to synthesize glutamate[102]. Preclinical studies have suggested that an excitatory-inhibitory imbalance of the glutamatergic and GABAergic systems might play a role in the etiology of PD[101]. Glutamatergic neurotransmission in the lateral nucleus of the amygdala is thought to be involved in fear-conditioning and extinction[104]. The results of animal studies have further suggested that glutamatergic and GABAergic transmissions are modulated by the NPS system. NPS receptors are widely distributed in the central nervous system with highest expressions in the cortex, thalamus, hypothalamus and the amygdala[106]. In a recent imaging genetic study, blunted glutamatergic ACC response due to CCK-4-induced panic was reported in *NPSR1* risk allele carriers[107]. The results of additional imaging genetic studies on genetic *NPSR1* variations will be presented below.

Imaging genetics

During the past decade, studies on the genetic basis of PD focused on genes related to classical neurotransmitters, mainly monoamines. More recently, other

groups of molecules have been identified, including genes involved in neurodevelopment and synaptic plasticity. More than twenty different genes were reported to confer susceptibility to - or modulate the pathological mechanisms of - PD[108]. Identified genes belong to different biological pathways and implicate inter alia the serotonergic, noradrenergic, neuropeptidergic (*e.g.*, NPS) or glucocorticoid system. Imaging genetic studies, as specified below, are designed to evaluate the impact of genetic variations (polymorphisms) on cerebral function in regions critical for PD. Most of the imaging genetic studies used functional magnetic resonance imaging. Some other studies assessed structural connectivity and structural alterations by DTI and VBM.

Serotonergic system: According to recent genetic studies, SERT polymorphisms are associated with fear learning deficits[113] and lowered quality of life measures[114] in healthy subjects. Imaging genetic studies in PD have demonstrated that there is a significant impact of genetic variations on severity of symptoms (5-HTR1A)[111] and response to CBT (MAOA)[115]. DTI revealed increased structural integrity within the left cingulum in patients carrying the 5-HTR1A risk allele[111]. In an fMRI study, PD patients with an *MAOA* risk allele (causing higher activity of MAOA) exhibited a blunted anterior cingulate response during a classical fear conditioning paradigm. After CBT treatment, differential brain activation patterns, primarily in the inferior parietal lobes, were described in high- and low-risk subjects[115].

Noradrenergic system: Specific polymorphisms of *COMT*[91] and *NET*[93-95] genes have been demonstrated to be associated with a diagnosis of PD. COMT risk allele carriers suffering from PD seem to exhibit increased symptom severity accompanied by disturbed WM connectivity in wide-spread areas of the right hemisphere[53].

Neuropeptidergic system: The T risk allele of the *NPSR1* gene is associated with PD in female patients. This genetic variation is also related to elevated anxiety sensitivity. Moreover, fMRI scans revealed decreased activity in the DLPFC, lateral OFC and ACC[119]. Healthy subjects carrying the risk allele exhibit increased amygdala and PFC responses to anxiety related emotional stimuli[121]. During a probe of alerting function, higher activations in the right PFC and the LC have been observed in healthy risk allele carriers[123]. Results of a very recent study suggest that the *NPSR1* T allele might be responsible for impaired top-down control of limbic structures during adolescence, therefore increasing the risk for possible anxiety-related traits[124].

CRH: Another neuropeptide that has attracted attention is the neurotransmitter CRH. CRH plays a central role in the regulation of the HPA axis. Preclinical and clinical studies have indicated that CRHR1 is a possible candidate gene for PD[125,126]. In a multi-level study by Weber *et al*[127], one allele was found to increase risk for PD in females. Aberrant fear conditioning due to *CRHR1* variation was demonstrated in PD as well as in healthy subjects. MRI scans in PD patients revealed that risk allele carriers exhibited aberrant fear conditioning with blunted activations in the bilateral prefrontal cortex. Moreover, during processing of safety cues, patients of this group showed elevated responses in the amygdalae compared to patients without the risk allele. Behavioral and neurofunctional findings of this study indicated an increased fear sensitization and sustained fear in this group. Postmortem analyses in risk allele carriers (brain tissue was obtained from a Tissue Bank) revealed decreased CRHR1 mRNA expression in the PFC and amygdala[127].

Human TransMEMbrane protein (TMEM123D): TMEM123D is expressed in neurons and colocalized with actin filaments that putatively function as a cell-surface marker for oligodendrocyte differentiation[130]. Recent association studies have linked variants of the *TMEM132D* gene with PD[131,132]. Morphometric analyses in healthy volunteers revealed that carriers of a specific risk allele show increased GM volume in the left amygdala. Moreover, these subjects had higher ratings for trait anxiety, behavioral inhibition, and negative affect[133]. Thus, the results of population genetic studies were confirmed by imaging genetic studies.

Amiloride-sensitive cation channel 2: Patients with PD exhibit increased sensitivity to inhaled carbon dioxide[136]. The amygdala acts as a chemosensor that detects hypercarbia and acidosis *via* the ACCN2[135]. In a recent multi-level study by Smoller *et al*[135] it was demonstrated that genetic variation of *ACCN2* is associated with PD as well as with amygdala structure and function. Two polymorphisms of the *ACCN2* gene showed association with PD. One of the detected PD risk alleles was associated with increased amygdala volume and elevated amygdala reactivity to fearful and angry faces. These results suggest that genetic variation of *ACCN2* may be involved in the pathophysiology of PD.

As stated above, the intention of imaging genetic studies is to evaluate the impact of genetic variation (polymorphisms) on cerebral function in regions critical for PD. Given the fact that PD is a multifaceted disease with various pathogenic pathways, the etiological effects of specific polymorphisms shall not be overestimated or generalized. Nevertheless, genetic imaging will help to understand the multitude and the interplay of pathogenic factors in PD. Moreover, future neuroimaging studies will become more sophisticated by including genetically defined patient and control samples. Regardless of the undeniable advantages of imaging genetics, some limitations of the studies presented above have to be mentioned: (1) results of studies in healthy subjects may not or only to some extent be transferable to patients suffering from PD; (2) given the wide variety of genes involved in the pathophysiology of PD, it is still

difficult to define homogenous samples and to control for interfering factors; (3) general methodological limitations of neuroimaging studies (*e.g.*, related to paradigms and assessment techniques; please see above) cannot be avoided; (4) identified genes often fail to find replication in larger cohort sets or in different populations; and (5) epigenetic factors and non-coding genomic elements may also play a role in the pathophysiology of PD[153]. Nevertheless, great progress has been made in the field of genetics of psychiatric disorders and by now there is a considerable amount of notable findings. In this light, it is conceivable that in the near future this research will lead to the development of clinically useful tools such as predictive biomarkers or novel treatment options.

Limitations and future directions

This review discusses the recently published neurofunctional, neurostructural and neurochemical alterations in PD.

However, the premise that PD is a single phenotype, might not be accurate. Studies on abnormal brain structure in PD revealed a relatively large heterogeneity of significant findings, which makes it difficult to relate specific regions or tracts with aberrant gray or WM to PD. Additionally, the application of functional MRI did not reduce the heterogeneity of reported findings, even if the brain's salience network, mainly composed of the amygdala, insula and ACC becomes increasingly important for the understanding of panic attacks.

On the other hand, the new era of imaging genetics provided first insights into the potential etiological heterogeneity of PD. Imaging genetic studies have not only confirmed the importance of serotonergic and noradrenergic transmission in the etiology of PD, but also indicated the significance of neuropeptide S receptor and CRH receptor gene variants. These new insights reveal possible targets for the development of drugs for personalized anxiolytic treatment. Furthermore, appropriate imaging genetics studies may lead to a better understanding of non-response to psychotherapy, *e.g.*, due to the variability of top-down control that the prefrontal/anterior cingulate cortex exerts on the amygdala/hippocampus, as well as on the brainstem in PD[154]. In the future the imaging genetics approach will be of major importance for the further development of the neuroanatomical model, because genetic risk variants may significantly influence fear network activity in PD[15]. Therefore, imaging genetic consortia are necessary to accumulate a sufficient number of functional and structural brain scans, which may allow researchers to detect genome-wide significant loci affecting brain function and structure in PD.

COMMENTS

Background

Panic disorder (PD) is a frequent psychiatric disease. Gorman *et al* (2000) proposed a comprehensive neuroanatomical model of PD, which suggests that fear- and anxiety-related responses are mediated by a so-called "fear network" which is centered in the amygdala and includes the hippocampus, thalamus, hypothalamus, periaqueductal gray region, locus coeruleus and other brainstem sites. It was further assumed that the serotoninergic system plays a pivotal role in the etiology of PD.

Research frontiers

The main focus of this systematic review was laid on recent neurofunctional, neurostructural, and neurochemical studies. Within this frame, special attention was given to the emerging field of imaging genetics.

Innovations and breakthroughs

Recent functional imaging studies revealed abnormal activation not only in the "fear network" proposed by Gorman *et al* (2000), but also in additional brain regions such as anterior and midcingulate cortex, insula, and prefrontal cortex. Thus, the so-called "salience" network of the brain becomes increasingly important for the understanding of PD. Advanced neurochemical studies have substantiated the major role not only of serotonergic, but also of noradrenergic and glutamatergic neurotransmission in the pathophysiology of PD. In addition, imaging genetic studies have confirmed the importance of serotonergic and noradrenergic transmission in the etiology of PD and, moreover, have indicated the significance of neuropeptide S receptor and CRH receptor gene variants.

Applications

Genetic imaging studies have revealed that genetic risk variants may significantly affect fear network activity in PD. Thus, the inhomogeneity of neuroimaging findings, as reported in this review, could be partly due to such influences. In future studies these effects will have to be considered carefully. Other practical applications of the genetic imaging approach could be the development of clinically useful tools such as predictive biomarkers or drugs for personalized anxiolytic treatment.

Terminology

All terms that may not be familiar to the majority of the readers are explained at the beginning of each major section.

Peer-review

This is, in summary, an interesting review manuscript aimed to provide a detailed and comprehensive overview of the current research in the functional neuroanatomy of panic disorder. The authors mainly focused on recent neurofunctional, neurostructural, and neurochemical studies about the specified topic. They concluded that it is conceivable that new research advances may lead in the near future to the development of clinically useful tools like predictive biomarkers or novel treatment options.

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SYSTEMATIC REVIEWS

Neuroimaging studies of cognitive remediation in schizophrenia: A systematic and critical review

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Abstract

AIM

To examine the effects of cognitive remediation therapies on brain functioning through neuroimaging procedures in patients with schizophrenia.

METHODS

A systematic, computerised literature search was conducted in the PubMed/Medline and PsychInfo databases. The search was performed through February 2016 without any restrictions on language or publication date. The search was performed using the following search terms: [("cogniti*" and "remediation" or "training" or "enhancement") and ("fMRI" or "MRI" or "PET" or "SPECT") and (schizophrenia or schiz*)]. The search was accompanied by a manual online search and a review of the references from each of the papers selected, and those papers fulfilling our inclusion criteria were also included.

RESULTS

A total of 101 studies were found, but only 18 of them fulfilled the inclusion criteria. These studies indicated that cognitive remediation improves brain activation in neuroimaging studies. The most commonly reported changes were those that involved the prefrontal and thalamic regions. Those findings are in agreement with the hypofrontality hypothesis, which proposes that frontal hypoactivation is the underlying mechanism of cognitive impairments in schizophrenia. Nonetheless,

great heterogeneity among the studies was found. They presented different hypotheses, different results and different findings. The results of more recent studies interpreted cognitive recovery within broader frameworks, namely, as amelioration of the efficiency of different networks. Furthermore, advances in neuroimaging methodologies, such as the use of whole-brain analysis, tractography, graph analysis, and other sophisticated methodologies of data processing, might be conditioning the interpretation of results and generating new theoretical frameworks. Additionally, structural changes were described in both the grey and white matter, suggesting a neuroprotective effect of cognitive remediation. Cognitive, functional and structural improvements tended to be positively correlated.

CONCLUSION

Neuroimaging studies of cognitive remediation in patients with schizophrenia suggest a positive effect on brain functioning in terms of the functional reorganisation of neural networks.

Key words: Cognitive remediation; Cognitive training; Neuroimaging; Cognition; Prefrontal cortex; Thalamus; Plasticity; Schizophrenia

Core tip: Cognitive remediation therapy for schizophrenia is an evidence-based psychological treatment that aims to improve cognitive dysfunction. However, its underlying neural mechanisms have not been established. Several neuroimaging studies have shown positive effects in terms of brain activation. However, the results have been heterogeneous and difficult to integrate. The primary aim of the present review was to analyse systematically all of the published trials that used neuroimaging procedures. Additionally, we performed a more qualitative analysis examining the possible influence of neuroimaging methods and the use of different theoretical frameworks.

Penadés R, González-Rodríguez A, Catalán R, Segura B, Bernardo M, Junqué C. Neuroimaging studies of cognitive remediation in schizophrenia: A systematic and critical review. *World J Psychiatr* 2017; 7(1): 34-43 Available from: URL: http://www.wjgnet.com/2220-3206/full/v7/i1/34.htm DOI: http://dx.doi.org/10.5498/wjp.v7.i1.34

INTRODUCTION

Cognitive remediation therapy for schizophrenia is a psychological treatment that proposes to ameliorate cognitive dysfunction. It has been defined as a behavioural training-based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalisation[1]. Although the described effects have been modest, several trials and two meta-analyses have established its efficacy, improving not only cognition but also daily functioning[1,2]. Nonetheless, the underlying neural mechanisms of this treatment have not yet been well established.

Over the past few years, several neuroimaging studies have been conducted with the intention of identifying the different brain mechanisms underlying cognitive recovery. Some positive effects in terms of brain activation have been described, although the results have been heterogeneous[3,4]. Owing to this heterogeneity among the studies presenting different hypotheses, different results and different findings, we understand the need to review systematically all of the published works to provide new insights that would help to generate a new hypothesis in the near future. Moreover, recent revisions in the field of neuroimaging have indicated the need to explore not only the results but also the methods and theoretical frameworks[5].

The objective of the present review was to analyse neuroimaging studies that have tested the effects of cognitive remediation on brain functioning in patients with schizophrenia. To do so, we systematically reviewed published trials that used a cognitive remediation treatment and neuroimaging procedures. Additionally, we performed a more qualitative analysis examining the possible influence of neuroimaging methods and the use of different theoretical frameworks.

MATERIALS AND METHODS

Literature search

A systematic, computerised literature search was conducted in different online scientific databases: PubMed/Medline and PsychInfo. The search was performed through February 2016 without any restrictions on language or publication date. The search was performed using the following search terms: [("cogniti*" and "remediation" or "training" or "enhancement") and ("fMRI" or "MRI" or "PET" or "SPECT") and (schizophrenia or schiz*)]. This search was accompanied by a manual online search and review of the references from each of the papers selected, and those papers fulfilling our inclusion criteria were also included.

The following inclusion criteria were applied. Studies in which any imaging technique was used to assess the effect of cognitive training were selected. Assessments had to be conducted both at baseline and also after therapy. We excluded those articles that did not report any results, for instance, presentations or descriptions of interventions or study designs. Regarding the intervention, we only included studies in which patients were provided with multiple sessions of cognitive training, and programmes focusing only on social cognition were excluded.

RESULTS

In total 101, studies were obtained, and 18 of them

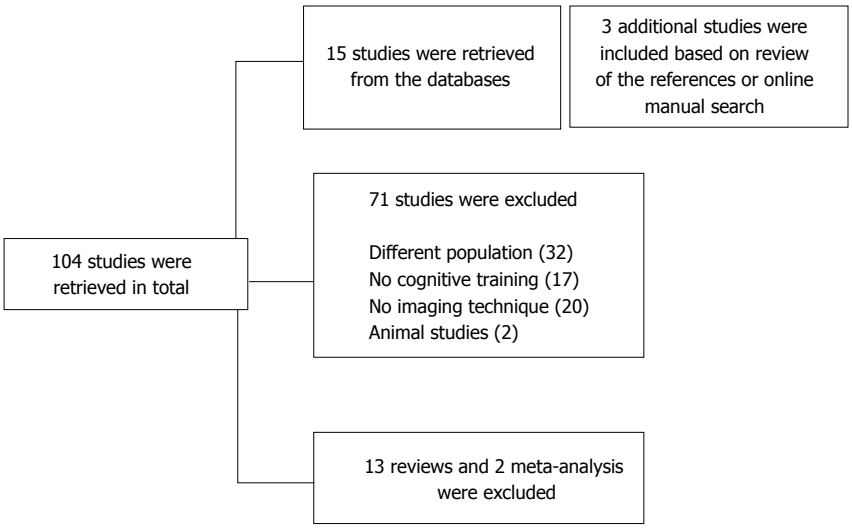

Figure 1 Diagram of literature search.

fulfilled the inclusion criteria (Figure 1). In addition to the differences in neuroimaging variables that will be analysed in subsequent paragraphs, an important heterogeneity in the characteristics of the retrieved studies was found (Table 1). Cognitive intervention approaches frequently differed among the studies, ranging from paper and pencil tasks, computerised cognitive training, training delivered in group format or individualised sessions with a therapist, simple auditory training, multimodal training and so on. The duration of the therapies ranged from less than one week to two complete years, with the mean duration of the training being 12.47 wk and 11 studies (64.7%) being between 10 and 16 wk in length. In addition, the cognitive remediation approaches focused on a single cognitive function to others focusing on all cognitive aspects possible, including social cognition. Because of the heterogeneity of the methodologies, interventions and assessments, we decided to rely on a qualitative description rather than a quantitative analysis.

First period: Improving brain activation

The first studies performed in the 1990s seemed to be inspired by the simple assumption that cognitive remediation would be able to cause some detectable effects on brain functioning. Thus, any visible changes in brain functioning would be considered a success. During that period, the use of functional neuroimaging techniques, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) procedures, were predominant. Both procedures helped to establish the hypothesis of hypofrontality. Hypofrontality was defined as a state of decreased cerebral blood flow or reduced utilisation of glucose in the prefrontal cortex of the brain[6,7]. Thus, testing cognitive remediation with PET or SPECT was the best option for researchers, more specifically in the context of the hypothesis of hypofrontality using analysis of regions of interest (ROIs), in this case, the prefrontal cortex. Thus, any detectable change in terms of brain activation indicating any sort of reduction of the hypofrontality would be proof that cognitive remediation was working well.

Thus, the first study to test the effects of cognitive remediation through SPECT procedures was performed by Wykes *et al*[8], who reported that two patients showed changes in frontal perfusion patterns after cognitive treatment. Penadés *et al*[9] found similar results, describing an increase in prefrontal blood flow during task performance following cognitive treatment in a case report study including two patients. These results were extended and confirmed in a later study with a small sample of eight patients[10]. However, two intriguing aspects from these studies raised questions that remain open. Firstly, not only increases but also decreases in the activation of some specific brain regions could be related to cognitive improvement. In the Wykes *et al*[8], not only increased but also decreased activity was found in the bilateral frontal, temporal, parietal and occipital regions. Secondly, another open question is the variables that could explain the intersubject variability, preventing the success of cognitive remediation in some patients. In a study by Penadés *et al*[9] with two patients, one had clearly improved prefrontal brain activation, while no significant changes were found in the other patient. Nonetheless, despite these and other possible open questions, this initial period offered promising results that were able to establish the idea that cognitive remediation is able to improve brain activation and eventually reduce hypofrontality. This line of thought was applied by Wexler *et al*[11] using a different methodology: Functional magnetic resonance imaging (fMRI). They described in a longitudinal study the progressive effects of cognitive remediation on brain functioning. In particular, they found increased task-related activation in the prefrontal cortex, which is the same brain region that was activated during memory tasks in healthy individuals. Improvement in brain activation was associated with cognitive changes, specifically verbal memory improvement.

In summary, in this initial period from 1998 to 2002, both SPECT and fMRI studies were able to

Table 1 Studies included in the systematic review

Ref.	Participants	Treatment	Treatment duration (wk)	Imaging method	Experimental task	Neural treatment effects	Direction of change
Cognitive remediation							
Wykes *et al*[8]	SCH = 2	CRT	12	SPECT	Verbal fluency	Bilateral frontal, temporal, parietal and occipital	↑
Penadés *et al*[9]	SCH = 2	CRT	12	SPECT	Tower of London	Prefrontal activity	↑
Wexler *et al*[11]	SCH = 8	CRT	10	fMRI	Auditory verbal memory	L inferior frontal	↑
Penadés *et al*[10]	SCH = 8	CRT	12	SPECT	Tower of London	Prefrontal activity	↑
Wykes *et al*[12]	SCH = 12 HC =6	CRT OC HC	12	fMRI	N-back	R inferior frontal gyrus and bilateral occipital activity	↑
Eack *et al*[20]	SCH = 53	CET EST	52	MRI	-	Loss of GM in temporal cortex, including the L parahippocampal gyrus, L amygdala, bilateral anterior cingulate, and L hippocampus	↓
						GM in L amygdala	↑
Haut *et al*[13]	SCH = 21 HC = 9	CRT CBSST	6	fMRI	N-back, lexical task	L prefrontal activity	Case report series
Rowland *et al*[15]	SCH = 17 HC = 17	CRT	< 1	fMRI, VBM		L amygdala, bilateral inferior parietal regions	↑
						Controls also exhibited activation reductions in region and spatial extent with relational learning proficiency	↓
Edwards *et al*[14]	SCH = 22 HC = 14	CRT	22	fMRI	Continuous performance task	R middle frontal R superior parietal cortex R inferior frontal junction R visual cortex Cerebellum	↑↓
Bor *et al*[16]	SCH = 20 HC = 15	CRT	8	fMRI	N-back	L inferior/middle frontal gyrus, cingulate gyrus and inferior parietal lobule activity	↑
Subramaniam *et al*[19]	SCH = 31 HC = 16	AT	13	fMRI	Word generation and recognition	Medial PFC activity	↑
Penadés *et al*[21]	SCH = 31 HC = 16	CRT SST	15	fMRI, DTI	N-back	L superior parietal lobule and bilateral middle frontal gyri activity	↑
						DMN activity in L precuneus and middle frontal gyrus	↓
						FA in CC and R posterior thalamic radiations	↑
Vianin *et al*[22]	SCH = 16	CRT	8	fMRI	Verbal fluency	Inferior parietal lobule, precentral gyrus, Broca's area, middle occipital cortex, middle cingulate cortex, and superior parietal lobule activity	↑
Subramaniam *et al*[23]	HC = 15 SCH = 30	AT	15	fMRI	N-back	Middle frontal and inferior frontal gyri activity	↑
Social-cognitive remediation							
Haut *et al*[13]	SCH = 20 HC = 10	TAR TAU	10	fMRI	Facial affect recognition	L middle and superior occipital lobe, R inferior and superior parietal cortex, and L and R inferior frontal cortex activity	↑
Combination of cognitive and social-cognitive remediation							
Hooker *et al*[17]	SCH = 22	AT + SCT	11	fMRI	Facial emotion recognition	Postcentral gyrus activity	↑
Hooker *et al*[18]	SCH = 22	AT + SCT	11	fMRI	Facial emotion recognition	L and R amygdala, R putamen and R medial prefrontal cortex	↑

SPECT: Single photon emission computed tomography; fMRI: Functional magnetic resonance imaging; GM: Grey matter; DMN: Default mode network; FA: Fractional anisotropy; CC: Corpus callosum; AT: Auditory-based cognitive training; SCT: Social cognitive training; SCH: Schizophrenia; HC: Healthy control.

detect changes in brain functioning after cognitive remediation. Data analyses were mainly based on particular regions of interest that were defined a priori and were mainly located in regions of the prefrontal cortex. Unfortunately, these studies had small samples and lacked control groups to exclude placebo effects.

Nonetheless, during this period, no other treatment was able to show any changes in brain functioning related to cognitive improvement in schizophrenia.

Second period: Testing the hypofrontality hypothesis

Wykes *et al*[12] conducted a controlled study in which 12 patients were randomly assigned to control therapy or cognitive remediation. The effects of the intervention were tested with fMRI procedures using the n-back task during the scanning. The intervention was delivered on an individual basis and involved a therapist and paper and pencil tasks. Not surprisingly, only the group receiving cognitive remediation showed a significant increase in the activation of brain regions associated with working memory, particularly the inferior frontal gyrus. Although the sample size was still small, this study confirmed the insights from the previous period using a convincing methodology. It could be said that it was the first time that brain activation changes were clearly associated with the cognitive remediation intervention by applying a reliable and rigorous methodology. In conclusion, cognitive remediation acted as an active treatment to improve cognition, and it was also able to improve brain functioning in prefrontal regions in patients with schizophrenia. Thus, the need to replicate these results appeared to be the main target of successive studies.

Subsequent posterior studies showed similar results. Haut *et al*[13] conducted a quasi-randomised study involving nine patients receiving cognitive remediation, nine patients receiving a control therapy in the form of social skills training, and nine healthy control subjects. The authors showed that patients receiving cognitive remediation presented some increases in the activity of the left dorsolateral prefrontal cortex, left dorsal prefrontal cortex, anterior cingulate, right and left prefrontal cortex. The authors used fMRI procedures and visual n-back tasks containing words or pictures, as well as a lexical decision task. Patients receiving cognitive remediation improved on the word and picture 2-back tasks, showing more improvement than the control treatment group. Unfortunately, only regions of interest were examined. Edwards *et al*[14] used event-related fMRI to analyse brain activity associated with cognitive remediation. The sample comprised 22 patients with schizophrenia and a matched control group of 14 healthy participants. The training protocol emphasised direct encoding of contextual cues and updating of response selection goals in accordance with cue information. Following training, increased activation was observed in several areas involving anterior and posterior brain regions, such as right middle frontal, right superior parietal cortex, right inferior frontal junction, and left inferior frontal and visual cortex. These effects on brain activation seemed to be related to both clinical and cognitive improvements. Unfortunately, the analyses were also based on previously defined regions of interest.

Rowland *et al*[15] conducted an interesting study investigating the effects of cognitive training in the context of a relational learning task and using fMRI procedures. The sample comprised 17 patients with schizophrenia and 17 healthy control subjects. The most important innovations of this study were the use of whole-brain analysis and the fact that the healthy controls were also tested after having undergone cognitive training. Firstly, the authors found different patterns in both groups before and after treatment. The controls engaged regions including the frontal, parietal, and medial temporal lobes. After the training, the controls showed activation reductions in these regions and spatial extent in areas related to learning improvement. These findings are commonly observed phenomena in successful learning, but they were new in the context of cognitive training. Conversely, thee subjects with schizophrenia displayed bilateral inferior parietal region activation, as the authors had predicted.

Bor *et al*[16] conducted a study that explored the impact of cognitive remediation in a sample of 17 patients and 15 healthy volunteers. Throughout the study, all of the patients were on stable doses of atypical antipsychotics. The authors used fMRI and a visual 2-back test after 28 h of computerised cognitive remediation, comparing baseline with after treatment measurements in a randomised, controlled trial. Following treatment, patients in the group that received cognitive remediation exhibited higher levels of activation for the left inferior-middle frontal gyrus, cingulate gyrus, and inferior parietal cortex. These changes were related to improvement in measures of strategic efficiency and sustained attention. Hooker *et al*[17,18], in two studies with the same sample, tested the effects of a cognitive remediation programme plus a social cognitive intervention together in a sample of 22 schizophrenia patients. The authors used an fMRI task of positive and negative facial emotion recognition, showing improvements in postcentral gyrus activity, the left and right amygdala, the right putamen and the right medial prefrontal cortex. The particular choice of the fMRI task and the use of a combined treatment made it difficult to interpret whether these effects on brain functioning were the results of the cognitive treatment or the social cognitive treatment or even of the combination of both treatments.

Finally, Subramaniam *et al*[19] performed a controlled study with 31 schizophrenia patients and 16 healthy controls, but randomisation was not performed Almost all of the patients were taking atypical antipsychotics throughout the study. During fMRI scanning, tasks of word generation and recognition of words were used. Computerised cognitive training was used to examine its effects on regions related to reality monitoring. The authors found that patients exhibited less activation in the medial prefrontal cortex during word recognition for words at baseline. After cognitive remediation, the patients somewhat normalised their activation patterns, although they still had less activity than healthy controls. One important thing to note in this study was the use of a more complex theoretical framework of brain

activation. However, owing to the use of the region of interest approach by the authors, the study precluded the detection of other possibly relevant changes in activity.

In summary, in this second period from 2002 to 2011, different studies consolidated that cognitive remediation acts by improving brain activation in the prefrontal lobes and other related regions. The use of fMRI totally replaced the use of other methods, such as SPECT or PET. Data analyses were still based mainly on predefined regions of interest, but whole-brain analysis opened a new pathway. The methodology was heterogeneous across the different studies, but some of them began to attain the highest standards. Moreover, hypofrontality is the current framework, and an increase of activity is always considered a success criterion. However, some studies have suggested going beyond the hypofrontality hypothesis because cognitive remediation may have some detectable effects in other brain areas. In addition, more brain activation does not necessarily indicate better brain functioning. At least in healthy people, a decrease in activation in some brain areas could be correlated with better cognitive performance.

Neuroprotection: Changes in brain morphology

Eack *et al*[20] conducted a study that was unique in many aspects, and it is probably one of the most influential works published in the field. The aim of the study was basically to test the option to detect changes in brain morphology after treatment by cognitive rehabilitation. A randomised, controlled trial was performed with a longitudinal design for 2 years, with annual assessments of cognition and structural MRI. Statistical analyses were based on a mixed effects model, while processing of the neuroimaging data was based on voxel-based morphometry methods. Volumetric analyses of regions of interest in different areas of the frontal and temporal regions were performed a posteriori. A sample of 53 patients with diagnoses of schizophrenia or schizoaffective disorder in the early course was included. They were symptomatically stable and, consequently, their doses of antipsychotics were also stable. Cognitive remediation was an integrated approach that combined cognitive computer training and group-based social cognitive exercises. A control group followed an active control based on supportive therapy to improve illness management. It provided psychoeducation and coping strategies training.

Astoundingly, patients who received cognitive remediation showed greater preservation of grey matter volume over 2 years. A main effect of time indicated loss of grey matter in some brain areas, such as the bilateral cerebellum, left medial and posterior cingulate. Additionally, an interactive effect of time and treatment suggested that patients showed less grey matter loss in the left parahippocampal and fusiform gyrus and even greater grey matter increases in the left amygdala following cognitive remediation. Interestingly, these changes were statistically related to cognition changes. The authors appealed to the possible neurobiologic protective effects of cognitive remediation, particularly in early schizophrenia. Unfortunately, this work has not yet been replicated.

Third period: Going beyond hypofrontality and testing connectivity changes

Penadés *et al*[21] conducted a trial using a whole-brain approach that combined fMRI and diffusion tensor imaging (DTI). They investigated the effect of cognitive remediation on brain functioning in a randomised, controlled trial with 30 schizophrenia outpatients with an experimental group and an active control group. Additionally, 15 healthy volunteers were also included as a second comparison group. Cognitive remediation consisted of an individual strategy-learning-based treatment implemented by a trained therapist, based on paper and pencil exercises. The control group used an active control with an identical duration based on an individual social skills training that provided information about illness management. Brain activation patterns were assessed during an n-back task using independent component analysis as implemented in multivariate exploratory linear decomposition into independent components. This analysis showed clear differences between schizophrenia patients and healthy participants. Despite having performed similarly on the n-back task, patients with schizophrenia showed two different networks that were overactive compared to the healthy participants: The central executive network and default mode network. After treatment, the activation pattern significantly changed only in the cognitive remediation group in the sense of normalising towards the patterns observed in healthy controls Thus, decreased activation was found in the left superior parietal lobule and bilateral middle frontal gyri. In addition, decreased activity in the default-mode network was found in the left precuneus and middle frontal gyrus, among other areas, allowing for activation of the central executive network and deactivating of the default mode network in a more proper manner, suggesting an improvement in the efficiency of both networks. Furthermore, analysis of white matter on DTI showed an increase in the fractional anisotropy index in the anterior part of the genu of the corpus callosum. Interestingly, after treatment, statistically significant correlations were found among cognitive, functional, and structural changes. Finally, the authors speculated that cognitive improvement could be based on an increase of interhemispheric information transfer between the bilateral prefrontal cortices *via* the corpus callosum.

Another interesting and innovative result was reported by Vianin *et al*[22]. The authors performed a single-blind, randomised trial with sixteen patients distributed into an experimental group of cognitive remediation and a treatment-as-usual control group.

Cognitive remediation was based on executive function training lasting 14 wk. The authors tested brain activation patterns using a covert verbal fluency task during fMRI. In addition to cognitive improvements, the authors reported increased activation in many areas, such as the inferior parietal lobule, precentral gyrus, inferior frontal gyrus (Broca's area), middle occipital cortex, middle cingulate cortex, and superior parietal lobule, in the cognitive remediation group compared to the control group after treatment. Particularly interesting was the increased activation in Broca's area. The authors hypothesised that the use of metacognitive techniques of verbalisation might be the main factor underlying these brain changes.

Finally, Subramaniam *et al*[23] used n-back tasks in an fMRI study comparing computerised auditory and sociocognitive training based on a video game with an active control group and a group of healthy controls. They observed baseline hypoactivation in the middle frontal gyrus at baseline for the patient group. After treatment, the sociocognitive group showed a greater increase in activity in the middle frontal and inferior frontal gyri. One striking and interesting finding in this study was the correlation between the increase in right frontal activation on the verbal n-back task and the increase in the activation in left frontal regions. These results could suggest a process of increased connectivity after cognitive treatment.

Summarising the period since 2013 until today, the studies have definitively gone beyond the hypothesis of hypofrontality. A new and wider theoretical framework is emerging, and it includes more recent discoveries, such as the connectivity between different brain networks (Figure 2). Now, the focus is not only on task-related performance but also on rest-related brain functioning, which involves different interconnected regions that should be highly active at rest but that should be deactivated during the performance of cognitive tasks, such as the default mode network. For this reason, improvement can no longer be expressed only in terms of simple activation increases. Another feature of this period is the focus on other nonspecific prefrontal cortex areas such as the ventral regions or Broca's area, which could be related to some aspects of the remediation process. These findings are changing the focus of neuroimaging studies and are possibly providing a more complex and accurate picture of the brain mechanisms underlying the effects of cognitive remediation.

Meta-analyses

Two meta-analyses have been performed. Ramsay *et al*[24] conducted an Activation Likelihood Estimation (ALE) meta-analysis. After a literature search, they identified 162 articles, but only 9 of them were included in the analysis. ALE analyses showed increased activity in several brain areas, such as the lateral and medial prefrontal cortex, parietal cortex, insula, and the caudate and thalamus. Wei *et al*[25], with the same number of studies, found similar but not identical results: Increased brain activation occurred in thee frontal and parietal lobes, including the left medial frontal gyrus, left inferior frontal gyrus, right middle frontal gyrus, right postcentral gyrus, and inferior parietal lobule. The main results of the meta-analyses confirmed the insights of previous studies. However, secondary analyses could add even more information to the state of art. For instance, an original secondary analysis in the Ramsay *et al*[24] study was performed to compare the brain areas involved in cognitive remediation with areas that had been previously associated with deficits in working memory and executive control in persons with schizophrenia. Surprisingly, they found that some areas, such as the left prefrontal cortex and thalamus, overlapped, but other areas did not, suggesting both restorative and compensatory mechanisms. Another interesting secondary analysis showed that cognitive remediation resulted in similar patterns of brain activation irrespective of the different treatment approaches.

Nonetheless, the results from these two meta-analytic studies should be interpreted with great caution. The number of the included studies (n = 9) was extraordinarily small. In addition, there was a risk of bias due to the heterogeneity among these nine studies. Beyond differences in remediation approach and neuroimaging methods, the studies used different types of control groups and different methods of randomisation, and also blinding was absent in some studies but not in others. Statistical analysis was performed using different methods, making the results difficult to compare because some studies used mixed models and others used a general lineal model; some used data substitution, and others did not; some used the intention-to-treat procedure, and others did not. In terms of neuroimaging processing, different software was used; some studies reported results in terms of interaction effects between time and treatment and others in terms of differences between baseline and posttreatment, and while some studies used whole-brain analysis, others were based on analysis of ROIs. Although Wei *et al*[25] found similar increased activation brain areas in analysis with or without ROI studies, they found that analysis including ROI studies yielded a higher ALE value**.** Future studies with larger numbers of studies and more homogenised methodologies will provide us with more consistent results.

DISCUSSION

Cognitive remediation seems to improve brain activation when it is tested by means of neuroimaging techniques. Changes involving the prefrontal and thalamic regions were the most commonly reported results in the reviewed studies as in other previous systematic reviews[3,4,26]. These findings were in agreement with the hypofrontality hypothesis, proposing frontal hypoactivation as the underlying mechanism of cognitive impairments in schizophrenia. Nonetheless, advances in neuroimaging methodology, such as the use of whole-

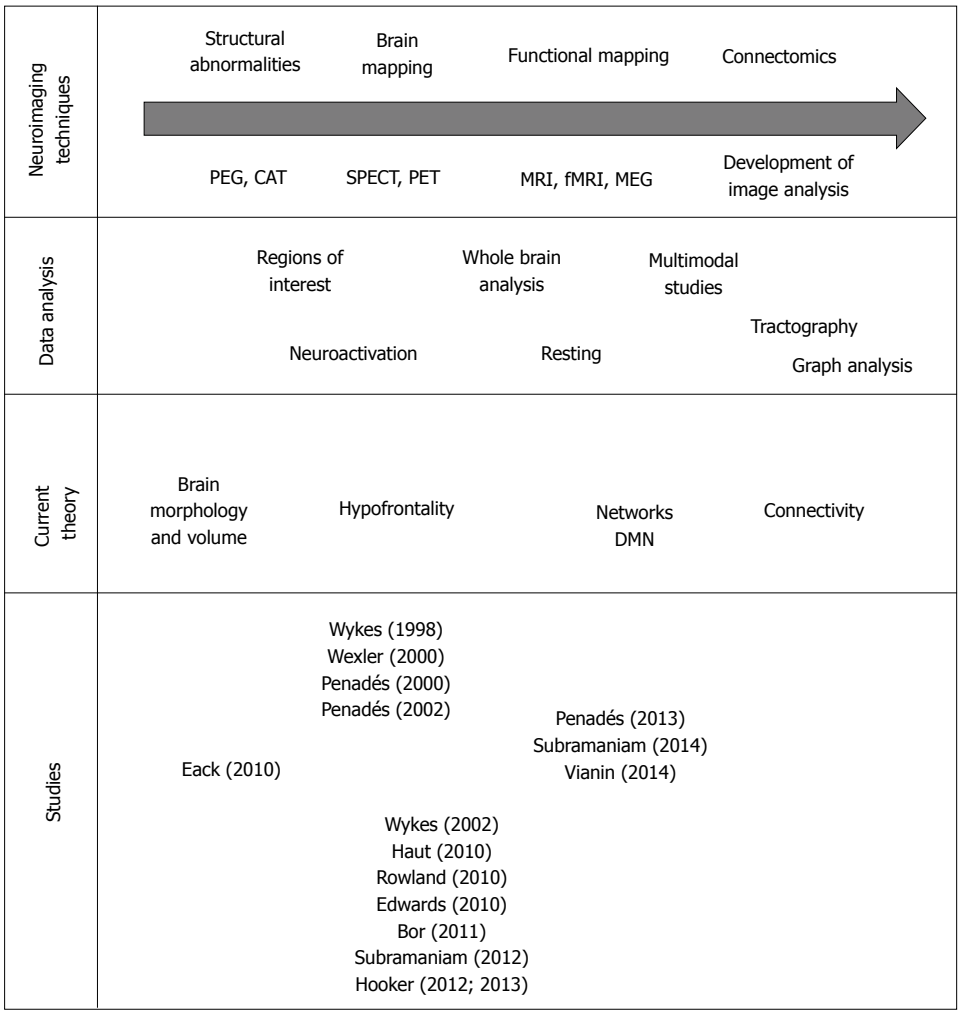

Figure 2 Evolution of neuroimaging studies, data analysis and theoretical frameworks. PEG: Pneumoencephalagraphy; CAT: Computed axial tomography; SPECT: Single-photon emission tomography; PET: Positron emission tomography; MRI: Magnetic resonance imaging; fMRI: Functional magnetic resonance imaging; MEG: Magneto encephalography; DMN: Default mode network.

brain analysis, tractography, graph analysis, and other sophisticated methodologies of data processing, might have conditioned the interpretation of results, generating new theoretical frameworks.

In fact, more complex theoretical frameworks are currently reinterpreting hypofrontality. Current theories are focusing on other aspects, such as the connectivity between different brain networks. In addition, not only task-related but also rest-related brain functioning is being considered. Consequently, different interconnected regions should be active at rest, but they should be deactivated during cognitive tasks. Improvement can no longer be expressed exclusively in terms of activation increases. Thus, the results of more recent studies are interpreting cognitive recovery within this framework, showing improvement in the efficiency of different networks. Additionally, structural changes have been described in both the grey and white matter suggesting a neuroprotective effect of cognitive remediation. Cognitive, functional and structural improvements have tended to appear positively correlated.

Results from meta-analytic studies have confirmed the active role of cognitive remediation in brain function involving the prefrontal and thalamic areas. However, other brain changes after treatment have been described. Consequently, cognitive recovery seems to be mediated by restoration and compensation mechanisms at the same time. Moreover, neuroimaging findings are not linked to a particular remediation approach, and all of the different cognitive remediation approaches act similarly in terms of brain functioning. Despite these findings, some limitations must be considered. Firstly, the evidence is tremendously incomplete because of the small number of studies and the lack of replicative studies. Secondly, different remediation approaches and different neuroimaging methods have made the comparison and generalisation of results problematic undertakings. Finally, the lack of a validated theoretical framework for the underlying neurobiological mechanisms of cognitive recovery has rendered the data difficult to interpret.

In conclusion, neuroimaging studies of cognitive remediation in patients with schizophrenia seem to have a positive effect on brain functioning in terms

of the functional reorganisation of neural networks. Currently, the most commonly reported changes involve the prefrontal and thalamic regions. Structural changes in the grey and white matter have been described, suggesting a neuroprotective effect of cognitive remediation. Cognitive, functional and structural improvements appear to be positively correlated. Further randomised, controlled studies are needed to confirm and clarify these results, possibly in the context of more complex theoretical models, including different brain networks, aspects of connectivity, whole-brain analysis and multimodal neuroimaging.

COMMENTS

Background

Neuroimaging studies have been conducted by many authors with the intention of identifying the different brain mechanisms underlying cognitive recovery. Even though some positive effects in terms of brain activation have been described, results have been heterogeneous and difficult to integrate. Some studies have described increased brain activation and others have shown decreased activation patterns. The primary aim of this review was to examine systematically all the published trials using neuroimaging procedures. Furthermore, the analysis was intended following a qualitative analysis in order to investigate the influence of neuroimaging methodology and the use of different theoretical frameworks.

Research frontiers

Nowadays, a comprehensive theoretical framework for cognitive recovery is needed. In order to integrate all the studies that have already been published and to guide future research we need to reflect on how the hypothesis and results are evolving and how neuroimaging methodology has conditioned the results of the studies.

Innovations and breakthroughs

Nearly all the recruited neuroimaging studies testing cognitive remediation in patients with schizophrenia have been based on the hypothesis of hypofrontality. In addition, they were always performed using a task-related paradigm and using the "region of interest" methodology. Nowadays, the use of different methodologies such as the brain networks framework and the whole brain analysis has brought to light some new insights reconceptualising the previous findings. Thus, improving frontal activation is now understood in a broader framework that points to an improvement of the networks efficiency.

Applications

Beyond the necessary replicative studies, future research needs to explore different hypothesis such as the putative changes in connectivity patterns of the different brain networks.

Terminology

The efficiency of a network is described in network science as a measure of how efficiently it exchanges information. Brain networks are efficient when they are able to show enough but not excessive activation during cognitive and resting states.

Peer-review

In this systematic review, the authors have presented a qualitative and critical analysis of the neuroimaging studies paying close attention to the theory of the brain networks connectivity.

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SYSTEMATIC REVIEWS

Attention-deficit/hyperactivity disorder and suicide: A systematic review

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Data sharing statement: The current manuscript does not describe a study, it is a systematic review.

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Abstract

AIM

To investigate suicidality and attention-deficit/hyperactivity disorder (ADHD), this paper aims to systematically review the literature as an extension of previous reviews.

METHODS

We searched five databases (Ovid MEDLINE, Psychinfo, PubMed, Scopus, Web of Science) with two categories of search terms: (1) suicide; suicidal; suicide behavior; suicide attempt; suicidal thought; and (2) ADHD.

RESULTS

The search resulted 26 articles. There is a positive association between ADHD and suicidality in both sexes and in all age groups. Comorbid disorders mediate between suicidality and ADHD.

CONCLUSION

Recognizing ADHD, comorbid conditions and suicidality is important in prevention.

Key words: Attention-deficit/hyperactivity disorder; Suicide; Systematic review

Core tip: This review of the last four years strengthens previous findings that there is a positive association between attention-deficit/hyperactivity disorder (ADHD) and suicidality in both sexes and in all age groups. Suicidality should screen in patients with ADHD. Comorbid disorders mediate between suicidality and ADHD. Recognizing ADHD and comorbid conditions can be important in suicide prevention as well.

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INTRODUCTION

Suicide prevention is a public health issue all over the world[1]. Recently, several studies have focused on attention-deficit hyperactivity disorder (ADHD) as a possible psychiatric disorder that may serve as a suicide risk factor as well[2-5]. One of the theoretical backgrounds of it is the construct of impulsivity, which is a well-know personality trait. Impulsivity is a core symptom of ADHD[6,7], moreover it is known, that it correlates to suicidal behavior[8]. Another theoretical background behind the possible association between ADHD and suicide is, that two-thirds of ADHD cases have at least one comorbid psychiatric diagnosis, which most often is conduct disorder, substance use or major depressive episode[9-11]. These comorbid disorders are well-known risk factors of suicide[12-15]. As ADHD is one of the most prevalent (2%-12%) psychiatric disorders among children and adolescents and in 40%-60% of the cases, it continues into adulthood[16,17], all additional knowledge on the possible association between ADHD and suicidality has high clinical importance and can add to suicide prevention.

The growing body of publications on ADHD and suicidality has already resulted in five review or summary papers on this topic. First, James *et al*[18] searched two electronic databases (MEDLINE, Psychlit) for the period from 1966 to 2003. In their review, they included psychological autopsy studies of teenage and young adult suicides and long-term follow-up studies of ADHD children. They found a positive association between ADHD and completed suicides in males, concluding that ADHD could increase the risk for suicide through comorbid conditions such as conduct disorder and depression. Second, Impey *et al*[19] performed a search for the period up to January 2011 using three main databases (MEDLINE, EMBASE and PSYCHINFO). They concluded from their review that most suicidal study groups showed a higher rate of ADHD than the controls: At least double the rate for suicidal ideation and around 1.5-2.0 times for suicide attempts and completion. The authors emphasized that comorbidity had a large influence, especially in the cases of delinquency and substance misuse. Third, Furczyk *et al*[20] published a selective review on the most important currently known associations between ADHD and suicidality. They concluded, similar to the previous reviews[18,19], that there is substantial evidence supporting an association between ADHD and increased suicide risk, and that it is at least partially mediated by comorbidities. They highlight the importance of raising the awareness of health professionals of the risk of suicide in ADHD patients, but further research on the long-term outcomes of the treatment of ADHD patients with a risk of suicide is needed. The selective review paper of Nigg[21] had a wider focus: He overviewed the current knowledge on the health-related impairments of ADHD, including smoking, drug abuse, accidental injury, sleep, obesity, hypertension and diabetes, as well as suicidal behavior. On the topic of ADHD and suicide, the author concluded that ADHD is associated with an elevated risk of suicide attempts (particularly in girls) and completed suicide (particularly in boys), and this risk is mediated by comorbid disorders, which may vary with gender: They include conduct and emotional problems in males and depression in females. Finally, we have to mention Renaud *et al*[22] summary paper: Based on some selected important research in the field, the authors concluded that there is not a direct link between ADHD and suicide, however, ADHD's constructs of impulsivity and aggression are related to the development of conduct and oppositional defiant disorders, which can lead to deviancy and drug abuse; all of these comorbid conditions increase the risk of suicide.

Knowing of the growing interest in this topic over the last couple of years, we found it useful to conduct an up-to-date systematic review, which can provide important extensions. The search of James *et al*[18] was conducted more than one decade ago, and even Impey *et al*[19] completed their search in January, 2011. The most recently published reviews were not systematic[20-22]. Additionally, all of the reviews have mainly been limited to males[18,19]. Moreover knowing more about the methodology of the studies can lead to a better understanding of the prevalence data. Considering all of this, the current systematic review aims to present an overview on suicidality and ADHD as an extension of the previous ones, not only in the time period of the search, but also by focusing on the following topics: (1) Is ADHD more common in people who are suicidal? (2) Is suicide more prevalent in people with ADHD? and (3) Which other identifiable risk factors can be associated with suicide in ADHD?

Additionally, to be able to compare the included studies, we investigated what kinds of assessments are used for measuring ADHD, suicidality and comorbid conditions.

MATERIALS AND METHODS

Selection of publications

A systematic literature search was conducted in the following five computerized literature databases on January 27, 2015: Ovid MEDLINE, Psychinfo, PubMed, Scopus, Web of Science from 2011 to 2015. Search terms from two categories were used: (1) suicide; suicidal; suicide behavior; suicide attempt; suicidal thought; and (2) ADHD; attention deficit hyperactivity disorder. Search terms within both categories were separated by the Boolean operator OR, and the categories were separated by the operator AND. Using prespecified inclusion and exclusion criteria, we screened

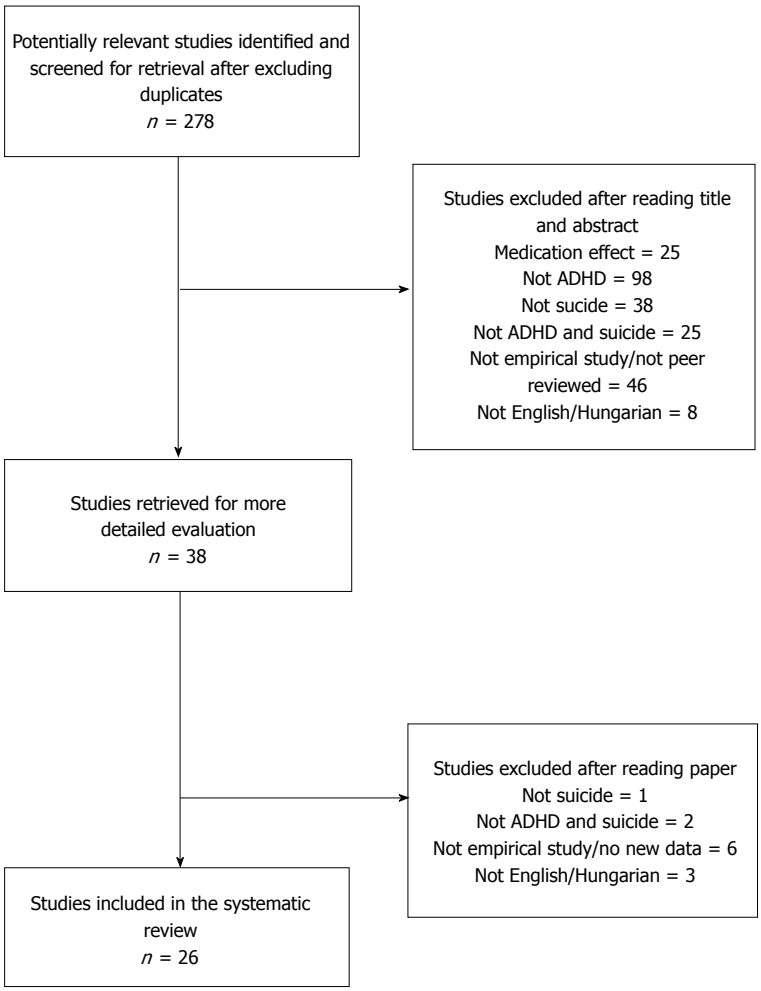

Figure 1 QUORUM flow chart detailing results of literature search. ADHD: Attention-deficit/hyperactivity disorder.

the titles and/or abstracts. The relevant full texts of papers that passed the first search were read, and the ones that met the inclusion criteria were collected. The reference lists of the retrieved papers were screened, and papers that possibly met the inclusion criteria were retrieved and studied. The inclusion criteria were: Peer-reviewed journals; publications written in English or Hungarian. The exclusion criterion was the lack of any empirical data. It was not in the focus of our study to examine suicidal behavior, as a safety concern about ADHD drug treatment. We excluded those studies, which aim was to examine pharmacological treatment (*e.g.*, atomoxetine) induced suicide in patients with ADHD, *e.g.*, Capuano *et al*[23], who present a series of cases of Italian children who experienced suicidal ideation during ADHD pharmacological therapy with atomoxetine.

RESULTS

Included studies

The search strategy resulted in a total of 278 articles (excluding duplicates), of which 26 were included in the systematic review after the screening process (Figure 1, Tables 1-3).

The 26 papers were written in 16 countries on four continents. Of the 26 studies, only two had a longitudinal design. Detailed information on the origin, design, sample and instruments of the studies can be found in Tables 1-3.

Is ADHD more common in people who are suicidal?

Table 1 summarizes the three studies on ADHD in suicidal patients[24-26].

Is suicide more prevalent in people with ADHD?

Table 2 includes the 14 studies, which examines suicidality in patients with ADHD[27-40].

Which other identifiable risk factors can be associated with suicide in ADHD?

Gender differences in suicidality and ADHD: Examining the gender distribution of ADHD cases among suicidal patients, only one study provided relevant data[24]: 8.6% of suicidal male adolescents had ADHD, and 4.7% of suicidal female adolescents had ADHD.

Focusing on the gender differences in suicidal cases among ADHD patients, in the above-described 12

Table 1 Included relevant articles examining attention-deficit/hyperactivity disorder and suicidality from January 2011 to January 2015: Attention-deficit/hyperactivity disorder in suicidal patients

ADHD in suicidal patients							
Ref.	**Country**	**Study design**	**Sample**	**Population at onset**	**Population's age at onset**	**Measures for ADHD, comorbid conditions and suicidality**	**Main findings**
Ben-Yehuda *et al*[24]	Israel	Cross-sectional	Clinical sample	The survey involved all minors (age < 18) (n = 266) who were referred to a psychiatric emergency department due to a suicide attempt or suicidal ideation during a 3-yr period (2005-2007)	Children: Age range: ⩽ 12 yr Adolescents: Age range: > 12 yr	The diagnosis was made by the examiner in the emergency department: diagnoses were coded using the ICD-10	The distribution of psychiatric diagnoses differed significantly in the two age groups ADHD was significantly more prevalent among suicidal children, while mood disorders were more prevalent among suicidal adolescents The second most prevalent diagnosis among suicidal children was ADHD (25.6%) (following adjustment disorder/38.5%/and followed by conduct disorders/23.1%) In adolescents ADHD was not among the most common diagnoses: it was found in only 5.7% in the adolescent group
Evren *et al*[25]	Turkey	Cross-sectional	Community sample	A representative sample of 10th grade students: n = 4938 (male ratio: 52.7%)	Mean age: 15.58 yr (SD = 2.85)	PSTA	Those with a lifetime suicidal thoughts had a higher mean ADHD symptom score than those without. Suicidal thoughts predicted the symptoms of ADHD
Soole *et al*[26]	Australia	Cross-sectional	Community sample	469 deaths by external causes were recorded in the Queensland CDR for children and adolescents aged 10-17 between 2004 and 2012	Between 2004 and 2012, 149 suicides were recorded: 34 of children aged 10-14 yr and 115 of adolescents aged 15-17 yr	Causes of death were categorized using the ICD-10	Mental and behavioral disorders were observed in 50% of children and 57.3% of adolescents who died by suicide. Disorders usually diagnosed in infancy, childhood, and adolescence, such as ADHD, were significantly more frequent in children than in adolescents. Mood disorders, such as depression, were significantly more common in adolescents compared with children

CDR: Child Death Register; ADHD: Attention-deficit/hyperactivity disorder; PSTA: Psychological screening test for adolescents.

papers, which examined the prevalence of suicidality among patients with ADHD, three studies focused on gender differences[27,35,37], and one study enrolled only girls[39].

Regarding suicidal ideation, Mayes *et al*[37] found no differences between boys and girls with ADHD with suicidal ideation (18% and 11%, respectively). All three studies examined the gender of those who attempted suicide among ADHD patients, and two did not find differences[28,37]. Agosti *et al*[27] found that 52.9% of patients with ADHD who had previous suicide attempts were male, while the rate of males was 58.3% in patients with ADHD without previous suicide attempts. Mayes *et al*[37] found no differences between boys and girls with ADHD and suicidal ideation (7% and 3%, respectively). Ljung *et al*[35] found that the risk of suicide attempts among ADHD patients differed significantly by gender (χ^2 = 1271.0; P < 0.001): The adjusted estimate was 2.93 (95%CI: 2.60-3.29) for males and 5.41 (95%CI: 4.60-6.36) for females. Only one study examined gender differences in ADHD patients who completed suicide[35] and found no gender differences.

Suicidality in patients with psychiatric disorders who have ADHD comorbidity: Table 3 summarizes the seven studies among the 26, which investigated ADHD, as a comorbid condition of other psychiatric disorders, and its association with suicidality[30,41-46].

Suicidality in ADHD patients who have psychiatric comorbidity: From the 26 papers of this review, the 10 studies, which investigated comorbidity in ADHD patients with suicidality are presented in Table 4[27,28,35-39,47,48].

Assessments for measuring ADHD, suicidality and comorbid conditions

Assessments for measuring ADHD: Table 5[49-55] summarizes assessments for measuring ADHD.

Assessments for measuring suicidality and

Table 2 Included relevant articles examining attention-deficit/hyperactivity disorder and suicidality from January 2011 to January 2015: Suicidality in patiens with attention-deficit/hyperactivity disorder

Suicidality in patiens with ADHD							
Ref.	**Country**	**Study design**	**Sample**	**Population at onset**	**Population's age at onset**	**Measures for ADHD, comorbid conditions and suicidality**	**Main findings**
Agosti *et al*[27]	United States	Cross-sectional	Clinical sample	Current ADHD: 365 adults: With Suicide attempts: *n* = 59 No suicide attempts: *n* = 306	Age range: 18-66 yr	CIDI, ACDS, DIS-IV	Sixteen percentage of participants with current ADHD diagnosis had previous suicide attempt. While ADHD increased the risk of previous suicide attempt only 1.5 fold, having one or more comorbid disorders increased the risk of previous suicide attempt 4 to 12 fold
Balazs *et al*[28]	Hungary	Cross-sectional	Clinical sample	ADHD and subthreshold ADHD children: *n* = 220 ADHD and subthreshold ADHD adolescents: *n* = 198	Children: Age range: 3-11 yr Mean age: 7.67 yr (SD = 2.03) Adolescents: Age range: 12-17 yr Mean age: 14.31 yr (SD = 1.67)	MINI-KID	The relationship between ADHD and suicidality was fully mediated by comorbid psychiatric disorders. In children, symptoms of anxiety disorders mediated this relationship, while in the adolescent group, symptoms of major depressive episode, dysthymia, and substance abuse/dependence were found to be significant mediators
Barbaresi *et al*[29]	United States	Cross-sectional	Community sample	Adults with childhood ADHD: *n* = 232 Non-ADHD controls: *n* = 335	ADHD group: Mean age: 27 yr Non-ADHD group: Mean age: 28.6 yr	MINI	The rate of death from suicide was significantly higher among adults with childhood ADHD compared to non-ADHD adults
Cheng *et al*[30]	Taiwan	Cross-sectional	Community sample	5405 University students: *n* = 5405 (male ratio: 64.8%) ADHD symptoms were elevated in 8.6% of the sample: (male ratio: 75.1%)	University students	ASRS, BSRS-5	Individuals with higher levels of ADHD symptoms were more likely to have higher suicidal ideation
Huntley *et al*[31]	United Kingdom	Cross-sectional	Clinical Sample	Participants from two in-patient alcohol and drug detoxification units: *n* = 226 (male ratio: 76.5%) Patient with alcohol/drug intoxication + ADHD: *n* = 11 Patient with alcohol/drug intoxication without ADHD: *n* = 183	Mean age: 39.0 yr (SD = 10.3)	DSM-IV 18-item self-report ADHD screening questionnaires for both current and childhood behavior Impairment questions from the Barkley scales DIVA	Patients with both substance use disorders and ADHD had significantly higher rates of prior suicide attempts than patients with substance use disorder without ADHD
Hurtig *et al*[32]	Finland	Longitudinal: 16 yr. First follow up: at ages 7, 8, second follow up at ages 15, 16	Community sample	ADHD adolescents: *n* = 104 Non-ADHD adolescents: *n* = 169	Adolescents from the same birth cohort	At 8 yr of age: Rutter B2 During the 15-16 yr follow up: SWAN, K-SADS-PL	Adolescents with ADHD had more suicide ideation, acts than adolescents without ADHD. The effect of ADHD on suicidal ideation remained strong after controlling for other variables
Kavakci *et al*[33]	Turkey	Cross-sectional	Community sample	980 university students (male ratio: 55.9%) ADHD: *n* = 48 Non-ADHD: *n* = 932	Age range: 17-44 yr Mean age: 21.4 yr (SD = 2.3 yr)	ASRS SCID I, SCID II, Adult ADHD Module of MINI Plus	Adolescents with ADHD reported significantly more lifetime suicide attempts than those without ADHD

Keresztény *et al*[34]	Hungary	Cross-sectional	Clinical sample	Children: *n* = 168 (male ratio: 87.5%) Adolescents: *n* = 43 (male ratio: 62.8%)	Children: Age range: 3-12 yr Mean age: 8.23 yr (SD = 2.22) Adolescents: Mean age: 14.65 yr (SD = 1.6 yr) boys: 27 (62.8%)	MINI-KID	The most common comorbid diagnoses with ADHD were oppositional defiant disorder, conduct disorder and suicide behavior in both age-groups. The rate of suicide behavior was 17% among children and 58% among adolescents
Ljung *et al*[35]	Sweden	Cross-sectional	Patient and prescribed drug registers and population-based registers	ADHD: *n* = 51707 (male ratio: 69.8%) Control: *n* = 258535	Age range: 3-40 yr	Discharge diagnosis of ADHD	Participants with ADHD had an increased risks of both attempted and completed suicide compared with control participants. This result was the same even after adjusting for comorbid psychiatric conditions. While the highest familial risk was reported among first-degree relatives, lower risk was observed among more genetically distant relatives. The results suggests that shared genetic factors are important for this association
Mayes *et al*[36]	United States	Cross-sectional	Community and clinical sample	1706 children and adolescents with psychiatric disorders and typical development: ADHD-C: *n* = 566 (male ratio: 74.6%) ADHD-I: *n* = 235 (male ratio: 57.4%) Other psychiatric disorders (autism, depression/ anxiety, eating disorder, intellectual disability): *n* = 719 (male ratio: 67.2%) Typical: *n* = 186 (male ratio: 43.5%)	Age range: 6-18 yr	All participants had a clinical diagnosis of ADHD made by a licensed PhD psychologist. The clinical diagnosis was based on a comprehensive psychological evaluation including diagnostic inter-views with the parent and child, parent and teacher rating scales, review of educational and medical records, extensive psychological testing PBS	All psychiatric groups had far more suicide behavior than typically developed children. ADHD-C: 20.7% had suicide ideation, 6.0% attempt ADHD-I: 7.3% had suicide ideation, 2.6% attempt
Mayes *et al*[37]	United States	Cross-sectional	Clinical sample	Children and adolescents with ADHD: *n* = 925 (male ratio: 68.5%) ADHD-C: *n* = 666 ADHD-I: *n* = 259	Age range: 3-16 yr Mean age: 8.8 yr (SD = 2.6)	All participants had a clinical diagnosis of ADHD made by a licensed PhD psychologist. The clinical diagnosis was based on a comprehensive psychological evaluation including diagnostic inter-views with the parent and child, parent and teacher rating scales, review of educational and medical records, extensive psychological testing PBS - suicide ideation and attempt items	For the total sample with ADHD, 15.8% had suicide ideation (sometimes or more) and 5.5% had attempts Ideation and attempts were more than twice as prevalent among participants with ADHD-C than among participants with ADHD-I ADHD-C: 19% had suicide ideation, 7% attempt ADHD-I: 7% had suicide ideation, 3% attempt Those, who had ADHD alone: 6% had suicide ideation and 2% had suicide attempt. Those, who had ADHD + co-occurring sadness and ODD, 46% had ideation and 21% had attempts
Park *et al*[38]	South Korea	Cross-sectional	Community sample	A total of 6081 subjects: Non-ADHD symptom group: *n* = 6012 ADHD symptom group: *n* = 69	Age range: 18-59 yr	K-CIDI Adult ADHD Self-Report Scale	Adult ADHD symptoms are significantly associated with lifetime suicidality. However, the association disappeared after adjusting for other comorbid psychiatric disorders

Swanson *et al*[39]	United States	Longitudinal: 10 yr: First 5 yr follow up and second 10 yr follow-up	Community and clinical sample	ADHD girls: *n* = 140 Non-ADHD girls: *n* = 88	Age range: 6-12 yr at ascertainment Mean age at 5 yr follow-up: 14.2 yr Mean age at 10 yr follow-up: 19.6 yr (range 17-24 yr)	At ascertainment: DISC-IV First follow up: SNAP-IV, Second follow up: SIQ, Barkley Suicide Questionnair, DISC-IV-YA	Women with a childhood diagnosis of ADHD-C, compared with those with ADHD-I and control group, were at higher risk for suicide attempts. Furthermore, women with a persistent ADHD diagnosis were at higher risk than women with a transient diagnosis and the control group
Van Eck *et al*[40]	United States	Cross-sectional	Community sample	Undergraduate psychology students: *n* = 627 (male ratio: 40%)	Mean age: 20.23 yr (SD = 1.40)	CSS BSI	ADHD indirectly increased suicidal ideation through depression. The moderator factors in the indirect effect of ADHD on suicidal ideation were emotion regulation deficits of accepting negative emotions, emotional awareness, and goal-oriented behavior

ADHD: Attention-deficit/hyperactivity disorder; CIDI: Composite International Diagnostic Interview; ACDS: Adult ADHD Clinical Diagnostic Scale; DIS-IV: The Diagnostic Interview Schedule for DSM-IV; MINI-KID: Mini-International Neuropsychiatric Interview for children and adolescents; PBS: Pediatric Behavior Scale; MINI: Mini-International Neuropsychiatric Interview; ASRS: Adult Self-Report Scale; BSRS-5: Brief Symptoms Rating Scale; DIVA: Diagnostic Interview for ADHD in Adults; SWAN: Strengths and Weaknesses of ADHD symptoms and Normal Behaviors; SCID-I: Structured Clinical Interview for DSM-IV Axis I Disorders; ODD: Oppositional defiant disorder; K-CIDI: Korean version of Composite International Diagnostic Interview; SNAP-IV: Swanson, Nolan, and Pelham Rating Scale; SIQ: Self-Injury Questionnaire; DISC-IV-YA: Diagnostic Interview Schedule for Children 4th ed., Young Adult version; ADHD-C: ADHD combined type; ADHD-I: ADHD inattentive type, ADHD-HKS Questionnaire.

comorbid conditions: Table 6[56-80] summarizes assessments for measuring suicidality and comorbid conditions.

DISCUSSION

This review of the last four years strengthens the recent finding that ADHD is related to high suicidality in all age groups and in both girls and boys.

Although our current systematic review was conducted only for the last four years, we still found 26 papers that presented data on ADHD and suicidality. Moreover, we know that several systematic review papers and overviews had been done previously. Impey *et al*[19], who performed a systematic search on the same topic, covering all studies up to January 2011, the starting point of our search period, found 25 papers. All of them support the view that research on the association of ADHD and suicidality is a subject of high and growing interest, and clinicians and researchers need to have access to up-to-date knowledge in this field.

The studies of this review are culturally diverse, as they come from four continents. This shows that this topic has relevance all over the world and that the conclusions can be used in wider aspects.

Regarding the age groups investigated on the topic of ADHD and suicidality, the studies have been balanced over the last four years: Exactly half of them investigated children/adolescents, and half of them examined adults. This reflects the growing interest in ADHD in adulthood among both healthcare professionals and researchers[81]. Considering the previous studies on this topic - which were included in the review of Impey *et al*[19] - a majority of them involved the 12-18 age group, although there were a few studies in older and younger age groups as well. Additionally, in their review, Impey *et al*[19] concluded that, based on the studies included in their review paper, age differences were not clearly definable. In this way, the current review extends our knowledge with further information on all age groups with ADHD and suicidality, including children under 12 and adults, and makes it possible to compare different age groups.

Systematically searching the literature of the last four years, we found only two studies that reported the prevalence data of ADHD among patients with suicidality[24,45]; however, there were a total of six studies addressing that study question in the review of Impey *et al*[19]. There were five in the review of James *et al*[18], but four of them were included in the review of Impey *et al*[19] as well. In both studies in the current review, the diagnoses of ADHD and suicidality were based on a clinician's opinion. A very important and new result shown in our review is that one-quarter of the suicidal children under 12 years old had ADHD. The prevalence rate of ADHD among suicidal adolescents was lower (5.7%) than in children, and it was lower than in previous studies[19]. One possible explanation could be that these studies did not use either diagnostic interviews or screening tools for the diagnoses of ADHD and suicidality. All of them show that there is still limited data on the prevalence of ADHD among patients with suicidality; however, all of the studies performed found a high prevalence of ADHD in this population, especially among young children. Further studies are needed, but based on the current knowledge, we suggest a routine screening for ADHD patients with suicidal thoughts and attempts, with a special focus on young children.

Table 3 Included relevant articles examining attention-deficit/hyperactivity disorder and suicidality from January 2011 to January 2015: Suicidality in patients with psychiatric disorders who have attention-deficit/hyperactivity disorder comorbidity

Suicidality in patients with psychiatric disorders who have ADHD comorbidity							
Ref.	**Country**	**Study design**	**Sample**	**Population at onset**	**Population's age at onset**	**Measures for ADHD, comorbid conditions and suicidality**	**Main findings**
Bácskai *et al*[41]	Hungary	Cross-sectional	Clinical sample	198 patients with drug dependence (male ratio: 76%) Drug dependent patients without ADHD: *n* = 154 Drug dependent patients with ADHD: *n* = 44	Age range: 18-40 yr Mean age of the whole sample: 27 yr (SD = 6.31)	ASRS, EuroADAD, BDI	Drug dependent patients with ADHD showed a significantly higher proportion of suicidal ideation, suicidal attempts and self-injuries associated with suicidal attempts than drug dependent patients without ADHD
Berkol *et al*[42]	Turkey	Cross-sectional	Clinical sample	Patients with BD type I and II Adult BP with ADHD: *n* = 23 Adult BP without ADHD: *n* = 32	BP adults with ADHD: Mean age: 35.1 yr (SD = 10.7) BP adults without ADHD: Mean age: 41.3 yr (SD = 13.0)	ADHD scale Mood disorder modul of SCID-I-CV	In the BP with ADHD group, the rate of suicide attempts (47.8%) was significantly higher than in the BP without ADHD group (21.9%)
Donev *et al*[43]	Germany	Cross-sectional	Clinical sample	Patients with schizophrenia according to ICD-10 criteria: *n* = 27 (14 male) Patients with schizophrenia and no ADHD: *n* = 15 Patients with schizophrenia and ADHD: *n* = 12	Age range: 18-44 yr Mean age: 25.7 yr (SD = 7.6)	ADHD-HKS Questionnaire	Among patients with both schizophrenia and ADHD there were significantly higher number of suicide attempts than among those with schizophrenia without ADHD
Huntley *et al*[31]	United Kingdom	Cross-sectional	Clinical sample	Participants from two in-patient alcohol and drug detoxification units: *n* = 226 (male ratio: 76.5%) Patient with alcohol/drug intoxication + ADHD: *n* = 11 Patient with alcohol/drug intoxication without ADHD: *n* = 183	Mean age: 39.0 yr (SD = 10.3)	DSM-IV 18-item self-report ADHD screening questionnaires for both current and childhood behavior Impairment questions from the Barkley scales DIVA	Patients with both substance use disorders and ADHD had significantly higher rates of prior suicide attempts than patients with substance use disorder without ADHD
Patros *et al*[44]	United States	Cross-sectional	Community sample	College students: *n* = 1056 (male ratio: 38.5%)	Age range: 18 yr of age or older; 96.4% aged 18-24 yr	CSS, HDSQ	Higher hyperactive/attention symptoms were associated with increase in suicidal thoughts, suicide attempts, and need for medical attention after suicide attempts, among participants with depressed mood
Penney *et al*[45]	Canada	Cross-sectional	Clinical sample	Clients who presented for treatment at an addictions facility: *n* = 5990 (male ratio: 63.1%) Clients who reported being hospitalized for attempting suicide in the past year: *n* = 76 All other clients: *n* = 5914	Age range: 11-86 yr Mean age: 32.60 yr (SD = 14.55)	Clients reported whether or not they had been diagnosed by a mental health professional in the last 12 mo and in heir lifetime	Compared to all other clients, clients who attempted suicide in the past year were significantly more likely to have ADHD (9.2% *vs* 2.5%)

Sáez-Francàs *et al*[46]	Spain	Cross-sectional	Clinical sample	Adult CFS patients: n = 158 CFS patients with adult ADHD: n = 33 (male ratio: 3.0%) CFS patients without adult ADHD (male ratio: 6.4%)	CFS + ADHD: Mean age: 47.55 yr (SD = 7.99) CFS: Mean age: 48.60 yr (SD = 8.88)	CAADID Suicide risk was studied with the Plutchick Risk of Suicide Scale (Plutchik et al, 1989), a 15-item self-report scale with dichotomous responses. Values above the cut-off point of 6 indicate a risk of suicide	CFS patients with adult ADHD had a higher risk of suicide than CFS patients without ADHD

CFS: Chronic fatigue syndrome; ADHD: Attention-deficit/hyperactivity disorder; ASRS: Adult Self-Report Scale; EuroADAD: European Version of the Adolescent Assessment Dialogue; BDI: Beck Depression Inventory; SCID-I-CV: Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version; DIVA: Diagnostic Interview for ADHD in Adults; CSS: Current Symptoms Scale–Self-Report Form; HDSQ: Hopelessness Depression Symptom Questionnaire-Suicidality Subscale; CAADID: Conners'Adult ADHD Diagnostic Interview for DSM-IV.

Almost half of the papers reported prevalence data on suicidality in ADHD patients. The results strengthen the findings of previous studies[18-21] that there is a positive association between ADHD and suicidality, including completed suicides, attempts, as well as ideation. We would like to highlight that, in adolescence, based on the studies of the last four years, more than half of the patients with ADHD had suicidal thoughts, and this prevalence rate is even higher than what has been described previously[19]. It is important to note that even in adulthood, one third of ADHD patients had suicidal ideation. Based on these results, we suggest the introduction of routine screening questions on suicidal thoughts in outpatient/inpatient ADHD clinics, both for those specializing in adults and those specializing in children/adolescents. This improvement in clinical practice can be an important step towards suicide prevention.

The rate of previous suicide attempts was the highest (16%) in the adult ADHD age group; however, adolescents need attention in this respect as well, as almost one-tenth of ADHD patients in this age group had a previous suicide attempt. As one of the strongest predictors of a completed suicide is a previous suicide attempt, close follow-up of these ADHD patients could be of core importance in suicide prevention.

When we examined, which identifiable risk factors can be associated with suicide in ADHD, first we focused on gender. There are still a limited number of studies examining gender differences within this topic. The only study[24] that reported data on the gender distribution of suicidal patients with ADHD is in agreement with the conclusion of previous reviews[18,19] that ADHD is present more often among suicidal men than suicidal women. However, when we examined the prevalence of suicidality (*e.g.*, ideation, attempts and completed suicides) in ADHD patients, two out of three of the studies did not find a difference between men and women[27,37], and one study reported an adjusted estimate for the risk of suicide attempts in females that was almost twice as high[35]. In his selected review paper, Nigg[21] reported that girls had an elevated risk of a suicide attempt as well; however, the author stated that boys have a higher risk of completed suicide among ADHD patients. It is important to note that there are very few studies that have focused on female patients with ADHD[82]. One of them was conducted during the search period of this review[39], while in the previous review on this topic, there were several studies in which only men were enrolled, as well as those in which both females and men were included[19]. Based on the currently available results, both females and males with ADHD need a special focus to recognize their possible suicide risk; however, further studies are needed to gain a better understanding of the gender differences in all age groups.

Second, when we examined identifiable risk factors, which can be associated with suicide in ADHD, we focused on comorbidities. One of the most exciting questions, which also has been raised in all of the previous review and summary papers[18-21], is whether there is a direct association between ADHD and suicidality or if ADHD increases the risk of suicide through comorbid conditions. In the current review, we examined two aspects of this question. First, we reviewed all of the papers within the examined period that measured the prevalence of ADHD in suicidal patients with other psychiatric disorders, such as mood disorders, schizophrenia, alcohol/drug intoxication and chronic fatigue syndrome. The results of all seven studies on this topic showed that the prevalence of suicidality is higher when psychiatric disorders are comorbid with ADHD than in their absence. These findings suggest that the presence of ADHD, as a comorbid condition, conveys an increased risk of suicide for patients with other psychiatric disorders. Second, we

Table 4 Included relevant articles examining attention-deficit/hyperactivity disorder and suicidality from January 2011 to January 2015: Suicidality in attention-deficit/hyperactivity disorder patients who have psychiatric comorbidity

Suicidality in ADHD patients who have psychiatric comorbidity							
Ref.	**Country**	**Study design**	**Sample**	**Population at onset**	**Population's age at onset**	**Measures for ADHD, comorbid conditions and suicidality**	**Main findings**
Agosti *et al*[27]	United States	Cross-sectional	Clinical sample	Current ADHD: 365 adults: With Suicide attempts: *n* = 59 No suicide attempts: *n* = 306	Age range: 18-66 yr	CIDI, ACDS, DIS-IV	Sixteen percentage of participants with current ADHD diagnosis had previous suicide attempt. While ADHD increased the risk of previous suicide attempt only 1.5 fold, having one or more comorbid disorders increased the risk of previous suicide attempt 4 to 12 fold
Balazs *et al*[28]	Hungary	Cross-sectional	Clinical sample	ADHD and subthreshold ADHD children: *n* = 220 ADHD and subthreshold ADHD adolescents: *n* = 198	Children: Age range: 3-11 yr Mean age: 7.67 yr (SD = 2.03) Adolescents: Age range: 12-17 yr Mean age: 14.31 yr (SD = 1.67)	MINI-KID	The relationship between ADHD and suicidality was fully mediated by comorbid psychiatric disorders. In children, symptoms of anxiety disorders mediated this relationship, while in the adolescent group, symptoms of major depressive episode, dysthymia, and substance abuse/dependence were found to be significant mediators
Daviss *et al*[47]	Lebanon	Cross-sectional	Clinical sample	Youth with ADHD: *n* = 101 (male ratio: 63.4%) Lifetime SBs *n* = 28 (male ratio: 42.9%) No lifetime SBs: *n* = 73 (male ratio: 71.2%)	Age range in the whole sample: 11-18 yr Lifetime SBs: Mean age: 14.6 yr (SD = 2.1) No lifetime SBs: Mean age: 13.5 yr (SD = 1.8)	K-SADS-PL ADHD Rating Scale	In this ADHD sample, after controlling for the age, female sex, and comorbid disorders, lifetime SB remained significantly associated with parent-child conflict, and impairment in nonacademic domains of function and breadth of exposure to victimization events Past and current ADHD symptoms and signs were not associated with lifetime SB
Ljung *et al*[35]	Sweden	Cross-sectional	Patient and prescribed drug registers and population-based registers	ADHD: *n* = 51707 (male ratio: 69.8%) Control: *n* = 258535	Age range: 3-40 yr	Discharge diagnosis of ADHD	Participants with ADHD had an increased risks of both attempted and completed suicide compared with control participants. This result was the same even after adjusting for comorbid psychiatric conditions. While the highest familial risk was reported among first-degree relatives, lower risk was observed among more genetically distant relatives. The results suggests that shared genetic factors are important for this association

Mayes *et al*[36]	United States	Cross-sectional	Community and clinical sample	1706 children and adolescents with psychiatric disorders and typical development: ADHD-C: *n* = 566 (male ratio: 74.6%) ADHD-I: *n* = 235 (male ratio: 57.4%) Other psychiatric disorders (autism, depression/anxiety, eating disorder, intellectual disability): *n* = 719 (male ratio: 67.2%) Typical: *n* = 186 (male ratio: 43.5%)	Age range: 6-18 yr	All participants had a clinical diagnosis of ADHD made by a licensed PhD psychologist. The clinical diagnosis was based on a comprehensive psychological evaluation including diagnostic interviews with the parent and child, parent and teacher rating scales, review of educational and medical records, extensive psychological testing PBS	All psychiatric groups had far more suicide behavior than typically developed children. ADHD-C: 20.7% had suicide ideation, 6.0% attempt ADHD-I: 7.3% had suicide ideation, 2.6% attempt
Mayes *et al*[37]	United States	Cross-sectional	Clinical sample	Children and adolescents with ADHD: *n* = 925 (male ratio: 68.5%) ADHD-C: *n* = 666 ADHD-I: *n* = 259	Age range: 3-16 yr Mean age: 8.8 yr (SD = 2.6)	All participants had a clinical diagnosis of ADHD made by a licensed PhD psychologist. The clinical diagnosis was based on a comprehensive psychological evaluation including diagnostic interviews with the parent and child, parent and teacher rating scales, review of educational and medical records, extensive psychological testing PBS - suicide ideation and attempt items	For the total sample with ADHD, 15.8% had suicide ideation (sometimes or more) and 5.5% had attempts. Ideation and attempts were more than twice as prevalent among participants with ADHD-C than among participants with ADHD-I. ADHD-C: 19% had suicide ideation, 7% attempt ADHD-I: 7% had suicide ideation, 3% attempt Those, who had ADHD alone: 6% had suicide ideation and 2% had suicide attempt
Park *et al*[38]	South Korea	Cross-sectional	Community sample	A total of 6081 subjects: Non-ADHD symptom group: *n* = 6012 ADHD symptom group: *n* = 69	Age range: 18-59 yr	K-CIDI Adult ADHD Self-Report Scale	Those, who had ADHD + co-occurring sadness and ODD, 46% had ideation and 21% had attempts Adult ADHD symptoms are significantly associated with lifetime suicidality. However, the association disappeared after adjusting for other comorbid psychiatric disorders

Swanson *et al*[39]	United States	Longitudinal: 10 yr: First 5 yr follow up and second 10 yr follow-up	Community and clinical sample	ADHD girls: n = 140 Non-ADHD girls: n = 88	Age range: 6-12 yr at ascertainment Mean age at 5 yr follow-up: 14.2 yr Mean age at 10 yr follow-up: 19.6 yr (range 17-24 yr)	At ascertainment: DISC-IV First follow up: SNAP-IV, Second follow up: SIQ, Barkley Suicide Questionnaire, DISC-IV-YA	Women with a childhood diagnosis of ADHD-C, compared with those with ADHD-I and control group, were at higher risk for suicide attempts. Furthermore, women with a persistent ADHD diagnosis were at higher risk than women with a transient diagnosis and the control group
Taylor *et al*[48]	New Zealand	Cross-sectional	Community sample	66 adults (43 men, 23 women ADHD: n = 35 (male ratio: 65.7%) Non-ADHD: n = 31 (male ratio: 64.5%)	Age range: 18-65 yr Mean age: 31.9 yr (SD = 1.6)	CAARS DSHI SCID-I (suicidality) CAADID	There was a significant associations between ADHD symptom severity and self-reported suicidal ideation and suicide attempts. These associations between suicidal behaviours and ADHD symptom severity were significantly and differentially mediated by psychosocial variables such as comorbidities (mood, anxiety, drug, and alcohol abuse disorders) and emotion-focussed coping style

SB: Suicidal behavior; ADHD: Attention-deficit/hyperactivity disorder; CIDI: Composite International Diagnostic Interview; ACDS: Adult ADHD Clinical Diagnostic Scale; DIS-IV: The Diagnostic Interview Schedule for DSM-IV; MINI-KID: Mini-International Neuropsychiatric Interview for children and adolescents; K-SADS-PL: Schedule for Affective Disorder and Schizophrenia for School-Age Children- Present and Lifetime Version; K-CIDI: Korean version of Composite International Diagnostic Interview; DISC-IV-YA: Diagnostic Interview Schedule for Children 4th ed., Young Adult version; SNAP-IV: Swanson, Nolan, and Pelham Rating Scale; SIQ: Self-Injury Questionnaire; CAADID: Conners'Adult ADHD Diagnostic Interview for DSM-IV; CAARS: Conners' Adult ADHD Rating Scale; DSHI: Deliberate Self-Harm Inventory; ADHD-C: ADHD combined type; ADHD-I: ADHD inattentive type, ADHD-HKS Questionnaire.

Table 5 Assessments for measuring attention-deficit/hyperactivity disorder

Ref.	Scale	Abbriviation
[49]	Adult ADHD Clinic Diagnostic Scale	ACDS
[50]	Adult Self-Report Scale	ASRS
[51]	Adult ADHD DSM-IV-Based Diagnostic Screening and Rating Scale, ADHD-C: ADHD combined type, ADHD-I: ADHD inattentive type, ADHD-HKS Questionnaire	ADHD scale
[52]	Conners' Adult ADHD Diagnostic Interview for DSM-IV	CAADID
[53]	Conners' Adult ADHD Rating Scale	CAARS
[54]	Diagnostic Interview for ADHD in Adults	DIVA
[55]	Strengths and Weaknesses of ADHD symptoms and Normal Behaviors	SWAN

ADHD: Attention-deficit/hyperactivity disorder; DSM-IV: Diagnostic and statistical manual of mental disorders fourth edition; ADHD-HKS: Attention deficit hyperactivity disorder - hyperkinetic syndrome.

investigated the role of comorbidity in ADHD patients with suicidality. The majority of the studies (7/9) found that comorbid disorders mediate between suicidality and ADHD[27,36,38-41,49], which is in line with the conclusion of previous review papers[18-21]. It highlights the importance of raising clinicians' awareness of the need to screen and treat comorbidity in ADHD, which may reduce suicidality as well.

These findings are limited in that only studies published in English and in Hungarian were included. Three potentially relevant studies were excluded because they were neither in English nor in Hungarian. The vast majority of the studies included in this review have a cross-sectional design, which limits the possible conclusions. Additionally, most of the studies that were conducted before this review paper have a cross-sectional design as well[19]. This should draw the attention of the researchers that, in the future, more studies are needed with a longitudinal design. Additionally, similar to the previous review of Impey *et al*[19], the measurement methods for both ADHD and suicidality in the studies included in the current review are very different, *i.e.*, diagnostic interviews, rating questionnaires and clinician-made diagnoses - which means that a comparison of the

Table 6 Assessments for measuring suicidality and comorbid conditions

Ref.	Scale	Abbriviation
[56]	Beck Depression Inventory	BDI
[57]	Brief Symptoms Inventory	BSI
[58]	Brief Symptoms Rating Scale	BSRS-5
[59]	Composite International Diagnostic Interview	CIDI
[60,61]	Current Symptoms Scale-Self-Report Form	CSS
[62]	Deliberate Self-Harm Inventory	DSHI
[63]	Diagnostic Interview Schedule for DSM-IV	DIS-IV
[64]	Diagnostic Interview Schedule for Children	DISC-IV
[65]	Diagnostic Interview Schedule for Children 4th ed., Young Adult version	DISC-IV-YA
[66,67]	European Version of the Adolescent Assessment Dialogue	EuroADAD
[68]	Hopelessness Depression Symptom Questionnaire-Suicidality Subscale	HDSQ
[69]	Korean version of Composite International Diagnostic Interview	K-CIDI
[70]	Schedule for Affective Disorder and Schizophrenia for School-Age Children- Present and Lifetime Version	K-SADS-PL
[71]	Psychological Screening Test for Adolescents	PSTA
[72]	Rutter's Behaviour Scale for Children (Teacher's Scale)	Rutter B2
[73]	Mini International Neuropsychiatric Interview	MINI
[73,74]	Mini International Neuropsychiatric Interview Kid	MINI Kid
[75]	Pediatric Behavior Scale	PBS
[76,77]	Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version	SCID-I-CV
[78]	Structured Clinical Interview for DSM-III-R Personality Disorders	SCID-II
[79]	Self-Injury Questionnaire	SIQ
[80]	Swanson, Nolan, and Pelham Rating Scale 4th ed.	SNAP-IV

numerical results is not possible.

In conclusion, our systematic highlights that the early recognition and treatment of ADHD - either as a comorbid condition or as a main diagnosis- and the co-occurring psychiatric disorders, can play an important role in the secondary prevention of suicide. Additionally, it could be useful to incorporate routine measurements of suicidality in the daily practice of ADHD clinics.

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COMMENTS

Background

Recently, several studies have focused on attention-deficit/hyperactivity disorder (ADHD) as a possible psychiatric disorder that may serve as a suicide risk factor as well. This paper presents a systematic review of suicidality and ADHD as an extension of previous reviews for the search period and with study questions.

Research frontiers

Suicide prevention is a public health issue all over the world. As ADHD is one of the most prevalent psychiatric disorders among children and adolescents and in 40%-60% of the cases, it continues into adulthood. All additional knowledge on the possible association between ADHD and suicidality has high clinical importance and can add to suicide prevention.

Innovations and breakthroughs

Although this systematic review was conducted only for the last four years, the authors still found 26 papers that presented data on ADHD and suicidality.

Applications

This systematic review strengthens the finding that ADHD is related to high suicidality in all age groups and in both girls and boys. It highlights that the early recognition and treatment of ADHD - either as a comorbid condition or as a main diagnosis - and the co-occurring psychiatric disorders, can play an important role in the secondary prevention of suicide.

Terminology

Attention-deficit/hyperactivity disorder: ADHD is a neurodevelopmental disorder with ongoing pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development; Suicidality: It includes suicidal thought, suicidal plan, suicidal attempt and completed suicide; Systematic review: A systematic review is a type of literature review which aims to provide a thorough, complete, exhaustive summary of current literature relevant to a research question.

Peer-review

The authors have reviewed the evidence for an association between ADHD and suicide. This is a descriptive review that does not include meta-analysis.

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META-ANALYSIS

Consequences of bullying victimization in childhood and adolescence: A systematic review and meta-analysis

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Abstract

AIM

To identify health and psychosocial problems associated with bullying victimization and conduct a meta-analysis summarizing the causal evidence.

METHODS

A systematic review was conducted using PubMed, EMBASE, ERIC and PsycINFO electronic databases up to 28 February 2015. The study included published longitudinal and cross-sectional articles that examined health and psychosocial consequences of bullying victimization. All meta-analyses were based on quality-effects models. Evidence for causality was assessed using Bradford Hill criteria and the grading system developed by the World Cancer Research Fund.

RESULTS

Out of 317 articles assessed for eligibility, 165 satisfied the predetermined inclusion criteria for meta-analysis.

Statistically significant associations were observed between bullying victimization and a wide range of adverse health and psychosocial problems. The evidence was strongest for causal associations between bullying victimization and mental health problems such as depression, anxiety, poor general health and suicidal ideation and behaviours. Probable causal associations existed between bullying victimization and tobacco and illicit drug use.

CONCLUSION

Strong evidence exists for a causal relationship between bullying victimization, mental health problems and substance use. Evidence also exists for associations between bullying victimization and other adverse health and psychosocial problems, however, there is insufficient evidence to conclude causality. The strong evidence that bullying victimization is causative of mental illness highlights the need for schools to implement effective interventions to address bullying behaviours.

Key words: Bullying; Victimization; Systematic review; Meta-analysis; Child; Adolescent

Core tip: There is convincing evidence of a causal association between exposure to bullying victimization in children and adolescents and adverse health outcomes including anxiety, depression, poor mental health, poor general health, non-suicidal self-injury, suicidal ideation and suicide attempts. It is probable that bullying victimization also causes an increased risk of cigarette smoking and illicit drug use. This review highlights that bullying victimization is associated with a wide and diverse range of problems and reinforces the need for effective interventions to be implemented in schools to address the high prevalence of children and adolescents engaging in bullying behaviours.

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INTRODUCTION

Bullying victimization among children and adolescents is a global public health issue, well-recognised as a behaviour associated with poor adjustment in youth[1]. There is evidence suggesting bullying victimization in children and adolescents has enduring effects which may persist into adulthood[2-4]. Bullying victimization is most commonly defined as exposure to negative actions repeatedly and over time from one or more people, and involves a power imbalance between the perpetrator(s) and the victim[5]. Traditional bullying includes physical contact (pushing, hitting) as well as verbal harassment (name calling, verbal taunting), rumour spreading, intentionally excluding a person from a group, and obscene gestures. In recent years cyberbullying has emerged as a significant public health problem[5-8].

The estimated prevalence of bullying victimization is wide-ranging, with 10% and 35% of adolescents experiencing recurrent bullying victimization[9-16]. While contextual and cultural differences influence prevalence estimates[17], this variation is most frequently explained by differences in measurement strategy[18-20]. As a result, researchers continue to call for greater consensus in the definition and measurement of bullying behaviours[17,21,22]. Cook *et al*[17] examined the variability in prevalence of bullying victimization in a meta-analysis, and more recently Modecki *et al*[20] synthesised studies measuring both traditional bullying and cyberbullying. Mean prevalence was 36% for traditional bullying victimization and 15% for cyberbullying victimization[20]. There was significant overlap between bullying victimization in traditional and online settings[20]. A meta-analysis by Kowalski *et al*[23] showed that the strongest predictor of cyber-victimization was traditional bullying victimization.

Many studies have examined adverse health and psychosocial problems associated with bullying victimization. Those most commonly reported are mental health problems, specifically depression, anxiety, self-harm, and suicidal behaviour[2,14,24-28]. Over the past two decades researchers have conducted a number of systematic reviews to examine the relationship between bullying victimization and ill mental health.

The first systematic investigation by Hawker and Boulton[1] was a meta-analysis of cross-sectional studies of peer victimization published between 1978 and 1997. The authors reported victimization was significantly associated with depression, loneliness, reduced self-esteem and self-concept, as well as anxiety. To understand the temporal sequence between peer victimization and mental health problems, Reijntjes and colleagues conducted a pair of meta-analyses of longitudinal studies to examine internalizing (depression, anxiety, withdrawal, loneliness, and somatic complaints) and externalizing behaviours (aggression and delinquency) and peer victimization[29,30]. They examined two prospective paths: (1) peer victimization at baseline and changes in internalizing and externalizing problems at a second time point; and (2) internalizing and externalizing problems at baseline and changes in peer victimization at follow-up. The two meta-analyses demonstrated internalizing and externalizing behaviours are both antecedents and consequences of bullying victimization[29,30].

Another meta-analytic review on bullying victimi-

zation and depression by Ttofi *et al*[31] found those children who were bullied at school were twice as likely to develop depression compared to those who had not been bullied. In addition, another meta-analytic review found those children involved in any bullying behaviour were more likely to develop psychosomatic problems[32]. Finally, three systematic reviews have shown an association between bullying victimization and increased risk of adolescent suicidal ideation and behaviours[33-35].

In contrast to mental health, there is mixed evidence for the relationship between bullying victimization and substance use. Some studies report that bullying victimization is associated with a reduced risk of engaging in harmful alcohol use in later life[16,28], whereas others suggest that being bullied may result in an increased probability of later harmful alcohol use[36,37]. Similarly, some studies have shown an association between being bullied and later illicit drug use and smoking[36-39], whereas others have found no association at all[2,14,24,40].

The association between bullying victimization and psychosocial problems, such as academic achievement and school functioning/connectedness and criminal behaviour has also been examined. A meta-analysis by Nakamoto and Schwartz[41] found a small but significant negative association between bullying victimization and academic achievement. However, Kowalski *et al*[23] found no significant relationship between cyberbullying victimization and academic achievement. Another study found those exposed to bullying victimization in adolescence were at increased risk of involvement in criminal behaviour such as carrying a weapon[40].

There are now a large number of studies examining associations between bullying victimization and a wide range of adverse health and psychosocial problems. However, many of these have not been systematically examined and many existing systematic reviews did not include cyberbullying. Furthermore, although associations exist, it is unclear if there is a causal relationship. It is plausible that there are common factors that predispose individuals to being bullied in childhood but independently also increase the risk of adverse health and other psychosocial problems. Rigorous appraisal is required to consider both the possibility of a causal association but also other plausible explanations for any significant associations. Given the variation between studies, this study aimed to investigate adverse outcomes of both traditional and cyber bullying victimization and conduct a meta-analysis to summarize each association. Furthermore, we critically evaluated whether sufficient evidence existed to establish a causal relationship between bullying victimization and each of the adverse health and psychosocial problems. This is the first study to complete a summary of the evidence for all adverse health and psychosocial problems that are potentially a consequence of traditional and cyber bullying victimization.

MATERIALS AND METHODS

This study followed the recommendations from the PRISMA 2009 revision[42] and the guidelines outlined by the Meta-analysis of Observational Studies in Epidemiology[43] (Supplementary material S1). Methods and inclusion and exclusion criteria were specified in advance in the review protocol (Supplementary material S2).

Inclusion and exclusion criteria

This systematic review and meta-analysis included studies meeting the following inclusion criteria: (1) reported original, empirical research published in a peer reviewed journal; (2) examined the relationship between exposure to bullying victimization as a child or adolescent and one or more consequences of the bullying exposure; and (3) is a population based study. This study did not examine a particular type of bullying victimization therefore all direct and indirect forms of bullying including cyberbullying were included. Included studies reported odds ratios (ORs) and confidence intervals (CIs) comparing those exposed to bullying victimization and those not exposed to bullying victimization or, alternatively, provided information from which effect sizes (ORs and CIs) could be calculated between those exposed to bullying victimization and an outcome.

Search strategy

Four electronic databases (PsycINFO, ERIC, EMBASE and PubMed) were used to search for literature on the adverse correlates of bullying victimization as either a child or adolescent from inception up to 28 February 2015. The search was not restricted to the English language nor by any other means. The searches of the databases were conducted using the terms: "bullying", "bullied", "harassment", "intimidation", "victimization" along with "child" and "adolescent". As this study aimed to examine all correlates that were potentially a consequence of bullying victimization, the search terms used in conjunction with those above were broader terms such as "outcome" "harm" "consequence" and "risk". In addition, reference lists of selected studies were screened for any other relevant study and articles in languages other than English were translated (Supplementary material S2).

Data collection and quality assessment

The full text of articles that met all inclusion criteria were retrieved and examined. Data extracted using a data extraction template included publication details, country where study was conducted, methodological characteristics such as sample size and study design, exposure and outcome measures, type of bullying and frequency (Supplementary material S2). Each study was then subjected to a quality assessment in order for the reviewers to rate the quality of each study.

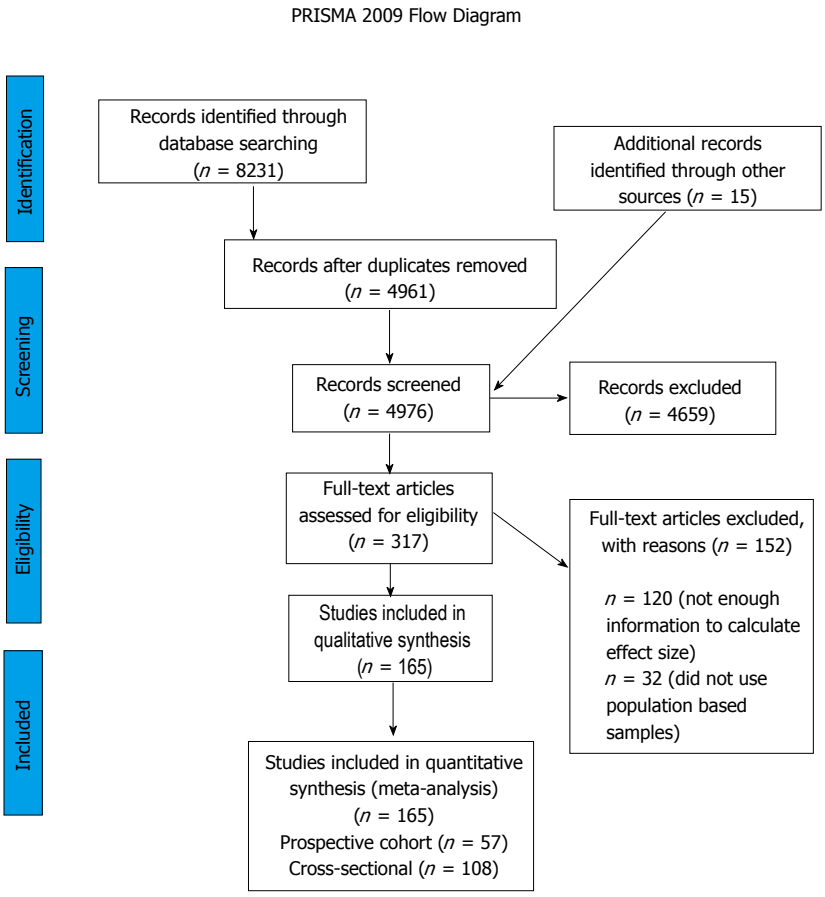

Figure 1 PRISMA flow diagram showing process of study selection for inclusion in systematic review and meta-analyses.

Two reviewers independently reviewed the included articles and completed the quality assessment and any disagreements were resolved by a third reviewer. The quality assessment tool was based on the Newcastle-Ottawa Scale for assessing the quality of observational studies[44] as used by Norman *et al*[45] (Supplementary material S2).

Statistical analysis

Following the method used by Norman *et al*[45], MetaXL version 2.1[46], an add-in for Microsoft Excel was used in this study to conduct the meta-analysis. ORs were chosen as the summary measure. Heterogeneity was assessed using the Cochran's Q and I^2 statistics[47]. This meta-analysis used a quality effects model[48], a modified version of the fixed-effects inverse variance model that additionally allows greater weight to be given to studies of higher quality *vs* studies of lesser quality. The quality effects model avoids the limitation in random-effects models of returning to equal weighting irrespective of sample size if heterogeneity is large[47,48]. Furthermore, in order to address the effects of important study characteristics and explore heterogeneity this study conducted subgroup analyses, dependent on data availability, for sex of participants in the sample, geographic location and income level (high income *vs* low-to-middle income as per the World Bank classification criteria), severity of the bullying (frequent - at least once a month, *vs* sometimes - less than once a month), age of bullying victimization (before 13 years of age *vs* after 13 years of age), and type of study (prospective *vs* cross-sectional).

RESULTS

A total of 8231 articles were primarily identified by the search, of which 3270 were duplicates. Titles and abstracts for the 4961 remaining unduplicated references were reviewed and 15 additional articles were found from reference lists. From reviewing the title and abstracts a further 4659 articles were excluded. This left 317 articles meeting the following criteria: (1) original research extracted from a peer reviewed journal; and (2) examined the bullying victimization as a child or adolescent and one or more outcomes. Of the 317 articles reviewed, a further 152 articles were excluded as they did not use a population based sample or did not report enough information to calculate an effect size. The remaining 165 articles provided evidence of an effect size for bullying victimization and an outcome (Figure 1) - either odds ratio with confidence intervals or provided data which enabled the calculation of effect sizes. The majority (n = 142) were from high income regions. There were far fewer studies (n = 22) from

low- and middle-income countries, and only one study utilized cross-national samples from different income-level countries. Of the articles included, 57 had a prospective cohort design and the remaining 108 were cross-sectional. The majority of studies measured self-reported bullying victimization. Some were from samples collected from a state or regions where as others were nationally representative (Supplementary material S3).

Bullying victimization in children and adolescents and mental health

Bullying victimization in children and adolescents was associated with a wide range of adverse mental health outcomes (Table 1) including poor mental health (OR = 1.60; 95%CI: 1.42-1.81), syndromes such as depression and anxiety, and symptoms and behaviours such as psychotic symptoms, suicidal ideation and attempts. Specifically, those exposed to bullying victimization had an increased risk of depression (OR = 2.21; 95%CI: 1.34-3.65). This association remained significant for all the sub-group analyses including prospective studies, age bullying occurred, sex and severity of the bullying. A dose response existed between being "sometimes bullied" and "frequently bullied" and depression (OR = 1.78; 95%CI: 1.39-2.28 and OR = 3.26; 95%CI: 2.45-4.34 respectively). In comparing high- and low-to-middle income countries, there was no significant difference in the odds of developing depression. Those exposed to bullying victimization were significantly more likely to experience anxiety (OR = 1.77; 95%CI: 1.34-2.33) and exposure to bullying victimization was associated with a wide range of anxiety spectrum disorders such as social phobia and post-traumatic stress disorder. This association remained after conducting subgroup analyses including study type, sex and severity of the bullying; however, the association between bullying victimization and anxiety was not significant in children under 13 years (Table 1).

Bullying victimization was also associated with non-suicidal self-injury (OR = 1.75; 95%CI: 1.40-2.19) and increased risk of suicidal ideation (OR = 1.77; 95%CI: 1.56-2.02) and the association remained significant for all subgroup analyses (Table 1). A dose response existed between being "sometimes bullied" and "frequently bullied" and suicide ideation (OR = 1.53; 95%CI: 1.28-1.82 and OR = 2.59; 95%CI: 2.06-3.25 respectively). Bullying victimization was associated with an increase in suicide attempts (OR = 2.13; 95%CI: 1.66-2.73). Subgroup analysis showed both males and females were approximately three times more likely to attempt suicide if they were bullied (OR = 2.93; 95%CI: 1.65-5.18 and OR = 2.89; 95%CI: 1.52-5.49 respectively). There was nearly a fourfold increase in suicide attempts for individuals who experienced frequent bullying victimization (OR = 3.77; 95%CI: 2.55-5.58) (Table 1). When comparing high income countries to those with low and middle income, the odds of bullying victims developing suicidal ideation or attempting suicide were similar.

Although bullying victimization in children and adolescents was associated with the pooling of all behavioural problems (OR = 1.37; 95%CI: 1.18-1.59), this association was not significant in prospective cohort studies and no dose-response was observed. Diagnoses of disruptive behavioural disorders were not associated with bullying victimization in children and adolescents (Table 1).

Bullying victimization in children and adolescents and substance use

Table 2 presents the associations between bullying victimization and substance use. When all studies were pooled together there was a significant association between bullying victimization and alcohol use (OR = 1.26; 95%CI: 1.00-1.58). A subgroup analysis showed a significant association between bullying victimization and the risk of tobacco use for prospective studies (OR = 1.62; 95%CI: 1.31-1.99). Furthermore, a dose response was present with frequent bullying victimization being associated with tobacco use (OR = 3.19; 95%CI: 1.19-8.58), whereas no significant association was found with those who were "sometimes bullied" (Table 2).

Bullying victimization was associated with an increased risk of illicit drug use (OR = 1.41; 95%CI: 1.10-1.81). Subgroup analysis revealed that the association between bullying victimization and increased risk of using illicit drugs was significant in both cross-sectional (OR = 2.43; 95%CI: 1.42-4.15) and prospective studies (OR = 1.27; 95%CI: 1.12-1.44). A subgroup analysis also revealed bullying victims in low-to-middle income countries are at an increased risk of illicit drug use (OR = 4.05; 95%CI: 2.18-7.55) compared with bullying victims in high income countries (OR = 1.31; 95%CI: 1.15-1.48). No significant association was found in a sub group analysis examining cannabis and bullying victimization in children and adolescence (Table 2).

Bullying victimization in children and adolescents and other health outcomes

Table 3 presents the association between bullying victimization and other health outcomes. Bullying victimization was associated with increased risk of somatic symptoms, the most common being stomach ache (OR = 1.76; 95%CI: 1.53-2.03), sleeping difficulties (OR = 1.73; 95%CI: 1.46-2.05), headaches (OR = 1.64; 95%CI: 1.38-1.94), dizziness (OR = 1.64; 95%CI: 1.38-1.95), and back pain (OR = 1.67; 95%CI: 1.43-1.95). Bullying victimization was also associated with an increased risk of being overweight and obese (OR = 1.68; 95%CI: 1.21-2.33 and OR = 1.78; 95%CI: 1.42-2.21, respectively). These associations were significant for cross-sectional studies only and there was no dose response.

When all studies were pooled, bullying victimization in children and adolescents was associated with increased

Table 1 Associations between bullying victimization in children and adolescents and mental health outcomes

	Data points	Pooled OR	95%CI lower bound	95%CI upper bound	Cochran's *Q*	I^2 (%)	Test for heterogeneity (*P* value)
Poor mental health							
Pooling all	39	1.6	1.42	1.81	303.79	87.49	< 0.01
Study type							
Retrospective/cross-sectional	25	1.8	1.44	2.25	211.78	88.67	< 0.01
Prospective cohort	14	1.39	1.29	1.49	22.12	41.24	0.05
Sex							
Male	3	2.49	1.86	3.32	0.44	0	0.8
Female	3	2.38	1.41	4	6.95	71.22	0.03
Twins	3	1.41	1.27	1.56	2.5	20.09	0.29
Severity of bullying							
Sometimes	8	1.5	1.27	1.76	47.68	85.23	< 0.01
Frequent	8	1.52	1.18	1.95	51.4	86.38	< 0.01
Anxiety							
Pooling all	58	1.77	1.34	2.33	3816.23	98.51	< 0.01
Anxiety	32	1.56	1.39	1.75	434.61	92.87	< 0.01
Social phobia	8	2.48	1.59	3.86	11.01	36.41	0.14
Generalised anxiety disorder	2	2.83	1.38	5.84	0.11	0	0.74
PTSD	12	6.41	1.93	21.22	497.11	97.79	< 0.01
Specific phobia	1	2.4	1	5.6	-	-	-
Separation anxiety disorder	1	4.6	2	10.6	-	-	-
Panic disorder	1	3.1	1.5	6.5	-	-	-
Agoraphobia	1	4.6	1.7	12.5	-	-	-
Study type							
Retrospective/cross-sectional	39	2.02	1.21	3.38	3697.48	98.97	< 0.01
Prospective cohort	19	1.29	1.06	1.55	84.03	78.58	< 0.01
Age of bullying							
Less than 13 yr	13	1.4	0.58	3.41	123.12	90.25	< 0.01
Older than 13 yr	45	1.81	1.29	2.56	3688.82	98.81	< 0.01
Sex							
Male	16	1.84	1.3	2.59	112.23	86.63	< 0.01
Female	15	2.46	1.74	3.48	124.39	88.74	< 0.01
Severity of bullying							
Sometimes	7	1.46	1.06	2	43.41	86.18	< 0.01
Frequent	25	2.47	1.94	3.14	122.47	80.4	< 0.01
Geographic location and income level							
Low-to-middle income	22	2.41	1.75	3.32	175.97	88.07	< 0.01
High income	36	1.67	1.24	2.25	3441.17	98.98	< 0.01
Depression							
Pooling all	92	2.21	1.34	3.65	14525.32	99.37	< 0.01
Major depressive disorder	2	2.27	0.68	7.57	2.07	51.63	0.15
Study type							
Retrospective/cross-sectional	63	1.95	1.24	3.07	2594.97	97.61	< 0.01
Prospective cohort	29	3.03	1.31	6.98	4583.05	99.39	< 0.01
Age of bullying							
Less than 13 yr	36	2.11	1.63	2.72	544.9	93.58	< 0.01
Older than 13 yr	56	2.29	1.24	4.23	13806.72	99.6	< 0.01
Sex							
Male	27	2.07	1.48	2.89	443.84	94.14	< 0.01
Female	21	2.13	1.18	3.86	313.5	93.62	< 0.01
Severity of bullying							
Sometimes	15	1.78	1.39	2.28	78.61	82.19	< 0.01
Frequent	28	3.26	2.45	4.34	224.43	87.97	< 0.01
Geographic location and income level							
Low-to-middle income	13	2.53	1.75	3.68	143.98	91.67	< 0.01
High income	79	2.15	1.26	3.68	14351.72	99.46	< 0.01
Psychotic symptoms							
Specific psychiatric symptoms	6	2.07	1.49	2.87	20.57	75.69	< 0.01
Non-clinical psychotic experiences	9	2.68	2.03	3.54	15.1	47.03	0.06
Psychotic symptoms	5	2.73	1.97	3.77	10.86	63.16	0.03
Personality disorders							
Anti-social personality disorder	2	0.58	0.15	2.28	2.53	60.48	0.11
Borderline personality disorder	3	2.2	1.4	3.46	4.8	58.31	0.09
Eating disorders							
Bulimia nervosa	1	3	1.4	6.2	-	-	-
Anorexia nervosa	1	0.004	0	251	-	-	-

Non-suicidal self injury							
Pooling all	30	1.75	1.4	2.19	749.02	96.13	< 0.01
Study type							
Retrospective/cross-sectional	21	1.55	1.09	2.22	721.15	97.23	< 0.01
Prospective cohort	9	1.65	1.34	2.02	19.39	58.75	0.01
Sex							
Male	6	4.86	3.35	7.07	13.56	63.12	0.02
Female	4	2.7	2	3.65	8.92	66.37	0.03
Twins	2	2.57	1.79	3.7	0.12	0	0.73
Severity of bullying							
Sometimes	6	1.57	1.09	2.25	34.04	85.31	< 0.01
Frequent	7	2.52	1.6	3.97	54.49	88.99	< 0.01
Suicidal ideation							
Pooling all	105	1.77	1.56	2.02	2093.5	95.03	< 0.01
Study type							
Retrospective/cross-sectional	86	1.8	1.56	2.09	2037.46	95.83	< 0.01
Prospective cohort	19	1.68	1.38	2.05	38.98	53.82	< 0.01
Age of bullying							
Less than 13 yr	22	1.85	1.48	2.3	74.4	71.77	< 0.01
Older than 13 yr	83	1.75	1.51	2.03	1984.06	95.87	< 0.01
Sex							
Male	21	1.95	1.64	2.32	76.6	73.89	< 0.01
Female	18	2.15	1.84	2.52	33.15	48.72	0.01
Severity of bullying							
Sometimes	16	1.53	1.28	1.82	35.19	57.38	< 0.01
Frequent	21	2.59	2.06	3.25	49.83	59.87	< 0.01
Geographic location and income level							
Low-to-middle income	11	1.31	1.06	1.61	60.02	83.34	< 0.01
High income	94	1.8	1.43	2.26	1894.91	95.09	< 0.01
Suicide attempt							
Pooling all	48	2.13	1.66	2.73	1110.46	95.77	< 0.01
Suicidal attempt/non-suicidal self injury	3	2.97	1.68	5.23	6.33	68.42	0.04
Study type							
Retrospective/cross-sectional	40	2.03	1.46	2.84	1105.65	96.47	< 0.01
Prospective cohort	8	2.04	1.38	3.01	4.34	0	0.74
Age of bullying							
Less than 13 yr	11	2.11	1.65	2.69	11.49	12.98	0.32
Older than 13 yr	37	1.52	0.82	2.83	579.75	93.79	< 0.01
Sex							
Male	7	2.93	1.65	5.18	15.38	54.5	0.02
Female	7	2.89	1.52	5.49	24.23	71.11	< 0.01
Severity of bullying							
Sometimes	9	2.19	1.71	2.8	7.52	0	0.48
Frequent	12	3.77	2.55	5.58	28.31	61.14	< 0.01
Geographic location and income level							
Low-to-middle income	4	1.91	1.07	3.43	22.18	86.47	< 0.01
High income	44	2.17	1.69	2.8	1084.61	96.04	< 0.01
Behavioural problems							
Pooling all	54	1.37	1.18	1.59	862.4	93.85	< 0.01
Study type							
Retrospective/cross-sectional	29	1.18	0.99	1.41	311.21	91	< 0.01
Prospective cohort	25	1.56	0.94	2.58	413.53	94.2	< 0.01
Sex							
Male	9	1.35	0.68	2.67	450.06	98.22	< 0.01
Female	7	1.99	0.97	4.1	88.07	93.19	< 0.01
Twins	2	1.19	0.94	1.5	7.31	86.31	0.01
Severity of bullying							
Sometimes	8	1.95	0.92	4.1	243.71	97.13	< 0.01
Frequent	8	2.26	0.76	6.69	163.51	95.72	< 0.01
Externalising behaviours	20	1.29	1.12	1.5	157.09	87.9	< 0.01
Delinquent/deviant behaviour	24	1.99	1.24	3.2	423.78	94.57	< 0.01
Missed school	7	1.49	0.99	2.23	38.4	84.37	< 0.01
Disruptive behavioural disorders							
Attention deficit hyperactivity disorder	1	2.6	0.8	8.5	-	-	-
Oppositional defiant disorder	1	0.8	0.3	2.5	-	-	-
Conduct disorder	1	2.6	0.8	8.8	-	-	-
Other mental health outcomes (not included above)							
Nervousness	9	1.82	1.51	2.2	135.59	94.1	< 0.01
Powerlessness	2	1.06	0.95	1.18	1.64	39.18	0.2
Feeling low	7	2.26	1.66	3.08	299.47	98	< 0.01
Irritability or bad temper	7	1.82	1.51	2.2	125.07	95.2	< 0.01
Feel helpless	5	3.2	2.01	5.09	273.51	98.54	< 0.01

Feeling tense	3	3.07	2.06	4.56	3.02	33.75	0.22
Unhappy/sad	12	1.25	0.55	2.84	668.61	98.35	< 0.01
Worried	4	1.27	1.09	1.47	314.35	99.05	< 0.01
Afraid	3	2.68	1.18	6.09	9.49	78.92	0.01

Table 2 Associations between bullying victimization in children and adolescents and substance use

	Data points	Pooled OR	95%CI lower bound	95%CI upper bound	Cochran's *Q*	I^2 (%)	Test for heterogeneity (*P* value)
Alcohol use							
Pooling all	53	1.26	1.00	1.58	10328.18	99.5	< 0.01
Study type							
Retrospective/cross-sectional	38	1.28	0.88	1.84	10256.15	99.64	< 0.01
Prospective cohort	15	1.19	0.87	1.62	67.87	79.37	< 0.01
Sex							
Male	6	0.61	0.49	0.77	4.89	0.00	0.43
Female	4	0.88	0.50	1.57	6.36	52.86	0.1
Severity of bullying							
Sometimes	6	1.72	0.84	3.50	86.17	94.20	< 0.01
Frequent	13	1.53	0.78	3.03	332.27	96.39	< 0.01
Frequency of alcohol consumption							
Sometimes	24	1.52	1.08	2.13	8416.94	99.73	< 0.01
Frequent	29	0.99	0.86	1.14	251.81	88.88	< 0.01
Age of bullying							
Less than 13 yr	16	1.23	0.93	1.63	1618.14	99.07	< 0.01
Older than 13 yr	37	1.31	0.96	1.80	6896.71	99.48	< 0.01
Geographic location and income level							
Low-to-middle income	11	1.37	0.75	2.49	8328.21	99.88	< 0.01
High income	42	1.08	0.91	1.27	462.84	91.14	< 0.01
Tobacco use							
Pooling all	35	1.36	0.96	1.92	418.71	91.88	< 0.01
Study type							
Retrospective/cross-sectional	26	1.17	0.59	2.31	394.92	93.67	< 0.01
Prospective cohort	9	1.62	1.31	1.99	11.48	30.33	0.18
Sex							
Male	3	0.97	0.59	1.58	8.23	75.7	0.02
Female	3	0.51	0.37	0.68	1.78	0	0.41
Severity of bullying							
Sometimes	4	1.89	0.83	4.33	71.38	95.8	< 0.01
Frequent	4	3.19	1.19	8.58	39.85	92.47	< 0.01
Frequency of smoking							
Sometimes	28	1.36	0.89	2.06	400.72	93.26	< 0.01
Frequent	7	1.35	1.00	1.84	16.28	63.16	0.01
Illicit drug use							
Pooling all	34	1.41	1.10	1.81	677.62	95.13	< 0.01
Study type							
Retrospective/cross-sectional	11	2.43	1.42	4.15	297.3	96.64	< 0.01
Prospective cohort	23	1.27	1.12	1.44	67.23	67.28	< 0.01
Sex							
Male	7	1.04	0.81	1.33	32.84	81.73	< 0.01
Female	5	1.17	1.03	1.33	3.26	0.00	0.52
Severity of bullying							
Sometimes	7	1.22	0.78	1.90	160.47	96.26	< 0.01
Frequent	8	1.14	0.43	3.00	465.43	98.50	< 0.01
Geographic location and income level							
Low-to-middle income	5	4.05	2.18	7.55	98.61	95.94	< 0.01
High income	29	1.31	1.15	1.48	103.73	73.01	< 0.01
Cannabis only all	9	1.42	0.96	2.12	23.32	65.70	< 0.01
Study type							
Retrospective/cross-sectional	1	2.46	1.53	3.95	-	-	-
Prospective cohort	8	1.36	0.90	2.05	18.14	61.41	0.01

risk of sexual behaviour problems (OR = 1.51; 95%CI: 1.01-2.25) which included teenage pregnancy, early onset of sexual activities and risky sexual behaviour. Subgroup analyses were not significant with the exception of those frequently bullied. Although bullying victimization was associated with increased likelihood of

Table 3 Associations between bullying victimization in children and adolescents and other health outcomes

	Data points	Pooled OR	95%CI lower bound	95%CI upper bound	Cochran's *Q*	I^2 (%)	Test for heterogeneity (*P* value)
Somatic symptoms							
Unspecified psychosomatic symptoms	25	2.00	1.54	2.60	232.02	89.66	< 0.01
Stomach ache	25	1.76	1.53	2.03	138.73	82.7	< 0.01
Sleeping difficulties	24	1.73	1.46	2.05	574.91	96	< 0.01
Headache	26	1.64	1.38	1.94	169.16	85.22	< 0.01
Bedwetting	3	2.51	1.44	4.37	4.93	59.45	0.08
Feeling tired	2	2.68	1.39	5.19	1.22	17.87	0.27
Poor appetite	2	2.23	1.60	3.12	0	0	0.95
Back pain	8	1.67	1.43	1.95	73.53	90.48	< 0.01
Skin problems	1	1.82	1.33	251	-	-	-
Dizziness	9	1.64	1.38	1.95	76.57	89.55	< 0.01
Eating and weight related problems							
Binge eating	2	2.66	1.68	4.22	0.57	0	0.45
Non-diet soft drink consumption	1	1.21	1.04	1.41	-	-	-
Skips breakfast	6	1.41	1.20	1.65	11.89	57.94	0.04
Underweight							
Pooling all	2	1.27	0.73	2.21	0	0	0.96
Sex							
Male	1	1.28	0.69	2.37	-	-	-
Female	1	1.24	0.19	2.29	-	-	-
Overweight							
Pooling all	14	1.68	1.21	2.33	82.69	84.28	< 0.01
Study type							
Retrospective/cross- sectional	12	1.99	1.39	2.85	65.45	83.19	< 0.01
Prospective cohort	2	0.98	0.64	1.49	1.92	47.97	0.17
Sex							
Male	7	1.22	0.99	1.49	8.04	25.4	0.23
Female	7	2.22	1.28	3.84	50.17	88.04	< 0.01
Severity of bullying							
Sometimes	2	1.32	1.00	1.74	0.09	0	0.77
Frequent	6	1.14	0.88	1.47	7.37	32.2	0.19
Obese							
Pooling all	13	1.78	1.42	2.21	14.68	18.28	0.26
Study type							
Retrospective/cross-sectional	10	1.97	1.53	2.53	7.22	0	0.61
Prospective cohort	3	1.57	0.89	2.77	6.89	70.97	0.03
Sex							
Male	6	1.94	1.45	2.60	4.88	0	0.43
Female	6	2.15	1.57	2.94	2.22	0	0.82
Severity of bullying							
Sometimes	2	1.63	1.11	2.38	0.52	0	0.47
Frequent	6	2.09	1.59	2.75	5.26	4.86	0.39
Sexual behaviour problems							
Teen parent	5	1.26	0.81	1.97	15.11	73.53	< 0.01
Risky sexual behaviour	4	2.28	0.95	5.48	23.43	87.2	< 0.01
Early onset of sexual activities	3	1.44	0.90	2.30	7.38	72.91	0.02
Pooling all	12	1.51	1.01	2.25	85.66	87.16	< 0.01
Study type							
Retrospective/cross-sectional	3	1.77	0.42	7.52	54.97	96.36	< 0.01
Prospective cohort	9	1.34	0.98	1.84	23.88	66.51	< 0.01
Severity of bullying							
Sometimes	2	0.81	0.51	1.28	2.46	59.32	0.12
Frequent	4	2.38	1.05	5.41	27.55	89.11	< 0.01
Health services utilised							
Pooling all	16	1.20	0.99	1.45	34.37	56.36	< 0.01
Study type							
Retrospective/cross-sectional	14	1.14	0.94	1.39	27.91	53.42	0.01
Prospective cohort	2	1.54	0.65	3.61	4.43	77.43	0.04
Sex							
Male	7	1.17	0.95	1.43	3.54	0	0.74
Female	7	1.41	1.12	1.77	11.16	46.25	0.08
General medication use							
Pooling all	12	1.16	0.80	1.70	117.98	90.68	< 0.01
Study type							
Retrospective/cross-sectional	11	0.99	0.56	1.75	112.26	91.09	< 0.01

Prospective cohort	1	1.67	1.09	2.58	-	-	-
Sex							
Male							
Medication for headache	2	1.43	1.06	1.93	2.34	57.21	0.13
Medication for stomach-ache	2	1.09	0.72	1.65	1.9	47.5	0.17
Female							
Medication for headache	2	1.19	0.98	1.45	1.33	24.79	0.25
Medication for stomach-ache	2	1.23	1.01	1.5	0.27	0	0.61
Severity of bullying							
Sometimes	5	1.26	0.99	1.59	15.46	74.13	< 0.01
Frequent	5	1.72	1.11	2.67	24.9	83.93	< 0.01
Over the counter drug misuse	3	0.95	0.19	4.66	76.34	97.38	< 0.01
Psychotropic medication use							
Pooling all	13	1.28	0.72	2.26	205.76	94.17	< 0.01
Study type							
Retrospective/cross-sectional	11	0.95	0.32	2.8	195.34	94.88	< 0.01
Prospective cohort	2	1.31	0.66	2.6	5.61	82.18	0.02
Sex							
Male							
Medication for nervousness	2	1.32	0.42	4.1	14.98	93.32	< 0.01
Medication for sleeping	2	1.89	1.33	2.67	1.59	37.28	0.21
Female							
Medication for nervousness	2	1.97	1.49	2.59	1.06	5.88	0.3
Medication for sleeping	2	1.83	1.42	2.36	0.27	0	0.6
Severity of bullying							
Sometimes	6	1.66	1.26	2.18	18.54	73.04	< 0.01
Frequent	6	1.88	1.17	3.03	31.93	84.34	< 0.01
Prescription drug misuse	3	0.92	0.17	5.07	88.16	97.73	< 0.01
Poor general health							
Pooling all	29	1.83	1.45	2.31	133.31	79	< 0.01
Study type							
Retrospective/cross-sectional	22	1.71	1.21	2.42	112.06	81.26	< 0.01
Prospective cohort	7	1.56	1.07	2.28	19.72	69.57	< 0.01
Sex							
Male	9	1.95	1.16	3.27	20.5	60.98	0.01
Female	9	2.36	1.11	5.04	52.78	84.84	< 0.01
Severity of bullying							
Sometimes	4	2.16	1.10	4.26	9.15	67.21	0.03
Frequent	4	6.96	2.17	22.35	16.72	82.05	< 0.01

poor general health (OR = 1.83; 95%CI: 1.45-2.31) and this association persisted when restricted to prospective cohort studies (OR = 1.56; 95%CI: 1.07-2.28). There was no consistent increase in utilisation of health services or medications in those exposed to bullying victimization during childhood or adolescence (Table 3).

Bullying victimization in children and adolescents and academic and social functioning

The association between bullying victimization and functioning at school was inconsistent. There was a robust association between bullying victimization in childhood or adolescence and poor academic achievement. Those who had exposure to bullying victimization were more likely to have poor academic achievement (OR = 1.33; 95%CI: 1.06-1.66), whilst those with good academic achievement were less likely to have been exposed to bullying victimization (OR = 0.71; 95%CI: 0.60-0.85); however, all studies except one were cross-sectional. Bullying victimization was not associated with later financial or occupational functioning.

Similarly, there were inconsistent associations between bullying victimization and social problems. Those exposed were approximately twice as likely to report loneliness (OR = 1.89; 95%CI: 1.39-2.57) and poor life satisfaction (OR = 2.26; 95%CI: 1.41-3.60) and were significantly less likely to have a good quality of life (OR = 0.85; 95%CI: 0.78-0.93). Bullying victimization was not consistently associated with low self-esteem, social problems, or criminal behaviours (Table 4).

DISCUSSION

This paper provides the most comprehensive critical analysis of the association between bullying victimization and a wide range of health and psychosocial problems. The primary and sub-group analyses allow for interpretation of the evidence of causality within the Bradford-Hill Framework, based on the following: Biological plausibility, the temporal relationship of the association, strength and consistency of the association, the presence of a dose-response relationship, and whether an alternate explanation for the associations is possible[49]. We used the grading system developed by the World Cancer Research Fund[50] as used in the Global Burden of Disease study as a guideline for evaluation of the level of

Table 4 Associations between bullying victimization and academic and social functioning

	Data points	Pooled OR	95%CI lower bound	95%CI upper bound	Cochran's *Q*	I^2 (%)	Test for heterogeneity (*P* value)
Poor school functioning							
Pooling all	6	1.10	0.87	1.38	82	93.9	< 0.01
Study type							
Retrospective/cross-sectional	3	1.24	1.22	1.27	0.33	0	0.85
Prospective cohort	3	0.90	0.76	1.08	8.15	75.46	0.02
Severity of bullying							
Sometimes	1	0.96	0.88	1.04	-	-	-
Frequent	1	0.98	0.76	1.19	-	-	-
Academic achievement							
Poor academic achievement							
Pooling all	6	1.33	1.06	1.66	11.17	55.25	0.02
Study type							
Retrospective/cross-sectional	6	1.33	1.06	1.66	11.17	55.25	0.02
Good academic achievement							
Pooling all	4	0.71	0.60	0.85	8.81	65.97	0.07
Study type							
Retrospective/cross-sectional	3	0.86	0.8	0.92	2.89	30.69	0.58
Prospective cohort	1	0.46	0.28	0.76	-	-	-
Sex							
Male	2	1.24	0.88	1.74	2.49	59.8	0.65
Female	2	1.32	0.99	1.75	1.4	28.7	0.84
Severity of bullying							
Sometimes	1	0.88	0.83	0.93	-	-	-
Frequent	1	0.80	0.70	0.93	-	-	-
Poor financial and occupational functioning							
Pooling all prospective cohort	16	1.14	0.87	1.50	92.97	83.86	< 0.01
Severity of bullying							
Sometimes	3	1.00	0.9	1.11	0.04	0	0.98
Frequent	3	0.81	0.61	1.07	2.68	25.32	0.26
Social isolation							
Loneliness							
Pooling all	13	1.89	1.39	2.57	3120.66	99.62	< 0.01
Study type							
Retrospective/cross-sectional	13	1.89	1.39	2.57	3120.66	99.62	< 0.01
Sex							
Male	4	2.58	1.62	4.10	222.21	98.65	< 0.01
Female	3	3.92	1.95	7.90	19.53	89.76	< 0.01
Severity of bullying							
Sometimes	2	2.09	1.98	2.20	0.39	0	0.53
Frequent	4	4.12	2.24	7.60	23.32	87.13	< 0.01
Self esteem							
Pooling all	14	0.99	0.92	1.07	93.73	86.13	< 0.01
Study type							
Retrospective/cross-sectional	4	1.13	0.83	1.54	76.58	96.08	< 0.01
Prospective cohort	10	0.97	0.93	1.01	12.32	26.93	0.2
Sex							
Male	5	0.96	0.88	1.06	20.65	80.63	< 0.01
Female	4	0.95	0.88	1.03	5.74	47.7	0.13
Severity of bullying							
Sometimes	5	0.99	0.95	1.04	1.61	0	0.81
Frequent	5	0.95	0.87	1.04	9.65	58.54	0.05
Social problems							
Pooling all	22	1.02	0.74	1.42	427.13	95.08	< 0.01
Study type							
Retrospective/cross-sectional	5	2.86	1.42	5.76	38.09	89.5	< 0.01
Prospective cohort	17	0.89	0.74	1.06	72.36	77.89	< 0.01
Sex							
Male	1	2.89	1.45	5.73	-	-	-
Female	1	8.10	4.60	14.26	-	-	-
Severity of bullying							
Sometimes	3	0.9	0.83	0.96	0.5	0	0.78
Frequent	3	0.81	0.72	0.92	3.67	45.49	0.16
Criminal behaviour							
Pooling all	33	1.04	0.78	1.39	133.36	76.01	< 0.01
Carrying a weapon	8	1.59	1.27	1.98	19.16	63.47	0.01

Violent offense/behaviour	6	1.25	1.01	1.56	2.46	0	0.78
Study type							
Retrospective/cross-sectional	9	1.01	0.47	2.14	106.83	92.51	< 0.01
Prospective cohort	24	1.05	0.92	1.19	25.72	10.58	0.31
Sex							
Male	11	1.00	0.82	1.22	13.78	27.43	0.18
Female	4	0.70	0.46	1.04	0.38	0	0.94
Severity of bullying							
Sometimes	5	0.97	0.75	1.26	7.37	45.74	0.12
Frequent	8	1.22	0.86	1.74	16.33	57.13	0.02
Other outcomes reported							
Good quality of later life	6	0.85	0.78	0.93	17.42	71.29	< 0.01
Poor life satisfaction	6	2.26	1.41	3.60	3.79	0	0.58
Problematic internet usage	1	2.36	1.58	3.54	-	-	-
Picked on by siblings	1	1.69	1.38	2.07	-	-	-

evidence.

Temporality

In this meta-analysis, both longitudinal (n = 57) and cross-sectional (n = 108) studies showed associations between bullying victimization and many adverse health and psychosocial problems. Prospective studies provided evidence of a temporal relationship showing bullying victimization preceded the later adverse consequences.

A temporal relationship exists between bullying victimization and outcomes such as anxiety, depression, non-suicidal self-injury, suicide ideation and suicide attempts. As poor mental health is also a known risk factor for bullying victimization[51], it is with caution we say that an independent temporal relationship exists between bullying victimization and these adverse mental health outcomes. Many studies did not control for pre-existing mental health and could be reporting a continuation of pre-existing psychopathology and not a direct outcome of the bullying victimization. Nonetheless, two recent studies have found that even when controlling for pre-existing mental health, bullying victimization was strongly associated with later adverse mental health consequences such as non-suicidal self-injury and depression[27,28].

Strength of the association

Both prospective and population-based studies demonstrated significant associations between bullying victimization and adverse health and psychosocial problems. After adjusting for confounding variables, there was generally a reduction in the strength of these associations. Furthermore, the magnitude of the associations diverged depending on the sub-group analysis performed. Despite some variability, bullying victimization was found to significantly increase the likelihood of mental ill health suggesting significant and robust associations.

Consistency of the association

Consistency of the associations between bullying victimization and mental ill health was demonstrated in the estimated effect sizes across studies. It is possible that publication bias affected the results for some of the outcomes. Direction of the association (as estimated through risk estimates) was consistent across different geographic regions, samples, study designs, and income levels investigated, particularly for anxiety, depression, non-suicidal self-injury, suicide ideation and suicide attempts (Supplementary material Figures S4, S5, S7, S8, S9). Inconsistent associations were observed for certain outcomes such as behavioural problems (Supplementaty material Figure S6).

Dose-response relationship

Available evidence suggests that experiencing more severe or frequent forms of adversity in childhood increases the risk of adverse outcomes compared to a lower exposure to adversity[45,52-56], particularly for mental health problems. Similarly, this study demonstrated a dose-response relationship between bullying victimization and detrimental effects on health, in particular for mental health problems. After summarizing the evidence through a meta-analysis, dose-response relationships were observed between bullying victimization and depression, suicide ideation, cigarette smoking and loneliness[45,52-56]. An increase in the dose of bullying victimization (frequent *vs* sometimes) resulted in non-significantly greater point estimates for other problems such as anxiety, medication use (general and psychotropic), suicide attempts and non-suicidal self-injury.

Plausibility

Due to a lack of animal models, the majority of inferences for biological plausibility arise from observational rather than experimental data. However, one model of social defeat in rats has been used to understand bullying victimization[57,58]. Two male rats are placed into a cage together, and after fighting, one rat becomes dominant and the other subordinate. The subordinate rat experiences social defeat and after a single experience demonstrates signs of stress. One study found that the subordinate rat demonstrated behaviours representative of depression in humans when exposed to multiple social defeats over several weeks[59].

Observational data has also been used to explain the association between bullying victimization in childhood

Table 5 Strength of evidence for a causal relationship between bullying victimization and adverse health or psychosocial problems

Strength of evidence	Adverse health or psychosocial problem
Convincing	Anxiety; depression; poor mental health; poor general health; non-suicidal self-injury; suicide attempts; suicide ideation
Probable	Tobacco use; illicit drug use
Possible	Alcohol use; psychotic symptoms; increased use of health services in females; lower academic achievement; social isolation; loneliness; psychosomatic symptoms, overweight and obesity
Insufficient	Binge eating; bulimia nervosa; borderline personality disorder; behavioural problems; carrying a weapon; general medication use; health services sought; poor financial and occupational functioning; psychotropic medication use; poor school functioning; sexual behavioural problems; poor life satisfaction

and adolescence and the later development of mental health problems. First, early adverse experiences (*i.e.*, bullying victimization) that occur during vulnerable developmental periods can cause neurobiological[60,61] or inflammatory[62] changes expressed as illnesses in later life[61]. Moreover, those individuals exposed to frequent bullying victimization who develop mental health problems may self-medicate their distress and negative emotions with alcohol, illicit drugs, medications, tobacco or disengaging from school.

Taking into account both the limited animal studies[57-59] and observational studies[60-62], it can be understood as to why bullying victimization can affect the immediate and long-term health and non-health related outcomes of the individual.

Consideration of alternate explanations

The relationship between bullying victimization and adverse health and psychosocial problems are thought to be complex and influenced by both genetics and environmental factors; however, there are limited twin studies available to inform these associations[27,63-66]. One study[64] found that being bullied in childhood is an environmentally mediated contributing factor to poor childhood mental health. Another found victimized twins were more likely to self-harm than their non-victimized twin sibling[27]. Exposure to bullying victimization has also been found to be associated with socioeconomic status[51,67] which is also known to play a role in the development of mental health problems and other health and non-health related outcomes[68].

It is further acknowledged that the association between bullying victimization and adverse outcomes is not necessarily an independent relationship. As early emotional and behavioural problems are known risk factors for bullying victimization, without adequate statistical adjustment, some studies may risk reporting pre-existing psychopathology rather than a direct outcome of bullying. The available evidence suggests a complex relationship between genetics and environment and neither can solely explain the relationship between bullying victimization and adverse outcomes. Even though some of the effects of bullying victimization on adverse outcomes reported may be a result of confounding factors, generally the association with mental health problems was significant after controlling for potential confounding factors.

Assessment of causality

Using the grading system developed by the World Cancer Research Fund (WCRF)[50] as a guideline for evaluation of the level of evidence, we concluded that there was "convincing evidence" for a causal relationship between bullying victimization and anxiety, depression, poor general and mental health, non-suicidal self-injury, suicide attempts, and suicide ideation. This evidence was based on a substantial number of epidemiological studies identified in this systematic review including prospective observational studies of sufficient size, duration, and quality showing consistent effects. In addition, the association was considered biologically plausible. We concluded that "probable evidence" of a causal relationship existed between exposure to bullying victimization and illicit drug and tobacco use based on the epidemiological evidence. Possible causal associations existed between bullying victimization and lower academic achievement, alcohol use, loneliness, obesity, overweight and psychosomatic symptoms. This evidence was based mainly on findings from cross-sectional studies and a few prospective studies showing inconsistent associations between exposure and disease. More studies are needed to support these tentative associations, which are also considered to be biologically plausible.

All other significant associations reported in this study were classified as having insufficient evidence of a causal relationship (Table 5). This is not suggesting that there is no causal relationship. Further research is needed to better examine if any associations that exist are causal or due to other confounding factors. Furthermore, the use of WCRF grading system, although appropriate for dietary risk factors, might not be adequate for psychosocial factors particularly newly emerging risks.

Limitations

While we followed rigorous methodological steps, some limitations are notable. As studies with non-significant findings are less likely to be published, there may be a publication bias within this meta-analysis resulting in the association between bullying victimization and some adverse outcomes being overstated[69,70]. Additionally, inconsistencies would have occurred in the analysis due to methodological differences in the way bullying victimization is defined and measured throughout the studies as there is no consensus on the best way to

measure bullying victimization[18,19]. In order to address this, a quality effects model was used giving higher scores to those studies which provided respondents with a definition and utilised a validated measure of bullying. There are also methodological issues in regards to the adverse outcomes reported, as some have been self-reported, while others were reported by teachers, parents, clinicians or through objective measures. This issue was also addressed with the use of a quality effects model in which higher quality scores were given to those studies where standardised validated diagnostic instruments were used to assess the outcome relative to those where outcomes were self-reported on a non-validated scale[44]. In spite of this methodology, the assessment of exposure to bullying and the assessment of a wide range of outcomes remains a challenge. In particular, there will always be some uncertainty pertaining to the measurement of bullying, especially when retrospectively reported as a result of the respondent's subjective perception of the actions and behaviours of others.

As a research question involving bullying victimization can only be observational and not experimental, a further limitation of this meta-analysis are those limitations that come with observational studies[71]. First, we acknowledge the issue of confounding. It is appropriate to adjust for these confounders in the statistical analyses by either stratification or multivariate analysis[71]. Although many studies controlled for socio-demographic and other variables[2,27], some reported unadjusted odds ratios between bullying victimization and adverse outcomes, or provided only basic adjustment for sex and age[72,73]. This was addressed in this meta-analysis through the use of the quality score of studies where confounding factors were not adequately adjusted and by conducting further analyses where data were available[44]. Generally, after controlling for the effects of confounding variables, the associations between bullying victimization and adverse outcomes were attenuated. The majority of studies included in this meta-analysis did not identify individuals who were both victims and perpetrators of bullying. Previous research has suggested those who are both perpetrators and victims are at even greater risk of adverse mental health outcomes[28]; however, we were unable to confirm this with the current study.

In the majority of primary analyses of the association between bullying victimization and adverse outcomes, significant heterogeneity was present. This heterogeneity remained significant in most subgroup analyses even after controlling for study quality in the quality effects models[44].

In conclusion, evidence suggests a causal relationship between bullying victimization and mental health outcomes. There were also associations between bullying victimization and other adverse health and psychosocial problems which require further research to accurately measure the negative impact of bullying victimization and the broad health and economic costs. Through the implementation of school wide interventions that involve the entire school community (*i.e.*, staff, students, and parents) bullying behaviour is considered a modifiable risk factor[25,74]. This review highlights the increased likelihood of a wide and diverse range of problems that are experienced by those exposed to bullying victimization. These findings reinforce the need for implementation of effective interventions in schools to address the high prevalence of children and adolescents engaging in bullying behaviours.

COMMENTS

Background

Bullying victimization (including traditional and cyberbullying) among children and adolescents is a global public health issue, well-recognised as a behaviour associated with poor adjustment in youth. There is evidence suggesting bullying victimization in children and adolescents has enduring effects which may persist into adulthood.

Research frontiers

There have been many studies examining the association between bullying victimization in children and adolescents and adverse health and social problems. However, many of these have not been systematically examined and existing systematic reviews did not include cyberbullying. Furthermore, although associations exist, it is unclear if there is a causal relationship.

Innovations and breakthroughs

The authors found convincing evidence of a causal relationship between bullying victimization in children and adolescents and adverse health outcomes including anxiety, depression, poor mental health, poor general health, non-suicidal self-injury, suicidal ideation and suicide attempts. It is probable that bullying victimization also causes an increased risk of cigarette smoking and illicit drug use.

Applications

Given the convincing evidence of a causal association, there is an urgent need for effective interventions to be implemented in schools to address the high prevalence of children and adolescents engaging in bullying behaviours.

Peer-review

This is an important topic on consequences of bullying victimization in childhood and adolescence. This area for sure needs more attention. The authors have done a great job presenting a large systematic review and meta-analysis of studies correlating the history of bullying victimization with different mental health problems in childhood and adolescence.

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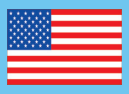

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REVIEW

Understanding the pathophysiology of postpartum psychosis: Challenges and new approaches

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Abstract

Postpartum psychosis is a severe psychiatric condition which affects 1-2 of every 1000 mothers shortly after childbirth. Whilst there is convincing evidence that the condition is precipitated by a complex combination of biological and environmental factors, as yet the pathophysiological mechanisms remain extremely poorly defined. Here, I critically review approaches that have been, or are being, employed to identify and characterise such mechanisms; I also review a recent animal model approach, and describe a novel biological risk model that it suggests. Clarification of biological risk mechanisms underlying disorder risk should permit the identification of relevant predictive biomarkers which will ensure that "at risk" subjects receive prompt clinical intervention if required.

Key words: *CCN3*; Immune system; Steroid sulfatase; Nephroblastoma-overexpressed; Mouse; Animal model; Risk factor

Core tip: Postpartum psychosis is a severe psychiatric condition affecting a small proportion of women shortly after childbirth. The pathophysiological mechanisms underlying risk for the condition are extremely poorly-defined, but may include perturbed immune function, altered tryptophan metabolism and serotonergic dysfunction. Here, I critically review evidence underlying these assumptions, and discuss a novel model for postpartum psychosis risk, involving maternal deficiency for the enzyme steroid sulfatase, and overexpression of the *CCN* gene family, based upon emerging data from a recently-developed mouse animal model. Identifying

and characterising predictive biomarkers for postpartum psychosis risk will help to ensure prompt clinical intervention if required.

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INTRODUCTION

What is postpartum psychosis?

Postpartum, or puerperal, psychosis (PP) is a severe psychiatric disorder which typically manifests within days of childbirth in a small proportion of women (1-2 in every 1000 new mothers)[1,2]. The main symptoms of PP include hallucinations and delusions, cognitive disorganisation and confusion, anxiety and sleep problems[1,2]; rarely, affected mothers may attempt to injure themselves or their child, with maternal suicide and infanticide observed in some cases. Pharmacological treatments are relatively efficacious if administered promptly and in combination with psychotherapy and psychoeducation[1,2]: These include a range of typical and atypical antipsychotic drugs and mood stabilisers (given that mood fluctuations, or bipolarity, may precede and/or be exacerbated by PP); prophylactic pharmacotherapy may also be used judiciously in women at high risk of PP[1,2].

Risk and protective factors

The single largest risk factor for PP is a personal, or family, history of bipolar disorder or related psychotic disorder (seen in about 40%-50% of PP cases[1,2]). Other risk factors that have been suggested as modulators of PP risk include: Primiparity, maternal age, stress levels in the puerperium, and maternal sleep problems[1-4]; in contrast to postpartum depression, adverse early-life events do not appear to significantly enhance risk of developing PP in women with bipolar disorder[5]. The condition is associated with obstetric complications, notably pre-eclampsia[6], a potentially-damaging increase in maternal blood pressure. In common with other psychotic spectrum conditions such as schizophrenia, psychosis-related phenotypes in the perinatal period seem to be higher in immigrant populations, possibly as a function of being exposed to new infections, or to high levels of stress[7]. A recent intriguing study has tentatively suggested that women who smoke exhibit reduced risk of developing PP[8], although the questions as to whether this association is genuine, whether cigarettes somehow confer biological protection, or whether the smoking and non-smoking groups differ on some other critical demographic, biological or psychological measure unrelated to smoking remain to be directly addressed.

A biological basis to risk?

The temporal proximity of PP onset to childbirth, its high relapse rate, and its relatively stable prevalence and nature across societies and cultures, indicates that risk for the condition may be substantially influenced by biological factors[1,2]. The maternal body undergoes extreme physiological changes in the postpartum period, notably a massive drop in circulating oestrogens upon expulsion of the placenta. It has been suggested that abnormal sensitivity to this endocrinological disturbance may confer vulnerability to PP in some women[1,2], an idea supported by the fact that oestrogen supplementation may be beneficial to some patients[9,10]. The fact that PP is often responsive to antipsychotic treatment indicates that abnormal serotonergic and/or dopaminergic function may play a role in its pathogenesis; there is a well-established link between oestrogen levels and serotonergic function[11]. An increasing body of literature has implicated immune system dysfunction in psychotic disorders in general[12] and in PP specifically[13], whilst thyroid system abnormalities[14] and other autoimmune conditions[15] have been reported in some cases of PP.

Although the epidemiology, risk/protective factors, and comorbid phenotypes associated with PP have been systematically investigated and several have been consistently replicated (albeit by a small number of research groups), the molecular, cellular and neural pathophysiology of the condition is currently very poorly understood. Below, I list some contemporary approaches aimed at addressing this issue and their successes and limitations. Understanding the biological factors that confer PP risk will be important for identifying and characterising novel drug targets for more efficacious, less toxic, pharmacotherapy; however, given the reasonable efficacy of currently available medications this is perhaps not the main goal. A more pressing aim once biological risk pathways have been identified will be to describe predictive biomarkers which may be used to classify individuals at risk of the condition early in their pregnancy, and to ensure that they are closely monitored and have prompt access to appropriate clinical expertise and facilities if required.

CURRENT APPROACHES TO UNDERSTANDING POSTPARTUM PSYCHOSIS AND THEIR LIMITATIONS

There are a number of diverse approaches that have been employed in trying to understand the pathophysiology of PP. These investigational methods, and their relative advantages and limitations are summarised in Table 1.

Clinical biochemistry

One conceptually-simple approach to understanding the biology of PP is to compare the biochemistry of patients diagnosed with PP with that of appropriate controls

Table 1 The advantages and limitations of methods for investigating biological risk factors in individuals with postpartum psychosis

Investigational method	Advantages of method	Limitations of method
Clinical biochemistry or gene expression analyses	Direct assessment in patient or "at risk" groups Possibility of identifying peripheral biomarkers for PP risk	Difficult to access central nervous system; peripheral changes may not reflect central functional abnormalities Potential issues with obtaining consent for samples Substantial fluctuation of markers with participant demographics, experiences and treatments Possible issues related to reverse causation, *i.e.,* are abnormalities a cause or consequence of the disorder?
Neuroimaging	Direct assessment of brain structure, function or chemistry in patient or "at risk" groups	Cannot easily be performed during psychotic episodes Substantial exclusion criteria for procedure Limited resolution; cannot provide information on most neurochemical, cellular or molecular abnormalities Substantial fluctuation of measures with participant demographics, experiences and treatments Possible issues related to reverse causation, *i.e.,* are abnormalities a cause or consequence of the disorder?
Genetics	DNA can be readily obtained from patient or "at risk" groups from peripheral tissues DNA sequence is stable and unaffected by variability in patient's circumstances Possibility of identifying biomarkers that can predict risk at an early stage Few issues with reverse causation	Low power of genome-wide studies as a consequence of low prevalence of the condition; possibility of false positives and negatives
Porcine infanticide model	Some degree of face validity Direct access to brain tissue for detailed examination and DNA for genetic studies	Questionable relevance of animal behavioural phenotypes to PP symptoms Difficult and expensive to breed and maintain Not readily amenable to pharmacological studies; predictive validity unclear Difficult to systematically assess all brain regions
STS-inhibition mouse model	Some degree of face and predictive validity Direct access to brain tissue for detailed examination Relatively cheap to breed and maintain Amenable to pharmacological and genomic studies	Questionable relevance of animal behavioural phenotypes to PP symptoms Face and predictive validity require further confirmation STS deficiency unconfirmed in PP cases, hence construct validity unsubstantiated

PP: Postpartum psychosis; STS: Steroid sulfatase.

(either postpartum mothers without psychosis, or non-postpartum females). Studies to date have focussed on levels of tryptophan and its metabolites (*i.e.,* precursors of serotonin)[16], and the immune[13] and thyroid[14] systems, the latter two systems being in considerable flux during pregnancy and in the perinatal period. The main findings of these studies may be summarised, respectively, as: (1) deficient tryptophan breakdown, and lower kynurenine production, is evident in women with postpartum mood disorders; (2) abnormally low T cell numbers, and over-activation of the monocyte/macrophage arm of the immune system is evident in the postpartum period in women diagnosed with PP; and (3) patients with PP have a higher prevalence of autoimmune thyroid disease than controls.

Whilst this type of study undoubtedly provides clinically-relevant knowledge about the abnormal biology associated with PP, it is limited in several key ways. First, it is difficult to obtain biological samples from psychotic patients, particularly where these patients lack capacity to consent to experimental procedures, and where they may be socially and geographically isolated from individuals who can give consent on their behalf. Second, the biological samples that can be obtained are peripheral (typically blood or serum); accessibility to more relevant tissue from patients [brain, or even cerebro-spinal fluid (CSF)] is very limited or impossible. Whilst this may not be a major concern with regard to developing predictive peripheral biomarkers, the relationship between any peripheral tissue changes and abnormal brain function underlying behavioural phenotypes is difficult to characterise. Finally, biochemical measures can fluctuate substantially as a function of demographic variables, physiological and general health status, psychosocial factors and drug regime; hence, identifying physiological measures which definitively and reliably differentiate individuals with PP from healthy individuals, and establishing exactly how these measures correlate with phenotype, is extremely challenging. Moreover, there is the potential issue of reverse causation whereby it is difficult to establish unambiguously whether specific biochemical differences between individuals with PP and healthy controls are a cause or a consequence of the condition and its treatment.

Neuroimaging

The biochemical studies above are limited by their ability to directly assay brain function. The development of elegant neuroimaging techniques, including functional magnetic resonance imaging (fMRI) and Diffusion Tensor Imaging over the past couple of decades, has opened up the possibility of identifying neural substrates associated

with PP vulnerability. Neuroimaging studies in this area are scarce, presumably due to issues with participant recruitment and testing. To date, no brain circuitry has consistently be shown to develop or function abnormally in cases of PP. A recent case-control study has suggested that individuals developing PP have a reduced anterior cingulate cortex (ACC) volume[17]. As the ACC plays an important role in cognitive and emotional processing, including in impulse control, decision-making and cognitive organisation, it represents an interesting neural candidate for further study. Rare cases with PP who have been imaged have reported altered ventricular morphology[18], abnormal orbitofrontal cortex reactivity[19] and structural abnormalities of the corpus callosum[20].

Imaging studies, like biochemical studies, are limited in several ways. First, for practical reasons, it is not possible to examine brain function during psychotic episodes, and this has to be assessed in "recovered", or "at risk" participants - hence, the relevance of findings from, *e.g.,* fMRI studies to psychotic experiences is questionable. Moreover, imaging measures, particularly "snapshot" studies, may be confounded by a patient's demography, life history and comorbid diagnoses, and current and previous medication regimes. Finally, whilst neuroimaging can identify brain regions and circuits that may be of potential interest, and sophisticated techniques like magnetic resonance spectroscopy might identify reasonably highly spatially-resolved changes in limited brain neurochemistry, such approaches cannot identify most changes in neurochemistry, nor altered cellular or molecular function.

Genetics

Psychiatric genomics has recently come of age, with genetic risk variants associated with psychosis risk now being reliably identified *via* genome screens in patients with psychotic and mood disorders such as schizophrenia and bipolar disorder[21]. Genetic studies offer two key advantages over the above approaches: First, genomic material (DNA) can be reliably obtained from accessible tissues (typically saliva or blood), and DNA sequence is essentially conserved between these peripheral tissues and the brain. Second, genetic sequence is stable throughout life, and unlike biochemical or brain function measures, is not affected by environmental, psychosocial or pharmacological influences.

The robust identification of common risk variants that increase risk of complex psychiatric disorders by a small amount, or of rare variants that confer greater risk, necessitates the use of large sample sizes (conceivably up to 100000 cases to detect a high proportion of risk variants). For relatively common psychiatric disorders such as schizophrenia and bipolar disorder obtaining this number of cases is feasible through collaborative enterprises such as the Psychiatric Genomics Consortium[22]. For rare disorders such as PP it is unlikely that such large numbers of participants can be recruited, even with extensive inter-institutional working. Based upon our existing knowledge, it seems likely that, in common with related mood and psychotic disorders, genetic risk for PP will be complex and polygenic; hence, genomic analyses in PP, even with several thousand cases, will be limited by relatively low power.

Genetic studies that have been performed in PP to date have employed small sample sizes (< 1000 cases), and hence their conclusions should be regarded with caution: Low power implies a high rate of both false positive and false negative findings. A seminal genetic (linkage) study in bipolar affective postpartum psychosis suggested evidence for significant and suggestive risk loci at 16p13 and 8q24 respectively[23]; the regions implicated contained multiple genes, many of which could theoretically have mediated PP risk. Efforts are currently underway to undertake a sufficiently-powered genome-wide association study (GWAS) in bipolar affective postpartum psychosis, but as yet these have not yielded significant findings. Candidate gene-led studies in PP have focussed upon serotonergic system genes given the therapeutic efficacy of antipsychotics; one study provided suggestive evidence for association within the serotonin transporter and serotonin 2A receptor genes[24]. However, candidate gene association studies, which focus upon genes of likely biological relevance to a condition, often have low replication rates and are inevitably biased by our very limited current knowledge base[25]. Other candidate gene association studies in PP have examined a number of genes important in serotonergic and oestrogenic signalling, and the immune response, but, as yet, these have yielded mixed findings with little consistent evidence for robust risk variants[1]. Genomic techniques such as exome, or even whole-genome, sequencing are feasible in the relatively small number of PP samples available, but here again, low power will make drawing any conclusions about the pathogenicity of any potentially-causal genetic variants difficult.

Besides looking at the DNA sequence *per se*, insights into PP pathogenesis may be obtained by comparing the epigenome or gene expression profiles in individuals with PP and controls. One such study focussed upon microRNAs known to regulate the immune response and demonstrated altered expression of miR-146a and miR-212 in patients with PP relative to healthy controls[26]. However, whether these changes were a cause or consequence of the disorder (and associated medications) is unclear. Moreover, like with candidate gene association studies, expression studies focussing on just a handful of pre-selected genes provide limited information on the specificity of the changes or on general risk pathways; for example, it could feasibly be the case that the expression of a large proportion of microRNAs is perturbed in PP.

The porcine infanticide model of PP

A further approach towards understanding the biological basis of PP risk is through the use of animal models. Animal models permit a degree of experimental control that cannot be achieved in clinical, or other human,

studies and allow procedures that would be ethically prohibited in humans to be conducted; however, there is some resistance to the use of animals, and particularly non-primate species, for modelling complex psychiatric phenotypes characterised by deficits in "uniquely-human" aspects of behaviour and cognition. The first published animal model for PP is the infanticidal sow pig, which exhibits several epidemiological, behavioural and endocrinological traits associated with the condition[27]. An early quantitative trait locus (QTL) study in this model identified four possible genomic loci of interest on chromosomes 2, 10 and X, corresponding to human chromosomal loci 5q14.3-15, 1q32, Xpter-Xp2.1, and Xq2.4-Xqter respectively[27]; an independent linkage study confirmed an association between X-linked loci and maternal aggression, and suggested regions of interest on chromosomes 2, 6, 14 and 15[28]. Examination of hypothalamic gene expression in the maternal infanticide model identified multiple genes, the expression of which was altered in pigs showing aberrant behaviour; several of these mapped to the previously-implicated QTL regions [of particular note were the *HTR2C* (serotonin receptor 2C), *DRD2* (dopamine receptor 2) and *PRL* (prolactin) genes, the first two encoding antipsychotic drug targets[29]]. A genome-wide association study in this model indicated candidate regions on porcine chromosomes 3, 4 and 15, syntenic with human chromosomal regions implicated in bipolar disorder and postpartum psychosis (including 16p13)[30], whilst a candidate gene association study suggested preliminary evidence for association with oestrogen receptor (*ESR1*), excitatory amino acid transporter 2 (*EAAT2*) and dopamine receptor 1 (*DRD1*) genes, but not *HTR2C*[31].

The fact that the pig model described above shows some superficial phenotypic similarities to patients with PP ("face validity"), and that it indicates genomic regions, and specific gene candidates, of possible functional relevance, suggests that it may represent a reasonable model for PP. However, it should be acknowledged that the model is compromised in a number of ways which may limit its utility. First, there is a relatively poor correlation between the clinical and animal behavioural profiles, in that the vast majority of women with PP are not aggressive, and even those who are aggressive will not attempt infanticide. Second, this large animal model is difficult and expensive to breed, maintain, and analyse experimentally. Of particular note, it is difficult to test whether the infanticide phenotype is sensitive to antipsychotic administration - hence it is difficult to determine the extent to which this phenotype is analogous to PP, and to assess whether or not the model has any degree of predictive validity. Another main issue is that, because the brain of the pig is relatively large, it is difficult to investigate all regions where abnormal activity may be observed; whilst previous work has understandably focused on the hypothalamus given its known role in maternal behaviour, there is, as yet, little convincing evidence for impaired hypothalamic function in PP cases.

PATHWAYS TO PROGRESS

Despite decades spent studying the illness, and the availability of cutting-edge experimental techniques and research hardware, we are still far from understanding the biological and psychological risk factors underpinning PP and hence how to identify women at greatest risk for the condition. Below, I briefly outline what I believe is required in order to make progress in this area over the next decade.

Perhaps the main factor hindering progress in PP research is sample size. It is now well recognised in psychiatry that groups from around the world must collaborate in order to generate an adequately-powered, consistently and deeply-phenotyped cohort of patients (and their affected and non-affected relatives) in which genetic, biochemical and neuroimaging analyses can be undertaken; such a large sample will permit factors such as drug treatment, demography and symptomatology to be covaried for, and hence for robust genotype-biology-phenotype correlations to be ascertained. There are ongoing collaborative efforts in the field of PP research involving centres of excellence across Europe and the United States, and these should soon begin to bear fruit. One research area that has been relatively neglected to date is deciphering the fundamental psychological processes that distinguish mothers who develop PP from: (1) those who have bipolar disorder and do not develop the condition; or (2) from healthy mothers. Specifying how "at risk" women differ from "protected" women on measures of behaviour and cognition, may feasibly permit the development of a simple screening test to be applied prior to childbirth, and may provide clues as to underlying neurobiology.

Even with larger numbers of cases available for genome-wide genetic analyses, there is a strong possibility that only a handful of polymorphisms or mutations associated with PP risk will be identified, and that many will not reach genome-wide levels of significance after the requisite stringent multiple testing corrections. Hence, there may still be a role for sensible candidate gene association studies comparing variant frequency in cases and controls, where higher levels of alpha (as a consequence of reduced multiple testing) are more likely to give rise to statistically significant findings. However, as discussed above, traditional candidate gene studies based upon theoretical causal or therapeutic mechanisms have frequently been shown to be irreproducible, or to give rise to findings of a much smaller magnitude than initially suspected[25,32]. Moreover, genome-wide association studies have repeatedly demonstrated that genetic variants robustly associated with disorder risk are often poorly-annotated and have unknown effects on biology, and hence would not have been prioritised in candidate-led approaches[32]. Bearing in mind these caveats, proposals for candidate *PP* genes should be supported by multiple converging lines of evidence, and should ideally exhibit both positional and functional relevance. In the following section, I describe a candidate gene backed by

such evidence.

There is also clearly a need for more experimentally-tractable animal and cellular models, in which molecular, cellular and circuit mechanisms that may influence PP risk can be characterised. In terms of animal models, ideally these should be available to be tested in large, well-defined batches, be neurobiologically-amenable, and exhibit some degree of face, construct and predictive validity (the latter in contrast to the porcine infanticide model). In terms of cellular models, the advent of induced pluripotent stem cell technology technology now means that "pathological" samples such as brain cell cultures can ultimately be generated from patient fibroblast, or other peripheral, cells[33]. Any data generated from *in vitro* studies in which derived-brain cells are examined in isolation, should be extrapolated cautiously given that PP risk, in common with the risk of related psychiatric conditions such as schizophrenia and depression, is likely to be modulated by complex ongoing interactions between a multitude of intra-brain and extra-brain (*e.g.,* hormonal, placental or immune system) factors[34].

A NEW CANDIDATE GENE

I have previously proposed, based upon numerous lines of clinical and basic scientific evidence, that maternal deficiency for the enzyme steroid sulfatase, encoded by the X-linked *STS* gene, may represent one candidate risk mechanism for PP[35]. The STS enzyme cleaves sulfate groups from a variety of steroid hormones, notably dehydroepiandrosterone sulfate (DHEAS), thus allowing them to be used as precursors for a variety of androgens and oestrogens; hence it is a key modulator of the steroid hormone axis. There are a number of criteria that candidate genes and pathways for PP may be expected to meet based upon our existing knowledge; the *STS* gene and the processes which it modulates meet many of these.

One might expect the candidate system to be in flux in the postpartum period, and to influence immune function at this time; in mice, and perhaps also in man, brain levels of STS are elevated specifically shortly after giving birth[36]. In healthy women, reduced levels of serum DHEA in the postpartum period are associated with activation of the immune system[37]; conceivably, in STS-deficient women, abnormally low levels of postpartum DHEA (as a consequence of impaired DHEAS desulfation) may result in hyperactivation of the immune system.

The steroid hormone axis has repeatedly been implicated in the pathogenesis of PP given the sudden drop in circulating oestrogen levels in the mother following birth, and the suspected protective effects of oestrogens against psychosis[38]; indeed, early candidate gene association studies focussed upon those regions of the genome thought to be regulated by oestrogens[39]. STS is a key player within this axis. STS is highly expressed in key reproductive tissues (testis, mammary gland, placenta, uterus, brain[40]) and hence its dysfunction may, a priori, be expected to impact upon normal reproductive physiology. Recently, placental mis-expression of the *STS* gene has been implicated in pre-eclampsia risk[41]. It is plausible that in STS-deficient mothers, where baseline oestrogen levels may already be low[42], expulsion of the oestrogenic placenta precipitates psychosis vulnerability. There is also some evidence that women who are carriers for *STS* mutations, and who are STS-deficient, are at increased risk of psychological abnormalities (unpublished results) and of delayed, or prolonged labour, and related obstetric complications[43]; such complications, and the accompanying psychological stress, may be one precipitant of postpartum psychiatric distress, although a specific link to PP remains unconfirmed[1,44].

In the developing and adult brain, *STS* is expressed in regions implicated in postpartum psychosis. Specifically, it is highly expressed in the thalamus (involved in the integration and usage of sensory information) and throughout the cortex (including the cingulate cortex)[45,46]; it is also highly expressed in the hypothalamus, and outside the brain in the thyroid gland[45,46]. Hence, its absence may feasibly give rise to abnormal hypothalamic-pituitary-adrenal or hypothalamic-pituitary-thyroid function, consistent with notions of an abnormal stress response, or thyroid pathology, in cases of PP.

Parallel clinical and animal model studies have demonstrated that STS deficiency (or genetic variation within *STS*) gives rise to behavioural phenotypes of relevance to PP including psychosis, cognitive disorganisation, anxiety, depression and, rarely, aggression (unpublished results and ref.[46-49]). Moreover, there is a positive correlation between serum levels of DHEAS and psychoticism (anxiety, paranoia, psychosis) in healthy women and women exhibiting postpartum psychiatric distress[50,51]. Data from genetic and pharmacological rodent models suggest that deficiency for STS may impact upon neurochemistry of relevance to psychosis vulnerability including altered levels of hippocampal serotonin (and Htr2c receptors) and acetylcholine[52,53].

Finally, *STS* was explicitly suggested as a candidate gene underlying significant X-linked QTLs in the porcine maternal infanticide model of PP[27].

INSIGHTS FROM A NEW MOUSE MODEL

The only existing animal model for PP, the porcine maternal infanticide model, is sub-optimal. We have recently attempted to develop a more experimentally-tractable mouse model for the condition, based upon the idea that maternal steroid sulfatase deficiency is a putative risk factor[54].

Briefly, we showed that pharmacological inhibition of the steroid sulfatase enzyme in new mouse mothers resulted in behavioural, endocrinological and genetic phenotypes partially mirroring those seen in PP ("face validity"). Whilst STS inhibition did not affect gross health, maternal behaviours or activity, it did have subtle effects on

exploration of the elevated plus maze (increased rearing and reduced latency to enter the exposed open arms) and the startle response (reduced with enzyme inhibition); a reduced startle response is a feature of patients with bipolar disorder[55]. These observations support the notion of STS as a modulator of postpartum maternal behaviour. STS inhibition did not seem to influence levels of the main stress hormone corticosterone in mice, consistent with data indicating that women with PP show normal cortisol levels[56].

Previous work had suggested that a small genomic region on mouse chromosome 15 harboured a QTL influencing rearing and open arm latency measures in the elevated plus maze[57]; excitingly, this region of chromosome 15 was syntenic with human chromosome 8q24, a region implicated in PP pathogenesis by linkage[23]. Expression screening of the small number of genes within the mouse chromosome 15 interval revealed just one, *Nov*/*Ccn3*, whose expression was significantly altered (upregulated) in STS-inhibited brain; the expression of two other genes from the Ccn family (*Ctgf/Ccn2* and *Wisp1/Ccn4*), as well as genes whose products may be co-regulated with *Nov/CCN3* (*Arhgdig*, *Adcy8* and *Ccl2*) was also increased in STS-inhibited brain tissue[54].

An advantage of the mouse model is that it is possible to test whether putative PP-relevant behavioural and molecular features are sensitive to antipsychotic administration, *i.e.,* to test whether it has potential predictive validity. We showed that administration of clinically-relevant doses of the atypical antipsychotic ziprasidone reverses the deficient startle response, and tempers the over-expression of *Nov/Ccn3* in the STS-inhibited mouse, indicating that these facets of the model may be relevant to psychotic pathophysiology[54].

Although the STS-inhibited mouse shows some degree of promise as a model for PP, its face validity needs to be defined more thoroughly. For example, does it show the abnormalities in the tryptophan-kynurenine pathways and immune system that have been reported in PP cases? One limitation of the current pharmacological model is that steroid sulfatase is solely inhibited in the postpartum period - if STS deficiency is truly a risk factor for PP, it would likely be genetic in origin, and operate throughout life (including pregnancy and the postpartum period). Hence, it would be useful to examine the behaviour and physiology of new mouse mothers that lack one (or both) functional *STS* alleles, and hence have reduced constitutive STS expression; such knockout mice have historically proved difficult to generate due to the complex genomic architecture around the *STS* locus, but this difficulty may potentially be overcome with new genetic engineering technologies such as CRISPR.

A NEW PATHWAY TO PATHOLOGY AND TREATMENT?

The new mouse model described above indicates, on the basis of analyses agnostic to gene function, that dysregulation of the *CCN* gene family arising downstream of dysfunction of the STS axis may be implicated in PP risk. Is this a reasonable concept? If so, can this evaluation suggest molecular, cellular and neural pathways that could be perturbed in PP and that could feasibly be targeted *via* re-purposing of existing drugs, or through developing new drugs?

The *CCN* gene family encodes a number of secreted extracellular matrix-associated proteins that are highly-expressed in the brain[58]; impaired function of the extracellular matrix, and the subsequent abnormal cell-cell interactions, have recently received attention as a possible pathophysiological mechanism in a number of mood disorders[59]. This gene family is also known to be important in female reproductive function[60], exhibits dynamic brain expression throughout pregnancy and the puerperium[61], and modulates Notch and Wnt signalling pathways[57] that are disrupted in bipolar disorder[62] and cases of postpartum psychiatric disturbance[63]. Interestingly, the expression of CCN family members may also be altered by the administration of substances that induce psychosis-like states[64,65], by social stress[66] and by small molecules including cytokines and serotonin[67] suggesting these members as possible mediators of analogues of psychosis.

CCN3 is of particular interest as a candidate modulator of PP risk given the location of the associated gene directly under the 8q24 linkage peak. There is also emerging evidence from a study in human female (cervical cancer) cells that STS and DHEA can directly influence the expression of the integrin β1 molecule[68], a known interactor with CCN3 in the brain and a putative mediator of CCN3-induced effects on cytokine secretion[69].

The CCN3 protein exhibits a variety of additional features that strengthen its candidacy. First, it regulates intracellular calcium signalling[70] a process that goes awry in both bipolar disorder[71] and PP[72]. Second, it is highly expressed in the brain's cortex and limbic system[58], and its expression is dampened by circulating oestrogens[73]. It is apparently a regulator of axonal outgrowth of callosal projection neurons[74], a finding of interest in light of possible corpus callosum abnormalities in cases of PP[20]. The fact that CCN3 modulates placental angiogenesis[60], that the associated gene is located 70kb from a GWAS hit for hypertension[75] and that it, and its family members, are regulated by thyroid hormone derivatives in the cortex of the brain[76], is consistent with the epidemiological studies showing overlap between PP, pre-eclampsia and thyroid abnormalities. Given the preliminary findings regarding a potential attenuation effect of smoking on PP risk, it is interesting to note that the *CCN3* gene lies close to a single nucleotide polymorphism nominally associated with smoking cessation[77], and that in female mouse tissues *Ccn3* expression is reduced upon exposure to cigarette smoke[78]. The protein DDR1 is a putative receptor mediating CCN3 signalling[79]; there is some evidence suggesting association of genetic variants within DDR1 with psychotic illness[80,81].

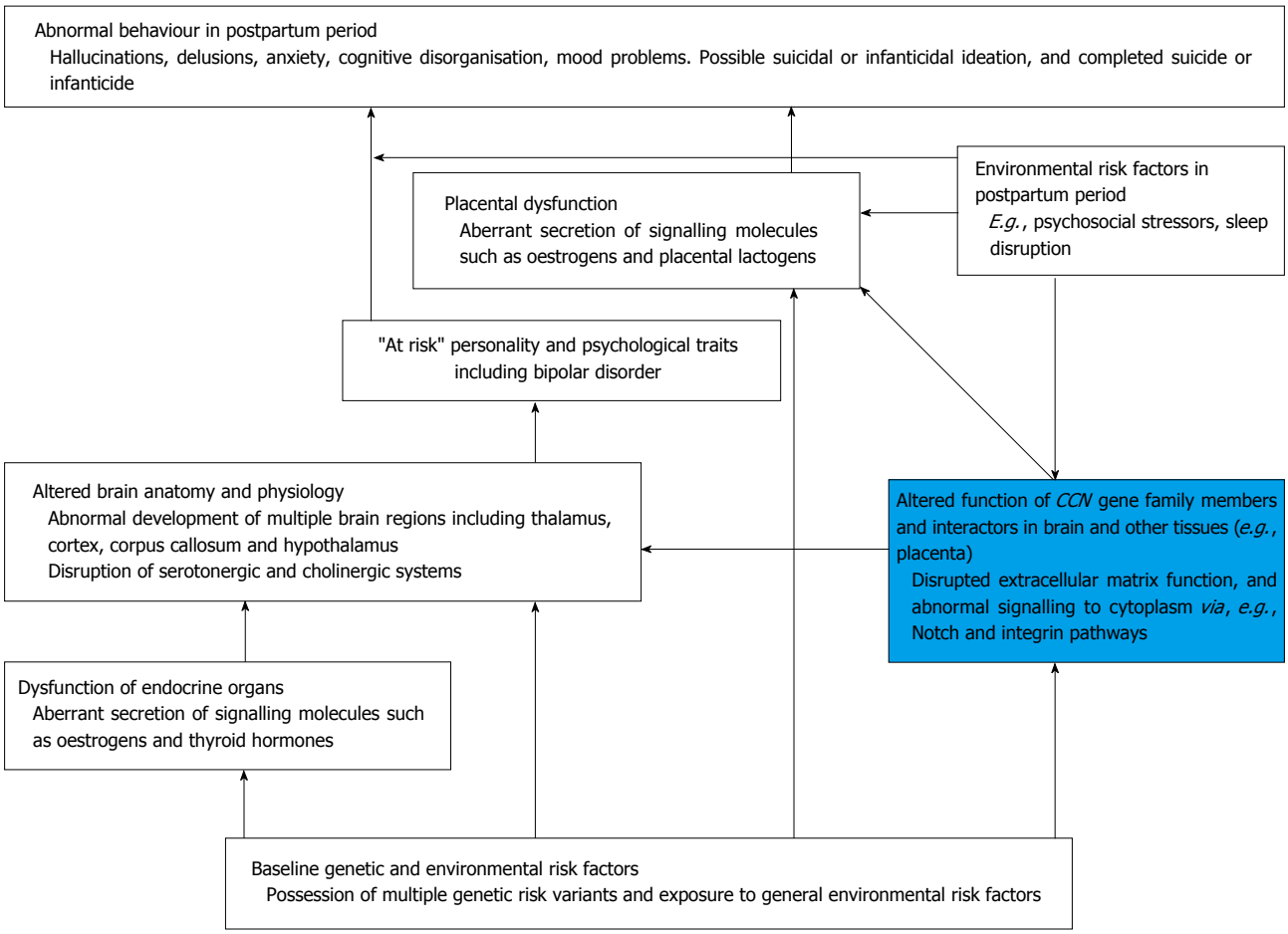

Figure 1 A revised model for postpartum psychosis risk. We suggest that multiple genetic risk variants (potentially influencing STS and CCN family member function), in combination with environmental risk factors, adversely affect the function of multiple endocrine organs (notably placenta and thyroid gland) and increase expression of CCN family members in brain and placenta, to elicit functional changes in brain architecture and neurochemistry which predispose to postpartum psychosis risk. This risk may be further exacerbated by acute environmental risk factors acting within the postpartum such as psychosocial stressors (plausibly also acting *via* CCN-mediated pathways). Putative and well-characterised protective factors such as smoking and antipsychotic administration respectively could potentially exert their effects *via* normalisation of CCN family member function.

Finally, converging evidence from a genetic mouse model is consistent with the notion that *Ccn3* over-expression is associated with abnormal maternal behaviour. Specifically, wildtype mouse mothers carrying pups with genetic modifications which affect placental (spongiotrophoblast) function exhibit abnormal maternal and anxiety-related behaviours in the postpartum period and significantly increased hippocampal *Nov/Ccn3* gene expression[54,82]; this finding is intriguing as it suggests the possibility that the secretion (or lack thereof) of one or more circulating factors from the placenta can indirectly affect brain expression of *Nov/Ccn3*, and subsequently maternal behaviour. The spongiotrophoblast is involved in the synthesis and secretion of multiple compounds which have been shown to influence maternal behaviour in rodent models and which may plausibly mediate this effect (*e.g.,* placental lactogens and pregnancy-specific glycoproteins[83]). Interestingly, in humans, placental lactogen is secreted by the syncytiotrophoblast of the placenta[84], a site of high STS expression[85].

An integrated model showing how PP risk may conceivably be influenced by STS deficiency, placental dysfunction, and disruption to CCN family members based upon current knowledge is presented in Figure 1. This model may be updated and refined as new data emerge from avenues including larger genomic screens, hypothesis-free gene expression screens in model systems, and physiological measurements in patients with PP. The model makes several readily-testable clinical predictions for PP cases relative to control subjects: (1) there will be an excess of genetic variants that reduce STS function and enhance CCN3 expression; (2) there will be an increased DHEAS:DHEA tissue ratio; and (3) there will be elevated levels of CCN3 in accessible fluids including serum, cerebrospinal fluid and urine[86]. In parallel to these clinical studies, we could potentially demonstrate whether or not CCN3 contributes significantly to abnormal maternal behavioural phenotypes in mice by administering an STS inhibitor to wildtype mice and readily-available *Ccn3* knockout mice[87], with the prediction being that wildtype mice would exhibit behavioural abnormalities whereas knockout mice would not.

Should CCN family member over-expression be confirmed as a PP risk factor by future clinical and basic

studies, it may be amenable to pharmacological amelioration by, amongst other approaches, antibody-targeting or knockdown strategies[88]; such interventions may have therapeutic benefits and offer an alternative to more conventional mood stabiliser and antipsychotic approaches.

CONCLUSION

Numerous features of postpartum psychosis (notably its low prevalence, its high degree of heterogeneity, its relative unpredictability and a lack of relevant animal and cellular models) make understanding its pathophysiology difficult. Whilst research to date has provided tantalising hints at pathways and systems that may be perturbed in the condition, the questions as to whether or not they are truly pathogenic remains to be addressed. Undoubtedly, there are many more risk pathways to be discovered.

To make meaningful progress in understanding the molecular, cellular, neural and psychological mechanisms underlying PP risk it will be necessary to adopt a converging experimental approach comprising large-scale genetic (association, copy number variations and sequencing), gene expression and genetic neuroimaging studies, clinical studies correlating behavioural phenotypes with physiological markers of immune, neurochemical and neuroendocrine dysfunction, and animal (pig and mouse) and cellular (*e.g.,* induced pluripotent stem cells) model studies, bearing in mind the many caveats raised above. Importantly, hypothesis-free approaches such as the genomic and animal/cellular model approaches may identify non-obvious risk pathways which can then be followed up in more focussed clinical analyses. The prioritisation of candidate pathways may be informed by work examining the physiology of related conditions and behaviours including bipolar disorder, other postpartum mood disorders, pre-eclampsia and smoking.

A main goal in PP research is to identify biomarkers within easily accessible tissues that can be sampled before, or during, pregnancy (*e.g.,* blood, saliva) that can accurately predict risk, a substantial challenge for such a rare condition; early identification of "at risk" individuals should facilitate rapid access to appropriate facilities and medical care (including close monitoring, administration of psychological or pharmacological treatments, and counselling). The experimental analyses proposed above are likely to result in the identification and characterisation of such biomarkers.

A recent study has shown that the expression of *Nov*/*Ccn3* in rat tissues is sensitive to the administration of the mood-stabilising drug lithium which has clinical efficacy in some cases of PP[89].

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ORIGINAL ARTICLE

Basic Study

Development of an instrument to measure patients' attitudes towards involuntary hospitalization

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Abstract

AIM

To construct and assess the psychometric properties of an instrument to measure patients' attitudes towards involuntary hospitalization.

METHODS

This is a two phase study. In the first phase, based on comprehensive literature review, a twenty one item scale to measure patients' attitudes to involuntary admission was constructed. Forensic and inpatient Psychiatrists, patients' advocates and legal experts (n = 15) were invited to participate in the validation process of the written instrument, by formally rating each item of the instrument for its relevancy in measuring patients' attitudes to involuntary admission. In the second phase of the project, the instrument was administered to a sample of eighty consecutive patients, who were admitted involuntarily to an acute psychiatric unit of a teaching hospital. All patients completed the constructed attitudes towards involuntary admission scale, and the client satisfaction questionnaire.

RESULTS

Responses from psychiatry and advocacy experts provided evidence for face and content validity for the constructed instrument. The internal consistency reliability of the instrument is 0.84 (Chronbach' alpha), factor analysis resulted in three correlated, and theoretically meaningful factors. There was evidence for content, convergent, and concurrent validity.

CONCLUSION
A reliable twenty one item instrument scale to measure patients' attitudes to involuntary admission was developed. The developed instrument has high reliability, there is strong evidence for validity, and it takes ten minutes to complete.

Key words: Scales; Mmeasurements; Patients' attitudes; Involuntary admission; Psychiatric

Core tip: Examining patients' attitudes towards involuntary hospitalization is crucial for making clinical decisions and is required to administer quality patient care. This project involved the development and psychometrical assessment of a reliable instrument with demonstrated evidence of validity, to measure patients' attitudes towards involuntary hospitalization. The developed instrument consists of a 21-item, 5-point Likert questionnaire. The internal consistency reliability of the instrument is 0.84 (Chronbach' alpha), and there is an evidence for content, convergent, and concurrent validity.

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INTRODUCTION

Promoting for patient care is the most important objective of mental health. This should include both effective patient day to day care, and advocating for patients' rights. Involuntary admission is one of the most ethically challenging practices in medicine, which touches patient's rights and freedom. Yet we are only beginning to learn more about patient's perspective by utilizing a reliable instruments with evidence for validity. The prevalence of patients' involuntary hospitalization, factors associated with coercion, and patients' dissatisfactions were examined internationally especially Europe. In one large of Swiss inpatients study, about 25% were admitted on an involuntary basis and there were substantial number of patients were exposed to coercion. It was demonstrated that the severity of the psychiatric disorder was the main risk factor to predict appling force during admission[1].

The prevalence of involuntary hospitalization significantly varies from country to country. For example, Zinkler and Priebe[2] (2002) found in a review that there were nearly 20-fold variations in involuntary admission rates in different European countries. However the criteria for detention of the mentally ill are broadly similar when it comes to patients at risk to themselves or others[2].

Risk factors for involuntary admission are numerous. Results from research, suggested that the diagnoses and the intensity of psychiatric illnesses were the most important risk factors for being subjected to any form of coercion[2-4].

In a cross-sectional survey, there were significant proportions among both voluntarily and involuntarily admitted patients who felt that they were forced to be hospitalized. However the majority felt that their admission was necessary[5]. Involuntary admissions were found to be associated with a history of previous hospitalizations[6], presence of psychotic symptom[7], lower levels of social functioning[8], and linguistic communication problems[9]. However, those who were admitted involuntarily were more likely to report significantly more adverse circumstances around the admission procedures such as exposure to verbal or physical force[10-13].

Both clinical outcomes and future adherence to treatment appear to be negatively affected by involuntary hospitalization or by the experience of coercion. For example, Katsakou *et al*[14] (2010), examined 778 involuntary psychiatric inpatients admissions. Perception of coercion was associated with less satisfaction with treatment. Also Swartz *et al*[15] (2003), reported that only 36% of consumers with chronic psychiatric disorders, reported fear of coerced treatment as a barrier to seeking help.

Objectives of the present study

To the best of author's knowledge, there is no published reliable scale with evidence of validity that was developed to measure patients' perceptions towards involuntary hospitalization.

The objective of this study is to examine the reliability, and validity of an instrument that was constructed to measure patients' attitudes towards involuntary hospitalization.

MATERIALS AND METHODS

Participants

Expert participants (psychiatrists, review panel, and patient advocate experts): Fifteen experts from both males and females, volunteered to participate in the validation process of the scale. Among participants, there were nine psychiatrists affiliated with the University of Calgary, three provincial mental health advocacy staff, one lawyer, and two community mental health coordinators. Among psychiatrist experts, there were two at the rank of professor, four at the associate professor in the area of forensic psychiatry, and three at the level of assistant professor in general psychiatry. Table 1 describes the demographicc details of patient participants.

Letters of invitations were delivered inviting experts to participate in the validation process. In addition to the formal validation, there was one-on-one discussion, and feedback, about each item of the proposed scale with regard its relevancy to sample attitudes of patients

Table 1 Demographics of the participating experts (n = 15)

Variable	mean (SD)
Age (yr)	52 (9.5)
Sex: Male/female	11/4
Years of experience as independent Psychiatrist, consultants, lawyers or advocate	22 (12.5)
Professorial experts' professions	*n*
Psychiatrists affiliated with the University of Calgary	9
Professors of psychiatry	2
Associate Clinical Professors (U of C)	4
Assistant Professors	3
Mental Health Advocacy Staff	3
Community order coordinators	2
Lawyers of the Mental health Review Panel	1

towards involuntary admission of psychiatric patients.

Patient participants

Invited to participate in this study, consecutive sample of consenting patients, who were involuntarily admitted to an acute psychiatry teaching unit within the University of Calgary. Patients were included if they were admitted at least on one certificate under section 2 of the Alberta Mental Health Act (2010)[16]. Form one certificate of section 2 is completed by a physician allows detention of a patient up to 24 h. When a person is detained in a facility under a form one certificate, the detained person must be examined as soon as possible by a physician who is on staff, at the receiving facility. According to the Act, these two admission forms (certificates) are sufficient authority to detain and control the person in a facility for 30 d, to allow diagnosing, care for, observation, assessments, and treatments (section 7 of the Act). If a second admission certificate is not signed within 24 h of the person's arrival at the designated facility, the person can no longer be detained involuntarily and shall be released (section 5 of the Mental Health Act)[16].

The researchers approached eligible, consenting patients and invited them to participate in the study. All patients who participated in this study were diagnosed with formal psychiatric disorders, and were deemed danger to themselves or others, on admission. Excluded from the study, patients who are mentally handicapped, the severely ill or aggressive patients, suicidal patients, and those who deemed unable to provide consent. For the purpose of this study, we excluded patients with a score > 50, on The Brief Psychiatric Rating Scale (BPRS) total maximum score[17]. The Mini-International Neuropsychiatric Interview (M.I.N.I. Screen 2001-2005) was utilized to confirm the diagnosis of each included patient[18].

Instruments administered to patients

In addition to the constructed attitudes towards involuntary admission (ATIA) scale Hospitalization scale ATIA (Table 2), all patients completed the following questionnaires: (1) The Client Satisfaction Questionnaire (CSQ)[19]. The CSQ is intended to measure satisfaction with healthcare services. The scale consists of eight items, has a high levels of internal consistency, with alphas ranging from 0.86-0.94; and (2) The Brief Psychiatric Rating Scale (BPRS)[17]. The BPRS is an 18 - item scale that measures symptom severity of major psychiatric disorders, with ratings on a seven point scale (1 = not present, 7 = extremely severe). The rating is made on observations during a 15 to 30 min interview to assess attention, emotional withdrawal, psychomotor symptoms, anxiety, psychotic symptoms depressed mood, and hostility. All patients consented to the study, and provided their demographics including; age, education, occupation, if they were brought to hospital by police force, and if mechanical restraints were used.

Procedure

The procedure of the project aimed at examining the psychometric properties of a developed scale to measure patients' perceptions towards involuntary admissions to acute psychiatric unit. The project was granted an approval by the Conjoint Health Research Ethics Board (CHREB), of the University of Calgary.

Phase 1 of the study: This phase of the study included the construction of the scale items, and the validity assessment by experts. Following literature review using PubMed, and MEDLINE, a table of specification with the initial items describing patients ATIA was prepared as a reference for writing the items of the newly developed scale. The literature was searched for recent evidence from published research projects and reviews to adequately cover the domain of patients' perceptions towards involuntary hospitalization. This was the first step of the project to improve content validity of the items selected. We were able to identify twenty one items that best describe patients' perceptions of involuntary admission[20].

Measuring attitudes is always challenging because attitudes represent such subtle affective domain Applying a scale such as a 5-point liket scale best assesses this domain[20,21]. The twenty one item list of patients' attiudes to involuntary hospitalzation were converted to a 21-item, 5-point Likert scale, resulting in the ATIA scale (Table 2).

Administration to experts

Face validity, was assessed by inviting the experts to provide their views on the overall layout and the content of the instrument. Formal content validity was assessed by asking the volunteer panel of experts to review each items and to examine its relevancy and clarity. Investigators invited experts which included forensic and general psychiatrists, independent mental health advocacy specialists, community health coordinators, and lawyers, to assess each item of the scale for its relevance in measuring patients' attitudes to involuntary admission, on a five-point Likert scale (1 = extremely irrelevant, 2 = irrelevant, 3 = slightly relevant, 4 = relevant, and 5 =

Table 2 The administered version of the constructed attitudes towards involuntary admission scale

	1	2	3	4	5
Instructions: Please rate your perception about the following statements in relation to your involuntary admission to hospital (1 = strongly disagree and 5 = strongly agree)					
I think that being detained as an involuntary patient has averted further harm to me					
I believe that I was offered the opportunity to recover in a safe place					
I could not recognize that I needed help when I was very ill					
I felt that I was pressured excessively					
My problem could have been managed without being pressured					
I think that my hospitalization was not necessary at all					
I think that my hospitalization was unfair					
I think that hospitalization was against my rights					
I felt that I was not heard					
Hospitalization against my will posed a permanent threat to my independence					
My problems might have been managed through a voluntary hospitalization					
My problems might have been managed through a shorter hospitalization					
This admission had a negative impact upon the relationship with my family					
My relationship with my psychiatrist was negatively impacted by this involuntary admission					
I felt that that my current or future job could be affected by being in hospital against my will					
I know my rights as an involuntary patient					
I was given passes and other privileges outside the unit when my doctors felt it was ok					
Admission to hospital was a humiliating experience					
I was given the chance to appeal my involuntary admission					
Overall, I was treated with respect					
I think my family should have been involved in the decision about my admission					

strongly relevant). All participating experts also provided their ratings on the clarity of each item, about absence of abrasive language and about the overall comprehensives of the instrument.

Phase Ⅱ of the study: This phase of the study included the administration of the instrument (Table 2) to patients, data collection, and examining the psychometric properties of the scale. While administration to experts was utilized to assess face and content validity, the administration to patients aimed at establishing internal consistency reliability, and exploring evidence for validity. The scale was pilot tested with four patients. Patients were asked to comment on the clarity of each item, and the time that needed to complete the scale.

After patients' feedback and experts' reviews of each item, the constructed ATIA Scale (ATIA = 21 items), was administered to eighty consenting adult consecutive patinets who were admitted involuntararily to a psychiatric teaching unit. Patients rated ATIA scale on a 5-point Likert type scale (from 1 = strongly disagree to 5 = strongly agree), their perceptions and experiences towards involuntary admission.

Table 3 shows the constructed scale after revision. Seven items scoring were reversed to avoid response patterns. All patients completed the ATIA scale, and the CSQ. A semi structured interview with patients was conducted to complete the BPRS to assess eligibility for inclusion in the study, and to confirm psychiatric diagnoses. Patients were also asked to provide their demographics including age, marital status, education, employment status and all patients were asked if force was used to bring patient to hospital, and if mechanical restraints were used to hold them during hospitalization.

RESULTS

Participated in the study eighty patients who were admitted on an involuntary basis. There were fifty two males, and twenty eight females (M/F = 65%/35%), with mean age 38 (SD = 13.0). Twenty three patients (28.7%) suffered from schizophrenia and schizoaffective disorders, thirty three patients (4.3%) from mood disorders, fourteen patients (17.5%) suffered from alcohol and substance abuse, and ten patients (12.5%) were diagnosed with adjustment disorder. In eleven patients (13.8%), mechanical restraints were applied (Table 4) displays the details of patients' demographics.

The internal consistency reliability (Cronbach's alpha) was 0.84 for the 21 items of the ATIA. Between group differences were analyzed employing Analyses of Variance. There were no significant differences, between males and females, marital status, different age groups, occupational and diagnostic categories, or any difference between the mechanically restrained groups, in the attitudes mean scores of the instrument.

Experts' responses

There were no significant differences ($P < 0.08$) in ratings among experts based on their length of experience. Expert's ratings for all items on the scale ranged from 4.2/5 to 4.8/5. The mean rating the instrument' items was 4.5/5, which results in an overall 90% agreement of experts for the relevancy of the ATIA instrument as a measure for patients attitudes towards involuntary hospitalization (Tables 5 and 6).

Patients' responses

Table 5 displays patients' attitudes mean scores on each

Table 3 The Final version of the attitudes towards involuntary admission scale

	1	2	3	4	5
Please rate your perception about the following statements (1 = strongly disagree to 5 = strongly agree)					
I think that hospitalization was against my rights					
I felt that I was not heard					
Admission to hospital was humiliating experience					
I think that my hospitalization was unfair					
My relationship with my psychiatrist was negatively impacted by this involuntary admission					
This admission had a negative impact upon the relationship with my family					
I felt that my current or future job could be affected by being in hospital against my will					
My problem might have been managed through a shorter hospitalization					
My problem might have been managed through a voluntary hospitalization					
Hospitalization against my will posed a permanent threat to my independency					
My problem could have being managed without being pressured					
I felt that I was pressured excessively					
I think that my hospitalization was not necessary at all					
I think my family should have been involved in the decision about my admission					
Please rate your perception about the following statements (1 = strongly agree to 5 = strongly disagree)					
I know my rights as an involuntary patient					
I was given the chance to appeal my involuntary admission					
I think that being detained as an involuntary patient has averted further harm to me					
I could not recognize that I need help when I was very ill					
Overall, I was treated with respect					
I believe that I was offered the opportunity to recover in a safe place					
I was given passes and other privileges outside the unit when my doctors felt it was ok					

Table 4 Demographics of patients (n = 80)

Categorical variables	Frequency (%)
Sex	
Male	52 (65)
Female	28 (35)
Marital status	
Single	48 (68)
Married	14 (17.5)
Divorced	17 (21.3)
Widow	1 (1.3)
Education	
Elementary	4 (5.0)
Junior high	3 (3.8)
High school	35 (43.8)
College	20 (25.0)
University degree	18 (22.5)
Occupation	
Unemployed	37 (46.3)
Own business	9 (11.3)
Non-skilled/temporary	3 (3.8)
Skilled	26 (32.5)
Professional	5 (6.3)
Brought to hospital by police	
Yes	35 (43.8)
No	45 (56.2)
Psychiatric diagnosis	
Mood disorders	33 (41.3)
Psychotic disorders	23 (28.7)
Alcohol and substance abuse	14 (17.5)
Adjustment disorder	10 (12.5)
Mechanical restraints	
Mechanical restraints used	11 (13.8)
Mechanical restraints not used	69 (86.2)
Continuous variables	M (SD)
Age	37.7 (13.0)
Number of psychiatric admission	3.4 (2.9)
Number of involuntarily admission	2.2 (2.0)

item towards involuntary admission. There were mixed patients' perceptions about involuntary hospitalization. Overall, there was an average rating for all the instruments' items of 2.9/5. However, in the current study, there were some important items which received a favorable positive attitude scores (> 3/5), including the following four items; "Being detained as an involuntary patient has prevented further harm to me", "I believe that I was offered the opportunity to recover in a safe place", "overall, I was treated with respect during this admission", and "I was given the chance to appeal my involuntary admission". In contrast, there were items that overall, received negative attitudes (< 3/5) scores from patients such as the following items; "My hospitalization was unfair", "I think that the hospitalization was against my rights", "I felt that I was not heard", and "Hospitalization against my will posed a permanent threat to my independence" (Tables 5 and 6).

Factor analysis

Exploratory factor analyses were performed on the 21-item scale. Three-factors were extracted, accounting for 44% of the variance in responses related to patients' perceptions of involuntary hospitalization.

Factor 1: Violation of legal rights and autonomy: This factor consists of thirteen items, has an internal consistency of 0.85, and explains 25.6% of the observed variance. It refers to the perceptions that involuntary admission violated legal rights, was not justified, and unfair. There were perceptions of threat to independency, feelings of humiliation, and of being stigmatized by others.

Factor 2: Ambivalent perceptions: This factor consists of six items, has an internal consistency of 0.68, and

Table 5 Experts' ratings, and patient's responses to the items (n = 21) of the attitudes towards involuntary admission scale

Items of the constructed list of specifications patients' and experts' ratings of the	Experts ratings for the relevancy of items[a]		Patients' responses[b]	
	Min-Max	mean (SD)	Min-Max	mean (SD)
I think that being detained as an involuntary patient has prevented further harm to me	3-5	4.6 (0.65)	1-5	3.1 (1.90)
I believe that I was offered the opportunity to recover in a safe place	3-5	4.5 (0.66)	1-5	3.9 (1.21)
I could not recognize that I needed help when I was very ill	4-5	4.8 (0.38)	1-5	2.7 (1.50)
I felt that I was pressured excessively	4-5	4.7 (0.44)	1-5	2.5 (1.46)
My problem could have been managed without being pressured	4-5	4.6 (0.65)	1-5	3.3 (1.38)
I think that my hospitalization was not necessary at all	4-5	4.5 (0.66)	1-5	2.4 (1.36)
I think that my hospitalization was unfair	3-5	4.4 (0.96)	1-5	2.4 (1.47)
I think that the hospitalization was against my rights	3-5	4.3 (0.63)	1-5	2.4 (1.45)
I felt that I was not heard	2-5	4.4 (0.96)	1-5	2.5 (1.45)
Hospitalization against my will posed a permanent threat to my independence	3-5	4.3 (0.63)	1-5	2.3 (1.50)
My problems might have been managed through a shorter hospitalization	2-5	4.3 (0.85)	1-5	3.6 (1.40)
My problems might have been managed through a voluntary hospitalization	3-5	4.6 (0.66)	1-5	2.9 (1.44)
This admission had a negative impact upon the relationship with my family	2-5	4.4 (0.96)	1-5	2.2 (1.41)
My relationship with my psychiatrist was negatively impacted by this involuntary admission	3-5	4.4 (0.65)	1-5	1.9 (1.29)
I felt that that my current or future job could be affected by being in hospital against my will	3-5	4.2 (1.2)	1-5	2.5 (1.48)
I know my rights as an involuntary patient	2-5	4.7 (0.48)	1-5	3.4 (1.51)
I was given passes and other privileges outside the unit when my doctors felt it was ok	3-5	4.5 (1.1)	1-5	4.3 (1.12)
Admission to hospital was a humiliating experience	1-5	4.3 (0.85)	1-5	2.6 (1.48)
I was given the chance to appeal my involuntary admission	4-5	4.5 (0.66)	1-5	3.2 (1.50)
Overall, I was treated with respect during this admission	2-5	4.6 (0.51)	1-5	3.9 (1.20)
I think my family should have been involved in the decision about my admission	1-5	4.6 (0.51)	1-5	3.2 (1.51)
Mean (SD) for the total samples	2.8-5	4.5 (0.70)	1-5	2.9 (1.2)

[a]Experts' responses: 1 = extremely irrelevant to 5 = very relevant; [b]Students' responses: 1 = strongly disagree to 5 = strongly agree.

Table 6 Experts' ratings of the attitudes towards involuntary admission scale format

Experts' ratings (n = 15)	Min-Max	mean (SD)
Clarity of the items (1 = not clear, 5 = very clear)	4-5	4.4 (0.65)
Absence of abrasive language (1 = presence of abrasive, 5 = absence of abrasive language	4-5	4.5 (0.52)
Comprehensiveness of the instrument (1 = not comprehensive, 5 = comprehensive)	4-5	4.5 (0.66)

explains 10% of the observed variance. This factor refers to mixed perceptions. Despite the recognition that there was a need for treatment and that the admission have averted further harm, patients felt that the admission could have been carried out on a voluntary basis and without pressure.

Factor 3: Appreciating procedural justice: This factor consists of five items has an internal consistency of 0.57 and explains 8.8% of the observed variance. It refers mainly to the positive attitudes that the admission was justified, and that there was appreciation for being treated with respect, for being provided the opportunity to appeal their involuntary admission, and for being allowed privileges outside the psychiatry unit when appropriate (Table 7).

There were significant correlation (P < 0.05-0.01) between the three factor scores on the Pearson product moment correlations (Table 8), providing an evidence for convergent validity.

There was significantly negative correlations (r = -0.44, P < 0.01) between the CSQ mean score, and ATIA factor 1 score, "violation of legal rights and autonomy". Also, there were negative correlations between the CSQ mean score, and the other two ATIA factor scores (Table 8).

DISCUSSION

In the present study, patients' ATIA, were included in a 21-Likert-type item scale that have an overall reliability internal consistency of 0.84. There was 95% overall agreement among experts about the relevance of its contents to measure patients' perceptions towards involuntary admission, providing an evidence for content validity. The scale was administered in a timely manner, when patients were able to make fair judgement about their perceptions. This was guided by ensuring a low scores (< 50) of the BPRS.

In the current study, patients who completed the ATIA scale, reported variable perceptions on the 21 item questionnare administered. There is strong evidence from published research to support the same findings and to suggest that the negative attitude towards involuntary hospitalization changes over time. For example, in number of studies, authors found retrospectively that, between 33% and 81% of patients regarded the admission as justified and the treatment as beneficial. Also, patients with more marked clinical improvement had more positive retrospective judgments[22-24].

It was demonstrated in the EUNOMIA prospective research project which included involuntary (n = 2326)

Table 7 Rotated factor matrix, attitude towards involuntary hospitalization scale scores[1]

Items perceptions of involuntary hospitalizations scale (n = 21)			
Factors extracted	**Factor loadings**		
	F1	**F2**	**F3**
I think that my hospitalization was unfair	0.80		
I think that hospitalization was against my rights	0.71		
I think that my hospitalization was not necessary at all	0.70		
Hospitalization against my will posed a permanent threat to my independency	0.59		
I felt that I was not heard	0.60		
Admission to hospital was humiliating experience	0.58		
I believe that I was offered the opportunity to recover in a safe place	0.56		
This admission had a negative impact upon the relationship with my family	0.54		
My relationship with my psychiatrist was negatively impacted by this involuntary admission	0.51		
My problem might have been managed through a shorter hospitalization	0.51	0.46	
I felt that my current or future job could be affected by being in hospital against my will	0.51		
I think my family should have been involved in the decision about my admission	0.40		
My problem might have been managed through a voluntary hospitalization		0.74	
I could not recognize that I need help when I was very ill		0.65	
My problem could have been managed without being pressured	0.39	0.52	
I think that being detained as an involuntary patient has averted further harm to me		0.51	
I was given the chance to appeal my involuntary admission			0.67
I was given passes and other privileges outside the unit when my doctors felt it was ok			0.59
I know my rights as an involuntary patient		0.55	0.56
Overall, I was treated with respect			0.56
I felt that I was pressured excessively			0.48
Internal consistency (Cronbach's alpha) for each factor	0.85	0.68	0.57
Proportion of observed variance for each factor (%)	25.6	10.0	8.8

[1]Principal components extraction, Varimax rotation with Kaiser Normalization. Rotation converged in twelve iterations, factor loadings < 0.35 have been excluded. Factor 1: Violations of legal rights and autonomy; Factor 2: Ambivalent perceptions; Factor 3: Appreciating procedural justice.

Table 8 Pearson product moment correlations between factor scores and client satisfaction questionnaire scores

PIH factors	Factor 2	Factor 3	Client satisfaction questionnaire
Factor 1	0.48[2]	0.27[1]	-0.44[2]
Factor 2		0.36[2]	-0.07
Factor 3			-0.21

[1]Correlation is significant at the 0.05 level (2-tailed); [2]Correlation is significant at the 0.01 level (2-tailed).

patients that between 39% and 71% considered that their admission was justifiable after one month, and this positive attitude changed to 86% after three months[25].

Perceptions of coercion

In the current study, significant proportion of patients perceived being pressured to the admission, or perceived humiliation. These findings replicate findings from other studies. For example, it was demonstrated that negative experiences of being coerced such as by exposure to physical or verbal force during the admission process were more common among patients with involuntary admission. However, coercion was also observed among those who were voluntarily admitted[22,23,26]. Also, Kallert *et al*[27] (2011), reported that perceptions of coercion were found to be significantly more prevalent (89%) among the involuntarily admitted patients, than among the voluntarily admitted patients (48%)[11,28].

It was emphasized by other authors that minimizing patient's perception of coercion during hospital admission may impact positively on the course and adherence to treatment. Authors emphasized that there is need, to minimize the patient's perception of coercion during hospital admission which may affect treatment course and adherence to it[28].

The results from the current study, demonstrated that the Scale's items, on atitudes towards involuntary admission clustered into three constructs (*i.e.*, factors), which resulted in three components. The factors are theoretically meaningful and cohesive, as it was demonstrated by the significant correlations between their scores, supporting evidence for convergent validity.

The three extracted factors, factor 1, "violations of legal rights and autonomy", factor 2, "ambivalent perceptions", factor 3, and "appreciating procedural justice", are consistent with previous research, and theoretically provide a meaning to our hypothseis, which provide evidence for construct valididty. Findings from the current study replicate the findings from other studies. For example, Katsakou *et al*[29] (2011), identified three groups of patients with distinct views on their involuntary hospitalization: Those who believed that it was right, those who thought it was wrong and those with ambivalent views.

Evidence for content validity

The evidence from the published literature leading to the development of a list of patients' ATIA, the cohesive construct of the scale items, and the formal input from experts, provide an evidence for content and construct validity of the scale.

Evidence for concurrent validity

This was demonstrated by the negative correlations between the mean scores of the three factors, and the CSQ mean score. There was significantly (r = -0.44, P < 0.01) negative correlation between the mean score of factor 1, and the CSQ mean score. This negative relationship is meaningful and expected, and supports the findings that patients who had negative perceptions were significantly less likely to be satisfied with services.

Limitations of the study

There was a small sample size, and all patients were recruited from the same psychiatric inpatient sitting.

Conclusion

Advocating for patients should include both effective patient day to day care, and advocating for patients' rights. It is crucial to ensure that patients' rights during hospitalization is protected. In the current study, an instrument to measure patients' perceptions towards involuntary hospitalization was developed. The instrument has a strong reliability. Utilizing confirmatory factor analysis in future research, should be performed to explore the construct validity of the instrument. Also, future research should examine the relationship between involuntary admission risk factors and the clinical outcomes associated with involuntary hospitalization.

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COMMENTS

Background

This project explored the most prevalent perceptions of patients who were admitted to an acute psychiatric unit involuntararily. It aimed at the development and psychometric assessment of an instrument to reliably measure attitudes towards involuntary hospitalization.

Research frontiers

In the first phase of the study, to ensure content validity of the instruemt, all items were written carfefully after a thourough literature review, and psychiatry experts provided a formal ratings on each item of the instrument with regard its relevancy in measuring patients' attitudes, before the instrument was administered to patients.

Innovations and breakthroughs

To the best knowledge of the author, this is the first developed instrument with acceptable reliability to systematically examine patients' attitudes to involuntary psychiatric hospitalization. Results from this study, might shed further light into providing better patient care while protecting patients' legal rights.

Applications

Future researchers, should consider testing the reliability and validity of this instrument in larger sample of patients, from different cultures and in different inpatient settings. There are number of recommendations that could be made which might include the following; better understanding of patients attitudes towards involuntary hospitalization, emphasizing the need to providing psychoeducation to patients and their relatives about the reasons that led to hospitalization and its expected duration; protecting patients' rights during their hospital stay, and improving the communication between relatives and professional hospital staff.

Peer-review

This is a highly relevant paper dealing with the assessment of patient satisfaction in the case of involuntary admission. The authors developed a reliable 21-item likert scale questionnaire with evidence of validity that seems well constructed.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Group psychological intervention for maternal depression: A nested qualitative study from Karachi, Pakistan

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Abstract

AIM

To understand the experience of maternal depression, the factors implicated in accessing health, and the acceptability of the psychosocial intervention.

METHODS

The participants were recruited from the paediatrics outpatient department of Civil Hospital Karachi, Pakistan. The study started in December 2009 and completed in December 2010. Women with maternal depression, aged 18-44 years with children aged 0-30 mo who had received nutritional supplements, and participated in the intervention programme [called Learning through Play (LTP) plus] were included in the study. Qualitative interviews were conducted with 8 participants before the intervention and 7 participants after the intervention. A semi structured topic guide was used to conduct the interviews.

RESULTS

Framework analysis procedures were used to analyse the qualitative data. Four themes emerged: (1) the women's contextual environment: Interpersonal conflicts, lack of social support and financial issues being the major barriers in assessing healthcare; (2) women's isolation and powerlessness within the environment: Sense of loneliness was identified as a restricting factor to access healthcare; (3) the impact of the intervention (LTP-Plus): Women felt "listened to" and seemed empowered; and (4) empowered transformed women within the same contextual environment: The facilitator provided a "gardening role" in nurturing the women resulting in a positive transformation within the same environment. The women's homes seemed to be more happy homes and there was a positive change in their behaviour towards their children.

CONCLUSION

Findings informed the further development and testing of culturally-appropriate psychosocial intervention (LTP^{+}) for addressing maternal depression.

Key words: Low income Country; Thinking Healthy Program; Learning through play; Maternal depression; Framework analysis; Exploratory analysis

Core tip: To our knowledge this is the first qualitative study from Pakistan exploring the experiences of depressed mothers participating in a group psychosocial intervention trial. This was part of a randomized control trial testing the acceptability and feasibility of a parenting intervention Learning through Play (LTP)-Plus among depressed women in a low-income setting. The LTP^{+} intervention focused on two key objectives. First was to stimulate early child development through a pictorial calendar among children from birth to 3 years. Second was to change negative thoughts patterns of mothers through culturally adapted cognitive behavioural therapy intervention. The intervention was acceptable and the qualitative data informed the further development of the intervention.

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INTRODUCTION

Childbirth has been recognized as an important life event that alters responsibilities of a woman permanently[1]. The transition to motherhood is characterized by rituals, prohibitions, and guidelines that facilitate mothers' adaptation to their new roles[2]. However, lack of social support and stressful life events during this significant transition may lead to depression[3,4]. In the West, 10%-15% of women are affected by maternal depression[4] and its prevalence is much higher in developing countries such as India (28%)[5] and South Africa (34.7%)[6]. The prevalence rate is even higher among Pakistani women, *i.e.*, 36%[3]. Increased psychological distresses during the antenatal period[3,5], worry about debt[7] poverty, and disturbed marital relationships[5] have been identified as risk factors for maternal depression.

Furthermore, a phenomenological study in Hong Kong highlighted feelings of "being trapped" in women with postnatal depression and explained that lack of support in the form of uncaring husbands and controlling in-laws were emergent themes along with mothers' ambivalent feelings of love and hate towards their baby[8]. The mother is responsible for breastfeeding, maintaining hygiene for the child, and immunization. She is expected not only to recognize illness, but also to seek appropriate care and treatment for her child[9]. Symptoms of maternal depression such as tiredness, inability to concentrate, preoccupation with guilt, worthlessness, and hopelessness adversely affect a mother's ability to provide adequate care[10]. This may have a long-term impact on the child's physical as well as psychological and cognitive well-being[11]. Results of cohort studies from developing countries including South Africa, Pakistan and India report strong associations between maternal depression and stunted growth[5,12,13]. Similarly, the damaging effects of maternal depression on intellectual and psychological development are also well documented[14,15].

The effectiveness of different psychological interventions such as cognitive behavioural therapy (CBT), interpersonal psychotherapy, and problem-solving therapy is well

established in the treatment of depression in developed[16] as well as developing countries[17]. A multicomponent intervention that involved psychoeducational treatment adherence, support, and pharmacotherapy was found to be effective in reducing depression in women with postnatal depression in Santiago[18]. In Pakistan, intervention based on the principles of CBT was found to be effective in reducing depression and disability and in improving social functioning[19].

A qualitative systematic review by Dennis and Chung-Lee[20] highlighted inability to disclose feelings, the presence of myths and lack of knowledge as barriers to help-seeking behaviours in women suffering from depression. Furthermore, this review also reported a preference for "talking therapies" for the treatment of postnatal depression[20].

As far as we are aware, the present study is the first qualitative research in Pakistan which explores the experiences of women suffering from maternal depression in Pakistan and their related experiences of participation in a group psychosocial intervention trial. A mixed-method study was conducted that comprised a randomized controlled trial (RCT) to test a psychosocial intervention for reducing maternal depression and improve child outcomes. A qualitative method was also used to understand the experience of maternal depression, factors implicated in accessing help, and the acceptability of the group psychosocial intervention in the participants.

MATERIALS AND METHODS

A qualitative approach was adopted as the research design. This approach was chosen in order to understand the experience of maternal depression in the cultural context of these participants, and to explore the antecedents, manifestation, and consequences of depression. Another area that was targeted in this study was the experience of participation in a group psychosocial intervention by particularly focusing on the helpful parts of the intervention, and the difficulties faced by the participants. The participants were interviewed before and after taking part in the intervention. Data was analysed using framework analysis principles[21,22]. All the mothers aged 18-44 years with children between 0-30 mo, diagnosed with depression on Edinburgh Postnatal Depression Scale (EPDS score $\geqslant$ 14) and residents in the trial catchment site were included in the study. Mothers with a medical disorder that could prevent their participation in the trial and those with active suicidal ideation or any other severe physical/mental disorder were excluded.

Ethical approval for the study was sought from the Institutional Review Board of Dow University of Health Sciences, Karachi, Pakistan. A Participant Information Sheet was provided to all participants at the time of recruitment and queries were addressed. After providing a detailed description of the study, written informed consent was obtained from all participants. Participants were assured of confidentiality and permission was obtained to audio record interviews. Codes were assigned to each participant and all transcripts were anonymised during transcription to keep personal data confidential. Data was kept safe on encrypted and password protected computers and were transferred electronically using encrypted files. A Lone Working Policy was used by Pakistan-based researchers in order to ensure their safety in the field. Furthermore, a Distress Policy was in place to enable the researchers to have a framework for accessing further support for participants when it was clear that someone could be at risk. The participants were interviewed at Civil Hospital Karachi, because it was a convenient place for the participants.

This study was a part of an RCT in which the acceptability and feasibility of a group psychosocial intervention [Learning through Play (LTP) Plus] was tested to reduce maternal depression and improve child outcomes. The LTP program focuses on the strategies to stimulate early child development. A pictorial calendar is the main feature of this program that is designed for parents and includes eight successive stages of child development from birth to 3 years. The second component of the psychosocial intervention was cognitive behaviour therapy (CBT) that was aimed at changing negative thought patterns. This study comprised of 98 participants; half of whom were randomized into the intervention group (n = 49) and half into the control group (n = 49). Participants were included in an in-depth interview study through convenient sampling. Interviews were conducted with 7 participants from the routine treatment group and 8 participants from the LTP plus in addition to routine treatment. Initially, 25 participants were invited at random to participate in qualitative interviews; 10 refused to participate because they did not want their interviews to be recorded whereas 15 participants consented. In-depth, semi-structured interviews were conducted by trained researchers. All were trained psychologists and received additional training on qualitative research and data analysis. All interviews were audio recorded after obtaining participant consent. Two separate topic guides were prepared for pre-intervention interviews and post-intervention interviews. The purpose of the interviews with the routine treatment group was to explore experience of maternal depression, its causes and manifestation, and the state of available treatment options. However, interviews conducted with the LTP Plus group were focused on exploring the experience of participation in a group psychosocial intervention, and to identify facilitators and barriers to accessing the intervention. After each interview, field notes were made by the researcher to document the body language of the participant in response to questions along with any other relevant information.

All interviews were transcribed verbatim in Urdu and then translated into English for data analysis. The routine treatment group data and LTP plus group data were analysed separately and then integrated during the mapping and interpretation phases[23]. The five stages of

framework analysis were used to analyse data[21]. During the initial familiarization stage, three researchers (HF, TK, BF) read through the transcripts and field notes collected during the interviews several times to fully immerse themselves in the data. After all data were familiarized, and in order to identify the key themes, a draft theoretical framework was constructed in which major and minor themes were identified from all interviews. Indexing was then carried out in order to apply the draft theoretical framework systematically to the data. Here the data from transcripts were copied and pasted alongside the relevant themes that were listed in the draft theoretical framework. Data and themes were then compared again and the draft theoretical framework revised. During the charting process, data were summarized into table developed using MS Word software for each theme listed in the draft theoretical framework[24]. This process provided a clear and concise overview of the data. Finally, these tables were reviewed during the mapping and interpretation phase. This enabled all key ideas and the data to be compared and discussed by researchers and supervisors, and to identify the final theoretical framework that synthesized and interpreted the data as a whole. To maintain credibility and trustworthiness of the data and subsequent findings, the researchers in Karachi were supervised by experienced mental health and qualitative researchers (NC, FL, CF) based in the United Kingdom. Regular fortnightly Skype meetings were held to discuss progress with the study team during the data collection and analysis phases. Drafts of analyses were electronically mailed to researchers in the United Kingdom who were able to study these before the Skype meetings. The organization (structure and pace) of the supervision process enabled the Pakistan-based researchers to develop experience, skills and confidence in qualitative methods. Engagement in discussion and regular reviews by all researchers ensured fit of the data to the final analysis, and supported minimization of bias[24]. Team members met for the final review of the theoretical framework, and came up with similar ideas. Furthermore, translations from Urdu to English were back-translated to ensure accuracy. For respondent validation[25], 15 participants were approached for feed-back, out of those 9 agreed to give feedback on accuracy of the data. Researchers and group members agreed on the key themes and interpretations.

RESULTS

All participants were home maker women aged 36-40 years, married, with children aged of 0-36 mo. After completion of data analysis, the following 4 key themes were identified in the final theoretical framework.

Context-the women's environment

This theme identifies the psychosocial factors that co-existed with women suffering from maternal depression. Interpersonal conflict and lack of support from extended family members were highlighted in many interviews. For example, the data suggest that several women were experiencing financial hardship which was the main barrier to accessing healthcare facilities. In this setting, it is common for healthcare to be paid for by the service user as state-funded services are minimal. The following quotes illustrate these points.

My sister-in-law often has arguments with me. She does not take care of my children when they cry (Participant 1). Who will understand? My husband thinks that I am bad. My children also think that I am bad (Participant 3). Participants reported that they were suffering from severe financial hardship because of their partners' unemployment and were unable to access treatment for their ill children which they also had to pay for. My husband stays at home not doing anything. He has not been going to work for the last 2 years (Participant 6). Yes he earns but how much can an ill person earn? (Participant 4). My child falls ill very frequently (Participant 1). There is illness but the actual problem is poverty. We don't have money (Participant 2). Children are becoming timid and frightened; they cry because of the circumstances (Participant 5). Participants were unable to contribute financially to the household because of cultural attitudes against their going out to work[16]. It does not happen in our home (community) that women go for work and men do not go. I will go secretly after my husband will leave for work (Participant 8).

Participants also expressed dissatisfaction with the healthcare services available to them. The participant reported that most of the doctors did not provide adequate attention and appropriate treatment to the patients. She does not provide (proper) treatment; simply gives medicine and injection (Participant 1). Sometimes when a good doctor is available he attends us well, but most of the time they just ignore (Participant 2). He (doctor) does not check properly. Here doctors are just like this. No one checks, they just come and leave (Participant 3). You know well how doctors in the government setup are. They do not listen to us. There are so many patients and doctors do not bother with them (Participant 4). What kind of treatment? I had spiritual treatment but it did not have any benefit; reduced my anger just a little bit (Participant 6). Treatment can be provided by a doctor. He should give medicine and also listen to us (Participant 8).

Women isolated and powerless within the environment

The data suggest that prior to the intervention, women were thinking very little about themselves and felt very alone. They were unable to seek support outside the home and described a sense of "paralysis". Some women reported symptoms of physical illness. They were keeping themselves isolated and felt they had no support. There is no use to share this. Who will understand our problems? (Participant 3). I do work. What can I do? There is no one else who can do my work (Participant 4). Whom should I talk to, who would understand, who

would help? (Participant 7). Because of the lack of support and feelings of helplessness, the participants experienced sadness. Before (intervention) I felt sadness and a lot of anxiety and also felt myself alone (Participant 7). I remained sad and worried all the time before (intervention) and I could not find a solution for any of my problems (Participant 6). Because they were keeping themselves isolated and little support was available to them, the participants expressed this sadness in the form of anger. I get very angry (Participant 1). I cry, remain worried. What else can I do? (Participant 2). I get upset, not knowing what to do. I pray but also get angry (Participant 8). I feel like I want to take poison and kill myself and my children too (Participant 7). I started fighting with others without trying to understand what they were saying. If my husband said anything I would start fighting immediately. I used to say anything in state of anger (Participant 4). Furthermore, because of their emotional state, the participants lost interest in participating in routine activities of their daily life, such as looking after the house and their children. I just sit at home, cannot do anything. I just sit idle (Participant 6). I did not have interest in anything (Participant 1). I do not want to play with my children although I know it's important but still I am not interested in doing this (Participant 5). The disturbed emotional state often provoked them to beat their children which consequently made them feel more upset and guilty. When I was angry, I often used to beat my children (Participant 3). Earlier I used to think bad about myself (Participant 2).

The impact of the intervention

After completing the intervention, the participants were clearly demonstrating a more positive nurturing role. They appeared lesser isolated and were interacting more positively with others. They displayed a sense of empowerment following the intervention and demonstrated that the intervention enabled them to be more confident in their roles.

Now I have become more confident (Participant 2). They appeared now to have the strength and courage to attend to and interact with their children. They were more involved in the care of their children, for example, washing them adequately, teaching them etiquette, and playing with them. Some misconceptions seemed to be present in the community such as mothers believing that showing children their reflection in the mirror will make them ill-that if they showed a mirror to their child, he/she will get mad or get diarrhoea. After participating in the LTP Plus intervention, mothers learned to challenge this belief and appreciate the positive outcomes of using a mirror during child play. These quotes explain these behaviours. Now I feel good, take care of myself and the children as well. Now I do not get obsessed with worries like I was before (Participant 3). Through this program I got more information regarding children; like I did not show mirror to my child before but now I show them mirror (Participant 2).

Yes, we should play with children. They like their parents behaving like a child in front of them. This makes children happy and me as well (Participant 1). What I learned about children is that we should teach them etiquette when they are young. When elders use abusive language children understand that and also repeat that in their mind (Participant 4). I liked the part related to children because I feel happy when my child is happy (Participant 6). I liked the part related to children because before (intervention) I did not treat my children well, dealt with them harshly, but after attending the intervention I learned how to spend time with children and how to understand them (Participant 7). They also developed skills in observing and evaluating others and themselves, and also thinking about others. They were now able to solve problems when faced with difficulties and appeared to be more rational in their thinking about daily life activities. They were now thinking more outwardly, rather than inwardly. My mind has been changed since I participated in the program; now I try to solve my problems myself (Participant 5). We should keep on looking for other solutions; at least one (solution) will definitely work. This encouraged me a lot (Participant 7). Yes, all negative thoughts are gone away (Participant 1).

Empowered, transformed women within the same environment

The facilitator was seen as the catalyst for the change in the women. This was a novel experience for the participants as; previously, many of them did not have anyone to share their personal feelings with. They were happy that the facilitator was a female, and they felt that she provided more support and understood them and their feelings well. The facilitator's role can therefore be likened to a "gardeners role", nurturing the women to enable them to foster and transform within their environment.

She focused on each and every point, talked slowly and thoughtfully (Participant 1). Yes, doctor (interventionist) elaborated things very well and I did not have any problem in understanding. She tried to teach us things very calmly and in a good manner (Participant 2). I liked her style of teaching the most. She used to tell everything very slowly and calmly (Participant 3). No, there was no difficulty (in understanding session) (Participant 5). Sister (interventionist) used to teach us slowly and with love. She repeated the things we did not understand (Participant 6). She tried to teach slowly and with love (Participant 7).

To summarize these findings, the environment that these women lived in before taking part in the intervention can be likened to an "infertile garden landscape" where flora is not able to grow and thrive. Furthermore, the "gardeners", or healthcare providers in this case, are not able to provide any support freely, or to nurture their inhabitants in the surrounding area. When medical help was sought by these women, the assistance was not appropriate and did not meet their needs. This

can be likened to the "gardeners" being somewhat irresponsible and reckless as they did not pay adequate attention to these women and their health concerns. Before the intervention these women can be described metaphorically as "closed, dormant rosebuds in the garden", who were experiencing feelings of loneliness and sadness. However, the data indicate that after participating in the LTP Plus intervention the women can be compared to a "vase of blossoming roses" who are now blooming and prominently emitting confidence, knowledge, and self-assurance. Furthermore, the facilitator or deliverer of the intervention was observed as a nurturer/cultivator who attended to their needs with care, love, and attention. Hence, this role can be likened to a "nurturing gardener" who tends carefully to the plants and foliage in their surrounding landscape. Following the LTP Plus intervention, most of the women's homes (the landscape) were transformed into happy homes where the women were interacting more positively with their children.

DISCUSSION

The qualitative approach and framework analysis method of data analysis has clearly identified themes that provide a detailed explanation for the participants' feelings of psychological distress before the intervention. The method has also enabled the changes to be identified after participating in the study. The participants' environment was characterized by deprivation of financial and economic support. Worry about the employment of the partner and interpersonal conflict have been reported by the participants as a contributing factor for maternal depression. Social adversity has been reported to be associated strongly with maternal depression in differing contexts in previous studies[7]. A study in India reported economic deprivation as a risk factor for maternal depression[26]. Studies reported that unhealthy social environment and experiencing lack of social support (including difficulties in relation to people: Friends, partners, trusted people, and relatives) have strong associations with maternal depression[27]. Results of a qualitative study conducted in four cities of south-western Finland reported that lack of a caring attitude from the husband and controlling and powerful in-laws were associated factors for symptoms of hopelessness. Helplessness and loss of control were noted among Chinese women in Hong Kong suffering from maternal depression[8]. A previous study conducted in Pakistan reported that social support and stress contributed greatly to postnatal depression compared to poverty and financial issues[3]. Women in the present study reported that they were unable to contribute financially as many women in their culture are not allowed to go out for work. South Asian women are dependent on men socially and economically[28] and are restricted not only in their mobility but also in decision-making and use of resources[29]. A qualitative study of postnatal depression across countries and cultures reported that a universally accepted remedy to deal with postnatal depression was to increase social support from the family and emotional support from the husband[1].

A second theme of this study was related to women being isolated and powerless in their environment. This theme was basically about the expression of depression among women. They expressed their depression in the form of sadness, hopelessness, anger, physical symptoms, and lack of interest in the environment. They also reported that they directed their anger to their children. Depression has been reported to be a debilitating disorder with symptoms of low mood, low self-esteem, tiredness, and lack of interest[30]. Research also supports that depressed mothers are tired and unable to concentrate and they experience feelings of guilt, worthlessness, and hopelessness[10]. As these women were often unable to provide proper attention to their children because of their depression, they directed anger towards their children and ultimately felt guilty. Moreover, medically unexplained symptoms (MUS) have been recognized as the most prevalent type of symptoms in primary care[31]. MUS can be the representation of recognized psychiatric disorders such as depression or anxiety and can be manifested in various forms including chronic fatigue syndrome, irritable bowel syndrome, fibromyalgia, or simply as symptoms that exist in the absence of a defined organic diagnosis. Evidence suggests that MUS being more common in Asian and African cultures[32]. Findings from a previous study conducted in Pakistan reported that although the proportion of MUS (35%) was similar to what is reported in the West, unlike western studies MUS were twice as common in women than in men and these symptoms led to inability to perform work[32]. Results of a previous qualitative study reported that women with postnatal depression felt helpless and they somatised their depression[33].

The third theme was related to women reporting the positive effects of the LTP Plus intervention. They felt that they became more empowered after the intervention and their knowledge about child rearing improved. They reported better ways of dealing with their children and improvement in problem-solving and their feelings after attending the intervention. In an earlier qualitative study assessing the role of psychosocial intervention in postnatal depression, women described the intervention as a positive experience and found it acceptable and successful. They also reported a positive impact of the CBT approach in influencing thought patterns that led to positive and negative feelings[34]. The LTP intervention was reported to be effective in increasing mother's knowledge of child development[35]. Results of a previous study testing the Thinking Healthy Program (THP) based on the principles of CBT reported that rates of depression were reduced among women receiving this intervention compared to those receiving enhanced routine care. Women in the intervention group experienced more symptomatic relief, and better social adjustment than the comparison group[19]. This was the first time a combination of both interventions was tested, *i.e.*, LTP and CBT (THP).

It led to improvement in mother-child interaction and reduction in depression, as reported by the participants.

The final theme was about the satisfaction of the participants with the LTP Plus group facilitator. They reported that the facilitator helped them to feel empowered even within their difficult environment. Participants appreciated the communication style and patience of the facilitator. The relationship between the role of communication and the effectiveness of intervention for reducing depression in primary care has already been explored[36]. It is recommended that all the healthcare providers dealing with maternal depression should adopt a non-judgmental and accepting approach[34].

Strengths and limitations of the study

There was a high participation rate, with 15 out of 25 (60%) eligible women agreeing to participate in the study. The framework analysis process and the integral phases work well when supervising at a distance as each stage provides a logical opportunity for discussion and review with team members. This fostered a thorough and comprehensive consideration of all aspects of the research process. The multidisciplinary backgrounds of the research team (mental health, midwife, clinical psychologist, research) facilitated emergence of key ideas in the data. Because of the small sample size, the findings cannot be generalized. Moreover, female facilitators were more acceptable to the participants. The findings from women with mild to moderate depression may not be extrapolated to women with severe depression. Some interviews were not as detailed as others because women in this context are not used to accessing services and discussing their problems. Seeing health professionals is not a common practice and thus they are not familiar with talking about their feelings. Thus, the interview experience is slightly novel to them.

Reducing child mortality and morbidity has received attention as a Millennium Development Goal worldwide. However, in low and middle-income countries the process of development of cost-effective psychosocial interventions to achieve such a goal is slow. The present study gives direction in developing and testing culturally-appropriate psychosocial interventions for reducing maternal depression in order to work towards the sustainable development goal.

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COMMENTS

Background

Prevalence is much higher in developing countries such as India (28%) and South Africa (34.7%). The prevalence rate is even higher among Pakistani women, *i.e.*, 36%. Results of cohort studies from developing countries including South Africa, Pakistan and India report strong associations between maternal depression and stunted growth. In Pakistan, intervention based on the principles of cognitive behaviour therapy (CBT) was found to be effective in reducing depression and disability and in improving social functioning. However studies highlighted inability to disclose feelings, the presence of myths and lack of knowledge as barriers to help-seeking behaviours in women suffering from depression.

Research frontiers

Major changes occur during the postnatal period which determines the well-being of mothers and newborns, but unfortunately this is the most neglected period in terms of provision of quality services. Maternal depression accounts for the largest proportion of burden associated with mental or neurological disorders and have strong association with increased child mortality. There is now evidence from some low income countries that effectively delivered psychosocial interventions that are cost effective for improving maternal and child health.

Innovations and breakthroughs

This study was a part of a randomized controlled trial in which the acceptability and feasibility of a group psychosocial intervention [Learning through Play (LTP) Plus] was tested to reduce maternal depression and improve child outcomes. The LTP program focuses on the strategies to stimulate early child development. A pictorial calendar is the main feature of this program that is designed for parents and includes eight successive stages of child development from birth to 3 years. The second component of the psychosocial intervention was CBT that was aimed at changing negative thought patterns. CBT based intervention called Thinking Healthy Program (THP) was successfully tested to reduce postnatal depression in rural area of Pakistan. A parent based intervention LTP was also tested in the same setting that led to the improvement in knowledge, attitude and practices of depressed mothers about child development, however no reduction was found in maternal distress. Therefore the aim of the present study was to explore the acceptability and feasibility of combination of two interventions, *i.e.*, LTP plus THP (LTP Plus) to reduce maternal depression and improve child health.

Applications

The present study is the first qualitative study conducted in Pakistan to explore the role of culturally adapted intervention to improve maternal mental health and child health outcomes for undernourished children brought to paediatric units. There is a need to conduct such studies so that this low cost culturally appropriate intervention can be integrated into the existing health care system to improve maternal and child health in Pakistan and other low income countries.

Terminology

Framework analysis: Framework analysis is a method of qualitative analysis and it is case and theme based approach, reduces data through summarization, retains links to original data, and allows comprehensive and transparent data analysis; THP: THP is based on principles of CBT like listening, identifying and changing negative thoughts and emotions, problem solving skills, *etc.*; Cultural adaptation: Cultural adaptations are changes to intervention content or process that addition, deletion, or alteration to the components, changes in intensity of the intervention and cultural or other contextual modifications.

Peer-review

It is well written.

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ORIGINAL ARTICLE

Observational Study

Childhood trauma and factors associated with depression among inpatients with cardiovascular disease

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Abstract

AIM

To identify factors associated with depressive symptoms

among inpatients with cardiovascular disease (CVD).

METHODS

This is a cross-sectional study performed in a subsample of a large cross-sectional research that investigated affective disorders and suicide behaviour among inpatients hospitalized in non-surgical wards of the University Hospital of the Federal University of Minas Gerais from November 2013 to October 2015. Sociodemographic and clinical data were obtained through a structured interview and medical record review. Depression was assessed by the depression subscale of the Hospital Anxiety and Depression Scale, with scores $\geqslant$ 8 considered as positive screening for depression. We used the Fagerström Test for Nicotine Dependence to characterize nicotine dependence. For assessing resilience and early-life trauma, we used the raw scores of the Wagnild and Young Resilience Scale and Childhood Trauma Questionnaire, respectively.

RESULTS

At endpoint, we included 137 subjects. Thirty-eight (27.7%) subjects presented depressive symptoms and nine (23.7%) of those were receiving antidepressant treatment during hospitalization. The female sex; a lower mean educational level; a greater prevalence of previous suicide attempts; a higher level of pain; a higher prevalence of family antecedents of mental disorders; a lower resilience score; and higher childhood trauma score were the factors significantly associated with screening positive for major depression ($P < 0.05$). Multivariate analysis demonstrated that the factors independently associated with the depressive symptoms were a higher childhood trauma severity (OR = 1.06; $P = 0.004$); moderate to severe nicotine dependence (OR = 8.58; $P = 0.008$); and the number of previous hospital admissions (OR = 1.11; $P = 0.034$). The obtained logistic model was considered valid, indicating that the three factors together distinguished between having or not depressive symptoms, and correctly classified 74.6% of individuals in the sample.

CONCLUSION

Our results demonstrate that inpatients presenting both CVD and a positive screening for depression are more prone to have antecedents of childhood trauma, nicotine dependence and a higher number of previous hospitalizations.

Key words: Inpatients; Depression; Cardiovascular disease; Depressive symptoms; General hospital

Core tip: The prevalence of depression is considerably higher among individuals with cardiovascular diseases (CVD) when compared to the general population. Both major depression and depressive symptoms are predictors of poor outcome in patients with CVD. Depressive disorder is frequently overlooked and untreated in individuals with CVD. Our results demonstrate that inpatients presenting both CVD and a positive screening for depression are more prone to have antecedents of childhood trauma, nicotine dependence and a higher number of previous hospitalizations. Clinicians may consider these factors in the assessment of CVD inpatients at risk for major depression. This measure can improve their treatment approach and patients' prognosis.

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INTRODUCTION

The prevalence of major depressive disorder (MD) is four times higher among individuals with cardiovascular diseases (CVD) when compared to the general population[1-4], and MD is a predictor for future CVD. MD increases the risk for coronary arterial disease (CAD) by 56%, independent of other traditional cardiovascular risk factors[1]. Moreover, MD and depressive symptoms are predictors of poor outcome in patients with CVD regarding morbidity and mortality[2,3].

Maltzberg[4] first reported the bidirectional relationship between MD and CVD in 1937. This author observed an increase in mortality from CVD in patients with severe depression. More recently, some authors reported that post-myocardial infarction depression increases the risk of all-cause mortality (RR = 2.25) and of cardiac events (RR = 1.59) within 24 mo after the event[5]. Even in the absence of depressive symptoms, a positive history of depression in first-degree relatives may influence the cardiovascular risk profile in adulthood, comparing to control group[6].

Various biological modifications, previously found in patients with depression, may explain these findings. An increased concentration of inflammatory biomarkers (C-reactive protein, interleukins 1 and 6), metabolic dysregulation, dysfunctions in the platelet clotting cascade, decreased variability in heart rate, hyperactivation of hypothalamus-pituitary-adrenal axis and reduction in circulating endothelial progenitor cells are some of the factors that may be at the pathophysiological origin of the association between depression and CVD[2,7-9]. Finally, both depression and CVD have notorious genetic determinants, which may underlie the development of one and another as shared risk factors[2,10]. Even acute and chronic life stressors may increase the risk for developing one of these diseases[2,10]. Adverse events in early life can directly affect genome through epigenetic mechanisms and contribute to the expression or exacerbation of a genetic susceptibility for depression, CVD or both in adulthood[2].

During hospitalization, depression decreases inpatients'

treatment adherence, increases functional disability and extends hospital length of stay[11,12]. Inpatients with CVD presenting positive screening for depression at discharge have a 2.5 fold increase in relative risk of experiencing a CVD-related hospitalization, even after adjustment for traditional cardiovascular risk factors and measures of disease severity[13].

Depression is still a frequently overlooked and untreated condition among individuals with CVD[14,15]. The same applies for those admitted to general hospitals, a population in which 28% present criteria for depressive disorders[16]. Less than one in four cases of major depression among inpatients are correctly diagnosed by assisting physicians[14]. In addition, only half the members of the American College of Cardiologists treat depression properly, according to a national survey[17].

Inpatients with CVD have increased vulnerability for depression. Improving the knowledge on how much risk factors influence the chances of becoming depressed may improve identification of MD among this population in the general hospital setting. We hypothesized that inpatients presenting both CVD and a positive screening for major depression are more prone to be of female sex; to present personal and familiar antecedents of psychiatric disorders (*e.g.*, suicide attempts, addictions); to present worse indicators of CVD (*e.g.*, increased number of previous hospital admissions, present pain and a worse score of functionality); and present lower resilience and antecedents of childhood trauma. Our primary goal was to assess the factors mentioned above in a population of inpatients with CVD in a university hospital.

MATERIALS AND METHODS

This cross-sectional design study encompassed a subsample of a larger study that investigated suicide behaviour among general hospital inpatients. We included all inpatients admitted to the wards of the University Hospital of the Federal University of Minas Gerais (UH-UFMG), hospitalized from November 2013 to October 2015. The UH-UFMG is a tertiary regional reference centre.

The Committee of Ethics in Research of UFMG approved the protocol, registered with the number CAAE 13605213.3.0000.5149. We obtained written informed consent from all participants, after providing a complete description of the study. All subjects screening positive for a psychiatric disorder received consultation-liaison psychiatric evaluations.

Subjects

For the initial study, we included inpatients aged 18-year-old or older, hospitalized in a clinical ward and excluded patients hospitalized with surgical indication. In the present study, we selected all patients with a diagnosis of CVD (*e.g.*, CAD, congestive heart failure, Chagas cardiomyopathy, cardiac arrhythmia or any other cardiac disease that required hospitalization) and excluded subjects screening positive for delirium and mild to severe cognitive impairment or dementia as well as those unable to comprehend, illiterate or with major visual or hearing impairment. We summarized the inclusion procedure in the flowchart (Figure 1).

Instruments and procedures

After a clinical assessment and stabilization, we included all subjects at admission. Experienced psychiatrists, trained to perform the assessments foreseen in the study protocol, evaluated the subjects. All the scales used in this study had been previously translated and culturally adapted to Brazilian Portuguese.

We screened delirium using the Confusion Assessment Method[18] and cognitive impairment through the Montreal Cognitive Assessment[19] using 17 as a cut-off point[20].

For screening MD, we used the Hospital Anxiety and Depression Scale (HADS-d). This scale has acceptable properties for use in inpatients with CVD[21]. Scores of $\geqslant$ 8 indicate a positive screening for depression, according to the Brazilian validation study that issued a sensibility of 84.6% and specificity of 90.3%[22].

We used the visual analogue scale to assess pain intensity[23]. We determined the basic and instrumental activities of daily living (ADL) using the Katz Index and the Pfeffer's Functional Activities Questionnaire (PFAQ), respectively[24]. We considered scores $\geqslant$ 5 in the PFAQ as characteristic of dependence on instrumental ADL[25].

We considered a score $\geqslant$ 8 on the Alcohol Use Disorders Identification Test to assess problematic alcohol use[26] and a score $\geqslant$ 4 on the Fagerström Test for Nicotine Dependence to characterize moderate to severe nicotine dependence[27].

We considered the levels of positive psychosocial adjustment given major life events, like resilience, and used the Wagnild and Young Resilience Scale (WYRS) to evaluate resilience level. The WYRS is a paper-and-pencil scale, composed of 25 likert-type items[28] and, as the validation study did not establish a cut-off point, we used the raw results in our analysis. For assessing early-life trauma we used the Childhood Trauma Questionnaire (CTQ)[29]. The CTQ is a 28-item self-report inventory that provides a valid screening for early life abuse or negligence.

Statistical analysis

In the descriptive analysis, we calculated measures of central tendency and dispersion. The Shapiro-Wilk test assessed data normality. For univariate analysis, a χ^2 test was considered for categorical variables and Mann-Whitney test for continuous variables. To determine which factors had a greater association with positive screening for depression in our sample, we conducted a multiple logistic regression with stepwise selection. Those variables with P value $\leqslant$ 0.2 in univariate analysis were apt to enter the model. The χ^2 test model and Nagelkerke's R^2 used to evaluate the predictive ability of the logistic model obtained. Calculation of odds ratios (OR) considered a 95%CI and significance of $P < 0.05$.

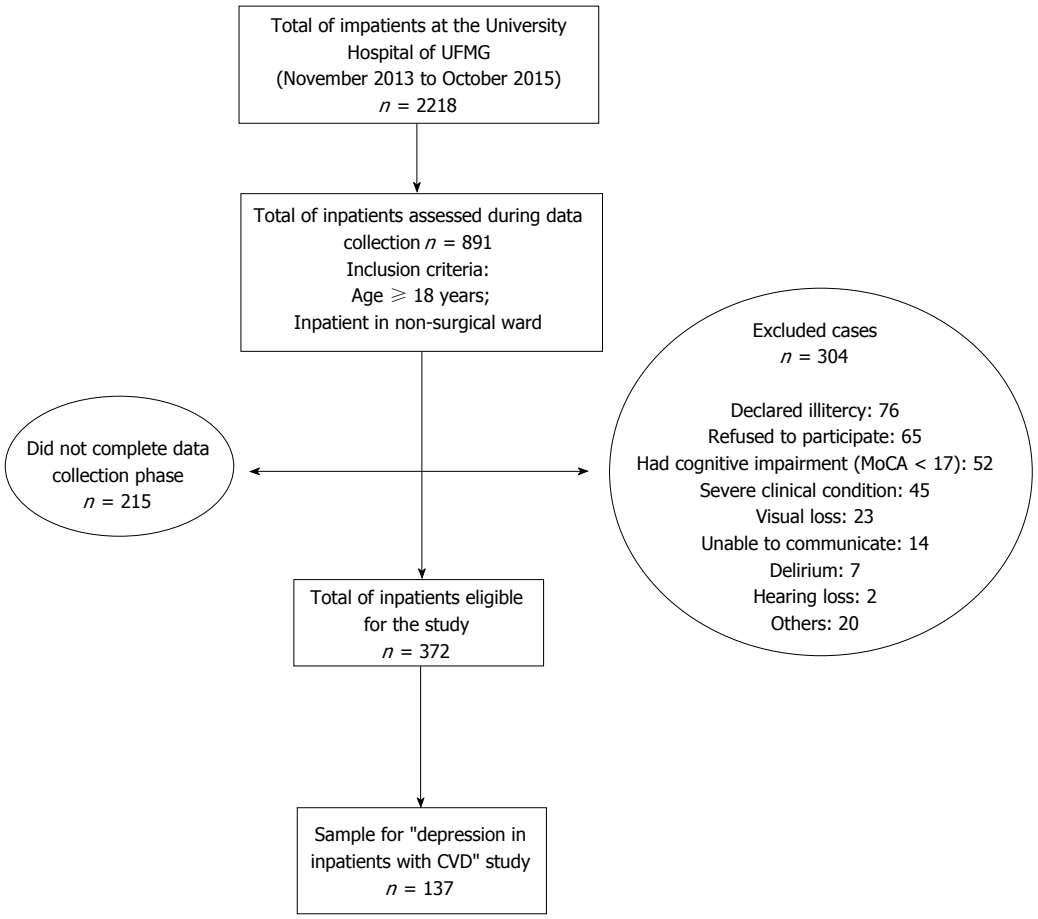

Figure 1 Flowchart of subjects included in the study. UFMG: The Federal University of Minas Gerais; CVD: Cardiovascular disease.

All analyses were performed using SPSS software version 20 (IBM Corporation© 2011).

RESULTS

Sample description

At endpoint, we included 137 subjects and found a higher prevalence of males [*n* = 92 (67.2%)], a mean age of 52.1 ± 12.5 years old and a mean educational level of 8.5 ± 4.4 years. The most prevalent CVD diagnoses were CAD (*n* = 76; 55.5%), congestive heart failure (*n* = 43; 31.4%) and cardiac arrhythmia (*n* = 15; 10.9%). CAD, the most frequent cardiovascular diagnosis, was not associated with positive screening for major depression. Seventy-five (54.7%) and 23 (16.8%) subjects presented hypertension and diabetes mellitus, respectively.

Factors associated with positive screening for depression

Thirty-eight (27.7%) subjects screened positive for depression and nine (23.7%) were taking antidepressants during hospitalization. Female sex, lower mean educational level, greater number of previous suicide attempts, higher level of pain, higher prevalence of family antecedents of mental disorders, lower resilience score and higher childhood trauma score were the factors significantly associated to screening positive for major depression (Table 1).

Three factors remained statistically associated with a positive screening for depression (Table 2) in multivariate analysis: (1) childhood trauma; (2) moderate or severe nicotine dependence; and (3) the number of hospital admissions.

Patients with moderate and severe nicotine dependence were 8.58 times more prone to screen positive for depression ($P = 0.008$).

The chance to screen positive for depression increased 11% for each hospital admission ($P = 0.034$) and 6% for each point of increase in the CTQ score for childhood trauma ($P = 0.004$).

The logistic model indicated that the three factors together distinguished between positive screening for depression or not, and correctly classified 74.6% of individuals in the sample (χ^2: 17.974, $P < 0.001$, D.F. = 1; Nagelkerke R^2: 0.33).

DISCUSSION

This study assessed the influence of the factors associated with positive screening for depression in a sample of patients with CVD hospitalized in a university hospital. After multiple comparisons, we found that positive screening for depression was significantly associated with

Table 1 Factors associated with positive screening for depression (Hospital Anxiety and Depression scale - depression subscale score ≥ 8) in inpatients with cardiovascular diseases (*n* = 137) *n* (%)

	Screening for depression		Missing data (%)	*P* value
	Yes	No		
Sociodemographic variables				
Gender				
Male	15 (39.5)	77 (77.8)	-	< 0.001[a]
Female	23 (60.5)	22 (22.2)	-	
Age, mean (SD)	53.7 ± 11.4	51.5 ± 12.8	-	0.444
Elder (aged ≥ 60 yr)	15 (39.5)	24 (24.2)	-	0.077
Educational level in years (mean ± SD)	7.4 ± 4.4	8.5 ± 4.3	1.5	0.035[b]
Married/lives with partner	25 (65.8)	70 (70.7)	0.7	0.723
Lives alone	3 (8.1)	9 (9.1)	0.7	0.857
Any son	34 (91.9)	83 (84.7)	1.5	0.272
Unemployed	9 (24.3)	23 (23.5)	1.5	0.917
Religion	35 (94.6)	91 (91.9)	0.7	0.595
Clinical variables				
N° of previous hospital admissions, mean (SD)	7.6 ± 9.1	5 ± 5.2	5.8	0.07[b]
CAD	18 (47.4)	58 (58.6)	-	0.237
Congestive heart failure	12 (31.6)	31 (31.3)	-	0.976
Cardiac arrhythmia	5 (13.3)	10 (10.1)	-	0.76
Hypertension	19 (50)	56 (56.6)	-	0.489
Diabetes mellitus	5 (13.2)	18 (18.2)	-	0.481
Pain level, mean (SD)	2.2 ± 2.9	1.3 ± 2.4	0.7	0.136
Propranolol	8 (21.1)	12 (13.5)	8.0	0.255
Dependence in basic ADL	10 (26.3)	14 (14.1)	0.7	0.09
Dependence in instrumental ADL	2 (22.2)	4 (17.4)	76.6	0.753
Psychosocial variables				
Family history of mental disorder	18 (47.4)	20 (20.2)	-	0.001[a]
Previous suicide attempt	11 (28.9)	8 (8.2)	0.7	0.002[a]
Moderate to severe nicotine dependence	7 (18.4)	10 (10.1)	-	0.186
Problematic alcohol use	7 (30.4)	13 (18.84)	32.8	0.243
Resilience score, WYS mean (SD)	138.5 ± 14.5	144.9 ± 14.9	2.9	0.029[b]
Childhood trauma score, CTQ mean (SD)	46.4 ± 20.1	37.5 ± 12.6	8.8	0.004[b]

[a]χ^2 test significant if $P < 0.05$; [b]Mann-Whitney test significant if $P < 0.05$. CAD: Coronary arterial disease; ADL: Activities of daily living; WYS: Wagnild and Young Scale; CTQ: Childhood Trauma Questionnaire.

Table 2 Logistic regression analysis of factors associated with positive screening for depression (Hospital Anxiety and Depression scale - depression subscale score ≥ 8) in inpatients with coronary arterial disease

Variable	B	EP	Wald	OR	95%CI	*P*
Moderate to severe nicotine dependence	2.15	6.91	7.135	8.58	1.77-41.57	0.008
N° of previous hospital admissions	0.106	0.06	4.505	1.11	1.01-1.23	0.034
High childhood trauma severity (CTQ)	0.06	0.02	8.2	1.06	1.02-1.11	0.004
Constant	-4.664	0.01	16.141	0.01	0.00-0.09	< 0.001

χ^2: 17.974, $P < 0.001$, D.f. = 1; Nagelkerke R^2: 0.33. CTQ: Childhood Trauma Questionnaire.

childhood trauma, the severity of nicotine dependence, and the number of previous hospital admissions. These results partially agree with our initial hypothesis as no association was found with some of the factors previously related with major depression, such as: Personal and familiar antecedents of psychiatric disorders (*e.g.*, suicide attempts, addictions), pain perception, a worse score of functionality, and a lower resilience level. To the best of our knowledge, only one study reported risk factors associated with depression in patients with CVD[30]. However, no study evaluated such a vast array of epidemiological, clinical and psychological factors associated with depression in patients hospitalized with CVD.

Our results should be regarded considering a few issues. First, our study has a cross-sectional design and, as such, hinders the evaluation of causality between the factors evaluated and major depression. Second, our sample included patients with different types of CVD. We have grouped the distinct disorders in a unique group as they share common risk factors and etiological mechanisms associated with inflammatory processes; previous studies have adopted this same strategy[30]. Finally, we have not been able to assess the severity of CVD with an objective measure within this study.

Our sample presented a rate of 27.7% of patients screening positive for depression. This result is comparable with previous studies, which reported a prevalence of

13.5% to 47% of major depression in inpatients with CVD[16,30-33]. Different from previous studies, that reported only 5% of patients with CVD and depression were being treated with antidepressants[33], in our sample, 23.7% of the subjects were taking an antidepressant.

Stressful experiences during the lifespan have been associated with CVD[34] and depression[35]. Childhood trauma is one of the most significant predictors of health problems, life expectancy, psychiatric disorders and the severity of clinical diseases' courses[36]. The occurrence of childhood trauma can influence the development of CVD through changes in metabolic, cardiovascular risk factors like dyslipidemia, central obesity, and hyperglycemia. A Dutch cohort study found that among the childhood trauma subtypes and personality traits, sexual abuse was the primary factor that correlated negatively with serum cholesterol and abdominal circumference measurements[37]. Recurrent stressful events may induce a subtle chronic inflammatory response, enough to contribute to the progression of atherosclerosis and increased the risk of developing CAD[38]. Our results highlight the importance of the assessment of childhood trauma in patients with CVD, as the severity of trauma may predict depression in this population. Clinicians must consider that one possible mechanism of the association between childhood trauma, depression and CVD is the disruption of the key stress-response system, such as the catecholamine system, the hypothalamic-pituitary-adrenal axis, and neurotrophic factors, in early stages of child development. The impairment of the stress response system can influence arousal and emotional behaviour and contribute to increase the allostatic load, impairing brain development and increasing the risk for psychopathology[36].

As reported in the paper of Caro *et al*[30], our results point that nicotine dependence is associated with a positive screening for depression in CVD inpatients. Nicotine dependence is more prevalent in individuals with depression, possibly because these subjects are less prone to engage in smoking cessation programs[9] and tend to use nicotine to alleviate anxiety and dysphoria[39]. As other risk factors for CVD, cigarette use has been associated with damage of the arterial wall. Moreover, the intensification of cigarette use maintains inflammatory response, like chronic stress, and increases risk for depression and CVD[2]. Also, both depression and CVD increase the systemic pro-inflammatory state[2,7], aggravating the pathophysiological mechanisms related to CVD and closing a vicious cycle[38].

Presenting a greater number of previous hospital admissions was another factor associated with positive screening for depression in our study. These results agree with previous findings regarding inpatients with several medical illnesses[32]. Compared to those without depression, medical inpatients suffering from depression have longer hospital stays and higher readmission rates. Both factors underline the burden of this affective disorder among CVD patients, including the financial burden[12,40]. Moreover, each hospital admission can represent an acute stressor for those who experience it, raising negative feelings about an individual's current health state and prognosis, augmenting depressive symptoms. In the same manner, a higher number of hospitalizations may represent a proxy for CVD severity. Other CVD severity measures were significantly associated with depression in inpatients, namely having an implantable cardioverter defibrillator or being in functional class Ⅲ or Ⅳ[33].

How can we link these three factors to CVD and major depression? In our view, either childhood trauma, nicotine dependence and the number of previous hospitalizations have been associated with stress arousal and pro-inflammatory states. Both conditions are well-known risk factors for major depression and CVD[36].

Our results demonstrate that inpatients presenting both CVD and a positive screening for major depression are more prone to have antecedents of childhood trauma, nicotine dependence and a higher number of previous hospitalizations. Clinicians may consider these factors in the assessment of CVD inpatients at risk for major depression. This measure can improve their treatment approach and patients' prognoses.

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COMMENTS

Background

The prevalence of depression is considerably higher among individuals with cardiovascular diseases (CVD) when compared to the general population. Both major depression and depressive symptoms are predictors of poor outcome in patients with CVD. Depressive disorder is frequently overlooked and untreated in individuals with CVD.

Innovations and breakthroughs

This study assessed the influence of the factors associated with positive screening for depression in a sample of patients with CVD hospitalized in a university hospital. After multiple comparisons, the authors found that positive screening for depression was significantly associated with childhood trauma, the severity of nicotine dependence, and the number of previous hospital admissions.

Applications

The results demonstrate that inpatients presenting both CVD and a positive screening for major depression are more prone to have antecedents of childhood trauma, nicotine dependence and a higher number of previous hospitalizations. Clinicians may consider these factors in the assessment of CVD inpatients at risk for major depression. This measure can improve their treatment approach and patients' prognoses.

Peer-review

This is a cross-sectional survey of risk factors associated with depression in patients hospitalized in non-surgical wards and suffering in cardiovascular disease. As both cardiovascular diseases and depression are frequent and possessing a great burden on the family and the society, the study is relevant and interesting.

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ORIGINAL ARTICLE

Observational Study

Relation of binge eating disorder with impulsiveness in obese individuals

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Abstract

AIM

To investigate the levels of impulsiveness, and the relationship between the binge eating disorder (BED) and the levels of impulsiveness in obese individuals.

METHODS

Two hundred and forty-one obese patients who were included in the study and candidate for bariatric surgery (weight loss surgery) were clinically interviewed to identify the BED group, and patients were divided into two groups: Those with BED and those without BED. The comorbidity rate of groups was determined by using structured clinical interview for DSM-Ⅳ (SCID-Ⅰ). A sociodemographic data form including the story of previous psychiatric treatment, structured clinical interview for DSM-Ⅳ (SCID-Ⅰ), Beck Anxiety Inventory, Beck Depression Inventory (BDI) and Barratt Impulsiveness Scale-11 were applied to both of the groups.

RESULTS

In regard to 241 obese individuals included in the study, total score and score of attention subscale for BED (+) group were significantly high ($P < 0.05$). In addition, suicide attempt, story of psychiatric consultation, and score for BDI were again significantly high in the BED (+) group ($P < 0.05$).

CONCLUSION
In assessment of obese individuals, assessment of associated psychopathology such as impulsive characteristics and suicide attempt in addition to disrupted eating behaviors will allow to have a more extensive view.

Key words: Binge eating; Obesity; Impulsiveness

Core tip: Impulsiveness is a multidimensional personality trait that leads to uncontrolled and excessive intake of food, thus contributing to development and maintenance of obesity. Obese patients who were included in the study and candidate for weight loss surgery were clinically interviewed to identify the binge eating disorder (BED) group and patients were divided into two groups: Those with BED and those without BED. Impulsivity, suicide attempt, story of psychiatric consultation, and score for depression were significantly high in the BED (+) group. Impulsive characteristics and suicide attempt in addition to disrupted eating behaviors will allow to have a more extensive view.

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INTRODUCTION

Over the past 30 years, the prevalence of obesity has been gradually increased worldwide and the obesity is regarded as one of the major problems for community health[1,2]. Furthermore, obesity is a condition associated with reduced life expectancy[3]. Impulsiveness is a multidimensional personality trait that leads to uncontrolled and excessive intake of food, thus contributing to development and maintenance of obesity[4,5].

After defined by Albert Stunkard for the first time[6], research on binge eating disorder (BED) has been increasingly growing in time. While BED is included in the eating disorder not otherwise specified in the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders 4th revised edition), it is reclassified alone[7] under a separate title for diagnosis in the DSM-5[8] published in May 2013. So, the BED is classified as a standard eating disorder as Anorexia Nervosa and Bulimia Nervosa[9]. Redefining BED has not changed the diagnostic criteria, but time criteria for incidence of BED attacks is reduced in order to facilitate diagnosis of BED. Such changes may be seen as increased importance of BED diagnosis category.

The binge eating behavior is largely associated with obesity and defines a subgroup of individuals with excessive eating that shows significant differences[10]. The BED may be seen in general society, but is mostly seen in obese individuals and in groups seeking a therapy for obesity[11]. The BED is characterized by compulsively eating a large amount of food without balancing behavior and it is the most common eating disorder in the obese patients[7]. Although the prevalence of BED varies in a wide range in the obese population, it may be as high as 30%-57% in obese individuals seeking for a therapy and morbidly obese individuals who are candidate for bariatric surgery[11-14]. In a multi-center fieldwork including 1984 cases, the prevalence of BED was 2% in the general population and 30.1% in the population participating in hospital-supported weight control programs[15]. The rate for BED was 23.1% in a study including 281 non-obese university students in our country[16]. In other studies performed on obese patients in our country again, the rates for BED were 22.4% and 23%, respectively[17,18].

Failures in the bariatric surgery are attributed to psychological factors and/or eating disorders rather than technical causes[19]. Impulsiveness may be a predictor for poor prognosis and negative outcomes in eating disorders[20,21]. The presence of BED may cause to regain the weight that has been lost after bariatric surgery[22-24]. However in our study, there was no significant differences between the mean body mass index (BMI) of BED (+) and BED (-) groups. The reason for this result can be related with that BED might be affecting the recovery of the lost body weight, not the initial weight loss.

Increasing number of literatures suggest that eating disorders are associated with impulsiveness especially when binge eating is prominent[25,26]. The literature has studies indicating that those with BED have higher impulsive characteristics[27-31]. There is a study performed in our country that found that impulsiveness was higher in the obese individuals than that of normal control group and overweight[32]. Another Turkish study showed that morbidly obese patients had higher impulsiveness than healthy control[33].

The obesity is an area where increasingly more studies are performed about the relationship between BED and impulsiveness. Our study has relatively higher number of patients, including morbidly obese and super morbidly obese patients who were candidate for bariatric surgery. The objective of this study was to investigate the relation of BED with impulsiveness in obese patients and to provide a more extensive view on assessment of disrupted eating behavior based on the obtained results.

MATERIALS AND METHODS

Methods

Two hundred and forty-one obese patients were successively included in the study, who admitted to Bagcilar Training and Research Hospital for bariatric surgery between July 2012 and October 2013 and transferred to psychiatry service for consultation. Thirty-four (14.1%) of 241 morbidly obese patients were obese, 150 (62.2%) were morbidly obese, and 57 (23.7%) were super-

morbidly obese. These individuals were included in this study performed as part of a comprehensive review on disorders associated with obesity. Among the individuals included in the study, 60 (24.9%) were males and 181 (75.1%) were females. A clinical interview was performed with obese patients to identify the BED group. The patients were divided into two groups according to administrated structured clinical interview for DSM-IV (SCID-I) BED comorbidity rate. The age range for patients was between 16 and 61 years. The individuals who were illiterate, who stated that they were unable to complete the scales, and who voluntarily wished to discontinue during the study were excluded from the study. The exclusion criterias were: Having a psychological disease affecting reasoning, substance use, pregnancy, and any disease restricting ability to move.

The participants were administrated a sociodemographic assessment form including eating habits and diet characteristics, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Barratt Impulsiveness Scale-11 (BIS-11).

The volunteers participated in the study were asked to sign an informed consent form. It was clearly explained in detail that responses to scales provided by participants would not affect the surgical process. Approval of ethics committee of Bagcilar Training and Research Hospital was obtained for the study.

Materials

The sociodemographic data form: Developed by the researchers to collect research data, this form included sociodemographic characteristics of volunteers (age, gender, education and marital status) and questions about disease-related characteristics.

The structured clinical interview for DSM-IV Axis I disorders: A diagnostic scale developed by First *et al*[34] (1997). SCID-I has been translated into Turkish and validity and safety studies have been performed[35].

The BDI: One of the most frequently used scales for mental health screening or research on depression. It was developed by Beck in 1961. It is a self-report measure and has 21 items with 15 including psychological symptoms and 21 including somatic symptoms. The highest score to get is 63. A higher score indicates increase in complaints for depression. The cutoff score was 17 in the study performed by Hisli for validity and safety, and the author reported that scores equal to or higher than 17 were able to differentiate a depression requiring therapy with 90% of accuracy[36,37].

The BAI: This inventory comprises of 21 questions. It is a self-report measure. Each question is assessed between 0 and 3 scores and the high scores indicate the severity of anxiety experienced by individual. So, total score to get from this inventory ranges from 0 to 63. This inventory was developed by Beck (1988) and standardized for Turkish version by Ulusoy[38] (1993).

The BIS-11: Developed by Patton *et al*[39] in 1995. It is completed by patients to assess impulsiveness. Four different sub-scores are obtained from BIS-11; total score includes non-planning, attention and motor impulsivity. The higher total score from BIS-11 indicates the higher level of impulsiveness of the patient. The validation and safety study for Turkish version of BIS-11 was performed by Güleç *et al*[40].

Statistical analysis

The data were entered into the computer using SPSS 15.0 (Statistical Package for Social Science). The data were assessed by parametric and non-parametric statistical analyses based on the distribution of data. For quantitative evaluation, Mann-Whitney *U* or Student-*t* test was used for pairwise comparison. Kruskall-Wallis test was used for triple comparisons. χ^2 test was performed for qualitative evaluation. $P < 0.05$ was considered significant.

RESULTS

After psychiatric interviews conducted, 75 (31.1%) of 241 obese patients were diagnosed with BED. The BED (+) group was composed of 62 (82.7%) female and 13 (17.3%) male patients. The mean of BMI of BED (+) and BED (-) groups was compared and there were no significant differences between values which were 46.6 and 45.5 respectively. In comparison of sociodemographic data, no statistically significant differences were found between groups (Table 1). Ceasing smoking cigarette in the last six months was assessed for groups in order to exclude the influence of ceasing smoking on the weight, and no statistically significant differences were found.

The comparison of rates for previous psychiatric admittance of BED (+) and BED (-) groups of obese individuals were 49.3% and 30.1% respectively. The differences were statistically significant ($P < 0.05$). However, no statistically significant differences were found in comparison of BED (+) and BED (-) groups 8.0% and 3.0% respectively, for psychiatric comorbidity at the time of study ($P > 0.05$) (Table 2).

The difference was statistically significant in comparison of thinking of suicide in any phases of life of BED (+) and BED (-) groups of obese individuals 34.7% and 15.7% respectively and previous attempts to suicide 21.3% and 8.4% respectively ($P < 0.05$) (Table 2).

The scores of BED (+) and BED (-) groups were 20.04 ± 11.08 and 14.77 ± 8.40, respectively, in comparison of scores from BDI of two groups. The difference was statistically significant ($P < 0.05$) (Table 3).

The groups were compared for scores from BAI and the scores of BED (+) and BED (-) groups were 16.72 ± 11.76 and 13.70 ± 9.78, respectively. The difference was not statistically significant ($P > 0.05$) (Table 3).

While no significant differences were found between BED (+) and BED (-) groups in non-planning 26.59 ± 5.32 and 25.82 ± 4.34 respectively and motor sub-scales

Table 1 Comparison of the sociodemographic and clinical characteristics of the binge eating disorder (+) and binge eating disorder (-) group

		Overall		BED (+) group		BED (-) group		*P*
Age		36.49 ± 10.14		35.05 ± 9.61		37.13 ± 10.33		0.141
Sex	Females	181	75.1%	62	82.7%	119	71.7%	0.068
	Males	60	24.9%	13	17.3%	47	28.3%	
Marital status	Maried	154	63.9%	48	64.0%	106	63.9%	0.983
	Single	87	36.1%	27	36.0%	60	36.1%	
Education level	Primary	81	33.6%	28	37.3%	53	31.9%	0.62
	Middle	107	44.4%	30	40.0%	77	46.4%	0.62
	High	53	22.0%	17	22.7%	36	21.7%	0.62
Physically active	Yes	179	74.3%	55	73.3%	124	74.7%	0.874
	No	62	25.7%	20	26.7%	42	25.3%	
Weight (kg)		124.82 ± 18.23		124.37 ± 17.57		125.03 ± 18.57		0.796
BMI		45.89 ± 6.08		46.69 ± 6.69		45.53 ± 5.76		0.195
Cigaret (yr)		6.23 ± 8.35		5.45 ± 7.56		6.58 ± 8.68		0.331
Quit smoking in the last six months		31 (12.9%)		6 (8%)		25 (15.1%)		0.130

BED (+): Group with binge eating disorder; BED (-): Group without binge eating disorder; BMI: Body mass index.

Table 2 Comparison of the psychiatric and suicidal features of the binge eating disorder (+) and binge eating disorder (-) group

		Overall		BED (+) group		BED (-) group		*P*
Previous psychiatric admittance	Yes	87	36.1%	37	49.3%	50	30.1%	0.004
	No	154	63.9%	38	50.7%	116	69.9%	0.004
Psychiatric comorbidity	Yes	11	4.6%	6	8.0%	5	3.0%	0.086
	No	230	95.4%	69	92.0%	161	97.0%	0.055
Thinking of suicide	Yes	52	21.6%	26	34.7%	26	15.7%	0.001
	No	189	78.4%	49	65.3%	140	84.3%	0.001
Previous attempts to suicide	Yes	30	12.4%	16	21.3%	14	8.4%	0.005
	No	211	87.6%	59	78.7%	152	91.6%	0.005

BED (+): Group with binge eating disorder; BED (-): Group without binge eating disorder.

21.36 ± 4.86 and 20.21 ± 3.79 respectively of BIS-11, total score 64.84 ± 9.75 and attention sub-scale 17.03 ± 3.24 were statistically significantly higher in the BED (+) group ($P < 0.05$) (Table 4).

DISCUSSION

In our study, general psychopathologic and impulsive characteristics were evaluated and examined based on the BED in obese patients (including 34 obese, 150 morbidly obese and 57 super-morbidly obese patients).

The previous psychiatric admittance of BED (+) group was higher. The relevant literature has similar results[11]. In addition, the BED (+) group has statistically significantly higher depressive symptoms in our study. This is again in agreement with previous studies[14,41-44]. The depression itself may contribute to persistence of symptoms of eating disorder[45]. Furthermore, depressive symptoms may predispose individuals to develop binge eating behavior[11]. However, there were no significant differences between the current rates for psychiatric comorbidity diagnosis in groups during the performance of study. This result, which is not consistent with the literature, was attributed to the fact that study sample included individuals who felt healthy enough to attempt seeking for treatment of obesity.

In the present study, the rate for attempting suicide, defined as an impulsive behavior, was statistically significantly higher in the BED (+) group. There are data that the rate for attempting suicide is high in eating disorders where obesity and binge eating are prominent[46-48]. In addition, a Turkish study reported that self-destructive behavior was significantly high in the group of eating disorders[49].

The relation of eating disorders with impulsiveness is complex. Impulsiveness may be characteristic only for a specific subgroup of eating disorders[26] or may manifest after eating disorder occurs[50]. Nonetheless, there is only little information about the influence of impulsiveness on the eating habits of obese individuals and individuals with BED[51]. In the present study, BIS-11 total score and score from attention sub-scale were statistically significantly higher in the BED (+) group. Inattention or cognitive impulsiveness assesses making quick decisions without thinking attentively on the matter or cognitive instability[39]. Obese individuals have an inhibition problem against stimulus in the form of food and problem with focusing attention, and such cognitive deficits are much severer in obese individuals with BED[52]. Among eating disorders, the BED may be seen as a different impulse control disorder[49]. Moreover, those with BED (+) may form a subgroup that has specific impulsive

Table 3 Comparison of the Beck Depression Inventory and Beck Anxiety Inventory between binge eating disorder (+) and binge eating disorder (-) group

	Overall	BED (+) group	BED (-) group	*P*
Beck depression inventory	16.41 ± 9.61	20.04 ± 11.08	14.77 ± 8.40	0.000
Beck anxiety inventory	14.64 ± 10.50	16.72 ± 11.76	13.70 ± 9.78	0.064

BED (+): Group with binge eating disorder; BED (-): Group without binge eating disorder.

Table 4 Comparison of the Barratt Impulsiveness Scale-11 between binge eating disorder (+) and binge eating disorder (-) group

	Overall	BED (+) group	BED (-) group	*P*
BIS-11 total	62.84 ± 8.83	64.84 ± 9.75	61.93 ± 8.25	0.018
BIS-11 attention	16.22 ± 3.28	17.03 ± 3.24	15.85 ± 3.25	0.010
BIS-11 motor	20.57 ± 4.18	21.36 ± 4.86	20.21 ± 3.79	0.072
BIS-11 non-planning	26.06 ± 4.67	26.59 ± 5.32	25.82 ± 4.34	0.275

BED (+): Group with binge eating disorder; BED (-): Group without binge eating disorder; BIS-11: Barratt Impulsiveness Scale-11.

characteristics across all obese patients[53]. In addition, there are studies establishing that individuals who have both obesity and BED more commonly have comorbid mental disorders associated with impulsiveness such as drug dependency and attention deficit/hyperactivity disorder, and many behavioral patterns[54-56].

In studies performed on eating disorders, motor impulsivity[57,58] and inattention[59] were higher in the groups with prominent binge eating. In addition, many research showed increased score for impulsiveness in individuals with BED and obesity[10,31,60,61]. In a study performed by Nasser *et al*[51] using BIS-11, individuals with BED had higher motor impulsivity and criteria for BED were positively correlated with scores from BIS-11. Furthermore, the same study identified a relationship between the variables of motor impulsivity and mood, and suggested that this relationship might be associated with possible serotonin transmission disorder in the BED[51].

Two characteristic features of BED are associated with impulsiveness, which are inability to stop eating, sense of lost control, and eating in a certain time unit in which most people would simply eat more than they could eat. Especially, impulsive characteristics were found to be high in those with BED[62]. In addition, higher rates for suicide attempt, an impulsive behavior, in the BED (+) group suggest that it might be associated with higher impulsiveness in this group. Although the BED (+) group had higher scores for depression and story of psychiatric admittance than those of other group, there were no significant differences between the rates for current psychiatric comorbidity at the time of study. In assessment of data obtained from this study, it will be reasonable to place an emphasis on impulsiveness.

For clinical efficiency, it would be useful that professionals working on eating disorders and obesity include the presence and quantity of underlying impulsive characteristics in addition to disrupted eating behavior in the assessment process. In current research on the obesity, approach to preservation of weight lost after bariatric treatment rather than losing weight is included in the research phases that become prominent. Among many important causes, inclusion of impulsive personality traits in the assessment process may increase the success rate in the field.

Limitations of our study include absence of a control group and use of a self-report scale rather than more objective methods to assess impulsiveness of participants. It would be useful that results obtained from this study should cover a larger group of cases, not only hospital samples seeking for treatment, and that this study should be repeated with more objective diagnostic instruments that are able to measure impulsiveness in the behavioral dimensions.

COMMENTS

Background

Over the past 30 years, the prevalence of obesity has been gradually increased worldwide and the obesity is regarded as one of the major problems for community health. Furthermore, obesity is a condition associated with reduced life expectancy. Impulsiveness is a multidimensional personality trait that leads to uncontrolled and excessive intake of food, thus contributing to development and maintenance of obesity. The objective of this study was to investigate the levels of impulsiveness, and the relationship between the binge eating disorder (BED) and the levels of impulsiveness in obese individuals.

Research frontiers

In assessment of obese individuals, assessment of associated psychopathology such as impulsive characteristics and suicide attempt in addition to disrupted eating behaviors will allow to have a more extensive view.

Innovations and breakthroughs

The previous psychiatric admittance of BED (+) group was higher. The relevant literature has similar results. In addition, the BED (+) group has statistically significantly higher depressive symptoms in our study. This is again in agreement with previous studies. The depression itself may contribute to persistence of symptoms of eating disorder. Furthermore, depressive symptoms may predispose individuals to develop binge eating behavior. There are data that the rate for attempting suicide is high in eating disorders where obesity and binge eating are prominent. In addition, a Turkish study reported that self-destructive behavior was

significantly high in the group of eating disorders.

Applications

For clinical efficiency, it would be useful that professionals working on eating disorders and obesity include the presence and quantity of underlying impulsive characteristics in addition to disrupted eating behavior in the assessment process.

Terminology

Bariatric surgery; weight loss surgery, binge eating disorder; is characterized by compulsively eating a large amount of food without balancing behavior and it is the most common eating disorder in the obese patients.

Peer-review

The manuscript is interesting, well written and provides important insights for understanding the characteristics of the impulsiveness that leads to uncontrolled and excessive intake of food.

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ORIGINAL ARTICLE

Observational Study

Three-dimensional stereotactic surface projection in the statistical analysis of single photon emission computed tomography data for distinguishing between Alzheimer's disease and depression

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Abstract

AIM

To evaluate usefulness of single photon emission computed tomography (SPECT) with three-dimensional stereotactic surface projection (3D-SSP) in distinguishing between Alzheimer's disease (AD) and depression.

METHODS

We studied 43 patients who presented with both depressive symptoms and memory disturbance. Each subject was evaluated using the following: (1) the Minimal Mental State Examination; (2) the Hamilton Rating Scale for Depression; (3) Clinical Global Impression-Severity scale (CGI-S); and (4) SPECT imaging with 3D-SSP.

RESULTS

The MMSE scores correlated significantly with the maximum Z-scores of AD-associated regions. CGI-S scores correlated significantly with the maximum Z-scores of depression-associated regions. Factor analysis identified three significant factors. Of these, Factor 1 could be interpreted as favouring a tendency for AD, Factor 2 as favouring a tendency for pseudo-dementia, and Factor 3 as favouring a depressive tendency.

CONCLUSION

We investigated whether these patients could be categorized as types: Type A (true AD), Type B (pseudo-dementia), Type C (occult AD), and Type D (true depression). The factor scores in factor analysis supported the validity of this classification. Our results suggest that SPECT with 3D-SSP is highly useful for distinguishing between depression and depressed mood in the early stage of AD.

Key words: Alzheimer's disease; Three-dimensional stereotactic surface projection; Single photon emission computed tomography; Pseudo-dementia; Depression

Core tip: The present study aimed to evaluate whether statistical analysis of single photon emission computed tomography images by three-dimensional stereotactic surface projection (3D-SSP) is useful for distinguishing between Alzheimer's disease (AD) and depression. The Minimal Mental State Examination, the Hamilton Rating Scale for Depression, and Clinical Global Impression-Severity scale findings correlated significantly with the Z-scores of AD-associated and depression-associated regions as determined using 3D-SSP analysis. Furthermore, factor analysis identified three significant factors: Factor 1, a tendency for AD; Factor 2, a tendency for pseudo-dementia; and Factor 3, a depressive tendency.

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INTRODUCTION

It is important to distinguish between depression and the depressed mood characteristic of early stage Alzheimer's disease (AD), but it can be difficult to make this distinction based solely on clinical symptoms. Brain images obtained by magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT) may be useful for distinguishing between these two conditions even at relatively early stages. Among the different imaging modalities, SPECT has been introduced clinically for making a differential diagnosis of early stage AD because it can detect brain function abnormalities before the appearance of organic changes in the brain better than other techniques. The accuracy of SPECT for diagnosing AD is reportedly 88%[1]. A meta-analysis found that SPECT has a superior specificity to clinical criteria (sensitivity 74% *vs* 81%, specificity 91% *vs* 70%) in discriminating AD from vascular dementia, fronto-temporal dementia and non-dementia subjects[2].

Three-dimensional stereotactic surface projection (3D-SSP) is a technique used for the statistical analysis of SPECT images. This technique converts images of the brains of patients with inter-individual variances in morphological features using standard brain coordinates to extract functional information (projected onto the brain surface), followed by statistical processing of the data for visual representation of the extent and severity of the reduction in brain metabolism or brain perfusion[3]. This technique was initially developed to analyze positron emission tomography (PET) images, and Minoshima *et al*[4] used 3D-SSP to show that patients with AD had reduced glucose metabolism in the posterior cingulate gyrus. H2150-PET analysis of patients with AD also showed reduced perfusion in the posterior cingulate gyrus[5], indicating that this technique can be used not only for the evaluation of brain metabolism but also for brain perfusion. 3D-SSP was first applied to SPECT by Bartenstein *et al*[6].

The present study aimed to evaluate whether statistical analysis of brain perfusion SPECT images by 3D-SSP was useful for distinguishing between AD and depression.

MATERIALS AND METHODS

Subjects

This study included 43 patients who presented with both depressive symptoms and memory disturbance (13 men and 30 women with a mean age of 67.7 years). All were clinically diagnosed with depression or AD and were ambulatory patients at the Department of Psychiatry, Juntendo University Shizuoka Hospital, Shizuoka Japan. The presence or absence of depressive symptoms was checked using the 2-item Patient Health Questionnaire depression module[7]. Depressive symptoms were considered present when either the patient or a family member reported that the patient had at least one of the symptoms suggesting "depressed mood" or "loss of interest or joy". Memory disturbance was considered present when at least one of the signs on the observation list for early signs of dementia[8] was noted. Patients showing evident signs of non-AD type dementia (vascular dementia, dementia with Lewy body, fronto-temporal lobar degeneration, *etc.*), according to clinical symptoms or diagnostic imaging findings, were excluded from the study. The study was approved by the Juntendo University Shizuoka Hospital Ethics Committee. All participants provided written informed consent.

Evaluation plan

Each patient was evaluated with following: (1) the Minimal Mental State Examination (MMSE); (2) the Hamilton Rating Scale for Depression (HAM-D); (3) Clinical Global Impression-Severity scale (CGI-S) (for evaluating AD); and (4) N-isopropyl-p-[I-123]iodine amphetamine (I-123I IMP) SPECT images with 3D-SSP. Using the CGI-S, AD severity was rated on a 7-point scale: 1 (normal), 2 (borderline), 3 (mild), 4 (moderate), 5 (moderately severe), 6 (severe), and 7 (most severe).

SPECT

Imaging was carried out while each patient lay still in a supine position, awake but with eyes closed. 111 MBq [3 mCi] of 123I-IMP (Perfusamin® Injection: IMP) was intravenously injected *via* the right cubital vein, followed by SPECT imaging 15 min later using SYMBIA-E (Siemens) with a Low-Medium Energy General Purpose collimator. The data were projected with the following parameters: Energy window, 159 KeV ± 15%; acquisition mode, step and shoot; acquisition time, 30 s × 36 Views (18 min); acquisition angle, 10°/view; rotation radius, 13.5 cm; matrix size, 128 × 128; magnification ratio, × 1.45; and pixel size, 3.3 mm.

Image reconstruction

Tomographic data were pre-processed with a Butterworth filter (order, 8; cut-off, 0.26 Nyquist) and then reconstructed from the 128 × 128 matrix of the transverse section. The Chang method was used for attenuation correction. The attenuation coefficient was set at μ = 0.06. Scatter correction was not used. Filtered back-projection by a Gaussian filter was employed for image reconstruction.

Statistical analysis

The SPECT images were statistically analysed by 3D-SSP and stereotactic extraction estimation (SEE)[9].

3D-SSP: 3D-SSP is a technique that is well-established in usefulness for the statistical analysis of images, as shown by previous studies[3,4,10] and the Society of Nuclear Medicine. Transaxial images were selected from the transaxial, coronal, and sagittal SPECT images for statistical analysis using NEUROSTAT® brain image analysis software. Image conversion was performed using standard brain coordinates followed by extraction of functional information using brain surface projection to determine the Z-score relative to the normal database (NDB).

The results of analysis with 3D-SSP can vary markedly depending on the NDB that is used. The NDB for this study was derived from data for healthy volunteers aged 50-79 years old; the data were collected at facilities equipped with the same type of SPECT system that we use. The construction of NDB was approval by ethics committee of each facility, and each participant provided written informed consent. Individuals with MMSE scores of 27 or higher and MRI/magnetic resonance angiography findings corresponding to their age were considered healthy. The SPECT device and the settings for image acquisition and reconstruction used to create the NDB were identical to those used in the present study.

SEE: SEE[9] classifies 3D-SSP brain surface projection data to regions based on neuroanatomy and Brodmann's classification. This procedure involves the assignment of anatomical and functional information to each pixel in a given image. The coordinate system for the brain surface projection data is identical to the Talairach brain coordinates[11]. Anatomical information was assigned to the 3D-SSP brain surface projection data by applying the "Talairach Daemon", which is designed to assign anatomical information to each pixel in accordance with this coordinate system[12,13]. The statistical standard deviation (Z-score) was determined for each region.

AD-associated and depression-associated regions were defined as the brain regions that exhibit characteristic perfusion reductions in the presence of AD[3-6] and depression[14] (AD-associated regions: Superior parietal lobule, inferior parietal lobule, precuneus, and posterior cingulate gyrus; depression-associated regions: Superior frontal gyrus, middle frontal gyrus, and inferior frontal gyrus).

Correlation coefficient

Spearman correlation coefficients (two tailed) were used to evaluate whether the maximum Z-scores of the AD-associated and depression-associated regions correlated with the HAM-D, MMSE, or CGI-S scores.

Factor analysis

Principal axis factor analysis with varimax rotation (df = 21) was performed for the following variables: Age, sex, HAM-D score, MMSE score, CGI-S score, and the maximum Z-scores of the AD-associated and depression-associated regions. The statistical analyses were performed in PASW® version 18 for Windows.

Evaluation criteria

Patients with HAM-D scores of 10 or higher were considered to have depressive symptoms (HAM-D-positive). Patients with MMSE scores of 24 or lower were considered to have symptoms of dementia (MMSE-positive). In evaluating the SPECT Z-score with 3D-SSP, the rating "AD-positive" was made in cases with reduction of perfusion that were 2 standard deviations (SDs) or greater (Z-score $\geqslant$ 2.00) in at least one of the AD-associated regions. Similarly, a "depression-positive" rating was given to cases showing 2 SDs or greater reductions of perfusion in at least one of the depression-associated regions.

RESULTS

MMSE-positive was confirmed in 19 cases and MMSE-negative in 24. HAM-D-positive in 14 cases and HAM-D-negative in 29 was also confirmed. The CGI-S score was 1 in 3 cases, 2 in 11 cases, 3 in 13 cases, 4 in 13 cases, 5 in 2 cases, and 6 in 1 case. In the SPECT 3D-SSP analysis, AD-positive in 9 cases and AD-negative in 34, and depression-positive in 13 cases and depression-negative in 30 was observed. The 3D-SSP results of two representative cases are presented in Figure 1.

Correlation analysis

The maximum Z-scores of AD-associated regions correlated significantly with MMSE (Spearman *r* =

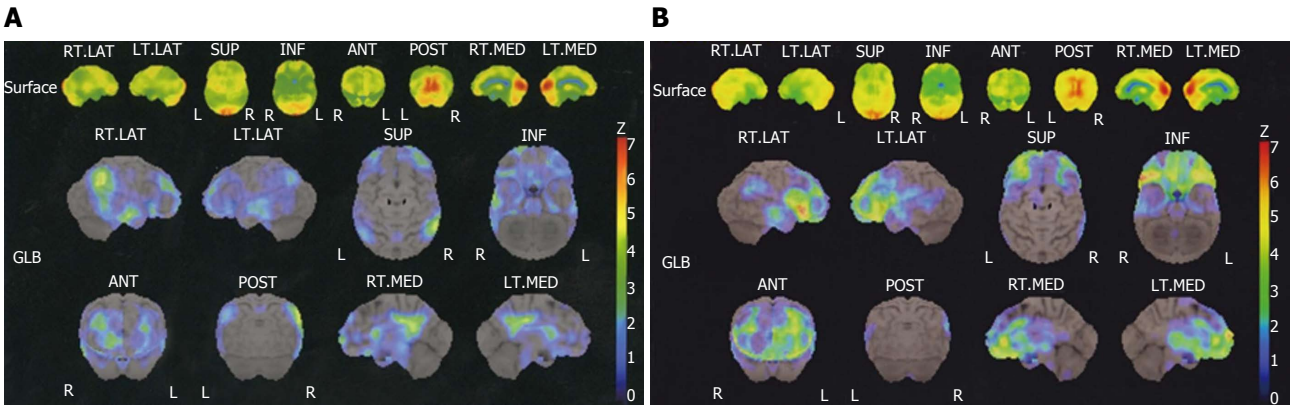

Figure 1 The three-dimensional stereotactic surface projection results of two representative cases. A: Female, 59 years old; MMSE 26, HAM-D 18, CGI 3; showed significant reduction of perfusion in the AD-associated region (the superior parietal lobule and posterior cingulate gyrus); B: Female, 64 years old; MMSE 28, HAM-D 9, CGI 2; showed significant reduction of perfusion in the depression-associated region (the inferior frontal gyrus). HAM-D: Hamilton Rating Scale for Depression; MMSE: Minimal Mental State Examination; CGI: Clinical Global Impression; AD: Alzheimer's disease.

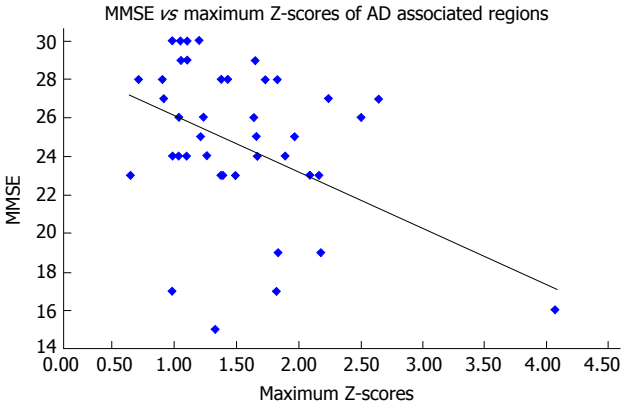

Figure 2 Correlations between Minimal Mental State Examination scores and the maximum Z scores of Alzheimer's disease-associated regions. The MMSE scores correlated significantly with the maximum Z-scores of AD-associated regions. MMSE: Minimal Mental State Examination; AD: Alzheimer's disease.

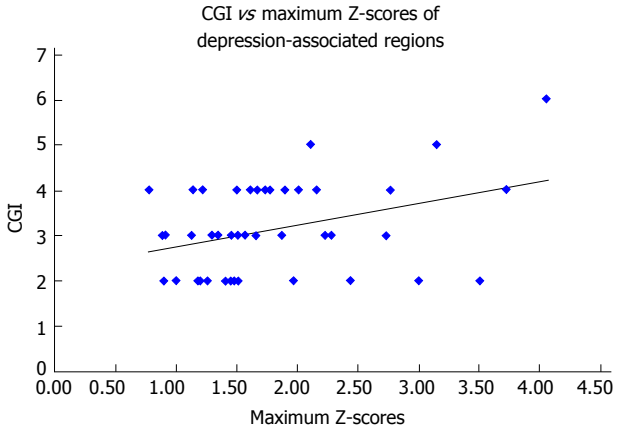

Figure 3 Correlations between Clinical Global Impression-Severity scale scores and the maximum Z scores of depression-associated regions. The CGI-S scores correlated significantly with the maximum Z-scores of depression-associated regions. CGI: Clinical Global Impression.

-0.333, n = 43, P = 0.029) (Figure 2), but not with the HAM-D score (Spearman r = 0.014, n = 43, P = 0.928) or the CGI-S score (Spearman r = 0.275, n = 43, P = 0.074). The maximum Z-scores of depression-associated regions correlated significantly with the CGI-S score (Spearman r = 0.309, n = 43, P = 0.043) (Figure 3), but not with the MMSE score (Spearman r = -0.189, n = 43, P = 0.224) or HAM-D score (Spearman r = 0.047, n = 43, P = 0.763).

Factor analysis

Three significant factors with eigenvalues over 1 were identified (Table 1). Factor 1, a tendency for AD, *i.e.*, negative correlation with MMSE and positive correlations with CGI-S and the Z-scores of AD-associated and depression-associated regions; Factor 2, a tendency for pseudo-dementia, *i.e.*, more marked in women, positive correlations with age and HAM-D and a negative correlation with MMSE; and Factor 3, a depressive tendency, *i.e.*, negative correlation with age and positive correlations with HAM-D and MMSE (Table 2).

DISCUSSION

Classifying cases in which it is difficult to distinguishing between AD and depression: Four-type classification system

In the 14 HAM-D-positive cases in which it was difficult to distinguish between AD and depression, we investigated the use of a four-type classification system (2 × 2 = 4), based on the AD rating (positive/negative) and the MMSE rating (positive/negative). The maximum Z scores of depression-associated regions correlated strongly with Factor 1 (tendency for AD) but only weakly with Factor 3 (tendency for depression). Thus, the maximum Z score of depression-associated regions was not adopted as a criterion for evaluation (Figure 4).

Each type was interpreted as follows. Type A (2 cases, both women) was interpreted as being "true AD accompanied by depressive symptoms" because both AD and MMSE were positive. Type B (3 cases, all women) was interpreted as being "pseudo-dementia" because AD was negative and MMSE was positive. Type C (3 cases;

Table 1 Results of principal axis factor analysis (df = 21)

Factors	Total of explained variance								
	Initial eigenvalues			Sums of squares of loadings after sampling			Sums of squares of loadings after rotation		
	Total	Proportion of explained variance (%)	Cumulative proportion of explained variance (%)	Total	Proportion of explained variance (%)	Cumulative proportion of explained variance (%)	Total	Proportion of explained variance (%)	Cumulative proportion of explained variance (%)
Factor 1	2.422	34.603	34.603	1.961	28.017	28.017	1.805	25.780	25.780
Factor 2	1.223	17.478	52.081	0.982	14.025	42.041	1.067	15.248	41.029
Factor 3	1.166	16.656	68.738	0.484	6.920	48.961	0.555	7.932	48.961
Factor 4	0.805	11.502	80.240						
Factor 5	0.598	8.538	88.778						
Factor 6	0.500	7.144	95.922						
Factor 7	0.285	4.078	100.000						

Methods to extract factors: Principal axis factor analysis. Principal axis factor analysis with varimax rotation (df = 21) was performed for age, gender, HAM-D score, MMSE score, CGI, and the maximum Z-scores of AD-associated and depression-associated regions. Three significant factors with eigenvalues over 1 were identified. HAM-D: Hamilton Rating Scale for Depression; MMSE: Minimal Mental State Examination; CGI: Clinical Global Impression; AD: Alzheimer's disease.

Table 2 Factor loading after varimax rotation

Factors	Factor 1	Factor 2	Factor 3
Age	0.103	0.171	-0.504
Sex	0.061	0.960	-0.107
HAM-D	0.135	0.241	0.350
MMSE	-0.679	-0.178	0.399
CGI	0.763	-0.082	-0.048
AD regions	0.674	0.078	0.063
Depression regions	0.523	0.119	0.042

Factor 1 was interpreted as indicating a tendency for AD (negative correlation with MMSE score and positive correlations with CGI-S score and maximum Z-scores of the AD-associated and depression-associated regions). Factor 2 was interpreted as indicating a tendency for pseudo-dementia (more marked in women; positive correlations with age and HAM-D score and negative correlation with MMSE). Factor 3 was interpreted as indicating a depressive tendency (negative correlation with age and positive correlations with HAM-D and MMSE scores). Colored columns represent significant correlation between the variables and Factors. HAM-D: Hamilton Rating Scale for Depression; MMSE: Minimal Mental State Examination; CGI: Clinical Global Impression; AD: Alzheimer's disease.

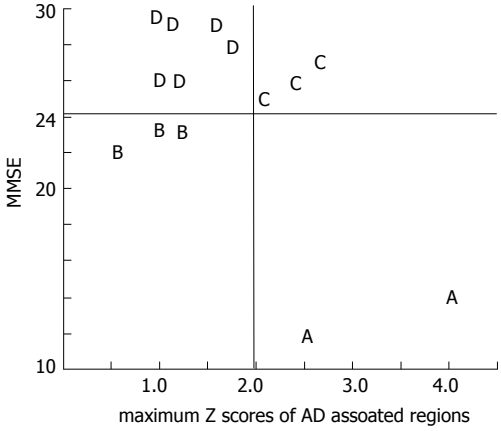

Figure 4 Schematic representation of the classification system. Types (2 × 2 = 4 types) were determined based on the AD rating (positive/negative) and on the MMSE findings (positive/negative). Data from individual patients are plotted by type (A, B, C, and D) on the graph. The X-axis indicates the AD-associated region Z-scores and the Y-axis indicates the MMSE scores. A: True AD; B: Pseud dementia; C: Occult AD; D: True depression. MMSE: Minimal Mental State Examination; AD: Alzheimer's disease.

2 women and 1 man) was interpreted as being "occult AD" because AD was positive and MMSE was negative. Type D (6 cases; 3 women and 3 men) was interpreted as being "true depression (non-AD)" because both AD and MMSE were negative (Figure 4). In the analysis of the score for each factor for each type, Type A (true AD) had high scores for Factor 1 (tendency for AD), type B (pseudo-dementia) had high scores for Factor 2 (tendency for pseudo-dementia), and type D (true depression) had high scores for Factor 3 (depressive tendency). This finding seemed to validate the use of this classification system. All of the Type B cases were women and Factor 2 loaded the variable "sex" to a greater amount (0.96), indicating that women have a higher tendency for pseudo-dementia. Type C cases (occult AD) had high scores for Factors 1 and 3, suggesting that Type C cases have a strong tendency for AD while also presenting with a depressive tendency (Figure 5).

The results of the present study indicate that the Z-scores of AD-associated regions have high sensitivity for the diagnosis of AD, while the Z scores of depression-associated regions correlated only weakly with the depressive tendency in factor analysis and lacked specific sensitivity for depressive symptoms.

Limitations

This study had some limitations, and more work needed. First, only 14 patients were included in the classification analysis, so this classification system needs to be tested in a larger number of patients. There were differences between sexes, and this, too, merits further study in a larger population. Second, we excluded patients with non-AD dementia according to their clinical symptoms or diagnostic imaging findings. A more detailed structured interview or more sophisticated evaluation for differential diagnosis would help more rigorously rule out non-AD dementia. Third, concerning the AD-associated and depression-associated regions, it would be better to

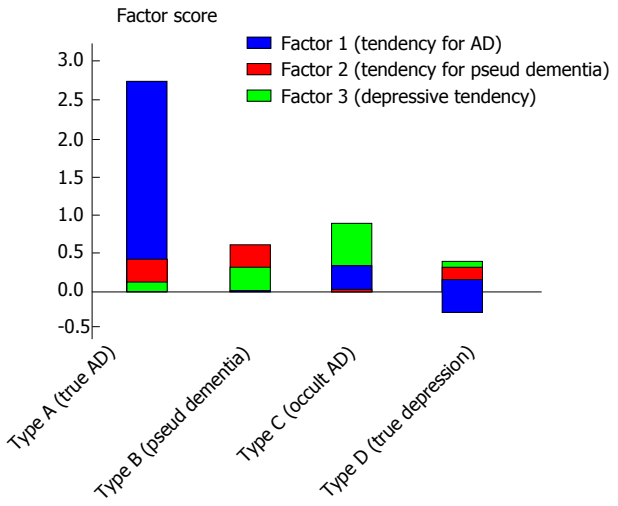

Figure 5 Scores for each factor for each type. Type A cases (true AD) had high factor scores for Factor 1 (tendency for AD); Type B cases (pseudo-dementia) had high factor scores for Factor 2 (tendency for pseudo-dementia); and Type D cases had high factor scores for Factor 3 (depressive tendency), thus validating the type determination method. Type C cases (occult AD) had high factor scores for Factors 1 and 3, suggesting that this type shows a strong tendency for AD while also presenting with a depressive tendency. AD: Alzheimer's disease.

conduct a more detailed analysis of the individual areas. The definition of depression-associated regions needs to be reviewed because the Z-scores of these regions failed to show specific sensitivity. The validity of the definition of these regions for distinguishing between AD and depression must be established based on future evaluations or meta-analyses of larger samples. Kang *et al*[15] used SPECT and found that AD patients with clinically significant depression had significantly lower perfusion in the right orbitofrontal and inferior frontal gyri than non-depressive AD patients, whereas AD patients with clinically significant apathy had had significantly lower perfusion in the right amygdala, temporal, posterior cingulate, right superior frontal, postcentral, and left superior temporal gyri than non-apathetic AD patients[15]. Thus, there may be some overlaps between AD- and depression-associated regions. On the other hand, Terada *et al*[16] investigated the cerebral blood flow of AD patients with depressive symptoms, excluding the effect of apathy and anxiety. They found that the dorsolateral prefrontal area was significantly involved in the pathogenesis of depressive symptoms in AD, and that the area on the left side in particular may be closely related to depressive symptoms[16]. In the future, AD- and depression-associated regions should be better defined to differentiate between depression and anxiety/apathy. Fourth, the use of this classification system to identify Types A-D requires validation by prospective observation. Fifth, although clinicians often find that cognitive impairment symptoms respond to treatment for depression, a substantial proportion of patients with pseudo-dementia will develop dementia during follow-up. Therefore, the use of SPECT findings to distinguish between AD and depression should be viewed with caution in terms of the clinical implications.

Conclusion

This study found that MMSE, HAM-D, and CGI-S findings correlated significantly with the Z-scores of AD-associated and depression-associated regions as determined using SPECT imaging with 3D-SSP analysis. Factor analysis identified three significant factors: (1) Factor 1, a tendency for AD; (2) Factor 2, a tendency for pseudo-dementia; and (3) Factor 3, a depressive tendency. Our results indicated that patients presenting with both depressive symptoms and memory disturbance could be divided into four types: (1) Type A, true AD; (2) Type B, pseudo-dementia; (3) Type C, occult AD; and (4) Type D, true depression. The scores for the three factors validated the identifications of these types. Thus, statistical analysis of I-123 IMP perfusion SPECT images using 3D-SSP shows great promise for distinguishing between depression and the depressed mood that is characteristic of early stage AD.

COMMENTS

Background

In clinical practice, it is often difficult to distinguish between depression and the depressed mood seen in the early stage of Alzheimer's disease (AD). Among the different imaging modalities, brain perfusion single photon emission computed tomography (SPECT) has been introduced clinically for making a differential diagnosis of early stage AD because it can detect brain function abnormalities before the appearance of organic changes in the brain better than other techniques.

Research frontiers

Three-dimensional stereotactic surface projection (3D-SSP) is a technique used for the statistical analysis of SPECT images.

Innovations and breakthroughs

The present study aimed to evaluate whether statistical analysis of brain perfusion SPECT images by 3D-SSP was useful for distinguishing between AD and depression. As results, factor analysis identified three significant factors. Of these, Factor 1 could be interpreted as favouring a tendency for AD, Factor 2 as favouring a tendency for pseudo-dementia, and Factor 3 as favouring a depressive tendency. Furthermore, the authors investigated whether these patients could be categorized as types: Type A (true AD), Type B (pseudo-dementia), Type C (occult AD), and Type D (true depression). The factor scores in factor analysis supported the validity of this classification.

Applications

The authors' results suggest that SPECT with 3D-SSP is highly useful for distinguishing between depression and depressed mood in the early stage of AD.

Terminology

3D-SSP: Three-dimensional stereotactic surface projection is a technique used for the statistical analysis of SPECT images. This technique converts images of the brains of patients with inter-individual variances in morphological features using standard brain coordinates to extract functional information (projected onto the brain surface), followed by statistical processing of the data for visual representation of the extent and severity of the reduction in brain metabolism or brain perfusion.

Peer-review

This is an interesting study on the use of SPECT in differentiating depression from dementia.

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CASE REPORT

Cognitive correlates of neuroimaging abnormalities in the onset of schizophrenia: A case report

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Author contributions: Grassi S and Orsenigo G collected data; Serati M revised report; Caletti E performed neuropsychological tests; Altamura AC designed the report; Buoli M wrote the paper.

Institutional review board statement: This case report was exempted from IRB standards of University of Milan.

Informed consent statement: Patient gave his written informed consent and permission for disclosure of his protected health information.

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Abstract

Increasing evidence shows that cognitive impairment and brain abnormalities can appear early in the first episodes of schizophrenia, but it is currently debated how brain changes can correlate with clinical presentation of schizophrenic patients. Of note, this report describes the case of a young schizophrenic male presenting parietal magnetic resonance/positron emission tomography abnormalities and cognitive impairment, documented by specific neuropsychological tests. In our knowledge only few studies have investigated if neuropsychological abnormalities could be concomitant with both structural and functional neuroimaging. This case shows that impairment in specific cognitive domains is associated with structural/functional brain abnormalities in the corresponding brain areas (frontal and parietal lobes), supporting the hypothesis of disconnectivity, involving a failure to integrate anatomical and functional pathways. Future research would define the role of cognitive impairment and neurodegeneration in psychiatric nosography and, in particular, their role in the early phases of illness and long-term outcome of schizophrenic patients.

Key words: Positron emission tomography; Magnetic resonance; Schizophrenia; Neuropsychology

Core tip: Schizophrenia is associated with impairment in executive function, verbal memory, verbal fluency and attention. Neuropsychological tests are associated with structural and functional brain alterations. This

case report is an example of the potential correlation between clinical symptoms (*e.g.*, cognitive impairment) and brain changes. These data may help in the prediction of possible outcome of schizophrenia patients.

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INTRODUCTION

A number of data would indicate schizophrenia as a progressive neurodegenerative disorder[1] whose outcome is influenced by many biological and clinical factors[2]. Of note, recent literature shows that neuropsychological deficits at onset may predict the clinical course of illness[3] being often associated with frontal and parietal lobe dysfunctions[4-6]. Moreover, a recent trial found that brain abnormalities of schizophrenic patients change according to age at onset. In particular, early onset patients show parietal abnormalities, while adult onset patients exhibit frontal and temporal ones[7].

To our knowledge there are few studies[8-10] associating cognitive frontal and parietal deficits with structural [magnetic resonance (MR)] and functional neuroimaging [positron emission tomography (PET)] and the anatomical and functional relationships underlying this deficit remain to be elucidated. Dysconnectivity, a failure in functional integration, is considered a key mechanism in the pathophysiology of cognitive impairments (in particular working memory performance) in individuals with schizophrenia[11].

The present paper deals with a recent diagnosed schizophrenic patient showing frontal and parietal lobe MR/PET abnormalities clinically associated with deficits in the corresponding cognitive domains.

CASE REPORT

The patient was a 19-year-old man admitted in our department. The patient showed nor psychiatric comorbidity with an Axis Ⅰ disorder neither personality disorders. A neurological exam, performed by a neurologist, was negative. Diagnosis of undifferentiated schizophrenia and exclusion of comorbid conditions were assessed through the administration of semi-structured interviews based on DSM-Ⅳ criteria (SCID Ⅰ and Ⅱ). Patient had family history for psychiatric disorders: The father was an alcohol abuser, one schizophrenic uncle (father's brother) committed suicide and the grandmother in mother line was affected by bipolar disorder. At the admission in our ward the patient was drug-naïve and showed persecutory delusion, auditory hallucinations, thought/behavioural disorganization and a duration of untreated psychosis of 9 mo[12]. Baseline score at Positive and Negative Syndrome Scale[13] was 84, while baseline score at Brief Psychiatric Rating Scale was 55[14]. In the first days of admission patient underwent to neuropsychological tests, cerebral MR and cerebral PET.

A neuropsychological battery was designed to encompass the areas believed to be affected by Schizophrenia[15]. Results and standard scores are summarized in Table 1. Patient's neurocognitive performances provided evidence for impairment in the following domains: Executive function (Cognitive Estimation, Verbal fluency, Trail Making Test), verbal memory, verbal ability (Boston Naming Test, phonemic Verbal Fluency) and attention (Visual Search, Trail Making Test). In addition, the patient failed in two Wechsler Adult Intelligence Scale[16] subscales: Verbal Comprehension Index and Perceptual Organization Index.

MR was performed using a circular polarized head coil and included Turbo Spin-Echo T1-weighted sequences, T2-weighted sequences and FLAIR. Imaging in three planes was performed using 5-mm slice thickness. MR revealed normal-sized ventricles, normal-sized subarachnoidal spaces, no abnormalities in gray matter, but bilaterally soft hyper-intensities in superior parietal lobe[4] periventricular white matter.

Fluorodeoxyglucose (FDG) was injected in condition of rest and fasting and after 30 min three-dimensional scan was performed. The images were compared to a cohort of normal ones. Fluoro-D-Glucose PET (Figures 1 and 2) showed glucose frontal and parietal lobes hypometabolism bilaterally. No further abnormalities in FDG distribution were observed.

MR and PET were performed by neuroradiologists collaborating within our department.

Of note, neuropsychological results are consistent with outlined MR abnormalities and PET images (fronto-parietal abnormalities)[17].

DISCUSSION

The present case report confirms data from literature of early cognitive deficits in the course of schizophrenia[18,19] and neuroimaging parietal abnormalities in early onset schizophrenic patients[7,20,21]. In addition, the correspondence between cognitive deficits and morphological/functional brain alterations[22] contributes to clarify the influence of brain changes in schizophrenia clinical presentation as well as to support the hypothesis of schizophrenia as a neurodegenerative disorder[23,24]. Recent trials found that brain abnormalities are more severe in patients with a longer duration of illness[25-27], novel antipsychotics are promising molecules for their efficacy in stopping the neurodegenerative process[28,29]. In this context cognitive and neuroimaging follow-up of our case can be useful to discriminate if neurodegenerative process of schizophrenia progresses in the course of illness or it is specific of early stages[24,30,31]. Finally, it would be important in the future to define the role of neuroimaging abnormalities in influencing outcome. MR

Table 1 Neuropsychological results

Test	Patient score	Normal value	Result	Z-score
Mini-mental state examination	27.19	24-29.19	Normal	0.45
Executive functions: Tower of London	25	20-36	Normal	-0.75
Frontal assessment battery	15.98	13.5-17.3	Normal	-0.95
Cognitive estimation task	19.97	0-18	Failed	2.43
Bizarreness	6	0-4	Failed	4
Problem solving: Raven's progressive matrices	29.05	18.6-33.05	Normal	0.89
Assessment of cognitive impairment in memory				
Verbal memory and learning				
Digit Span	5.75	3.75-8.75	Normal	-0.4
Verbal Learning	10.50	6.50-21.50	Normal	-0.93
Recall of prose: Immediate and after 10 min	3.50	8.00-27.50	Failed	-2.92
Spatial short-term memory (Corsi test)	4.50	3.50-8.50	Normal	-1.20
Attention and speed information processing				
Trail making test				
Part A	33	< 93 s	Normal	
Part B, dual task	161	< 282 s	Normal	
Part B-A	128	< 186 s	Borderline score	-1.36
Visual search	34.25	31-51.25	Borderline score	
Verbal fluency				
Phonemic	23	17-59	Borderline score	-1.43
Categories	32	25-58	Normal	-1.15
Language				
Boston naming test	31	43-60	Failed	-4.82
Token test	32	29-36	Normal	-0.29
Wechsler adult intelligence scale-revised	General IQ = 75 (verbal IQ = 81; performance IQ = 74) VCI = 5.5; POI = 6.25	80-120	Borderline score	-2.50

The standard scores, reported in the second column, are calculated considering a normal population. Our patient's scores, adjusted for age, sex and education are shown in the first column next to each test. A score is considered pathological when the score is present less than 5% of the normal population. Sometimes normal scores are considered pathological due to the clinical condition and the global performance. VCI: Verbal comprehension index; POI: Perceptual organization index.

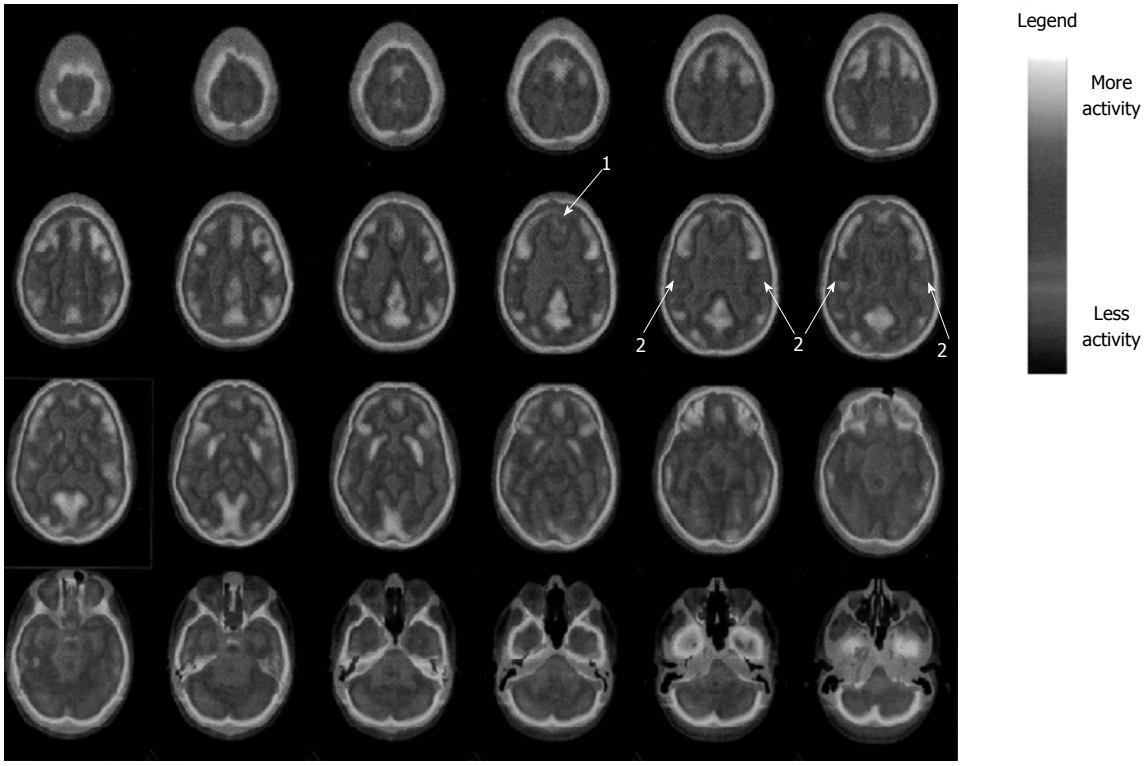

Figure 1 D-glucose (fluorodeoxyglucose) positron emission tomography, transversal sections. Pointer 1 displays the frontal lobe hypo-metabolism; pointer 2 displays the parietal lobe hypo-metabolism.

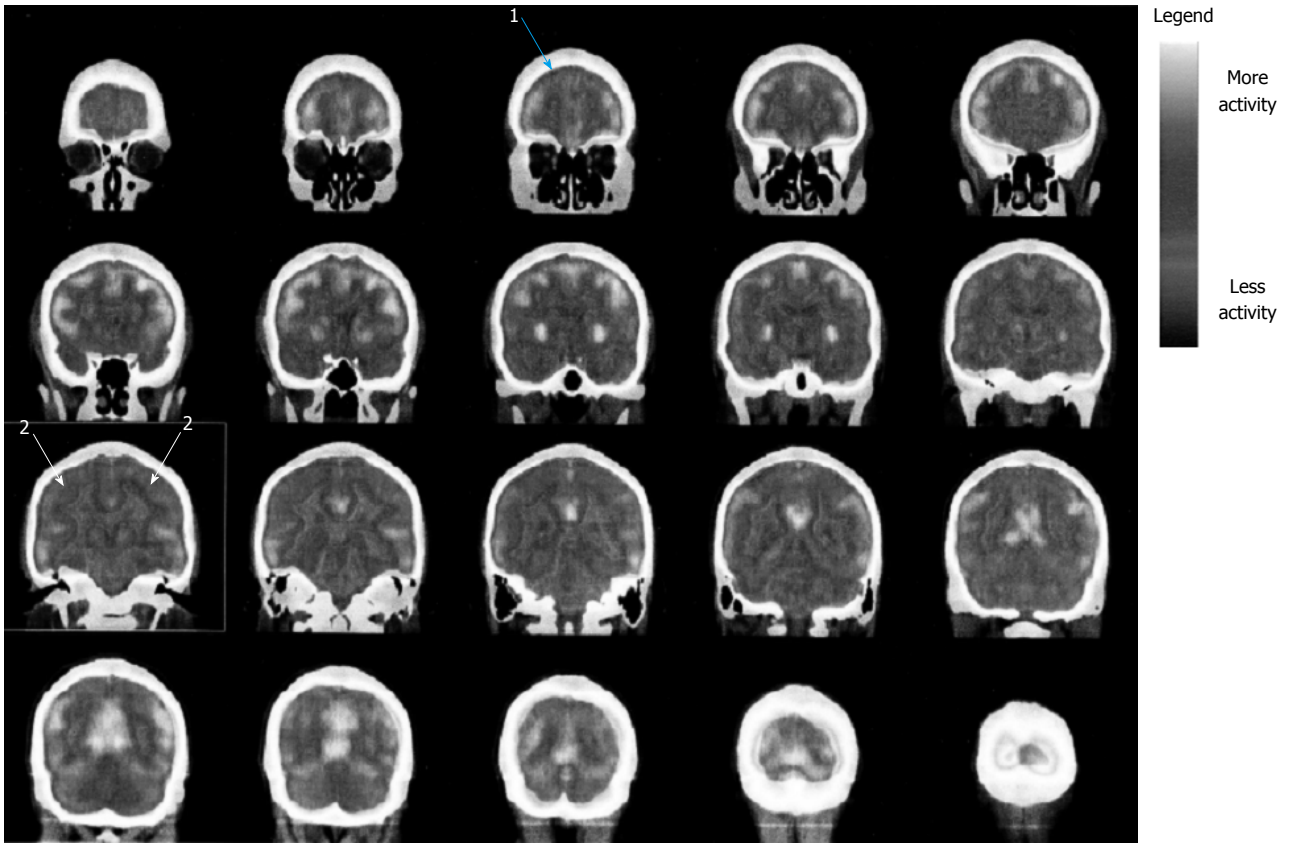

Figure 2 Fluoro-D-glucose (fluorodeoxyglucose) positron emission tomography, coronal sections. Pointer 1 displays the frontal lobe hypo-metabolism; Pointer 2 displays the parietal lobe hypo-metabolism.

and PET could be useful tools to make diagnosis and to predict long-term course of schizophrenic illness.

COMMENTS

Case characteristics

A 19-year-old male patient with severe schizophrenia presentation.

Clinical diagnosis

Patient was hospitalized because of prominent persecutory delusion, auditory hallucinations, aggressiveness and thought/behavioural disorganization.

Differential diagnosis

Bipolar disorder, substance use disorder.

Laboratory diagnosis

Routine blood tests were resulted within normal limits.

Imaging diagnosis

At magnetic resonance imaging bilaterally soft hyper-intensities in superior parietal lobe periventricular white matter were detected, while positron emission tomography showed glucose parietal lobes hypo-metabolism bilaterally.

Pathological diagnosis

Schizophrenia, acute episode.

Treatment

Ziprasidone 80 mg × 2 and Gabapentin 300 mg × 3.

Related reports

Severe cognitive impairment as showed by neuropsychological tests.

Term explanation

Dysconnectivity means abnormal functional integration among brain regions resulting in impaired modulation of neurotransmitters.

Experiences and lessons

It is important to perform imaging evaluation and neuropsychological tests to better define long-term outcome of schizophrenia patients.

Peer-review

This case report is novel and well designed.

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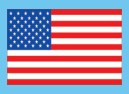

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REVIEW

Biobehavioral assessment of the anxiety disorders: Current progress and future directions

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Abstract

It is difficult to accurately assess and differentially diagnose the anxiety disorders. The current system of assessment relies heavily on the subjective measures of client self-report, clinical observation, and clinical judgment. Fortunately, recent technological advances may enable practitioners to utilize objective, biobehavioral measures of assessment in a clinical setting. The current body of literature on two of these biobehavioral tools (eye-tracking and electrocardiogram devices) is promising, but more validation and standardization research is needed to maximize the utility of these devices. Eye-tracking devices are uniquely capable of providing data that can be used to differentially diagnose anxiety disorders from both other commonly comorbid and misdiagnosed disorders. Both eye-tracking and electrocardiogram devices are able to provide change-sensitive assessment information. This objective, real-time feedback can assist clinicians and researchers in assessing treatment efficacy and symptom fluctuation. Recently developed wearable and highly portable electrocardiogram devices, like the wearable fitness and behavior tracking devices used by many consumers, may be particularly suited for providing this feedback to clinicians. Utilizing these biobehavioral devices would supply an objective, dimensional component to the current categorical diagnostic assessment system. We posit that if adequate funding and attention are directed at this area of research, it could revolutionize diagnostic and on-going assessment practices and, in doing so, bring the field of diagnosis out of the 20th century.

Key words: Biobehavioral; Assessment; Diagnosis; Anxiety; Electrocardiogram; Electrocardiogram; Eye-tracker

Core tip: Anxiety disorders are some of the most commonly comorbidly- and mis-diagnosed disorders in the DSM-5. The current system of assessment and diagnosis depends on clinician and client report measures, which are subjective and prone to bias. Recent technological advances make it possible to utilize the biobehavioral measures from eye-tracking and electrocardiogram devices in clinical settings. These devices can provide a much needed dimensional, objective, and change-sensitive component to current diagnostic and treatment-efficacy assessment protocols. This article summarizes the

status of and outlines future directions for research on this important topic.

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INTRODUCTION

While the Diagnostic and Statistical Manual of Mental Disorders (DSM) has been the guidebook to the assessment for psychiatric disorders for more than half of a century, its system of diagnosis has been fraught with flaws, concerns, and issues since its inception. Each revision of the DSM has sought to correct the flaws of the preceding revision, resulting in so many changes that the first edition of the text bears little resemblance to the most recent edition, the DSM-5[1]. Each of these editions have been built on the same principle: Developing a system of discrete categorical diagnoses which are determined by a list of symptom criteria-the presence or absence of which are determined by tools of client self-report, clinical observation, and clinical judgment[2]. Once a diagnosis is determined, those three tools are used in the ongoing assessment of symptom severity to determine treatment efficacy. Despite the advances made over the past several decades, there are still serious problems with this current system of assessment. Excitingly, recent technological advances and research breakthroughs in biobehavioral tools of assessment may help address these issues to build a sounder system of diagnosis and a sensitive system for assessing the fluctuation of symptom severity, particularly in the realm of anxiety.

The DSM-5's categorical system presumes that mental disorders are discrete issues with distinct boundaries[1], however this concept is not reflected in the research[3]. For people with anxiety disorders having comorbid disorders may be more common than having a single, discrete disorder. For example, one study found that 89% of people with an anxiety disorder were also diagnosed with a disorder of a different category[4]. One reason for this is that there is considerable overlap in the diagnostic criteria between some of the anxiety disorders and other categories, such as the depressive disorders[5]. While many people who are diagnosed with dual or multiple disorders may truly have two (or more) discrete disorders, a dual diagnosis in some people can instead be due to a single underlying issue that presents in such a way to cause a dual diagnosis with the current nosology[6]. A separate study indicated that approximately one third of participants with at least one anxiety disorder diagnosis also qualified for at least one or more additional anxiety disorder diagnosis[7]. Comorbidity in anxiety disorders is associated with difficulties in determining treatment path[8] and worsened clinical outcomes related to course of treatment[9].

While the DSM-5 was being developed, the task force considered adopting a dimensional model of psychopathology, in contrast to the current categorical system[2,10,11]. The dimensional model looks at disorders as not having a single distinct cut off point, and allows for multiple dimensions in a diagnostic model, such as intensity, duration, and level of disruption caused by a disorder's symptoms and components[10]. Most advocates for this system suggested the integration of a dimensional component into the categorical system to provide a fuller diagnostic picture that would be more functional for clinical application[2,12]. Some sections of the DSM-5 diagnostic structure included a quasi-dimensional element, by including specifiers that categorize severity of symptoms as "Mild", "Moderate", or "Severe"[1]. Unfortunately, the dimensional model was not incorporated into the DSM-5 diagnostic structure for anxiety disorders in any way, shape, or form[1]. Since its publication, the debate has continued as to whether the DSM's categorical model should continue to be revised to a more dimensional structure[13].

One reason the dimensional model was not incorporated into the DSM-5 was the lack of a single, standard, empirically-supported, and widely-agreed upon measurement of assessment for the dimensional system for the anxiety disorders to be based upon[10]. This issue may be tied to another problem in the current system of assessment for anxiety disorders: Dependence on accurate self-reports by the client and accurate clinical observation and judgment. Reflecting this, there was disagreement about whether a dimensional scale would rely primarily on clinician ratings or client self-ratings[10]. Both sources of information are subjective, of course, and thus highly flawed. As but one example, client self-report and clinician-report on psychological measures do not necessarily agree with one another[14]. Accurate self-report requires high levels of insight and complete honesty on the part of the client. Many clients cannot or will not accurately perceive their thoughts and feelings or the reasonableness of those thoughts. This is widely understood, as evidenced by the DSM-5's addition of a level of client insight specifier for disorders like obsessive compulsive disorder (OCD)[1]. Even if clients do have a clear understanding of their symptomatology, one study found that 93% of clients purposely lie to their mental health practitioners, with the most frequent lies being about the severity of the symptoms and how badly the client feels[15]. Additionally, there is considerable error in self-reporting for observable behaviors such as physical activity[16], so even the reports of clients trying to be accurate with fair insight into their psychological state may be inaccurate due to biases and memory errors.

Similarly, clinical judgment is also prone to errors and biases. Clinicians are susceptible to the all common human information processing errors[17-19]. One of the most notable information processing errors in assessment

is stereotyping[18]. Clinicians often make decisions of diagnosis based upon how much a client resembles their own personal prototype, a mental conception for the most typical client with that diagnosis[19]. As such, clinicians' diagnoses can be influenced by client characteristics that are not related to diagnostic criteria, such as race, sex, and occupation[20-22]. The inflexibility of this prototypical stereotype bias can quite often lead to misdiagnosing clients[19]. Unfortunately, the issue of practitioner information processing errors is not easily remedied; clinical judgment improves only slightly with education, training, and/or experience[23,24]. This may partially be since it is rare for clinicians to receive timely and effective feedback about their decisions[17]. Clinicians may engage in faulty strategies when hypothesis testing[24], often falling prey to confirmation bias by unwittingly seeking information that confirms the accuracy of their judgment as opposed to seeking out information that would refute it[25]. Accurate feedback may be essential to the process of learning from experience[26], though the literature is still unclear as to whether this is true specifically for clinical judgment[23].

The concerns of client self-report and clinician judgment extend beyond just the initial diagnosis. Disagreement between client self-report and clinical judgment occurs before treatment and at the end of treatment[14], impacting treatment efficacy assessment. This is true for both clinical trials and individual case formulation, and can lead to erroneously continuing ineffective treatment, discontinuation of effective treatment, or prematurely terminating treatment with individuals who would benefit from further services. A more objective and change-sensitive method of assessment would provide the clinician with immediate feedback to reduce the prevalence of these treatment plan errors.

In summation, the DSM-5 used a categorical system for diagnoses whose severity and type appear to be better represented on a dimensional scale[27,28] and the standard practice of assessment uses a variety of kinds of client self-report and clinical judgment measures, which are both highly subjective. In addition to these general issues, the problems with the current diagnostic and assessment system for anxiety disorders specifically are many and varied. This has led in part to the anxiety disorders being among the most misdiagnosed[29]. Because of the flaws in the current system, we suggest that the development, integration, and adoption of a more objective and change-sensitive measure of diagnostic status is imperative. We propose that one or more standardized biobehavioral methods of assessment may be the solution.

Why do we use the term biobehavioral? Years of medical and psychological research have demonstrated that psychological conditions have significant physiological impacts, and vice versa[30]. For example, many people suffering from clinical depression show cellular alterations that result in lower levels of immunity than healthy populations[31]. Many diseases progress more rapidly when accompanied by poor mental health[32]. Inversely, physical conditions such as chronic pain can have deleterious effects on mental health[33]. Integrating psychological, behavioral, and biological factors when studying or improving mental health is referred to as the biobehavioral approach[30]. This approach affords clinicians and researchers quantitative information about an individual, and increases the resources available for treating mental health conditions.

Vast advances in a variety of biobehavioral measurement tools have been developed and refined across the last 30 years. Biobehavioral devices provide unbiased reports of physical behavior and biological processes. Electrocardiogram (ECG) and eye tracking devices are powerful and sensitive tools of biobehavioral assessment that were traditionally limited to only top of the line medical and research facilities due to their once exorbitant cost. Recently, more cost effective versions of these devices have been developed which greatly increases the accessibility and utility of such tools for clinical settings. Despite their greatly decreased cost, the sensitivity of these tools are very promising for identifying unique symptoms of anxiety disorders salient to accurate differential diagnoses[34]. Incorporating a biobehavioral, dimensional component to the DSM's categorical system of diagnosis would make psychiatric classification more in line with other medical classification systems[13]. For instance, hypertension is diagnosed partially based upon a doctor's clinical judgment, but is accompanied by physiological, dimensional measures, namely systolic and diastolic blood pressure reading[13].

The purpose of this paper is to discuss the current research status of two of the most well-researched and easily accessible biobehavioral tools and suggest future research directions to be taken to validate and incorporate their use in both diagnostic assessment and treatment outcome evaluations. First, the basic characteristics of several anxiety-related disorders and commonly co-occurring disorders will be reviewed. Second, a summary of the data captured by eye-tracking technology and a description of several affordable tools that are currently available is provided, followed by a review of the available literature on the discriminative ability of eye-tracking research. Third, descriptions of the most relevant information captured through ECG devices and affordable devices available are presented, along with how this data can assist in monitoring real-time change in symptomology.

ANXIETY AND RELATED DISORDERS

The DSM-5 taxonomy is loosely based on clustering disorders by similar symptomatologic features, but not necessarily by similarities in clinical presentation such as age of onset[13,35]. The specified DSM-5 disorders placed in the category for anxiety disorders are separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder (SAD), panic disorder (PD), agoraphobia, and generalized anxiety disorder (GAD).

A more accurate term for this group may be fear and anxiety disorders, because while these constructs are interrelated, they are different, and some of these disorders have a much more prominent fear component while others are more anxiety-based[2,35]. Fear is an emotional, cognitive, and physiological response to and directed at a present threat[36]. Anxiety is also a distressing emotion, but it is typically characterized by future-oriented, threat-focused cognitions and a perceived state of ambiguity or uncertainty[36]. Both anxiety and fear states are characterized by heightened autonomic arousal which is demonstrated through multiple physiological reactions.

There is little to no research on the biobehavioral reactions of individuals with separation anxiety disorder, selective mutism, PD, and agoraphobia. For this reason, this paper focuses on GAD, specific phobia, and SAD. GAD is characterized by excessive and uncontrollable worry. The symptoms are the result of the interaction between cognitive and physiological responses to imagined or perceived threats[37]. Individuals with GAD are consumed by monitoring and avoiding potential sources of threat and danger. Specific phobias are characterized by an immediate, extreme, and persistent fear toward an object or situation, and thus are more fear-based than anxiety-based[1]. SAD is characterized by persistent fears of social interactions or situations in which criticism and rejection by others is possible[1]. Individuals with SAD are extremely critical of their social performance and are anxious about whether they will be able to make positive impressions or live up to social expectations[38].

The anxiety disorder cluster is, by no means, a comprehensive grouping of all disorders with a significant anxiety component. Several other disorders are also defined in part by extremely high levels of anxiety. Most notably, posttraumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD) are comprised of symptoms that clearly denote high levels of anxiety. To qualify for a post-traumatic stress disorder diagnosis a person must experience a traumatic event and then experience intrusive dreams, memories, dissociative, distressing, and/or physiological reactions and hyperarousal that lasts for at least one month in duration after experiencing the traumatic event[1]. Obsessive compulsive disorder is characterized by obsessions and/or compulsions. Obsessions are unwanted and intrusive images, impulses, thoughts, or ideas that are threatening, nonsensical, disgusting, or obscene[39]. These obsessions are categorized into six categories: Contamination, violence, sex, religion, the need for exactness, or responsibility for harm[40,41]. Each type of obsession causes distress and functional impairment. Most people with OCD also experience compulsions, the strong urge to engage in an action, whether mental or physical, to reduce the anxiety caused by the obsession[39]. The overlap in diagnostic criteria for PD, agoraphobia, social phobia, specific phobia, GAD, OCD, and PTSD can make diagnosis based on self-report and clinical judgment difficult. For example, a fear of dirt can either be part of a specific phobia or a component of OCD for an individual with a contamination obsession. Fear of a location could be associated with a specific phobia, be related to a fear of being unable to escape (as in Agoraphobia), tied to a traumatic event, or be due to fear of being judged by the people in that location (as in SAD). Under the current diagnostic system, accurate and thorough client self-report is imperative to correctly categorizing these symptoms into the appropriate diagnostic box, which as previously discussed, is unlikely to consistently occur.

In addition to the issue of co-occurrence and misdiagnosis within the fear and anxiety related disorders, the disorders also frequently co-occur with and are misdiagnosed for disorders from other categories. There are relatively high rates of co-occurrence between major depressive disorder (MDD) and each of the disorders mentioned above, particularly with GAD[42]. Major depressive disorder has so much in common with GAD and PTSD, that an alternate empirically-based structure was proposed for the DSM-5 with MDD, GAD, and PTSD in a category together called "Distress Disorders", while the other disorders listed above were placed in a separate "Fear Disorders" category[13,35]. There is also significant overlap between the anxiety disorders and attention-deficit/hyperactivity disorder (ADHD), with nearly half of the individuals with an ADHD diagnosis having a comorbid anxiety disorder[43]. However, this is, likely, partially due to misdiagnosis[44]. ADHD is characterized primarily by impulsivity and inattention[1]. People with high levels of anxiety often have difficulty concentrating and maintaining attention[45]. They may also act abruptly in ways that appear highly impulsive, due to their desire to avoid fear-inducing stimuli or, in the case of OCD, due to a compulsion to complete certain behaviors. Understanding a client's internal processes related to these behavioral symptoms is imperative to accurate differential diagnosis between these disorders. Self-report can be a helpful tool to this end, but biobehavioral measures of physiological markers through eye-tracking can provide insight into internal processes which may assist in differentially diagnosing ADHD and MDD from disorders like OCD, PTSD, GAD, SAD, and specific phobia, especially in cases where a client has a lack of insight or where there are barriers to accurate verbal communication. Eye-tracking and ECG devices can also provide clinicians with detailed and change-sensitive measures of symptomatology which can assist in evaluating the course of a disorder and efficacy of treatment.

EYE TRACKING AND ANXIETY

Eye-tracking technology has made it possible to measure certain physiological markers, that contain covert information about individuals, such as pupil dilation, eye-movements, and fixations[46]. For example, due to the established relationship between dopamine

and blinking, blink rate has been frequently used as a marker for dopamine[47]. Additionally, changes in pupil size when viewing sad stimuli has served as a predictor for depression[48]. The eye has many behaviors, each one indicative of other things happening within the individual. For our purposes, there are three important behaviors of the eye that eye-trackers are successful in accurately measuring. First are saccades, those rapid eye-movements that occur consciously and unconsciously when changing fixation points[45]. These are one of the most common types of eye-movements and the ones typically measured when using eye-tracking technology[49].

Second are fixations, purposeful stops of the eye on a specific part of the visual environment and represent where visual attention is being allocated[45]. A fixation occurs between saccades when the eye is stationary, and are valuable for several reasons. First, they show the type of stimuli on which a person is focused (*e.g.*, sad faces). Second, the frequency and duration of fixations can yield information about an individual's condition (*e.g.*, fixation duration can be indicative of current mood)[50]. Lastly, different stimuli can change an individual's fixation patterns, which can in turn influence how the stimuli are perceived by the viewer[51,52].

The third behavior is pupillary size, which has served as an indirect measure of neurological functioning for many years in the medical field[53]. Pupillometry, the method of recording pupil diameter, has made its way into other fields and is now commonly used as an indirect measure of cognitive load, attention, and emotional arousal in psychology[34,54]. As previously discussed, clients are not always honest, and many times, they are unaware of certain relevant information about themselves. The pupil is a gateway to certain aspects of the brain and can make this hidden information accessible. For example, pupil diameter increases when a person is looking at emotionally arousing stimuli as opposed to neutral stimuli[34]. This can expose how certain things may influence more emotional arousal than others, even if the client has no desire or ability to communicate these differences. Incorporating measures of pupil diameter into a treatment plan would also be beneficial in instances where a client is experiencing anxiety, but is unable to pinpoint the major sources responsible for his anxiety. Tracking his pupil dilation while looking at stressful stimuli could reveal the primary areas of struggle.

The evolution of eye-trackers has paralleled that of computers. They have transformed from machines of massive proportions and immense costs to easily portable and affordable devices. Eye-trackers today come in a wide variety of sizes, prices, and capabilities. Eye-trackers recording at the minimum of 60-Hz have been validated as capable of accurately measuring pupil dilation[55]. Most affordable eye-trackers on the market are capable of measuring at 60-Hz and above. One of the leading companies manufacturing portable eye trackers is Tobi. This Stockholm-based company sells small, easy to set up, portable eye trackers for as low as € 159.00. The company Smooth Eye offers an eye tracker that samples at 1000 Hz, and they can design a customized eye-tracker to meet the client's needs. Pricing varies depending on the features wanted by the client. The Pupil Headset by Pupil Labs (€ 1640) is a complete headset that the client can wear for hours at a time without worrying about wires or remaining in the same spot. It is also possible to simply make an eye tracker; many websites offer step-by-step guides to building affordable eye-trackers. These are only a sample of the companies offering affordable eye-tracking devices. There are many more and each one offers different services and software. The affordability and portability of current eye-trackers make it possible for eye-tracking to become a standard tool used in psychology, and it may almost be time to move them from the research laboratory to the clinician's office. There is a great deal of promising research wherein eye trackers demonstrate their ability to assess types of anxiety (Table 1), but a consistent method of doing so has yet to be developed.

Using eye tracking to assess type of anxiety

One of the most common and useful behaviors that eye tracking technology captures is attentional bias. Attentional bias is the tendency to attend to certain stimuli at the expense of others, and is one of the most commonly measured behaviors in mental health-related eye-tracking studies[56]. This bias is shaped by an individual's experiences and mental states. For example, people struggling with depression tend to focus on negative stimuli, while people with PTSD tend to focus on threatening stimuli[57,58]. Negative attentional biases often turn into a malfunctioning cycle because the mental state that developed these negative attentional biases is only receiving reinforcing feedback, thus maintaining the condition[59]. Fortunately, maladaptive attentional biases can change through treatment, and the progress of this change can be tracked through eye movements[60].

In addition to providing insight into cognitive aspects, eye-tracking methods can also yield useful data that can help distinguish between commonly confused conditions[61]. As previously mentioned, there is significant overlap between certain anxiety disorders and depression. People with anxiety display an orienting bias making them faster at detecting threatening stimuli[62]. Additionally, people with anxiety make more frequent eye movements[62]. Neither of these features are present in depressed or healthy populations[50]. People with GAD selectively attend to different stimuli than people with depressive disorder and nonclinical populations. Interestingly, individuals with GAD who are not depressed orient to threatening faces before neutral faces[63-65].

Eye-tracking studies on depression have found that depressed clients with no anxiety do not display hypervigilant eye-movements, but instead have longer

Table 1 Eye-tracking differences across DSM diagnoses

Eye tracker information pertinent to differential diagnosis	Anxiety	Generalized anxiety disorder	Depression	Phobia	SAD	Post-traumatic stress disorder	Obsessive compulsive disorder	Attention-deficit hyperactivity disorder
Attentional Bias (the tendency to attend to certain stimuli at the expense of others)		Tend to focus on threatening stimuli. Selectively attend to more threatening stimuli	Tend to focus on mood-congruent stimuli (*e.g.*, SAD, negative)	Tend to avoid feared stimuli	More sensitive to faces showing emotion over neutral faces	Tend to focus on threatening stimuli	Tend to focus on aversive stimuli	
Orienting Bias (faster detection of certain stimuli)	Faster detection of threatening stimuli	Faster detection of threatening stimuli. Orientation to threatening faces before neutral faces	Slower to detect threatening stimuli (compared to anxiety or generalized anxiety disorder)	Faster orientation to feared stimulus		Faster detection of threatening stimuli		
Frequency of eye movements	Higher frequency of eye-movements	Higher frequency of eye-movements	Slower frequency of eye movements than in anxiety or generalized anxiety disorder				More fixations during a visual search task than anxiety and nonclinical populations	Higher frequency of eye movements
Engagement/ disengagement of stimuli				After detecting feared stimulus, quick disengagement with the stimulus	Takes longer to disengage from a threatening facial expression than other expressions	Do not show the same type of disengagement as people with a phobias		
Stimulus avoidance			Lack of interest in positive stimuli - focus instead on mood-congruent stimuli	After detecting feared stimulus - quick disengagement and avoidance of feared stimulus	Avoidance of eye-contact and faces in general, even if faces are pleasant. Correlation between severity of SAD and the amount of gaze avoidance			
Fixations, saccades, and pupil dilation	Make less fixations (closer to nonclinical populations) than people with obsessive compulsive disorder during a visual search task		Longer fixations on mood-congruent stimuli than those who have anxiety			Greater pupil dilation in general than nonclinical populations	Longer and more frequent fixations towards aversive stimuli. Deficits in goal-oriented visual tasks (higher error rates, inaccurate eye movements for the specific task)	Premature saccades occur more frequently than in nonclinical populations. Higher error rates on anti-saccades tasks than non-clinical populations

SAD: Social anxiety disorder.

fixations on mood-congruent stimuli (*e.g.*, sad faces), and show a lack of interest in positive stimuli[50,66,67].

Some researchers refer to these tendencies as the double attentional bias, increased attention to sad faces along with decreased attention to happy faces[68]. Clients with comorbid anxiety and depression pay attention to both types of stimuli[66,67].

Phobics show specific orienting biases as well. People with phobias are faster at detecting their feared stimulus than normal populations[69]. Unlike in people with PTSD, people with phobias tend to disengage with the threatening stimulus and avoid looking at it. While this behavior can occur in people with other types of anxieties, it is most pronounced when an individual with a phobia is presented with the feared stimulus[50].

Gaze avoidance, or not looking at a stimulus, is easily measured with an eye-tracker, and is a physiological response that can consistently discriminate SAD from other disorders. Socially anxious individuals avoid making eye contact and looking at faces, whether a face is happy, negative (*e.g*., angry or sad), or neutral[70]. Despite this consistent avoidance, these individuals rate these smiling faces as pleasant. This discrepancy between self-reported information and biobehavioral observable reaction exemplifies the unfortunate difficulty experienced by clinicians relying on self-report.

People with SAD avoid eye contact when receiving feedback whether it is positive or negative, a behavior not seen in people with GAD, depression, or PD[71]. Although people with SAD avoid eye contact, they are more sensitive to faces showing emotion than neutral faces, and take longer to disengage attention from threatening facial expressions, such as faces expressing disgust[72] and anger[73]. Additionally, there is a correlation between the severity of SAD and the amount of gaze avoidance, making it possible to determine a client's level of social anxiety through eye-tracking tests[63].

Eye-tracking studies show that people suffering from PTSD orient faster to threatening stimuli and show greater pupil dilation than nonclinical populations[74]. People with PTSD show an attention bias towards trauma-related stimuli over general threatening stimuli, a bias not seen in healthy populations[74]. For example, one study showed that people with a PTSD diagnosis made more initial fixations to threatening words than people who had experienced a trauma but did not qualify for a PTSD diagnosis[51]. Pupil dilation differences in PTSD populations have also been reported, but more research is necessary for consistency. One study reported that people with severe symptoms of PTSD showed greater change in pupil dilation when viewing negative versus neutral images, followed by people with mild symptoms of PTSD, with nonclinical populations showing the least amount of change in pupil dilation[75]. Another study failed to replicate this result, and found that people with a clinical diagnosis of PTSD had greater pupil dilation when viewing both neutral and threatening images than people who had experienced trauma but did not have enough symptoms for a PTSD diagnosis. There were no differences in baseline pupil dilation between groups, indicating higher levels of autonomic arousal in the PTSD group[51], which can be measured using pupil dilation as a marker.

There are inconsistencies in the research on the type of attentional biases displayed by populations with PTSD. Three different types have been reported: Facilitated attention (attending to threatening stimulus first), delayed disengagement (difficulty disengaging from threatening stimulus), and/or attentional avoidance (avoiding the threatening stimulus after it has been detected)[76]. While some have found evidence for attentional avoidance, most studies have seen facilitated attention and delayed disengagement[75]. A likely reason for this divide is the different experimental methods used in the studies. The inconsistencies in the methodology, type of stimuli, and type of task performed by participants are a likely reason for this disparity. Eye-tracking studies using similar methodologies have seen more consistent results[74].

People with OCD have shown deficits in performance on goal-oriented visual tasks in eye-tracking studies, particularly higher error rates and inaccurate eye movements[77]. Populations with OCD also tend to make longer and more frequent fixations towards aversive stimuli, a finding that could help identify obsession-type for clients[78]. Another eye-tracking study by Toffolo *et al*[79] found that participants with OCD searched for longer and made more fixations during a visual search task than either participants with anxiety or a control group, a finding that helps differentiate the diagnosis of OCD and other anxiety disorders with biobehavioral data.

ADHD and anxiety disorders can often look similar at first glance. This can lead to mistakes in diagnoses and inefficient treatment plans for clients. Some of the deficits experienced by ADHD sufferers can be seen using eye-tracking methods. Eye-tracking studies have consistently found that people with ADHD make premature saccades more frequently and have higher errors on anti-saccades tasks than normal populations[80,81]. These patterns reflect difficulties with inhibition, which is reciprocally related to impulsivity, and could be used to help avoid misdiagnosis.

Eye-tracking data have also demonstrated an impressive predictive ability. Several studies have found that difficulties disengaging visual attention predicts negative affect[82,83]. Difficulty disengaging visual attention, especially from negative stimuli, is characteristic of people suffering from depression or dysphoria[84-86]. Another study found that the eye-movements of anxious teenagers were more successful in predicting depression two years later than their own self-reported symptoms[82]. While additional research is needed, these promising findings on predictability show yet another potential component of eye-tracking methodology.

Eye-tracking research is beginning to shed light on new ways to differentiate diagnoses. However, there are contradictions in the literature that merit focused

attention and more research. For example, some studies have found that people with anxiety were slower in naming words related to their anxieties when compared to words that had nothing to do with their anxieties[59,87]. This contradicts the more common notion that people are faster at detecting stimuli related to their anxiety. Although these findings are contradicting, they still show that differences exist between participants with anxiety and healthy controls. It is necessary to conduct more research so that consistent findings can allow for the implementation of eye-tracking techniques in clinical settings.

HEART RATE VARIABILITY RESEARCH

The autonomic nervous system (ANS) regulates adaptive behavioral and physiological responses to environmental stress. Individuals with mood and anxiety disorders exhibit dysfunctional ANS regulation. The heart is an ideal and widely measured organ for assessing the influence of the ANS[88], with heart rate variability (HRV) having been studied extensively. HRV is the variation of heart period over time, measured by ECG, and is a physiological indicator of cardiovascular health, predictor of mortality, and an important biomarker of psychological well-being[89]. There are several heart rate frequencies and each of them are influenced by different factors[90]. High-frequency HRV (HF-HRV) is associated with respiratory rhythm and it is regulated by parasympathetic neuroanatomical structures[91]. HF-HRV is reduced in participants with anxiety disorders compared to healthy controls[92].

Higher resting HF-HRV is associated with greater ability to regulate stress, attention, and emotional arousal[93,94]. Low levels of HF-HRV regulation indicate poor social and emotional regulation, and in some cases have been associated with psychiatric disorders[95]. For example, children with behavioral problems have lower HF-HRV, while children with reliable and stable HF-HRV display fewer behavioral problems, decreased negative affectivity, and better social skills[96]. Higher HF-HRV has also been correlated with greater affect expressivity[97]. Outside of mental health, physical factors including cardiovascular risk[98], diabetes, and obesity are related to low HF-HRV[99].

The 12-lead electrocardiogram has been used for diagnosis of heart disease and cardiac screening measure for over 100 years[100]. However, a smaller number of ECG leads are sufficient to gather the required information to guide clinical practice and decisions. Advances in wireless technology and mobile communications enables real-time ECG recording directly from smartphones and tablets without the need for ECG machines, cumbersome leads, or trained professionals. Currently, there are several small cost-friendly devices that can record, monitor, and transmit ECG signals. These devices allow the possibility to record ECGs outside the laboratory in cost-efficient and timely manner. These mobile ECG work without electrodes attached to the skin and burdensome experimental demands on the participant.

The AliveCor ($99) device consists of a bipolar electrode case that fits on a smartphone to record cardiac electrical activity and software to process the information from the single lead ECG. The QardioCore ($449) is a wearable ECG strap that is worn below the chest. The QardioCore records ECG measurements and sends them directly to a user-friendly application for mobile devices. The Cronovo ($150) is a smartwatch with the capability of recording ECG and translates the data in real time for the consumer. The Lief Smart Patch ($229) is a device that is worn directly on the skin that is capable of continuously recording HRV and providing direct biofeedback relaxation exercises.

The AliveCor can record accurate baseline measurements and detect cardiac abnormalities[100]. Furthermore, participants preferred the mobile ECG devices to conventional 12 lead ECG because it less burdensome and allows data to be shared directly with their healthcare providers. Mobile ECG acquisition is more cost-friendly, faster, less burdensome, and allows clinicians to review data remotely. The mobile technologies make it easier to record ECG at any time and allows for clinical studies to be conducted on a new scale. It is now possible to collect ECG data from individuals from several different countries and populations quickly and cheaply. However, some of the devices are unable to continuously record ECG data, but those devices would dovetail nicely with ecological momentary assessment studies and provide an objective measurement along with self-report. Several of these devices have not been fully vetted by empirical studies. Therefore, future research is necessary to support the usage of these devices for diagnostic assessment and treatment outcome.

The wearable health and fitness device market is growing; it is estimated that 19 million people will be wearing this technology in the next 5 years[101]. In October 2014, the FDA approved the use of smartphone ECG, before devices were restricted to heart rate and activity monitoring. Future technological advancements in wearable health monitoring will more than likely include continuous ECG recording.

Clinical applications of measuring HRV

Coupling mobile HRV with biofeedback is an effective treatment for anxiety disorders[102,103]. HRV biofeedback reduces autonomic hyperactivity and helps the individual learn how to regulate homeostatic mechanisms. HRV biofeedback promotes relaxation and increases vagal activity[104]. Mobile biofeedback devices are beneficial because they provide patients with an objective measure of their physiology, rather than only relying on subjective self-report.

In the anxiety related disorders there are symptoms that denote the involvement of the ANS[105]. These include rapid breathing, suppressed digestive processing, pupil dilation, endorphin release, heart palpitations, and reflex acceleration[104,106]. These

physiological responses prepare the body for action and are adaptive responses when real danger is present, but this response system is maladaptive when no actual danger is present, as often occurs in the anxiety disorders[106]. Individuals with clinical levels of anxiety exhibit less suppression of HF-HRV[107]. Poor HF-HRV regulation in adults has also been associated with greater social anxiety[108]. The close link between HF-HRV and anxiety disorders has been examined in PD[109,110], in GAD[111,112], SAD[110], and PTSD[113].

The subjective experience of SAD is extremely distressing, as are the physiological sensations associated with the disorder (*e.g.*, palpitations, sweating, tremors, muscle tension, blushing, diarrhea, gastrointestinal discomfort). SAD is characterized by social avoidance and disengagement, which are associated with dysfunctional autonomic processes. These dysfunctional autonomic processes are exhibited through social inhibition, emotional dysregulation, and fear. Individuals with SAD exhibit diminished HRV during baseline measures compared to healthy controls[114].

GAD is associated with physical symptoms of restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance[1]. Individuals with anxiety disorders such as GAD, do not show typical cardiac vagal activity in response to threat. Individuals with GAD display a reduction in HRV through a lack of autonomic reactivity[115]. Individuals with GAD have high stable heart rate and low HRV[88]. Empirical studies find that worry suppresses HF-HRV in non-anxious controls[116]. Worrisome thinking before exposure to imagery inhibits cardiovascular activity[117]. Inducing worry suppresses HF-HRV in both non-anxious and anxious individuals[118].

There is some variability among the anxiety disorders in physiological response. For PD there is some degree of fight-flight behavioral and physiological reaction. Individuals with PD exhibit reduced HRV[119,120] and dysregulated respiratory system[115-116], which suggests dysfunctional vagal activation and hyperactive sympathetic processes during challenging situations[105]. Conversely, during non-challenging situations individuals with PD exhibit increased vagal withdrawal and hyperactive parasympathetic activation[120]. Several studies have found conflicting results between individuals with PD and healthy controls on HRV[105,121]. The incongruent findings may be due these studies having different methodological approaches and forms of analysis than other. Nonlinear dynamical theory may provide additional insight into the nonlinear relationship between heart rate variability and psychopathology[121].

Specific phobias are characterized by increased heart rate and skin conductance when the individuals with the disorder are confronted with the fear object[122]. Increased arousal is common among the specific phobias, while blood-injection-injury phobias have a unique physiological response that includes fainting. Individuals with dental phobia when exposed to phobia similar stimuli exhibit decreased HRV[123].

Individuals with OCD are characterized by intrusive thoughts and irresistible urges to perform ritualized behavior. When individuals attempt to control these thoughts or behaviors, autonomic nervous system (ANS) activity increases. HRV has not been extensively studied in OCD and the few studies that have been performed have produced conflicting results. Some studies found increased levels of heart rate and skin conductance[124], while other found no justifiable differences between controls[125,126]. Using spectral analysis Slapp *et al*[105] found no differences between individuals with OCD and healthy controls on resting HRV. However, this study reported null findings on HRV between PD and healthy controls, which contradicts the established literature. Pittig *et al*[112] found that individuals with OCD exhibited diminished HRV during experimental tasks. These results need to be interpreted with caution because of a small sample size and the researchers did not account for the effects of medication. It is evident from the dearth of research on OCD and HRV that more work needs to be done to examine this relationship.

Physiological reactivity to reminders of a traumatic event is a characteristic feature of PTSD[89]. PTSD populations have an average heart rate resting rate approximately five beats per minute faster than control groups[127]. Higher resting heart rate and greater heart rate activity to trauma cues in individuals with PTSD have been explained as over activation of the ANS[89,128]. The inability to regulate levels of arousal and distress is central to PTSD[129]. The psychophysiological symptoms of PTSD include hyperarousal (*e.g.*, excessive startle reflex, hypervigilance) and exaggerated reactions to trauma cues, which indicate a dysfunctional physiological stress system in individuals with PTSD[130].

The role of cardiac activity in the ANS has been extensively studied in trauma research[131,132]. Abnormalities in heart rate to trauma related a stimulus has been exhibited in a plethora of PTSD samples[89,113,130]. Individuals with PTSD exhibit elevated tonic cardiovascular activity[113,127] and excessive heart rate reactivity to trauma reminders[113,128]. In contrast, some trauma-exposed individuals respond with a reduced basal HR (hypoarousal) or even dissociation when confronted with trauma cues[133]. Individuals with PTSD compared to trauma-exposed individuals without PTSD exhibited amplified heart rate, attenuated respiration, and decreased HF-HRV[134]. These differences are exaggerated when individuals are exposed to trauma-specific stimuli. Individuals with PTSD tend to remain physiologically aroused and fail to return to baseline levels[113].

In summary, the majority of anxiety disorders exhibit significantly reduced HF-HRV than healthy controls during baseline measurement[112]. Individuals with PD demonstrate the strongest differences between healthy controls on HRV[109,112]. Individuals with GAD and SAD exhibit smaller effect sizes and exhibit less diminished HRV. Meta-analysis revealed significantly reduced HRV in individuals with PTSD, GAD, PD, SAD, and Specific Phobias compared to healthy controls[91]. Therefore,

the anxiety related disorders exhibit unique biomarkers of psychopathology that are useful for diagnostic assessment, particularly differentiating from those without anxiety disorders. Additionally, HRV can be used effectively to objectively track treatment outcome for the anxiety-related disorders.

Heart rate variability has been extensively studied and validated as a biomarker of the anxiety related disorders[135]. HF-HRV is a change-sensitive marker that parallels positive effects of treatment, with increases in HF-HRV following treatment for depression[136]. Successful completion of cognitive behavioral therapy reduces psychophysiological activity in PTSD[128,137], PD[138,139], OCD[140], GAD[103], SAD[141], and specific phobias[142]. Therefore, HF-HRV is a potential biomarker of treatment efficacy for the anxiety related disorders[135]. However, more research is needed to examine the efficacy of psychotherapy on HRV. Heart rate has been established as a biomarker of the efficacy of CBT on PTSD[128,135,137]. Therefore, future research should examine the efficacy of CBT on the other anxiety disorders and if HRV can be considered a potential biomarker of treatment outcome.

DISCUSSION

Making accurate mental health diagnoses is not an easy task, especially when clinicians must rely primarily on client self-report, which can be inaccurate or misleading. Many disorders have similar symptomatology, and it can be difficult to untangle the many components to make an accurate diagnosis. Additionally, the DSM-5's categorical system can lead clinicians to make multiple diagnoses when there may be only one underlying condition responsible for the client's symptoms. While many clinicians have advocated for a dimensional model to solve these entanglements, the categorical model remains as the standard in the field. A promising solution to this quagmire would be to use biobehavioral assessments in clinical settings. The ample amount of research on heart rate variability and eye-tracking methodologies make it evident that these two measures are valuable for obtaining physiological data that is indicative of different aspects of mental health. These methods provide accurate and unbiased data (as opposed to self-report) that are useful in discriminating between disorders for diagnosis or evaluating treatment efficacy.

The multiple biomarkers that eye-trackers record provide abundant amounts of valuable data that can be used to differentially diagnose many anxiety-related disorders[57,58,71]. ECG technology can provide clinicians with a clear visual of treatment efficacy for the anxiety related disorders[135]. Integrating these biobehavioral devices into assessment will allow clinicians to make use of recent technological advancements in psychophysiology, years of research in biobehavioral markers, and assist clinicians in overcoming issues with self-report and human information processing errors. Using these methods could help psychological assessment overcome the systemic flaws that have been endemic to psychological assessment and bring the system of psychological diagnosis out of the 20th century.

Imagine a common scenario, a mother brings her fidgety son, Jimmy, to her family doctor stating that he isn't doing well in school and seems distracted. She asks the physician for medication to help. Instead of the doctor asking a few hypothesis-congruent questions and prescribing ADHD medication, the physician instead asks Jimmy to put a watch on his wrist and look at a few pictures on the computer screen. A few minutes later, the doctor informs Jimmy's mom that it appears Jimmy has high levels of anxiety and is at-risk for future depression. The doctor subsequently refers Jimmy to a nearby mental health professional, who takes a closer look at the information and can see what types of attentional biases Jimmy exhibited during the assessment. Based upon this information, she can look more closely at the disorders Jimmy is most likely to have. The mental health practitioner also has information that can help her develop an accurate case formulation and determine which treatment is most likely to be effective. She also has established baseline anxiety levels that can be compared with later assessments to determine the efficacy of her treatment. This swift and objective assessment tool has the added benefit of fostering clear communication between medical professionals and mental health practitioners.

To make this vignette possible, several steps must be taken in this direction. While biobehavioral measures are becoming more prevalent, more research is needed to use these measures as resources for clinical settings. For instance, some of the research has yielded different results when analyzing the same constructs[51,64,75,121]. One potential reason for some of the incongruent results on these studies is that each study utilized its own stimuli and methodological practices[64]. To implement the use of these devices in a clinical setting, a standardized set of stimuli and methodology must be developed and validated. To do so, large scale studies with diverse populations comprised of clinical and healthy participants are needed. This requires funding and cooperative research relationships on a large scale. To this end, we exhort institutions to secure grants and other funding for this imperative research. Likewise, the United States Food and Drug Association (FDA) and European Medicines Agency (EMA) could encourage pharmaceutical and digital therapeutic companies to include biobehavioral measures as outcome measures when they file investigational new drug (IND) clinical plans. This could provide a more thorough picture of a treatment's efficacy and help standardize the use of biobehavioral measures in research and clinical practice.

Once a standardized set of stimuli and methodology are developed, new software would need to be developed to easily analyze the data for clinical use. It would be unrealistic to expect any general practitioner or master's level clinician considering a treatment path to painstakingly statistically analyze all the data involved

in these forms of assessment. A software program with the ability to print out easily discernible raw and standard scores would allow ECG and eye-tracker data to be interpreted in a similar manner to blood sugar readings or IQ test results.

There are several obstacles and opportunities for clinical psychology as a science and as a practice. Making these tools standard practice will be difficult, but it is possible and could resolve many of the issues currently plaguing clinical psychology. The fields of psychology and psychiatry can be serving people with anxiety disorders more efficiently and effectively, but a paradigm shift will need to occur. It would be best that as a discipline we can keep up with emerging technology instead of waiting for the current paradigm to be replaced by a better one[143]. The process of implementing a difficult paradigm shift to incorporate the fruit of years of empirical research and technological advancement is well worth the discomfort of change and the inconvenience of validating and learning a new system of assessment.

In conclusion, many of the most troubling issues of the current system of mental health diagnosis and assessment would be greatly ameliorated by developing and utilizing a standard, objective, dimensional system through the use of eye trackers and electrocardiograms. Successfully changing the diagnostic system to include this new standard can be assisted by the concerted efforts of researchers, grant providers, government agencies, and clinicians. The benefits of including biobehavioral measures in mental health assessment far outweigh the effort it will take to make it a standard practice.

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MINIREVIEWS

Tattoos as a window to the psyche: How talking about skin art can inform psychiatric practice

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Abstract

Tattooing the skin as a means of personal expression is a ritualized practice that has been around for centuries across many different cultures. Accordingly, the symbolic meaning of tattoos has evolved over time and is highly individualized, from both the internal perspective of the wearer and the external perspective of an observer. Within modern Western societies through the 1970s, tattoos represented a cultural taboo, typically associated with those outside of the mainstream such as soldiers, incarcerated criminals, gang members, and others belonging to marginalized and counter-cultural groups. This paper aims to review the more recent epidemiology of tattoos in Western culture in order to establish that tattooing has become a mainstream phenomenon. We then review psychological and psychiatric aspects of tattoos, with a goal of revising outmoded stigmas about tattooing and helping clinicians working with tattooed patients to facilitate an exploration of the personal meaning of skin art and self-identity. We suggest that as a kind of augmentation of the physical exam, looking at and talking to patients about their tattoos can provide a valuable window into the psyche, informing clinical practice.

Key words: Tattoos; Military psychiatry; Deviance; Skin art; Psychopathology; Psychology

Core tip: Although traditionally associated with deviance and psychopathology in modern Western culture, tattoos have evolved into a mainstream phenomenon, especially among younger adults. While there are myriad motivations for obtaining a tattoo, most individuals seek tattoos as a means of personal expression that provides a potential window into the psyche that can be used to facilitate psychiatric treatment. By reviewing the literature on psychological and psychiatric aspects of tattooing, we suggest that tattoos should be viewed not as signs of

pathology, but as opportunities to explore core aspects of self-identity that can be valuable in clinical work.

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CASE STUDY

Mr. A is a 31-year-old Caucasian United States Army veteran with post-traumatic stress disorder (PTSD) based on military combat experiences while deployed to Iraq and Afghanistan. He is a divorced father of two, currently in law school, with overall high functioning despite significant life challenges. A tumultuous childhood, including neglect and trauma at the hands of his mother and within the foster care system, led to several suicide attempts as a pre-teen and one psychiatric hospitalization where he was diagnosed with intermittent explosive disorder, bipolar disorder, and obsessive compulsive disorder. While medication titration was attempted during that hospitalization, he was never followed consistently by mental health as a child or adolescent, nor did he take psychiatric medication. Despite these developmental barriers, Mr. A was considered a gifted child with an intellectual capacity well beyond his years and background. At the age of 31, he presented for treatment of PTSD with bilateral full arm tattoos along with visible tattoos on his hands, knuckles, and the back of his neck. Later, he revealed that most of his body was covered with tattoos.

Discussions in psychotherapy revealed that he started getting tattooed at the age of 11, when his father forced him to learn how to fight, subjecting him to physical beatings in order to prepare him for the violent realities of his neighborhood. His first tattoos declared affiliation with his ethnic background, depicting themes of racial affiliation and violence that reflected long-time engagement with racially-based groups for the purpose of enhancing survival on the dangerous streets of his childhood home and within the juvenile corrections system. Other tattoos, including women in bondage, wizards, and skulls, were described as "filler", while others displaying religious symbols, weapons, references to Greek philosophy, and military themes seemed to be more personal. One tattoo referenced the names of fellow soldiers who were killed in action during the wars in Iraq and Afghanistan.

When asked about his motivation for joining the military he replied, "I needed to find a way to maintain masculinity without being a convict". Although he claimed to have thrived within military culture, he often clashed with superiors when he felt disrespected. During deployments, he accumulated extensive combat experience where he expected to die. However, he ultimately completed his military service and after an initial period of instability that included intoxicated fighting and divorce, he obtained sobriety and decided to go to law school. At the time of enrolling in treatment, he was living with a long-time girlfriend while maintaining partial custody of two children from his previous marriage. As psychotherapy began, he demonstrated notable difficulty discussing his emotions and was resistant to the therapist's attempts to delve further into past and current relationships and his symptoms of PTSD.

REVIEW METHODOLOGY

An online search of PubMed and PsycInfo databases was performed using the search terms "tattoos", "tattooing", "tattoo", "skin art", "epidemiology", "stigma", "psychiatric disorders", "psychology", "perception", "self-perception", "removal", "depression", "anxiety", "self-harm", "deviance", "psychopathology", "prison", "military", and "veterans". Criteria for inclusion were original research involving human subjects, meta-analyses, reviews, published in the English language between January 1, 1990 and February 1, 2016 (with the exception of reference 7 which was included for historical purposes). The bibliographies of articles identified through electronic search were also reviewed for additional relevant publications including online resources such as the Harris Poll and military service regulations. Dissertations were excluded. Articles with a primary focus on dermatological/physical/physiological reactions to tattooing and tattoo removal or on diagnosis and treatment of the infectious sequelae of tattoos were excluded.

EPIDEMIOLOGY

Until recently, tattoos have represented a cultural taboo in modern Western societies, typically associated with those outside of the mainstream such as sailors, soldiers, incarcerated criminals, gang members, prostitutes, and others belonging to marginalized and counter-cultural groups[1,2]. Over the past two decades however, epidemiologic studies have demonstrated that tattooing has become more of a mainstream phenomenon, with decreasing associations with stigma.

A survey of 500 population-representative United States respondents age 18-50 years old performed in 2004 revealed that 24% (n = 120) had tattoos with an additional 21% reporting that they had considered obtaining one[3]. Overall, 65% of tattooed respondents reported obtaining their first tattoo by age 24, with women more likely than men to be > 30 years old when they obtained their first tattoo. Tattooed respondents mostly had their tattoos done within the United States (98%), usually in professional tattoo parlors (80%),

with tattoos obtained *via* homemade tattooing devices or sewing needles more likely to have been obtained at < 18 years of age. No tattooed respondents ever had a tattoo removed. Very few tattooed respondents reported being treated differently in work or social settings due to tattoos, suggesting that stigma surrounding tattoos has faded along with increasing popularity.

A more recent Harris poll of 2225 United States respondents performed in 2015 found that 29% of Americans had at least one tattoo, an increase from 14% in 2008 and 21% in 2012[4]. Tattoos were slightly more common among United States women (31%) than men (27%). Younger respondents were more likely to have tattoos, with nearly half (47%) of those 18-35 years old reporting that they had a tattoo. Regret about having a tattoo was reported in 23% of respondents, an increase from 14%-17% in previous years. Based on limited sample sizes from these two surveys, it therefore appears that tattooing has become much more common in the United States, particularly among young adults where rates may approach 1 in 2.

Looking more globally at industrialized Western societies, Kluger published a review of epidemiologic studies performed in the United States, Canada, Australia, Europe, and South America, reporting that the prevalence of tattooing is around 10%-20%[5]. Consistent with data from the United States, tattooing is more common among younger people globally, with the "tattooed generation" born in the 1970s and early 1980s. Being in a tattooed peer group or having a tattooed family member was linked to higher rates of possessing tattoos (75% and 29% respectively). Although tattoos have been traditionally more common among men, gender divides have lessened to the degree of extinction in recent decades in some countries, with tattooing now more common in women overall compared to men in the United States and more common among women 20-29 years old in Australia. However, women tend to have smaller and less visible tattoos overall and prevalence data might be skewed by the inclusion of cosmetic or "permanent make-up" tattoos.

In addition to general prevalence data, Kruger noted that tattoos remain common in groups most traditionally associated with tattooing[5]. For example, the prevalence of tattoos among United States Navy personnel in World War Ⅱ was 65%, while the modern prevalence of tattoos among those in the military is cited as ranging widely from 10%-44%. Differences in rates may reflect variations in sanctioning within separate settings, with peer group pressure playing a significant role. In Brazil for example, tattooing was not introduced until 1959 and the practice is illegal for minors in some states[6]. A survey conducted among a sample of 18-year-old Brazilian military recruits (n = 1968) revealed that about 11% of recruits had tattoos, of which 66% had a single tattoo and 21% had two tattoos, with the remainder having > 2 tattoos[6]. A large majority of tattooed recruits (80%) had obtained their first tattoo before the age of 18.

Despite the illegality of getting tattooed in most prisons worldwide, tattooing remains a common practice among inmates, with prevalence rates ranging from 9%-70%, depending on location, and some 40% of all inmates obtaining a tattoo while incarcerated[5]. Tattoos in the incarcerated population serve to align the wearer with a specific group, as a remembrance, as a sign of strength or aggressiveness, or to simply help to pass the time. Due to the makeshift nature of prison tattooing, inmates are at high risk for obtaining blood borne illnesses such as hepatitis C and human immunodeficiency virus (HIV).

WHAT DO TATTOOS TELL US ABOUT THEIR WEARERS?

Evolutionary and historical perspectives

Tattooing has been a human practice for more than 5000 years, leading Carmen *et al*[2] to examine tattoos through an evolutionary lens. They hypothesized that, regardless of the proximal motivations for getting a tattoo (*e.g*., commemorating an event or relationship, designating group affiliation, or serving as a marker of individuality), the ultimate evolutionary purpose is by definition rooted in sexual selection. The authors offered two hypotheses to explain how tattooing might have been favored in evolution that they call the "human canvas" and the "upping the ante" theories. The former postulates that tattooing is an expression of human culture based in "symbolic thought", with the artistic canvas as a means to illustrate one's personal story and to document history, moving from cave walls to the skin over time. The "upping the ante" theory suggests that tattoos evolved as a fitness indicator, enhancing one's appearance in the context of intersexual competition, similar to a peacock's tail. In tracing the evolution of tattooing across history starting from its ritualistic tribal origins, the authors note that the modern rise in the popularity of tattoos within Western culture emerged from individual niches such as military culture during World Wars Ⅰ and Ⅱ, the subsequent countercultural movements of the 1960s and 1970s, and the current cultural mainstream as a status quo. Over time, social stigmas have lessened and technical innovations have reduced the infectious risk of tattooing, such that it has become a less "costly" and therefore more common fitness indicator.

Psychoanalytic perspectives

Like Carmen *et al*[2], Grumet[7] tracked the development of tattoos throughout history, but did so through a lens of psychodynamic psychiatry as opposed to evolution. Although he acknowledged that tattoos could proclaim identity and group allegiance (as with military tattoos), he argued that "tattoo analysis" ought to be used as a kind of "dermal diagnosis", with tattoos almost uniformly serving as a sign of psychopathology. For example, he

suggested that tattoos are rooted in antisociality and exhibitionism and that "outcasts and outlaws" obtain tattoos in order to bolster low self-esteem. He concluded that tattoos should be viewed as "a psychic crutch aimed to repair a crippled self-image, inspire hope, keep noxious emotions at bay, and reduce the discrepancy between the individual and his aspirations"[7].

In a more recent analytic summary of unconscious motivations for tattoos, Karacaoglan[8] utilized a case series to illustrate that "the painful penetration of the skin in the process of tattooing… is a form of acting out" and that tattoos symbolize "an attempt to actively represent and recompense, as it were, an early deficiency" and a "dialectical record of the mother-father relationship". Highlighting the masochistic nature of tattooing, the author interprets tattooing as an alternative form of expression that patients "resort" to when unable to verbalize "unendurable affect" through language. Like Grumet[7], Karacaoglan[8] ultimately concluded that tattooing is a "form of perversion".

While we agree on the potential value "dermal diagnosis" in exploring unconscious motivations for obtaining tattoos, these uniformly pathologic interpretations now seem, in light of the ubiquity of tattoos in mainstream culture, like antiquated generalizations. While an individual's tattoos could indeed be used to inform psychodynamic psychotherapy by tapping into personal self-representation through symbolism, their interpretation need not be restricted to the realm of psychopathology.

Motivations for tattooing

In keeping with the view that tattoos should not be solely regarded as reflections of psychopathology, Wohlrab *et al*[1] reviewed studies exploring the myriad motivations for obtaining tattoos. The desire to create and maintain a distinct self-identity by controlling one's appearance is cited as one of the most common reasons for tattooing. This motivation may be especially age-relevant and helps to explain the desire to obtain a tattoo during adolescence and young adulthood. In addition to the more identity-based, personal narrative, and group-oriented motivations for getting tattoos, some studies suggest that tattoos can also be viewed as a means to embellish the body as a fashion accessory or piece of art to wear on the body. Others have noted that tattooing can serve as a kind of badge that reflects pain tolerance and physical endurance, as a means of emphasizing sexuality, and as an affiliation with a religious or spiritual tradition, while tattoos are also sometimes obtained impulsively for no specific reason.

Based on a literature review, Dickson *et al*[9] likewise enumerated a variety of motivations for getting tattoos, including body adornment and personal decoration, expressions of individualism and markers of identity, and overcoming difficult emotions as a means of affect management. Motivations for tattooing vary between genders, with women more likely to seek tattoos for personal decoration and to feel more independent, and men more likely to use them as symbols of group identity. Contrary to traditional stereotypes, most adults with tattoos do not associate them with rebelliousness or cultural alienation, do not usually obtain them impulsively or while intoxicated, and do not regret getting them afterwards.

In order to test these generalizations, Dickson *et al*[9] administered a survey about tattoos to 458 United States college students, including 43% with at least one tattoo. The survey results confirmed that most tattooed respondents had taken months to decide what tattoo to get, obtained the tattoo in a reputable tattoo parlor, spent a significant amount of money on it, and tended to have been $\geqslant$ 18 years old at the time of their first tattoo. Respondents tended to view their tattoos as a means of self-distinction, rating them as having significant personal meaning as opposed to symbols of rebelliousness. While respondents reported very high levels of satisfaction with their first tattoo, those with multiple tattoos (60% of the tattooed sample) tended to rate their second or third tattoos, typically obtained a few years after their first, as favorites. This suggests that the process of obtaining multiple tattoos reflects a self-concept that continually evolves with time. For the majority of survey respondents who didn't have tattoos, reasons cited to forgo tattooing included not liking tattoos, concerns about permanency, anticipated disapproval from family, fear of pain, and not knowing what kind of tattoo to get.

Psychopathology and personality traits in tattooed individuals

Although several studies have indicated a greater prevalence of tattoos among psychiatric samples compared to the general population, the data to support this conclusion are largely drawn from older studies based on comparisons of cross-sectional measures of psychopathology among tattooed individuals in either non-psychiatric settings or psychiatric settings with inadequate controls between samples[10]. For example, Birmingham *et al*[11] reported an association between tattoos and a diagnosis of schizophrenia, but their study was based on a limited sample of male prisoners with visible tattoos. Two studies have reported an association between tattoos and a history of abuse, but both included individuals with body piercings[12,13] and one was based on responses to a survey published in a German body modification magazine[12]. Studies of such specialty populations may have limited generalizability due to other confounds that might better explain associations with psychopathology. Similarly, reported associations between tattoos and risk-taking behaviors such as drug use, early sexual activity, gang affiliation, and violent behavior have typically been drawn from small studies of adolescents, with methodological problems related to sample population and size, survey techniques, and the potential for type I error[5,14]. Taken in aggregate,

now that tattooing has become more common and is well-represented amongst adults, any associations with psychopathology are much less clear.

Looking again at recent epidemiologic data from the United States cited above, Laumann *et al*[3] reported that compared to non-tattooed individuals, tattooed respondents were more likely to use recreational drugs, more likely to have spent ⩾ 3 d in jail, and less likely to claim religious affiliation, even when controlling for age[3]. The percentage of tattooed respondents was lower among those who had never consumed alcohol. Among current drinkers, those with tattoos drank significantly more alcohol, although only a small minority of those tattooed had ever obtained their tattoos while intoxicated. Beyond the United States however, Kluger[5] noted that an association between tattoos and alcohol usage has not been detected in surveys from other countries and is therefore not well established. On the other hand, associations between tattoos and both cigarette smoking and recreational drug use (especially cannabis) may be more consistent.

A number of studies have used psychological rating scales to explore potential personality differences between tattooed and non-tattooed individuals, with mixed results[15]. Swami *et al*[15] administered a battery of inventories measuring various personality traits to a sample of 540 subjects from the southern German-speaking region of central Europe and found that those with tattoos only scored higher on measures of extraversion, experience seeking, and need for uniqueness. Although effect sizes were small to moderate, these results highlight that, if personality differences do exist among those with tattoos compared to the general population, they may not necessarily be dysfunctional or pathological. This conclusion is in keeping with recent findings from the United States in which the Community Body Modification Checklist was given to 213 adult subjects with and without tattoos or non-ear body piercings[16]. Defying hypothesized expectations, Giles-Gorniak *et al*[16] reported that the only significant difference in mental health history and behavioral choices between the two groups was that those with body modifications were more likely to engage in social and healthy behaviors. Likewise, an Australian study employed the Loyola Generativity Scale to assess "concern for and commitment to the next generation" among 710 adult women and found that those with and without tattoos had equivalent levels of psychosocial health according to this measure[17].

In contrast to these studies involving adults across the lifespan, much of the work to date on personality differences between tattooed and non-tattooed individuals has been performed in samples of college students, with limited generalizability. In order to avoid the methodological limitations of earlier studies, Tate and Shelton measured personality traits with validated scales that assessed for the Big Five Factors of personality (neuroticism, extraversion, openness to experience, agreeableness, conscientiousness), the need for uniqueness, and the desire to be perceived favorably by others[14]. Tattooed participants, as compared to their non-tattooed counterparts, scored significantly lower on agreeableness and conscientiousness and higher on need for uniqueness. However, while these differences were statistically significant, effect sizes were small and personality scores found among tattooed individuals were, with a single exception among women, within published norms. The authors therefore concluded that "it is untenable to refer to tattoos, per se, as signs of social deviance or personality and character flaws"[14].

Suicide, self-injury, and tattoos

Tattooing is an inherently painful ritual that is usually voluntary, with a history of other acts of self-injury and of suicidal ideation sometimes noted anecdotally by recipients. A survey of 432 German adults with tattoos or non-ear body piercings found that 27% of respondents had a history of self-cutting during childhood[18]. Comparing those with and without a history of self-cutting, self-cutters had the same average number of tattoos, but significantly more piercings. Curiously, some respondents reported feeling "healed" and stopping self-injurious behavior following body modification, leading the authors to hypothesize that some use body modification as a "therapeutic substitute" for "autoaggressive acts"[18]. However, the inclusion of those with body piercings and the lack of a control group without body modification limits the generalizability of this conclusion to those with tattoos.

A possible association between eating disorders, self-injury, and tattoos was explored in a study of 65 female patients referred to a specialized unit for the treatment of anorexia, bulimia, and binge eating disorder[19]. In this sample, a history of self-injury was reported in 51% of patients, while 27% had at least one tattoo. Having a tattoo was significantly associated with a history of burning, supporting the authors' conclusion that body modification might represent a form of self-punishment among those with eating disorders. However, 27% of the sample had tattoos and/or piercings without a history of self-injury and this subgroup had more positive feelings towards their bodies, higher levels of self-esteem, and less impulsivity, depression, anxiety, and social dysfunction than those with a history of self-injury. Therefore, tattoos may sometimes represent positive modifications of body image as opposed to markers of self-injurious behavior.

An association between tattoos and suicide was suggested in a study of 134 completed suicides over a 3-year period in Mobile County, Alabama[20]. In this sample, 21% had one or more tattoos at time of death, with 57% of "young, white suicide" completers having tattoos compared to only 29% for matched accidental deaths. Another study involving a larger series of 438 autopsies in Linn County, Iowa over a 15-year period included 32% subjects with tattoos[21]. Having a tattoo was associated with a significantly younger age at death and greater risk of death by an unnatural manner

(*e.g.*, gunshot wound or drug overdose), but not suicide. Taken together, these small, regional studies offer conflicting evidence for tattoos being associated with suicide. Both studies did speculate that tattoos might be a potential marker of risk-taking behaviors and substance use that could in turn be associated with early mortality, but larger, epidemiologic studies are needed to more clearly elucidate associations between tattoos, self-injury, and early death.

Self-perception in tattooed individuals

Given the intimate and relatively permanent nature of tattooing, a tattoo is expected to alter the new wearer's perception of their body and their identity. However, the effect of the tattoo could depend on motivations for tattooing and the type and meaning of the tattooed image. A 2015 Harris Poll found that although most respondents did not feel that tattoos made them feel more sexy, attractive, rebellious, or spiritual, having a tattoo also did not make them feel less intelligent, respected, employable, or healthy[4]. However, a substantial minority did report that having a tattoo made them feel more sexy (33%), attractive (32%), and rebellious (27%). Tattoos therefore seem to have the ability to positively impact one's sense of self, with individual variation and many aspects of identity potentially affected.

In an attempt to examine effects of tattoos on self-perception, Swami conducted a prospective study of adults from London who were planning to get their first tattoo by recruiting them in a tattoo shop[22]. Participants (n = 82) were assessed before and after getting their first tattoo and asked to rate or provide information about the following aspects of self-perception: Their own overall physical appearance, anxiety about 16 different body sites, measures related to a positive body image, self-attributed need for uniqueness, social physique anxiety, self-esteem, desire to stand out with appearance, reasons for obtaining the tattoo, schematic outlines of the front and back of their bodies to ascertain tattoo visibility and percentage of body covered by the new tattoo, satisfaction with the tattoo, and likelihood of obtaining future tattoos. Assessments were conducted immediately before and after obtaining the tattoo, and then again after 3 wk. Immediately after getting the tattoo, both men and women reported reduced anxiety and less dissatisfaction around their appearance, effects that were sustained at 3-wk follow up. On 3-wk follow up, both genders also reported an overall increase in self-esteem. This suggests that tattoos can mitigate negative attitudes a wearer might hold about one's appearance. However, while men demonstrated a sustained decrease in social physique anxiety after obtaining a tattoo, female participants had higher social physique anxiety after 3 wk. The reason for this gender difference is unclear, but may be related to more negative perceptions towards women with tattoos in society. Still, no differences were found between participants with visible tattoos and those easy to conceal, such that "corporeal meaning" appeared to be a more important predictor of self-perception than appearance, or how others might view them.

While this survey reported individuals' experiences and self-perception immediately before and after being tattooed, it did not examine self-perception in a more longitudinal fashion. It therefore remains unclear whether tattoos truly fulfill one's need for self-expression or if this need remains unfulfilled over time for some, leading them to find other means, or more tattoos, to validate uniqueness. Collectively however these findings suggest that at least in the short-term, tattoos have the power to improve self-esteem and satisfaction, with their appearance providing fertile ground for exploration in the therapeutic setting.

Tattoo removal

The data presented thus far give lie to the ever-present stereotype of tattoos being obtained by intoxicated youth who regret the act the next day, with up to 83% of wearers satisfied with their tattoos[23]. Still, that leaves an estimated 20% of wearers who are dissatisfied with their tattoos and 6% who eventually opt for removal *via* surgical excision, dermabrasion, cryosurgery, chemical peels, and laser ablation with scarring, hypopigmentation, and incomplete removal as potential risks.

Armstrong *et al*[23] surveyed a sample of 196 subjects who sought tattoo removal from 4 clinics across the United States and found that the average person waited 10 years to do so. Frequent reasons for removal included "just decided to remove it", "suffered embarrassment", "got tired of it", "just grew up", and the need to hide the tattoo due to workplace stigma. Issues surrounding stigma were especially prevalent among women (see below for additional discussion).

Tattoo removal may be on the decline as societal acceptance of tattoos increases, with a 23% reduction in tattoo removal procedures reported by The American Society for Aesthetic Plastic Surgery between 2012 and 2013[24]. This decrease is in contrast to a 52% increase reported by the American Society of Dermatologic Surgery over the same time period. However, tattoo removal does not necessarily reflect an overall dissatisfaction with tattoos. In the study by Armstrong *et al*[23], a third of subjects seeking removal were interested in getting more tattoos in the future, suggesting that for some the desire of ablation is more about specific tattoos rather than tattoos in general.

TATTOOS IN SPECIFIC POPULATIONS

Adolescents and tattoos

It is important to distinguish between tattoos among adolescents and adults, since motivations for obtaining tattoos may be significantly different between the two groups. In addition, while tattoos have become a more mainstream phenomenon among adults, considerable

stigma remains with tattooing as an adolescent[25]. Significant research has been devoted to the study of tattoos in adolescents, highlighting negative associations with risk-taking behaviors such as substance abuse, smoking, sexual activity, violent behavior, and problems in school[5]. However, such associations in adolescents < 18 years old are confounded by the fact that it is illegal for a minor to obtain a tattoo in all 50 of the United States. This suggests that tattooing may indeed be a signal of risk among minors, but those risks should not necessarily be extended to those obtaining tattoos as adults[25].

With these demographic differences in mind, a prospective, longitudinal study followed a national sample of 13101 United States 7th-12th graders over 12 to 18 mo, looking at predictors of getting a tattoo[25]. In their sample, adolescents who reported lower levels of parental and/or school attachment, lower grade point averages, and lower religiosity levels were more likely to have tattoos on follow up approximately 1-2 years later. The study also found that adolescents who used alcohol or marijuana and engaged in violent behavior were more likely to be tattooed at follow up. A history of violent victimization was also a significant antecedent of getting a tattoo, suggesting that some adolescents obtain tattoos as a method of self-protection. The authors conceded that the number of adolescents surveyed who later acquired tattoos was small (only 3.6% of sample), precluding any analysis of interaction effects[25]. In addition, they did not take tattoo size, type, or location into account, which is potentially salient since such specifics might reflect different motivations for getting a tattoo (*e.g.*, tattoos signaling affiliation with "conventional institutions" such as a sports team or school likely have very different meanings compared to a gang tattoo on one's neck). This caveat highlights that specific features of tattoos may have different implications about an individual, such that asking wearers about their tattoos may be a valuable source of information in terms of risk assessment, diagnosis, and general understanding. Methodological limitations aside however, it does appear that tattoos in adolescents can be thought of as representing a potential signal of risk among American adolescents.

Tattoos in the military

In modern Western culture, tattoos have been associated with soldiers for nearly a century, dating back to World Wars Ⅰ and Ⅱ[2]. This may have contributed to early associations with tattoos as symbols of machismo or with tattooed individuals being tougher or more dangerous. Among current soldiers, the motivations for getting tattoos and their meanings are varied and diverse, with some important potential distinctions from the general population.

Recent data indicate that about a third of United States soldiers enter the military with pre-existing tattoos[26], potentially reflecting character traits such as increased novelty seeking, extraversion, and a drive for self-individualization that might be associated with both getting a tattoo and joining the military. A survey of tattooed soldiers (n = 122) in the United States Armed Forces found a wide variety of tattoo types, including tattoos reflecting themes of self-identification (military branch or unit designations, patriotic images, ethnic/cultural/tribal symbols), martial themes (weapons, symbols of death), spirituality (religious symbols and quotations, angels, devils), and nature (animals, trees/flowers/plants, and moon/sun/planet/stars)[26].

Gadd conducted a survey of 445 British soldiers who presented to a military-run health clinic in 1990 and found that almost half had tattoos[27]. Peer influence, moreso from male than female friends, was frequently cited as a motivating factor (64%). Nearly a third of tattooed soldiers reported regret associated with their tattoo and considered its removal, with such sentiments significantly more likely among those ⩾ 26 years old. These findings suggest that military personnel may face peer pressure to get tattoos that results in higher levels of regret than is reported in the general public. Regret among older soldiers might likewise reflect a change in identity with which the tattoo did not keep pace, or represent reminders of military experiences one might prefer to forget. Tattoos among military personnel and veterans seeking psychiatric treatment might therefore offer especially valuable avenues to gain access to self-identities transformed by war and personal loss.

The United States military has a long history of maintaining strict standards about personal appearance and grooming, with exacting guidelines governing proper attire and hair length. With the modern frequency of tattoos among potential recruits and the evolution of tattoos away from a sign of rebellion, the United States Armed Forces have recently revised their rules about tattoos, representing a shifting balance between codes of discipline or uniformity and evolving societal views about tattoos.

No branch of the United States Armed Forces allows tattoos that are sexist, racist, extremist, or derogatory in content. The United States Army recently provided general rules prohibiting tattoos on the neck, head, face, or wrists, but personnel are allowed to have tattoos everywhere else on their bodies, including the arms and legs, which were historically forbidden[28]. Hand tattoos are only permitted in the form of one ring on each hand in order to allow for tattooed wedding rings. The United States Marine Corps is currently updating its rules, but Marines are still not allowed to have tattoos covering the whole arm ("sleeves")[29]. The United States Navy's regulations specify that no tattoos are allowed on the face, neck, scalp, or head[30]. Tattoos exposed by wearing a short sleeve navy uniform shirt may be no larger in size than the wearer's hand with fingers extended and joined with the thumb touching the base of the index finger. In contrast to the other branches of the United States Armed Forces, the United States Air Force has relatively

strict rules, prohibiting excessive tattoos (partially defined as any tattoo that exceeds ¼ of the exposed body part) from being exposed or visible while in uniform[31].

Concerns about tattoos in the United States Armed Forces seem to reflect an emphasis on discipline, uniformity, and a respect for command that might be compromised by obvious external markings that set an individual apart. However, as tattoos have become increasingly common and more societally acceptable, the military has in turn become more tolerant, allowing that tattoos might provide an acceptable symbol not of defiance, but individuation and a potential source of group cohesion.

HOW DO OTHERS PERCEIVE THOSE WITH TATTOOS?

General perceptions

Despite the rapidly changing societal views of tattoos, explicit and implicit biases continue to affect how tattooed individuals are perceived. A 2015 Harris Poll revealed that the majority of respondents stated that there was no difference in perceptions of rebelliousness, sexiness, spirituality, respectability, intelligence, or health for people with or without tattoos[4]. However, for the substantial minority of respondents who did perceive a difference, people with tattoos were rated as more rebellious, but less attractive, sexy, spiritual, respectable, intelligent, and healthy.

Tattoo perceptions appear to vary according to the profession of the wearer, with more discomfort associated with visible tattoos on presidential candidates, judges, primary school teachers, and doctors compared to athletes, information technology technicians, and chefs[4]. Due to the persistent disapproval of visible tattoos in some professional settings, some individuals might forgo tattooing altogether or hide their tattoos at work in order to avoid stigma. In the reverse direction, a 1998 survey found that physicians and registered nurses demonstrated negative biases against those with tattoos[32]. Although the survey did not measure providers' actual attitudes towards their patients, it is important to be aware of the potential for negative bias as a clinician working with individuals with tattoos.

In reviewing the literature on tattoo perception, Burgess and Clark[33] have noted that most tattoo perception studies to date have failed take into account the type of tattoo a participant possessed. This is an important omission that has likely contributed to generalizations about tattoos that are misleading in current society, where tattoos of all sizes, locations, and thematic imagery can be found. Tattoos can range from those that are concealed or visible only in more casual or intimate settings to prominent markings on the face, neck, and extremities. Designs can range from "small, trendy, and fun"[33] fashion accessories to more complex tattoos displaying more provocative or sexual themes covering large portions of the wearer's body. Intuitively, such widely varying differences in tattoos are expected to be salient in terms of impacting the perceptions of others. Such perceptions would also be expected to vary based on the gender or age of a wearer.

In order to test such hypotheses, Burgess and Clark[33] performed a study in which 300 British university students were shown images of hypothetical male and female job applicants with either "cute" tattoos, "tribal" tattoos, or no tattoos. No tattoos and cute tattoos were associated with applicants being rated as more friendly and therefore suitable for the job in comparison to those applicants with tribal tattoos, who were perceived as more aggressive and less well suited. Negative dispositional characteristics were attributed exclusively to tribal tattoo wearers, which in turn negatively affected their perceived job suitability. This perception was more strongly held in respondents without tattoos compared to those with tattoos, or those who had considered getting one. This study therefore confirms that the content of a tattoo affects how the wearer is perceived, while also highlighting that tattooed individuals are generally less likely to infer negative attributes about another tattooed person. Therefore, while certain types of tattoos continue to trigger inferences about aggression and deviance, such attitudes may be shifting as more of the populace becomes tattooed.

Gender specific perceptions

Despite the increasing acceptance of tattoos in modern Western culture, women with tattoos still tend to be more negatively perceived than tattooed men. A 2004 survey of Canadian undergraduates reported that both male and female respondents had negative attitudes towards descriptions of women with visible tattoos, and that tattoo size was a predictor of disapproval for respondents who did not have tattoos themselves[34]. Swami *et al*[35] extended upon this research by using line drawings of women with tattoos that allowed manipulation of tattoo location and the number of tattoos to assess effects on an observer's ratings of attractiveness, sexual promiscuity, and alcohol consumption. Based on a study sample of 160 British undergraduates, 14% of whom had tattoos, depictions of women with tattoos were rated as significantly less attractive, more sexually promiscuous, and heavier drinkers compared to women without tattoos. The likelihood of these perceptions increased with the number of tattoos, with figures bearing 3 tattoos estimated to drink more than twice the amount of alcohol as those without any tattoos. While the study was limited by the artificiality of the line drawings and the lack of a male figure control, it appears that tattoos among female college undergraduates may signal an increased likelihood of drinking alcohol and sexual activity. Despite these associations, 73% of the sample indicated that they would consider getting a tattoo in the future, and 53% of the sample was female. These caveats might therefore reflect not only less stigmatizing views of tattoos, but

also of alcohol and sexual activity (*e.g.*, casual sex and multiple partners) among undergraduates.

Resenhoeft *et al*[36] similarly used color photographs in two different experiments to assess United States undergraduates' perception of tattooed women. Participants viewed a photograph of a woman with or without a tattoo and then rated her on 13 personality traits including attractiveness, caring, athleticism, honesty, religiosity, and intelligence. The first experiment found that a photograph of a woman with a large, visible dragon tattoo on her upper arm was perceived as less attractive, fashionable, athletic, caring, intelligent, but more creative compared to a control photograph of the same woman without a tattoo. These differences were not significant in the second experiment that used a photograph of a woman with a smaller, less visible tattoo of a pair of dolphins, with the exception of higher ratings of honesty and religiosity for the non-tattooed control. Although the study findings may have been influenced by using photos of different women dressed in different clothes in the two experiments, the results again seem to indicate negative biases against women with tattoos, even among young college students who might be expected to be more accepting of tattoos.

In an attempt to examine the impact of tattoos on sexual attraction between genders, Wohlrab *et al*[37] performed an experiment using computer generated virtual images depicting both women and men wearing bathing suits that revealed tribal tattoos in various locations. German university students (n = 278) were asked to rate these images on measures of attractiveness, dominance, aggression, masculinity or femininity, and health. In this study, images of tattooed women were rated as less healthy than women without tattoos, whereas images of men were rated as more dominant than those without. Sex differences among raters were important, with men rating images of women with tattoos as more attractive, while women rated them as more dominant. Conclusions about these findings may be limited to heterosexual perceptions of tribal tattoos among young people, but when considered along with other studies, they support the possibility that ratings of female attractiveness by men reflect biases about tattoos signaling sexual availability.

This conclusion was reinforced by a study performed in France using real women who were rated as highly attractive and who, under experimental conditions, displayed a temporary butterfly tattoo on their lower back while lying on a beach in a swimsuit. The field experiment measured how long it took for anonymous men to approach them[38]. Compared to non-tattooed controls, women with tattoos were more likely to be approached by men and were approached within a shorter time. Subsequent interviews with the men revealed that although tattooed women were not rated as more attractive compared to controls, men gave higher probability estimates of being able to get a date with a tattooed woman and to have sex on the first encounter.

Drawing firm conclusions based on these studies is difficult, given that each utilized different methodologies and featured different women with different clothing and different tattoos. Within-study controls suggest that tattoos in young women have the potential to be interpreted as a signal of sexual availability to young men, but across studies, and in reality, visible tattoos are only one of many aspects that might influence female attractiveness. In addition, the use of different types of tattoos across various studies highlights that different tattoos seem to carry different meanings for both wearers and observers, and cautions against overgeneralization.

Looking beyond the narrow scope of the tattoo effects on ratings of female attractiveness in young people, tattoos may have different implications in other contexts, such as within older populations or professional settings. For example, one study found that female nurses with tattoos were perceived more negatively and rated as less caring, skilled, and knowledgeable than their tattooed male colleagues[39]. Observers' perceptions of tattoos in women are therefore influenced by a large number of variables, including setting, age, and other aspects of a woman's appearance, along with tattoo size, location, and content. While such variables are important in considering perceptions about tattoos in both men and women, the impact of such variables can be very different between genders.

CASE STUDY

As psychotherapy progressed, the value of discussing Mr. A's tattoos first emerged when the therapist asked about the tattooed faces of his children which had been embellished to appear more sinister. With prompting, Mr. A admitted that this was intended to maintain a look of stoic masculinity while still bearing reminders of his children on his body, and he agreed that this reflected a strong aversion to vulnerability. Once this was interpreted, he opened up further. The tattoo referencing fellow soldiers killed in combat, visible on the back of his neck, later proved to be a useful topic of exploration when he explained that it was placed in that location so that he would keep the reminder on his body but would not have to see it unless he wished to do so. He admitted that he felt deep, intolerable grief for the loss of these friends and used the tattoo to project this loss out onto the world because he felt incapable of dealing with it in any other way. This facilitated an actual discussion of Mr. A's grief, allowing him to share his feelings for the first time. He reported to the therapist that her interest in his tattoos and non-judgmental questioning increased his sense of a therapeutic alliance and his overall engagement in treatment for PTSD. With additional work in therapy, it appeared that for Mr. A tattooing represented a kind of outward manifestation of intellectualization as a defense that prevented others from having emotional access to the fragile and sensitive person beneath his adorned skin.

In further interpreting Mr. A's tattoos in the context of the modern literature on tattooing, his skin art can be viewed as a "human canvas" which tells the story of his childhood and subsequent formative military experiences. His tattoos overwhelmingly demonstrate dark themes of violent masculinity and pain tolerance, suggesting the need to portray an outward appearance of danger-seeking fearlessness that serves to intimidate or ward off others and that provides some insight into why he was drawn to military service. Now, as a law student and father trying to reconstruct his life with the help of psychotherapy, his tattoos represent a visual depiction of themes relevant to both his past life and present inner existence. While tattoos offer a window into the psyche, it is a window that only tells a partial story. Ultimately, tattoos represent what the patient purposefully reveals on the surface, inviting the therapist to explore that portal in order to access deeper emotions, motivations, and meanings contained within.

CONCLUSION

Over the past century in Western society, tattoos have evolved from cultural taboo to mainstream fashion. Accordingly, historical biases and pathological implications about tattoos warrant revision for present-day tattoo wearers. Although the literature to date on tattooing is informative, the available data are limited to subpopulations drawn from Western industrialized cultures and offer a narrow perspective on the interactions of other characteristics of tattoo wearers (*e.g.*, age, ethnicity, socioeconomic status) on public perception. Clinicians are therefore cautioned against overgeneralization, and are instead encouraged to explore the personal meaning associated with individual patients and their different tattoos. We suggest that as a kind of augmentation of the physical exam, doing so with individuals who are engaged in psychiatric treatment provides a valuable window to the psyche that can reveal core aspects of self-identity and hidden emotions with the potential to facilitate and enhance clinical work.

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MINIREVIEWS

Developmental psychopathology: A primer for clinical pediatrics

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Abstract

Developmental psychopathology (DP), broadly defined as the scientific discipline that has as its primary goal the integration of developmental science and psychopathology into a coherent approach to explanatory models for psychopathological development, has become the dominant approach in the past decade for understanding the origins of mental disorders among children and adolescents. Hence, it is incumbent upon those working in the field of clinical pediatrics to have at least a basic understanding of its core principles of DP. This article provided such an understanding (*i.e.*, a primer) in an exposition of the four principles that are generally considered be core elements of with examples illustrative of each of the principles.

Key words: Developmental psychopathology; Developmental cascades; Developmental pathways

Core tip: Developmental psychopathology is an expansive approach to understanding the processes and pathways to normal and abnormal development. The minireview articulated the four central principles upon which approach is based. Perhaps the most important tip which these principles point to is an expansion on the notion of developmental cascades as a way of advancing the sophistication and comprehensiveness of the understanding of developmental pathways. Namely the notion of developmental cascades proposes that early appearing problems can have effects that spread across multiple levels of functioning in a multiplicity of ways over time and thus provides a promising direction for the constructing developmental models for pathways of cascading effects.

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INTRODUCTION

Developmental psychopathology (DP), broadly

defined as the scientific discipline that has as its primary goal the integration of developmental science and psychopathology into a coherent approach to explanatory models for psychopathological development, has become the dominant approach in the past decade for understanding the origins of mental disorders among children and adolescents[1-3]. This approach emphasizes psychobiological vulnerabilities in interplay with environmental risk factors that shape developmental processes involved in psychopathology. The importance of understanding these processes is anchored in the robust consensus among clinicians and researchers that most adult manifestations of mental disorder have their origins, if not outright symptoms presentations, prior to age 18[3]. Hence, it is incumbent upon those working in the field of clinical pediatrics to have at least a basic understanding of the core principles of DP. The purpose of this article is to provide such an understanding (*i.e.*, a primer) on this discipline by focusing on four principles that are generally considered be core elements of DP[3]. Readers who may be interested in a much more comprehensive exposition of DP should consult the current, authoritative multi-volume work edited by Cicchetti[4].

The article will begin with a presentation of a more expanded definition of DP and then proceed to discuss four principles that are central to the DP model with examples illustrative of each of the principles.

DEFINITION OF DP

To reiterate, DP has as its primary goal the infusion of development into the study of psychopathology and its diagnosis and treatment. It has as its primary objective, the scientific understanding how and why, and for whom and when, processes related to psychopathology develop. In so doing it emphasizes the role of developmental and contextual processes in the origins and course of various juvenile mental disorders. This emphasis has historically distinguished DP from the disciplines of clinical and abnormal child psychology which focused on the classification of childhood mental disorders rather than the complex interplay of factors affecting the dynamic processes of abnormal development. Thus, in the DP approach, psychopathology is viewed not "as a static set of diagnostic entities but rather as the product of the failure to obtain core developmental competences, leading to a progressive veering from normal developmental trajectories and an accumulation of behavior patterns considered maladaptive in most contexts, even though at least some of these behaviors may have been adaptive in the context of deprived or harsh early environments"[3]. Lastly, since the predominant focus is on understanding the complex interplay among biological, psychological, and contextual aspects of development, DP is by definition interdisciplinary, as it draws on findings from multiple disciplines involving the medical, biological, psychological, and sociological sciences.

CORE PRINCIPLES OF DP

DP thus has a very broad approach and can considered a "macroparadigm that acts as a type of framework for understanding developmental processes from multiple perspectives"[1]. Next, we discuss four of the core principles that undergird this framework. Note that although these principles are separately discussed, they are inherently interrelated.

CONSIDERING THE NORMAL AND ABNORMAL DEVELOPMENTAL PROCESSES TOGETHER

In a nutshell, this principle posits that normal and abnormal developmental processes are mutually informative and thus should be considered together. Thus, as previously mentioned, since phenomena defined as abnormal from the DP perspective represent aberrations in normal developmental processes, knowledge of pathways and processes of normal development are essential for understanding pathology. A crucial corollary of this concept is that nearly all forms of psychopathology are best understood from a quantitative/dimensional, not a qualitative/categorical perspective. Namely, since almost no mental disorder constitutes a clearly demarcated, qualitatively distinct category (*i.e.*, a disorder is either present or absent) but rather is an extreme expression on a dimension/continuum, then processes applying to individuals near the center of the continuum are likely to apply to those at the extreme end of the continuum. Thus, psychological problems are "diagnosed" when there is evidence of deviations from the normal healthy course of development with a key issue being the determination of when and how the normal processes become disrupted and channeled into maladaptive functioning. An example of how the knowledge of normal development can inform an understanding of abnormal development such as chronic physical aggression comes from the study of the developmental origins of physical aggression[5]. Research has shown that humans, rather than having to learn how to use physical aggression, spontaneously start such usage towards the end of the first year after birth when they have acquired the physical coordination to push, pull, hit, kick, *etc,*. This usage peaks in frequency somewhere between 2 and 4 years of age and then begins to decline. Therefore, this finding from normal development clearly indicates that in order to properly understand the small group of children (almost all male) who become chronically physically aggressive the focus needs to on the reasons why they fail to learn alternatives to physical aggression with age rather than why physical aggression has become part of their behavioral repertoire.

Conversely, knowledge of abnormal development can also inform an understanding of normal develop-

ment for the same reason that an knowledge of normal development can inform and understanding of abnormal development. Namely, in the continuum model of abnormal development, processes that apply to individuals at the extreme end of the continuum (abnormal behavior) are likely to be applicable to those near the center of the continuum (normal behavior).

An example comes from the studies of infants and toddlers that were subject to brutal deprivation in Romanian orphanages in the 1980s of varying duration (*e.g.*, 6 mo to 3.5 years) and subsequently adopted into high quality homes in England[6]. Perhaps the most striking finding in these studies was an apparent 6-mo threshold in that when the deprivation lasted for 6 mo or less there was no detectable impairments in functioning across 7 domains at various follow-ups to age 11 when these children were compared to adopted children who had not experienced such savage deprivation. However, pervasive impairment was found in most children if the duration of deprivation extended beyond the 6-mo cut-off. In addition, there was also the unexpected finding of no significant dose-response effect of deprivation of ranging from 6 mo to 3.5 years. Thus, findings from the extremely abnormal circumstance of brutal deprivation uncovered what appears to be threshold relevant to normal development in that infants are relatively invulnerable during the first 6 mo of life to long-lasting impairments if their subsequent care-taking is of high quality.

In sum, DP's ultimate goal is the weaving studies of normal and abnormal development into a comprehensive synthesis.

DEVELOPMENTAL PROCESSES ARE RECIPROCAL AND TRANSACTIONAL

In contrast to a linear model of developmental processes in child factors respond to environmental factors in a static invariant manner, the DP model posits that developmental processes are almost always reciprocal and transactional in nature in that: (1) Child level factors influence environmental factors and vice versa; and (2) Such mutually reciprocating influences cause changes in both child and environmental factors. For example, in a child with Attention-Deficit/Hyperactivity Disorder, impulsivity greatly increases the risk for eliciting coercive, oppositional interchanges with significant others in the child's life. Indeed, it is estimated that a typical child with ADHD has an astonishing half a million of these negative interchanges each year. This change in the environment in turn has a reciprocal influence on the child's behavior in that there is an acceleration of the use by the child of aversive behaviors to attain access to rewarding resources and to reduce unpleasant experiences. These reciprocal and transactional processes can result in a developmental cascade which refers to the cumulative consequences for development of the many reciprocal and transactional processes that result in spreading effects across many child level and environmental level factors. Developmental cascades can explain why some problems in children (particularly conduct problems) can cause widespread difficulties in adulthood[7].

DEVELOPMENTAL PATHWAYS

Since psychopathology is conceptualized as resulting over time from reciprocal and transactional processes that result in successive and changing pattern of maladaptation of the juvenile in relationship to their environment, the articulation of developmental pathways is "at the heart of the DP perspective"[1]. A developmental pathway refers to a sequence and timing of behavioral continuities and transformations across development with individuals differing in their propensity to progress along the successive behavior represented by the pathway. Progress along the pathway is probabilistic, not deterministic[8]. Although change is seen as always possible because of the dynamic nature of developmental processes, there is likely to be continuity and stability in maladaptive behavior because past structures and organizations in the individual and the transactional processes surrounding constrain change. The resultant stability in highly similar overt behaviors over time is referred to as homotypic continuity. An example of such continuity would be the depressed, withdrawn, fearful behavior of a maltreated child who continues to be reared in an abusive environment. However, in many cases the specific behavioral manifestations will change but there is continuity and stability at the level of an underlying trait. This process is termed heterotypic continuity. For example, in a case of youth on an early onset pathway for antisocial behavior, the initial manifestations are likely to be tantrums and non-compliance in preschool, followed by impulsivity and aggression during childhood; a variety of covert (*e.g.*, theft) and overt (violence) antisocial behaviors including substance abuse problems and delinquency; and criminality in adulthood. Thus, seemingly disparate behaviors are different manifestations on a continuous antisocial pathway.

Lastly, a corollary of the developmental pathway principle is the concept of multiple pathways and outcomes. That is, multiple pathways can lead to the same development outcome (equifinality); and a given risk factor can cause multiple different outcomes (multifinality). An example of equifinality would be aggressive behavior which can have multiple different causes such as maltreatment, traumatic brain injury, a heritable tendency to impulsive, disinhibited behavior, and prenatal and perinatal risk factors[9]. An example of multifinality would ADHD which poses a significant risk for multiple adverse outcomes such as criminality, substance abuse, academic and occupational failure[10].

MULTIPLE LEVELS OF ANALYSIS

Following directly from the preceding principles, the last principle to be considered posits that a comprehensive

understanding of the developmental processes and pathway involved in the origins and maintenance of psychopathology requires a simultaneous analysis on multiple levels ranging from the neurobiological (*e.g.*, neural systems) to the individual (*e.g.*, temperament) and to all the contexts in which the individual is embedded (*e.g.*, family, school, social). Needless to say, the implementation of this principle for any particular pathology is in its infancy, with perhaps the best example of this principle being the ontogenic process model of antisocial behavior articulated by Beauchaine and colleagues[11-13]. In this model the biologically based temperamental trait of impulsivity, expressed early in life as the hyperactive/impulsive and combined presentations of ADHD, is conceptualized as a vulnerability to the development of antisocial behavior. The neurobiological substrate of this trait is a hyporesponsive mesolimbic dopamine (DA) system caused by chronically low levels of dopamine and diminished DA reactivity to rewards. In turn, this dysfunction provokes psychological states (irritability, discontentment) that motivate excessive impulsive reward-seeking behaviors that temporarily upregulate DA hyporesponsivity. This vulnerability elicits and interacts with various environment risk factors (*e.g.*, aversive family and social interactions, school failure) leading to a developmental pathway of increasingly more severe antisocial behaviors.

CONCLUSION AND FUTURE DIRECTIONS

DP is an expansive approach to understanding the processes and pathways to normal and abnormal development. The preceding discussion, which articulated the four central principles upon which approach is based, also provides the basis for future directions of DP. Perhaps the most important direction which these principles point to is an expansion on the notion of developmental cascades as a way of advancing the sophistication and comprehensiveness of the understanding of developmental pathways[1]. As previously discussed, the notion of developmental cascades proposes that early appearing problems can have effects that spread across multiple levels of functioning in a multiplicity of ways over time and thus provides a promising direction for the constructing developmental models for pathways of cascading effects.

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MINIREVIEWS

Taking care of suicidal patients with new technologies and reaching-out means in the post-discharge period

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Abstract

Suicide is a global public health problem with over one million people dying by suicide each year worldwide. Research efforts have focused on developing and testing novel suicide prevention strategies employing recent technological advances. In order to provide a review regarding the role of new technologies (*e.g.*, postcards/letters, text messages, crisis cards, telephone contacts, online interventions) in suicide prevention, we searched PubMed, ScienceDirect, ResearchGate, and Crisis to identify all papers in English from 1977 to 2016. Our results indicated that brief contact interventions show promise in reducing the number of episodes of repeated self-harm and/or suicide attempts following discharge from the Emergency Department or psychiatric units. Innovative methods of contact (*e.g.*, text messages) are easily implemented by clinicians and received by patients in the period of post discharge and have been shown to be beneficial. However, more research employing randomized clinical trials investigating the potential benefits of these novel suicide prevention methods is warranted. Future researchers should continue improving and testing new technologies in the prevention of suicide.

Key words: Suicide; Letters; Postcards; Emails; Sms; Telephone

Core tip: Several studies have shown that several reaching-out means (*e.g.*, letters, postcards, sms, emails)

are useful and beneficial for healthcare professionals in preventing suicide and self-harm attempts. In this review we wanted to evaluate how these means could influence the number of episodes of repeated self-harm and/or suicide attempts after discharge from emergency department or psychiatric wards. We have shown that these innovative methods of contact are well accepted by patients in the post-discharge period and are easily used in preventing suicide and self-harm reattempts even though future researchers should continue improving and testing new technologies in the prevention of suicide.

Falcone G, Nardella A, Lamis DA, Erbuto D, Girardi P, Pompili M. Taking care of suicidal patients with new technologies and reaching-out means in the post-discharge period. *World J Psychiatr* 2017; 7(3): 163-176 Available from: URL: http://www.wjgnet.com/2220-3206/full/v7/i3/163.htm DOI: http://dx.doi.org/10.5498/wjp.v7.i3.163

INTRODUCTION

Suicide is a severe public health problem with more than one million deaths reported per year internationally[1]. Moreover, suicide ranks among the ten major causes of death worldwide and it is a leading cause of death among youth and young adults in many countries[2-5]. Individuals who have been admitted to psychiatric inpatient units are at a particularly high risk for suicide[6-8]. For these patients, the highest risk period for a relapse is immediately following discharge[9-20]. Cutcliffe *et al*[21] aimed to understand why this time period has been identified as the highest risk. In their study, participants indicated a sense of feeling lost, disorientated, and uncertain after discharge. Some patients reported feeling "disoriented" in their daily lives. Accordingly, there is significant usefulness in making a post-discharge treatment plan in collaboration with the client, which can subsequently explore pragmatic issues such as "what will I have to do next?", "what issues must I face first?", and "where will I seek help?"

Some patients recognize an increased risk of reattempt following discharge because they become lonely when they return home. Indeed, patients recognize the need to interact with individuals (patients and staff) while on the unit. Even the mere presence of other patients and health care professionals is beneficial to those who have attempted suicide and need support. The hospitalization of a patient following a suicide attempt may be considered the first step in a long prevention strategy. It is critical that mental health professionals acknowledge that a substantial portion of recovery in suicidal patients occurs at the end of the acute period especially when they prepare for discharge and in the post-discharge period. Beautrais[22] observed that for many patients who have attempted suicide, the situation has not changed following a suicide attempt because they do not receive the help they need. Patients who are discharged post-suicide attempt often encounter barriers during their recovery and may seriously consider suicide and/or make another attempt. Also, these patients often want to start over, but do not know where to begin, do not know what to do, and frequently do not know who to ask for help solving their problems. Individuals who have received some form of aid in the post-discharge period consider this a form of security. According to Cutcliffe *et al*[21], this kind of help is more useful when it is offered by mental health professionals. Moreover, it turns out to be very useful to the patient and professional(s) develop a treatment plan collaboratively, which includes determining which support method should be employed (*e.g.*, telephone calls, e-mails, letters, SMS, *etc.*) immediately following discharge.

There is the need for the suicidology community to perhaps revisit what should be considered an appropriate timeframe for managing suicidality. In such a model, clinicians and researchers would acknowledge that the majority of the rehabilitation work for reducing suicide risk is likely to be undertaken in post-discharge period. All suicides and suicide attempts affect others, particularly "survivors", such as spouses, parents, children, relatives, friends, colleagues, and peers of those who have made a suicidal gesture, both immediately and in the long term. Suicide represents a major challenge for health care providers and society as a whole, especially in terms of prevention. New technologies have entered the field of suicide prevention with high expectations for the future, despite a relatively slow start.

Over the last decade, the internet has played an increasingly influential role in people's lives, particularly among young adults in middle and high income countries. Internet users now access the social media platforms to create, exchange and share their own content and experiences[23,24]. The Internet, mobile phones and self-help programs have the strong potential to achieve, sustain and help people who attempt suicide, their families, health professionals, and the suicide survivors. Globally, the use of new technologies have been demonstrated to be a useful and easily applicable approach to suicide prevention, which can be implemented by volunteers and professionals, from crisis lines, suicide prevention centers, mental health centers, researchers, and politicians[25].

The aim of the present review is to understand the role of new technologies for reducing self-harm, suicide attempt, and death by suicide, while paying particular attention to post-discharge from an Emergency Department (ED) or Psychiatric Ward. We also assess usability, validity, and effectiveness of letters, text messages, crisis cards, telephone contacts, and online interventions compared to current prevention techniques.

MAIN OUTCOME MEASURES

The primary outcomes considered in this review were: (1) The occurrence of any subsequent episode of self-

harm and/or suicide attempt post-discharge; (2) The number of repeated episodes of self-harm and/or attempted suicide per person post-discharge; and (3) the total number of suicide deaths.

POSTCARD/LETTERS/CRISIS CARD/ GREEN CARD

Motto *et al*[26] assessed the efficacy of a long-term contact program on the prevention of suicide. They randomly divided 843 patients hospitalized because of a depressive episode and/or suicidal state who had declined or discontinued treatment during the last 30 d (a total of 3005 individuals were contacted 30 d after discharge about follow-up treatment). Patients in the experimental group (n = 389) were contacted through a short letter correspondence for five years. The schedule for these contacts was sent monthly for four months, then every two months for eight months, and finally every three months for four years (a total of 24 letters for five years). The control group (n = 454) received no further contact. The authors found that patients in the intervention group had a lower suicide rate across all five years as compared to the control group, suggesting a preventative influence of the contacts. Conversely, reducing and/or discontinuing contacts may decrease and eventually eliminate this effect.

Hassanian-Moghaddam *et al*[27,28] conducted a RCT to evaluate the efficacy of a postcard intervention plus treatment as usual (TAU) *vs* TAU of three primary outcomes: suicidal ideation, suicide attempts, and self-cutting (or self mutilation) in a follow up of 12 and 24 mo in two separate studies. They sent nine postcards over 12-24 mo to 1150 patients discharged from the Loghman-Hakim Poison Hospital. Eight postcards were sent at 1, 2, 3, 4, 6, 8, 10 and 12 mo after discharge. In the second study, a postcard was also sent 24 mo after discharge. Each participant received a ninth postcard on his birthday, with the other 1150 patients receiving TAU. The researchers found that suicidal ideation and suicide attempts were reduced by a postcard intervention. Specifically, there was a beneficial effect on suicidality during the 12-24 mo follow-up period.

Carter *et al*[29] conducted a RCT to evaluate the effectiveness of an intervention using postcards (postcards from Edge project) in reducing repetitions of hospital treated deliberate self-poisoning in a follow up period of 1[29], 2[30] and 5 years[31]. Participants (n = 772) were randomized into an intervention group (n = 378) and a control group (n = 394). The intervention group received a postcard at 1, 2, 3, 4, 6, 8, 10 and 12 mo after discharge from the toxicology service with deliberate self-poisoning. The rate of hospital-treated-self-poisoning events was reduced by 50% over a 1-year, 2-years and 5-years period through the use of a postcard intervention, although it did not significantly reduce the proportion of individuals who repeated self-poisoning.

Beautrais *et al*[32] conducted a RCT to determine if a postcard intervention reduced repeated self-harm in persons aged 16 and older, who admitted to psychiatric emergency services at Christchurch Hospital, New Zealand, following self-harm or attempted suicide. Participants (n = 327) were randomized into two groups, one of which (n =174) received TAU; whereas, the other (n = 153) received TAU plus the postcard intervention. The postcard intervention consisted of a set of six "postcards" sent by mail during the 12 mo following discharge at 2 and 6 wk; 3, 6, 9 and 12 mo. No significant differences were found between the control and intervention groups with regards to the proportion of participants re-presenting with self-harm to the psychiatric emergency department, ED, or to either the psychiatric emergency or ED. Moreover, the use of this intervention had not shown a reduction in the total number of re-presentations for self-harm to the ED or to either the psychiatric emergency service or the ED. However, a reduction in the total number of re-presentations to the psychiatric emergency service was associated with postcard intervention, although the significance of this effect must be considered marginal given that the significance level exceeded the adjusted boundary P value.

Evans *et al*[33] conducted a RCT to evaluate, through a follow-up of 6 mo[33] and 12 mo[34], the usefulness of crisis cards in the repetition of a self-harming group of hospital-admitted patients. In the RCT, the researchers recruited 827 patients admitted to hospital following self-harm. Approximately half of the study participants received a card crisis while all others received standard treatment. In addition to treatment as usual, the intervention group was offered telephone support should any further crises arise. The main outcome assessed in this study was represented by repetition of deliberate self-harm within 6 mo and 12 mo of the index event. At 6-mo follow-up, the authors had shown that sending a card offering 24-h crisis telephone consultation is not effective on the repetition of self-harm. However, among those presenting following a first episode, a possible benefit was reported. At 12 mo follow up, the results confirmed no overall benefit of the intervention. Among those with a first episode of self-harm, the possible benefit of the intervention had diminished although only a modest effect was detected.

Cotgrove *et al*[35] evaluated the usefulness of an intervention for the prevention of suicide reattempts using green cards in adolescents 16 years of age or younger who were discharged from the hospital following a suicide attempt. After discharge, these adolescents were randomized into an experimental (n = 47) and a control group (n = 58). A green card which served as a passport to readmission into a pediatric ward at their local hospital was sent to the participants in the experimental group. If adolescents felt suicidal, they would be able to obtain immediate admission to the hospital. Adolescents in the control group received

standard treatment from their clinic or child psychiatric department. For one year after the suicide attempt, information was collected through green cards. In the year of follow up, only 3 (6%) patients in the experimental group made a suicide attempt and 5 (11%) made use of their green cards; whereas, in the control group, 7 (12%) attempted suicide. Although the repeat rate for those without green cards was twice that of those with green cards (12% *vs* 6%), this difference did not reach statistical significance (P = 0.26). It was observed that adolescents used the green card properly, considering it as a solution to their problems, knowing that they could be hospitalized if necessary.

LETTERS AND TELEPHONE CONTACT

Mouaffak *et al*[36] developed a follow-up intervention program called the organization of a suitable monitoring for suicide attempters (OSTA), which aimed to test the efficacy of a 1-year RCT. In this study individuals (n = 320) admitted to the psychiatric ED and the Psychiatric Department of the University Hospital of Bicêtre, France, were randomly assigned to receive either the OSTA program (n = 160) or a control treatment (n = 160). On an intention to treat basis, the proportion of patients who reattempted suicide did not differ significantly at 12 mo, between the intervention arm and the control arm. There was also a nonsignificant difference found between the two groups in the number of suicide attempts in the intervention *vs* the control group. For the repeaters, the percentage of those who have attempted suicide in the experimental group is only slightly higher than that of the control group (23.4% *vs* 23.3%).

Kapur *et al*[37] carried out a pilot RCT to evaluate if periodic contact after an act of self-injury can influence self-destructive behavior. Participants were admitted to the ED after self-harm and then randomized to the control (n = 33) or intervention group (n = 33). The intervention included an information leaflet listing sources of help, two telephone calls during the first 2 wk, and letters sent at 1, 2, 4, 6, 8 and 12 mo. After 12 mo, the rate of repetition of self-harm behavior was higher in the intervention group than control group.

TELEPHONE CONTACT

De Leo *et al*[38] conducted a study that showed encouraging results regarding the use of telephone contact to reduce suicidal behavior. The researchers compared the suicide rate between people connected to the service and the general population in the Veneto region of Italy. Tele-Help/Tele-Check included both an active help system to call and a service that provided a phone call about twice a week. During the 4 years of follow up, only one death by suicide was reported in the intervention group compared with the expected value of 7.44 for the general population. This study was replicated by De Leo *et al*[39], which evaluated the impact of telephone contact after 10 years of follow up (from 1988 to 1998). Only 6 deaths by suicide occurred during this time period, which were less than expected (n = 20.86) and confirmed the benefit of the Tele-Help/Tele-Check service.

Cedereke *et al*[40] conducted a randomized controlled trial to determine if telephone contacts can have an effect on suicidal behavior after a suicide attempt. Patients (n = 107) received a telephone call at 4 and 8 mo following discharge from a Medical Emergency Inpatient Unit and 109 subjects did not receive the intervention. Two suicide deaths occurred during the 12 mo-follow up: One woman belonging to the intervention group and one man belonging to the control group. There were no significant differences in subjects who died by suicide: 14 subjects in the intervention group (17%) and 15 in the control group (17%).

Vaiva *et al*[41] conducted a randomized controlled trial in order to demonstrate that a telephone call can reduce numbers of reattempted suicide. Subjects discharged from the ED after a suicide attempt by drug overdose were randomly assigned to three different groups: One group received telephone contact at one month; another group received telephone contact at three months and the last group did not receive any telephone contact (control group). Numbers of reattempted suicides was significantly lower in the group that received a telephone call after one month than the control group (12% *vs* 22%). For people contacted at three months, the difference was not significantly lower than control group (17% *vs* 22%).

Fleischmann *et al*[42] recruited 1867 suicide attempters from emergency departments at 5 different countries: (Brazil, India, Sri Lanka, Islamic Republic of Iran, China) and conducted a RCT to investigate the role of periodic contact on suicidal behavior. All participants were randomly assigned to receive 1 h of brief intervention as close to the time of discharge as possible and nine follow-up contacts after discharge or to receive only treatment of somatic symptoms related to a suicide attempt (control group receiving treatment as usual - TAU). The primary outcome measure was the number of deaths by suicide. At 18-mo follow-up, 18 participants (2%) in the control group died by suicide *vs* 2 subjects (0.2%) in the intervention group.

Bertolote *et al*[43], starting from the RCT of Fleischmann *et al*[42], evaluated rates of repeated suicide attempts as the secondary outcome during 18-mo of follow up. No significant difference between the two groups was shown in the results of this study. This result did not confirm the encouraging reduction of suicide mortality previously demonstrated by Fleischmann *et al*[42].

Cebrià *et al*[44] conducted a case-control study to evaluate the efficacy of a telephone contact program. Patients discharged from the ED following a suicide attempt were included. Participants of the intervention group (n = 296) received a telephone call after 1 wk, thereafter at 1, 3, 6, 9 and 12-mo intervals.

The patients in the control group (n = 218) received treatment as usual without additional telephone contact during 1-year follow-up. Results showed that the telephone contact program was associated with a low rate of patients who reattempted suicide compared to the previous year and to the control population. The telephone management program also delayed suicide reattempts in the intervention group compared the control population. Cebria *et al*[45] called all the participants in the previous study again after 5 years in order to evaluate the benefit of telephone contact on the suicidal behavior over the long term. There was not a statistically significant difference in the number of people who reattempted suicide after 5 years (intervention group: 31.4% *vs* control group: 34.4%). This result suggests that telephone contact after a suicide attempt was effective after one year, but this benefit was not maintained after 5 years.

Amadéo *et al*[46] conducted a RCT to test the efficacy of brief intervention and telephone contact after a suicide attempt. Two hundred patients admitted to the ED for self-harm behaviors were randomly assigned to the control group (n = 100) or to the intervention group (n = 100). Participants of the control group received treatment as usual. Patients in the intervention group received care as usual plus one hour of information session and 9 telephone contacts at 1, 2, 4, 7 and 11 wk and at 4, 6, 12 and 18 mo. It was found no significant difference in the frequency of suicidal behavior between the two groups. Two deaths by suicide occurred in the control group *vs* none in the intervention group.

TELEPHONE, EMAIL, TEXT MESSAGE, LETTERS

Hvid *et al*[47] conducted a quasi-experimental prospective design study to evaluate the utility and efficacy of a Baerum-model like intervention after attempted suicide. The Baerum model is a form of cooperation between Baerum hospital and the municipal health services in Asker and Bærum municipalities. The Bærum model consists of four stages: Medical treatment and monitoring; psychosocial/psychiatric intervention; aftercare by a public health nurse; continued residential or non-residential treatment. In this prospective study, patients who attempted suicide (intervention group; n = 93) were provided follow-up care by a program offering home visits and contacts. The patient identified a primary contact while in the hospital and follow-up visits were conducted after discharge by personal contact, telephone calls, letters, text messaging and e-mails. A control group (n = 58) received TAU, which included a psychiatric assessment followed by a decision on whether to offer the patient psychiatric treatment. Results revealed a significantly lower repetition rate in the intervention group; the proportion of repetitive patients fell from 34% to 14%. There were also fewer suicidal acts, in total 37 acts in the control group and 22 acts in intervention group. The Baerum model like intervention has a good chance of being a suicide prevention intervention of high acceptability and adherence, and was found to have acceptable effectiveness in the follow-up period of 1 year. As Hvid *et al*[48] have found encouraging results from the previous quasi-experimental prospective study conducted on the Baerum model, they decided to assess this model also through an RCT. They decided to evaluate the above-mentioned model based on the same model of intervention to assess it on the prevention of new suicide attempts in patients who had already made an attempt. During a two year period, 133 participants were randomized to the experimental group (n = 69) and they received the OPAC program and 64 to the (non-intervention) control group. The intervention in the experimental group was implemented as soon as possible following the suicide attempt. In the intervention group was observed a significantly lower proportion (proportion 8.7%) of patients who repeated a suicide attempt than in the control group (proportion 21.9%). Also the number of repetitive acts was significantly lower (8 repetitions in the intervention group *vs* 22 in the control group) (Table 1).

DISCUSSION

The present review sought to shed light on the role of new technologies as a means of preventing suicide in patients discharged from EDs and/or psychiatric wards. A systematic and meta-analytic review was conducted by Milner *et al*[49] to synthesize the evidence regarding the efficacy in reducing self-harm, suicide attempt and suicide deaths of brief contact interventions (*e.g.*, letters, green cards, telephone calls and postcards). However, unlike our study, Miller and colleagues did not focus on the evaluation of these means of prevention in the post discharge from an ED or psychiatric ward. Although the results of this review demonstrated how brief contact interventions have had a significant effect on the number of episodes of repeated self-harm or suicide attempts, these brief contact interventions cannot yet be recommended for widespread clinical implementation.

Based on the main findings of the present review, different types of new technologies have been used and evaluated in several studies as a means of suicide prevention. From this review, 10 studies examined the role of postcards, letters, crisis cards/green cards, 9 studies investigated the role of telephones, 2 studies the role of the telephones and letters (simultaneously) and 2 assessed the role of the telephones, letters, and text messages (simultaneously).

Regarding studies based on the use of postcard/crisis card/green card as a means of suicide prevention, only three of these studies have shown that these means may reduce the rate of suicide[26] and suicide ideation[27,28] in the experimental group to follow up. The other seven studies found that the intervention does not

Table 1 Summary of studies reporting contact with patients involving new technologies and reaching-out means in the post-discharge period

Ref.	Study design	Sample	Criteria	Methods	Outcomes	Follow-up	Results
Postcard/ letters/crisis card/green card							
Motto *et al*[26], 2001	RCT	843 participants	843 patients who had refused ongoing care after hospitalization because of a depressive or suicidal state	843 patients randomized to Intervention group: (n = 389) contacted by short letter for five years (a total of 24 letters for five years); control group: (n = 454) received no contact	Suicide rate	5 yr (contact period) and 10 yr	Patients in the contact group had a lower suicide rate in all five years of the study Intervention group: Suicide rate: 0.77% Control group: Suicide rate: 1.32% only for the first two years (P value = 0.043). Differences gradually decreased and at 15-yr no differences were observed
Hassanian-Moghaddam *et al*[27], 2011	RCT	2300 participants	Subjects admitted to the Loghman-Hakim Poison Hospital from March to June 2006, above 12 yr of age with self-poisoning defined by exclusion of poisoning classified as recreational, habitual misuse, accidental or iatrogenic by the treating medical toxicologist	2300 patients randomized to Intervention group: (n = 1150) received nine postcards sent over 12 mo. Eight postcards are mailed at 1, 2, 3, 4, 6, 8, 10 and 12 mo after discharge. A ninth postcard is sent for each participant's birthday Control group: (n = 1150) received no contact	Suicidal ideation; suicide attempt; cutting or self-mutilation; deaths	12 mo	A postcard intervention reduced suicidal ideation and suicide attempts. Sustained, brief contact by mail may reduce suicidal ideation and suicide attempts in individuals who self-poison Suicidal ideation: Intervention group: 29.0%. Control group: 41.7% Relative risk reduction: 0.31 (0.22 to 0.38). Number needed to treat: 7.9 (6.0 to 11.5) Suicide attempt: Intervention group: 3.0%. Control group: 5.1% Relative risk reduction 0.42 (0.11 to 0.63). Number needed to treat 46.1 (26 to 203.7) Self-cutting: Intervention group: 4.0%. Control group: 4.7% Relative risk reduction 0.14 (-0.29 to 0.42) Number needed to treat NA
Hassanian-Moghaddam *et al*[28], 2017						24 mo	There was a beneficial effect demonstrated for suicidal ideation and suicide attempt during the 24 mo follow-up period (after cessation of the intervention), however, there was no effect on self-cutting behavior during the same period Suicidal ideation: Intervention group: 46.6%. Control group: 58.6% ARR: 11.93% (95%CI: 7.58-16.27), OR: 0.62 (95%CI: 0.52-0.74) Suicide attempt: Intervention group: 6.2%; control group: 9.1% ARR: 2.85% (95%CI: 0.52-5.17), OR: 0.67 (95%CI: 0.48-0.93) Self-cutting: Intervention group: 1.5%; control group: 1.5% ARR: 0.00% (95%CI: -0.01-0.01), OR: 1.01 (0.49-2.07)

Carter *et al*[29], 2005	RCT	772 participants	Participants (> 16 yr) presented to the toxicology service with deliberate self poisoning from April 1998 to December 2001	772 patients randomized To Intervention group: (n = 378) received a postcard at 1, 2, 3, 4, 6, 8, 10 and 12 mo after discharge Control group: (n = 394) received no contact after discharge	Proportion of patients who repeat episodes of deliberate self poisoning; the number of repeat episodes of deliberate self poisoning per person	12 mo	A postcard intervention reduced repetitions of deliberate self poisoning, although it did not significantly reduce the proportion of individual repeaters Proportion of patients who repeated episode of self poisoning: Intervention group: 15.1%; control group: 17.3% N° of repeat episodes: Intervention group: 101; control group: 192 Incidence risk ratio of repetition: Intervention group: 0.55 *vs* Control group: 1.00 [ES = 0.13 (CI: 0.35 to 0.87); P value = 0.010]
Carter *et al*[30], 2007					Proportion of patients who repeat episodes of deliberate self poisoning; number of repeat admissions	24 mo	A postcard intervention maintained the halving of the rate of hospital-treated-self-poisoning events over 2-yr period, although it did not significantly reduce Proportion of patients who repeated episode of self poisoning: Intervention group: 21.2%; control group: 22.8% N° of readmissions: Intervention group: 145. Control group: 310 Incidence risk ratio of repetition: Intervention group: 0.49; control group: 1.00 [ES = 0.10 (CI: 0.33 to 0.73); P value = 0.010] The treatment was effective only for women: Intervention group: 0.49; control group: 1.00 [ES = 0.12 (CI: 0.30 to 0.80); P value = 0.004]
Carter *et al*[31], 2013					Proportion of patients who repeat episodes of deliberate self poisoning; number of repeat admissions; proportion of patients admitted to the hospital for any psychiatric reason; number of readmissions to a psychiatric hospitals; all-cause mortality; suicide deaths	5 yr	A postcard intervention halved self-poisoning events and reduced psychiatric admissions by a third after 5 yr Proportion of patients who repeat episodes of deliberate self poisoning: Intervention group: 24.9%. Control group: 27.2% Number of repeat admissions: Intervention group: 252; control group: 484 Incidence risk ratio of readmission: Intervention group: 0.54; control group: 1.00 (CI: 0.37 to 0.81; P value < 0.01) The treatment was effective only for women: Intervention group: 0.55; control group: 1.00 [CI: 0.34 to 0.88); P value = 0.01] Proportion of patients admitted to the hospital for any psychiatric reason: Intervention group: 38.1%. Control group: 35.5% Number of readmissions to a psychiatric hospital: Intervention group: 447; control group: 710 All-cause mortality: Intervention group: 5.8%; control group: 5.6% Suicide deaths: Intervention group: 1.3%. Control group: 1.5%

Beautrais *et al*[32], 2010	RCT	327 participants	Participants (> 16 yr) admitted to psychiatric emergency services at Christchurch Hospital, New Zealand, following self-harm or attempted suicide during the period August 1, 2006 to April 6, 2007	327 participants randomized to Intervention group: (*n* = 153) received treatment as usual + postcard intervention (six "postcards" sent by mail during the 12 mo following) Control group: (*n* = 174) received treatment as usual	Percentage of patients re-submitted at the psychiatric emergency service and at the emergency department for self-harm; numbers of self-harm re-presentations	12 mo	There were no significant differences between the control and intervention groups in the proportion of participants re-presenting with self-harm or in the total number of re-presentations for self-harm Percentage of patients re-submitted at the psychiatric emergency service and at the emergency department for self-harm: Intervention group: 25.5%; control group: 28.2% Numbers of self-harm re-presentations: Intervention group: 56.9%; control group: 78.2% (IRR 0.73; CI: 0.5-0.95; *P* value < 0.03)
Evans *et al*[33], 1999	RCT	827 participants	Patients admitted to hospital following deliberate self-harm between November 1994 and July 1996	827 patients randomized to Intervention group: (*n* = 417) received the green card offering 24-h crisis telephone consultation with an on-call psychiatrist for up to 6 mo Control group: (*n* = 410) received standard treatment	Patients who repeated self-harm	6 mo	At 6 mo, there was no effectiveness of the provision of a card offering 24-h crisis telephone consultation on repetition of self-harm but there was a possible benefit among those presenting following a first episode Patients with repeated self-harm: Intervention group: 16.8%; control group: 14.4% Median time to repetition: Intervention group: 33 d; control group: 40 d Intervention with green card seemed to have a protective effect on self-harm first timers *vs* people with history of previous self-harm. First timers: 18 (OR: 0.64; 0.34-1.22) Previous history of self-harm: 52 (OR: 1.85; CI: 1.14-3.03)
Evans *et al*[34], 2005						12 mo	At 12 mo there was no overall benefit of the intervention. Among those with a first episode of self-harm, the possible benefit of the intervention had diminished Patients with repeated self-harm: Intervention group: 21.6%; control group: 18.8% Median time to repetition did not differ between the two groups Among those with a first episode of self-harm, the possible benefit of the intervention had diminished compared to Evans *et al*[33] 1999 (OR: 0.89, CI: 0.52-1.52)
Cotgrove *et al*[35], 1995	RCT	105 participants	Adolescents (aged 16 yr or under), admitted to the study hospitals between January 1987 and January 1990 for a suicide attempt (all acts of deliberate self-poisoning and deliberate self-harm are also considered)	105 participants randomized to Intervention group: (*n* = 47) received a token, a green card, which acted as a passport to re-admission into a pediatric ward in their local hospital Control group: (*n* = 58) received standard treatment	Rate of further suicide attempts; rate of the use of the token	12 mo	There were lower rates of repeat suicide attempts in the intervention group. The differences between two groups did not reach the level of statistical significance Further suicide attempts: Intervention group: 6%; control group: 12% Rate of repetition: Intervention group: 6%; control group: 12%

Letters and telephone contacts							
Mouaffak *et al*[36], 2015	RCT	320 participants	Adult subjects (men and women > 18 older) surviving a suicide attempt, discharged from the Emergency Department from January 2009 until December 2011	320 participants randomized to Intervention group: (n = 160) destined to OSTA program (provided a card with a telephone number of a psychiatrist available 24 h a day and telephone calls at 2 wk post discharge, at months 1 and 3) Control group: (n = 160) received no contact	Proportion of patients who reattempted suicide; proportion of patients who started a medical follow-up	12 mo	There were no significant differences, between the two groups, in the number of patients who reattempted suicide and in suicide attempts Proportion of patients who reattempted suicide: Intervention group: 14.5%; control group: 14% Number of suicide attempts: Intervention group: 0.2 ± 0.58. Control group: 0.23 ± 0.84 Patients who started a medical follow-up: Intervention group: 24.2%; control group: 31%
Kapur *et al*[37], 2013	RCT	66 participants	Participants (> 18 yr), resident in Manchester, who presented to 2 of the 3 Emergency Department in the city with self-harm during November 2010 to May 2011	66 participants randomized to Intervention group: an information leaflet listing local and national sources of help mailed as soon as possible after consent, two telephone calls within the first 2 wk, and then a series of letters over a 12-mo period (at 1, 2, 4, 6, 8 and 12 mo). Control group: Received treatment as usual	Proportion of patients with at least one repeat episode of self-harm resulting in hospital attendance within 12 mo; number of repeat episodes during the same time period	12 mo	The rate of repetition of self-harm behavior was higher in the intervention group than control group. Repeat rate of self-harm over 12 mo: Intervention group: 34.4%. Control group: 12.5% (OR: 3.67, 95%CI: 1.0-13.1; P = 0.046) Total number of episodes of repeat self-harm over 12 mo: Intervention group: 41; control group: 7. [IRR = 5.86, 95%CI: 1.4-24.7; P value = 0.016] Adjusting for baseline clinical factors (centre, method of harm (self-poisoning *vs* other), previous self-harm, previous psychiatric treatment): repetition: (adjusted OR: 4.35, 95%CI: 0.9-19.8; P value = 0.057) repeat episodes: (adjusted IRR = 7.16, 95%CI: 1.6-32.8, P value = 0.011)
Telephone contact							
De Leo *et al*[38], 1995	Ecological study	12135 participants	Participants (> 65 years old) who were living in the Veneto region of Italy connected to the Tele Help/ Tele-Check service from January 1, 1998 and December 31, 1998	Authors compared the rate of suicide between Tele-Help/Tele Check users and the general population	Rate of suicide	4 yr	Only one suicide death occurred among elderly service users than expected. Ratio: 1:7.44 between observed and expected suicides. Standardized mortality ratio: (1/7.44 × 100%): 13.44% (χ^2 = 2.54, df = 1, 95%CI: 0.3%-74.8%; P value < 0.05)
De Leo *et al*[39], 2002	Ecological study	18641 participants		Comparison between observed and expected suicide rates among older Tele-Help/Tele-Check users		10 yr	Significantly fewer suicide deaths occurred among elderly service users than expected. Suicide deaths: Observed n = 6; expected n = 20.86, χ^2 = 10.58, df = 1; P value < 0.001 with an SMR for users of 28.8% (95%CI: 11.5-62.5)
Cedereke *et al*[40], 2002	RCT	216 participants	Patients treated after a suicide attempt at the Medical Emergency Inpatient Unit of the University	216 participants randomized to Intervention group: (n = 107) received telephone call at 4 and 8 mo	Attendance to treatment; repetition of suicide attempts; GAF, CSI, SSI score	12 mo	At follow-up, attendance and repetition of suicide attempts did not differ between the two groups Attendance to treatment repetition of suicide attempts: At baseline: Intervention group:

			Hospital of Lund between February 1995 and April 1997	Control group: (n = 109) destined to no such interventions			76%, Control group: 72% At follow-up: Intervention group: 72%. Control group: 65% Repetition of suicide attempts: Intervention group: 17% made 26 suicide attempts. Control group: 17% made 27 suicide attempts GAF: Intervention group: 1st month = 50.5 ± 19.9. 12th month = 61.4 ± 20.4 (P value < 0.001) Control group: 1st month = 50.3 ± 21.1. 12th month = 58.6 ± 20.2 (P value < 0.01) SSI score Intervention group: 1st month = 7.9 ± 8.4 (P < 0.10). 12th month = 5.8 ± 7.8 (P value < 0.05) Control group: 1st month = 5.0 ± 6.8 (P < 0.10). 12th month = 4.0 ± 6.2 (P value < 0.05) SCL90-GSI Intervention group: 1st month = 1.05 ± 0.74. 12th month = 0.82 ± 0.78 (P value < 0.05) Control group: 1st month = 1.02 ± 0.77. 12th month = 0.88 ± 0.72
Vaiva *et al*[41], 2006	RCT	605 participants	People (18-65 yr) discharged from an emergency department after attempted suicide by deliberate self poisoning	605 participants randomized to Intervention group: (n = 147) received telephone contact at one month after a suicide attempt Intervention group: (n = 146) received telephone contact at three months Control group: (n = 312) without telephone intervention	Proportion of participants who reattempted suicide, number of deaths by suicide and losses to follow up at 13 mo	13 mo	For participants contacted at one month, the number of who reattempted suicide is significantly lower than that of controls. For participants contacted at three months, the number who attempted suicide was not significantly lower than that of control Proportion of participants who reattempted suicide: At 1 mo: Intervention groups: 16%. Control group: 19% At 3 mo: Intervention group: 14%). Control group: 19% Number of deaths by suicide: At 1 mo: Intervention group: 0 %. Control group: 1% At 3 mo: Intervention group: 1%. Control group: 1% Lost to follow up: At 1 mo: Intervention group: 7%. Control group: 10% At 3 mo Intervention group: 10%. Control group: 10%
Fleischmann *et al*[42], 2008	RCT	1867 participants	Suicide attempters identified by medical staff in the emergency units of eight collaborating hospitals in five different countries	1867 participants randomized to Intervention group: (n = 922) received treatment as usual plus brief intervention and contact (which provided a standard 1-h individual information session combined with periodic follow-up phone calls or visit) Control group: (n = 945) received treatment as usual	Deaths from suicide	18 mo	Significantly fewer suicide deaths occurred in the intervention group than in the control group. Suicide deaths: Intervention group: 0.2%. Control group: 2.2% (P value < 0.001)

Bertolote *et al*[43], 2010					Repeated suicide attempts		At follow up, repeated suicide attempts did not differ between the two groups. Repeated suicide attempts: Intervention group: 7.6%. Control group: 7.5%
Cebrià *et al*[44], 2013	Case-control study	991 participants	Patients without age limit treated for attempted suicide during the years 2007-2008. They were identified following a systematic review of electronic medical records of the emergency departments of psychiatry, medicine, traumatology, surgery and pediatrics in the area of Sabadell	991 participants randomized to Intervention group: (n = 604) received telephone call for 1-yr after discharge from Emergency Department for suicide attempt Control group: (n = 387) received treatment as usual	Days to first reattempt; rate of patients who reattempted suicide	12 mo	The rate of patients who reattempted suicide was lower in the intervention group compared to the previous year Mean time in days to first reattempt Intervention group: Baseline: 316.64; Intervention year: 346.47 (Baseline *vs* intervention years log rank P value < 0.0005) Control group: Baseline: 273.05; Intervention year: 300.36 Intervention group *vs* control group during the intervention year (respectively 346.47 *vs* 300.36; log rank P value < 0.0005) Rate of patients who reattempted suicide Intervention group: Baseline: 14%; Intervention year: 6% (Baseline *vs* intervention years log rank P value < 0.0005) Control group: Baseline: 21%; Intervention year: 14% Intervention group *vs* control group during the intervention year (respectively 6% *vs* 14%; log rank P value = 0.005)
Cebrià *et al*[45], 2015	Nonrandomized, controlled, parallel study	514 participants		All participants (Cebria *et al*[45] 2013) were called after 5 yr	Rate of reattempts; time to recurrence	5 yr	There was a reduction of the rate of reattempts in the first year. The effects of the intervention was not be maintained at 5 yr Rate of reattempts Intervention group: 0.864. Control group: 0.839 Time to recurrence Intervention group: 1429 d. Control group: 1332 d
Amadéo *et al*[46], 2015	RCT	200 participants	Participants admitted to the Emergency Department of the Centre Hospitalier de Polynésie Française for intentional self harm over the period 2008-2010. All patients included in this study had a short psychiatric hospitalization (minimum 24 h)	200 patients Randomized to Intervention group: (n = 100) received treatment as usual plus brief intervention and contact (which provided nine follow-up phone calls Control group: (n = 100) received treatment as usual	Number of suicides and repeated non-fatal suicidal behavior	18 mo	There were a reduction in the number of suicides and episodes of non-fatal suicide behaviour in the intervention group Episodes of non-fatal suicide behaviour: Intervention group: 26.7% *vs* Control group: 21% Suicide: Intervention group: 0% *vs* Control group: 2.0%
Telephone, e-mail, text message, letters							
Hvid *et al*[47], 2009	Cohort study	151 participants	Participants arrived at the hospital's emergency rooms and clinical departments of	151 participants are randomized to Intervention group: Cohort of 2004 (n = 93) received a primary	Participation by acceptance and adherence;	1 yr	There were a significant lower repetition rate and fewer suicidal acts in the intervention group. The programme had a high acceptability Acceptability:

			Copenhagen University Hospital Amager for attempted suicide and self-harm actions through spring 2002 and spring 2004	contact while the patient was in hospital and followed-up visits (8) after hospital discharge, by personal contact, telephone calls, letters, text messaging and emails. The intervention period was limited to 6 mo Control group: Cohort of 2002 (n = 58) received no contact	repetition of suicide attempt and suicide; number of repetitive acts in 1 yr after the attempted suicide episode		65 of 94 patients of the Cohort of 2004 remained in the programme (70% participation) Repetitions during 1 yr: Cohort of 2002: 18 repetitive patients and 1 suicide (32.8%) 37 repetitive acts Cohort of 2004: 12 repetitive patients and 1 suicide (13.9%), 22 repetitive acts RR = 0.427 (95%CI: 0.228-0.797)
Hvid *et al*[48], 2011	RCT	133 participants	Subjects admitted to the emergency room and clinical departments and screened for attempted suicide and self-harm actions during a period from 2005-2007	133 participants randomized to Intervention group: (n = 69) received home visit and additional contact (telephone calls and text messages) Control group (n = 64) received no contact	Proportion of patients who repeated suicide attempt; number of suicidal acts	12 mo	There were a significant lower proportion who repeated a suicide attempt the intervention group and the number of repetitive acts was also significant lower Proportion of patients who repeated suicide attempt: Intervention group: 8.7%; Control group: 21.9% (Fewer events for intervention group vs control group; log rank P = 0.0414) Number of suicidal acts: Intervention group: 8; Control group: 22 (log rank P = 0.0037)

RCT: Randomized controlled trial.

significantly reduce the repetition of self-poisoning[29-31], self-harm[32-35] and suicide[35]. However, although Beautrais did not find a statistically significant reduction in repetition of self-harm, she noted a reduction in the total number of new admissions to the ED for self-harm.

Regarding the two studies included in this review which examined both letters and telephone contacts, one[36] showed no significant differences in the number of new suicide attempts in the two groups of intervention and control with the proportion of patients who reattempted suicide not differing significantly at 12 mo. The other study[37] demonstrated a higher rate of self-harm in the experimental group compared to the control group after 12 mo of follow up.

Nine studies that used only telephone contacts as a means of prevention of suicide in the post discharge period were included in our review. Of these, four studies showed a benefit in terms of suicide risk reduction[38,39] with a significant decrease in the number of suicide reattempts[41] at one month follow-up and a decrease in the number of deaths by suicide at 18 mo[42]. One study demonstrated a statistically significant decrease in the rate of patients who reattempted suicide at 1 year[44], but not at 5 years[45]. Three other studies, however, found no significant differences[40,43,46] in terms of suicide risk reduction through the use of telephone contact, therefore, they cannot be considered a useful means of suicide prevention. Some authors have also assessed the simultaneous use of multiple media such as telephone calls, emails, text messages and letters[47,48], and have found promising results regarding the reduction in the risk of reattempting suicide. Thus, we can conclude that approximately half of the studies considered in our review (11 of 23) have shown that new technologies can be used with some benefit to decrease the risk of new attempts of suicide or self-harm in the post discharge period. It was also observed that telephone contacts, postcard, text message, *etc*., are easily used by patients in the period of post discharge and allow a contact that is thought to beneficial. Future researchers should continue to improve and test new technologies in the prevention of suicide. For example, an online, unguided, self-help intervention for reducing suicidal ideation was recently found to be useful, usable, and cost effective[50]. Also Berrouiguet *et al*[51] designed a 2-year multi-center randomized controlled trial which will assess the efficacy of a text message intervention on reducing the risk of suicide attempt repetition among adults after self-harm. This intervention is called SIAM (suicide intervention assisted by messages) and it represents an easily reproducible intervention that aims to reduce suicide risk in adults after self-harm. Also Vaiva *et al*[52] have developed and examined the effectiveness of "ALGOS algorithm", an intervention based on systematic telephone contacts and a crisis card, which aims to reduce the incidence of repeated suicide attempt during the 6 mo following discharge. The authors suggest that this intervention will be easily reproducible and will supply guidelines for assessment and management of this high-risk population.

LIMITATIONS

This paper does not present a systematic review or a meta-analysis. It is also possible that studies were missed or excluded. Our review focused on a range of interventions (telephone, postcards, letters, green/crisis cards, text messages, email) that may have a different effect. We examined the role of these interventions on suicide and on self-harm, acknowledging that these are two very different and distinct behaviors. Our focus was on English language literature and more important source of data may be available in other languages.

CONCLUSION

Through our review of the literature concerning the new technologies and the prevention of suicide, we have concluded that it is necessary to reach out and initiate contact with the patient who has attempted suicide following hospital discharge. Moreover, we observed that new technologies and brief contact interventions (*e.g.*, letters, green cards, telephone calls, postcards) are valuable in the prevention of suicide and should be employed in conjunction with standard treatments. Patients who are utilizing these methods consider them usable, effective, efficient, and secure. We have determined that new technologies have the potential to be important suicide prevention resources; however, it is necessary to further examine the possible benefits of these efforts through well-designed clinical trials.

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MINIREVIEWS

Catatonia as a putative nosological entity: A historical sketch

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Abstract

Kahlbaum was the first to propose catatonia as a separate disease following the example of general paresis of the insane, which served as a model for establishing a nosological entity. However, Kahlbaum was uncertain about the nosological position of catatonia and considered it a syndrome, or "a temporary stage or a part of a complex picture of various disease forms". Until recently, the issue of catatonia as a separate diagnostic category was not entertained, mainly due to a misinterpretation of Kraepelin's influential views on catatonia as a subtype of schizophrenia. Kraepelin concluded that patients presenting with persistent catatonic symptoms, which he called "genuine catatonic morbid symptoms", particularly including negativism, bizarre mannerisms, and stereotypes, had a poor prognosis similar to those of paranoid and hebephrenic presentations. Accordingly, catatonia was classified as a subtype of dementia praecox/schizophrenia. Despite Kraepelin's influence on psychiatric nosology throughout the 20th century, there have only been isolated attempts to describe and classify catatonia outside of the Kraepelinian system. For example, the Wernicke-Kleist-Leonhard school attempted to comprehensively elucidate the complexities of psychomotor disturbances associated with major psychoses. However, the Leonhardian categories have never been subjected to the scrutiny of modern investigations. The first three editions of the DSM included the narrow and simplified version of Kraepelin's catatonia concept. Recent developments in catatonia research are reflected in DSM-5, which includes three diagnostic categories: Catatonic Disorder due to Another Medical Condition, Catatonia Associated with another Mental Disorder (Catatonia Specifier), and Unspecified Catatonia. Additionally, the traditional category of catatonic schizophrenia has been deleted. The Unspecified Catatonia

category could encourage research exploring catatonia as an independent diagnostic entity.

Key words: Catatonia; Psychomotor disturbances; DSM-5; Nosology; History

Core tip: Kahlbaum was the first to propose catatonia as a separate disease, whereas Kraepelin concluded that persistent catatonic symptoms (particularly negativism, bizarre mannerisms, and stereotypes) were hallmarks of the catatonic subtype of dementia praecox/schizophrenia. Although the Wernicke-Kleist-Leonhard school attempted to comprehensively elucidate the phenomenology and genetics of psychomotor disturbances associated with major psychoses, the complexity of the Leonhardian catatonia concept has hindered its acceptance in mainstream psychiatry. Kraepelin's influence on psychiatric classifications led to the appearance of catatonia only as a subtype of schizophrenia in the first three editions of the DSM. Progress in this field is illustrated by the inclusion of three forms of catatonia in DSM-5, thus paving the way toward an exploration of Kahlbaum's original concept of catatonia as a distinct disease entity.

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INTRODUCTION

Catatonia, which is generally conceptualized as a syndrome and characterized by a variety of autonomic, behavioral, and psychomotor abnormalities, occurs at high frequencies of 2.7%-17% among psychiatric inpatients[1]. The existence of different diagnostic criteria for catatonia may explain the diverse range of reported prevalence rates. For example, the simultaneous application of the Bush-Francis Catatonia Rating Scale (BFCRS)[2] and the DSM-IV and DSM-5 criteria to the same 130 acutely ill inpatients yielded catatonia diagnosis rates of 63%, 25% and 17%, respectively[3]. This paper outlines the historical development of the concept of catatonia as a distinct disease entity.

FIRST DESCRIPTION OF CATATONIA

Most classical authors, including Guislain, Pinel, Kiesel, Griesinger, and Arndt, described clinical pictures such as "Katalepsie und Psychose", "Melancholia attonita" and "Melancholie avec stupeur"[4]. These descriptions partly overlap with Kahlbaum's view of catatonia as a condition characterized by unusual motor behavior, affective changes, impaired volition and vegetative abnormalities[5,6]. Kahlbaum was the first to propose that catatonia is a separate disease following the example of general paresis among the insane, which served as a model for establishing a nosological entity[5]. The oft-cited definition of catatonia clearly refers to a distinct disease: "Catatonia is a brain disease with cyclic, alternating course, in which the mental symptoms are, consecutively, melancholy, mania, stupor, confusion and eventually dementia. One or more of these symptoms may be absent from the complete series of psychic symptom complexes. In addition to the mental symptoms, locomotor neural processes with the general character of convulsions occur as typical symptoms"[5]. Later in the book, however, Kahlbaum was uncertain about catatonia's nosological position and also considered it "a temporary stage or a part of a complex picture of various disease forms"[5], that is, a syndrome. Kahlbaum's attempt to describe catatonia as a distinct disease entity received mostly critical comments in the international literature, which failed to question his pioneering efforts to coalesce seemingly disparate psychopathological phenomena into a single clinical concept[7-16].

A factor analysis of 26 cases reported by Kahlbaum in his 1874 book yielded both "neurological" and "psychotic depression" factors: 11 cases exhibited neurological signs, 9 exhibited epileptic seizures, 2 cases each involved tuberculosis and general paresis, and 1 case was affected by delirium due to peritonitis[17]. This re-analysis led to the conclusion that "There is a difference between what Kahlbaum actually described and what he thought he was describing at the time"[17].

In the decades following the publication of Kahlbaum's groundbreaking book, catatonic symptoms were described for a host of psychiatric disorders and medical disorders, including mania[11,13,15,18], depression[13,14], infectious diseases, toxic states, delirium, mental retardation and syphilis[8,11]. By the time that seminal papers on catatonia by Seglas and Chaslin[8], Urstein[11], Kirby[15] and Schneider[19] appeared, the concept of catatonia as a separate disease had largely been discarded and, with the exception of a few authors[7], the ubiquitous nature of catatonic signs/symptoms and of the catatonic syndrome itself had been generally accepted in classical continental psychopathology, *i.e.*, mainly German and French psychiatry during the second part of the 19th century and the first few decades of the 20th century.

The concept of catatonia as a syndrome in Anglo-Saxon (English and American) psychiatry was revived and confirmed by Gelenberg[20] some 60 years later. Until recently[1,2,6], the issue of catatonia as a separate diagnostic category was not entertained, mainly owing to the misinterpretation of Kraepelin's influential views.

Catatonia as part of dementia praecox (schizophrenia)

In addition to the symptoms, illness course, and autopsy findings, the final outcome was a principle used

by Kahlbaum[5] to construct his nosology. The outcomes of Kahlbaum's 26 catatonia cases were inconclusive: 8 experienced remission and 8 died or became chronic ("demented"), whereas no follow-up information was available for 10 cases[5].

Kraepelin[21] followed Kahlbaum's nosological principles. However, only one of his 63 catatonic patients, who were followed up for an average of 4 years, completely recovered. An additional 39 never remitted, and even those who remitted showed residual symptoms. In his 1908 textbook, Kraepelin estimated that 13% of catatonia patients would remit[22]. A study of 200 catatonic patients observed between 1901 and 1905 reported a remission rate of 19%[23]. Based on these data and his own clinical experience, Kraepelin concluded that patients presenting with persistent catatonic symptoms he called "genuine catatonic morbid symptoms", particularly negativism, bizarre mannerisms and stereotypes, had a similarly poor prognosis as did those with paranoid and hebephrenic presentations. Thus, catatonia became a subtype of dementia praecox/schizophrenia[22]. While acknowledging the catatonic symptoms associated with mood-related and other psychiatric illnesses, Kraepelin emphasized that the above symptoms were "more characteristic (and) scarcely accompanying any other morbid process in a pronounced form throughout a long period"[22]. Kraepelin also emphasized that catatonic symptoms were not diagnostic criteria for dementia praecox and that the inclusion of the catatonia subtype in his classification was temporary: "So far as judgment on the subject is possible today, we may regard the catatonia of Kahlbaum as in the main a form, though peculiar, of dementia praecox. On the other hand, catatonic morbid phenomena are undoubtedly also observed in many quite different morbid processes to a greater or lesser extent, so that its appearance alone does not justify the conclusion that catatonia in the sense just indicated (*i.e.*, as a dementia praecox subtype) is present"[22].

In conclusion, Kraepelin devised a rather nuanced clinical concept of catatonia, as briefly outlined above. This concept was glossed over for decades, which ascribed to him the simplified view that catatonia equals schizophrenia[6].

DISTINCT CATATONIA SUBTYPES AS PUTATIVE NOSOLOGICAL ENTITIES

Despite Kraepelin's decisive influence on psychiatric nosology throughout the 20th century, only isolated attempts have been made to describe and classify catatonia outside of the Kraepelinian system.

Lethal (malignant) catatonia

In 1934, Stauder based a description of "lethal catatonia" on 27 cases, with the intent to delineate a separate clinical entity[24]. Stauder noted that sudden death in a catatonic state with or without autopsy findings had been well recorded in the psychiatric literature under different names such as acute delirium, Bell's mania, delirious mania, or amentia. Currently, the preferred term is malignant catatonia[25]. Stauder's lethal catatonia was characterized by a sudden, acute onset occurring mostly in young adults presenting with severe excitement ending in stupor, confusion alternating with mutism, rigidity and other catatonic signs and symptoms, vegetative disturbances, fever, dehydration, cardiovascular collapse and negative findings at autopsy[25]. Although the outcome in most of Stauder's cases was fatal, mortality has become relatively rare, with a rate of 9% among the 77 cases published since 1986[25,26]. The consensus view is that malignant catatonia is not a separate entity but a severe form of catatonic syndrome[25,26]. Advances in neurosciences and clinical neurology have led to the determination of the etiologic agents in cases of malignant catatonia, such as paraneoplastic encephalitis[27] or anti-NMDA encephalitis[28].

Most but not all[29] modern authors regard neuroleptic malignant syndrome (NMS) as an antipsychotic drug-induced variant of spontaneously occurring malignant catatonia[30]. While the two syndromes share several clinical characteristics and possibly an underlying pathophysiology, notable differences include the lack of a prolonged excitement phase in NMS and the dynamics how the symptoms develop; typically, a few days of extreme excitement ushers in malignant catatonia followed by exhaustion and stupor[25].

Wernicke-Kleist-Leonhard school of psychiatry

The Wernicke-Kleist-Leonhard school of psychiatry has made a comprehensive attempt to elucidate the complexities of psychomotor disturbances associated with major psychoses[31,32]. Following Wernicke and Kleist's path-breaking work, Leonard devised the final classification of psychomotor disturbances[31,32]. While a variety of motor signs and symptoms may appear in several neurological and psychiatric conditions, catatonic symptoms aggregate into persistent, stable syndromes associated with specific cognitive, affective, and psychotic patterns that sharply delineated categories within the schizophrenic and cycloid psychoses. Leonhard's system differentiates two major groups of psychomotor syndromes: Cycloid motility psychosis and the systematic and non-systematic catatonic schizophrenias. Motility psychosis, described originally by Wernicke, presents with akinetic and hyperkinetic poles both characterized by episodic course, good prognosis and motor symptoms which, although excessive, differ only quantitatively from normal movements, *i.e.*, lack odd/bizarre qualities). Most modern authors would undoubtedly regard motility psychosis as catatonia[33].

The six subtypes of systematic catatonias and non-systematic periodic catatonia are distinguished from normal psychomotor patterns by their qualitative and quantitative differences. Unlike motility psychosis,

these catatonia subtypes have a poor prognosis. Once they emerge, systematic catatonias never remit, and the initially episodic course of periodic catatonia may also become chronic. The sophisticated descriptions of catatonic and akinetic-hyperkinetic syndromes cover 57 psychomotor signs and symptoms[31,32]. A number of cross-sectional and large-scale, long-term (15-20 years) follow-up studies conducted by Kleist, Leonhard and their co-workers confirmed the reliability and stability of Leonhard's classification[31,32,34-37].

Due to its complexity and dissimilarity to mainstream classifications, Leonhard's nosological system has never been subjected to the scrutiny of investigations using modern methods to validate these putative disease entities beyond the works of dedicated proponents of the Wernicke-Kleist-Leonhard school.

Although Leonhard's catatonia subtypes have been subsumed under the group of schizophrenias, they form distinct entities and have been sharply delineated form the rest of schizophrenia subtypes, thereby constitute relatively independent, albeit putative catatonic disease entities.

Periodic catatonia

Periodic catatonia is not recognized by the ICD-10 or any version of the DSM. This nosological category is not well established, and there is no consensus regarding the relevant diagnostic criteria except for the Wernicke-Kleist-Leonhard classification, which has hardly been acknowledged by mainstream psychiatry. Discussions regarding periodic catatonia have always raised two continuously unresolved nosological issues: Whether it is a separate disease entity or just a variant of catatonia with an episodic course and whether it is a clinical form of bipolar affective disorder[22,26].

Catatonia with episodic presentation was recognized as early as 1894, when Nacke coined the term "Katatonie alternans"[38]. Bleuler[38] described similar cases and stated that "we recognize catatonias which run a periodic course". Kraepelin[22] presented several vignettes on periodic catatonia while discussing periodic, agitated, and circular dementias, and the catatonic forms of dementia praecox, but concluded rather dismissively that "some of the smaller groups will in course of time to be got rid of [...] namely for the cases [..] with a periodic course"[22]. However, he did not proceed with an argument regarding why these cases should not be included among the catatonias[22].

Despite its marginal place in nosology, in clinical practice periodic catatonia attracted the first rigorous investigations in biological psychiatry that spanned more than four decades. The father and son duo Rolv and Leiv Gjessing devoted a lifetime of research to periodic catatonia, a special form of schizophrenia. The subjects of their investigations were patients in whom catatonic stupor and excitement occurred with rhythmic periodicity over long periods and were regarded as two facets of the same pathophysiological process. The catatonic condition was painstakingly recorded and correlated with biochemical variables. Cyclic alternations in the nitrogen balance were observed to follow changes in the clinical presentation simultaneously with the catecholamine metabolism, autonomous nervous system, and EEG findings[39,40]. These findings have not been confirmed or refuted by other investigators using modern methods of neurobiology. The treatment of periodic catatonia with large doses of thyroid hormone to correct the nitrogen imbalance was made obsolete by the introduction of antipsychotics and lithium, which proved to be effective[41].

The Wernicke-Kleist-Leonhard school paid much attention to the clinical and genetic aspects of periodic catatonia, one of the three non-systemic schizophrenic psychoses characterized by polymorphous clinical presentation and a cyclic/bipolar course, which not infrequently becomes chronic[31]. In addition to psychotic symptoms, the specific catatonic features include the tendency of the two poles (stupor and excitation) to alternate, or appear simultaneously with signs/symptoms of impulse/aggression preparedness, affective tension, parakinesis, stiff/choppy movements, grimaces (particularly in the upper part of the face), iterative motor stereotypes, and negativism. Extensive clinical genetic studies conducted by Leonhard and his pupils confirmed the high familial incidence of homotypical psychoses in periodic catatonia, yielding a cumulative morbidity risk of 26.9% among first-degree relatives[32,42]. Subsequent and ongoing genome-wide linkage investigations identified two susceptibility loci on chromosomes 15q15 and 22q13[43]. These findings await replication by independent investigators.

Idiopathic catatonia

Ever since Kahlbaum conceptualized catatonia as a putative disease entity, there have been proponents of this idea although it has never gained currency in mainstream psychiatry. Recent reports suggest that in a significant minority of cases a catatonic syndrome appears without any underlying diagnosable psychiatric disorder or medical condition[33,44-49]. Case reports of presumably idiopathic catatonia describing clinical presentations that did not meet modern diagnostic criteria for any psychiatric illness[33,47-49] correspond to the traditional Leonhardian categories of periodic catatonia or motility psychosis[33]. Two studies from India compared idiopathic catatonia with catatonic schizophrenia (n = 13 *vs* n = 21)[45] and depression with catatonic schizophrenia (n = 30 *vs* n = 35)[46]. Idiopathic cases differed from the controls by shorter duration of illness, a preponderance of female patients[45], reduced overall psychopathology as measured by the Brief Psychiatric Rating Scale (BPRS), and higher scores regarding specific catatonia features, particularly negativism, waxy flexibility, Mitgehen, and ambitendency[46]. Further studies are warranted to replicate and extend these preliminary findings. The new DSM-5 diagnosis of Unspecified Catatonia will be the

appropriate category for idiopathic catatonia in psychiatric classification.

CATATONIA IN SUCCESSIVE EDITIONS OF DSM

In the first three editions of DSM catatonia appeared only as a subtype of schizophrenia following a narrow and simplified version of Kraepelin's catatonia concept.

A landmark paper by Gelenberg[20] heralded the rediscovery of catatonia as a syndrome based on knowledge known since Kahlbaum's time that catatonic signs/symptoms are found in several medical and neurological conditions. Reflecting this paradigm shift in modern psychiatry, the new category of Catatonic Disorder Due to a General Medical Condition was introduced in DSM-IV while still retaining the category of Schizophrenia, Catatonic Type[50]. As catatonic syndromes were observed with increasing frequency in patients with mood disorders[51], Catatonic Features was added as a specifier to describe mood disorders more accurately. Catatonic features could be diagnosed if 2 of the 5 composite signs/symptoms were present. Over the past 20 years, the number of publications on catatonia has grown significantly[52]. Rating scales[53] have been constructed and clinical[54], treatment[55], and biological studies[56] have appeared. Books[26] and review papers[57-59] have helped made clinicians cognizant of the clinical significance of catatonia. The development in the field is mirrored in DSM-5[60], which includes three forms of catatonia: Catatonic Disorder Due to Another Medical Condition, Catatonia Associated with Another Mental Disorder (Catatonia Specifier) and Unspecified Catatonia. The traditional category of catatonic schizophrenia was deleted. The diagnostic criteria for the first two categories are identical and require the presence of 3 out of 12 common catatonic signs/symptoms, including stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerism, stereotypy, agitation, grimacing, echolalia and echopraxia.

Unspecified Catatonia, an independent category in DSM-5, is an entirely new, potentially important development in the recognition of catatonia as a distinct diagnostic entity[61]. However, this category remains ambiguous toward catatonia as a separate diagnosis because it was intended to be applied to conditions where "either the nature of the underlying mental disorder or other medical condition is unclear, full criteria for catatonia are not met, or there is insufficient information to make a more specific diagnosis". Uncertainty about the nosological position of catatonia is demonstrated by the placement of the three catatonia diagnoses in the Schizophrenia and other Psychotic Disorders section. Nevertheless, the catatonia concept espoused by DSM-5 constitutes a major step forward and will stimulate the exploration of a separate catatonia diagnosis in clinical practice. Additionally, this concept will foster research[1], particularly if the soon-to-be published ICD-11 follows a similar path.

CONCLUSION

The validity and clinical utility of catatonic schizophrenia in the traditional Kraepelin-Bleuler classificatory system is limited. In an attempt to replace the Kraepelin-Bleuler model, the dimensional approach reaches beyond the classical concept of catatonic schizophrenia. Complex neurobiological and clinical investigations, including the quantification of individual or clusters of catatonic signs and symptoms, have recently taken shape within broadly defined groups of mood disorders and psychoses[62-64]. This dimensional approach reduces bias attributed to the narrow and uncertain nosological categories.

The catatonia concept espoused by DSM-5 constitutes a promising step forward by stimulating the exploration of a separate catatonia diagnosis in clinical practice. It could also foster research[1], such as whole-genome association, epigenetic, and metabolomics studies, particularly if the soon-to-be published ICD-11 is similar to DSM-5.

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SYSTEMATIC REVIEWS

Transition to school for children with autism spectrum disorder: A systematic review

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Abstract

AIM

To identify factors that promote a positive start to school for children with autism spectrum disorder (ASD).

METHODS

Web of Science, MEDLINE, Scopus, and PsychINFO searches were conducted to identify literature published after 1991 and relevant to school transition processes in children with ASD. Twenty studies were deemed eligible for inclusion. These studies evaluated a range of factors including school readiness, parent and teacher perspectives on transition practices, characteristics of children with ASD that are associated with successful transition to school and the impact of school based intervention programs.

RESULTS

A review of these studies showed that children with ASD are less school ready emotionally than their peers and those children with ASD appear to have more externalising behaviours and self-regulation difficulties that affect their school engagement and their relationships with their teachers. There was a paucity of research looking at interventions targeting school readiness. However, school-based behavioural interventions appear to improve cognitive, language and daily living skills, but have less impact on socialisation and peer inclusion.

CONCLUSION

Children with ASD face more challenges transitioning

to school, particularly with social interaction. Further development and implementation of specific school-based interventions is needed in order to assist children with autism to maximise their success in starting school.

Key words: Autism spectrum disorder; School transition; School readiness; School preparation; School based intervention

Core tip: This systematic review examines current school transition research for children with autism spectrum disorder (ASD), focusing on school readiness, parents and teachers school transitions expectations and experiences, individual factors affecting school transition and school-based interventions. Research in this area is disparate and sparse, but suggests that children with ASD have more difficulty adjusting to school, particularly in relation to active engagement and social interactions with the teachers and peers. Teachers and parents agree comprehensive transition processes are needed throughout the first years. School-based intervention programs in the first years can improve cognitive, language and daily-living but more interventions are needed targeting social interaction.

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INTRODUCTION

Starting school is a major event in any child's life and while for children with disabilities this transition can be challenging[1], this is particularly significant for children with autism spectrum disorder (ASD). The unique social, communication and behavioural difficulties that children with ASD experience may present additional barriers to a positive start to school[2,3]. This is particularly relevant as teachers rate social skills as more important than academic skills for successful kindergarten adjustment[4]. An increasing body of evidence supports the notion that children who have a positive start to school are likely to engage well and experience academic and social success[2,3]. Children with ASD have a greater risk of poor school outcomes including emotional and behavioural problems[5] and bullying[6] that result in school exclusion[7] or peer rejection[8]. It is therefore critical that protective factors, as well as barriers to positive school transition in children with ASD are identified and understood[2,3].

The transition process begins at pre-school age whereby the child is prepared for school while also evaluating if the child is "ready", described as "school readiness". Typically, the focus has been on the child "gaining competence" in a range of areas; emotional, behavioural, social and academic[9]. However, it is equally important that parents, schools and teachers are prepared for the special needs of children with ASD. Consequently, it is important to identify the strengths and deficits of children with ASD before they start school, as well as obtaining multiple perspectives from all parties. For this transition process to be successful, intervention and support needs to go beyond the preparation stage and continue after the commencement of school. Decades of research has demonstrated the positive effects of early intervention programs for children with ASD and also the success of later intervention programs for school-aged children. However, substantially less research has specifically evaluated school-based interventions[10,11]. Additionally, much of this research has focused on the later years and not the critical "transition to school" period in the first years of primary school[11]. Finally, for children with ASD, interventions targeting socialisation and communication skills are critical. In order to provide a successful start to school for these children, it is therefore important to develop school-based programs that target a range of skill development across behavioural and social as well as academic domains. However, to develop evidence-based programs, it is important to first establish what aspects of current school-based interventions have been successful in targeting a wide range of skills and behaviours.

While there has been considerable research undertaken on typically developing children's transition to primary school, there is a paucity of empirical studies that examine transition to school for children with ASD[4,12]. Additionally, the research available is not disseminated and there is a lack of synthesis of the available evidence that means that strengths and weaknesses in our current knowledge base are not readily apparent. Thus, there is a great need to establish and consolidate the current evidence on how and when children with ASD are ready for school, the types of supports required by children with ASD, their families and schools, and specific interventions and individual factors that serve to enable a positive start to school. This paper will review the existing research on the preparation and transition of children with ASD to primary school. Specifically, this systematic review aims to examine: (1) School readiness of children with ASD; (2) Parents' and teachers' views and experiences of the school transition process for children with ASD; (3) The characteristics related to positive school transition experiences for children with ASD, such as individual characteristics of the child as well as family variables and teacher, classroom and school characteristics; and (4) School-based interventions to enhance school readiness and transition in the first years of school that were associated with successful school transition for

children with ASD.

MATERIALS AND METHODS

Search strategy

Studies included in this review were located by searching the following electronic databases; Web of Science, MEDLINE, Scopus, and PsychINFO from January 1991 and April 2016. The search was limited to articles published after January 1994, given the adoption of the Individuals with Disabilities Education Act in the early 1990s by the federal government in the United States of America with autism included as a special education category[13], as well as the DSM expanding the definition of autism to include Asperger syndrome. The search was also limited to English language articles only. Secondary searches outside the official databases listed above were undertaken of relevant government and not for profit organisation websites, and ancestral searches were undertaken of the reference lists and reverse citations of included studies.

Searches were undertaken using a combination of the following descriptors: Autism, ASD, pervasive developmental disorder, pdd-nos, ASD, Asperger's syndrome, school transition, school readiness, school preparation, school adjustment, school engagement school entry, school based intervention, elementary school, primary school, kindergarten, preschool, educational interventions, early education, learning/mathematics/reading/literacy ready, learning/mathematics/reading/literacy achievement, learning/mathematics/reading/literacy acquisition and learning/mathematics/reading/literacy development. This broad range of keywords was used in an attempt to capture all articles relevant to the school transition process for children with autism.

Inclusion and exclusion criteria

Inclusion eligibility was based on the following seven criteria. First, only studies that specifically examined children with autism were included. Second, the age for starting school varies from country to country but generally is between 3 and 8 years. Any articles outside of this age range were excluded. Articles with children over 8 years were included if it was a longitudinal study with a baseline within the appropriate age range or if the study was cross-sectional with a younger age group identified and examined as a separate condition within the appropriate age range. Third, survey and interview studies must have targeted parent and teacher views of school transition experiences or school readiness experiences. Fourth, studies assessing and/or monitoring functioning and adjustment in the first year of school were included. Fifth, school based intervention studies in the first year were included if they targeted school readiness or school transition. Intervention studies did not need to discuss school transition specifically but had to be school based with outcome measures that targeted school transition factors (*e.g.*, general academic progress and/or social development). Intervention studies in first years of school only targeting very narrow and specific outcome measures (*e.g.*, word learning) were excluded. Intervention studies prior to school commencement must have used specific school readiness outcome measures and school readiness needed to be assessed at critical time point. Sixth, single-subject studies with small sample sizes (< 5) were excluded. Finally, PhD dissertation studies that had not been subsequently published as a peer reviewed journal article were included (dissertations that had been rewritten as a published manuscript were excluded).

Data extraction and synthesis

The titles and abstracts of the initial search were screened to identify potentially relevant articles. The first and second authors independently assessed the full-text of these publications for eligibility and any disagreements about inclusion were resolved through discussion and consensus. Study characteristics, number of participants, participant data including diagnosis, age range, intervention, and outcome measures were extracted and recorded on a data extraction form.

RESULTS

Studies identified and included

The initial search identified 1575 publications (excluding duplicates). After screening, 137 were identified for full-text review and of these, 20 met the selection criteria and were included in this review (Figure 1). These articles were grouped according to four criteria: School readiness (n = 4); parents' and teachers' school transition expectations and experiences (n = 4); individual factors affecting school transition (n = 5); and school based interventions (n = 7). An overview of the included articles is presented in Table 1.

School readiness

Three studies examined school readiness in children with ASD. However, there was substantial heterogeneity in the study designs and outcome measures. Nonetheless, these studies appear to indicate that while children with ASD show basic academic school readiness, they do not appear to be ready in the areas of social skills and daily living skills. A study by Crane[14] demonstrated that children with ASD enrolled in special education in pre-school through second grade had significantly poorer self-help skills, self-control and relationships than children with learning disabilities, speech/language impairments, emotional difficulties, and health problems. Moreover, a recent study by Klubnik *et al*[15] examined understanding of school-based concepts and self-/social awareness concepts in children with ASD and Intellectual Disability (ASD/ID) and ID. Results revealed that when controlling

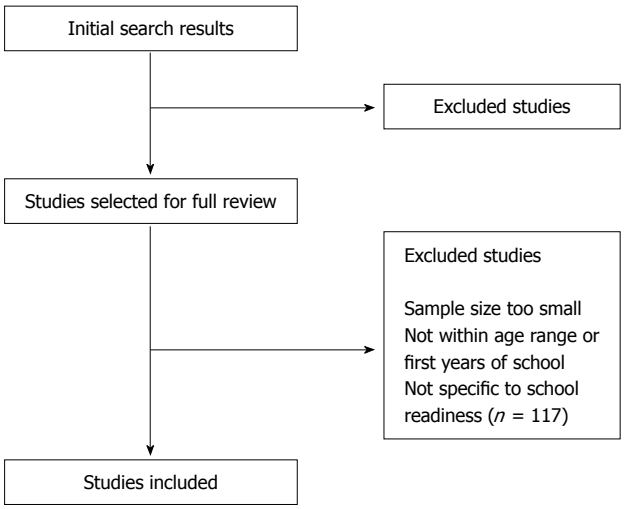

Figure 1 Search flow chart.

for age, IQ and communication skills, children with ASD/ID had significantly poorer understanding of self-/social awareness concepts than children with ID. Additionally, within the ASD/ID group, understanding of academic concepts (*e.g.*, numbers, letters) exceeded understanding of self-/social awareness concepts by more than one standard deviation, suggesting that although children with ASD may have a relative strength in academic readiness, they appear to be significantly behind their non-ASD peers in terms of social readiness.

Matthews[16] examined the link between early childcare experiences, friendship quality, Theory of Mind (ToM), and school readiness in children with ASD and their typically developing peers, and found poorer positive friendship quality, ToM, and school readiness in children with ASD. For all children, more positive friendship quality was associated with higher social-emotional school readiness and self-help school readiness, and was positively related to ToM in children with ASD, but negatively related ToM in controls. Child care experiences were not associated with ToM in either group. In fact, more time spent in child care was associated with poorer school readiness for children with ASD. Finally, ToM was also positively related to cognitive/motor school readiness, mediated by receptive language ability, for children with ASD.

Waddington and Reed[17] was the only study found that looked specifically at an intervention that prepared children with ASD for school. This study examined the Preschool Inventory of Repertoires for Kindergarten (PIRK; Greer and McKorkle, 2003 as cited in[17]) to determine its effectiveness in transitioning children to primary school. Specifically, they investigated whether using the PIRK teaching program had an impact on skills and behaviour and enabled children to transfer from special to mainstream schools. Children's progress in the PIRK program, a program based on Applied Behaviour Analysis (ABA) targeting individual children's specific curriculum deficits, was compared with the progress of children with ASD in an education as usual group, which had eclectic intervention approaches. Children in the PIRK program displayed improved communication and daily living skills. Importantly these improvements facilitated the transition process and continued in mainstream schools for these children. However, the children's social skills did not appear to improve as a result of the PIRK program[17].

Overall, these studies indicate that children with ASD are less school ready in social-emotional areas than both typically developing and developmental delayed peers. In addition, there is a preliminary suggestion that interventions targeting school readiness can improve communication and self-help skills. However, further intervention targeting social skills may be required.

Parents and teachers school transition expectations and experiences

In total, four autism-specific studies investigating teachers' and parents' perspectives of children with ASD on particular transition practices were identified in the literature. The elements for successful transition to school were fairly consistent across these studies[1,2,4,18]. These centred around the following themes: "Child visit, parent information, teacher sharing, placement identification, decision support, sending teacher, support identification, evaluation administrator, visit support, and peer preparation"[18] (p. 135). These studies also consistently showed that parents, carers, preschool and primary school teachers strongly endorse all of these practices for transitioning children with ASD into primary school[1-3,18]. Unfortunately, while all the relevant stakeholders consider these practices important, teachers report that few of these practices are actually implemented in real-life settings[1,3,4]. Quintero and McIntyre[1] surveyed 96 parents and teachers of children with disabilities, 19 of whom had ASD. They found that teachers had substantially more concerns about children with ASD regarding transition to kindergarten than they had for children with other disabilities. While parents and teachers, particularly preschool teachers, were highly involved in the transition process for all children with a disability, transition practices were generic and rarely individualised to each child's particular needs[1]. Parents reported kindergarten teachers engaged in some settling practices at the beginning of the school year but did not implement transition practices with on-going transition programs nor regular meetings[1].

One particular transition process highlighted in the literature, as being particularly important, is regular and detailed communication between the relevant stakeholders. Quintero and McIntyre[1] reported that this process rarely occurs between preschool staff and kindergarten teachers. Preschool teachers reported concerns about the lack of collaboration with kindergarten staff for children with disabilities leading up to school entry and during the transition process. Equally important is parent-teacher communication. There also appears to

Table 1 Summary of studies examining school transition for children with autism spectrum disorder

Author (yr)	Country	Sample	Intervention	Measures	Findings
School readiness					
Crane[14] (2010)	United States	91 children with ASD; 1338 children with ASD and other disabilities	Children received special education services	(DECA; LeBuffe and Naglieri, 1999); (LAP-D; Nehring, Nehring, Bruni and Randolph, 1992), Early Learning Accomplishment Profile (ELAP; Glover, Preminger and Sanford, 2002), (SRUSS), ESI-K, DIBELS, SAT-10	Children with ASD (and developmental delay group) showed the slowest gains over time in the language, cognitive and fine motor domains. Children with ASD had significantly lower scores on the initiative, self-control and attachment scales than all groups except the developmental delay group
Klubnik, Murphy, Campbell, Reed and Warner-Metzger[15] (2014)	United States	Exp group: 76 children with ID and ASD, M = 53.60 mo. Comp Group: 47 children with ID, M = 59.25 mo		Standford-Binet Intelligence Scales, Fifth Edition (SB5; Roid, 2003), Childhood Autism Rating Scale, Second Edition (CARS-2; Schopler, Van Bourgondien, Wellman, and Love, 2010), Vineland Adaptive Behaviour Scale, Bracken Basic Concept Scale- Third Edition: Receptive (Bracken, 2006)	Receptive understanding of self-/social awareness concepts was significantly lower for the ASD/ID group. ASD/ID group had significantly higher school readiness scores than the ID group. The ASD/ID group's the School Readiness Composite was greater than their Self/Social-Awareness subtest
Matthews[16] (2014)	United States	Exp: 63 children with a parent-reported diagnosis of ASD, M = 5.16 yr (4-6 yr). Comp Group: 33 TD children, M = 5.35 yr (4-6 yr)		Background information; History of child care; Friendship quality; School readiness - parent report of social-emotional and self-help school readiness; Theory of Mind (ToM Developmental Scale (Wellman *et al*, 20016; Wellman and Liu, 2004); Appearance-reality (Wellman and Liu, 2004); Second-order false belief (Targer-Flusberg and Sullivan, 1994); School readiness - Cognitive/motor (Cognitive: Concept tasks; Cognitive: Language tasks; Motor tasks); Verbal ability [Peabody Picture Vocabulary Test-III (Dunn and Dunn, 1997)]	Children with ASD, experiencing centre-based care was not associated with cognitive/motor school readiness, social-emotional school readiness, or level of self-help school readiness. Children with ASD who demonstrated more advanced ToM performance had higher cognitive/motor school readiness and levels of self-help school readiness. Both groups, children with more positive friendship quality had higher levels of social-emotional school readiness and self-help school readiness
Waddington and Reed[17] (2009) (Study 2)	United Kingdom	Exp group (PIRKS): 12 children with ASD, Baseline, M = 6.7 yr (4.3-10.5 yr), Comp Group (Treatment as usual (TAU)): 15 children with ASD, Baseline, M = 9.1 yr (5.2-15.0 yr)	PIRKS prepare children for inclusion in a mainstream kindergarten; based on ABA; 5 skill areas: Academic literacy, communication, listening, speaking, social self-management, school self-sufficiency, community, physical/motor. Individualised. Teaching takes place 1:1 or small groups	Gilliam Autism Rating Scale (GARS; Gilliam, 1995), Vineland Adaptive Behavior Scale, Mainstreaming Social Skills Questionnaire (MSSQ: Salend and Lutz, 1984), Strengths and Difficulties Questionnaire (SDQ: Goodman, 1987)	Children who had experienced PIRKS prior to attending mainstream schools demonstrated improvements in communication, socialisation, and daily living skills (not compared with comparison group just significant improvements within group) with these skills continuing at mainstream school
Parents'/teachers' views/experiences of school transition process					
Beamish, Bryer and Klieve[18] (2014)	Australia	91 intervention and advisory (specialised preschool) teachers		Transition practices online survey: 36 practices items identified from review of literature (including Forest *et al*, 2004). Themes: Child visit, Parent information, Teacher sharing, Placement identification, Decision support, Sending teacher, Support identification, Evaluation administrator, Visit support, Peer preparation	All 36 practices highly endorsed
Denkyirah and MAgbeke[2] (2010)	United States	Exp group: 306 preschool teachers. Comp group: 82 preschool		Survey developed from Forest *et al*, 2004. Themes: Timing for planning and preparation; Sharing information with family; Discussing placement with family; Helping families fin school	All themes endorsed by teachers in both countries

		teachers from Ghana	and community resources; Preparing and receiving school and teachers; Relationships between sending and receiving schools; Assistive technology; Home visit; Parent taring	
Fontil and Petrakos[4] (2015)	United States	Parents of 10 children (aged 53.8-87.4 mo) with or suspected of having ASD	Interview questions adapted from Kindergarten Transition Parent Interview - Preschool (Pianta and Kraft-Sayre, 2003). Themes: child's experiences at school, their peer contact, their activities at home, and parents' personal activities with the school. Measure of Processes of Care (MPOC-20; King, King and Rosenbaum, 2004)	Empathy, Caring, and Understanding: Relationships with preschool teachers more positive than with kindergarten teachers. Knowledge and Expertise: More sharing of information with parents at preschool than school. Less educational opportunities and resources at school than preschool
Quintero and McIntyre[1] (2011)	United States	Exp group: Parents and teachers of 19 children with ASD (M = 58.84 mo). Comp group: Parents and teachers of 76 children with Developmental Difficulties, M = 58.66 mo	Time 1 - end of preschool; Parents: Family Experiences and Involvement in Transition (FEIT; McIntyre *et al*, 2007); Preschool teachers: Teachers' Perceptions on Transition (TPOT), Open Ended Questions in TPOT. Time 2 - kindergarten entry; Parents: Family Experiences and Involvement in Transition (FEIT; McIntyre *et al*, 2007)	Teachers' Perceptions on Transition: Teachers significantly more likely to report higher concerns (some, many, or very many concerns) for children with ASD than children with DD. Teachers endorsed visiting students' assigned kindergarten classroom more for children in the ASD group than the DD group. Parent Involvement: Parents of DD group reported participating in a transition planning meeting significantly more than parents in the ASD group. Parents of DD group reported to have received written communication regarding the transition from the kindergarten program significantly more than parents in the ASD group
Protective and risk factors in first year of school				
Charman *et al*[19] (2004)	United Kingdom	Cohort 1: 73 children with ASD, Cohort 2: 52 children with ASD; Baseline both cohorts M = 56.6 mo	Vineland Adaptive Behavior Scales-Screen Version (VABS-S; Sparrows, 2000), Social Communication Questionnaire (SQC; Berument *et al*, 1999), Autism Treatment Evaluation Checklist (ATEC; Rimland and Edelson, 1999)	Group made more rapid development progress in the 11 mo in school than they had preschool. Pattern of change on the ATEC was mixed. On the social, language and communication subscale the scores did significantly reduce over time. The best developmental progress was made by children with better communication skills at the outset
Esienhower, Blacher and Bush[12] (2015)	United States	166 children with ASD (M = 5 yr 8 mo, 4-7 yr) and one parent per child	Demographics, ADOS, abbreviated WPPSI-II, Student-Teacher Relationship Scale (STRS; Pianta, 2001), Caregiver-Teacher Report Form and Teacher Report Form (CTRF and TRF; Achebach and Rescoria, 2000, 2001)	High externalising behaviour predicted poor STR and was not moderate by cognitive abilities.
Jahromi, Bryce and Swanson[20] (2013)	United States	Exp group: 20 children with HFASD, M = 58.95 mo. Comp group: 20 typically developing children, M = 50.20 mo	Measures: Preschool Language Scale 4 (PLS-4; Zimmerman, Steiner, and Pond, 2002), Differential Abilities Scale II (DAS-II; Elliot, 2007), Autism Diagnostic Interview-Revised (ADI-R; Lord *et al*, 1994), Social Communication Questionnaire (SCQ; Rutter *et al*, 2003), Emotion Regulation Checklist (ER Checklist; Shields and Cicchetti, 1997), Day/Night Task (Gerstadt, Hong, and Diamond, 1994), Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P; Gioia, Isquith, Guy, and Kenworthy, 2000), Parent–child joint engagement states and child-initiated joint engagement (Bakeman and Adamson, 1984), Child Behavior Questionnaire–Short Form (CBQ-SF; Putnam and Rothbart, 2006; Rothbart, Ahadi, Hershey, and Fisher, 2001), School Liking and Avoidance Questionnaire (Ladd *et al*, 2000), parent-report version of the Teacher Rating Scale of School Adjustment (Buhs and Ladd, 2001), Child Behavior Scale (CBS; Ladd and Profilet, 1996)	Children with HFA were rated significantly lower in emotion regulation and effortful control than their typically developing peers. Behavioural engagement: children with HFA had significantly less cooperative and independent participation. Emotional engagement: Executive function emerged as the significant predictor of emotional school engagement. For children with HFA, effortful control promoted greater prosocial behaviour with peers

Prino, Pasta, Giovanna, Gastaldi and Longobardi[23] (2016)	Italy	Exp group: 14 children with ASD, M = 85.75 mo; 18 children with Down Syndrome, M = 85.75 mo, teacher or teaching assistant per child (n = 32). Comp group: 128 TD children (classmates), M = 78.54 mo[1]		Student-Teacher Relationship Scale (STRS; Pianta, 2001)	No difference between teachers' perceptions of children with Down Syndrome and their TD classmates. Teachers' reported significantly higher conflict scores and significantly lower closeness scores for children with ASD than their TD peers
Sparapani *et al*[21] (2016)	United States	196 children with ASD, M = 6.36 yr		ADOS, Standford-Binet Intelligence Scale - 5th Ed (SB-5; Roid, 2003), Peabody Picture Vocabulary Test - 4th Ed (PPVT-4; Dunn and Dunn, 2007), Expressive One Word Vocabulary Picture Test - 4th Ed (EOWVPT-4; Brownwell, 2000), Social Skills Rating system (SSRS; Gresham and Elliott, 1990), Teacher Report Form (TRF; Achenbach and Rescorla, 2001), 60-min classroom observations. Five themes: Emotional Regulation, Classroom Participation, Social Connectedness, Initiating Communication, and Flexibility	No difference between children in general education and special education classes. Students spent less than 50% of time in a well-regulated state, productively and independently participating in classroom activities. Students only responded to half of verbal bids for interaction, infrequently directed communication, and rarely used generative language
Grindle *et al*[10] (2012)	United Kingdom, 4-5 yr	Exp group (ABA): 11 children with ASD, baseline: Age range 43 to 68 mo (M = 58.2 mo). Comp group [Education as usual (EAU)]: 18 children with ASD baseline: Age range 54 to 72 mo (M = 63.89 mo)	School-based comprehensive behavioural intervention features: (1) Parents generalize skills at home; (2) One-to-one intervention at desks in a shared classroom; (3) Education for a maximum of 6 h per day for 38 wk of year; (4) Matched school timetable; (5) Generalise skills to mainstream classes; and (6) based on the United Kingdom National Curriculum	IQ: Standford-Binet Intelligence Scale -Fourth Edition or Leiter International Performance Scale-Revised; Vineland Adaptive Behavior Scale-Survey Form (VABS); ABLLS/ABLLS-R assesses skills such as effective social and communicative functioning, imitation, and cooperation	Positive changes were observed for the majority of children enrolled in the ABA class - moderate to large-sized effects found for standardized test outcomes after 1 yr of intervention. Outcomes for ABA class were positive compared with the treatment as usual
Kamps *et al*[11] (2015)	United States	Exp group (Peer Networks Intervention): 56 children with ASD, baseline: Age M = 5.8 yr. Comp group (EAU): 39 children with ASD baseline: Age M = 5.8 yr	Peer network intervention: peer training and direct instruction. Five skills: (1) Requests and shares; (2) Comments about one's own play; (3) Comments about others' play; (4) Niceties, *e.g.*, please, thank-you; and (5) play organizers, *e.g.*, to give ideas about setting up games and rules	Dependent measures from direct observations consisted Clinical Evaluation of Language Fundamentals-4, Core Language Scores (CELF-4; Semel *et al* 2003); the Vineland Adaptive Behaviour Scale Teacher Report-Communication subtest (VABS; Sparrow *et al* 2006); and teacher ratings of classroom social behaviours [The Teacher Impression Scale (TIS); Odom and McConnell, 1997]	Peer intervention group improved more in initiations to peers during non-treatment social probes and during generalization probes in natural settings than the comparison group participants. Standard scores for language performance and communication (teacher report), and teachers ratings of peer network participants social communication behaviours greater for peer intervention group than for comparison group children
Locke *et al*[26] (2014)	United States	192 children with ASD, M = 6.1 yr (5-8 yr),	Strategies for Teaching based on Autism Research	ADOS, Differential Ability Scales-Second Edition (DAS-II; Elliott, 2009), Adaptive Behavior Assessment System-Second	Modest increases in global cognitive ability scores. Negligible changes in social functioning

		grades Kindergarten to second	(STAR), which incorporates discrete trial training (DDT, Smith 2001, from ABA), pivotal response training (PRT; Koegel *et al*, 1989) and functional routines	Ed (ABAS-ii; Harrison and Oakland, 2003), Pervasive Developmental Disorder Behavior Inventory (PDDBI; Cohen and Sudhalter, 2005)-Teacher Form	
McKeating[28] (2014)	United States	Exp group: 39 children with ASD, M = 6.21 yr (5-7 yr). Comp Group: 39 children with other disabilities, M = 6.26 yr (5-8 yr) (Footnote: 73 teachers of children in sample)	Children received Itinerant, supplemental or full-time special education services	Inclusive Classroom Profile (ICP; Soukakou, 2010), Autism Evaluation Treatment Checklist (AETC; Rimland and Edelson, 1999), Teacher Perception Survey (TPS)	Children receiving full time special education services made substantially greater progress in sociability and behaviour, but not in communication, sensory or cognitive abilities, than children receiving supplemental and itinerant services. All children, regardless of placement achieved higher sociability scores at post-test. Teacher perceptions of inclusion predicted higher ATEC scores
Pellecchia *et al*[25] (2016)	United States	152 children with ASD, M = 6.0 yr (5-8 yr), grades Kindergarten to second	Strategies for Teaching based on Autism Research (STAR), which incorporates discrete trial training (DDT, Smith 2001, from ABA), pivotal response training (PRT; Koegel *et al*, 1989) and functional routines.	ADOS, Differential Ability Scales–Second Edition (DAS-II; Elliott, 2009), Adaptive Behavior Assessment System-Second Ed (ABAS-ii; Harrison and Oakland, 2003), Pervasive Developmental Disorder Behavior Inventory (PDDBI; Cohen and Sudhalter, 2005)-Teacher Form, Child Symptom Inventory-4 (CSI-4; Gdaow and Sprafkin, 2002)	Modest mean change in DAS GCA scores. Several measures of adaptive behaviour; functional academics, health and safety, self-direction, social skills, and the overall adaptive composite predicted changes in DAS scores. Social anxiety symptoms predicted changes in DAS scores. Higher social anxiety symptoms and increase in student age significantly predicted a decrease in DAS scores
Sainato *et al*[27] (2015)	United States	Exp group (Inclusive kindergarten program): 41 children with ASD, baseline: Age M = 75.7 mo. Comp group (Eclectic intervention): 21 children with ASD, baseline: Age M = 74.1 mo	Experimental group participated in general education classroom taught by trained teachers. Curriculum addressed core deficits of children with ASD using evidence-based strategies and behaviour management	Leiter International Performance Scale-Revised (Leiter-R; Roid, and Miller, 2002); Kaufman Test of Educational Achievement, Second Edition (KTEA-II; Kaufman and Kaufman, 2004); The Test of Language Development (TOLD-P: 3; Newcomer and Hammill, 1997); Vineland Adaptive Behavior Scales-Classroom Edition (Sparrow, Balla, and Cicchetti, 1985)	Experimental group made significant gains in nonverbal intelligence, academic achievement, and language scores compared with comparison group. Comparison group exhibited either no improvement or decreases. Both model and comparison groups demonstrated similar improvement in pre- and post-test outcomes on the Vineland Adaptive Behavior Scales-Classroom Edition (Sparrow *et al*, 1985)
Whalen *et al*[24] (2010)	United States	Exp group (preschool and K-1 students): 22 children with ASD, range 3 to 6 yr. Comp group (preschool and K-1 students): 25 children with ASD, range 3 to 6 yr	TeachTown: Basics', a CAI program that includes computer lessons and natural environment activities (Connection Activities) for developmental ages 2-7 yr. The student is taught in a discrete trial format where they receive reinforcement for correct responses. Treatment group used TeachTown: Basics for approximately 20 min a day on school days over three months	Peabody Picture Vocabulary Test, 3rd Edition (PPVT; Dunn and Dunn), Expressive Vocabulary Test (EVT, Williams, 1997), The Brigance Inventory of Early Development (Brigance, 2004), Childhood Autism Rating Scale (CARS), Ongoing Automatic Data Collection (TeachTown: Basics)	Children in the TeachTown: Basics group performed better across all language and cognitive outcome measures than the children in the control group. Additionally, students who used TeachTown: Basics demonstrated significant progress overall in the software and those students who used the program for more time demonstrated larger gains within the software and in outcome measures

[1]Footnote: Other research populations examined separately not reported in this systematic review. DECA: Devereux Early Childhood Assessment; LAP-D: Learning Accomplishment Profile-Diagnostic; SRUSS: School Readiness Uniform Screening System; ASD: Autism spectrum disorder.

be a dramatic decrease in parent-teacher communication in kindergarten (formal primary school), as well as this contact being more negative compared to the supportive environments of specialized preschools[4]. Therefore, differences between preschools and mainstream primary schools are amplified for parents of children with ASD

through reduced explanatory communication and collaborative decision-making occurring between parents and teachers.

Individual factors affecting school transition

In total, five studies were included that examined the characteristics of children with ASD that may influence their adjustment to school in the first years. Three studies examined the functioning of children with ASD as well as their school and social engagement. Charman *et al*[19] assessed the functioning of children with ASD on entry to school and then again the end of their first year. They found that as a group the children' s symptom severity did not change over the first year regardless of educational setting. Encouragingly, their language and communication improved, but there was no improvement in their sociability, sensory issues, cognitive development, or behaviour. In terms of the individual characteristics associated with change over time, children with better communication skills and lower symptom severity made more positive changes in their daily living skills in their first year of school[19].

Jahromi *et al*[20] explored individual differences in self-regulation in 20 children with ASD compared with 20 of their typically developing peers, and how self-regulation related to their school and peer engagement in the first year of school. Prior to starting school, children's self-regulation and autism symptoms were assessed. The children's behaviour was assesses at the end of the year. The authors found that found that children with ASD had significantly less emotion regulation and effortful control than their typically developing peers. They also scored lower than their typically developing peers on many important components for school success, such as cooperative and independent class participation and prosocial peer engagement. For children with ASD, greater effortful control was associated with better prosocial behaviour[20]. This suggests that these children might have a protective factor that will allow them to form better relationships with their teachers and peers, and perhaps therefore experience a smoother transition to the school environment.

Sparapani *et al*[21] developed a more generalised measure, the Classroom Measure of Active Engagement (CMAE) that addressed five areas of active classroom engagement including emotion regulation, classroom participation, social connectedness, initiating communication and flexibility[21]. The authors reported that the children with ASD had substantial difficulties with active engagement in class and that this was not helped by participation in a special education class as opposed to a general education program[21]. Observational data revealed that children with ASD spent less than half of the time in an emotionally-regulated state, being time productive and independently participating in classroom activities. Children rarely directed communications or used generative language and were only able to shift their attention to new tasks following verbal requests about 50% of the time[21]. One area where they showed greater flexibility was shifting to different materials. Children with better social skills had more positive active engagement in almost all areas measured, while externalising behaviours and higher repetitive and restricted behaviours were associated with less flexible classroom behaviour[21]. Therefore, as a group, children with ASD had much difficulty with active classroom engagement, and children with poorer social skills and more repetitive and restrictive behaviours, and more externalised behaviours had the most difficulty with active engagement[21].

Two studies were identified that examined the quality of student-teacher relationships in children with ASD. These studies indicated that children with ASD had substantially higher conflict and lower closeness with their teachers than typically developing or intellectually disabled peers[22,23]. Eisenhower *et al*[22] examined the relationship between student-teacher relationship quality and externalizing behaviour problems for children with ASD in the first years of school. They found that children with ASD appeared to have poorer student-teacher relationships than those reported among typically developing children. Children in their study continued to have poor student-teacher relationships in new classrooms with new teachers, suggesting that the children's behaviour might be the more significant contributor to the student-teacher relationship. Prino *et al*[23] also found that teachers' relationships with children with ASD were more difficult than those they form with typically developing children, finding teachers reported higher conflict and less closeness with their students with ASD.

Overall, this research indicates that children with ASD appear to have externalising behaviours and self-regulation difficulties that affect their school engagement and their relationships with their teachers.

School-based interventions

Seven studies were identified that investigated the impact of school-based programs in the first years of school on children's functioning. Five of these studies examined ABA-based and teacher trained interventions in school. Whalen *et al*[24] examined discrete trial format Computer Assisted Instruction intervention; "TeachTown: Basics". This study found that children with ASD in the intervention program had higher language and cognitive skills than those who did not receive the intervention. However, this study did not examine broader social and behavioural skills.

Two studies evaluated the effectiveness of an ABA-based behavioural school-based intervention program called Strategies for Teaching based Autism Research (STAR) which involves intensive teacher training and support with the intervention focusing on three processes; discrete trial training, pivotal response training, and teaching within functional routines[25,26]. This program also targeted language, academic, social

skills, and adaptive daily living skills. Locke *et al*[26] found that while children in the program had a modest improvement in their cognitive abilities, there was no improvement in their social functioning. Pellecchia *et al*[25] examined child characteristics that were associated with these cognitive gains. They reported that children in the program who had social anxiety symptoms, such as social avoidance and social fearfulness, made the least gains in their cognitive abilities. Given the fact that ASD and anxiety commonly co-exist, the authors suggested that it is important to identify children at risk of poor school adjustment and ensure that school-based intervention practices incorporate an anxiety-focus[25].

Sainato *et al*[27] examined a school-based intervention with fully trained teachers that centred on full inclusion of children with ASD with their typically developing peers without individually assigned teaching aides. They developed a model kindergarten classroom that was organised to support a wide range of diverse learning needs for all children. Both children with ASD and typically developing peers experienced the same learning environment, curriculum and behaviour management. Children with ASD in the model classrooms made significant gains in a number of areas including performance IQ, academic achievement and language, while children in mainstream classrooms either did not improve or in some cases their scores decreased[27]. However, there were no significant differences between the groups in adaptive behaviour and socialisation.

Another school-based ABA intervention program was evaluated by Grindle *et al*[10]. This program specifically focused on targeting socialisation in the second year of the intervention. Eleven children with ASD were in ABA-supported classrooms that approximated the mainstream timetable integrating children with their typically developing peers during breaks and extra-curricular activities. Children in the ABA-based intervention group made considerable gains in almost all areas except for socialisation in their first year[10]. However, the focus of the intervention shifted in the second year to socialisation and communication, with the majority of children spending more time in mainstream classrooms. Children in the ABA-based program displayed a substantial improvement in daily living skills and socialisation skills in the second year, while their IQ remained stable. Overall, children in the ABA-based intervention made significantly more progress in their daily living and socialisation than children in the comparison group. However, the was no significant difference between the groups in academic progress. Nevertheless, after two years in the intervention program children with ASD remained predominately in the specialised support classrooms, only spending at most 6 h a week in mainstream classes[10].

Consequently, it seems that children with ASD may require more than instruction and inclusion to improve their social skills and interactions with their typically developing peers. Only one study was identified that examined school-based interventions that used combination of direct instruction and peer-mediated approaches. Kamps *et al*[11] randomised controlled study found that children from the intervention group were observed in natural settings to make more social initiations and frequency of communication with their peers than children in the education as usual group. Children in the intervention group also appeared to make greater gains in all areas of their language, communication and social skills than children in the comparison group[11]. Therefore, it appears that children with ASD may make the greatest gains in their socialisation when they have direct and structured interactions with their typically developing peers that generalise out to other settings.

One final study was identified that looked at special education services in the first years more generally. McKeating[28] found that children with ASD who attended full-time special education services made the largest gains in their behaviour and sociability, but not in communication, sensory or cognitive domains.

Therefore while school-based behavioural interventions appear to improve many skills and behaviours such as cognitive, language and daily living skills, children with ASD need to adjust and develop in the school environment, these interventions alone do not improve socialisation and peer inclusion for these children. There is a preliminary suggestion from Kamps *et al*[11] that school-based interventions incorporating direct instruction and peer-mediated interactions can assist children with ASD in developing vital social skills for a positive transition to the school environment.

DISCUSSION

Currently, there is a lack of systematic longitudinal studies evaluating the success of evidence based school transition programs for children with ASD. There are number of reasons for this. First, research on the school transition process for children with ASD is sparse and disparate, particularly in relation to school readiness. Only one study based on ABA specifically examined a school readiness intervention program[17]. This study suggested that behavioural-based intervention programs in preschool may not provide children with ASD with the social skills they need to socialise with their peers in primary school. This was also evident in school based intervention programs in the early years of school. However, while these behavioural and instructional school-based intervention programs appear to improve skills in a number of areas for school success, such as learning and cognition, behaviour and adaptive living skills, they do not appear to target peer inclusion and socialisation[10,25,26]. The results of one study suggested that peer modelling and instruction in the first year of school may help children with ASD form positive relationships with their peers and improve their socialisation[11]. Therefore, incorporating peer modelling and social instruction into behavioural interventions may provide the best support for children with ASD when

transitioning to school.

Children with ASD present with unique social and communication deficits and behavioural difficulties, which can present unique learning and adjustment challenges[21]. However, few studies have specifically investigated the impact of these difficulties on transitioning to school and engaging in the school environment. The few studies that have evaluated this suggest that children with ASD have poorer relationships with their teachers, poor self-regulation and difficulty being actively engaged in the classroom. This literature also established some individual child characteristics that may present as risk factors for poorer transition to school. Repetitive and restricted behaviours, social anxiety, less effortful control, poor social skills, and dislike of school appear to be associated with greater difficulty settling and engaging in school. The need for on-going and individualised school based interventions was also emphasised

Implications for school transition best practice

To date, no studies have specifically evaluated the success of a school transition program specifically for children with ASD. However, survey studies that have examined opinions of parents and teachers on best practices for school transition identified a number of key areas: (1) Transition team established; (2) parent involvement in planning; (3) child and parent visit to school; (4) visit support; (5) placement identification; (6) parent communication and information; (7) teacher sharing between preschool and kindergarten teacher; (8) child preparation (*e.g*., social stories); (9) decision support; (10) support identification; (11) transition administrator to supervise and evaluate the transition; and (12) peer, classroom and school preparation[18].

The authors of these studies identified these relevant practices from the literature as well as government guidelines. Many school transition policies and guidelines are generic and rarely individualised to the child's particular needs[1]. As can been seen from this review, children with ASD experience specific social, behavioural and communication difficulties that result in them being particularly vulnerable to a poor school transition. Additionally, teachers are more concerned about the ability of children with ASD to successfully transition to school than other children with disabilities. Therefore, children with ASD require comprehensive and individualised transition plans specifically tailored to suit their needs[1]. However, there are elements that should also potentially be incorporated into all transition plans for children with ASD based on the current evidence. For example, while children's learning and academic development is currently monitored in most Australian schools through learning plans, social skills, communication and behaviour may not be adequately monitored. Therefore, transition plans for children with ASD should include regular monitoring and evaluation of a broad range of areas including active engagement, socialisation and student-teacher relationships. Also, behavioural interventions with peer modelling may need to be incorporated into transition plans for these children. Finally, these programs need to be developed and implemented while children are in preschool and continue through the first year of school.

Implications for future research

There is a paucity of empirical studies that examine transition to school for children with ASD, particularly in longitudinal monitoring from specific school readiness preparation through to the end of the first few years of school[22]. While a number of recent studies have examined specific school-based interventions, existing research on the process of primary school transition has tended to adopt cross-sectional survey based methodology[2-4,18] rather than longitudinal designs with specific measurement of children's social-emotional, adaptive, and cognitive/academic progress. A large number of school transition practices have been identified and endorsed from these survey studies. However, the adequacy of these practices has not been established. There is a need for further research aimed at developing evidence-based strategies to enhance the school transition process and these strategies need to be formulated into guidelines and policies specifically for children with ASD due to their unique needs and difficulties. Additionally, while the academic progress of children is monitored through systems such as learning plans, for children with ASD more systematic monitoring of developmental and behavioural progress, using standardised instruments is needed to measure the effectiveness of well-developed, evidence-based individualised, long-term transition programs[19].

Limitations

There were a number of limitations to this systematic review. The main limitation was the small number of studies available and the vast variability in the research design and quality of the studies included. The studies included were also from a limited number of countries, with papers predominantly from the United States. Given that school transition practices can vary substantially, different approaches and outcomes may not be addressed and examined in this systematic review. Additionally, publications that were not in English and single-subject case study design studies were excluded, therefore, some relevant studies may have been overlooked.

This systematic review suggested that children with ASD face more challenges, particularly in relation to social-emotional development and active engagement, when starting school than their typically developing peers and even their peers with disabilities. Like many systematic reviews there was substantial variation in the quality of studies and research design of the primary studies. Additionally, the number of studies investigating the school transition process for children with ASD

was disparate and sparse. Nonetheless, it appears both parents and teachers agree that structured and individualised transition plans are needed for children with ASD when starting school, but also during the first years. More structured processes at school and communication between schools, teachers and parents is needed to assist these children and their families adjust to the new school environment. This review also suggests that children with ASD experience more difficulty actively engaging in the classroom and forming positive relationships with their teachers and peers than their typically developing and developmentally delayed peers. Preliminary evidences suggests that individualised intervention programs targeting social skills, incorporating peer modelling, both prior to starting school but also school-based programs in the first years would assist children with ASD to adjust to and succeed in the school environment.

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COMMENTS

Background

Increasingly children with autism spectrum disorder (ASD) attend mainstream schools. Children with ASD experience social, communication and behavioural difficulties unique to their disability. The presence of these deficits indicates that children with ASD have greater risk of poor school outcomes. Children who experience a positive start to school are more likely to experience academic and social success.

Research frontiers

There is a paucity of empirical studies examining the transition to school for children with ASD. The research available is not disseminated and there is a lack of synthesis of the available studies. Thus there is a great need to establish and consolidate the current evidence on how and when children with ASD adjust to the new school environment.

Applications

This review can be used to guide practices during the school transition process for children with ASD.

Terminology

The terms used to describe early education programs (*e.g.*, preschool, nursery school) and the first year of school (*e.g.*, reception, prep, kindergarten) vary throughout the world. As the authors of this paper are situated in New South Wales, Australia, the term "kindergarten" is used to describe the first year of school and the term "preschool" is used to describe early education programs.

Peer-review

This is a well written and comprehensive review.

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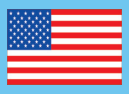

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ORIGINAL ARTICLE

Observational Study

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Effect of educational intervention on attitudes toward the concept of criminal responsibility

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Abstract

AIM

To evaluate the effect of educational intervention on individuals' knowledge of and attitudes toward forensic mental health.

METHODS

We conducted a questionnaire regarding attitudes toward various ideas about forensic mental health. The respondents attended a 1-h seminar regarding forensic mental health after answering the questionnaire. On completion of the seminar, the respondents answered another questionnaire containing many of the same questions as contained in the pre-seminar questionnaire.

RESULTS

A total of 86 individuals attended the seminar, and 78 responded to the questionnaire. Only 13 (18.8%) participants were supportive of the concept of criminal responsibility initially, and there was a statistically significant increase in those who became more supportive after the seminar, with 22 (33%) being supportive after the seminar (Wilcoxon signed-rank test, $P < 0.001$). Logistic regression analysis revealed that participants who were skeptical about forensic mental systems and those with fewer opportunities to see media reports regarding psychiatry were likely to become supportive of criminal responsibility after the intervention.

CONCLUSION

These results suggest that public attitudes toward criminal responsibility and mental health can be influenced *via* educational interventions.

Key words: Forensic psychiatry; Criminal responsibility; Psychiatry, Law and Ethics; Public policy; Education in psychiatry; Anti-stigma in psychiatry

Core tip: Many people have an unsympathetic attitude against offenders with mental disorders. However, this seems, to some extent, to be attributable to a lack of precise knowledge about forensic mental health. We prove that public opinion toward criminal responsibility and relevant ideas regarding forensic mental health can be amended *via* brief educational interventions. Access to accurate information can help to reduce discrimination against offenders with mental disorders.

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INTRODUCTION

Most legal systems and societies require that the criminal responsibility of the offender be proven before they are subject to sanctions. Thus, offenders who commit crimes when they are considered legally insane because of a mental disorder should not be punished. This concept is considered as rational in most developed countries for a number of reasons. First, people under the overwhelming influence of psychiatric symptoms cannot control their behavior. It is inappropriate to demand that they regulate their acts. Second, punishment is not effective to prevent recidivism for people who have committed a crime directly caused by psychiatric symptoms such as delusion. Third, the provision of immediate and appropriate psychiatric treatment, that is, diverting them from the criminal justice system to the mental health care system, is an effective way to reduce the risk of reoffending.

Despite recognition of the concept in various contexts internationally, many citizens have difficulty accepting or understanding criminal responsibility. When an individual with a confirmed or suspected mental disorder commits a sensational crime, a broad discussion is typically ignited regarding the criminal responsibility of the offender[1-4]. Consequently, many countries are struggling to establish their own forensic mental health systems to deal with mentally disordered offenders (MDOs), while also taking into consideration the unique cultural background of each country[5].

In the Japanese legislation, an act of insanity is not punishable, and that an act of diminished responsibility shall lead to the punishment being reduced, according to the article 39 of the Penal Code. Insanity is defined by the Supreme Court as a state without ability to recognize the difference between good and evil, and to control oneself due to mental disorders. Diminished responsibility is defined as a state with those abilities strongly impaired due to mental disorders[6].

For many years, Japan had no specific legal provision for MDOs[7]. Therefore, MDOs were treated under the Mental Health and Welfare (MHW) Act. After some debate, the Act on Medical Care and Treatment for Persons Who Have Caused Serious Cases under the Condition of Insanity (abbreviated to the Medical Treatment and Supervision Act, or the MTS Act) came into force in 2005[2], coinciding with the widespread reform of the Japanese forensic mental health system. Under this new scheme, individuals committing a serious criminal offense while insane or having a diminished responsibility are dealt with within a judicial, administrative framework. The enactment of the MTS Act also meant that clinical psychiatrists would have an opportunity to collaborate with legal professionals such as judges and lawyers in the treatment of MDOs. Additionally, judges faced the necessity of learning about clinical psychiatry for appropriate decision making

under the MTS Act.

On the other hand, for those offenders that are not identified as not guilty by reason of insanity (NGRI) nor as having diminished responsibility, they are treated the same as in the past. Therefore, the degree of criminal responsibility of each offender plays a crucial role in determining their treatment. It is for this reason that significant attention is paid to the criminal responsibility of offenders in Japan.

Previously, citizens in Japan had few opportunities to be involved in discussions regarding the criminal responsibility of offenders. However, this changed with the introduction of the Lay Judge Act in 2009. This act regulates the role of lay judges, who are selected from Japanese citizens for certain legal trials. For the first time, citizens had the opportunity to take a role in the criminal trials of MDOs. Furthermore, court judges and psychiatrists, as expert witnesses, were now required to explain the concept of criminal responsibility to lay judges using precise and easy-to-understand language.

Because of the above, an awareness of citizens' levels of understanding of forensic mental health is now important. To date, there are very few reports regarding the attitudes of citizens toward the concept of criminal responsibility. A literature review from an earlier study, which was accompanied by a survey of psychiatric outpatients, only identified two unpublished online surveys on this issue. Furthermore, the validity of those surveys is questionable because of small sample sizes and biased sampling. That study suggested that more than 70% of participants were opposed to the concept of criminal responsibility, whereas psychiatric patients and their family members were generally supportive of the concept[8].

Based on this situation, we considered it essential to examine the degree of understanding of forensic mental health among citizens in Japan using an appropriate method. We especially wanted to determine the degree to which they respected the concept of criminal responsibility. We assumed that the majority of citizens, although they may be curious about forensic mental health, have negative attitudes regarding this concept. Existing evidence suggests that Japanese citizens hold a stronger stigma against patients with mental disorders than do Australians[9], and are more reluctant to mention mental disorders than are British citizens[10]. His evidence points to the possibility that Japanese citizens have relatively negative attitudes toward MDOs.

We were also interested in whether individuals' opinions and attitudes can be changed *via* an educational intervention. This idea is derived from the estimation that unsympathetic attitudes toward MDOs may originate from a lack of knowledge regarding forensic mental health. Japanese people have little opportunity to learn about the situation of MDOs unless they are directly involved. Meanwhile, the media tends to sensationally report a few extreme criminal acts committed by patients with mental disorders, and these extraordinary cases are often generalized in the mind of the public. Therefore, some people may incorrectly conclude that numerous MDOs are released out into the public without any follow-up after receiving an NGRI verdict. In reality, there are only a few NGRI verdicts annually[6]. The situation is similar in the United States; an informal survey suggested that people have difficulty understanding the real situation regarding NGRI verdicts. Thus, they believed that 5%-20% of defendants were found NGRI, despite this rate being only 1% in reality[11].

Considering these facts, it is expected that after learning that NGRI verdicts are very rare and that such cases receive special forensic psychiatric treatment under the MTS Act, we believe citizens will become more supportive of the concept of criminal responsibility. A more supportive attitude by citizens toward MDOs will alleviate the emotional conflict around mental disorders, and will contribute to the realization of a society that is less discriminatory against people with mental disorders.

Based on the background descried above, we hypothesized that providing some specific knowledge about forensic mental health may change citizens' attitudes regarding MDOs. We planned an educational seminar on the concept of criminal responsibility and NGRI, the current situation of forensic mental health, and how MDOs are treated in special facilities. We considered a 1-h lecture would be adequate to accomplish the outcome, referring to a previous study in which a 1-h session on psychiatry was effective in changing individuals' attitudes toward mental disorders[12].

MATERIALS AND METHODS

Overview

To test the hypothesis mentioned above, we conducted a study that combined a series of questionnaires and a seminar. This study was a single-group, open-labeled interventional confirmatory trial. We presented a seminar on forensic mental health titled "What is forensic mental health: psychiatry, psychiatric testimony, mental disorders and crimes." The seminar was held at the Inohana Festival, a college campus festival administered by the Graduate School of Medicine, Chiba University, on November 1 and 2, 2014. The seminar was open to all interested attendees. We asked the audience to answer a questionnaire before the seminar started. We then administered a further questionnaire after the seminar concluded. We compared the results of the two questionnaires (pre- and post-seminar) using statistical analysis.

Participants

The subjects of this study were the seminar attendees. Inohana Festival is a well-known campus festival within the local area. Thousands of people, mainly local residents, the families and relatives of college students and workers, and high school students who are

Table 1 Pre-seminar questionnaire

Section	Question	Answer options
Knowledge about forensic mental health	Have you heard the term "Forensic psychiatry?"	Yes or No
	Do you know the content of the MHW Act?	Well known, a little, or No
	Have you heard the concept of criminal responsibility?	Yes or No
	Did you know about the introduction of the MTS Act?	Yes or No
	Did you know about the introduction of the Lay Judge Act?	Yes or No
Opinion about forensic mental health	Opinion toward OIH	Definitely agree, relatively agree, neutral, relatively disagree, or definitely disagree
	Opinion toward the concept of criminal responsibility	Definitely agree, relatively agree, neutral, relatively disagree, or definitely disagree
	Opinion toward the MTS Act	Definitely agree, relatively agree, neutral, relatively disagree, or definitely disagree
	Opinion toward the Lay Judge Act	Definitely agree, relatively agree, neutral, relatively disagree, or definitely disagree
About the relationship between psychiatry and the mass media	Opportunity to see media reports regarding psychiatry	Many, relatively many, neutral, relatively few, or few
	Opinion toward the optimal frequency of media reports regarding psychiatry	More than now, neutral, or less than now
	Opportunity to see media reports about the relationship between psychiatry and crimes	Increased, no change, or decreased
	Opinion toward the optimal frequency of media reports regarding the relationship between psychiatry and crimes	More than now, neutral, or less than now
About the responder	Should the media maintain anonymity in reporting crime cases with mental disorders?	Definitely agree, relatively agree, neutral, relatively disagree, or definitely disagree
	Age	< 20, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, or > 79
	Sex	Male or female
	Occupation	Medical practitioner, medical student, or other

MHW Act: Mental Health and Welfare Act; MTS Act: Medical Treatment and Supervision Act; OIH: Official Involuntary Hospitalization.

interested in Chiba University, visit each year.

We recruited attendees through an advertisement of the seminar on the festival website and a poster explaining the theme of the seminar. Any people who came to Inohana Festival were permitted to attend the seminar. All of the individuals who attended the seminar and completed the pre-seminar questionnaire were included as participants in this study. There were no exclusion criteria regarding participation.

Pre-seminar survey

We designed an anonymous self-reporting questionnaire sheet to deliver to the seminar audience. On this sheet, we disclosed the title and funding information of the study. We guaranteed that those who refused to answer the questionnaire could still attend the seminar.

Seminar attendees were given the two questionnaires (pre-seminar and post-seminar) at the same time. The components of the pre-seminar questionnaire are shown in Table 1. This questionnaire was originally created for a previous study examining the attitudes of psychiatric patients toward forensic mental health[8]. We decided to use a slightly modified version of this questionnaire because we expected to be able to compare the results of this study with those of the previous survey. In addition to the degree of knowledge about and attitudes toward forensic mental health, we also wanted to clarify the relationship between participants' perceptions about forensic mental health and their degree of exposure to media reports. We sought to do so because reporting on criminal cases with MDOs is sometimes sensationalized. Furthermore, we were curious about the opinions of citizens toward the practice of anonymous reporting about MDOs in the media. Whether the name of a suspect should be concealed when the suspect seems to be an MDO is often discussed in Japan. Attitudes expressed in the media are mixed[13] (Science Council in Japan, 2005), but patients with mental disorders and their families tend to approve of the practice of anonymous reporting[8].

The questionnaire was composed of four sections: (1) knowledge about forensic mental health; (2) opinions regarding forensic mental health; (3) the relationship between psychiatry and the mass media; and (4) information about the responders. Several items were included in each section. Most of the items were ranked using a five-point scale. A serial number was attached to each pair (pre- and post-seminar) of answer sheets in advance to identify which two sheets were completed by the same participant.

We explained the purpose of the study to the audience and then asked them to complete the pre-seminar questionnaire. After completion, we collected the pre-seminar answer sheets before the seminar began. The participants retained the post-seminar answer sheets during the seminar. Those who refused to answer the questionnaire were deemed to have dropped out of the study, but they could still attend the seminar if they wished.

Educational intervention

The seminar was 1 h in duration and comprised two

lectures: "criminal responsibility" and "forensic psychiatric treatment." For each seminar, a leading psychiatrist with a judgment physician license gave a presentation. In the first lecture, the lecturer explained how the concept of criminal responsibility was interpreted in Japanese legislation. Next, he explained the mechanisms through which mental disorders can be a cause of behaviors that harm others. An outline of the psychiatric evaluation of an MDO was then introduced. In the second lecture, another lecturer began by introducing the designated medical facility. He also presented the content of the treatment program provided in the facilities. Finally, data regarding the outcome of special treatment for MDOs were shared. After each lecture, the presenters answered questions from the participants.

Post-seminar survey

After the seminar concluded, we asked the attendees to answer the post-seminar questionnaire. Sections 1-3 from the pre-seminar questionnaire were included in the post-seminar survey; section 4 was omitted. Upon completion, we collected the answer sheets.

Ethical issues

This survey focused only on the opinions of individuals and did not deal with any patients. We gathered no personal information from the participants. The return of the questionnaires was deemed to indicate consent to participate in this anonymous survey. We registered this study with the Clinical Trials Registry of the University Hospital Medical Information Network (UMIN, Tokyo, Japan) with the unique trial number UMIN000015725.

Statistical analysis

We counted the questionnaire sheets returned to calculate the response rate. We then compiled the ratings for each item of the pre-seminar questionnaire. Furthermore, we examined the correlations between each item regarding knowledge and opinions (in sections 1, 2 and 3) and the demographic data collected on respondents (in section 4) using a chi-square test.

We also examined the change in participants' opinions about forensic mental health. Using the serial numbers on the answer sheets, we identified which sheets were paired. In these comparisons, pairs missing either pre-seminar or post-seminar responses were excluded from the analysis. The pairs for each item were statistically analyzed using a two-tailed Wilcoxon signed-rank test.

We then applied a logistic regression analysis to our data to identify factors predicting the plasticity of opinions on criminal responsibility. To conduct this analysis, we categorized the participants into two groups: (1) those whose pre-seminar opinion on criminal responsibility became more supportive; and (2) those whose opinion did not change or who became less supportive. This binary variable was set as the dependent variable, and all other items answered in the pre-seminar questionnaire were set as independent variables. Cases with missing data on opinions toward criminal responsibility either pre- or post-seminar were excluded from this analysis. We applied a logistic regression analysis using the forward stepwise (Wald) method.

The collected data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, United States). We set the level of significance at $P < 0.05$ before conducting the analyses.

RESULTS

Of the 86 people attending the seminar, 78 (91%) answered at least one item in the questionnaire, of which 69 people completed the both pre- and post-questionnaire. We included all 78 answers in the initial analysis. The number of valid answers in each item is described in each table.

The largest age group was those aged 50-59 years, with only four attendees aged over 60 years. Thirty-seven (47%) attendees were men, and 48 (62%) were neither medical practitioners nor medical students.

In the pre-seminar questionnaire, only half (n = 39) of the respondents stated they had previously heard the term "forensic psychiatry," and 48 (62%) had no knowledge of the contents of the MHW Act. In contrast, 74 (95%) respondents had previously heard the term "criminal responsibility." Furthermore, 53 (68%) respondents did not know about the introduction of the MTS Act, compared with 63 (81%) who were aware of the Lay Judge Act coming into force.

In the pre-seminar questionnaire, 37 (47%) and 35 (45%) respondents definitely agreed with the concept of official involuntary hospitalization (OIH) and the MTS Act, respectively. In contrast, only 13 (17%) had a positive attitude ("definitely agree" or "relatively agree") toward the concept of criminal responsibility, and 37 (47%) were against it ("relatively disagree" or "definitely disagree"). Regarding the Lay Judge Act, 34 (43%) had a favorable opinion, whereas 17 (22%) had a negative one. The responses reflected varied opportunities for exposure to media reports on psychiatry, while 59 (76%) participants believed that the media should report more frequently on mental health issues. The majority (55%) of participants answered that they had seen more recent media reports regarding the relationship between psychiatry and crime than in the past, and 45 (58%) believed that the media should intensify the frequency of reports explaining this topic. Opinions regarding anonymous reporting about suspects with mental disorders were split. These results are presented in Table 2.

We compared the results of the answers between the pre- and post-seminar questionnaires in the pre- and post-pairs (n = 66). More respondents had a positive opinion regarding the concept of criminal responsibility after the seminar than before (Wilcoxon

Table 2 Pre-seminar opinions of respondents regarding forensic mental health issues

Question	Answer	Number
Have you heard the term "Forensic psychiatry?"	Yes	39 (50%)
	No	39 (50%)
Do you know the content of the MHW Act?	Know in detail	11 (14%)
	A little	19 (24%)
	No	48 (62%)
Have you heard the concept of criminal responsibility?	Yes	74 (95%)
	No	4 (5%)
Did you know about the introduction of the MTS act?	Yes	25 (32%)
	No	53 (68%)
Did you know about the introduction of the Lay Judge Act?	Yes	63 (81%)
	No	15 (19%)
Opinion toward OIH	Definitely agree	37 (47%)
	Relatively agree	24 (31%)
	Neutral	12 (15%)
	Relatively disagree	0
	Definitely disagree	1 (1%)
	No answer	4 (5%)
Opinion toward the concept of criminal responsibility	Definitely agree	6 (8%)
	Relatively agree	7 (9%)
	Neutral	19 (24%)
	Relatively disagree	23 (29%)
	Definitely disagree	14 (18%)
	No answer	9 (12%)
Opinion toward the MTS Act	Definitely agree	35 (45%)
	Relatively agree	23 (29%)
	Neutral	12 (15%)
	Relatively disagree	3 (4%)
	Definitely disagree	2 (3%)
	No answer	3 (4%)
Opinion toward the Lay Judge Act	Definitely agree	12 (15%)
	Relatively agree	22 (28%)
	Neutral	24 (31%)
	Relatively disagree	9 (12%)
	Definitely disagree	8 (10%)
	No answer	11 (14%)
Opportunity to see media reports regarding psychiatry	Many	8 (10%)
	Relatively many	19 (24%)
	Neutral	11 (14%)
	Relatively few	18 (23%)
	Few	22 (28%)
Opinion toward the optimal frequency of media reports regarding psychiatry	More than now	59 (76%)
	Neutral	17 (22%)
	Less than now	1 (1%)
	No answer	1 (1%)
Opportunity to see media reports about the relationship between psychiatry and crimes	Increased	43 (55%)
	No change	32 (41%)
	Decreased	3 (4%)
Opinion toward the optimal frequency of media reports regarding the relationship between psychiatry and crimes	More than now	45 (58%)
	Neutral	30 (38%)
	Less than now	2 (3%)
	No answer	1 (1%)
Should the media maintain anonymity in reporting crime cases with mental disorders?	Definitely agree	11 (14%)
	Relatively agree	17 (22%)
	Neutral	27 (35%)
	Relatively disagree	13 (17%)
	Definitely disagree	10 (13%)

MHW Act: Mental Health and Welfare Act; MTS Act: Medical Treatment and Supervision Act; OIH: Official Involuntary Hospitalization.

signed-rank test, Z = -3.6758, P < 0.001). In addition, respondents' opinions toward OIH (Wilcoxon signed-rank test, Z = -2.017, P = 0.044) and the Lay Judge Act (Wilcoxon signed-rank test, Z = -2.467, P = 0.014) were also changed to be more favorable. No significant differences between pre- and post-seminar were detected for opinions toward the MTS Act (Wilcoxon signed-rank test, Z = -0.498, P = 0.619). Compared with pre-seminar attitudes, the post-seminar questionnaire answers showed that more respondents wanted to see more frequent media reports on the relationship between psychiatry and crimes (Wilcoxon

Table 3 Changes in opinions on psychiatry: Pre- and post-seminar

Question	Answer	Pre	Post	Stat[1]
Opinion toward OIH (n = 66)	Agree	33[2]	38[2]	Z = -2.017
	Relatively agree	21[2]	23	P = 0.044
	Neutral	11	4	
	Relatively disagree	0	1	
	Disagree	1	0	
Opinion toward the concept of criminal responsibility (n = 60)	Agree	5	9	Z = -3.797
	Relatively agree	6	13	P < 0.001
	Neutral	18	18[2]	
	Relatively disagree	19[2]	13	
	Disagree	12	7	
Opinion toward the MTS Act (n = 66)	Agree	32	29	Z = -0.498
	Relatively agree	19[2]	26[2]	P = 0.619
	Neutral	10	7	
	Relatively disagree	3	3	
	Disagree	2	1	
Opinion toward the Lay Judge Act (n = 66)	Agree	9	15	Z = -2.463
	Relatively agree	19	18[2]	P = 0.014
	Neutral	22[2]	21[2]	
	Relatively disagree	9	5	
	Disagree	7	7	
Should the media report more frequently on psychiatry? (n = 69)	Agree	54[2]	49[2]	Z = 1.291
	Neutral	14	19	P = 0.197
	Disagree	1	1	
Should media report more frequently on the relationship between psychiatry and crimes? (n = 69)	Agree	41[2]	51[2]	Z = -3.051
	Neutral	26	17	P = 0.02
	Disagree	2	1	
Should the media maintain anonymity in reporting crime cases with mental disorders? (n = 68)	Agree	9	11	Z = -2.185
	Relatively agree	15	17	P = 0.029
	Neutral	22[2]	25[2]	
	Relatively disagree	12	7	
	Disagree	10	8	

[1]Two-tailed Wilcoxon signed-rank test; [2]The median for each item is indicated by underscoring. MHW Act: Mental Health and Welfare Act; MTS Act: Medical Treatment and Supervision Act; OIH: Official Involuntary Hospitalization.

signed-rank test, Z = -3.051, P = 0.02), and more respondents had a positive opinion concerning the anonymous reporting of suspects with mental disorders (Wilcoxon signed-rank test, Z = -2.185, P = 0.029). No significant changes were detected regarding the level of reporting on psychiatry (Table 3).

The logistic regression analysis with the forward stepwise (Wald) method showed two independent variables as being associated with the positive change of opinion toward the concept of criminal responsibility: "opinion toward the MTS Act" [coefficient (B) = -0.540, odds ratio = 0.583, 95%CI: 0.341-0.997, P < 0.05] and "opportunity to see media reports regarding psychiatry" [coefficient (B) = -0.394, odds ratio = 0.674, 95%CI: 0.456-0.997, P < 0.05]. Thus, participants who were not supportive of the MTS Act before the seminar and those who had fewer opportunities to see media reports regarding psychiatry were more likely to become more supportive of criminal responsibility after attending the seminar.

DISCUSSION

In this study, we conducted a questionnaire survey regarding forensic mental health with two key aims. First, we identified participants' level of awareness and opinions about the current situation of forensic mental health in Japan. Second, we examined the possibility of changing participants' opinions *via* a 1-h educational intervention, based on our hypothesis that citizens' opposition to the concept of criminal responsibility derives from a lack of knowledge on forensic mental health.

The participants of the present study were voluntary seminar attendees. Thus, it is likely that most were interested in or at least curious about psychiatry. Nevertheless, only half of the participants had previously heard the term "forensic psychiatry." In addition, the majority of participants had no knowledge of either the MTS or MHW Act. These results show that the participants did not have even a superficial knowledge of forensic mental health. In contrast, most of the participants had previously heard the term "criminal responsibility." This might be because the mass media sometimes reports cases in which criminal responsibility is questioned[14]. However, the depth of the participants' understanding about criminal responsibility was uncertain. It is possible that Japanese citizens' knowledge

about forensic mental health is very limited.

Very few studies similar to ours have been performed in Japan. Ando *et al*[15] conducted a mail survey of 3000 citizens to investigate their knowledge regarding forensic systems. In that study, respondents had a good knowledge of psychiatric testimony, but the majority had little awareness of the MTS Act. These results are consistent with our findings.

In contrast, citizens' recognition of the Lay Judge Act has been repeatedly investigated by both government[16] and media organizations[17,18]. Previous studies suggest that over 90% of citizens are aware of the enactment of the Lay Judge Act. The percentage is higher than that found in the present study; however, it is highly likely that the Lay Judge Act is better known than the MTS and MHW Acts. This fact may reflect a lack of clarity among citizens about mental health in Japan.

In 2010, we conducted a survey of psychiatric outpatients using a questionnaire with content similar to the questionnaire used in the present study[8]. In the 2010 survey, 86.7% of patients and 91.4% of their families had previously heard of the term "criminal responsibility." We found a similar percentage in the present study. The participants in this study, as well as psychiatric outpatients and their families, can be considered to be more concerned about forensic mental health than are citizens in general. Therefore, we consider the degree of awareness of forensic mental health among the public to be lower than these results.

In this study, approximately 60% of respondents opposed the concept of criminal responsibility before the seminar. Considering the small sample size and convenience sampling method of this study, it is difficult to generalize this result. However, to date no other structured research evaluating the national opinion on this concept has been reported[8]. A nationwide survey with non-biased samples is required to certify our result.

It is possible that more than a few citizens consider it unfair that patients with mental disorders are not deemed criminally responsible (partially influenced by media reports), although it is very rare that an insanity defense is successful in court[6]. Indeed, some researchers insist on abolishing the concept of criminal responsibility because it is seen as a form of discrimination[19]. However, in the post-seminar questionnaire, we saw a statistically significant increase in the number of respondents who were supportive of the concept of criminal responsibility, and these supporters became the majority group. Thus, a considerable proportion of the audience changed their opinions regarding criminal responsibility after attending the 1-h seminar.

In other words, some people originally opposed to the concept of criminal responsibility may have simply lacked a good understanding of mental disorders and forensic mental health systems. This hypothesis is consistent with the finding from the logistic regression analysis that participants with fewer opportunities to see media reports on psychiatry were more likely to become more positive toward the concept of criminal responsibility after the educational intervention.

It is noteworthy that participants who were unsupportive of the MTS Act tended to change their opinion, becoming more supportive of criminal responsibility. It is hypothesized that those who previously held a negative view of forensic psychiatric treatment changed their attitude after gaining knowledge on forensic mental health, resulting in a more positive attitude about the concept of criminal responsibility.

In contrast, the majority of respondents were supportive of OIH and the MTS Act before the seminar. After the seminar, the proportion of supporters increased; this increase was statistically significant for OIH but not for the MTS Act. These results suggest that a challenge remains regarding how to teach citizens about special treatment for MDOs. This seminar did not include case presentations of MDOs. Exposure to patients with mental disorders in a clinical setting is considered beneficial in reducing stigma against mental illnesses[20]. However, it is technically and ethically difficult to organize a session in which citizens can interact with MDOs. A case presentation with a realistic atmosphere that enables audiences to imagine an MDO and their process of recovery is desirable to maximize the effect of seminars.

We found that after the seminar, more respondents were willing to be exposed to media reports regarding the relationship between psychiatry and crime. This increase was statistically significant and may indicate motivation on the part of the participants to learn about forensic mental health.

There is some debate as to whether the media should report criminal cases and name the alleged offender when he or she may suffer from a mental disorder. Traditionally, Japanese media have maintained anonymity in such cases. In this study, the number of respondents supporting this kind of anonymous reporting increased following the seminar. This suggests that a considerable number of participants considered the risks of naming alleged offenders suspected to suffer from a mental disorder.

Regarding study limitations, this study was a non-controlled trial. The participants, recruited through convenience sampling, may have already been motivated and interested in our lecture. Thus, it is unclear to what level the general population understands forensic psychiatry and how rigid their opinions against forensic mental health are. However, it seems unfeasible to force citizens who are indifferent to this issue to attend the seminar. Further studies should be conducted using larger and less biased samples to achieve more precise results. Additionally, randomized controlled trials are needed to evaluate the power of influencing the opinions of attendees with more precision. For example, an interventional trial in school settings with cluster sampling may contribute to confirming our hypotheses.

General discrimination against patients with mental disorders still exists in Japan. People in Japan have a

stronger tendency to judge patients with schizophrenia as unfamiliar and risky to the community than people in the United Kingdom[10] or the United States[21]. These results indicate the necessity of education not only on forensic mental health but also regarding general psychiatry.

In conclusion, in Japan, the enactment of the MTS Act and the Lay Judge Act opened a door to a new age for forensic mental health. The MTS Act aims for the early reintegration of MDOs into the community, and the Lay Judge Act provides greater opportunities for citizens to be involved in criminal trials in Japan, many of which involve MDOs. However, the level of concern of citizens about forensic mental health still appears to be low. Even among participants attending our seminar about forensic mental health, many knew very little about the legislation concerning MDOs. Additionally, the present study shows that the majority of citizens seem unsupportive of the concept of criminal responsibility. However, the results demonstrated the possibility that an educational intervention can change the opinions of citizens regarding these issues. After providing the participants with proper information and knowledge, they became more supportive of the concept of criminal responsibility, admitting the necessity of proper treatment for MDOs with NGRI rather than harsh punishment. This result is consistent with our hypothesis that a lack of knowledge about forensic mental health is associated with unsympathetic attitudes toward MDOs. As mentioned above, however, there are several elements that should be examined to confirm our hypothesis. A national survey with larger and non-biased samples is required to fully clarify public opinion toward forensic mental health. Interventional studies should employ random sampling methods to identify the exact effect of such seminars. The longitudinal effect of the intervention also needs to be examined with a follow-up session. Controlled trials will be beneficial to specify which elements are essential to help attendees alter their opinions. In terms of research settings, schools can be advantageous because of the availability of homogeneous subjects and participants' readiness to attend seminars. The content of these seminars should include case presentations.

COMMENTS

Background

There is scarce evidence regarding citizens' attitude to forensic mental health in Japan. Also, discrimination toward mentally disordered offenders seems to be strong in many countries.

Research frontiers

The authors provided a one-hour seminar to offer precise knowledge about forensic mental health to citizens. This kind of attempt is very rare in Japan.

Innovations and breakthroughs

The results suggest people's biased recognition about mentally disordered offenders will be amended by brief educational intervention. It means that providing precise knowledge can reduce citizens' discrimination toward mental disorders.

Applications

Educational intervention to citizens will be effective for constructing a collaborative society. Developing a series of seminar in school education is also promising.

Terminology

Mentally disordered offenders mean people who violated a law at least partially due to their psychiatric symptoms such as delusion. How to deal with them is a crucial issue for secure and effective community.

Peer-review

This is a very interesting manuscript aimed to identify participants' level of awareness and opinion about the current situation of forensic mental health in Japan, and how it can be changed through psychoeducation. Although the manuscript uses simple methodology, the results may have an important impact on negative attitudes and stigma towards mentally ill persons and mentally ill offenders. This kind of research should be encouraged.

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