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EDITORIAL

So if we like the idea of peer workers, why aren't we seeing more?

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Author contributions: Gordon J was the lead author and was responsible for conducting and reporting the original research study described herein; Bradstreet S was responsible for describing progress in recovery thinking and practices within Scotland and internationally; the reflections and arguments were jointly developed by the authors.

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Conflict-of-interest: Simon Bradstreet is the Director of the Scottish Recovery Network who has a strategic interest in the promotion of peer working. Jacki Gordon is an independent researcher commissioned by the Scottish Recovery Network for this research.

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Abstract

The employment of peer support workers is widely encouraged in recovery-oriented mental health systems and services, providing a tangible example of how to translate recovery values and principles into actions. In Scotland, despite a long-term policy commitment to recovery approaches, the creation of peer worker roles has been slow and patchy. This paper describes findings from a study on the levers and barriers to the development of peer worker roles in two Scottish health board areas. Findings suggest that new evidence on effective implementation and cost effectiveness should be prioritised to support potentially complex role development in time of reduced resources. We argue that additional evidence on effectiveness is unlikely, by itself, to lead to country-wide employment of peer workers. We therefore suggest that a policy commitment to peer working would be reinforced by not only a strengthened evidence base but also strengthened accountability mechanisms. In the absence of such accountability, decision-makers and planners might reasonably continue to ask "why bother"?

Key words: Peer support; Recovery; Mental health policy; Role adoption; Workforce development

Core tip: Recovery approaches are widely and increasingly promoted internationally in mental health policy and services. Peer support working is a new professional role in mental health services and provides a tangible example of recovery principles being applied within the context of these services. As a consequence, there is a great deal of interest in emerging evidence around this role, and whether/how evidence might support increased and more effective involvement of peer workers. Our editorial presents findings from research

in Scotland and on the basis of these, poses some "big questions" concerning what needs to happen to accelerate progress in not only the employment of peer workers but also in mental health services' recovery approaches more generally.

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INTRODUCTION

In this editorial, we report and discuss levers and barriers to local health boards' employment of peer workers to promote mental health service users' recovery drawing on findings from recent research in Scotland. We reflect on the implications of these findings not only for Scotland but also for other jurisdictions seeking to increase their mental health services' involvement of peer workers.

RECOVERY: AN INTERNATIONAL PERSPECTIVE

The integration of the concept of recovery into mental health policy has become increasingly widespread around the world[1,2]. This development has been most notable in English-speaking countries although more recently recovery ideals and principles feature in mental health policies and practices more widely across Europe and in some parts of Asia[3]. The renewed emphasis on recovery in modern mental health has been primarily driven through documented first person accounts of recovery from people in receipt of mental health services, initially in the United States but then more widely[4,5]. These personal accounts indicate that recovery is generally interpreted in holistic terms. Furthermore recovery is often viewed as a process (or "journey"). People therefore can describe themselves as being "in recovery". These experiences and conceptualisations contrast with a narrower and more clinical understanding within mental health services of recovery as an outcome, characterised by a greater emphasis upon the cessation of symptoms than quality of life[1].

The holistic and multi-faceted nature of recovery can present challenges in more precisely operationalising recovery. A systematic review of international literature identified connectedness, hope and optimism, identity, meaning and purpose and empowerment (creating the acronym CHIME) as central elements in personal recovery[6]. In recognition of mental health services' needs for (increased) clarity on what constitutes recovery focused practice, another international study sought to identify and distil the key characteristics of such practice. These were identified as: "promoting citizenship, organisational commitment, supporting personally defined recovery, and working relationship"[7].

While there is increasing consensus on the practices and interventions of recovery focused service systems, the implications of adopting recovery focused approaches are significant and suggest substantial change to the culture and organisation of services[8]. Promoting recovery requires appropriate, and in many cases, new skills, competencies and practices for mental health professionals. It also requires renegotiated roles for people in receipt of services, whereby their expertise, garnered through their live experience, is given enhanced recognition and self-management is encouraged[9].

WHAT IS PEER WORKING?

Peer workers are people who have personal experience of mental health problems who are trained and employed to work in a formalised role in support of others in recovery. Peer workers are willing and able to share their personal experiences on an equal level that supports, empowers and brings hope to the people with whom they partner. The peer worker role involves: (1) Developing mutually empowering relationships; (2) Sharing personal experiences in a way that inspires hope; and (3) Offering hope and support as an equal[10].

The type of activities that peer workers undertake depends on the setting in which they are working but includes working one to one with people, running recovery education and mutual support groups and supporting people to use self-management tools.

For many years, people who experience mental health problems have described the importance and value of support from others who have had similar experiences and how it brings something different to that which is found in professional support relationships. Similarly, proponents of recovery consider that the employment of peer workers provides an opportunity to complement and enrich the provision of mental health services.

At the same time robust evidence of the effectiveness of support provided by peers in comparison to non-peer equivalents is in its infancy internationally[11] and extremely rare in the United Kingdom[12].

RECOVERY AND PEER WORKING IN SCOTLAND

The mental health system in Scotland is underpinned by a raft of legislation, strategies, policies and targets that share a commitment to human rights, including participation and empowerment of those who use services. Thus, there is a legislative duty for local government (known as local authorities) to provide care and support services for people with a recognised

mental disorder who are not in hospital and to provide services to promote their wellbeing and inclusion. Similarly there are duties on Scotland's 14 regional health boards (*i.e.*, the National Health Service in Scotland) which are responsible for the protection and the improvement of their population's health, to provide care and treatment for people with mental health problems. Third sector organisations (both national and local) are recognised as key players in delivering mental health care and support, and their involvement is actively encouraged by the Scottish Government.

In the last decade there has been significant activity related to the promotion and support of mental health recovery in Scotland. Much of this activity has been linked to the work of the Scottish Recovery Network (SRN). During this time, recovery might reasonably be described as having moved from the margins of Scotland's mental health system to the mainstream. It has become part of the accepted discourse, seen as a predominant means of improving experiences and outcomes for people in receipt of mental health services in Scotland[13]. Through this process Scotland has gained a reputation as a world leader in putting the principles and values of recovery into practice in mental health systems[1].

Within this context, the development of peer worker roles has been consistently identified as tangible demonstration of the adoption of recovery principles and values in mental health policy and practice[14,15]. SRN have been working since 2005 to promote peer working through the development of implementation and practice guidelines and nationally accredited training. This has been complemented by a Scottish Government policy commitment to the development of peer worker roles since 2006[16]. This commitment is made explicit in the current Mental Health Strategy for Scotland which indicates a focus on increasing and embedding peer working across Scotland[17].

It should be noted however that the recovery movement in Scotland is largely a "bottom-up" one insofar as decisions regarding recovery practices are taken at a local level. While the Scottish Government supports and endorses recovery, and indeed funds SRN to promote recovery values and practices, it is largely a matter for local areas to decide the degree to which they incorporate recovery principles, including peer working, into their service design and delivery.

MOVING PEER WORKER EMPLOYMENT FROM THE MARGINS TO THE MAINSTREAM

As outlined above, the employment of peer workers is encouraged in recovery-oriented services. It also provides a tangible example of how to translate recovery values and principles into actions (although, of course, it is not the only way that services can realise recovery). Given the focus on recovery in Scotland and the endorsement of peer workers as a policy priority, our editorial reflects on the possible reasons for why progress has been patchy and asks - how do we move from simply having examples of peer support working across the country to widespread provision?

We consider how to achieve this shift by drawing on a recent piece of research in Scotland that we describe below. This research was intended to identify whether decision-makers in local areas have, or were perceived to have, any evidence needs that, if met, might increase the use of peer workers across the country. The findings point to not just what types of evidence decision makers might find useful, or even persuasive, but importantly, what else needs to happen for Scotland to see peer workers being employed across local health board areas.

OUR RESEARCH: EXPLORING ISSUES, INCLUDING BARRIERS, TO EMPLOYING PEER WORKERS

The research on which we draw was commissioned by SRN to help it understand the basis for local decisions regarding the introduction (or not) of peer workers. SRN was particularly interested in identifying whether/how it might engender their wider use through distilling and disseminating evidence to those who are responsible for making decisions locally regarding service design and redesign.

The research was carried out by one of the editorial authors (JG) who is an independent researcher and whom SRN contracted to deliver this research within that capacity.

RESEARCH

The research methods were qualitative and involved 19 one-to-one telephone interviews with local stakeholders and one focus group with a pre-existing national advisory group that has a remit for increasing and embedding service user involvement. The interviews were conducted with local decision makers in one of two (selected) Scottish health board areas. We used pseudonyms for these health boards in order to protect anonymity. One of these health boards ("Mags") was selected because of its known progress in using peer workers. The other health board area ("Cluny") was selected because it was known to have not (yet) employed people with lived experience to perform this role within their (statutory) mental health services. A total of 19 interviews were conducted: ten from Cluny and nine from Mags.

The research aimed to explore the views of individuals with responsibility (in the health board, local authority or third sector) for making decisions on the design or development of mental health services

Table 1 Details of interviewees' roles

Cluny		Mags	
NHS	General Manager for mental health Clinical lead and director for mental health OT service manager Lead for mental health nursing Strategic planning and commissioning manager (across NHS and Local Authority) Manager in service development/quality improvement Inpatient services manager	NHS	Performance manager Nurse with responsibility for practice improvement in mental health Associate director of nursing OT lead in mental health nursing Public mental health manager
Council	Head of Adult Social work	Council	Service manager Senior Social worker
Third Sector	Two managers in third sector mental health organisations	Third Sector	Two managers in third sector mental health organisations

NHS: National Health Service.

and recovery initiatives. The first point of contact in each local area was with an individual who was known to have a leadership role for mental health. These individuals were asked to identify colleagues who had a remit as described above. The researcher then contacted these individuals to request their participation, and also asked them whom they would identify as fulfilling the eligibility criteria. This process was repeated until no further individuals were identified.

Interviewees spanned a number of roles, all senior. These included people with roles in commissioning, mental health service planning and leadership (in psychiatry, nursing, occupational therapy and social work), governance, and service specification, management and supervision (For a breakdown of interviewees by role, please see Table 1).

In addition to these interviews, a focus group was run with a Scottish Government multi-disciplinary advisory group on peer support working. These focus group participants included individuals working for the Scottish Government, local health boards, and third sector organisations (including peer workers).

Ethical principles were practised in line with the guidelines of the Social Research Association and the Respect Guidelines[18,19]. These included providing all participants with written information describing the purpose of the research, the focus of the interviews and their likely duration, their right to refuse to participate, details of how anonymity would be protected, and how findings would be used and reported.

The data analysis approach was informed by Framework - an approach devised for qualitative policy evaluation and used by the National Centre for Social Research[20]. This involved developing an analytical framework that reflected the research questions and the content of the collected data, and which used descriptive headings under which data were summarised.

RESEARCH FINDINGS

What sorts of evidence needs were indicated?

In the main, Cluny interviewees (particularly those at the most senior levels) acknowledged that they were not highly-informed about peer working. Nevertheless, even those who, by their own admission were less informed about peer working intuited what would be involved and talked of "theoretical benefits" for both the workers and for the individuals whom they would support. Thus they had an expectation that service users would appreciate talking to someone whom they felt was on a similar level to them, "had walked in their shoes" and, as a consequence, genuinely understood how they were feeling. There was therefore a general sense that the concept of peer support is a sound one, in principle at least, "The issue that we're talking about now is the sort of thing that even without the strongest evidence, it's worth considering because it's got a degree of face validity." (C.I1)

While there was an assumption that peer workers would be valued by patients, there was an identified need for evidence on the effectiveness of peer workers in achieving patient and service outcomes in comparison with the effectiveness of staff who perform other (more conventional) roles, *e.g.*, occupational therapists, nurses *etc*. This consideration was particularly acute in view of budgetary pressures.

"The question is - how could we afford this? How could we move towards it? What other posts would I have to cut in order to finance that kind of role? So what we always have to consider is not always just about the costing benefits of these peer support concepts, it's costing benefits of developing a peer support concept in combination with the cost benefits of making changes and probable reductions to something else within the services, in order to pay for it." (C.I1)

As a consequence, there was a view that evidence on cost-effectiveness and on cost-benefits would be compelling to decision makers in those health boards that have not gone down the route of employing peer workers. In fact, there was triangulated evidence across research participants from both of the health boards and from the Scottish Government focus group that in order to increase adoption of peer working, there was a need to build a costed argument (or

a "business case" as some called it) and for this to complement evidence on service users' perspectives.

"We're talking about commissioners here, we're taking about bean counters, we're talking about procurement teams, and senior executive management teams. … If you could demonstrate by the introduction of a peer worker into an acute admission unit, that your average length of stay dropped by 7% over the course of the year following the introduction and there were no other attributable factors, then that would move people to introduce them, because they were getting a cost saving then." (M.I5)

In addition to unmet evidence needs regarding costed "arguments", the need for evidence on (successful) implementation also emerged. This need arose from identified challenges in establishing and/or delivering peer support services. Particular challenges were raised about how to ensure workers' compliance with professional requirements (such as patient confidentiality, information sharing with the wider multi-disciplinary team), maintenance of workers' wellbeing and risks to service continuity in the event of workers becoming unwell. In fact, there was a view that the significant challenges involved in establishing a service of this sort could lead to a "why bother?" attitude.

As a consequence, there were calls for information/evidence on how to go about employing peer workers and then how to ensure their ongoing and productive role within the multi-disciplinary team.

"There's not a lack of evidence around about its appropriateness and effectiveness… there is a lack about then "how do we go about making it happen?" (M.I4)

In view of the unmet needs reported above, focus group participants (*i.e.*, those in the Scottish Government advisory group) felt that a two-pronged approach would be advantageous: creating a business case (detailing aspects like cost-benefits, including the contribution of peer support working to other agendas such as person-centred care); and, partnering evidence on implementation with resources (such as job descriptions, employment contracts, supervision protocols, *etc.*) in order to make the establishment of a peer support service a less daunting prospect.

If decision makers had the "right" evidence, would we then see universal provision?

As previously explained, decisions about the inclusion of recovery values and practices in mental health service design and delivery are made at a local level in Scotland. Such devolved decision making on recovery issues is not a Scotland-specific phenomenon and is likely to be the case internationally. The question here therefore is - if decision makers were to be given the evidence that they say they are lacking, then would they go on to employ peer workers in their local areas?

The findings from this research indicated that this is unlikely, at least in Scotland just now. Rather, there are a number of other, and potentially stronger, drivers that can underpin decisions at a local level.

Insights from this research revealed that a key reason for Cluny having not introduced peer support working was because there was no requirement for it to do so.

"I think XXXX (civil servant) has pushed it a little bit, but clearly not very hard, otherwise…you know, normally when the Scottish Government say 'jump' the health board says 'how high?', and the last mental health review meeting that we've had in XXXXX (Cluny), they just were not interested in some of the softer stuff; it was all about meeting Health, Efficiency, Access, Treatment (HEAT) targets and stuff like that." (CI.2)

Interviewees-both in Cluny and Mags, were of the opinion that that if the Scottish Government went beyond simply asserting peer support working as a priority in policy documents and made local health boards more accountable for delivering on this, peer working would no longer be relegated to a position of "competing" with other priorities. Instead, local decision makers would be compelled to design their services accordingly.

"If there's a Government directive, then of course we have to work towards that." (C.I9)

"Until there's an ultimatum, I don't think people are going to just do it". (C.I4)

So, in the absence of any governmental requirement, why had Mags opted to introduce peer workers?

Mags interviewees described how the local decision was taken because peer support was seen to be wholly consistent with the health board's and strategic partners' recovery principles and practices. Furthermore, despite the relative lack of evidence on successful implementation, in Scotland at least, Mags' interviewees talked of taking a "leap in the dark"- a leap that they were willing to take because their health board area was a forward thinking and enterprising one that was not limited by the highly risk averse attitudes and judgements that were considered to be typical elsewhere. In other words, Mags' decision cannot be explained purely in terms of evidence-based considerations. Better evidence, while desirable, was not a pre-requisite for Mags' decision: employing peer workers was seen as an evolutionary development-a logical, highly acceptable and obvious next step that was consistent with its value-base. Mags' decision was a hearts and minds affair.

DISCUSSION

Our research was based on the assumption that providing better evidence to those responsible for making decisions on service design and delivery at a local level would encourage wider-scale adoption of peer workers. Certainly there was some support for the notion that a basket of evidence might be useful, and therefore that SRN might usefully review, distil and disseminate evidence in a manner that targets key decision-makers and tailors this evidence to their particular requirements. Thus, a sound and reasoned cost-benefit analysis that pointed to both improved

patient and service outcomes over existing or more conventional models and staff teams would provide the information that was likely to go some way to meeting the needs of decision-makers with responsibilities for budget allocation. In the same way, SRN might target those with a role in commissioning and service governance with tailored evidence on what works well in terms of establishing a service, attending to issues such as maintenance of workers' wellbeing, procedures to ensure adherence to confidentiality codes *etc.*

Participants in this research spoke about making decisions in the context of contracting and pressurised budgets and services. Furthermore, the Scottish experience and the feedback from the participants involved in the research project described in this paper clearly suggest that the development of peer worker roles is complex and challenging for those who have made a commitment and potentially daunting for those who have yet to commit. Clearly the question of "why bother" has to be emphatically answered and there are indications here that people would value specific evidence (and associated outputs such as job descriptions and templates) to help them navigate and effectively address the challenges of establishing and sustaining the peer worker role. Indeed this, along with evidence on the cost benefit of role creation, was more strongly emphasised than a need to demonstrate the effectiveness of peer workers. These needs suggest areas - perhaps even priorities - for future research and evaluation. They might also helpfully redirect energies from well-intentioned research on peer worker effectiveness (that casts them themselves as the intervention) rather than focusing on the effectiveness of the things they do. While we should certainly test the effectiveness of peer worker led interventions and support, we would argue that to treat peer workers as an "intervention", and a homogenous one at that, is unlikely to be helpful. We would argue in line with realist principles[21], that the key issue is not whether or not peer workers should play part of our (recovery focused) services but rather to identify the circumstances that make the involvement of peer workers more (and less) valued and effective. We consider that such insights are consistent with use-led research and thereby have the potential to be of value in shaping (real-life) decisions about service design.

The development of recovery approaches in Scotland has been notable internationally in that the main driver for systems change has come from outwith the statutory sector. While SRN is funded by the Scottish Government, it is based in the voluntary sector and acts more as a facilitator and bridge builder across groups and sectors than as an enforcer of policy. This facilitative approach has been broadly welcomed by stakeholders[22] yet it undoubtedly has its limits when it comes to encouraging the type of fundamental service redesign which the genuine application of recovery principles and values would suggest.

We did, though, note earlier that there has been a clear policy commitment to the adoption of peer working for some time in Scotland so support and encouragement from the top level has been consistent. We would however argue that given the perceived and real challenges in developing peer worker roles, to effectively challenge the "why bother" question we need more than one-off commitments, which, according to decision makers in one area of our study, did not feature highly on the list of policy priorities at local or national level. This suggests that to move beyond the current impasse, peer working must shift from being perceived as a "nice but not essential" feature of mental health service policy and provision to genuinely being a core and consistent one.

Furthermore, in the absence of mental health services being held to account on this issue, the "why bother" question has some credence, with or without evidence.

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EDITORIAL

What is schizophrenia? 25 years of research into schizophrenia - the Age Beginning Course Study

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Abstract

We studied a population-based sample of 232 first-onset cases of schizophrenia aged 12 to 59 years at first admission retrospectively back to illness onset and prospectively up to 11.2 years later. We compared them with psychiatrically healthy age- and sex-matched population controls and equally matched first-admission patients diagnosed with major depression. At schizophrenia onset women are several years older than men. The social factors tested did not explain the finding. Women's higher level of social development at onset is associated with a better medium-term functional and social outcome. Prodromal schizophrenia and depression are equal in length and diagnostically distinguishable only after the onset of positive symptoms. The sex difference in age at onset, invariable across cultures and ethnicities, is explained by a protective effect of oestrogen, which down-regulates D2 receptors. A higher genetic load antagonizes this effect. Long-term symptom-related illness course exhibits a plateau after three years, the positive symptom dimension after two years, the depressive and the negative dimensions do so after three to five years. The most prevalent symptom is depressive mood. Male first episodes are more frequent and more severe in the first half of life, female ones in the second half. Aetiological conclusions will be drawn.

Key words: Schizophrenia and depression; Symptom dimensions; Types of illness course; Sex; Age

Core tip: We studied schizophrenia from onset to 134 mo following first admission: age at onset is higher for women because of oestrogen. Prodromal schizophrenia and depression split diagnostically only after the onset of positive symptoms. Illness course exhibits a plateau after three years, positive symptoms do so after two,

depressive and negative symptoms after three to five years. Depressive mood is the most prevalent symptom. Male first episodes are more frequent and more severe in the first half of life, female ones in the second half. Late-onset schizophrenias feature paranoid delusions, early-onset illnesses various severe pathology. Aetiological conclusions will be drawn.

Häfner H. What is schizophrenia? 25 years of research into schizophrenia - the Age Beginning Course Study. *World J Psychiatr* 2015; 5(2): 167-169 Available from: URL: http://www.wjgnet.com/2220-3206/full/v5/i2/167.htm DOI: http://dx.doi.org/10.5498/wjp.v5.i2.167

INTRODUCTION

For more than one hundred years researchers have tried to answer the questions of what schizophrenia actually is and how it is related with affective disorder. Fascinating novel research methods have been developed and a considerable amount of knowledge has been amassed on different aspects, but we still lack conclusive answers to these questions. A quarter of a century ago (in 1987), as we launched our A (ge) B (eginning) C (ourse) Schizophrenia Study[1,2], the situation was very much the same. But we were daring enough to embark on a journey to gain insight into some aspects of the nature of the disorder.

STRATEGY AND AIMS

We proceeded from a finding already reported by Emil Kraepelin[3] and confirmed by numerous studies[4]: women's several years' higher age at first admission for schizophrenia compared with men's. After testing and confirming its transnational and transcultural validity on data from the Danish and the German case-register and the WHO ten-country study, with four sites in low-income developing countries and seven sites in industrialized countries, we set the first goals for our study: (1) finding an explanation for the sex difference in age of onset; and (2) collecting detailed information on the prodromal symptoms and demonstrating how the disorder unfolds prior to first admission.

This exceptional study was conducted by the same team of researchers in several consecutive steps from its planning and launch on January, 1st, 1987 to its completion on May 31st, 2012 and financed by the German Research Foundation (DFG) over those 25 years. Data analysis is still going on. Our aim was to produce generally valid results by applying a systematic, methodical approach and both traditional and advanced statistical techniques. For the sake of the generalizability of the results, the study was designed as a population-based, multiply controlled follow-up study. On the basis of the results achieved new research objectives were defined and novel hypotheses were tested. We studied symptoms, symptom dimensions and social parameters at the prodromal stage, in the first episode, over the medium- (5-year-) and the long-term (11.2-year) course of schizophrenia in the entire study sample and a subsample of 130 first admissions. We conducted eight cross-sectional assessments and mapped the illness course retrospectively on a monthly basis. We compared our population-based sample of 276 first admissions with a diagnosis of schizophrenia (= 232 first psychotic episodes) in age range 12-59 years with healthy controls drawn from the population of the catchment area and with age- and sex-matched first admissions for unipolar depression. We analyzed how age, sex, primary and secondary risk factors, hormonal factors, level of social development at illness onset and illness behaviour influence the disorder. We studied how symptomatology changes over the life-cycle in a sample of 1109 consecutively first-admitted patients with schizophrenia spectrum disorder.

Limited space permits us to present only excerpts from this large-scale study and to draw a few conclusions.

MAJOR FINDINGS

The prodromal stages of schizophrenia and moderately severe and major depression last for several years (in schizophrenia: mean 4.8 years, median 2.3 years) and cannot be discriminated from each other until positive symptoms appear. As long as this is the case, it is also impossible to make any predictions about the diagnosis-related illness course. The most frequent symptom over the entire course of schizophrenia, depressive mood, is also the most frequent initial symptom in both disorders. Prodromal depression in schizophrenia is associated with a greater amount of depressive and positive symptoms in the first illness episode, but not in the further course of the disorder.

Male incidence of schizophrenia shows a pronounced peak in age group 15 to 24 years, female incidence a lower peak in age group 15 to 29 years and a second - narrower and still lower - peak at menopausal age in age group 45 to 49 years. This finding is accounted for by the age-dependent protective effect of oestrogen, confirmed in animal experiments. Underlying it is probably a sensitivity-reducing effect on D_2 receptors. The protective effect is antagonized by genetic load - for example in co-twins and siblings of individuals diagnosed with schizophrenia. Beyond the menopausal age the sex ratio in the incidence of schizophrenia is reversed: in old age men develop psychosis more rarely and, when they do, present milder symptoms than their female peers.

Functional and social impairment appears at the prodromal stage. The severity of that impairment depends on the individual's sex and level of social development at illness onset. The social course of schizophrenia is less favourable for young males than females because of men's younger age at illness

onset and their greater prevalence of socially adverse behaviour. At higher age, when males have lost the socially adverse behavioural parameters frequent at younger age, men tend to develop milder, primarily paranoid symptoms and suffer less severe social losses. Schizophrenia is a disorder of all ages. Considering the entire lifespan, there is not any major sex difference in schizophrenia incidence, although there are numerous epidemiological studies, mostly based on lower age limits (45-55 years) and treated or hospitalized patients, and meta analyses reporting a higher lifetime risk for males[5].

The course of schizophrenia as such and the trajectories of the symptom dimensions as based on mean values show plateaus starting some two to five years after the first episode, and positive symptoms do so earlier than negative symptoms. Underlying these different patterns are irregularly occurring episodes of symptom exacerbation, which differ in duration depending on the symptom dimension.

CONCLUSION

Considering the remarkable finding that both the symptom-related and the social course of schizophrenia depend on age and sex, considering further the temporal variability of psychopathology and the fact that, according to mean values, the disorder does not progress, it seems reasonable to conclude that schizophrenia is not a unitary disorder. At its early prodromal stage, it is indistinguishable from mood disorder. Throughout the illness course, depressed mood is the most prevalent symptom in schizophrenia. Although the long-term trajectories of the individual symptom dimensions resemble each other, there is a certain degree of autonomy that cannot be overlooked in their remission following the first psychotic episode or in the frequencies and durations of their exacerbations. Schizophrenia does not convey the picture of a stable residual state caused by an early developmental disorder, nor does it look like a progressive neurodegenerative process. It rather gives the impression of a condition resulting from a susceptibility to recurrent crises in the neural functions that underlie the symptoms. Hence, rather than knowing what schizophrenia really is we have merely achieved a little better understanding of what it is not.

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REVIEW

Transcranial magnetic stimulation for geriatric depression: Promises and pitfalls

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Abstract

As the global population gets older, depression in the elderly is emerging as an important health issue. A major challenge in treating geriatric depression is the lack of robust efficacy for many treatments that are of significant benefit to depressed working age adults. Repetitive transcranial magnetic stimulation (rTMS) is a novel physical treatment approach used mostly in working age adults with depression. Many TMS trials and clinics continue to exclude the elderly from treatment citing lack of evidence in this age group. In this review, we appraise the evidence regarding the safety and efficacy of rTMS in the elderly. A consistent observation supporting a high degree of tolerability and safety among the elderly patients emerged across the Randomised Controlled Trials and the uncontrolled trials. Further, there is no reliable evidence negating the utility of rTMS in the elderly with depression. We also identified several factors other than age that moderate the observed variations in the efficacy of rTMS in the elderly. These factors include but not limited to: (1) brain atrophy; (2) intensity and number of pulses (dose-response relationship); and (3) clinical profile of patients. On the basis of the current evidence, the practice of excluding elderly patients from TMS clinics and trials cannot be supported.

Key words: Transcranial magnetic stimulation; Depression; Geriatric; Treatment resistance; Treatment resistant depression; Repetitive transcranial magnetic stimulation; Neuromodulation

Core tip: Depression in the elderly (geriatric depression)

is an emerging global concern. A major challenge in treating geriatric depression is the lack of robust efficacy for many treatments that are of significant benefit to depressed working age adults. An emerging intervention that shows promise in refractory depression is repetitive transcranial magnetic stimulation (rTMS). To date, most of the evidence for TMS in depression pertains to working age adults. We review the evidence regarding the safety and efficacy of rTMS in geriatric depression. In addition, we also review the literature on possible moderators of differential efficacy of rTMS in geriatric depression.

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INTRODUCTION

With an aging global population, depression in the elderly is emerging as a serious public health concern. At present it is estimated that nearly 8%-16% of the elderly (aged > 65) living in the community suffer from clinically significant depressive symptoms[1], a harbinger of significant morbidity and early mortality[2]. Older age of a depressed patient is a significant predictor of an unfavourable course with an increased risk of relapse[3], reduced likelihood of treatment response[4,5] and diminished chance of functional recovery[6]. Furthermore, the emergence of treatment resistant depression (TRD) is common among the elderly, with an estimated rate of between 26 and 41 per 100 person-years[7].

An important challenge in optimally treating geriatric depression is the reduced utility of conventional antidepressant treatments. Randomised Controlled Trials (RCTs) of antidepressants reveal a smaller size of treatment effect among the elderly compared to the younger age groups. The number needed to treat (NNT) for antidepressant *vs* placebo use for an acute response goes up steadily with age with estimated numbers of 6 in those aged < 55 years; 8 in those aged 55-65 years; and 14 in those aged > 65 years[5]. This difference may be related to the differences in the pathophysiology and phenomenology of depression among older people.

Whilst depression is mostly a disorder of young adults (peak age of onset in 20 s, with a trend towards more younger age of onset in younger cohorts), late-onset depression (after age 50) has a higher probability of medical comorbidity. There are 2 groups of individuals among those with geriatric depression: one with an early onset (< 50 years) recurrent depression and other in whom depression occurs after the age of 50 for the first time (late-onset). Compared to elderly patients with early-onset depression, patients with late-onset major depression often have greater vascular risk factors[8], show greater executive dysfunction[9], more psychomotor retardation, less agitation and guilt, and more disability[10]. These factors in general predict poorer response to antidepressants[10]. Furthermore, even among the elderly depressed with early-onset depression, the prevalence of treatment resistance is substantial[7], and the risk of relapse despite successful treatment is particularly high[3], highlighting the critical need to focus on alternative treatments that have fewer propensities to affect cognitive faculties and physical frailty while reducing the persistence of symptom burden.

Transcranial magnetic stimulation (TMS) involves the use of magnetic field applied on the surface of scalp to modulate brain function in a non-invasive manner. Repetitive TMS (also called rTMS) is a promising intervention for depression with a treatment effect size as large as the effect size seen when using antidepressant medications for depression[11-13]. Several treatment guidelines have endorsed the use of rTMS as a second-line intervention for treatment of depression in adults[14]. In particular, rTMS is often seen as complementary to electroconvulsive therapy (ECT) due to the reported lack of cognitive side effects, which may be highly advantageous when treating depression in older people. Nevertheless, with some earlier reviews dismissing its effectiveness[15], the place of rTMS in the treatment of depression in older people is unclear at present.

More than 35 RCTs have been published reporting on the efficacy of rTMS when compared to sham stimulation[16]. Most of these trials focus predominantly on working age adult samples. In recent times several meta-analytic syntheses of these trials have been published[17,18]. The mean age of the samples included in these syntheses, when reported, range from 27 to 61 years[19-26] (Table 1), indicating that very few cases of geriatric depression, if any, were included in the meta-analysed trials. Nevertheless, on the basis of sample mean values of 6 early RCTs (5 double-blind, one open-label), Fregni *et al*[27] concluded that older age is associated with poorer response to rTMS in depression. In line with this rTMS was considered to have no role in the management of geriatric depression[15]. Several subsequent meta-analyses have failed to replicate this finding[19,28,29]. Furthermore the inference based on Fregni *et al*[27]'s observation can be challenged on the basis of two important issues. Firstly, as highlighted earlier subjects with geriatric depression (age > 65) were not included in most individual trials. Secondly, moderator effects uncovered in meta-analytic studies are based on variances between sample means reported in studies, not variances between individuals who receive the treatment perse. Only by studying older subjects and estimating the influence of inter-individual age differences on the response, a firm inference regarding the effectiveness of rTMS in the

Table 1 Meta-analytic studies of the antidepressant efficacy of transcranial magnetic stimulation published on or after 2003

Ref.	No. of trials	Mean age	Effect size
Allan *et al*[29] 2011	25	Not presented	NNT = 5
Berlim *et al*[22] (bilateral) 2013	7	49.3 + 5.7	NNT = 6 (res); 7 (rem)
Berlim *et al*[47] (HF) 2013	29	47.6 + 7.1	NNT = 6 (res); 8 (rem)
Berlim *et al*[21] (LF) 2013	8	49.39 ± 7.0	NNT = 5 (res/rem)
Schutter[25] 2013 (add-on)	6	44.47 ± 7.55	NNT = 7
Couturier[91] 2005	6	Not presented	WMD = 1.1
Gaynes *et al*[76] 2014	18 (TRD)	Not presented	NNT = 9 (res); 5 (rem)
Gross *et al*[71] 2007	5	44.7 + 4.2	d = 0.76
Herrmann *et al*[28] 2006	33	49.14 (subgroups split at age 50)	d = 0.65
Lam *et al*[92] 2008	24	Not presented	NNT = 6
Lepping *et al*[16] 2014	22 (nTRD) 10 (TRD)	Not presented	d = 0.63 (nTRD) d = 0.74 (TRD)
Martin *et al*[20] 2003	14	41.8 - 60.9	d = 0.35
Schutter[25] 2009 (HF)	30	49.5 + 7.8	d = 0.39
Schutter[26] 2010 (LF)	9	50.0 + 6.3	d = 0.63
Slotema *et al*[13] 2010	40	Not presented	d = 0.55
Kedzior *et al*[19] 2014	14	27.0-53.0	d = 0.42

d: Cohen's d effect size; LF: Low frequency; TRD: Treatment resistant depression; nTRD: No treatment resistance; NNT: Number needed to treat; WMD: Weighted mean difference; res: Response; rem: Remission.

elderly can be made.

This review considers recent trials regarding the clinical utility of rTMS in depressed elderly patients. In particular we consider the: (1) evidence for efficacy and safety of rTMS in the elderly; (2) examine the moderators of efficacy; and (3) propose directions for clinical practice and future research.

LITERATURE SEARCH

Search strategy

This review is based on a literature search conducted primarily using the PubMed and Ovid databases in September 2014 with further searches including PsycINFO, CINAHL and Embase. Search terms used were "(Transcranial magnetic stimulation OR TMS OR rTMS OR brain stimulation) AND (geriatric OR elderly OR late life OR late onset OR age OR older) AND depress*." Articles in English published prior to the search date were included.

Eligibility criteria

RCTs evaluating the efficacy and safety of TMS (irrespective of pulse frequency) were included in this review. Due to paucity of research in this area we also included uncontrolled trials and retrospective reviews in the field. The primary outcome measure was chosen as a categorical response or a continuous change defined a priori in the individual trials on the basis of a standardised depression rating scale (*e.g.*, Hamilton Depression scale). In addition we also studied the adverse events reported in the trials. Only studies with a mean age of patient sample > 60 years were included. An exception to this rule was applied when subgroup analysis was performed with mean age > 60 for at least one subgroup.

Study selection

One reviewer (PS) assessed articles identified as a result of the search and where necessary, in cases of uncertainty, a second reviewer (LP) also considered the articles. Studies were initially screened for relevance in the title and abstract. Duplicate articles were removed and the remaining full text articles were reviewed. The final papers chosen for inclusion were also hand searched to ensure relevant references were not missed.

In addition to the systematic review focussing on efficacy and safety in geriatric depression, we also appraised the wider literature to investigate the known moderators of treatment efficacy in geriatric depression. For this purpose, a broader search was conducted using the above search terms, but without restricting studies to a specific mean age of the samples.

RESULTS AND DISCUSSION

Evidence for efficacy in the elderly

We identified 4 RCTs that specifically included older subjects, resulting in mean sample age > 60 years (Table 2). Of these 2 trials reported no benefit from rTMS when compared to sham[30,31] while 2 other trials (presented in a single manuscript) reported a substantial benefit[32]. Both Manes *et al*[30] and Mosimann *et al*[31] used stimulation intensity that was fixed at or lower than the motor threshold. In contrast, Jorge *et al*[32] employed a higher intensity. Jorge *et al*[32] have also shown that the delivery of a higher dose (larger number of pulses - 18000 instead of 12000) is more beneficial in the older than in the younger age group of patients with treatment resistant vascular depression[32].

Table 2 Randomised Controlled Trials investigating antidepressant effect of transcranial magnetic stimulation in older subjects (mean age of sample > 60)

Trial	Age range	TMS parameters	Sample size	Methodology	Results
Manes *et al*[30] 2001	60.7 ± 9.8	20 Hz; 80%MT; left DLPFC; 800 pulses/session; 5 sessions; no. of pulses = 4000	20 (sham = 10)	Double blind RCT with handle as sham in subjects with one antidepressant failure aged 50-70, withdrawn from antidepressants for 5 d	No sham *vs* active differences; in each group 30% responded. Non-responders had reduced frontal volume. No drop-outs due to adverse effects
Mosimann *et al*[31] 2004	62 + 12	20 Hz; 100%MT; left DLPFC; 1600 pulses/session; 10 sessions; no. of pulses = 16000	24 (sham = 9)	Double blind RCT with tilted-sham in 40-90 years old subjects with TRD	No sham *vs* active differences
Jorge *et al*[32] 2008 (Trial 1)	62.9 (7.2)	10 Hz; 110%MT; MRI-based target localisation of left DLPFC; 1200 pulses/session; 10 sessions; no. of pulses = 12000	30 (sham = 15)	Double blind RCT with look-alike sham coil in subjects > 50 yr age with vascular depression and failed at least one antidepressant; all patients medication-free for at least 4 d before TMS	Age inversely correlated with response; frontal volume positively correlated with response. Active treatment: 33.3% responders; sham: 6.7% responders. No drop-outs due to adverse events
Jorge *et al*[32] 2008 (Trial 2)	64.3 (9.4)	10 Hz; 110%MT; MRI-based target localisation of left DLPFC; 1200 pulses/session; 15 sessions; no. of pulses = 18000	62 (sham = 29)	Double blind RCT with look-alike sham coil in subjects > 50 yr age with vascular depression and failed at least one antidepressant; all patients medication-free for at least 4 d before TMS	Active treatment: 39.4% responders; sham: 6.9% responders. Older subjects had better response for higher dose. No drop-outs due to adverse events

DLPFC: Dorsolateral Prefrontal Cortex; MT: Motor Threshold; RCT: Randomised Controlled Trial; TMS: Transcranial magnetic stimulation.

Several uncontrolled trials that focus on the efficacy of rTMS in older samples (age > 60) have been published. We identified 5 uncontrolled trials with mean sample age > 60 (Table 3), and 2 trials that specifically studied the subgroup effect for patients aged > 60[33] or 65[34]. Response rates (defined as proportion showing a 50% or greater drop in HDRS score) greatly varied, ranging from 18% to 58.5%. Notable variation was also observed for the rTMS dose parameters, with some studies using 100% or less of Motor Threshold (MT: the intensity of magnetic pulse required to elicit an observable thumb movement)[34-36] and others using > 100% of MT[33,37]. One study employed an intensity adjustment for predicted frontal atrophy by measuring the MRI-based distance between the coil and the cortical surface[38]. Four studies explicitly studied the association between age and treatment response[33,34,37,38]. While 2 studies found a reducing treatment effect with increasing age[33,37], the other 2 studies failed to find a similar association[34,38]. Taken together, there is no consistent evidence negating the utility of rTMS in the elderly. The heterogeneity among studies suggests that several clinical and treatment-related factors may moderate the therapeutic effect of rTMS in the elderly.

Evidence for safety in the elderly

A consistent observation supporting a high degree of tolerability and safety among the elderly patients emerged across the RCTs and the uncontrolled trials. In most of the studied cohorts, there were no dropouts due to adverse effects. Only 2 studies reported loss of subjects due to adverse effects[33,39]. Out of 102 patients of various ages reported by Pallanti *et al*[33], dropouts occurred due to anxiety (n = 4), insomnia (n = 5), mood elevation (n = 1), discomfort of the scalp (n = 5), and hospitalization during treatment (n = 4). The 18.6% dropout rate reported in this study is unusually high, when compared to the overall 4.5% observed from other larger multisite studies[40]. Pallanti *et al*[33] did not study the influence of age on the dropouts. In the sample reported by Abraham *et al*[39] one subject dropped out due to local discomfort. Jorge *et al*[32] reported local discomfort in around 33% of the randomized sample. But no subjects discontinued treatment due to this effect, and the distribution of side effects was not significantly different between the sham and the active treatment groups[32].

Efficacy of rTMS in comparison with ECT in the elderly

ECT has an important role in the clinical management of geriatric depression. A substantial proportion of all referrals received by ECT clinics fall into the age group > 65[41]. ECT appears to be generally safe and highly efficacious in geriatric depression with response rates close to 70% reported in some studies[42,43]. Interestingly, older age is associated with a more favourable response to ECT[44,45]. In this context it is important to consider direct comparisons ECT and rTMS in treating geriatric depression.

We located 4 meta-analyses that synthesize the evidence from studies that compare rTMS and ECT (Table 4). The sample mean age of these studies span a range of 31.0 to 63.6 years[46-49]. All 4 meta-analyses find that ECT is superior to rTMS in short-term when categorical response is considered,

Table 3 Uncontrolled studies exploring the effect of age on the antidepressant effect of transcranial magnetic stimulation by recruiting older subjects (mean age of sample > 60) or undertaking analyses in subgroups with mean age > 60

Trial	Age range	TMS parameters	Sample size	Methodology	Results
Figiel *et al*[37] 1998	60.0 (22-89)	10 Hz; 110%MT; left DLPFC; 500 pulses/session; 5 sessions; no. of pulses = 2500	50	Uncontrolled trial in patients > 18 yr attending a Mood Disorder Clinic (most referred for ECT)	Age associated with treatment response; < 65 (n = 28) responded better (56%) than > 65 group (n = 22; 23% response). Overall 42% responded after the 5 sessions
Nahas *et al*[38] 2004	61.2 (7.3)	5Hz; 103%-141%MT (distance adjusted); left DLPFC; 1600 pulses/session; 15 sessions; no. of pulses = 18000	18	Uncontrolled trial in patients 55-75 yr; not selected for TRD	No correlation between age and response; 27% responded; 22% remitted; No drop-outs due to adverse events
Fabre *et al*[35] 2004	67.9 (6.7)	10 Hz; 100%MT; left DLPFC; 1600 pulses/session; 10 sessions; no. of pulses = 16000	11	Uncontrolled trial in patients age > 55 with vascular depression (first episode) and TRD but kept antidepressant free for 1 wk	5 out of 11 patients had clinically meaningful improvement in HDRS scores; response inversely related to frontal volume. No drop-outs due to adverse events
Abraham *et al*[39] 2007	66.8 (6.4)	10 Hz; 100%MT; left DLPFC; 1600 pulses/session; 10 sessions; no. of pulses = 16000	20	Uncontrolled trial in patients > 60 yr attending a specialist clinic - most referred for ECT	30% responded at the end of treatment; 1 dropout due to discomfort
Milev *et al*[78] 2009	69.0 (6.7)	Variable parameters: LF (1 Hz, 1200 pulses/session, n = 14), HF (10 Hz, 1600 pulses/session n = 31); both LF and HF (n = 4); 80%-110%MT; right or left DLPFC	49	Uncontrolled trial that includes patients with TRD referred to 2 specialist mood disorder clinics; all except 3 medicated	24.7% mean reduction in HDRS scores; 18% responders; 1 dropout due to discomfort out of 49. (Note: This sample includes n = 20 from Abraham 2007)
Pallanti *et al*[33] 2012	51.8 (14.1)	1 Hz; 110%MT; right DLPFC; 420 pulses/session; 15 sessions.; no. of pulses = 6300	102	Uncontrolled trial in consecutively enrolled nonpsychotic subjects in a TMS clinic with TRD	Age inversely related to response especially in patients > 60 yr; overall 56.9% responded. 62.1% of < 60 (n = 66) and 47.2% of > 60 (n = 36) responded at 3 wk. 18.6% drop-outs due to intolerance
Hizli Sayar *et al*[36] 2013	66.6 (5.8)	25 Hz; 100%MT; left DLPFC; 1000 pulses/session; 18 sessions; no. of pulses = 18000	70	Uncontrolled trial in patients > 60 yr with TRD	58.5% responded; 29.2% remitted; No drop-outs due to adverse events
Ciobanu *et al*[34] 2013	58.7 (14.0)	LF (1 Hz, 1200 pulses/session, n = 80), HF (10 Hz, 2000 pulses/session n = 13); 90%MT; right or left DLPFC; 15 sessions; no. of pulses = 18000	93	Uncontrolled trial in > 18 yr old subjects with TRD	Age not related to response; No difference between < 65 (n = 63; 53.3% responded) and > 65 age (n = 30; 46.7% responded) groups immediately and at 3 mo

DLPFC: Dorsolateral Prefrontal Cortex; MT: Motor Threshold; RCT: Randomised Controlled Trial; ECT: Electroconvulsive therapy; TRD: Treatment resistant depression; TMS: Transcranial magnetic stimulation.

though Ren *et al*[46] indicate that change in continuous Hamilton Depression Rating Scale (HAMD) scores do not significantly differ between the two treatments. Furthermore, Berlim *et al*[47] noted baseline differences favouring ECT (shorter duration and more severe illness). There is insufficient data to comment on medium or long-term efficacy[46]. Interestingly, two of the three individual trials showing significant difference in favour of ECT[50,51] included participants with higher mean age than the rest. When comparing ECT and rTMS, Janicak *et al*[52] noted that older subjects required a higher number of rTMS sessions to experience a favourable treatment response when compared to younger subjects. Nevertheless, when considered as a moderator in the meta-analytic setting, mean sample age did not significantly predict the effect size of rTMS v ECT differences[47]. An important predictor appears to be the presence of psychotic symptoms[46,47]; in the presence of psychosis, ECT appears to be significantly superior to rTMS[51]. But in samples with no psychosis, rTMS performs as well as ECT[53]. Given that many patients with geriatric depression have psychotic symptoms, this may partly explain the superior efficacy of ECT in this setting, though more focused studies are required to provide conclusive support to this notion.

Rapidity of response is an important factor for which ECT is sought in the elderly. Difference in speed of response has not been studied directly in the 4 meta-analyses, but an important observation suggests that ECT may be superior to rTMS in terms of the rapidity of response. Xie *et al*[48] observed that when rTMS treatment period was less than 4 wk, rTMS was significantly inferior to ECT. When the treatment period was increased to 4 wk, the difference between rTMS and ECT began to decrease, suggesting that ECT results in far more cases of early response than rTMS.

With respect to cognitive side effects in the relatively younger samples included in meta-analyses, ECT was associated with more impairment in several cognitive

Table 4 Summary of meta-analyses comparing transcranial magnetic stimulation and electroconvulsive therapy in depression

Meta-analysis	No. of studies/sample size	Mean age range	Summary of effect
Berlim *et al*[47] 2013	7/294	31.0-63.6	NNT = 6 favouring ECT for short-term response; at baseline, ECT samples had shorter illness duration and higher HAMD scores than rTMS samples. Age has no moderating effect on the differences
Ren *et al*[46] 2014	9/425	31.0-63.6	NNT = 7 for response; 6 for remission favouring ECT; No significant group difference when continuous change in HAMD scores is considered as outcome; In the absence of psychosis, rTMS as efficacious as ECT; Cognitive domains are better preserved after rTMS than ECT
Micallef-Trigona[49] 2014	9/384	34.0-63.6	Hedges'g = 1.28 for rTMS and 2.15 for ECT. rTMS produces a mean reduction of 9.3 points; ECT produces a mean reduction of 15.42 points on the HDRS
Xie *et al*[48] 2013	9/395	31.0-63.6	OR = 0.55 for response and 0.49 for remission in favour of ECT; rTMS is better tolerated than ECT (OR = 0.70); rTMS > 1200 stimuli/d is as efficacious as ECT

NNT: Number needed to treat; TMS: Transcranial magnetic stimulation; ECT: Electroconvulsive therapy; HAMD: Hamilton Depression Rating Scale.

domains[46], though the dropout rates (acceptability) did not differ between the two interventions.

Moderators for efficacy in the elderly

Studies included in this review examined the role of several moderators on clinical response as described below.

Age: Age itself is not a consistent predictor of the antidepressant effects of rTMS as shown by conflicting evidence from adult samples[29]. A large naturalistic study (n = 307) that included a broad age range (18 to 90) of patients receiving rTMS for depression concluded that age had no notable influence on the improvement in quality of life noted in patients[54]. Furthermore the RCTs and uncontrolled trials reviewed here defy the notion that rTMS is ineffective in geriatric depression. Given the wide range of response rates reported among the elderly, it becomes important to understand the factors that may influence treatment response in this group. Some of the important factors that have been identified in this context are: (1) brain atrophy; (2) intensity and number of pulses (dose-response relationship); and (3) clinical profile of patients.

Brain atrophy: Manes *et al*[30] first observed that the volume of frontal cortex was inversely related to the antidepressant response to rTMS in the elderly. This observation was later confirmed by Fabre *et al*[35] and Jorge *et al*[32]. In an atrophic brain, the distance between scalp and cortex (Scalp-Cortex Distance or SCD) increases. When applying rTMS the intensity of the magnetic field decays exponentially as we move from the scalp surface to the cortical surface[55]. Herbsman *et al*[56] have shown that nearly 60% of inter-individual variation in Motor Threshold can be explained by the distance between scalp and motor cortex alone (motor SCD). Using a simple linear model, Stokes *et al*[57] estimated that for every 1 mm increase in motor cortex SCD, a 2.8% increase occurs in consistent with this observation, the degree of rTMS induced change in frontal perfusion corresponds inversely with increasing frontal cortex SCD in depressed subjects[58].

One may argue that as the intensity of stimuli used in the treatment of depression is generally based on an individual's MT, the effect of brain atrophy is already taken into account by adjusting the intensity applied to frontal cortex on the basis of MT. But in fact, with age, a disproportionately higher volume reduction occurs in the frontal cortex compared to motor cortex[59]. As a result, the MT fails as a "benchmark" to calculate the intensity required for stimulating the frontal cortex. Several authors have proposed approaches to adjust the intensity of rTMS according to the measured SCD of the stimulated cortex[38,55,60,61].

But the utility of employing a SCD-adjusted intensity is questioned by other authors. Firstly, the relationship between SCD and treatment response is not a consistent one. Unlike Fabre *et al*[35], neither Kozel *et al*[62] nor Jorge *et al*[32] could find a relationship between frontal SCD and treatment response, though Jorge *et al*[32] noted that the volume of prefrontal cortex mediated the beneficial effects of treatment. Secondly, while higher SCD is a proxy for age-related (or pathological) atrophic process, the biological effect of brain atrophy is better reflected by a measure of cortical thickness or surface area. Interestingly, lower motor cortical thickness in older adults appears to be associated with lower (not higher) resting MT[63]. This indicates that brain atrophy could result in two contrasting changes 1. A reduction in the strength of the magnetic field that reaches the cortex upon the application of rTMS 2. An increase in the excitability of cortex, such that even smaller intensities are now sufficient to stimulate the brain. Taken together, there may not be any appreciable overall change in the MT with age. In fact, direct comparisons of the MT in the elderly and younger subjects have been so far inconclusive with some studies reporting age-related increase in MT, whereas others reporting no differences in MT between different age groups (reviewed by Rossini *et al*[64]). Most studies examining the effect of

rTMS on cognition in dementia employ < 100% MT on DLPFC but still observed notable improvements in cognitive performance[65]. It is likely that physiological effects of rTMS are induced despite notable cortical atrophy when stimulating frontal cortex in the elderly. On the basis of simulated models of brain atrophy that included both volume shrinkage and sulcal widening, Wagner *et al*[66] argue that SCD based correction of pulse dose/intensity[38,55,60,61] is an inaccurate oversimplification that fails to consider the geometrical changes and altered excitability of the shrunken brain.

Despite the limitation of distance adjustment approaches, a superior therapeutic response is noted when dose-adjusted intensity is employed in treating depression[38,67], when compared to conventional doses delivered as a fixed proportion of MT. The intensity adjustment approaches employed by Nahas *et al*[38] 2004 and Mosimann *et al*[67] require an anatomical MRI to calculate the SCD. A more pragmatic solution was put forward by Johnson *et al*[68], on the basis of a multisite RCT that studied 185 adults of age 22-69 years. The authors reported that most of the effect of frontal atrophy could be overcome by using an intensity that is 120% of MT[68]. This resulted in distance-adjusted intensities that ranged from 93% to 156% of MT and was found to be both safe and efficacious in patients. So far, no studies in the elderly have evaluated the efficacy of 120% MT protocol, though most TMS clinics are now employing an intensity of 120% MT for left prefrontal stimulation working age adults with depression[54,69].

Number of pulses delivered: In rTMS studies of depressed working age adults, a relationship between dose and response has been previously reported. A review by Gershon *et al*[70] noted that rTMS studies delivering higher doses (pulses/day) for longer duration of treatment were more effective than shorter studies using lower doses. In this context, it is worth noting that over the years, the total number of pulses delivered in treatment of depression has increased in general[11,19,71], partly explaining the increase in effect size of rTMS in depression over the years[71].

An interesting observation emerges from the TMS trials (both RCTs and uncontrolled trials) in the depressed elderly reviewed here; almost all studies that conclude in favour of efficacy of rTMS in the elderly use a high number of pulses (18000[32,34,36,38]) while most of the trials that found age-related reduction in efficacy employed smaller number of pulses (2500 to 6300[30,33,37]). Jorge *et al*[32] examined this issue closely by designing 2 experiments within a single trial. They noted that the elderly subjects with vascular depression who received 18000 stimuli in total responded more robustly than those who received only 12000 stimuli a day. While there are a number of other factors that could have influenced the heterogeneity of individual study results, the observation of lack of age-related reduction in efficacy when using higher doses (number of pulses) merits further consideration in clinical practice.

Clinical profile: Apart from age, several other features differentiate geriatric depression form the depression seen in working-age adults. These include the higher prevalence of treatment resistance[3,4], the excess of somatic/melancholic[72] and psychotic features[73], higher degree of cognitive impairment/dementia and medical comorbidity[74,75] among the elderly. Evidence for the influence of these factors on rTMS treatment response in the elderly is considered below.

Treatment resistance: Meta-analytic evidence in depressed working age adults supports the use of rTMS in the treatment of refractory depression (no. of studies = 18 with at least 2 antidepressant failures; duration 1 to 6 wk; sample sizes 12 to 74; NNT = 5 for remission)[76]. Some studies in depressed working age adults have observed a relationship between the degree of treatment-refractoriness and higher response rates for rTMS[77], though other studies have observed a reversed relationship[27,69]. Allan *et al*[29] reviewed this issue and concluded that the presence of TRD in a sample does not influence its response to rTMS. In line with this, there is a lack of a predictable association in either direction among the studies considered in this review as well. Of the 12 rTMS trials (RCTs and uncontrolled studies) in the depressed elderly reviewed here, 5 include samples with at least 2 antidepressant failures while the rest include samples with minimum 1 antidepressant failure. Studies concluding in favour of rTMS in treating geriatric depression have included samples both with TRD (2 antidepressant failure)[33,34,36,78] and 1 antidepressant failure[32,38]. Taken together, the influence of the degree of treatment refractoriness on therapeutic response to rTMS in the elderly is still uncertain. No focused studies directly comparing subjects with TRD and without TRD in geriatric depression have been reported to date.

Psychosis: Several studies in working-age samples support the notion that ECT achieves a superior treatment response in psychotic than non-psychotic depression. In their meta-analysis comparing ECT and rTMS, Berlim *et al*[47] reported that ECT was significantly superior to rTMS in primary studies where the samples had psychotic symptoms. Ren *et al*[46] concluded that rTMS works as well as ECT in the absence of psychosis. The study that reported one of the highest response rates for rTMS in patients > age 60 (47.2% response after 3 wk) only included patients without psychotic symptoms[33]. The mediating influence of psychosis on the antidepressant effect of rTMS in the elderly has not been directly investigated to date.

Melancholia: Melancholic features are more common among the elderly with depression. rTMS does have an alleviating effect on core melancholic features such as psychomotor retardation in working-age

adults[79]. A reduction in melancholic features occurs irrespective of overall clinical response, suggesting a symptom-specific effect of rTMS on melancholia[80]. In particular, psychomotor agitation, which is a common feature among the elderly, appears to respond to high-frequency rTMS[81]. While some rTMS studies in working-age samples suggest that the presence of melancholic features itself indicate poorer overall response to rTMS[82] other studies suggest the opposite[83]. Among the elderly, the specific effect of melancholic features on rTMS treatment response has not been examined so far.

Cognitive impairment: Patients with other comorbid psychiatric illnesses including dementia are often excluded from rTMS studies of depression. Geriatric depression is accompanied by a greater degree of cognitive impairment and a substantial number of patients, who are initially found to have depression with cognitive impairment, later develop dementia, suggesting that a subgroup of geriatric depression may indeed be a prodrome for dementia[84]. After an episode of depression, the risk of dementia increases by nearly 87% over a period of 25 years[85].

A number of studies indicate that rTMS may improve deficits and delay cognitive decline in Alzheimer's dementia[86], with some studies suggesting a therapeutic effect that lasts for nearly 3 mo[87]. Rutherford *et al*[88] suggest that some of the improvement in cognitive performance seen in patients with dementia after rTMS treatment can indeed be attributed to the antidepressant effect of rTMS. Furthermore, as concluded by Ren *et al*[46] in their meta-analysis comparing rTMS and ECT, rTMS appears to be superior to ECT in terms of cognitive side effects. Taken together, this suggests that contrary to the prevailing practice in most ECT clinics, there is no need to exclude elderly subjects with notable cognitive impairment from rTMS studies.

Medical comorbidities: To our knowledge, the moderating influence of medical comorbidities on the therapeutic response to rTMS has not been studied either in the working-age samples or the elderly. Most rTMS trials in working-age adults have excluded patients with significant medical illnesses; as a result the moderating effect of this variable has not been studied in the extant meta-analytic literature on the efficacy of rTMS. Among studies considering geriatric depression, some authors excluded patients with uncontrolled medical illnesses[31,33,38,39,78] while others included subjects with medical comorbidities[32,37]. rTMS has been investigated as a treatment modality in several neurological disorders that often present with comorbid depression in the elderly (*e.g.*, parkinsonism, stroke[89]), and has been found to be safe.

Pitfalls

While the potential of rTMS in the treatment of depression is acknowledged widely, it has not entered the standard stepped-care approach recommended for the treatment of depression in the elderly. An appraisal of the rTMS literature relevant to geriatric depression highlights several deficiencies and offers insight on the pitfalls of recommending routine use of rTMS in geriatric depression. Firstly, the practice of excluding older adults from rTMS trials has resulted in a dearth of good quality RCT data in this age group. The available evidence does not provide an unequivocal support for age related reduction in the antidepressant effect of rTMS. In contrary, it hints at several possible mechanisms for the inconsistently observed differential treatment response. Secondly, there is a scarcity of experimental studies investigating the variations in rTMS parameters to improve response rates in the elderly. Third, despite the numerous phenomenological and neurobiological differences between working-age adults and elderly with depression, moderators other than age have not been systematically studied in rTMS studies of geriatric depression.

Study limitations

We acknowledge that despite being broadly inclusive, several grey literature such as conference abstracts reporting on TMS efficacy for geriatric depression might have been missed. In addition, publications in languages other than English were not included in this search.

Direction for future research

Future studies are needed to replicate and confirm the hypotheses regarding the efficacy of higher number of pulses in the elderly. In addition, systematic exploration of the influence of various features (other than age) that differentiate geriatric depression from early-life depression is required to understand the moderating effect of these features.

Implications for clinical practice

Despite the limitations identified above, several clinical practice points emerge from this appraisal of rTMS focussed on older adults with depression. On the basis of the current evidence, the practice of excluding elderly patients from rTMS clinics and trials cannot be supported. Age-related reduction in antidepressant efficacy, even if present, is not specific to TMS[90]. Adjusted dosing schedules that deliver higher intensity and pulses appear to improve the therapeutic response in the elderly, and these dose variations must be made available for the elderly depressed seeking treatment. In contrast to working-age adult samples where TMS is considered as an alternative "in line" with ECT, for elderly depressed patients, given the indications for a superior efficacy of ECT, rTMS could be offered either after an unsuccessful or poorly tolerated trial of ECT. In some carefully selected cases of non-psychotic depression, rTMS could be a potential alternative to ECT when rapidity of response is not crucial but

undesirable cognitive side effects to ECT are highly likely. While it is premature to recommend rTMS for regular use in geriatric depression, continued exclusion of this group of depressed patients from a well-tolerated and safe treatment option for resistant depression on the basis of their age appears to be clearly untenable.

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REVIEW

Electroconvulsive therapy in catatonic patients: Efficacy and predictors of response

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Abstract

Recent evidence favors the view of catatonia as an autonomous syndrome, frequently associated with mood disorders, but also observed in neurological, neurodevelopmental, physical and toxic conditions. From our systematic literature review, electroconvulsive therapy (ECT) results effective in all forms of catatonia, even after pharmacotherapy with benzodiazepines has failed. Response rate ranges from 80% to 100% and results superior to those of any other therapy in psychiatry. ECT should be considered first-line treatment in patients with malignant catatonia, neuroleptic malignant syndrome, delirious mania or severe catatonic excitement, and in general in all catatonic patients that are refractory or partially responsive to benzodiazepines. Early intervention with ECT is encouraged to avoid undue deterioration of the patient's medical condition. Little is known about the long-term treatment outcomes following administration of ECT for catatonia. The presence of a concomitant chronic neurologic disease or extrapyramidal deficit seems to be related to ECT non-response. On the contrary, the presence of acute, severe and psychotic mood disorder is associated with good response. Severe psychotic features in responders may be related with a prominent GABAergic mediated deficit in orbitofrontal cortex, whereas non-responders may be characterized by a prevalent dopaminergic mediated extrapyramidal deficit. These observations are consistent with the hypothesis that ECT is more effective in "top-down" variant of catatonia, in which the psychomotor syndrome may be sustained by a dysregulation of the orbitofrontal cortex, than in "bottom-up" variant, in which an extrapyramidal dysregulation may be prevalent. Future research should focus on ECT response in different subtype of catatonia and on efficacy of maintenance ECT in long-term prevention of recurrent catatonia. Further research on mechanism of action of ECT in catatonia may also contribute to the development of other brain stimulation techniques.

Key words: Electroconvulsive therapy; Catatonia; Mood disorders; Schizophrenia; Benzodiazepines; Antipsychotics

Core tip: Catatonia is a treatable autonomous syndrome, frequently associated with mood disorders, but also observed in neurological, neurodevelopmental and toxic conditions. Electroconvulsive therapy (ECT) is effective in 80% to 100% of all forms of catatonia, even after pharmacotherapy with benzodiazepines has failed, and is considered first-line treatment in patients with neuroleptic malignant syndrome. Increasing the knowledge on the mechanism of action of ECT in catatonia may contribute to the development of other brain stimulation techniques, such as transcranial magnetic stimulation and deep brain stimulation. ECT response in different subtype of catatonia and efficacy of maintenance ECT in long-term prevention of recurrent catatonia deserve further research.

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INTRODUCTION

Originally described by Karl Kahlbaum[1] in 1874, catatonia is a severe neuropsychiatric syndrome characterized by prominent motor features including immobility, mutism, negativism, rigidity, posturing, staring, stereotypy, automatic obedience, echo-phenomena and mannerism. Mutism and stupor are generally considered the most typical symptoms of catatonia[2-4].

Although Kraepelin[5] admits the presence of catatonic symptoms in manic-depressive insanity, he marks catatonia as a principal sign of dementia praecox. The association of catatonia with dementia praecox[2] was suggested by its poor prognosis and its possible evolution toward a chronic deteriorative course. Kraepelin's position was essential for the development of subsequent psychiatric nosography until nowadays and the view of catatonia as a subtype of schizophrenia has hidden its recognition as an independent syndrome for more than a century[6].

In DSM-5[7], catatonia is still included in the chapter of schizophrenia spectrum and other psychotic disorders. The manual does not treat catatonia as an independent class but recognizes "catatonia associated with another mental disorder" (catatonia "specifier"), "catatonic disorder due to a general medical condition" and "unspecified catatonia". The catatonic subtype of schizophrenia has been deleted. According to the Manual, catatonia is considered only a specifier for schizophrenia, as for bipolar and major depressive disorders and for other additional disorders (schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, substance-induced psychotic disorder, neurodevelopmental disorders and others).

Currently, a large body of evidence seems to support the view of catatonia as an independent neuropsychiatric syndrome associated with several psychiatric disorders, and in neurologic, metabolic and endocrine conditions such as infections, toxic states, epilepsy, and traumatic brain injury[8]. Both catatonia associated with psychiatric disorders and with somatic conditions show similar clinical presentation, symptom severity, course and treatment indications[9,10].

Prevalence rates of catatonia range from 6% to 38% among psychiatric inpatients[8]; it is mainly associated with mood disorders (about 30% of cases), in particular with mania or mixed states[11]. Catatonic patients are at risk for severe complications including pneumonia, decubitus ulcers, malnutrition, dehydration, contractures, and thrombosis[12,13].

If correctly diagnosed, catatonia is a treatable syndrome. Intravenous benzodiazepines (generally lorazepam) are the most commonly used treatment, with a reported remission rate of about 60%-70%, regardless of the cause or of clinical manifestations[14]. Intravenous administration is preferred to assure adherence and rapid, complete absorption. As patients improve, they should be switched to oral medication. The dosing schedule varies with the severity of catatonia and the presence of fever and vegetative signs. For stuporous patients, dosing starts at 3 mg daily, increasing every one or two days to 6, 9, and 12 mg as tolerated, depending upon response and clinical urgency. A dose of 6 to 21 mg daily is effective for most patients, but a dose of 30 mg per day is occasionally necessary. A successful acute treatment course will take from 4-10 d[2,15,16]. Prolonged trials are not advised for severe catatonia, as complications have been reported[4]. Electroconvulsive therapy (ECT) is first-line treatment in malignant catatonia (MC) and in case of resistance to benzodiazepines[17].

The intimate relation between convulsive therapy and catatonia began in 1934 at Royal Hungarian State Psychiatric Institute in Budapest, where Laszlo Meduna induced for first time epileptic fit with intramuscular injections of camphor in five patients with catatonic features. These patients, diagnosed with catatonic schizophrenia were in stuporous state, requiring tube-feeding for several months; they were in serious physical condition and almost certainly destined to fatal outcome. After several sessions of convulsive therapy, the severity of catatonic stupor improved and tube-feeding was no longer necessary in any of the patients. In the early 1930s, this observation was regarded as a therapeutic breakthrough, given the lack of effective interventions for such severe mental illness[18]. Subsequently, ECT became the dominant method of convulsive treatment and the clinical experience of more than seventy years has shown that catatonia is a clinical condition with a rapid, dramatic and often life-saving response to ECT.

In the present article, we reported a systematic review of the literature about the use of ECT in catatonia, discussing available evidence on efficacy,

safety and predictors of response.

RESEARCH

A systematic review of the existing literature has been conducted through PubMed and Scopus using combinations of the following search terms: "catatonia", "electroconvulsive therapy", "treatment", "response", "von Meduna", "Cerletti", "schizophrenia", "mood disorder", "bipolar disorder", "depression", "neurodevelopmental disorders", along with terms related to each of the areas of focus listed above. Regarding ECT, Randomised Controlled Trial (RCT) only considering catatonia are not available. So we mash up information from available clinical studies, case-reports, case-series and expert descriptions. In particular we focus our attention on prospective and retrospective case series that included more than 10 patients. Reference lists from each article were assessed for additional citations of interest. Unless otherwise noted, the referred studies focus on adults. We excluded articles in languages other than English. Two reviewers evaluated the results of the searches on the basis of title and/or abstract, and assessed the citations for their suitability for inclusion based on the full publications.

CONCLUSION

The results of the 8 open observational studies including at least 10 patients with different form of catatonia are reported in Table 1. Few case series with 5 patients or less[19-21]; and a large number of single case reports have also been published describing the efficacy and tolerability of ECT in catatonia in a variety of clinical situations.

Efficacy

Retrospective observational studies report a response rate to ECT in catatonic patients ranging from 80% to 100%[22-26]. Hawkins *et al*[14] (1995) reviewed the treatments of catatonia in clinical records of 178 patients in 270 episodes. ECT alone was employed in 55 (about 30%) patients, obtaining the resolution of catatonic symptoms in 85% of the cases. When the presence of MC was suspected, the response to ECT was 89% (9 of 11). In another study[27] 50 catatonic patients where addressed to four step of treatment: in each ECT or drug treatment were administered, according to the patient and his/her family's choice, except for the last step where only ECT was administered. Response rates, defined as the number of patients who respond completely to ECT divided by the total (cumulative) number of patients, were equal to 100%. The Authors concluded that ECT should be the first choice treatment for catatonic symptoms, especially when doses of benzodiazepines above the upper limits cannot be applied, as in this study. In a recent observational study by our clinic (Medda *et al*[28], submitted to press) we observed a favorable response to ECT (measured as a CGI final score $\leqslant$ 2) in 21 (81%) out of 26 catatonic in-patients resistant to BZDs. This figure is in line with previous reports.

In a recent review of the ECT experience in a large Dutch teaching hospital[29], 27 cases of catatonia were identified among the 285 ECT treated patients over a 18-year period. Of the entire sample 48% presented mood disorders and 44% psychotic disorders. Although pharmacotherapy had failed in 85% of the patients, ECT was effective in improving 59% of the cases. The reduced treatment response in this study, compared with other reports (59% *vs* 85%-100%), may be related to the high prevalence of psychotic disorders, the delayed use of ECT (after two months of pharmacotherapy) and the previous use of antipsychotics in many of these patients. Finally, one third of the patients suffered from neurological comorbidity. The same study reported the benefit of daily ECT in catatonic patients with autonomic disturbances (that can be considered mild cases of MC). The need for daily ECT was already suggested in 1952, when a classic study by Arnold and Stepan reported that this procedure seems to avoid fatalities in MC[30].

Some authors approach neuroleptic malignant syndrome (NMS) and MC as separated entities[9]. However, once the overlap of the syndromes was recognized, ECT began to be applied to patients with NMS[31]. In a review of the most recent literature of 46 published reports describing experiences with 55 patients, ECT was effective in 40 (73%) patients with NMS[32]. Complete recovery of symptoms was reported in 25 (63%) of the cases, and partial recovery was noted in 11 (28%).

A literature review of ECT in children and adolescents[33], reporting data from the Paris clinic of David Cohen, identified 59 cases with 47% having mood disorders, 27%, schizophrenia, and 23% brain and pervasive developmental disorders. Favorable outcomes were reported in 76% of the treated patients, with only 1 patient considered as non-responder.

In conclusion, available empirical evidence clearly indicates that ECT is effective in 80%-100% of all forms of catatonia, even after pharmacotherapy have failed. ECT should also be first-line treatment in patients with MC, NMS, delirious mania or severe catatonic excitement, and in general in all catatonic patients that are refractory/partially responsive to benzodiazepines and amobarbital[17]. According to some Authors, ECT should be preferred to benzodiazepines as their effect on catatonic symptoms can be only transient and not every sign/symptom of an acute catatonic stupor responds well to benzodiazepines[34,35].

Administration and technique

Since catationic patients frequently present with compromised medical status, every effort should be made to optimize the patient's physical condition[36]. In malignant forms with hyperthermia and autonomic instability, ECT should be started within the first five days of hospitalization, to increase response rates and

Table 1 Studies that investigate efficacy of electroconvulsive therapy in catatonia (number of patients receiving electroconvulsive therapy ⩾ 10)

Ref.	Sample (*n*)	Patients receiving ECT *n* (%)	Diagnosis	Design	ECT technique	Outcome measures	Results	Variables associated with response
Unal *et al*[23], 2013	57	57 (100)	63% Mood disorders 29% psychotic disorders (including schizophrenia) 3.5% pts mental retardation 3.5% pts without psychiatric disorders	Retrospective All pts. received ECT in combination with oral BZDs	BL (bifrontal)	CGI, HDRS, YMRS, PANSS	Response = 100%	Not assessed
Tuerlings *et al*[64], 2010	34	34 (100)	59% mood disorders 77% schizophrenia and other psychotic disorders 37% somatic, toxic, post-traumatic stress disorder, mental retardation	Retrospective	Non specified	No standard diagnostic instruments or catatonia scales	58% pts treated with BZDs and/or ECT had clinically complete remission. 50% pts treated with ECT after unsuccessful medication trials recovered completely	Responders: Autonomic dysregulation Non-responders: Initial treatment with amantadine, bromocriptina and dantrolene More comorbid disorders
Van Waarde *et al*[29], 2010	27	27 (100)	48% mood disorders 44% psychotic disorder (including schizophrenia) 19% others (alcohol/substance abuse, mental retardation)	Retrospective	BL (bifronto-temporal) or UL (according to d'Elia)	Response defined as CGI ⩽ 2	Response = 59%	Responders: Younger age Autonomic dysregulation at baseline (especially higher body temperature) Daily ECT during the first treatment week Longer duration of motor and EEG seizure activity at the final ECT session Less morbidity in the year after ECT
Ravvendranathan *et al*[22], 2012	63	63 (100)	41% mood disorders, 49% psychotic disorders (including schizophrenia) 6% idiopathic catatonia	Retrospective	BL (bitemporal)	Response = complete resolutions of symptoms and/or BFCRS = 0	Response = 89%	The Authors divide the responders in faster (⩽ 4 sessions) and slower (⩾ 5 sessions) Faster responders: Lower duration of catatonia Greater severity of BFCRS Lesser electrical charge used overall Shorter duration of inpatient stay Waxy flexibility and gegenhalten. Lower responders: echophenomena
England *et al*[26], 2011	25	12 (48)	Total sample: 36% bipolar disorder 32% pts with psychosis NOS 4% depressive episode and anxiety disorder 16% schizophrenia 8% without previous psychiatric history	Retrospective	BL	BFCRS, clinical evaluation	83% pts treated with ECT definite beneficial effects > BZDs, APs, MS, ADs	Not assessed
Hatta *et al*[27], 2007	50	17 (34)	Total sample: 34% mood disorders 46% schizophrenia and other psychotic disordes 20% medical condition	Observational study I step: BZDs or ECT II step: APs (RIS or HAL) or ECT III step: CPZ or ECT IV step: ECT	BL (bitemporal)	"Partial response": disappearance of one or more catatonic symptoms; "complete response": disappearance of all catatonic symptoms	(Cumulative) ECT 100% > CPZ 68% > RIS 26% > HAL 16%	Not assessed

Dutt *et al*[24], 2011	51	42 (82)	75% psychotic disorders (including schizophrenia) 14% mood disorders 8% organic brain syndromes	Retrospective	Unspecified	Reduction of BFCRS assesses the response	Response = 100%	Not assessed
Rohland *et al*[25], 1993	22	22 (100)	59% mood disorders 32% schizophrenia and schizoaffective disorder 9% organic mental disorder	Retrospective	BL (bitemporal)	Response to ECT was assessed by not meeting Kahlbaum and Rosebush criteria for catatonia. Then, the number of single signs and symptoms prior and after ECT is another parameter	Response = 93%	Trend toward a better response in affective than psychotic pts (non statistically significant)
Medda *et al* (manuscript in preparation)	26	26 (100)	100% bipolar disorder	Observational	BL (bitemporal)	Response = CGI ≤ 2	Response = 81%	Non-responders: Older age at onset of mood disorders Lower number of mood episodes Higher BFCRS total score at baseline Less psychotic symptoms Higher rate of past treatment with anticholinergics and dopamine agonists and lower rate of past treatment with typical antipsychotics

APs: Antipsychotics; CPZ: Chlorpromazine; RIS: Risperidone; HAL: Haloperidol; ADs: Antidepressants; MS: Mood stabilizer; BZDs: Benzodiazepines; BFCRS: Bush-Francis Catatonia Rating Scale; CGI: Clinical Global Impressions scale; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; PANSS: Positive and Negative Symptoms Scale; ECT: Electroconvulsive therapy.

reduce mortality rate.

Systematic studies focused on electrode placement, stimulus dosing, frequency of session and other aspects of ECT technique for treating catatonia are lacking and these parameters have not been standardized. As regard electrode placement, there is a general consensus that bitemporal placement is the most effective[8]. The use of unilateral electrode placement is not recommended, although recently two case series illustrate successful use of right unilateral ECT in patients with catatonia[19,37].

To limit the possibility of sub-convulsive stimulation in patients with serious concomitant medical conditions, most of the authors suggest to use the half-age method to determine the stimulus intensity[8,38] and to measure the electroencephalographic (EEG) length of the seizures which should be at least 25 s. If the motor seizure duration decreased below 25 s, the stimulus setting was increased 1.5 times at the following session. The relief of catatonia often seems to require more frequent ECT session than in major depression and is generally given three times per week on alternating days. However, clinical urgency (MC, high risk of complications, delirious mania/excited catatonia with severe excitement and combativeness) may necessitate daily treatments until the patient is physiologically stable, which often occurs within 2 to 5 treatments. Then ECT is continued at more conventional frequencies[39].

The total number of ECT treatments that will be needed cannot be predicted. It was established on the basis of the clinical response after 5 or 6 treatments, and then again after 10 or 12 sessions. After that, termination of ECT should be considered when a full clinical response is achieved or when are not obtained further clinical improvement after two consecutive sessions. This number in usually between 12 and 20 treatments[21], however some patients manifest a complete remission after only a few treatments.

Usually all psychotropic medications were discontinued during the ECT course, however, as regard BDZs, literature is not consistent on this point. Some physicians describe discontinuing benzodiazepine treatment just prior to ECT, whereas others recommend continuing benzodiazepines during and beyond the ECT treatments and postulated a synergistic effect[40] (see Combined treatment: ECT plus benzodiazepines).

Succinylcholine has been traditionally the muscle relaxant of choice for ECT owing to its rapid onset of action and ultra-short duration of action. However, in catatonic patients the use of succinylcholine should be avoided for the increased risk of severe hyperkalemia[41] and the susceptibility to NMS and malignant hyperthermia (MH)[42]. Although rocuronium neuromuscular blockade can also be reversed with neostigmine, the use of rocuronium and sugammadex for the maintenance and reversal of neuromuscular blockade respectively, has the advantage of producing muscle relaxation similar to that of succinylcholine with regard to onset of action and duration of effect[43,44].

Combined treatment: ECT plus benzodiazepines

Because benzodiazepines are the first choice in the treatment of catatonia, patients treated with ECT are often receiving them. For patients with a partial but incomplete response to lorazepam, the drug should be continued during ECT to maintain the therapeutic effect[23]. Others authors recommended reducing or suspending the dose of BDZ when it interferes with ECT, increasing seizure threshold and shortening seizure duration, despite adjustments in ECT technique[15]. A case series of four hospitalized patients without catatonia prior to ECT who developed catatonic signs during ECT treatment, suggest that catatonia can emerge paradoxically when benzodiazepines were tapered or discontinued in preparation for ECT. This suggests that benzodiazepine withdrawal may be a risk factor for appearance of catatonia during ECT, in non catatonic patients[45].

In a recent study with a retrospective collection of 57 catatonic patients' records, the use of benzodiazepine-ECT combination achieved full recovery in the whole sample, composed by 63.2% of cases with mood disorders and 29.8% with psychotic disorders[23]. Some case-series describe a response to benzodiazepine-ECT combination, which seemed to be superior to monotherapy[40]. The Authors state that initially the patients showed a non-response to lorazepam, but lorazepam became effective at the same or lesser dosage after ECT was initiated. So, a synergistic effect of the combination ECT plus benzodiazepine has been hypothesized, suggesting that ECT may facilitate the therapeutic response to lorazepam. The converse is also supported, since the benefit of ECT is enhanced later in the treatment course after the addition of lorazepam[40]. Notably, the dosage of lorazepam varies among patients but was lower than that usually prescribed for catatonic states and the last dose was administered at least 12 h prior to ECT[46]. The short half-life of lorazepam and the absence of active metabolites may minimize possible antagonism with ECT. A synergism between the treatments could be explained by the common anticonvulsant properties of benzodiazepines and ECT (increase seizure threshold, decrease cortical excitability)[47,48].

ECT in maintenance treatment protocol

To prevent relapse, continuation treatment is necessary for most psychiatric conditions. In most cases ECT is stopped when catatonic symptoms are resolved, but sometimes a continuation phase is useful. No systematic data are available on the preventive efficacy of maintenance ECT (mECT) for periodic catatonia. Many patients have been sustained in the community with mECT at bi-weekly, monthly, and bi-monthly intervals, with or without daily benzodiazepine dosing[8]. There are no studies that suggest the optimal schedule for such treatment. For some patients with rapid cycling or in mixed affective states, mECT may be a better option than complex polypharmacy[8]. The successful use of continuation ECT without medication has been described in patients with catatonic schizophrenia[49] and with recurrent catatonia[50].

Safety

Questions are often raised as to the safety of ECT and general anesthesia in patients with general medical illnesses that are co-morbid with or the cause of catatonia. Safety concerns necessitate pre-procedure medical consultation to optimize the patient's general status and reduce risks. As an example, the motor immobility and muscle damage have been recognized as risk factors for hyperkaliemic states and may increase the likelihood of ventricular tachycardia (as torsade de pointes)[51], associated with the muscle relaxant succinylcholine. This risk can be reduced using a non-depolarizing muscle relaxant (*e.g.*, rocuronium). Furthermore, in catatonic patients deemed to be at high risk for the development of deep venous thrombus/pulmonary embolism (DVT/PE), a prophylaxis against DVT is recommended, by means of attempts to improve mobility, mechanical tools such as graduated compression stockings and intermittent pneumatic compression. Pharmacologic prophylaxis may be carried out with low-molecular weight heparin (*e.g.*, enoxaparin) or warfarin[52]. Warfarin should be continued in patients receiving ECT[53].

ECT results in significant cardiovascular effects, although they are generally transient and resolve without adverse sequelae. The initial electrical stimulus produces a vagally transmitted parasympathetic bradycardia or even asystole lasting several seconds[54]. As the seizure develops, this state is followed by sympathetic stimulation originating in the hypothalamus and descending *via* the brainstem, spinal cord, paravertebral stellate ganglia, and cardiac accelerator nerves. Adrenal stimulation leads to an abrupt increase in catecholamine release, which lasts several minutes postictally. A variety of cardiac dysrhythmias may occur, usually after the seizure, with reported incidences ranging from as low as 8% to as high as 80% or more in patients with known cardiovascular disease. Sympathetically mediated dysrhythmias include sinus tachycardia, bigeminy, trigeminy, and ventricular tachycardia and fibrillation. In healthy young people, the tachy-dysrhythmias seen are generally brief,

require no intervention, and do not preclude further ECT[55].

With modern anesthesiological procedures, ECT is remarkably safe even in the medically compromised, the elderly, and in pregnancy. In pregnant patients, in fact, during the first and second trimesters, ECT is a procedure with a ratio risk/benefits particularly favorable and may be used when a rapid benefit is needed or when medications are not tolerated or fail[54]. During the later stage of pregnancy, modification in ECT procedure should be considered in order to lower the risk for both the mother and the fetus (for instances, hydratation, monitoring of fetal heart and tocography, placing a wedge for displacing utero, *etc*.).

Although medical illnesses may limit the use of several drugs, there are no absolute controindications to the use of ECT in the widest range of patients with catatonia, with virtually any physical comorbidity and regardless the etiology. There are case reports of the effectiveness of ECT for treating catatonia in patients with comorbid medical illnesses such as lupus cerebritis, breast cancer, Graves' disorder and others[56-58]. ECT can be effective in treating children with catatonia, and it is estimated that half of children who receive ECT do so because of a diagnosis of catatonia[59].

Emergence of catatonia during ECT

The appearance of catatonia during ECT has been described in four patients[45]. Catatonia resolved with benzodiazepines and continuation of ECT. The emergence of catatonia after two sessions of ECT was also described in a patient with bipolar disorder[60]. When the patient was given a single unmodified ECT, three weeks later, after complete resolution of symptoms, catatonia reemerged.

Considering the universal efficacy of ECT in relieving catatonia, reports of the emergence of catatonia during ECT are puzzling. A possible explanation is that the patients experienced recurrence of their catatonic symptoms because of the rapid withdrawal of benzodiazepines prior to ECT. Rapid withdrawal from benzodiazepines may evoke catatonia[61].

Predictors of response

In a recent report, favorable response to ECT has been correlated with young age, presence of autonomic dysregulation at baseline (especially higher body temperature), daily ECT during the first treatment week, longer duration of motor and EEG seizure activity at the final ECT session and less morbidity in the year after ECT[29]. Acutely catatonic patients with an underlying mood disorder may respond more favorably to ECT than schizophrenic patients[25] and ECT does not appear to benefit chronic catatonia in some schizophrenic patients[62,63].

A fast response (within the first four sessions) is correlated with greater severity of catatonia symptoms as measured with specific rating scales, shorter duration of in-patient stay, psychopathological features like waxy flexibility and gegenhalten[22]. Slow responders showed greater number days of catatonia at presentation and echophenomena. Consistently with this observation, in a case series[21] three patients with prolonged catatonia (10-14 wk) have been treated with ECT with discrete success (two patients markedly improved, one partially), but they needed a great number of sessions.

Moreover, in the same study, the presence of cerebral pathology predicted a less good outcome. Catatonic patients previously treated with dantrolene, amantadine, and bromocriptine showed poor or no response with successive ECT[64]. In these cases it is possible to hypothesize the presence of underling neurological disorders. In fact, in a case series and review of literature, Swartz *et al*[20] reported the persistence of catatonia after an adequate (9 to 17 sessions) course of ECT in patients with a concomitant neurological condition, and a lack of stable remission. This suggests that chronic neurologic disease can provoke or exacerbate chronic or relapsing forms of catatonia. The Authors propose two explanations: the condition may be intrinsically less responsive to ECT or require exceptionally intense treatment. The latter may involve more ECT sessions, higher stimulus doses, and aggressive prophylaxis of catatonia after the ECT course. Moreover, it may involve adjunctive medication to mitigate the underlying neurologic condition. Finally, when a patient who shows signs of catatonia fails to achieve a good or stable remission with ECT, additional testing for an underlying neurologic condition may be considered. Consistently with these findings, in our study (Medda *et al*[28], submitted to press), we found that non-responders to ECT were characterized by older age at onset of mood disorders, lower number of mood episodes, higher Bush-Francis Catatonia Rating Scale (BFCRS) total score at baseline, less psychotic symptoms, higher rate of past treatment with anticholinergics and dopamine agonists and lower rate of past treatment with typical antipsychotics. We hypothesized that the use of dopamine agonists and the reduced use of neuroleptics in non-responders may be related to the presence of an extrapyramidal abnormality in these patients.

DISCUSSION

Catatonia has been erroneously considered as a subtype of schizophrenia during much of the twentieth century and is still included in the chapter of schizophrenia and other psychotic disorder in DSM-5. This diagnostic approach discourages the use of ECT as an early treatment option. On the contrary, the classification of catatonia within the frame of psychotic disorders encourages clinicians to treat catatonic patients with antipsychotic medications. Since the early 70's, however, catatonia was increasingly recognized as an

independent syndrome frequently associated with mood disorders and several neurologic conditions[11,65-68]. The most commonly used treatment is intravenous lorazepam, with a reported remission rate of about 70%, regardless of the clinical manifestations[69]. ECT is utilized when benzodiazepines fail to give adequate response[14] or rapid response is required. Since neither benzodiazepines nor ECT are effective for schizophrenia and since antipsychotic are usually ineffective or even dangerous, catatonia appears to be pathophysiologically different from schizophrenia and clinicians should avoid antipsychotic and other dopamine-blocking drugs in catatonic patients.

From our systematic review of the available literature, ECT resulted effective in all forms of catatonia, even after pharmacotherapy have failed. Response rates range from 80% to 100% and resulted superior to those of any other therapy in psychiatry. A reduced treatment response in 2 reports[29,64] might be explained by the delayed use of ECT, the previous use of antipsychotics in many of the selected patients, and the high rate of neurological comorbidity.

ECT should be considered first-line treatment in patients with MC, NMS, delirious mania or severe catatonic excitement, and in general in all catatonic patients that are refractory/partially responsive to benzodiazepines[17,70,71]. Early intervention with ECT is encouraged to avoid undue deterioration of the patient's medical condition. Some clinicians approach NMS and MC as different entities, reserving benzodiazepines and ECT for patients with MC and dopamine agonists and muscle relaxants for patients with NMS. However, ECT was also successfully applied to patients with NMS[72]. Likely the biggest obstacle for the appropriate use of ECT in catatonia, as well as in other clinical situations, is the social stigma against ECT. Society's wary stance regarding ECT stems from a combination of claims of overuse and misuse in its history. Furthermore, local laws on ECT often complicate the process of obtaining ethical consent in the severe and acute catatonic patient.

The rapid improvement of catatonic signs before the alleviation of the underlying illness indicates that the improvement of catatonia does not necessarily depend on the treatment of the psychotic or the mood symptoms. The dramatic picture of catatonia and its rapid relief by ECT and benzodiazepines suggest that catatonia may be the final common outcome pathway for abnormal brain seizure activity. It is conceivable that ECT relieves catatonia by raising the seizure threshold and inhibiting the propagation of abnormal electrical signals through cerebral synapses. Catatonia is prominent in patients with epilepsy, and non-convulsive status epilepticus is included in the differential diagnosis of catatonia. Against such association, however, is the absence of electroencephalographic seizure activity in catatonic patients. However, electroencephalograms of catatonic patients are frequently difficult to interpret because of muscle rigidity producing artifacts.

Little is known about the long-term treatment outcomes following administration of ECT for catatonia. However, it is clear that fatality rates from catatonia significantly decreased after the introduction and adoption of ECT as standard treatment in psychiatry[73]. One small retrospective study suggested that patients with catatonic depression who were treated with ECT in addition to a tricyclic antidepressant, lithium, bupropion, or high-dose venlafaxine had better long-term outcomes over the course of four years compared to patients who received ECT and selective serotonin reuptake inhibitors[74]. Cerebral pathology may predict a less favorable treatment outcome with ECT[20,45,75].

Catatonic patients with a poor outcome are often diagnosed at first as suffering from a neurologic illness of unknown etiology, and are intensively treated with anticonvulsants. This makes it almost impossible to achieve effective seizures, and may represent a possible explanation for the failure of ECT[8]. In some instances, catatonia may be late recognized with a delayed referral to ECT, after many weeks of unsuccessful or pejorative treatments (antipsychotics). In such circumstances, the number of ECT courses needed to effectively reduce catatonia is many times higher than the number usually employed to relieve acute catatonic syndromes. Moreover, the persistence of catatonia after ECT has been frequently reported to occur in patients with a neurological condition[20]. This subtype of catatonia may be intrinsically less responsive to ECT or require more intense treatment. In line with this observation, previous treatment with amantadine and dopamine agonists is associated with poor response to ECT[12,64]. The use of these drugs in non-responders, indeed, may be related to the presence of extrapyramidal abnormalities. It is likely that when catatonia is related to hypodopaminergic states, due to neurological conditions or antipsychotic treatments, ECT response may be less favourable.

On the other side, literature indicates that some clinical features such as young age, presence of autonomic dysregulation, severe psychotic underlying mood disorder, daily ECT during the first treatment week, longer duration of motor and EEG seizure activity at the final ECT session are associated with a favorable/faster response to ECT[25,29]. A faster response has been also correlated with greater severity of catatonia symptoms, shorter duration of in-patient stay, psychopathological features like waxy flexibility and gegenhalten[22].

In a recent review of the literature[76], different subtypes of catatonia have been hypothesized being based on the existence of deranged "top-down" or "bottom-up" modulation of cortical-subcortical connections devolved to the control of psychomotor activity. "Top-down modulation" may be described as a regulation of subcortical structures by cortical areas as reflected, for example, in the modulation of caudate and other basal ganglia by lateral orbitofrontal cortex.

Such a top-down modulation has to be distinguished from "bottom-up modulation" as reflected in the modulation of premotor/motor cortical areas by basal ganglia. In catatonia, GABAergic-mediated deficit in orbitofrontal cortex may lead to alterations in "top-down modulation" of caudate and other basal ganglia *via* the "orbitofrontal loop", whereas, in hypodopaminergic states, a mediated deficit in striatum may lead to alterations in "bottom-up" modulation of premotor/motor cortex. Both catatonia and NMS have been reported in response to both standard and novel antipsychotic medications. As a consequence motor symptoms, in some catatonic cases, may be directly related to a striatal D2 receptor blockade that modulates the motor loop to the supplementary motor area and to the orbitofrontal cortex[77]. Postulating the existence of different forms of catatonia, ECT would be more effective in "top-down" than in "bottom-up" variants of the syndrome.

Future research should focus on ECT response in different subtype of catatonia and on efficacy of mECT in long-term prevention of recurrent catatonia. Ultimately, a better understanding of the mechanism of action of ECT in catatonia may contribute to the development of other brain stimulation techniques.

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REVIEW

Auditory hallucinations: A review of the ERC "VOICE" project

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Abstract

In this invited review I provide a selective overview of recent research on brain mechanisms and cognitive processes involved in auditory hallucinations. The review is focused on research carried out in the "VOICE" ERC Advanced Grant Project, funded by the European Research Council, but I also review and discuss the literature in general. Auditory hallucinations are suggested to be perceptual phenomena, with a neuronal origin in the speech perception areas in the temporal lobe. The phenomenology of auditory hallucinations is conceptualized along three domains, or dimensions; a perceptual dimension, experienced as someone speaking to the patient; a cognitive dimension, experienced as an inability to inhibit, or ignore the voices, and an emotional dimension, experienced as the "voices" having primarily a negative, or sinister, emotional tone. I will review cognitive, imaging, and neurochemistry data related to these dimensions, primarily the first two. The reviewed data are summarized in a model that sees auditory hallucinations as initiated from temporal lobe neuronal hyper-activation that draws attentional focus inward, and which is not inhibited due to frontal lobe hypo-activation. It is further suggested that this is maintained through abnormal glutamate and possibly gamma-amino-butyric-acid transmitter mediation, which could point towards new pathways for pharmacological treatment. A final section discusses new methods of acquiring quantitative data on the phenomenology and subjective experience of auditory hallucination that goes beyond standard interview questionnaires, by suggesting an iPhone/iPod app.

Key words: Auditory verbal hallucinations; Perception; Executive functions; Brain imaging; Glutamate; Gamma-amino-butyric-acid; Schizophrenia

Core tip: Auditory hallucinations represent a major symptom in schizophrenia, and the present article reviews recent research with a focus on cognitive and brain markers. Auditory hallucinations are described in a neurocognitive model that sees such experiences

as initiated from temporal lobe hyper-activation, not inhibited due to frontal lobe hypo-activation. It is proposed that these patterns of brain activation are mediated by abnormalities of the neurotransmitter glutamate. A new way of collecting symptom data on-line is suggested, based on iPhone app-technology.

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INTRODUCTION

The research presented in this article was funded by an ERC Advanced Grant "VOICE" to Kenneth Hugdahl, and is thus a selective review. In this sense, this is not a formal review of the literature, nor a formal comparison of findings in the literature at large. The ERC "VOICE" project has also been reviewed in a conference proceedings volume from the 16th Conference for Philosophy, Psychiatry and Psychology, Golden Sands, Bulgaria, Edited by Stoyvanov D and to be published by Cambridge Scholars Publishing, Ltd. Schizophrenia is one of the most severe mental disorders, causing lifelong distress and social handicaps. The disorder is recognized as a leading cause of morbidity both globally and in particular in the Western world, and ranks as one of the most costly disorders that affect humans[1].

A key symptom in schizophrenia is auditory verbal hallucinations (AVHs), *i.e.*, the experience of "hearing voices" in the absence of an external auditory source. AVHs occur in 70%-80% of patients with schizophrenia and often produce distress, functional disability, and behavioral dys-control[2,3]. In some cases, hallucinations may also pose a threat to the patient or his/her family members, and even to society, if they the form of "hearing voices" commanding the patient to commit unwanted behaviors or acts[4].

SCHIZOPHRENIA AND AUDITORY HALLUCINATIONS

Because of the heterogeneity of the diagnostic phenotype of schizophrenia, which so far has escaped specification of underlying neuronal and molecular explanations[5,6], the ERC "VOICE" project has suggested an alternative approach by focusing on a single symptom, rather than on the diagnostic category itself[7]. There are several advantages with such an approach. First of all, by definition, it will reduce heterogeneity by increasing signal to noise ratio, since a symptoms is less heterogeneous than the diagnostic category as such. Second, it will better allow for the pursuit of explanations "upwards" to the clinical level of explanation and "downwards" to the neurobiological level of explanation since the symptom is closer to both the upward diagnosis and the downward neurobiological markers. Third, it will better allow for characterizations at the individual level, since symptoms can be (and typically are) quantified through the use of various symptom scales, like the Positive and Negative Syndrome Scale (PANSS)[8] and Scale for the Assessment of Negative Symptoms/Scale for the Assessment of Positive Symptoms (SANS/SAPS)[9], while a diagnosis cannot be and typically is not quantified. This means that parametric relationships can be obtained between, *e.g.,* degrees of cognitive impairment and scores on a specific symptom scale item, which is not possible for a diagnostic category. A fourth advantage is that a single symptom could also serve as an endophenotype, which can add to the genetic understanding of the broader phenotype of schizophrenia. At the brain level of explanation, a corresponding parametric relationship could be predicted for, *e.g.*, intensity of neuronal activation in a defined cluster of voxels and a symptom score, which could also be conducted in a parametric way for single symptoms, but not for a single diagnosis. I here disregard the identification of sub-diagnoses within a diagnostic category as seen in, *e.g.,* the DSM classification system, since such a procedure is still categorical and would not allow for the identification of parametric relationships to other domains, like cognition or pathophysiology. Fifth, unraveling the mechanisms involved in a single (or a few) key symptom(s) may provide a novel way of developing new symptom-specific treatment procedures, both pharmacological and non-pharmacological[10]. Sixth, since some of the symptoms seen in schizophrenia are also shared with non-psychotic individuals in the general population[11-13], studying auditory hallucinations and "hearing voices" respectively, will open for the possibility of specific symptoms as continuous dimensions rather than discrete categories[6,14].

AVHs

AVHs are the most characteristic symptom of schizophrenia and psychosis, and they "define" the disorder from a clinical and phenomenological point of view. Clinically, what drains the patient both cognitively, emotionally, and physically is the ongoing "dialogue" and typically negative comments and commands from the "voice", which recruits almost all available cognitive resources[7,15,16], and with the resulting typical signs of reality disorientation, and inward attentional focus[17]. From a phenomenological point of view, AVHs are characterized by a limited set of core features; the experience is auditory in nature, with a distinct perceptual quality of "hearing a voice". It is true that some schizophrenia patients may experience visual, olfactory or kinesthetic hallucinations, but such instances are rare and may actually be part of other symptoms, not sharing

explanations with the experience of hearing voices. The "voice" is typically localized outside of the head[18,19], although recent research has shown that hearing the "voice" as coming from the inside is more common than previously believed[4]. The "voices" also typically have negative emotional valence[20,21], which is in addition experienced as controlling the patient[7,22], revealing a lack of executive cognitive power by the patient.

AVHs and a dimensional approach to mental disorders

From a cognitive and neurobiological point of view, there is an emerging literature showing a likewise emerging picture of symptom specificity when it comes to AVHs[19,23,24]. Experiences of AVHs should therefore be an ideal target for research from a dimensional point of view since recent studies have identified that about 4%-5% of the general population experience "hearing voices"[11-13], also when excluding previous mental health problems, medication, drug use, and other potentially confounding factors in this group of individuals. Thus, by studying the phenomenology, cognition and neurobiology of healthy "voice hearers" in the same experimental context as patients with auditory hallucinations, and comparing with non-hearing, non-psychotic control subjects, it should be possible to map commonalities and differences across several dimensions[6,14]. In this sense, non-clinical "voice-hearers" may constitute a theoretically important third group, the "missing link" between clinical and non-clinical individuals who experience AVHs. Observing similarities and differences at cognitive and neuroimaging levels of explanation between such a third group and clinical AVHs may provide invaluable data for unraveling the underlying cognitive and neuronal mechanisms for the understanding of AVHs. Cuthbert and Insel[6] have elegantly reviewed the National Institute of Health (NIH), United States, initiative to find new ways of conceptualizing and classifying mental disorders as dimensional, rather than categorical illnesses. With this was meant that the aim is to find new ways of understanding mental disorders, and providing new avenues for treatment, that are based on dimensions of empirically observable behavior and recordings of neuronal activity. Cuthbert and Insel[6] provide a set of criteria that could aid researchers to identify dimensions of symptom-like behaviors including cognitive, emotional, and social dimensions that can be analyzed from the molecular to the clinical level of explanation (see also[1]). Badcock and Hugdahl[14] have applied these criteria to the understanding of AVHs from a dimensional point of view, focusing on the cognitive construct of inhibition, and the lack of inhibitory power that characterizes patients suffering from frequent and severe AVHs. The theoretical approach used by Badcock and Hugdahl[14] is a first attempt to apply the new NIH criteria to the understanding of a specific symptom.

THE PHENOMENOLOGY OF AVHs

AVHs are phenomenologically speaking a conviction that other individuals are talking to the patient despite the absence of an external auditory signal[8,15,16,18]. AVHs therefore have a different sensory quality than illusions, which are perceptual misinterpretations of an actual perceptual experience, although in some instances AVHs can take on an illusory quality, as when patients report that the "voices" they experience started as "hearing sounds" that over time develop into "voice" hallucinations. AVHs are often described as "misperception of inner experiences and thoughts"[25] or as "misattribution of speech"[26], or as "internally generated events that are interpreted as being externally generated"[27], further attesting to a speech perceptual nature of how AVHs are experienced phenomenologically by the patient (see also[7]). Other characteristics of AVHs are that the quality of the voice is often negative and condemnatory, and that it is out of the patients' control; in fact, many patients subjectively report that they "feel controlled by the voice". To this list should also be added an attentional dimension, and that AVHs have a profound influence on the patients' attentional capacity, with attention being drawn towards the "voices", with a corresponding loss of attentional awareness of the outer world. This inward attentional focus has been the target for different cognitive therapy approaches (see[28,29]), trying to train the patient to re-allocate attentional focus from the inner imaginary "voices" to the outer real voices. Thus, the subjective and phenomenological experiences of AVHs are that they: (1) are perceptual phenomena experienced as not belonging to one's self, irrespective of whether they are perceived as coming from the outside or the inside of the head; (2) typically have a negative emotional valence consisting of sinister comments and commands; and (3) that they are out of volitional control[30,31]. In addition, some patients also struggle with not complying with the commands given by the "voice", and this is what they sometimes experience as the most frightening and anxiety provoking aspect of having AVH experiences - that they would have to commit acts that they do not want to commit[32]. It may also be of interest to note the Bleuler in his 1911 book recognized these three dimensions in his writings where he writes about "voices" speaking to the patient, take the patient's thought away, and that threats or curses are common contents.

This also points to an emerging new research area; the cognitive and neurobiological aspects of patients failing to withstand the commands of the "voice" and who commit tragic acts with traumatic consequences[33]. This is an area unfortunately much neglected in hallucination research, and may shed important light on other aspects of AVHs and schizophrenia in general. McCarthy-Jones *et al*[4] used

a structured interview scale with questions about a variety of content dimensions of AVHs in order to describe in detail the phenomenology of AVHs in a relatively large sample of almost 200 patients. Items entered into the analysis were questions on duration, location and frequency, as well as questions related to past memories, gender, family relationship with the "voice", first, second or third person, and emotional content. The results showed a more complex relationship between the various domains or dimensions than previously acknowledged, which raises the question of whether AVHs should phenomenologically speaking be divided into sub-types with their own core characteristics. For example, the results showed that the localization of the "voices" as coming either from inside or outside of the head was about 50%, while command "voices" like "Did the voices ever tell you what to do?" accounted for 67% of positive answers from patients[4]. This finding attests to the saliency of commands and threats as part of the phenomenology of AVHs.

THEORETICAL MODEL OF AVHs

Probably the most influential model for the understanding of AVHs in schizophrenia is the suggestion by Frith *et al*[34-36] that AVHs are caused by a failure to adequately monitor and label verbal thoughts as coming from the inside rather than from the outside of the patient's head, often called an "inner speech" model. In addition to an inner speech model, it has been suggested[14,21] on the basis of the negative emotional content of AVHs that they may represent misinterpreted recall of strong emotional and traumatic memories that would act like intrusions, and that are mislabeled as coming from the outer world (see[8] for detailed overview over and discussion of theoretical models of AVH). However, as pointed out by Jones[8] (see also[7]), neither model fulfills the criteria of encompassing the full phenomenology of AVHs, common to all patients. Since both patients with auditory hallucinations and healthy individuals "hearing voices" subjectively report experiencing someone "speaking to them", not that they "speak to the voice" (although they may be engaged in a later dialogue with the "voice"), it seems that a perceptual model would better fit the actual phenomenology of "hearing voices" than a speech production model.

This is supported in a review by David *et al*[37] on AVHs which concluded that more than two thirds of patients with AVHs subjectively report that the "voice" is speaking in a different accent than their own, which is difficult to conceive of in an inner speech model. Electrophysiological and brain imaging data also show a pattern of responding more in congruence with a perceptual view, with recorded activity in temporal lobe speech perception areas[38-41]. In a recent review and meta-analysis, Jardri *et al*[18] moreover concluded that most studies support a view of aberrant speech perception as the core phenomenology of an AVH, and with a neuronal focus in the peri-Sylvian region in the auditory cortex (see also[7,42-45]. A speech perception view does however not exclude a speech production model. An inner speech model states that AVHs are related to a deficit in monitoring of one's own inner dialogue and thoughts, which then also includes a perceptual component in the monitoring aspect. What is different between the models is that a perceptual model gives rise to specific hypotheses about a neuronal origin in the speech perception areas in the upper posterior part of the temporal lobe, and primarily on the left side, while an inner speech model is less specific about a neuronal focus, (see however[12] who found activation in the right inferior frontal gyrus).

Similarly, since only about 10%-20% of the "voices" that patients experience "hearing" are about actual memories and previous experiences[46], it is difficult to reconcile this with a memory model for auditory hallucinations. It is however true that in some cases when the voices are very intrusive and threatening to the patient, there seems to be a correlation with previous trauma and sexual abuse and positive symptoms, like AVHs[47,48]. However, although there is no unique link between traumatic experiences and psychotic disorders, several studies have found a relationship between psychotic symptoms, including AVHs, and childhood trauma from sexual abuse as well as from having experienced increasing violence in war zones[48,49]. Such experiences are however not unique to causing AVH, since they more often lead to anxiety disorders, like PTSD. Furthermore, traumatic memories as causes of auditory hallucinations cannot explain the experience of benevolent voices, *e.g.*, when patients experience "listening to angels". If anything, the content of such hallucinations should be related to the trauma or abuse event if based on memories, which does not the fit their non-traumatic content. Also, as for inner speech models, memories need to be interpreted and "translated" into a perceptual experience in order to be congruent with what patients actually report, and this again points towards a perceptual basis for auditory hallucinations. To this should be added the characteristic perceptual quality of the "voice", which is typically experienced as a real person speaking with distinct perceptual qualities like accent, emotional valence, and timbre, as if in direct interpersonal communication[8].

EMPIRICAL EVIDENCE FOR A PERCEPTUAL DIMENSION

Hugdahl *et al*[50] used a dichotic listening task with simultaneous presentations of brief speech sounds consisting of a single vowel and a consonant, so called consonant-vowel syllables. One syllable is presented to the right ear and another simultaneously

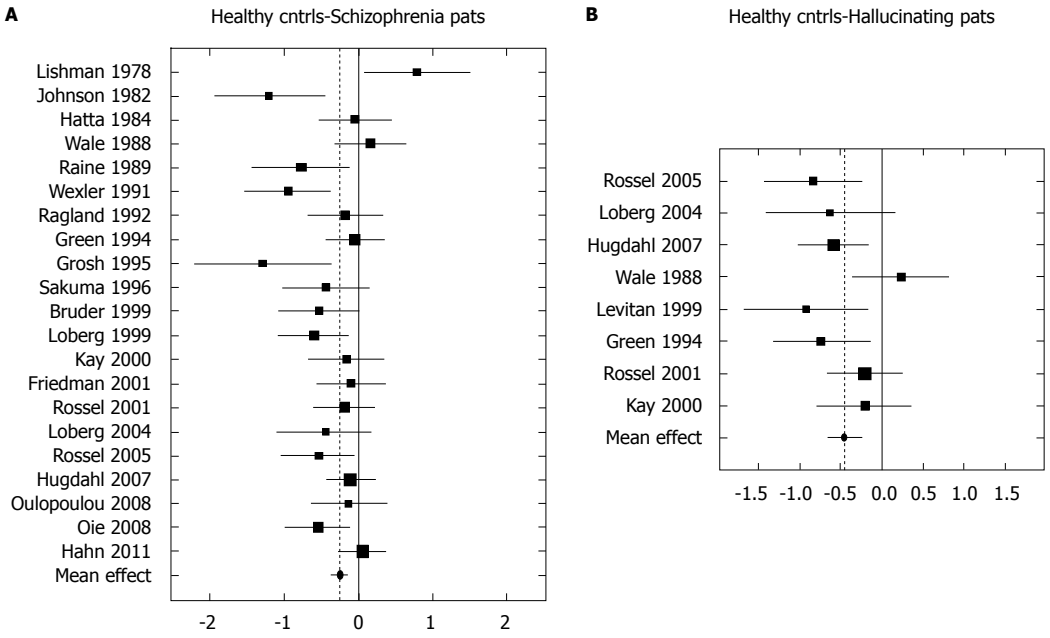

Figure 1 Graphic illustration of the meta-analysis done by Ocklenburg *et al*[55] on the relationship between the right-ear advantage in dichotic listening and schizophrenia (A), and between right-ear advantage and hallucinations (B). Reprinted with permission from the authors and the publisher.

to the left ear. This is a common procedure used in research on laterality and hemispheric asymmetry to investigate left hemisphere preference for speech sound perception. The result is typically a preference for reporting the right ear over the left ear syllable, reflecting a left hemisphere perceptual preference and processing of speech stimuli[51,52]. Hugdahl *et al*[50] predicted that AVHs would interfere with the processing of an external speech sound if a perceptual model is correct, and that the interference would increase with more frequent and severe AVHs. The authors therefore correlated the score on the hallucination item in the PANSS symptom scale with the right ear advantage in the dichotic listening task, predicting a negative correlation. The results confirmed the prediction with a significant negative correlation with the hallucination item, not found when a corresponding correlation was calculated for a negative PANSS symptom (see also[53,54]).

The notion that the magnitude of the right ear advantage in hallucinations would reflect the degree to which AVHs interfere with the perception and subsequent processing of an external auditory stimulus was further pursued by Ocklenburg *et al*[55] who conducted a meta-analysis of dichotic listening studies involving schizophrenia patients and in particular hallucinating patients. The total sample in the meta-analysis consisted of 700 patients and 700 healthy controls. The results showed that the patients had significantly reduced right ear advantage compared to controls (effect-size approximately 0.25) and that this was exaggerated when comparing patients with AVHs and healthy controls (effect-size 0.45). This is shown in Figure 1.

NEURONAL CORRELATES

Structural imaging

Ever since the pioneering work by Johnstone *et al*[56] which showed that schizophrenia patients had reduced grey matter volume compared to healthy controls, the use of magnetic resonance (MR) for the study of brain correlates of schizophrenia as a mental disorder (see meta-analysis by[44]), and AVHs in particular (see meta-analysis by[41,44]), has been a major research topic, using both structural and functional MR measures[57]. The fact that temporal and frontal lobe brain areas are implicated in auditory hallucinations has been repeatedly shown in functional and structural imaging studies. Using a voxel-based-morphometry (VBM) analysis method, Gaser *et al*[58] reported already in 2004 a reduction of grey matter in the left superior temporal gyrus and auditory cortex in hallucinating patients. This finding was followed by Neckelmann *et al*[59] who found a similar pattern, and in addition reported reductions in the frontal lobe, thalamus, and basal ganglia (Figure 2).

These results have later been strengthened by the results of a meta-analysis by Modinos *et al*[44] who concluded that: "Severity of AVHs was significantly associated with GMV reductions in the left and marginally with the right STG, including Heschl's gyrus" (p. 1046).

Frontal and temporal lobe grey matter reductions in schizophrenia patients have often been related to positive symptoms in general, and not only with AVHs[60-62] (see also[63] for review). It should be noted however, that in a very recent study by van Tol *et al*[45], grey matter reduction in the superior temporal gyrus was significantly reduced in both frequent and infrequent

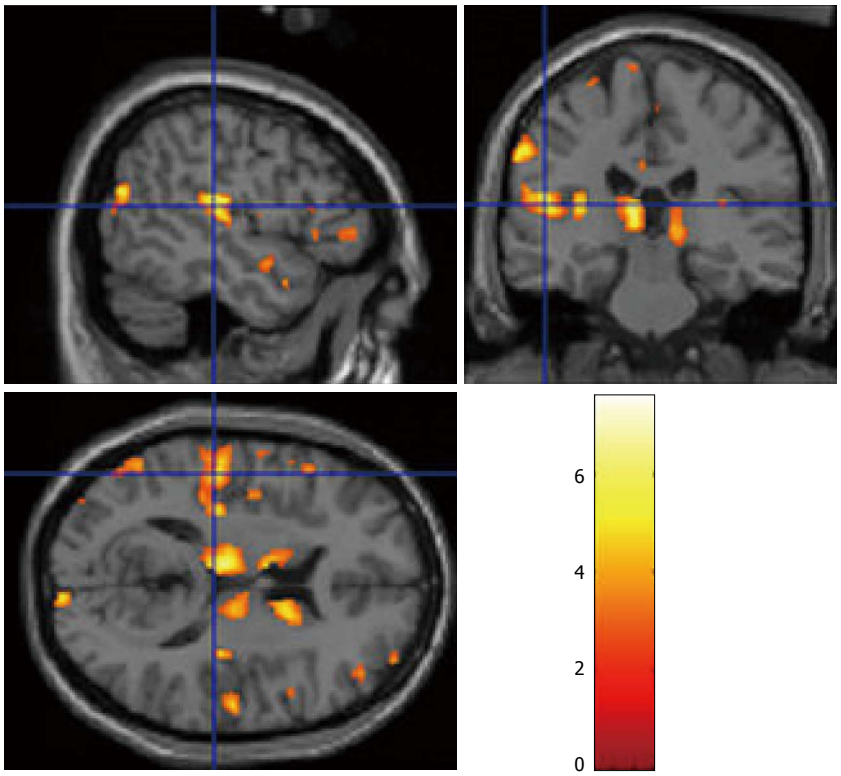

Figure 2 Structural magnetic resonance imaging, using Voxel-Based-Morphometry analysis of grey matter density in the brains of patients with frequent (PANSS P3 > 3), and infrequent (PANSS P3 < 4) hallucinations, shown in sagittal, coronal and axial slices. Data from Neckelmann *et al*[59] redrawn with permission of the authors and the publisher.

AVH patients compared to healthy controls, while reduction in the parahippocampal region was unique to AVH patients only. This could lend support to an intrusive memory account of AVHs[21,64], while at the same time weakening a speech perceptual model since temporal lobe area reductions did not differ between AVH and non-AVH patients. However, such a conclusion may be premature, since the results do not disprove that AVHs are related to temporal lobe pathology, but only say that this may be a more general characteristic of schizophrenia.

With regard to white matter changes and abnormalities in the brains of AVH patients, this is less known compared to grey matter abnormalities. Allen and Modinos[63] reviewed the white matter literature, based on diffusion tensor imaging (DTI), and fractional anisotropy (FA) which is an index of the difference in flow of water molecules along *vs* across axonal fibers. In general, these studies have shown both increased and decreased FA values in patients with schizophrenia, in particular for connections between anterior and posterior brain regions. Interestingly, schizophrenia patients experiencing AVHs show increased connectivity between frontal and temporal/parietal areas[65] which could be a white matter structural correlate to the verbal nature of AVHs.

Functional imaging

Functional imaging has likewise revealed temporal and frontal lobe abnormalities in patients with frequent AVHs[12,38-40,66,67]. See also[19,23] for meta-analyses, and[26] for an overview of both functional and structural imaging studies on AVHs. Thus, an understanding of the neuronal circuitry underlying AVHs is emerging, with new evidence coming from cognitive, behavioral, and brain imaging studies (see[26,68,69] for reviews). When reviewing the literature on functional imaging and AVHs, a distinction has to be made between "state" and "trait" studies. With "state" is meant studies that have compared patients during hallucination episodes with non-hallucination episodes while in the scanner, which may or may not be compared with healthy controls, and may or may not include the presentation of external stimuli. Patients typically indicate with a button-press or similar when they experience AVHs in the course of the scanning. With "trait" is meant that patients have been screened for frequency and severity of AVHs with typical symptom interview scales, like the PANSS, before the scanning, such that it is known in advance which patients could be labelled AVH-patients, and which could be labelled non-AVH-patients. Patients are then compared with healthy controls, typically in a paradigm with external stimuli, although this is not a requirement.

Resting-state brain activation

Northoff *et al*[70] suggested, after reviewing the literature, that AVHs may represent resting-state neuronal hyperactivity in the default-mode cortical network[71], a kind of spontaneous neuronal firing especially in the auditory areas, during AVHs in the absence of an external auditory stimulus. Northoff *et al*[70] summarized their review by stating that: "the findings suggest that the resting state activity in especially the anterior medial cortical regions is abnormally increased as indicated by the observations

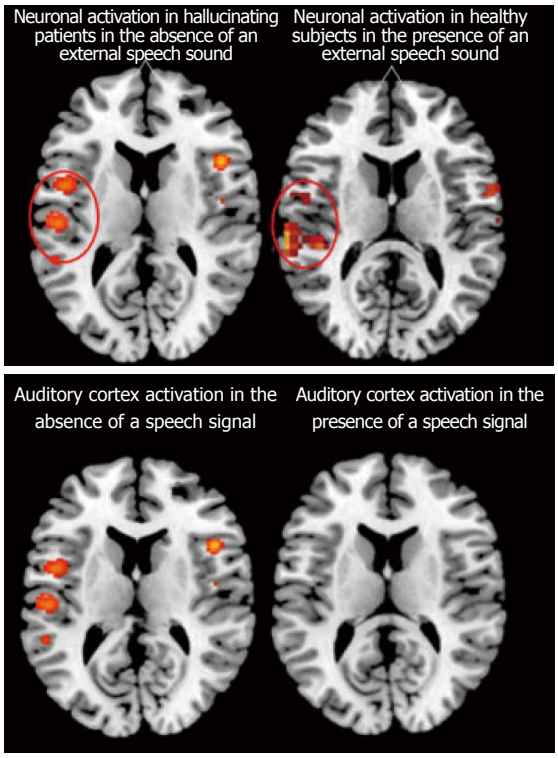

Figure 3 Functional imaging results for hallucinating patients based on the meta-analysis done by Kompus *et al*[24] which show activation in the absence of an external auditory stimulus (upper left panel) compared with healthy controls in the presence of an external auditory stimulus (upper right panel, data from van den Noort *et al*[117]). The lower left panel shows the same activation as in the upper left panel, spontaneous activation in hallucinating patients in the absence of an external auditory stimulus, but now compared with absence of activation in hallucinating patients in the presence of an auditory stimulus. Color-coded areas indicate significantly activated brain regions during active hallucinations and task-processing. Reprinted and redrawn with permission from the authors and the publishers.

of ... increased connectivity, and increased low-frequency fluctuations in schizophrenic patients." (p. 206).

Increased spontaneous activation in regions associated with the default-mode network may then interfere with processing of external speech, or an auditory stimulus, causing a kind of neuronal interference, *i.e.*, the internally generated neuronal activity during episodes of AVH interferes with the processing of an external stimulus. This is illustrated in Figure 3, which also shows in the lower panel a comparison between patients with frequent and severe AVHs and healthy controls in the presence of an auditory stimulus.

Neuronal interference was also observed by Hubl *et al*[72] and Ford *et al*[38] where the amplitude of the N1-component of the event-related electrophysiology potential to an external auditory stimulus in AVH patients was reduced. Based on these and other studies, (*e.g.*,[70,73-75]) it is suggested that the evidence show reduced rest-external stimulus interaction in AVHs, caused by failure of modulation of both resting state and stimulus-related activity. This is similar to the suggestion by Hugdahl *et al*[7] that AVHs may involve: "failure of down-regulation of a resting-state network and corresponding up-regulation of an effort network, thus upsetting the normal functioning of cognitive control mechanisms". (p. 41).

A paradoxical finding

Empirical evidence from functional neuroimaging studies, both electrophysiological and hemodynamic studies, point in the direction of AVHs being related to abnormal neuronal network architecture and interactions, with increased activation in auditory and speech perception areas in the absence of external auditory stimuli, and reduced activation in the same areas in the presence of external auditory stimuli. Kompus *et al*[24] labelled this the "paradoxical effect" since it is paradoxical that increased spontaneous activation in AVH patients in the absence of an auditory stimulus is not further increased when an auditory stimulus is actually presented, as if the perceptual system is "shut down". A major question is of course why this paradoxical effect occurs in the first place.

Northoff *et al*[70] suggested that the reduced resting-stimulus network interaction is the result of a mislabeling process where the abnormal processes that have occurred in the auditory cortex in AVH patients cause the patient to register an internally generated event as if it was an external stimulus, similar to faulty monitoring and labelling of an inner speech event as coming from the outside[35,36]. Similarly, Kompus *et al*[24] suggested that the paradoxical effect of reduced activation to an external auditory stimulus in the auditory cortex in AVH patients would fit a model of abnormal interaction between cortical networks, with too high activation in the default-mode network during episodes of external stimulus processing, causing neuronal interference[76], or resource competition[60].

Kompus *et al*[24] further discussed if this could be an attentional effect, in addition to a sensory processing effect, such that reduced activation to an external stimulus is caused by a failure to allocate attentional resources to an external source in the course of a hallucinatory episode. That schizophrenia patients are impaired on neuropsychological tests for attention is well-known[77-79], and it has recently also been shown that AVH schizophrenia patients fail to allocate attentional resources to the location of an auditory stimulus[23]. Thus, it is possible that the paradoxical effect seen in the meta-analysis by Kompus *et al*[24] is an attentional effect, with the cognitive system being "shut down". A third explanation is that it is a signal-gating effect, and that an auditory signal is not properly gated from the ear to the temporal lobe, possibly because of an abnormality at the thalamic or hippocampal levels[24], in which case it would be the thalamic system being "shut down". Several studies have shown that schizophrenia patients show

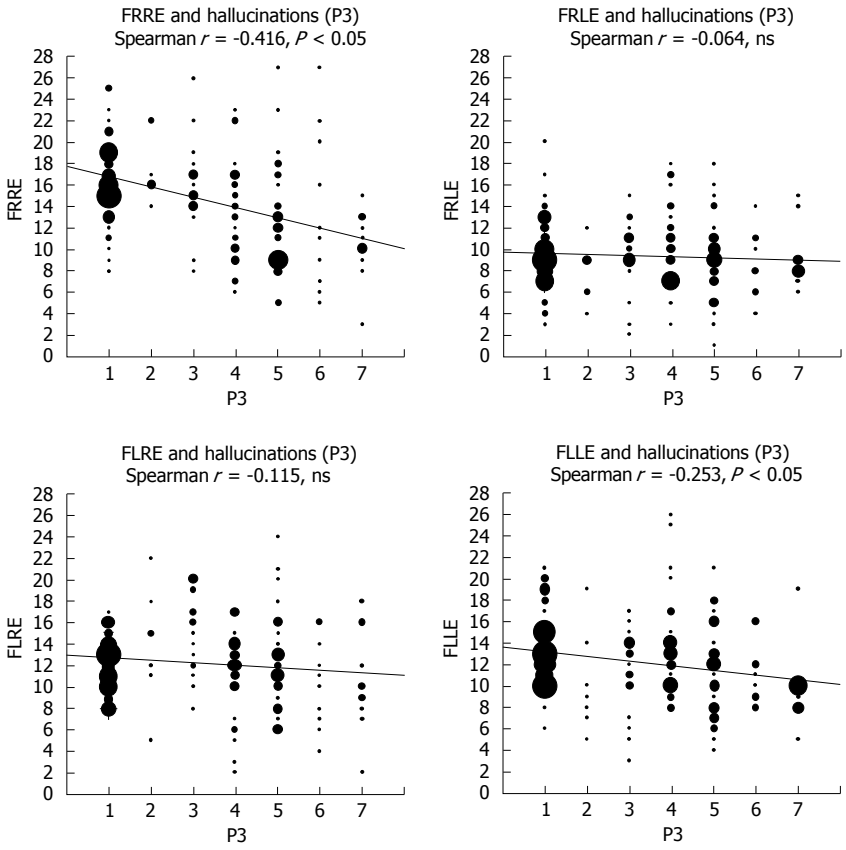

Figure 4 Correlations between the right and left ear scores on the forced-attention dichotic listening task and scores on the the PANSS P3 Hallucination item. Note the negative correlations for the FR and FL instruction conditions (upper left and lower right), respectively. See text for further explanations. From Hugdahl *et al*[23], reprinted with permission from the authors and the publisher. ns: Not significant.

aberrant sensory gating[38,80,81] such that the filtering function of sensory gating, *i.e.*, to filter out irrelevant stimulus noise at the sub-cortical level, with the aim of facilitating attention shifts at the cortical level to relevant aspects of an external stimulus, is impaired. If this mechanism is aberrant, it is not unreasonable to assume that the processing of an external stimulus is hindered by the noise created by the internally generated AVH, which is not inhibited by the incoming stimulus.

FAILURE OF TOP-DOWN INHIBITION

Irrespective of the theoretical model and neuroimaging data supporting either a perceptual model or other models, what may trouble patients the most is the failure to ignore the "voices" when they occur, and to focus on other things happening in their surrounding environment. It is as if the "voices" drain the patient of their cognitive capacity, leaving them in the hands of whatever malevolent comments or commands the "voice" may find it proper to try on. From a clinical point of view, this is probably what troubles, and not the least, scares the patient the most, being unable to control the "voice" and to withstand and ignore what they "say". This not only confuses the patient but also creates anxiety and fear when struggling not to comply with what the "voice" command. From a theoretical point of view this can be seen as a failure of top-down inhibitory control, or a failure of executive functions as it is typically called in classic neuropsychology[82,83]. Using a variant of the dichotic listening experimental paradigm, the forced-attention paradigm, as described in the perception section above, Hugdahl *et al*[23] found a negative correlation between scores on the PANSS hallucination item and the ability to shift attention to either side in auditory space (Figure 4).

The forced-attention dichotic listening task[84,85] is an experimental task that taps non-executive and executive attention in the same paradigm. As discussed above, due to the lateralization of speech sound perception, the right ear stimulus of the dichotic pair will be preferred for processing over the left ear stimulus since it has direct access to the left temporal lobe[51-52,86,87]. As also discussed above, this is called a bottom-up right-ear advantage (REA). The novel aspect of the forced-attention extension of the paradigm is that when the subject is instructed to explicitly attend to and report only from the right ear, this will create a non-executive attentional focus situation, since the bottom-up tendency to process the right ear stimulus acts synergistically with the top-down instruction to attend to the same ear, which results in a larger REA. When the subject is instructed to attend to and report only

from the left ear, the brain faces a cognitive conflict where the bottom-up and top-down processes are opposed to each other, and act non-synergistically. The conflict requires executive control resources, and the cognitively strong right ear stimulus has to be inhibited and the cognitively weak left ear stimulus has to be facilitated. Most healthy adults can overcome the bottom-up tendency and report the left ear stimulus of the dichotic pair, showing a left-ear advantage (LEA). The finding of a negative correlation between PANSS score for the hallucination item and the magnitude of the REA in the situation with attention focused on the left ear that was reported by Hugdahl *et al*[23] would then be evidence for a parametric inverse relationship between frequency and severity of AVHs and the ability to execute cognitive control.

Although the inability to suppress and inhibit the "voice" is a prominent feature of AVHs clinically, there are surprisingly few studies that have explicitly looked at the relationship between executive functions in general, and inhibition in particular, and AVHs. Executive functions in AVHs were reviewed by Waters *et al*[21], in particular in relation to what these authors called failure of "intentional cognitive inhibition", which is the inability to voluntarily monitor and inhibit intrusive thoughts. Such thoughts may be intrusive fragments from memory that are not inhibited and are then mislabeled as coming from the outer world in the form of someone speaking to the patient. Cognitive inhibition has been decomposed into different sub-components and sub-processes, voluntary *vs* involuntary inhibition[88], where the latter is the process of ignoring something without being aware of the process of doing it. Miyake *et al*[89] have proposed that inhibition in executive functions is related to the suppression of pre-potent responses and response-tendencies, which in addition requires the ability to shift attention set after inhibition. Applied to AVHs, it can now be suggested that the "voices" are intrusive and pre-potent thoughts that are not voluntarily inhibited and that take on an autonomous role once they are initiated and enter into the patients' awareness.

The failure of cognitive inhibition in AVH patients may have a neuronal localization in the frontal lobes, and a corresponding prefrontal inhibitory abnormality. Executive function and inhibition have been linked to the anterior cingulate cortex (ACC) in several studies, ranging from the early positron emission tomography (PET) studies by Pardo *et al*[90] with the Stroop task to later studies with fMRI using various auditory and visual tasks (see[24,91]). Thus, the prefrontal cortex and the ACC are areas critically involved in cognitive control and executive functions, and these regions have repeatedly been shown to be affected in patients with schizophrenia (see[26,92] for reviews).

LEARNING TO IGNORE THE "VOICES"

Failure of attention and executive control in AVH patients may also be the starting point for novel cognitive training attempts. Cognitive behavior therapy for schizophrenia and auditory hallucinations has long been directed towards giving the patient the skills necessary to voluntarily inhibit and shift attention away from the "voice" (see[28,93]). Recent approaches to cognitive therapy have been more focused on specific training procedures, rather than inducing a therapeutic change of strategy. Thus, a distinction can be made between treatments which in the case of schizophrenia will mean abolishing symptoms, therapies inducing new strategies on how to cope with stressful situations, and training which is specifically aimed at handling a single event, or symptom. We have developed an iPod/iPhone app[94] based on the dichotic listening paradigm, described above, as a tool to learn how to inhibit and ignore the "voice", also to be used in social situations, like riding on a bus, or being in other social situations, which can be used "there-and-then" whenever the patient feels the urge to have help in withstanding the "voice". Preliminary results from 15 patients show some promising effects that warrant further research on the use of app-technology for training and learning new mental skills in patients with schizophrenia.

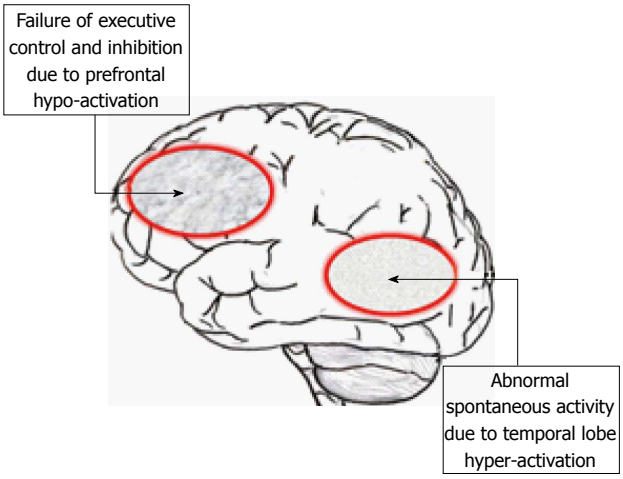

Figure 5 The ERC "VOICE" model showing impaired processing in a suggested pre-frontal and temporal lobe neuronal network, due to hyper-activation of temporal lobe regions, including the auditory cortex, which is not inhibited due to impairment of pre-frontal executive inhibitory functions. See text for further explanations. Redrawn from Hugdahl *et al*[7], with permission from the authors and the Publisher.

THE ERC "VOICE" MODEL

The results from the ERC project have provided the empirical input to a model that is graphically shown in Figure 5 (the model is also presented in[7]).

The purpose of proposing the model was to advance our understanding of the neuronal underpinnings of AVHs from the perceptual, attentional and cognitive control domains that have been reviewed and discussed above. The model derives from an assumption of the existence of two cognitive networks, or systems; one that acts as a bottom-up system that primarily

responds to stimulus features, and consists of perceptual and sensory processes, and another top-down system that responds primarily to the cognitive demands of the situation. The model further assumes that the bottom-up system is responsible for the actual initiation of AVHs, driven by neuronal hyper-excitation in the temporal lobes, while the top-down system is responsible for the maintenance of AVHs, and in particular failure of inhibition and attentional focus, localized to frontal and parietal lobe areas. As discussed above, AVHs are seen as the product of an abnormality in both the bottom-up and top-down systems characterized by hyper-activation of the bottom-up system, and hypo-activation of the top-down system, as illustrated in Figure 5. AVHs are therefore not inhibited once they occur because of impaired functioning of the prefrontal cortex. Finally, the model assumes that parietal lobe areas are activated for the direction of attentional focus towards the voices, and are also not inhibited through impaired frontal lobe executive and cognitive control functions. As also discussed above, the "VOICE" model will generate new hypotheses not only for the understanding of the underlying neuronal mechanisms for AVHs but can also contribute to novel hypotheses regarding cognitive training and learning of how to inhibit and ignore the "voice", by teaching the patient how to re-allocate attention away from the inner "voice" and towards real outer voices. From the networks outlined in the "VOICE" model, it is possible to derive the underlying cortical network representations by applying advanced connectivity analysis approaches to functional neuroimaging data, thus advancing our current understanding of the underlying mechanisms in a hypothesis-driven manner. The model moreover suggests new avenues that go beyond existing paradigms and methods, and move to the lower levels of explanation from the cognitive and imaging levels by asking questions about which neurotransmitters and receptors may be involved in the neuropathology. This is a new avenue in AVH research, and knowledge about transmitters and receptors may provide the inspiration for new pharmacological treatments. The "VOICE" model will also cover non-clinical individuals with AVHs, *i.e.*, individuals in the general population who share the experience of "hearing voices" but who are not clinically handicapped by their experiences[11]. A major difference between clinical and non-clinical AVH individuals is intact attentional top-down cognitive control of the "voices" in non-clinical individuals, coupled with intact frontal lobe functioning and increased activation in these regions[95,96]. Another difference between clinical and non-clinical individuals who experience AVHs is that the former lack a meta-cognitive understanding of the subjectivity of their experience and to a higher degree ascribes the experience to external factors.

THE NEUROCHEMISTRY OF AVHs

MR spectroscopy and glutamate/gamma-amino-butyric-acid interactions

A question that is seldom asked in the AVH literature is what transmitters and receptors may be causing or contributing to the neuronal activation abnormalities seen in AVH patients and reviewed above (see however[57]). We do not know what triggers an AVH at the cellular level, causing the subjective experience of perceiving a "voice" in the absence of an external stimulus. To answer this it is necessary to move down to the receptor and transmitter levels of explanation. The meta-analysis by Kompus *et al*[24], (see also[18]), revealed that areas in the posterior left temporal and right frontal lobes were hyper-excited during spontaneous AVHs, and at the same time hypo-excited to an external speech sound, when compared with healthy control subjects. Thus, AVHs seems to produce a neuronal paradox in the sense that the same brain areas that fire uncontrollably at the initiation of AVHs at the same time are refractory to the presentation of an external speech sound. Kompus *et al*[24] called this a "paradox" since one would expect activation in the auditory and speech perception regions in the absence of an auditory stimulus would actually be increased when an external stimulus is presented in addition. The spontaneous increase in neuronal activity in the auditory cortex in AVH patients was also recently shown by Homan *et al*[97] who found that cerebral blood flow was higher in this area in AVH patients, and remained so also after treatment with transcranial magnetic stimulation. Homan *et al*[97] suggested that increased blood flow may be a trait-marker of AVHs, which was also suggested by Kühn *et al*[98]. It is now suggested that the paradox could be explained by the differential actions of gamma-amino-butyric-acid (GABA) interneurons that produce hyper-excitation in the first case and hypo-excitation in the second case.

This can be empirically addressed through MR spectroscopy (MRS) to measure and quantify regional concentrations of brain metabolites, such as glutamate, which is excitatory and GABA, which is inhibitory. MRS thus allows for *in vivo* measurements of transmitter concentrations in patients which solves the problem of exclusive reliance on animal models. MRS allows for the near-simultaneous recording and quantification of both glutamate and GABA levels, and also other relevant metabolites, like *N*-acetyl-aspartate (NAA), choline, and creatine[99,100]. By adding an MRS sequence of 5-10 min to the fMRI sequence, it will therefore be possible not only to measure and quantify concentrations of glutamate and GABA in the hallucinating brain but also to correlate MRS metabolite concentrations in selected voxels with other clinical, cognitive and imaging data. A typical MR spectrum is shown in Figure 6.

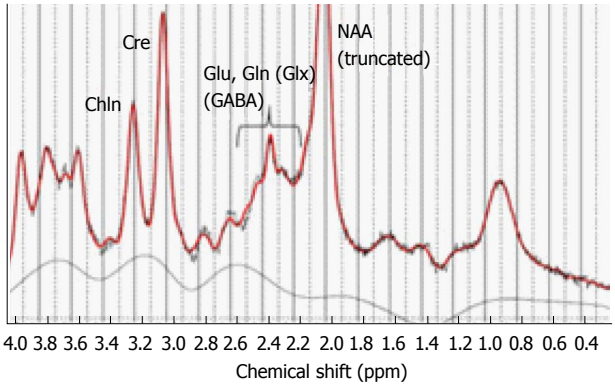

Figure 6 Example of a printout of the typical peak spectra from an MR spectroscopy sequence applied to a single voxel. Selected metabolites are indicated with respective acronym. Glu: Glutamate; Gln: Glutamine; Glx: Glutamate + Glutamine; GABA: Gamma-amino-butyric-acid; Cre: Creatine; Chln: Choline; NAA: *N*-acetyl-aspartate. From Hugdahl *et al*[111], reprinted with permission from the authors and the publisher.

Glutamate and schizophrenia symptoms

Glutamate is suggested to have an effect on positive symptoms associated with schizophrenia through balancing sub-cortical dopamine release (see[10,101] for overviews). The classic pathway for the involvement of glutamate in schizophrenia and in the regulation of positive symptoms is that reduced cortical glutamate levels, and/or dysfunctional N-methyl-D-aspartate (NMDA) receptors, hypo-activate GABA interneurons, which leaves striatal dopamine release uninhibited, resulting in dopamine excess in the schizophrenia brain[102]. The finding of reduced glutamate levels in schizophrenia patients would fit with a number of other studies which show that when healthy individuals are given ketamin and phencyclidin (PCP), which are drugs that act as NMDA receptor antagonists[103,104], they show signs and symptoms of a psychosis. The possible relationship between glutamate reduction and dopamine was described by Carlsson *et al*[105] such that prefrontal glutamate release will result in activation of GABA interneurons to balance too high levels of glutamate, which will also have an inhibitory effect on striatal dopamine release (see also[101]). When glutamate levels fall below critical levels or when GABA receptors are dysfunctional, GABA interneurons will consequently be hypo-activated and dopamine release will be correspondingly uninhibited. This will result in excess dopamine, and in particular dopamine D2-receptor activity, producing positive psychotic symptoms. It should be pointed out, however, that a more recent article concluded after reviewing the schizophrenia literature, with both decreases and increases of dopamine, particularly in frontal regions[106].

Interestingly there were no studies comparing glutamate levels in patients and controls in temporal regions in the Poels *et al*[106] review, which leaves the question of abnormal glutamate regulation in the auditory and speech perception areas currently unanswered. Falkenberg *et al*[107] moreover found a positive correlation between fMRI activation and glutamate in the anterior cingulate region in schizophrenia patients, while there was a corresponding negative correlation in control subjects. Falkenberg *et al*[107] also found that decreased glutamate levels were associated with impaired executive control functioning when the patients were tested on a cognitive control task[108]. It should be noted that the healthy control subjects did not show an association between task performance and glutamate levels. Thus, glutamate seems to be specifically involved in mediating frontal lobe executive functioning in schizophrenia patients, who also perform below the controls on this task. The study by Falkenberg *et al*[107] again raises the question as to whether glutamate levels are increased or decreased in temporal lobe areas, and whether patients with frequent AVHs differ from patients with less frequent AVHs.

Temporal lobe glutamate levels and AVHs - preliminary results

The only data, to my knowledge, on the role of transmitters in AVHs are from the study by Homan *et al*[97] who found that levels of NAA differed between patients and healthy controls, and a positive correlation between NAA levels and the frequency of positive symptoms (see however[109]). Again the MRS voxel placements were in the frontal lobes, and therefore it is not known what role glutamate may play for the frequency and severity of AVHs when measured in the temporal lobes. As argued above, an increase in temporal lobe glutamate levels may be predicted to go along with increased AVH frequency, considering the neuroimaging data which have shown increased activity in both hemodynamic and electrophysiology studies[18,24,49,110], although as for other brain metabolites that have been studied in schizophrenia patients, both increases and decreases could be expected. Hugdahl *et al*[111] recorded glutamate levels from four voxels, in the left and right auditory cortex, overlapping with Heschl's gyrus and in the left and right prefrontal cortex in the superior frontal gyrus. Symptom frequency and severity were quantified from the PANSS interview scale[8]. The results showed first of all that schizophrenia patients had reduced glutamate levels compared to the healthy controls, which would be predicted from previous studies (*e.g.*,[63,112,113]). Second, patients with a high symptom load for the AVH item in the PANSS had significantly higher glutamate level in both temporal and frontal lobe areas, thus for the first time demonstrating increased glutamate levels in these regions. The results were moreover specific for the AVH symptom when compared with the emotional withdrawal negative symptom. Figure 7 shows the relationship between AVH and glutamate levels in the temporal lobe. The glutamate data in Figure 7 are pooled for the right and left temporal lobes, with a voxel placement in the upper posterior portion, overlapping with Heschl's gyrus. The data are

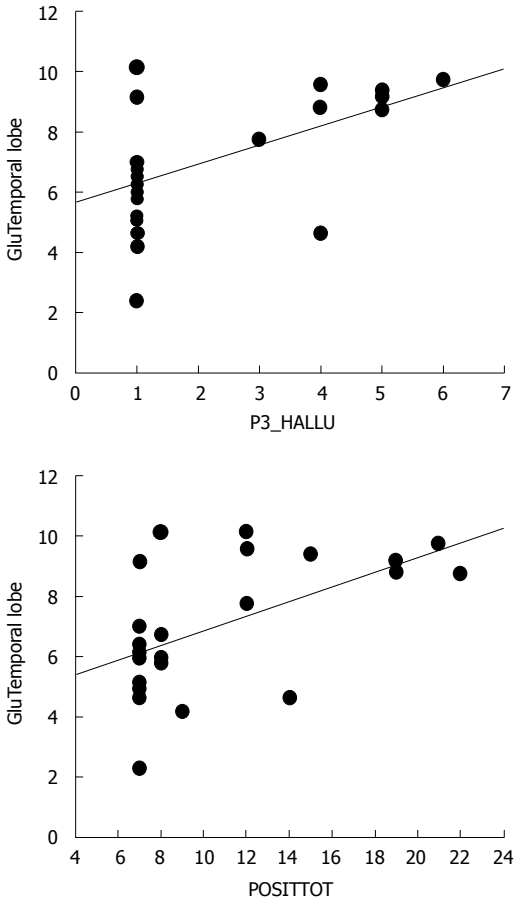

Figure 7 Scatter-plots of the correlations between scores on the PANSS P3 Hallucination item and Glutamate levels from a temporal lobe voxel, and between the sum total of positive symptoms and Glutamate levels from the same voxel. P3_Hallu: Score for the PANSS hallucination item; POSITTOT: Sum total of positive symptoms; Glu: Glutamate.

presented as correlations between mean glutamate levels in the voxel areas and PANSS AVH item scores, as well as for the sum total of all PANSS positive item scores, also including the AVH item (data re-plotted from Hugdahl *et al*[111]).

The results reported above thus extend the findings reported in Homan *et al*[97] who found altered levels of NAA in AVH patients, by showing that altered levels of brain metabolites in AVH patients are also related to glutamate. This may be a significant novel finding since NAA is involved in the metabolism of NAA-glutamate[114]. Thus, the two metabolites are functionally overlapping, and both could therefore be expected to be elevated in a state of neuronal hyper-excitation, as in auditory hallucinations.

The relevance of the findings by Hugdahl *et al*[111] is substantiated by the fact that while most studies have found reduced levels in schizophrenia patients in general[63], the same holds for NAA, which is also typically reduced in schizophrenia in general[115], but increased in hallucinating patients[110]. The demonstration that auditory hallucinations may be mediated by excessive glutamate levels in the same brain regions that have been previously implicated from fMRI studies is a finding that may have implications for new treatment targets and the development of new drugs that are tailored to counteract the experience of hearing voices rather than acting on the schizophrenia disorder as such. The MRS findings reported in Hugdahl *et al*[111] would also support a dimensional view advocated by[6] specifically targeting alterations in brain metabolites related to specific symptoms rather than to the schizophrenia disorder as such (see also[14]).

NEW WAYS OF SAMPLING SYMPTOM DATA IN REAL-TIME

The introduction of smartphone app technology

Data on frequency and intensity of auditory hallucinations are typically obtained from scores on a single item in structured interview scales, where the PANSS[8] is a commonly used scale. As previously mentioned, data on hallucinations are entered as a number between 1 and 7, with 1 = low frequency or non-existent, while 7 = high frequency. There is however a number of non-optimal and confounding factors with such interview scale data that may obscure the true frequency and variability over time on an individual basis. Data are obtained in a single, or few, sessions, typically in an artificial office environment, data are aggregated across several sub-symptom dimensions, processes, and verbal responses, and interpreted by the clinician before entering a score on the questionnaire. Questionnaire data are also by necessity retrospective in the sense that the patient is asked to recall past events, *e.g.*, whether they have had unusual or uncommon experiences lately, or whether they sometimes hear voices inside their head that others cannot hear, what these voices tell the patient, how often they hear them etc. Thus, there is a fairly long "distance" from the phenomenological experience in the patient's mind, and the data that the researchers are provided with and use for statistical analyses have therefore been filtered through several intermediate steps from the patient to the researchers. There is thus a pertinent problem of how to bridge, or shorten, the distance from the phenomenology of a personal experience to a score on the analysis computer. Our research group at the University of Bergen, Norway, has recently suggested the use of smartphone technology for acquisition of real-time data on cognitive and clinical parameters as well as for cognitive training to inhibit the "voice", as previously discussed (*e.g.*,[94]).

The idea is that the patient is equipped with an iPhone or iPod and after opening the app is confronted with a series of question shown on the display that will tap the three major dimensions in auditory hallucinations, a perceptual dimension (do the voices come from outside or inside the head), a cognitive dimension (does the patient have full or no control over the voices), and an emotional dimension (are

Figure 8 iPhone app for the sampling of real-time data on the three dimensions of auditory verbal hallucinations, cognitive control (upper slider), emotional content (middle slider), and perceptual locus (lower slider), developed by the ERC "VOICE" Group at the University of Bergen, Norway. See text for further explanations.

the voices negative or positive). In addition there are questions about frequency and intensity of the "voice". The patient responds to each question by moving the finger-slider from left (inside the head, no control, emotionally negative) to the right (outside the head, full control, positive) of the display, and the distance is then quantified in centiles.

There are several advantages with an app-approach to symptom data sampling: (1) data will be patient-driven, rather than therapist-driven; (2) data will be acquired in real-time, and data acquisition can be repeated over and over again during day, either at fixed or pre-determined intervals, or whenever the patient feels a necessity to enter data; (3) data will better reflect the "ebb and flow" of symptoms; and (4) this will allow examination of temporal relationships between variables with a short "life-cycle", not possible with standard interview questionnaires. A final advantage is also that an iPhone app will have high ecological validity in the sense that a patient going through these questions when, *e.g.*, sitting on a bus, will not stand out in any way. He or she will instead look like most other young people who listen to music or play games on their iPhones while on a bus, or elsewhere in today's digitized society. Figure 8 shows an example of a prototype display with the three dimensions shown in the display.

UNSOLVED ISSUES AND FUTURE DIRECTIONS

I have reviewed the current literature on the phenomenology, neuroimaging, and neurochemistry of AVHs. In particular the neuroimaging data, both structural and functional neuroimaging, support a view of AVHs as perceptual misrepresentations, caused by neuronal hyper-activation that results in a phenomenological experience as "someone speaking to the patient" despite the absence of an external auditory source for such an experience. In that respect AVHs are like perceiving sounds that do not exist. It is however quite conceivable that the phenomenological experience of a sensory event is caused by misinterpretations of inner speech and covert monologues, triggered by intrusive traumatic memories, which are two alternative models for the explanation of AVHs. Localization of the neuronal correlates of AVHs in the temporal lobes cannot however explain other cognitive aspects of AVHs, like the failure to cognitively inhibit and ignore the "voices", and focus attention to the outer world rather than inwards and engaging in a running commentary and dialogue with the "voice". The cognitive aspects of AVHs have been shown to implicate frontal and parietal brain regions, and a model is presented which sees AVHs as initiated by temporal lobe hyper-activation, not controlled due to frontal lobe hypo-activation in a cortical network. Despite the huge literature on AVHs, there are still unresolved issues and questions. One pertinent question is what cognitive and neuronal processes give the hallucination a negative emotional tone, which should be the focus for future research. One hypothesis is that the amygdala may play a critical role in the emotional flavoring of AVHs. Another unsolved issue is the possibility of a genetic predisposition for AVHs, orthogonal to genetic predisposition for schizophrenia in general (see[116] for an update on genetic factors in schizophrenia). The fact that AVHs also occur in the general population in individuals not in need of clinical care[11-12,96] provides a background against which it could be predicted that AVHs could be related to a genetic pathway orthogonal to genetic susceptibility for schizophrenia. These issues should be explored in future research, hopefully also in larger samples than has been the case so far.

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REVIEW

Olfactory function in psychotic disorders: Insights from neuroimaging studies

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Abstract

Olfactory deficits on measures of identification, familiarity, and memory are consistently noted in patients with psychotic disorders relative to age-matched controls. Olfactory intensity ratings, however, appear to remain intact while the data on hedonics and detection threshold are inconsistent. Despite the behavioral abnormalities noted, no specific regional brain hypoactivity has been identified in psychosis patients, for any of the olfactory domains. However, an intriguing finding emerged from this review in that the amygdala and pirifom cortices were not noted to be abnormal in hedonic processing (nor was the amygdala identified abnormal in any study) in psychotic disorders. This finding is in contrast to the literature in healthy individuals, in that this brain region is strongly implicated in olfactory processing (particularly for unpleasant odorants). Secondary olfactory cortex (orbitofrontal cortices, thalamus, and insula) was abnormally activated in the studies examined, particularly for hedonic processing. Further research, using consistent methodology, is required for better understanding the neurobiology of olfactory deficits. The authors suggest taking age and sex differences into consideration and further contrasting olfactory subgroups (impaired *vs* intact) to better our understanding of the heterogeneity of psychotic disorders.

Key words: Olfaction; Schizophrenia; Neuroimaging; Functional magnetic resonance imaging; Positron emission tomography; Single photon emission computed tomography

Core tip: Olfactory identification, familiarity, and memory deficits are consistently noted in patients with psychotic disorders relative to age-matched controls. Olfactory intensity ratings remain intact while olfactory hedonics and detection threshold show inconsistent findings. This review found no consistent differences in functional activity in amygdala and pirifom cortices in psychotic patients relative to control subjects.

Secondary olfactory cortices were abnormally activated in psychosis patients, however. Further methodologically consistent research is required for better understanding the neurobiology of olfactory deficits in psychotic disorders. The authors recommend examining sex differences contrasting olfactory subgroups (impaired *vs* intact) in future examinations.

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INTRODUCTION

Olfactory input, although mostly unconsciously processed and relatively ignored, colours our appreciation for food, influences our mood and warns us of impending danger (*e.g.*, spoiled food, smoke, chemical spill *etc.*). It is only when olfaction is impaired that humans begin to realize how much olfactory stimulation influences decisions in everyday life. In fact, olfactory compromise has been linked to depression[1] and for patients with traumatic brain injury, post traumatic anosmia is negatively linked to return to work after injury[2,3]. For individuals with neurodegenerative disorders, such as Parkinson's disease[4], Dementia (*e.g.*, Alzheimer's disease[5]), or psychotic disorders[6], olfactory decline may be one of the first symptoms subjectively noted. Consequently, formal assessment of olfactory function may allow for early identification of those at risk of developing these illnesses prior to the illness onset. Understanding the neurobiology of olfactory decline may prove useful to clinicians and allow for early detection, intervention and treatment.

In psychotic disorders, including schizophrenia, olfactory deficits are observable early in the course of illness, but progress very little, if any[7]. However, these olfactory problems may be a harbinger for poorer prognosis, both symptomatically and in terms of functional outcome[8,9]. A better understanding of olfactory compromise in these disorders is fundamental to better understanding the heterogeneity of illness course and symptoms. Further elucidating the neurobiology of olfactory deficits may provide further clues to the underlying brain abnormalities in this disorder.

The purpose of this paper, therefore, is to review the literature on olfactory function in patients with schizophrenia, paying particular attention to the neuroimaging data that has accumulated.

The olfactory system

Small postage stamp sized regions of superior aspect of each nasal cavity and upper portion of the nasal septum contain the olfactory epithelium. Within this region, specialized G-protein coupled olfactory receptors bind to inhaled volatile chemicals that have dissolved in the olfactory mucosa. Once odorants are bound to receptors, action potentials are initiated and are transmitted to the brain *via* the olfactory nerves. Axons project through fenestrations within the cribriform plate of the ethmoid bone and synapse on neurons (mitral and tufted cells) within the olfactory bulb. From here, signals project predominantly through the lateral olfactory tract to the primary olfactory cortex (including the piriform and entorhinal cortices, part of the amygdala and the olfactory tubercule). Collaterals from these axons project to the anterior olfactory nucleus. A minority of fibres project *via* the medial olfactory tract and cross, *via* the anterior commissure, to the contralateral olfactory bulb. However, the vast majority of olfactory projections are ipsilateral[10].

The olfactory system is unique among the senses as it projects initially to cortical regions, rather than thalamic nuclei. Thalamic connections occur post-cortically, along with projections from piriform cortex to other limbic regions, such as the hypothalamus and hippocampus. Projections to the orbitofrontal cortex can be either direct from primary olfactory cortex, or indirect *via* the dorsomedial nucleus of the thalamus[11].

A further differentiating factor that separates the olfactory system from other senses is that the signals from primary sensory receptors to higher processing regions are predominantly sent ispilaterally, rather than having a contralateral representation. This fact allows for the assessment of the relative contribution of each hemisphere to the processing of olfactory stimuli. If stimulus presentation is restricted to one nostril only, the ipsilateral hemisphere will be preferentially (initially) engaged. This anatomic detail has been exploited by some research groups and lateralized findings have been reported[12,13].

Olfactory dysfunction can occur as a result of damage at any level of the olfactory system, from destruction of the olfactory receptors due to exposure to inhaled chemical toxins, to deficits in olfactory detection threshold as a result of olfactory nerve/tract damage during closed head injury, to distinct higher level olfactory deficits (*e.g.,* olfactory agnosia) as a result of lesions to secondary olfactory cortex[14,15].

Olfaction in schizophrenia

Between 1%-3% of the population suffers from non-affective psychotic disorders, with schizophrenia being the most common form[16]. These disorders are associated with a diverse range of abnormal mental phenomena, including hallucinations, delusions, unusual thought content, anhedonia, social withdrawal and alterations in cognitive domains such as memory, attention, language and executive function. The typical age of onset of these disorders is relatively early, with most individuals presenting with their

first psychotic episode in late adolescence or early adulthood. For many, the course of illness is one of waxing and waning of symptomatology; few make a full recovery after one episode. The issue of whether olfactory sensitivity (detection threshold/acuity) is impaired in schizophrenia has not yet been resolved, with some studies showing normal acuity[17,18], others impaired[19,20] and still others demonstrating enhanced sensitivity[21,22]. As well, the issue of whether olfactory hedonics are abnormal in patients with psychotic disorders continues to be debated[19,23-27]. There is evidence that pleasantness ratings differ by sex[28,29] and are likely related to symptom presentation[30,31]. More consistent findings have emerged when olfactory discrimination (same as/different) and olfactory memory/familiarity are assessed. Patients with psychotic disorders appear to be impaired on both of these functions[26,32,33]. Odour intensity ratings, however, appear to be intact in patients with psychotic disorders[26].

The most robust difference between patients with psychotic disorders and control subjects has been noted in studies examining olfactory identification ability. In these investigations, consistently abnormal olfactory identification has been shown in psychosis patients[7,9,18,30,34]. Olfactory identification deficits do not appear to be influenced by age of illness onset[17,34], smoking history[17,35], exposure to antipsychotic medications[13,17,32] or cannabis use[7]. Olfactory identification deficits, however, are thought to correlate with measures of verbal memory function[36,37], and negative (but not positive) psychotic symptoms[7,9,34]. Recent research has shown that olfactory compromise may be a marker for poorer outcome. Good *et al*[8] examined symptomatic outcome in a group of patients who were antipsychotic drug naive at initial olfactory testing. Poorer negative and cognitive symptom outcome was associated with a lower baseline olfactory identification (UPSIT) test score. This same group prospectively followed a group of first episode patients for 4 years[9]. Those with poorer olfactory scores at initial assessment had worse symptom outcome and reduced functional outcome at follow up. Additionally, individuals who are at risk for developing a psychotic disorder (by virtue of having a first degree relative with the disorder and/or showing attenuated psychotic symptoms), having lower olfactory test scores appears to be related to the conversion to a true psychotic disorder[6]. Taken together, these findings suggest that not only may olfactory deficits predict transition to illness, but that subgroups may be identified, early in the course of illness, who may be at risk for a more severe illness course.

Overlap between olfactory processing and pathology in schizophrenia

That patients with psychotic disorders have olfactory dysfunction is not surprising given the overlap between olfactory processing regions and areas of the brain that have been consistently noted as abnormal in these patients. Abnormalities in medial temporal regions, including the hippocampus, amygdala and parahippocampal gyrus have been observed in patients with psychotic disorders. For a review, see[38,39]. Moreover, orbitofrontal and dorsomedial nucleus of thalamus have also been found to be both structurally and functionally abnormal[40,41]. Left sided abnormalities are more commonly reported[42].

NEUROIMAGING OF THE OLFACTORY SYSTEM IN HEALTHY INDIVIDUALS

The olfactory system has been well described anatomically (see above). However, recent neuroimaging studies have revealed a more widespread network of interrelated olfactory brain regions required for different aspects of olfactory processing. For example, although the piriform cortex is reciprocally connected with the olfactory bulb, functional magnetic resonance imaging (FMRI) studies have reported that piriform cortex activation is most robust during active "sniffing" of the odorants, and not during passive odours presentation such as when subjects are instructed not to purposely inhale the odorants[43] but see also[44]. However, the primary olfactory cortex appears to habituate more quickly than other brain regions and thus may be a better reason why consistent activation is not found in this brain region in all studies. The insula and anterior cingulate cortex are not necessarily associated with olfaction *per se*; however, activation in these regions has been demonstrated relatively consistently during odour presentation, suggesting a role in higher-order olfactory processing[45] (Table 1).

Passive Odour presentation

Brain regions that are activated after presentation of odours when subjects are instructed not to sniff or nor consciously process the odorants include areas associated with primary olfactory cortex [piriform cortex (however, see above), amygdala, hippocampus, entorhinal cortex] and secondary olfactory regions (thalamus, orbitofrontal cortex, cingulate and insula)[46-49]. These regions can be thought of as "core" olfactory regions. When olfactory-cognitive load is increased, other ancillary regions are also engaged.

Odour "sniffing" vs smelling

As previously mentioned, the piriform cortex may be activated solely in the presence of active "sniffing" or nasal airflow[43,50]. A more recent positron emission tomography (PET) study, however, did not confirm these results[44].

Odour hedonics: Humans are particularly poor at naming odours *de novo* (see section below). However, odours can evoke very strong emotional reactions, even without conscious awareness. Consequently,

Table 1 Description of the olfactory methods used to examine different olfactory domains

Olfactory domain	Methods by which this domain is assessed
Passive smelling	Odorant is presented passively to the subject. Imaging done without response or overt cognitive appreciation
Olfactory detection	Similar to passive smelling, however, the subject must press a button to signal the onset of the odorant perception
Odour "sniffing"	Subjects are given instructions to inhale the odorant during presentation
Olfactory intensity	Rating the odorant as to its perceived strength. Can be done by a button press (Is the odour "strong"?) Intensity may be assessed by ratings of odorants (*e.g.*, VAS) outside of the scanner and presenting odours that have been rated on opposite ends of the continuum (very strong *vs* very weak)
Olfactory familiarity	Recollect prior exposure without the exact autobiographical context and also without naming. Button press if odour is "familiar"
Olfactory hedonics (valence)	The determination of pleasantness of the odorant. Button press to rate whether an odorant is pleasant Pleasant/Unpleasant odorant rated (*e.g.*, VAS) outside of the scanner and presenting odours that have been rated on opposite ends of the continuum (very unpleasant to very pleasant)
Olfactory identification	Correct identification- those items that are correctly labeled *vs* those for which label is incorrect Olfactory identification test score used to capture most impaired, compared with normal sense of smell Forced choice odour naming during scanning

the primary dimension by which humans characterize odorants is according to the odour's pleasantness, and particularly when odorants are difficult to name[51]. Researchers have capitalized on this aspect of olfactory processing in imaging studies; but unfortunately, mixed findings have resulted. The data is clear on one point: pleasant and unpleasant odorants invoke activation in similar neural networks, (primary and secondary cortices). However, intensities and degree of engagement may differ and some unique brain regions may also be invoked[52], particularly for unpleasant/aversive odorants. Both pleasant and unpleasant odorants activate the bilateral piriform/amygdala[45,53,54] but see also[55], right[49] and bilateral insula[45,56], and orbitofrontal cortex[49,53,54,57,58]. Most contrasts between pleasant (P) and unpleasant (UP) odorants have shown a greater degree of activation in the UP-P subtraction, rather than the other way around (P-UP). To this end, aversive or unpleasant odorants appear to further engage orbitofrontal cortex[54] - but only when subjects are engaged in a hedonic estimation task, and the activation seems to be concentrated in the lateral aspect rather than medial subdivisions[58]. Moreover, the left insula[45,52], but see also[56] who showed insular activity predominantly during pleasant odour stimulation), the anterior cingulate[45,52,58], brainstem/hypothalamus[52], and piriform/amygdala[45] activation has been noted after unpleasant odor presentation over and above that demonstrated during pleasant odorant stimulation.

Odour familiarity: Determining whether an odour is familiar requires an implicit set of memory processes; the perceptual input needs to be compared with semantic odour associations[59]. The smeller must recollect prior exposure without the exact autobiographical context and also without naming. Only few studies have examined this aspect of olfactory processing. In 1999, Royet *et al*[60] examined, among other aspects of olfactory processing, odour familiarity in healthy subjects. In this study, they demonstrated right orbitofrontal cortex activation during odour familiarity ratings, suggesting a lateralization of secondary olfactory cortical function. In a later study by this same group, Royet *et al*[57] noted a larger network of olfactory brain regions associated with odour familiarity. Bilateral orbitofrontal cortex (OFC), anterior cingulate along with left superior and right middle frontal gyri were all active during a PET scan during which an odour familiarity task was compared to control activation (presentation of odorless air). When compared with odour detection, left superior and left inferior frontal gyri engagement was noted, suggesting a hierarchical process, with odour familiarity ratings at higher levels of processing. This group suggested that the lateral frontal activation may represent accessing stored representations.

Odour intensity: A further dimension of odour processing is that of rating odour intensity. Odour pleasantness ratings change as a function of an odour's perceived intensity. For example, the rose-like odorant (phenyl ethanol) tends to be perceived as pleasant at lower concentrations, but less pleasant at higher concentrations[61]. In many studies assessing olfactory hedonics, the intensity of presented odorants was not controlled. In order to dissociate intensity and valence, Anderson *et al*[54] focused on the amygdala and the orbitofrontal cortex. The amygdala has been reliably shown to activate during presentation of aversive stimuli[62]. The orbitofrontal cortex, as mentioned previously, appears to be invoked in higher order processing of olfactory stimuli. By presenting two different odorants at two different concentrations (high intensity-unpleasant, high intensity-pleasant, low intensity-unpleasant, low intensity-pleasant), Anderson *et al*[54] noted that that the orbitofrontal cortex engaged in relation to the valence of the odorant while the amygdala was preferentially engaged according to the intensity of the odorant. No ratings were performed during the scan; rather, subjects were only

instructed to "sniff" for the duration of a presented message and respond if an odour was detected. A more recent study lent some further explanation to this unexpected finding. Winston *et al*[63] replicated the Anderson *et al*[54] study, but included both high- and low-intensity neutral odours for comparison. In this study, the amygdala was engaged predominantly with both the pleasant and unpleasant high-intensity odors, but not the high intensity neutral odour (nor any of the low intensity odours either). A more parsimonious explanation was suggested by these researchers in that the amygdala is engaged when odours are encountered that may be relevant for survival. High intensity pleasant or unpleasant odours are more likely to be behaviorally salient than are neutral odours (or low intensity odours along the hedonic spectrum).

Olfactory identification: Odor naming, particularly when potential exemplars are not provided, is a difficult task for humans[64,65]. By providing a multiple-choice format, such as the University of Pennsylvania Smell Identification Test (UPSIT), performance is improved significantly[61].

In a recent study, Kjelvik *et al*[47] examined whether there were any differences in activation patterns when individuals were successful in naming odorants *vs* when they incorrectly named the odours. Odorants were presented to subjects (only women) during an FMRI scan. Post scanning, subjects were presented with these same odours and were instructed to spontaneously name them (no exemplars provided). Brain activation patterns differed between correctly identified odours *vs* those not correctly identified in left entorhinal cortex, bilateral temporal poles, orbitofrontal cortex (right moreso than left), right thalamus and left insula. Other, non-olfactory areas (*e.g.*, putamen, primary visual and auditory cortices, premotor cortex, SII and cerebellum, inferior frontal, and fusiform area) were also activated more during identified *vs* non-identified odours. When specifically examining the medial temporal regions, left entorhinal cortex, and bilateral posterior parahippocampal gyri were engaged. The data suggested that the entorhinal cortex and the hippocampus are more attuned to identifying odours.

Sex differences: Many of the studies mentioned above (*e.g.*,[47,55]) examined only female subjects as women reliably outperform men on olfactory detection, memory and identification tasks[66-68]. Three different research groups have examined whether this female olfactory superiority translates into enhanced brain activity. In an early FMRI study, Yousem *et al*[69] noted that female brains had significantly more active voxels in the perisylvian and inferior frontal regions during odour presentation. Levy *et al*[53], using a ratio of pixel activated to the number of pixels in a region, also showed sex differences; However, their findings were in the opposite direction (males > females). In contrast, Bengtsson *et al*[70] were unable to detect any male/female differences in brain activation during passive perception of odours. This group suggested that males and females engage similar networks during low level processing of olfactory stimuli. However, due to methodological inconsistencies, the intensity of activation was not examined in this PET study, making comparisons with other papers data difficult. In contrast, Royet *et al*[45] found that women activated the left orbitofrontal cortex over and above what was noted in male brains. The differences again may prove to be related to methodological differences, or rather due to the processing demands placed on the subjects during olfactory scanning (for part of the study, subjects in the Royet *et al*[45], study were asked to make an hedonic judgment regarding the odours presented while Bengtsson *et al*[70] were examining olfactory processing during passive administration). Nevertheless, these data taken as a whole, suggest that sex differences should be taken into account when examining olfactory brain activations.

Age

As the ability to perceive odours deteriorates with age, do functional alterations in brain regions associated with the sense of smell also accompany these changes? A study published by Wang *et al*[71] noted that there were significant differences in the processing of olfactory stimuli when comparing young and older subjects. Although for both groups, the same regions were activated by odorants, lower cluster volumes and intensities were noted in the aged group when compared to the younger group. This finding suggests that age should be taken into consideration when examining neural activation to olfactory stimuli (Table 2).

NEURAL SUBSTRATES OF OLFACTORY PROCESSING DEFICITS IN PATIENTS WITH PSYCHOTIC DISORDERS

Although many studies exist demonstrating olfactory deficits in patients with psychotic disorders, only few neuroimaging investigations have been published to date examining the relationship of olfactory deficits to neural abnormalities.

Passive odour administration

Odour activation patterns are similar between patients with psychotic disorders and control subjects during passive odour administration[25]. However, there are some differences regarding the intensity or cluster volume in these regions between patients and control subjects. Plailly *et al*[25] examined olfactory detection (passive odour administration), hedonics and familiarity using PET. A moderately sized sample of patients with schizophrenia and healthy controls were presented with odours during the scan and were instructed to press a button when they detected an odour (for the detection condition), if the odour was pleasant (for

Table 2 Olfactory studies

Ref.	Authors	Year	Modality	Subject group(s)	Finding
	Passive smelling				
[46]	Zatorre *et al*	1992	PET	Healthy subjects	Piri (B) and OFC (RH)
[53]	Levy *et al*	1997	FMRI	Healthy subjects	P and UP: piri, amyg, hippocam, cing and post inf front cortex (laterality not specified)
[43]	Sobel *et al*	1998	FMRI	Healthy subjects	Passive smelling, lat OFC; Sniffing-piri (B) and post OFC (B)
[48]	Savic *et al*	2000	PET	Healthy subjects	OFC (RH), amyg/piri (RH), thal (RH), insula (LH), ant cing
[49]	Gottfried *et al*	2002	FMRI	Healthy subjects	P and UP: Amyg (B), post OFC (B), post piri (B), insula (RH)
[45]	Royet *et al*	2003	FMRI	Healthy subjects	UP and P odorants-piri/amyg, hypothal, sup temp, insula and OFC, ant cing
[44]	Kareken *et al*	2004	PET	Healthy subjects	Piri (B), amyg (B), insula (B); sniffing lateral OFC (B)
[47]	Kjelvik *et al*	2012	FMRI	Healthy subjects	Piri (B), amyg (B), OFC (B) and thal (B) cing (RH), insula (LH)
[25]	Plailly *et al*	2006	PET	Psychosis patients	HC > SZ Piri (LH) and inf front (LH) SZ > HC insula (RH)
	Good *et al*	Under review	FMRI	Psychosis patients	HC > SZ thal (RH), caud (B), ant cing, OFC (B only midly greater), mid temp gyrus (B)
	Hedonics (Valence)				
[55]	Zald *et al*	1997	PET	Healthy subjects	Aversive odorant- amyg and OFC; less aversive- only OFC (LH)
[56]	Fulbright *et al*	1998	FMRI	Healthy subjects	Pleasant- BA 46/9 (RH), 32 (LH), 8 (B) 6 (RH) and insula (B); Unpleasant- 46/9 (RH), 32 (LH), 6 (B), insula (RH)
[57]	Royet *et al*	2000	PET	Healthy subjects	Hedonic judgement- ant cing, OFC (LH), sup front (LH), midd front gyrus (LH), inf midd temporal (LH)
[49]	Gottfried *et al*	2002	FMRI	Healthy subjects	UP: insula (RH), lat hypothal (LH), amyg (RH), post OFC (L); P: piri (RH), insula (RH), post OFC (RH)
[45]	Royet *et al*	2003	FMRI	Healthy subjects	Hedonic valence -UP > P: piri (LH), amyg (LH); P > U: cing (LH)
[58]	Rolls *et al*	2003	FMRI	Healthy subjects	P: med OFC; ant cing
[54]	Anderson *et al*	2003	FMRI	Healthy subjects	
[72]	Crespo-Facorro *et al*	2001	PET	Psychosis patients	HC > SZ P *vs* UP: insula (LH), para hipp (LH), sup temp gyrus (LH), accumbens (RH), lingual gyrus (B), cb. vermis (LH) SZ > HC Med OFC (B), DLPFC (B), med front (LH), lat front (RH), lat front (LH), front operculum (LH), parahipp (RH), post cing (LH)
[25]	Plailly *et al*	2006	PET	Psychosis patients	HC > SZ Insula (LH) and Inf front (LH)
[27]	Schneider *et al*	2007	FMRI	Psychosis patients	HC > SZ UP: Midd temp gyrus (RH) Midd front gyrus (RH) Insula; P: thal (L) SZ > HC UP: Midd front (RH) ant cing (RH)
	Intensity				
[54]	Anderson *et al*	2003	FMRI	Healthy subjects	Amyg (B)
[63]	Winsto *et al*	2005	FMRI	Healthy subjects	Amyg, (but only at the extremes of valence), OFC and piri
	Familiarity				
[60]	Royet *et al*	1999	PET	Healthy subjects	Med frontal (RH), inf front (LH), sup front(LH) cingulate (B)
[57]	Royet *et al*	2000	PET	Healthy subjects	OFC (B), ant cing, sup front (LH) midd front (RH)
[25]	Plailly *et al*	2006	PET	Psychosis patients	HC > SZ piri (LH), sup temp gyrus(LH), gyrus rectus(RH), OFC (LH), inf OFC (LH)
	Identification				
[47]	Kjelvik *et al*	2012	FMRI	Healthy subjects	Correctly identified entorhinal cortex (LH), Hippocam (RH), parahippocam gyrus (B), OFC and piriform cortices Incorrectly identified: OFC and piri cortices
[73]	Clark *et al*	1991	PET	Psychosis patients	HC > SZ front (B) parietal (B); Norm > Micro thal (RH) and basal ganglia
[33]	Malaspina *et al*	1998	SPECT	Psychosis patients	HC > SZ inf. Front (RH), sup temp (RH) supramarg/angular gyrus (RH) HC (but not SZ) hippocam(B), fusiform(RH)
	Genetic Trait				
[27]	Schneider *et al*	2007	FMRI	Psychosis patients	HC > FDR UP: mid front gyrus(RH) FDR > HC P: ant cing(LH)

FMRI: Functional magnetic resonance imaging; PET: Positron emission tomography; SPECT: Single photon emission computed tomography; HC: Healthy controls; SZ: Schizophrenia patients; FDR: First-degree relatives; UP: Unpleasant; P: Pleasant; B: Bilateral; LH: Left hemisphere; RH: Right hemisphere; ant: Anterior; post: Posterior; lat: LAteral; inf: Interior; sup: Superior; midd: Middle; temp: Temporal; front: Frontal; Amyg: Amygdala; piri: Piriform cortex; hippocam: Hippocampus; OFC: Orbitofrontal cortex; ant cing: Anterior cingulate; thal: Thalamus; hypothal: Hypothalamus; parahippocam: Parahippocampal; DLPFC: Dorsolateral prefrontal cortex.

the hedonic condition) and if it was familiar (for the familiarity condition). For the detection condition, this group noted that the piriform cortex and the orbitofrontal cortex (inferior frontal) were activated in both groups. However, small clusters remained in these two regions when a subtraction analysis (HC-SZ) was performed. So, although both primary and secondary cortices were activated in both groups, patients with psychotic disorders appeared to show less robust activity in these two regions. Our group has recently examined passive odour administration in a group of patients with non-affective psychosis (Good *et al*, under review). We noted that patients and controls had similar activation patterns in amygdala, OFC and left thalamus, but the subtraction analysis (HC-SZ) showed slightly greater activation in OFC and

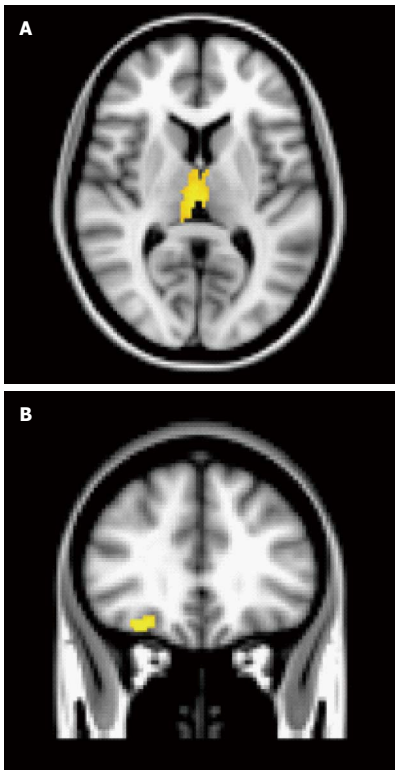

Figure 1 Neural activation for passive smelling in controls-patients. For both locations (thalamus and right orbitofrontal), controls showed significant activation relative to psychosis patients that was unrelated to sex. A: Thalamus; B: Right orbitofrontal. From Good *et al* (under review).

left thalamus. In contrast, controls, but not patients, activated right thalamus, caudate (bilateral), cingulate, middle temporal gyrus and frontal pole (Figure 1).

Hedonic processing

In contrast to passive odour administration, other aspects of olfactory processing appear to engage different brain regions between patients and control subjects. As previously mentioned, rating the pleasantness of odorants is an automatic process and may have survival significance, particularly if the odour is intense. As described above, in patients with psychotic disorders, their ability to rate odour pleasantness may be abnormal. In imaging studies, significant patient/control differences have emerged and show some contrasting findings. For instance, in the PET study published by Crespo-Facorro *et al*[72], patients were impaired on rating the pleasantness of pleasant odours, but no differences were noted between patients and control in neural processing of these same odours. In contrast, patients did not differ from control subjects on ratings of unpleasant odours; however, neural activation did differ. Control subjects engaged the left anterior insula, left parahippocampal gyrus, left superior temporal gyrus, lingual gyrus (bilateral) and left cerebellar vermis along with right accumbens when contrasted with unpleasant *vs* pleasant odorants, while patients did not. Interestingly, patients demonstrated higher metabolic rates in other brain regions relative to the controls, suggesting that patients invoked compensatory structures during processing. These regions included a number of right hemisphere regions (dorsolateral, lateral and parahippocampal gyrus) and left hemisphere activations (dorsolateral, medial and lateral frontal along with posterior cingulate). In a more recent PET study[25], where both positively and negatively valenced odorants were compared together, greater regional cerebral blood flow (rCBF) was noted in the left insula and left inferior orbitofrontal regions in control subjects relative to patients (Figure 2).

In an FMRI study, hypoactivity of right middle temporal and right middle frontal (BA 46) cortices in patients with psychotic disorders relative to controls during the presentation of a negatively valenced odorant; a relative hyperactivity was also seen in the middle frontal gyrus (in BA 9) and right anterior cingulate in patients. During presentation with a pleasant odorant, left thalamic hypoactivation was noted in patients relative to controls. In the presentation of both types of odorants, insular hypoactivation just missed statistical significance. Unfortunately, unpleasant and pleasant odours were never compared to each other in this study[27].

Taken together, despite different methodology and analytic techniques, the data presented suggest that dysfunction in secondary olfactory cortices and perhaps the insula may account for the olfactory hedonics dysfunction in patients with psychotic disorders. As no group noted differences in amygdala and piriform cortex activations suggest that primary olfactory cortices may be normally activated in these patients.

Odour intensity

The neural underpinnings of processing odour intensity have not been contrasted between patients and control subjects. But as mentioned previously, no differences between these two groups have been noted on odour intensity ratings. Nevertheless, future research should examine this dimension of olfactory processing.

Odour familiarity

Determining whether an odorant has been experienced before appears to further engage frontal brain regions (see above). When patients with psychotic disorders were compared with control subjects on a familiarity task, hypoactivity of piriform cortex, orbitofrontal and superior temporal gyrus (all on the left) was observed[25]. This study also noted that patients rated odours as less familiar than did healthy controls. It was suggested that impaired familiarity ratings may be accounted for by temporolimbic/orbitofrontal dysfunction.

Odour identification deficits

The neural underpinnings of olfactory identification have not been adequately examined in patients with psychotic disorders, despite the fact that olfactory identification deficits are the most robust finding in this patient group. Malaspina *et al*[33] were the first

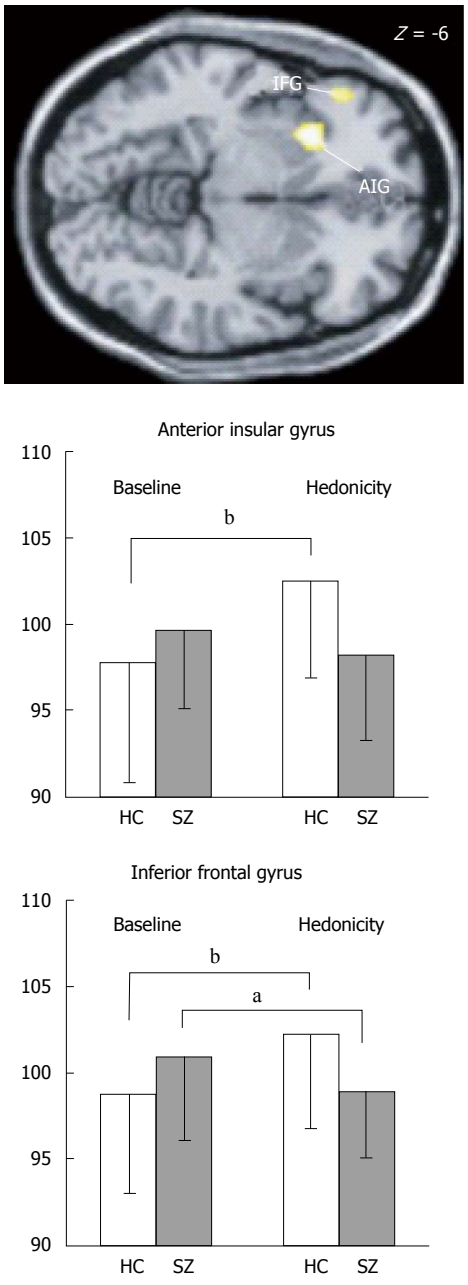

Figure 2 Figure showing difference between hedonic processing and baseline (air) for patients with psychotic disorders and control subjects. Differences in activation were noted between patients and control subjects in anterior insula and inferior frontal gyrus. Controls had enhanced activation in both sites for the hedonicity condition (relative to baseline) while for the anterior insula, patients showed no increase and for inferior frontal regions patients saw a statistically significant decrease in regional cerebral blood flow (H-B). Reprinted with permission from Plailly *et al*[25]. $^{a}P < 0.05$, $^{b}P < 0.001$.

to examine olfactory identification using SPECT. In this study, a small sample of patients with psychotic disorders and controls were scanned while engaging in a forced-choice odour identification test and a comparator picture matching test. Differences in rCBF between the two tasks included hypometabolism in patients in inferior frontal, superior temporal and supramarginal/angular gyri (on the right). Controls, but not patients engaged right fusiform gyrus and bilateral hippocampi during the odour activation task relative to the control task. The right-sided deficits are consistent with lesion data showing more severe deficits in odour identification after rights than left sided lesions. However, the data is not entirely consistent with the majority of neuropathological studies of schizophrenia showing a predominance of left sided structural abnormalities. Moreover, there was no examination of the differences in odour activation according to the correctness of identification of the odorants.

As it appears that only a proportion of patients demonstrate abnormalities on olfactory identification testing, dividing the groups of patients into those who are impaired *vs* those who have normal olfactory function, may have merit. Clark *et al*[73] examined glucose metabolism in three groups of subjects: a group of patients with olfactory agnosia (impaired olfactory identification ability and normal olfactory detection), a group of patients with normal sense of smell (normosmic) and healthy controls (age matched). PET scanning occurred in the absence of any olfactory stimulation (resting state). In all brain regions, the agnosia patient group had the lowest metabolic rates compared to the other two groups, followed by the normosmic patients and then controls. Controls had higher rCBF than both patient groups in bilateral frontal and parietal regions. The two patient groups differed from each other on right thalamus and basal ganglia metabolism (olfactory agnosia group lower than normal olfactory group). The results of this study are consistent with earlier reports of structural and functional abnormalities in thalamic and basal ganglia. As no olfactory task was presented, these data suggest an underlying hypofunction in regions of the brain that subserve olfactory processing, rather than a processing abnormality. Nevertheless, the heterogeneity of schizophrenia should be taken into account, or at least acknowledged, when examining the neural underpinnings of olfactory function in patients with psychotic disorders. Further investigation is required.

Genetic trait

Not only do patients with psychotic disorders exhibit abnormalities in olfactory processing, but their unaffected first-degree relatives also demonstrate mildly abnormal brain activation patterns when contrasted to non-related controls[27]. When presented with an unpleasant odour, patients' unaffected brothers demonstrated reduced frontal activation (relative to the healthy control group) and increased activation in anterior cingulate, but during the presentation of a pleasant odorant, no differences were noted. This group suggested that hypofrontality may be a genetic trait that is expressed to a lesser degree in the non-affected brothers.

Age

Despite age being considered an important factor to consider in olfactory neuroimaging research[71], to date, no studies have examined the difference in olfactory neural processing between young and older patients

with psychotic disorders. In all studies presented in this literature review, the age of the patients and that of control subject have been well matched and also relatively young (Mean ages < 35 years). Further research may be informative in this regard.

LIMITATIONS

While many olfactory neuroimaging studies of healthy subjects have recruited and assessed only female subjects, the data on patients with psychotic disorders has been strongly biased towards male patient data. Therefore, what is thought of as "normal" may be only normal for women and the comparison with male patients with psychotic disorders may not be appropriate. For example, only male patients were examined in the studies published by Schneider *et al*[27], Clark *et al*[73], and Plailly *et al*[25] and investigations by Crespo-Facorro *et al*[72] and Malaspina *et al*[33] contained samples that were predominantly male. Only Turetsky *et al*[20] (not described) and Good *et al* (under review) examined almost equal numbers of males and female subjects. The data on sex differences in olfactory processing is not fully developed; however, in patients with psychotic disorders, the overwhelming number of sex differences is a very important aspect of the disorder and is likely overlooked in neuroimaging studies of this population.

Not all patients with psychotic disorder are impaired on olfactory testing. Some of the data provided herein suggest that may be subgroups within the heterogenous diagnostic category "schizophrenia". Not only are there potential differences in brain activation, but there are within diagnostic group differences in symptomatology and outcome[8,9]. Further investigations are needed to tease out the differences within schizophrenia.

A further limitation on the data that were presented is that patients and controls differ on many variables that are related to brain activation patterns. Most patients are medicated with antipsychotic medications. Very few studies were upfront about how much this variable may have affected their results. Clark *et al*[73] showed hypoactivation in almost all brain regions across the three groups examined (olfactory agnosia-patient, normal sense of smell-patient, healthy controls), but pointed out that cerebellar metabolism did not differ among the groups. They argued that this evidence suggested that state variables may not be responsible. Moreover, since the two patient groups differed in metabolism in specific olfactory brain regions also argues against antipsychotic medication being a causative factor. No imaging studies have examined antipsychotic naïve or withdrawn patients. The effects of antipsychotic medications on neuroimaging outcomes continue to be unknown. Moreover, patients with psychotic disorders are also more likely to be heavy consumers of tobacco and caffeine. Both of these substances are found to impact on activation patterns. Very few studies have controlled for smoking status (and pack-years) and none have examined caffeine use (particularly prior to scanning). These two variables should be examined more closely to uncover any effects on resultant activation maps between patients and controls. Finally, examining the effects of age in this population may be worthwhile and may provide further insights into changes in brain activity in olfactory regions with aging.

Finally the unique and varied protocols used make for a more challenging task to understand the contribution to olfactory dysfunction in patients with psychotic disorders. Whether resting state activation abnormalities are similar to that noted when patients are engaged in different olfactory tasks (*e.g*., hedonic ratings *vs* passive presentation of pleasant and unpleasant odorants; PET *vs* FMRI *vs* SPECT) is unknown. Further, more extensive research is needed to parse out the effects of each type of odour presentation/protocol.

CONCLUSION

Psychosis is linked to observable olfactory deficits in many different olfactory domains. Olfactory identification deficits tends to be most commonly reported, likely because of the availability of standardized tests. Olfactory familiarity and memory are also robustly affected in this disorder. Olfactory intensity ratings are not noticeably impaired in these patients. Olfactory hedonics and detection threshold, however, are more troublesome as the methods by which researchers have examined these domains differ markedly. It is not surprising, therefore, that conflicting results have been published. Nevertheless, the noted deficits do not appear to be state-related and may be predictive of poorer outcome.

Olfactory pathways are overlapping with areas of the brain that are found to be abnormal in schizophrenia/psychosis an assessing this sense may provide a good indicator of the integrity of different brain regions. Adding in neuroimaging techniques, we may be better able to disentangle the varied neurobiological substrates of olfactory deficits. Moreover, olfactory assessment, along with neuroimaging methods may provide a way to further our understanding of the heterogeneity of psychotic disorders

The differing methodologies employed by neuroimaging studies hampers the ability to make firm conclusions about which brain regions are impaired in patients with psychotic disorders, particularly when presented with olfactory processing demands. Hypoactivation of various brain regions is a robust finding when patients with psychotic disorders are compared with healthy, age-matched controls. What regions are hyper/hypofunctional when faced with olfactory stimuli and cognitive assessment of these inputs is still under examination. One thing is clear: patients activate the same regions as controls when faced with olfactory processing demands.

However, the degree of activation may be reduced in patients with psychotic disorders. Furthermore, if compensatory regions are invoked in patients above and beyond control subject activation, this finding requires replication as it has only been examined in one study[72]. One interesting finding emerged, however. In olfactory imaging studies of healthy controls, particularly when subjects are presented with unpleasant odorants, the amygdala is typically engaged. In neuroimaging studies examining odorant processing in patients with psychotic disorders, the amygdala was not once identified as being abnormal. Piriform cortex, as well, was not noted to be abnormally activated in patients during hedonic processing. Secondary olfactory cortex (orbitofrontal cortex, thalamus and insula), on the other hand, was noted to be abnormally activated in the neuroimaging studies examined. The lack of amygdala abnormalities may have been as a result of an inability to discern the amygdala from piriform cortex. However, masking templates for use in neuroimaging research have reliably delineated this region. Moreover, given that piriform cortices have been noted to habituate more quickly than other brain regions, this fact may be responsible for the lack of abnormalities in piriform/amygdala activation (*i.e.*, no activity may be as a result of neurobiological constraints rather than a lack of difference between groups). However, given that this review encompassed data collection using many different imaging modalities and unique protocols (some with odor presentations in the range of 2 s), this explanation is unlikely. This interesting avenue of research will undoubtedly grow and provide more insights as imaging techniques continue to improve.

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Inter-relationships between isotretinoin treatment and psychiatric disorders: Depression, bipolar disorder, anxiety, psychosis and suicide risks

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Abstract

Isotretinoin (Accutane) is a treatment for severe acne that is resistant to other forms of treatment, including antibiotics and topical treatments. The prescription of this drug has been controversial ever since its initial marketing in 1982. It is the only non-psychotropic drug in the Food and Drug Administration top 10 drugs found to be associated with depression. Recently, Bremner *et al* published an extensive review (until 2010) of the evidence for the association of retinoic acid (RA) with depression and suicide. Some patients who are admitted in psychiatric hospitals report a history of present or past treatment with isotretinoin. Then, the imputability of the molecule in the occurrence of disorders represents necessarily an important question for both professionals and their patients. This paper aims to specify the links between the drug and specific psychiatric disorders. A review of the literature related to isotretinoin, RA, vitamin A, depression, suicide, anxiety, bipolar disorder, psychosis, schizophrenia was performed. Many studies demonstrated an increased risk of depression, attempted suicide and suicide following isotretinoin treatment. However, isotretinoin may have an antidepressant impact, according to some dermatological papers. They consider treating acne with this efficient treatment could improve self-image and make the patient feel better. Several studies showed that patients with bipolar disorder had an increased risk for a clinical exacerbation of symptoms undergoing treatment with isotretinoin. A few studies also seem to suggest a possible link between isotretinoin and psychosis. Nonetheless, studies point out a link between retinoid dysregulation and schizophrenia through modulation of dopamine receptors. From this review, we propose guidelines for isotretinoin prescription to healthcare professionals.

Key words: Isotretinoin; Retinoic acid; Vitamin A; Suicide; Anxiety; Bipolar disorder; Psychosis; Schizophrenia

Core tip: Isotretinoin is a treatment for severe acne. The prescription of this drug has been controversial ever since its initial marketing in 1982. This paper aims

to specify the links between the drug and psychiatric disorders such as depression, suicide, anxiety, bipolar disorder and psychosis. Many studies demonstrated an increased risk of depression, attempted suicide and suicide following isotretinoin treatment. Several studies showed that patients with bipolar disorder had an increased risk for a clinical exacerbation of symptoms undergoing treatment with isotretinoin. A few studies also seem to suggest a possible link between isotretinoin and psychosis. From this review, we propose guidelines for isotretinoin prescription to healthcare professionals.

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INTRODUCTION

Since 1982 the United States Food and Drug Administration (FDA) has approved isotretinoin for the treatment of cystic and nodular acne that is not responsive to other forms of treatment (including antibiotics). Isotretinoin [13-cis retinoic acid (RA)] belongs to retinoids, a group of compounds derived from the essential nutrient vitamin A, which performs a large number of functions in many systems among them the central nervous system (CNS). The majority of these functions are performed by RA, the most active form of vitamin A, which binds to retinoic receptors to control gene expression in the brain. Thirty years later, the prescription remains controversial[1]. Drug regulatory agencies worldwide are now warning isotretinoin-treated patients about the risk of potential psychiatric side effects, particularly of depression and suicide[2].

Since its first use, many studies alert about a possible correlation between the use of isotretinoin and psychiatric disorders. In 2005, the FDA established a black box warning for suicide, depression, aggression and psychosis. The first aim of this article is to list the literature (from pubMed) in order to specify links between isotretinoin and depression, anxiety, bipolar disorder, and psychosis. A lot of papers respond to the only two keys words isotretinoin and depression. Among all these papers, we chose to select those that enable to show the differences between both psychiatric and dermatological points of view. Thus, forty-one papers were included.

Finally, we propose guidelines for isotretinoin prescription to healthcare professionals.

Isotretinoin and CNS

It is now established that isotretinoin is highly teratogenic, especially regarding the CNS. Fetal malformations as exencephaly, prosencephaly and hydrocephalus have occurred[1]. More recent works suggested that RA may influence the adult brain.

Bremner *et al*[2] highlights RA function in the striatum, hippocampus, frontal cortex and hypothalamus, brain areas all involved in depression.

13-cis RA may cause a dysregulation of neurotransmitters in striatum and hippocampus (in particular the dopaminergic system) and an inhibition of hippocampal neurogenesis[2,3].

In 2005, Bremner *et al*[2,4] studied the influence of isotretinoin on brain metabolism measured by Positron Emission Tomography Fluorodeoxyglucose. They showed a significant reduction in orbitofrontal cortex (a brain region associated with depression) metabolism after a 4-mo of isotretinoin treatment.

The study exposed a correlation between decreased orbitofrontal metabolism and headache during the treatment. Subjects sensitive to isotretinoin-induced effects on the CNS such as headache may also be susceptible to other neuropsychiatric side effects, such as depression[2,4,5].

Retinoids may lead to a decrease in orbitofrontal functioning *via* their effects on the hippocampus, a brain area that modulates dopaminergic function in the orbitofrontal cortex. The hypothesis of a dysregulation in hippocampal-orbito-frontal function caused by isotretinoin could explain how it contributes to promote depression[4].

The RA has also an action in the hypothalamus[2,6]. Shearer *et al*[6] have identified the synthesis of RA in tanycytes (by the retinaldehyde deshydrogenase) and the presence of RA receptors in hypothalamus neurons. RA can be released into the hypothalamus and regulate a number of genes among them those implicated in corticotropin-releasing hormone (CRH) synthesis.

Chen *et al*[7] highlights an increased density of receptor acid retinoic α-expressing cells in the hypothalamic paraventricular nucleus of patients with affective disorders. Increased RA signaling promoted by isotretinoin may mimic the augmentation of the pathway resulting from the elevation in RA receptor α[4,7]. RA receptor α might contribute to regulating the activity of CRH neurons *in vivo* and by this mechanism may contribute for depression as this hormone is known for playing a key role in its pathogenesis.

Hypervitaminosis A and psychiatric disorders

Bremner *et al*[2] reported a number of cases of mental symptoms associated with vitamin A toxicity. For example, the rare < pibloktoq syndrome > in people living within the Arctic Circle (that may be secondary to consuming polar bear or seal liver, which contain very high vitamin A levels). This syndrome includes symptoms ranging from depression to violence outbursts.

To investigate the link between hypervitaminosis A and psychiatric disturbances, studies on mefloquine (an antimalarial drug) are of value. Mefloquine is

known for a long time to have neuropsychiatric side effects. It has been linked to severe anxiety and depression, cognitive disturbances, psychosis and violence. Mawson[8] presented the hypothesis that mefloquine toxicity is an endogenous form of hypervitaminosis A. It is the only drug that targets the liver-stage Plasmodium falciparum parasites. Mefloquine acts as a dehydrogenase inhibitor that causes accumulation of retinyl esters in the liver, resulting in hepatocellular damage and the destruction of malaria parasites *in situ*. This is followed by the discharge of stored retinoids into the circulation in toxic concentrations before their transportation to the brain. Neuropsychiatric adverse effects result thus, as manifestations of an endogenous form of hypervitaminosis A. Acute vitamin A toxicity includes nausea, vomiting, headache, vertigo, blurred vision, increased intracranial pressure, irritability and muscular incoordination[8].

LITERATURE REVIEW

Isotretinoin, anxiety and depression

The effect of isotretinoin on mood and suicide risk is a matter of concern.

Preliminary evidence of links between RA and depression has come from behavioral studies on animals. Researchers suggested administration of 13-cis-RA in mice during 6 wk increases depression-related behaviors [decreased swimming in a (forced swim) test and poorer performance in (tail suspension) tests][9].

In adults, Bremner, an American psychiatrist[2], published in 2012 an extensive review (until 2010) on RA and affective disorders. Bremner *et al*[2] have outlined a relationship between isotretinoin and depression. The evidence included case reports, temporal association between onset of depression and exposure to the drug, challenge-rechallenge studies (depression resolved after discontinuation of the drug and in some cases returned with its reintroduction), dose response, biologic plausibility and class effect (review of neuropsychiatric effects of hypervitaminosis A). Moreover, they reported that the incidence of depression in large studies of isotretinoin-treated patients ranges from 1% to 11%. For some researchers[10,11] it corresponds to the annual incidence of major depressive disorders in adolescents.

Between 1990 and 2001, pharmacologists, dermatologists and a psychiatrist (Sundström *et al*[12]) led an important retrospective cohort study with 5756 patients aged 15 to 49 years who were prescribed isotretinoin for severe acne. This Swedish cohort demonstrated an increased risk of attempted suicide up to 6 mo after the end of treatment. The authors specified that severe acne is an independent risk factor for attempted suicide. Furthermore, they reported that an additional risk may be present, but can't be established with certainty, during and up to one year after treatment, and for this reason recommend a close monitoring for suicidal behavior. They add that there is no reason to refuse this treatment for patients who have attempted suicide. Indeed, they observe fewer recurrences with the patients having such a history in comparison to those having started such behaviors in connection with the treatment.

The major part of the dermatology community[13-23] states that there is no causal link between isotretinoin and depression with this postulate: acne causes anxiety and depression; treating acne with isotretinoin is a way to manage depression (improved self-image and positive behavioral effects). For example, Halvorsen *et al*[15] support a link between acne and suicidal ideation, mental health problems, and social impairment based on a large cross-sectional study of Norwegian adolescents. On the contrary, Magin *et al*[24] found no relationship between presence of acne or acne severity and measures of depression and anxiety. Hahm *et al*[14] found no correlation between beck depression inventory (BDI) scores and acne grade, but they suggested that improvement in depression symptoms are caused directly by quality of life in connection with acne improvement (APSEA score: Assessment of Psychological and Social Effects of Acne) rather than by improvement in acne grade.

A recent prospective observational longitudinal study[20] with a sample of 346 subjects treated for moderate acne highlights a significant reduction of Hospital Anxiety and Depression Scale (HADS) scores for anxiety and depression after isotretinoin treatment. A prospective and uncontrolled study[22] conducted between 2006 and 2008 included 100 patients suffering from moderate to severe acne. Before the treatment, six percent of the patients had suffered from depressive symptoms. The isotretinoin treatment did not seem to make these symptoms worse. By contrast, the study demonstrated that isotretinoin treatment of acne significantly improved depressive symptoms. Comparisons of the BDI-Ⅱ scores indicate that improvement in mood was statistically significant between months 0 and 1, 4 and 7, and 0 and 9 during the isotretinoin course. No suicide risk was reported during follow-up. McGrath *et al*[21] shows that successful treatment of acne significantly improves quality of life, particularly in those with more depressive symptoms at the outset. Yesilova *et al*[25] showed that performance avoidance score in Liebowitz Social Anxiety Scale (LSAS), pain and social functioning scores in SF-36 (Short-Form) were significantly better at the end of isotretinoin treatment. In their conclusion, the authors state that isotretinoin treatment improves the quality of life and social anxiety symptoms in acne patients.

Thirty-three patients with acne vulgaris completed a study[10] led between 2010 and 2011; rumination (MOCQ), depression and anxiety symptoms (HADS) improved significantly after 6 mo of oral isotretinoin treatment. On the other hand, doubting, a dimension of obsessive-compulsive symptoms was significantly

worse after treatment.

Two recent comparative studies from dermatological papers should be mentioned: A prospective and comparative study[26] included 85 patients: 46 with moderate acne (20 treated with isotretinoin and 26 patients were a control group treated with vitamin C) and 39 with severe acne (21 with isotretinoin, and 18 with vitamin C). In moderate and severe acne patients, there was no significant difference between the patients taking isotretinoin and the control group in any of the psychological tests [Measure of Psychological Stress (MPS), BDI, State Trait Anxiety Inventory (STAI) and APSEA tests]. The use of isotretinoin in the treatment of moderate to severe acne did not increase the symptoms of depression and anxiety. Another study[18] compared during 4 mo quality of life, anxiety and depressive symptoms between two groups of patients suffering from acne: the first group received the isotretinoin treatment (n = 37) and the control group received a topical treatment (n = 41). The two groups were the same in terms of Dematology Life Quality Index (DLQI), BDI, Hospital Anxiety and Depression (HAD) scores at baseline. However, at the end of the second month, quality of life was significantly more impaired in the topical treatment group compared to the isotretinoin group. At the end of the fourth month, quality of life and all psychological test scores had a significantly greater improvement in the isotretinoin group. Depressive and anxiety symptoms did not increase in the isotretinoin treatment group in comparison to the topical group[18].

Nonetheless, Goodfield *et al*[27] published in 2010 guidelines concerning the isotretinoin prescription in the British Journal of Dermatology. They recommend: first, the inventory of psychiatric histories for all patients candidate for isotretinoin prescription. Then, patients and their families should be sensitive of the possible potential for mood change. Finally, a direct enquiry about psychological symptoms should be made at each clinic visit.

Isotretinoin and bipolar disorder

The first episode of bipolar disorders is frequent during late adolescence. Lithium is recommended as the first-line medication for this pathology. Acne is not an unusual side effect of lithium. As lithium-related acne is often resistant to usual treatments, isotretinoin is frequently prescribed for this particular resistant acne. Several studies showed that BD patients treated with isotretinoin are at risk for clinically significant exacerbation of mood symptoms, including suicidal ideation. This exacerbation could arise in spite of a concurrent use of maintenance psychiatric medicines.

Isotretinoin prescription in BD patients

In 1988, Bigby *et al*[28] described a BD patient taking lithium who became suicidal after six and a half weeks of isotretinoin treatment. In 1999, Cott *et al*[29] described a case report of a BD woman taking lithium who developed after 4 wk of isotretinoin treatment, signs of previous psychotic manic symptoms decompensations. The addition of an antipsychotic allowed the complete resolution of the episode.

In 2010, a retrospective chart review[30] of 300 BD patients identified 10 patients treated with isotretinoin. Nine of the ten patients experienced an exacerbation of mood symptoms: six mixed symptoms, two depressive symptoms and one hypomanic symptom. Three of them developed suicidal ideation. Symptoms began from 4 to 20 wk after initiation of therapy and resolved with discontinuation in all but 1 patient. Besides, seven of the nine patients were taking maintenance psychiatric medications for BD at the time of the apparent reaction.

Isotretinoin prescription in non BD patients

Barak *et al*[31] of 500 soldiers with no prior history of psychiatric diagnosis treated with isotretinoin for severe acne reported that five of these patients developed manic psychosis within 8 mo of exposure. This was accompanied by a suicide attempt for three of them. In three cases, they found a family history of BD in a first degree relative. A personal history of obsessive-compulsive disorder (OCD) was also found for three patients.

In 2010, Fornaro[32] described a 25-year-old patient who developed OCD following isotretinoin treatment. An unexpected mood switch was observed 1 mo after the introduction of an antidepressant (fluvoxamine). This points out to the possible link between an iatrogenic induced OCD and an increasing risk for bipolar disorder.

Isotretinoin and psychosis

Bremner *et al*[2] reported cases of hypervitaminosis A associated with psychotic symptoms. A few studies in the literature state a possible link between isotretinoin and psychosis[16,33].

The neurobiological hypothesis for schizophrenia and psychotic symptoms is an increase in dopaminergic stimulation or sensitivity in the limbic system[34].

In fact, Goodman[35-37] points out a link between retinoid dysregulation and schizophrenia. He suggested that dysregulation by retinoids may be an important factor in the etiology of this pathology.

The evidence of this association is based on three points, according to these studies. First, retinoid dysfunction produces congenital anomalies, the same found in schizophrenic patients. Additionally, schizophrenia and the retinoid cascade have been linked to the same gene loci. Finally, RA regulates the transcriptional activation of the Dopamine D2 receptor and other schizophrenia candidates (as serotonin and glutamate receptors)[35-37].

A microarray study of schizophrenia in human brains published by Goodman[38] reported that two proteins (aldehyde dehydrogenase 1A1 and albumin), both important for the transport and function of the

vitamin A are altered in these patients. Thus, RA, the final metabolic product of the retinoid cascade, would be insufficient in schizophrenia. Unavailability of RA impairs transcriptional regulation of retinoid target genes like the Dopamine D2 Receptor, which is a candidate gene in schizophrenia. The expression of dopamine receptors has indeed shown to be regulated by RA[38,39]. So, Citver *et al*[40] proposed retinoid analogs as candidates for the treatment of schizophrenia, by altering the downstream expression of dopamine D2 receptors. Furthermore, mutations for the acid retinoic receptors demonstrated in mice could reduce expression of D1 and D2 receptors and do impair dopamine signaling[38,41].

DISCUSSION

This paper aims to discuss the relationship of treatment with isotretinoin to depression, bipolar disorder and psychosis.

Literature studies have demonstrated two opposing views as to the role of isotretinoin from two differing clinical specialties. The psychiatric literature (cf Bremner) suggests a causal link between isotretinoin and depression. The dermatological literature suggests that acne is an independent risk factor for depression and isotretinoin could be used to improve depression by treating acne and improving self-image. These differing views could be explained by a recruitment bias. Dermatologists may not have been aware of the occurrence of psychiatric disorders.

There is strong evidence from the psychiatric literature that demonstrates an association of isotretinoin to depression, probable clinical exacerbation of bipolar mood disorder and possible links to psychosis.

It is important that isotretinoin be prescribed only for severe acne, resistant to several course of antibiotics. The patients that may be susceptible to these side effects may not be able to be predicted. However, an assessment of previous psychiatric histories (by means of questionnaires preliminary to the isotretinoin's prescription) and current psychiatric state may be helpful in identifying them.

Close monitoring of these patients for neuropsychiatric side effects seems to be very important during isotretinoin therapy. For example, headache symptoms could constitute an alert symptom. In patients undergoing lithium therapy who develop acne, a careful risk/benefit analysis on withdrawal of treatment should be undertaken. The responsibility of lithium in the occurrence of acne may be established with the highest certainty possible. Then, the mental state of the patient has to be evaluated: is its pathology balanced under lithium? In this case, it may be risky to stop lithium treatment, although there are many other pharmacological choices today such as anticonvulsants and atypical antipsychotics (please find adequate references). The optimal treatment may be discussed with both professionals and patient in order to choose the best option available.

There is also a debate between nephrologists and psychiatrists regarding lithium and renal insufficiency. Nephrologists recommend to stopping the treatment if the patient develops a renal insufficiency. Psychiatrists will tend to maintain the treatment, especially if they consider it's the only molecule able to stabilize the patient.

CONCLUSION

Opposing views as to the role of isotretinoin in the occurrence of depression are discussed. Even if the risks of suicide appear weak, a general principle of patient therapy monitoring should be introduced. Further studies to establish links to bipolar disorder and psychosis during isotretinoin therapy are required. Careful risk/benefit analysis of patients developing acne on lithium treatment should be undertaken.

A multidisciplinary approach of the patient (during the liaison psychiatry for example) is here particularly relevant in order to permit discussion between specialists about this treatment.

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ORIGINAL ARTICLE

Retrospective Study

Outpatient competence restoration: A model and outcomes

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Abstract

AIM: To describe a model outpatient competence restoration program (OCRP) and provide data on time to restoration of adjudicative competence.

METHODS: The authors tracked the process by which individuals are referred for outpatient competence restoration (OCR) by courts in the United States capital, describing the unique requirements of American law, and the avenues available for compelling adherence. Competence to stand trial is a critical gate-keeping function of the judicial and forensic communities and assures that defendants understand courtroom procedures. OCR is therefore an effort to assure fairness and protection of important legal rights. Multi-media efforts are described that educate patients and restore competence to stand trial. These include resources such as group training, use of licensed clinicians, visual aids, structured instruments, and cinema. Aggregate data from the OCRP's previous 4 years of OCR efforts were reviewed for demographic characteristics, restoration rate, and time to restoration. Poisson regression modeling identified the differences in restoration between sequential 45-d periods after entrance into the program.

RESULTS: In the past 4 years, the DC OCRP has been successful in restoring 55 of 170 participants (32%), with an average referral rate of 35 persons per year. 76% are restored after the initial 45 d in the program. Demographics of the group indicate a predominance of African-American men with a mean age of 42. Thought disorders predominate and individuals in care face misdemeanor charges 78% of the time. Poisson regression modeling of the number attaining competence during four successive 45-d periods showed a substantial difference among the time periods for the rate of attaining competence (P = 0.0011). The three time periods after 45 d each showed a significant decrease in the restoration rate when compared to the initial 0 to 45 d period - their relative rates were only 22% to 33% as high as the rate for 0-45 d (all P-values, compared to the 0-45 d rate, were 0.013 or smaller). However, the three periods from day 45 to day 135

showed no difference among themselves (P = 0.87).

CONCLUSION: The majority of restored participants were restored after 45 d, suggesting a model that may identify an optimal length of time to restoration.

Key words: Forensic psychiatry; Mental competence/ legislation and jurisprudence; Adjudicative competence; Competence restoration; United States

Core tip: Restoring a defendant's competence to stand trial is a cardinal element of public sector forensic services in the United States. The Washington DC outpatient competence restoration program (OCRP) is one of a number of state programs that offers a model of education and support for incompetent defendants. Using a combination of specialized assessment, multi-modal education, support, and court leverage, the DC OCRP is the first to identify the length of time most useful for restoring its referral population. Implications of these findings can affect the court calendar, further research, and inter-agency collaboration.

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INTRODUCTION

Outpatient competence restoration (OCR) is a function of United States law that provides outpatient competency education to non-dangerous defendants who are found incompetent to stand trial. Competency is defined by a 1960 United States Supreme Court case, Dusky v. United States, which affirmed a defendant's right to a competency evaluation before proceeding to trial. In this landmark case, the court outlined the basic standards for determining competency, ruling that a defendant must have a "sufficient present ability to consult with his lawyer with a reasonable degree of rational understanding" and a "rational as well as factual understanding of the proceedings against him"[1]. The standard draws on fundamental principles of fairness to establish that it is both unlawful and unethical for defendants to proceed in a criminal matter without an understanding of the proceedings, its consequences, and the ability to assist their attorneys.

The OCR program (OCRP) in Washington DC is unique in that it serves international defendants who travel for the express purpose of communicating with the White House or United States Congress. Cultural nuances are therefore a critical component of local competency restoration. Individuals from Romania, for example, cannot bear witness if their trial is heard in Romania. In the United States, they must be taught that they can indeed be a witness in their own defense. South African citizens may not be familiar with a jury-based system. Because of racial prejudice and inequality the jury system was formally abolished there in 1969[2]. In the District of Columbia, South African defendants facing a felony charge must be informed of the possible benefits and safeguards of having a jury of peers deciding their case.

There are an estimated 25000 to 39000 competency evaluations conducted annually in the United States[3,4]. After defendants are deemed incompetent by a judge applying the Dusky standard, they may be committed to restoration in an inpatient or outpatient setting. Dangerousness determines the location, but is also governed by the resources of the state and the judgment of the fact-finder (*i.e.*, the judge).

Thirty-five states have specific statutes that allow for OCR. However, only 16 states actually have a functioning OCRP. Some states, New York for example, only restore individuals who are charged with a felony, a serious charge generally carrying a sentence of over a year in prison. In the District of Columbia, a defendant can be ordered to participate in either inpatient restoration at Saint Elizabeths Hospital, the District's publicly funded hospital, or to outpatient restoration at the OCRP in the DC Department of Behavioral Health. The outpatient option adheres to the statutory requirement of providing the least restrictive alternative for mental health orders.

Other states with OCRPs include Arizona, Georgia, Louisiana, Ohio, Texas, Virginia, West Virginia and Wisconsin. Wisconsin provides one-on-one competency education to defendants for one hour twice a week. Competency restoration specifically includes case management services which are provided once a week to each participant. This assures that participant schedules are coordinated, appointments made, and that contact with the program is maintained. In 2012-13, Wisconsin served 121 defendants, restoring them at a rate of 75% - among the highest rates in the nation[5].

Texas follows a group-structured competency restoration program with the option of one-on-one service[6]. Groups meet daily for 1-1.5 h. Between 2008 and 2013, the overall rate of restoration was 42%. The stark difference between this program and the DC OCRP is the availability of involuntary medication in the outpatient setting. DC does not have this option, leading to delays in treatment that affect time to restoration. Programs with legal leverage of this kind can greatly increase restoration rates by enforcing the intense exposure and structure needed to teach defendants the critical elements of the legal system. Moreover, patient adherence to medication regimens decreases the symptoms of mental illness that interfere with the ability to order and retain new material.

Judicial responses to persons not adhering to the initial court order include an order to return to OCRP, an order for inpatient competency restoration, dismissal of charges, the issuance of a bench warrant, or a finding of unlikely to be restored. Bench warrants for a return to court are generally issued to participants who do not comply with the initial court order and do not appear for OCR.

Compared to inpatient restoration, OCRP provides easily recognizable benefits to the defendant and the healthcare system. It is conducted in a less restrictive environment, provides less encroachment on personal liberty, is less disruptive of daily life, and offers cost savings to defendants and the public health system alike.

The DC OCRP

DC evaluators are board-certified forensic psychiatrists and forensically experienced psychologists who must have completed a forensic psychiatry fellowship or supervised experience with a trained clinician. This includes observing competency evaluations and then conducting at least five evaluations under direct supervision. Successful completion of this additional course of training provides acculturation to the program and its constituents, improved understanding of regulations, familiarity with local cultures and interpretations of law, and the proper thresholds for ascribing competence.

The DC OCRP meets at an outpatient clinic in the center of the District of Columbia. Participants are court-ordered to participate and screened for suitability by a psychologist who performs a full introductory evaluation of competence to stand trial. Individuals with violent charges or who cannot be adequately contained in the community are not recommended for the program. However, 71% of those who participate receive mental health services while enrolled in OCRP. Individuals who do not adhere to their appointment schedule or who are disruptive to the group process are identified and the court is alerted in writing. The court ultimately decides whether the defendant continues in OCRP or whether an alternative option like hospitalization is appropriate.

MATERIALS AND METHODS

OCR takes place in a group setting. The group meets twice a week for 1.25 h at a time. The first visit essentially serves as an intake session where the group facilitator collects demographic information, obtains the defendant's signature on a formal participation agreement, and reviews the purpose of the program along with the expectations of those attending. These are essential elements of an informed consent process that discloses information about the program, contributes to the assessment process, and encourages the participant's engagement. If defendants are receiving community mental health services, they are asked to sign a release of information so that treatment needs and adherence can be confirmed.

Defendants are asked to read the program's main teaching tool, a 42-question survey loosely based on the Florida State Hospital CompKit[7]. Used broadly to assess the factual prong of the Dusky standard (*i.e.*, "a factual understanding of the proceedings against him"), the instrument ascertains the defendants' ability to read and understand the curriculum's competency information. This is an important adjunct to the initial competence evaluation.

The OCRP groups are facilitated by a licensed clinical mental health provider, currently a master's level social worker, as well as a mental health provider who provides support to the facilitator. Various teaching tools are utilized, depending on the needs of the group. The 42-question survey is studied in each session so that part-by-part review can improve recall and understanding of the material. In addition, the facilitator uses visual aids, like pictures of a courtroom on a magnetic board, to reach participants whose preferred learning modality is visual or who may be cognitively impaired (These materials are not publicly available so that attorneys and defendants do not gain unfair advantage before the formal assessment and restoration efforts).

Case vignettes drawn from the media are selected for discussion. The connection to current events anchors the curriculum in real-life events, lending an urgency and specificity to the curriculum. Feedback from participants over the years indicates that this is a particularly effective manner to underscore the identity of courtroom participants and engage group members. Role play is a useful strategy in this context as well, as participants act out the roles of courtroom members.

Each quarter, the facilitator shows the movie "My Cousin Vinnie", a Hollywood comedy recounting the adventures of an ersatz city lawyer trying to disentangle his cousin from a rural court. Participants consequently discuss the movie's relevance to the real courtroom. Finally, the facilitator uses word association and acronyms to help participants retain the material. This approach underscores the visual and kinesthetic elements of the program and offers mnemonics that can easily be recalled.

Each defendant is consequently evaluated by a forensic psychiatrist after 45 d (the length of the initial court order), and each 30 d thereafter. Reports are written by the same examiner to support reliability, and describe whether or not the defendant is competent to stand trial along with recommendations for continued restoration if needed.

Statistical analysis

Statistical analysis was overseen and conducted by biomedical statistician Robert W Wesley, PhD.

RESULTS

Outcomes for the DC OCRP

The cost to run the DC OCRP is $2006/wk in 2014 US dollars, compared to the cost of inpatient restoration at $6307/wk. Although the majority of costs are for personnel, considerable savings accrue from using licensed, clinical mental health professionals rather than medical doctors or psychologists to facilitate the group sessions. Physicians and psychologists are reserved for the competency evaluations themselves. Moreover, basing the program on a group treatment model creates an economy of scale that allows staff access to more individuals at one time. The subsequent analysis has been exempted from review by the DC Department of Behavioral Health institutional review board.

In the past four years, the DC OCRP has been successful in restoring 55 of 170 participants (32%), with an average referral rate of 35 persons per year[8]. Demographics of this group are presented in Figures 1 and 2, and indicate a predominance of African-American men.

With a mean age of 42, participants were largely in the 37-58 year age range, and faced misdemeanor charges 78% of the time.

Because they were frequently returned to the program by court order for continued competency restoration, the 170 participants generated 274 court orders. During 2009-2013, 70 of 170 total participants were ordered to return to OCRP after 45 d. This number dropped precipitously to 24 after 75 d in OCRP, and again thereafter as the rules of the program took hold. After 45 d of participating in bi-weekly OCRP, 28 participants were ordered to receive restoration and treatment on an inpatient basis (50 within 135 d). Three participants were ordered to inpatient restoration and treatment after being in OCRP for 135 d.

Forty-two of the 55 participants successfully restored were found competent after the first 45 d of participation. After 75 d of participating in OCRP, six more attained competence. After 105 d, four more were restored, and by 135 d all 55 participants were deemed competent to stand trial (Figure 3).

Poisson regression modeling of the number attaining competence during these four time periods, showed a substantial difference among the time periods for the rate of attaining competence (P = 0.0011). The three time periods after 45 d each showed a significant decrease in the restoration rate when compared to the initial 0 to 45 d period - their relative rates were only 22% to 33% as high as the rate for 0-45 d (all P-values, compared to the 0-45 d rate, were 0.013 or smaller). However, the three periods from day 45 to day 135 showed no difference among themselves (P = 0.87).

Eleven participants had their charges dismissed after being in the program for 45 d. This number dropped to ten participants after 75 d and four participants after 105 d of being ordered to the program. A total of 28 participants, 21 facing misdemeanors, had their charges dismissed by 135 d (only 9 more after 135 d).

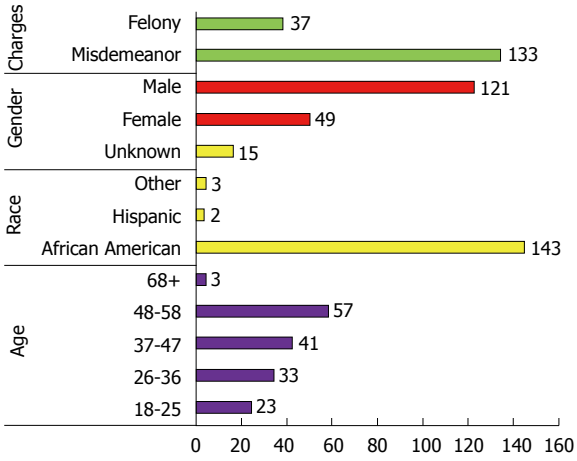

Figure 1 Demographics of outpatient competence restoration program 2009-2013. Totals may not add to 170 because of missing data for certain individuals.

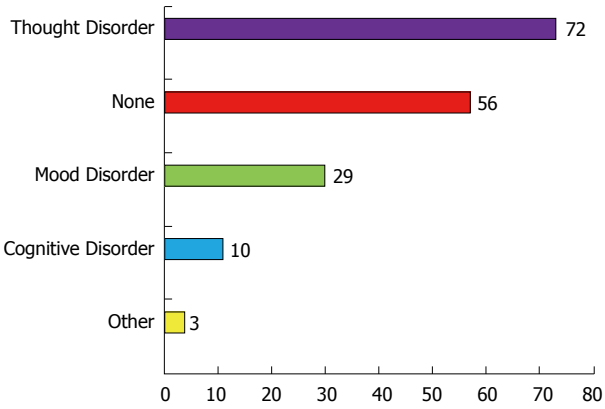

Figure 2 Outpatient competence restoration program Diagnoses 2009-2013. For the purposes of brevity "Cognitive Disorder" includes DSM-5's Neurocognitive Disorder (3 cases) and Intellectual Developmental Disorder (7 cases).

Five bench warrants were issued after the first 45 d, with an additional two bench warrants issued after 75 d, and only one after 135 d in the program.

Five participants were determined to be unlikely to be restored in the foreseeable future and a Jackson finding was issued after 45 d. This order is based on the United States landmark case of Jackson v. Indiana which requires that confinement for OCR bear some relationship to the initial reason for incarceration[9]. Defendants cannot be held indefinitely. Seven participants were determined to be unlikely to be restored after 75 d, with one additional participant added after 135 d, and another after 165 d.

DISCUSSION

These data indicate that the first 45 d of participation in the DC OCRP are the most productive. To our knowledge this is the first report to identify an optimal

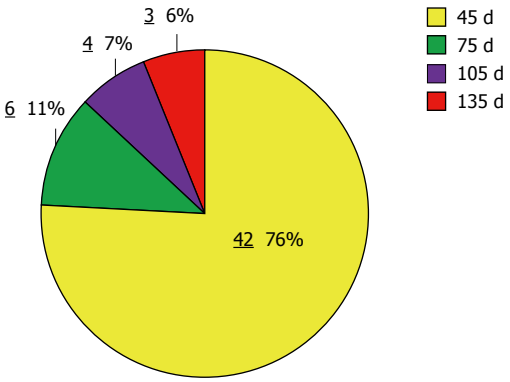

Figure 3 Outpatient competence restoration program participants competent to stand trial by decision of dc superior court.

length of time to restoration in the outpatient forensic setting. The substantial majority (76%) of participants found competent were restored after 45 d in the program. The type of leverage used by the courts (*e.g.*, bench warrants, return orders) decreased significantly after 45 d and another significant participant group had their charges dismissed. The increase in Jackson findings (*i.e.*, that participants are unrestorable) after 45 d indicates the power of the 45 d period to determine competence.

Twenty-eight defendants, mostly facing misdemeanor charges, had their charges dismissed by 135 d after their initial order into competency restoration. We hypothesize that judges recognize that defendants may spend more time attempting to become competent than serving the short sentence they are likely to face after a misdemeanor. It is not surprising, therefore, that this group faced dismissal despite not attaining competence.

The importance of adequate time for group education and multi-media efforts to take hold is an important predicate of outpatient restoration and matches findings in the psychiatric literature supporting multi-modal efforts for patient education[10,11]. The group process is critical here, as in other modalities for improving patient care, from cognitive-behavioral therapy to addictions[12,13].

Use of forensically trained evaluators who have undergone local supervision underscores familiarity with local statutes, cultures, and legal interpretations. The broad range of ethnicities and nationalities in Washington DC requires regular updating on cultural norms and legal experiences outside the United States. This is achieved by peer support and supervision among evaluators and educators.

There continue to be barriers for OCRP programs in general and DC in particular. The need for programming for those with cognitive limitations could be especially useful in a population that often suffers educational or developmental delays[14,15]. Growth of programs useful in other settings could be essential to restoring the participants who do not attain competence after initial attempts[16]. The local Department of Disability Services may be an especially effective partner, since it has already developed programs to support and educate their clients with developmental disabilities.

As effective as groups are in allowing education for a large number of participants, even group size can interfere with productivity. The size for schizophrenia therapy groups has often been reported at fewer than ten patients, with larger groups potentially interfering with group education and process[17,18]. Identifying the size at which restoration groups attain optimum performance may be an important outgrowth of research in this area.

As some states have recognized, case management services are critical for addressing restorability as well as assessing the use of clinical and forensic services. The factors known to affect one's ability to become competent include employment, treatment adherence, and abstinence from substance use[19,20]. Support in these areas can be health-affirming as well as cost-effective. Transportation assistance can be particularly useful in improving access to forensic and community services that assure the fairness of the judicial process.

As practiced in the District of Columbia, therefore, OCR is an effective intervention for assuring the fair use of the courts. Governed by landmark court cases and local law, the OCRPs in general offer a range of educational resources and support for those who cannot successfully navigate the judicial system. Frequently achievable within 45 d in DC, OCR relies on expert assessment, group process, multi-media interventions, and leverage from the courts. Future challenges arise from the presence of participants with cognitive difficulties and the need for more research on optimal group size, transportation needs, and inter-agency collaboration.

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COMMENTS

Background

This study examines an outpatient competence restoration program (OCRP) and its effectiveness in restoring adjudicative competence in the least restrictive environment. In a period when budgetary constraints influence clinical services, outpatient competence restoration (OCR) is an effective and cost-saving tool for providing a necessary service required by United States law. Providing multi-media group education in an outpatient setting alongside competency evaluation conducted by forensic clinicians is a cardinal feature of the OCRP in Washington DC. This study provides a look into a model OCRP and its data in hopes that jurisdictions not yet utilizing this service will develop programs that simultaneously meet the needs of the criminal justice system while protecting the civil liberties of the mentally ill.

Research frontiers

There is little information in the literature on the specifics of OCRPs. This is

the first time, to our knowledge, that the specific methods of an OCRP are described and its aggregate data examined. This project may consequently allow other jurisdictions to compare their methods and data as they develop or modify new programs.

Innovations and breakthroughs

The multi-media approach to education of persons diagnosed with mental illness finds a new application in the outpatient forensic setting. This combination of educational efforts and forensic resources represents a unique effort to protect the rights of vulnerable individuals interacting with the judicial system. The combination of specific educational methods and aggregate data offers a unique look at the inner workings of a potentially model program.

Applications

The specific educational and resource information offered here, as well as its effect on OCR, can provide the framework for jurisdictions seeking to develop evidence-based programs that protect the civil liberties of persons diagnosed with mental illness.

Terminology

Competency restoration: The educational process followed by defendants found incompetent to stand trial; Adjudicative competence or competence to stand trial: The critical elements of courtroom procedures, participants, and reasoning that allow defendants to collaborate meaningfully in the judicial process.

Peer-review

A well conducted study and the results are concise with a good discussion and literature survey.

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ORIGINAL ARTICLE

Observational Study

Audit study of the new hospitalization for assessment scheme for forensic mental health in Japan

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Author contributions: All authors contributed to the creation of the questionnaire; Hirata T collected the data; Shiina A analyzed the data and wrote the manuscript; Iyo M supervised the procedure of this study; Igarashi Y is the administrator of this study; all of the authors critically assessed the manuscript and finally approved this article.

Ethics approval: We did not gather any personally identifiable patient information in this study. No studies described in this paper were interventional. We reported the contents of this survey to the Ethical Council of the Graduate School of Medicine, Chiba University in advance, and the council has confirmed that each survey posed no ethical problems.
Informed consent: This study is a service evaluation study. The ethics council has approved that it is not required to obtain the informed consent of each patient in this study.
Conflict-of-interest: This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Health, Labour and Welfare of Japan, entitled "Iryo-kansatsu-ho seido no kantei-nyuin to senmonteki-iryo no tekiseika to kojo ni kansuru kenkyu [A research for optimization and improvement of Hospitalization for Assessment and Special Treatments in the MTS Act.]." We declare that we have no other conflict of interests related to this research.
Data sharing: There is no additional data available other than in this article.

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Abstract

AIM: To clarify the components of hospitalization for assessment (HfA) and the management changes from the beginning of the scheme to the present.

METHODS: This study is composed of two surveys. In 2013 survey, we created two paper questionnaires (facility and case questionnaires) for psychiatrists working in psychiatric hospitals accepting HfA patients. Questionnaires were sent to 205 hospitals that were identified as accepting the HfA cases, and responses were requested *via* mail. The facility questionnaire was designed to clarify the following specifications and characteristics of each facility: the facility organizer (public sector or private hospital), and the number of beds, psychiatrists, psychiatric nurses, occupational therapists, psychiatric social workers, psychotherapists, public health nurses, and patients treated through HfA during the survey period. The case questionnaire was then used to collect data of the patients under HfA based on the Medical Treatment and Supervision (MTS) Act who were discharged between July 1, 2012 and June 30, 2013. Gathered information included: legal information of each case, demographic data, past history of the offenders, issued offense and the relationship to the victim, information regarding past psychiatric testimonies, psychiatric diagnoses, contents

of the treatment during HfA, information regarding seclusion and restraint during the HfA, the verdict of the District Court panel, and so forth. Next, we compared those results with relevant data obtained in 2007. The 2007 survey comprised data of HfA patients from July 15, 2005 (the date the MTS Act was enforced) to January 15, 2007.

RESULTS: We obtained 171 cases, approximately a half of whole contemporary cases of HfA, from 134 facilities, of which 46 were national, prefectural, or semi-official hospitals, and 88 were private hospitals, in 2013 survey. The majority of subjects were male, schizophrenic, and experienced previous psychiatric treatment. The most frequent type of the offense was injury, followed by arson. Most of the subjects were medicated, and a few cases took psychotropic injection during the HfA. The frequency of injection was decreased in 2013 (χ^2 = 7.54, df = 1, P = 0.006) than in 2007. Psychiatric testimony was more likely to be conducted in 2013 (χ^2 = 8.56, df = 1, P = 0.004). The examiner psychiatrist was more likely to belong to the HfA facility to which the patient was hospitalized (χ^2 = 5.32, df = 1, P = 0.02). Hospitalization orders were more frequently selected in 2013 (χ^2 = 19.76, df = 3, P < 0.001), although the characteristics of the subjects had not changed.

CONCLUSION: Although the management of HfA has improved in recent years, structural problems remain.

Key words: Medical treatment and supervision act; Hospitalization for assessment; Forensic mental health; Audit study

Core tip: In 2005, the Medical Treatment and Supervision Act was enforced in Japan. In this scheme, offenders with mental disorders are hospitalized for assessment (HfA) to determine their treatment. We aimed to clarify the components of HfA and the management changes from the beginning of the scheme to the present. We obtained approximately a half of whole contemporary cases of HfA in the 2013 survey, and then compared the data to those in the 2007 study. The comparison revealed some changes in the HfA cases. This study clarified the improvement of HfA management, and remained some structural problems as well.

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INTRODUCTION

Forensic mental health is a topic of great concern and controversy[1]. Thanks to the global trend toward deinstitutionalizing patients with mental disorders, the need to develop sophisticated forensic mental health systems has increased[2]. Consequently, many countries have established their own forensic mental health systems, which link different disciplines according to their cultural backgrounds[3].

For many years, Japan had no specific legal provision for offenders with mental disorders[4]. Such offenders were treated under the Mental Health and Welfare Act. Under that legislation, patients with mental disorders who were potentially dangerous, being capable of harming themselves or others, were hospitalized under a prefectural government order. This system of official involuntary hospitalization was completely independent of the criminal justice system[5], which led some lawyers to argue that the human rights of these patients were not properly guaranteed. Similarly, some psychiatrists suggested the need for special hospitals with sufficient staff to provide appropriate care for offenders with mental disorders[6].

To address these problems, the Medical Treatment and Supervision (MTS) Act (the Act on Medical Care and Treatment for the Persons Who Had Caused Serious Cases under the Condition of Insanity) was enforced in 2005[7], and the Japanese forensic mental health system underwent reform. Under this new scheme, individuals committing a serious criminal offense in a state of insanity or diminished responsibility would be dealt with in a judicial, administrative framework. The public prosecutor is responsible for making allegations to the District Court to render judgment. The offender is sent to a hospital, usually soon after the public prosecutor makes an allegation to the court. In the term of hospitalization for 2 to 3 mo, psychiatric examination and treatment are implemented; this assessment period is known as hospitalization for assessment (HfA, *kantei-nyuin*)[8]. The District Court forms a judgment panel consist of one judge and one mental health reviewer (*seishin-hoken-shinpan-in*), with the latter being selected from a group of psychiatrists who hold a judgment physician license (*seishin-hoken-hantei-i*), which is a national license for forensic mental health specialists. A second psychiatrist with a judgment physician license is then appointed by the panel of the District Court to be an examiner psychiatrist (*kantei-i*), who is required to write a report on the psychiatric evaluation of the patient. At the end of HfA, the panel makes a final decision based on the reports written by the examiner psychiatrist and the rehabilitation coordinator (*shakai-fukki-chousei-kan*) working in a probation office, with refererence to the opinion of the mental health advisor (*seishinhoken-sanyo-in*) who is a discretionary member of the panel. The panel can arrive at three possible verdicts: hospitalization orders, community treatment orders, or no treatment/release. In the case of a hospitalization order, the offender is sent to a designated inpatient

facility by the government officials. If either of the first two options is selected, the offender is then obliged to submit to continuous supervision by a rehabilitation coordinator[9]. When the offender cannot adhere to treatment in the community, the probation office can make an allegation for a recall order, based on the deliberate assessment regarding the risk of recommitting.

In 2008, the Japanese Government published a list of 239 Japanese psychiatric hospitals for the purpose of HfA of mentally disordered offenders[10]. According to an official report, this has now increased to 286 hospitals[11]. However, the criteria used to elect these facilities are vague. The MTS Act provides little information on the regulation for even the minimum requirements these facilities must meet, which has led to marked variations in conditions[12]. To minimize this variation and improve the quality of assessments, we previously conducted a written mail survey of leading Japanese forensic mental health experts. This resulted in the development of expert consensus for many HfA treatment standards. We therefore concluded that these consensus statements should be widely publicized among practitioners to ensure better management during HfA[9].

Since the MTS Act was enforced some 9 years ago, several papers have been published on subsequent outcomes[13,14]. In contrast, the status of HfA is rarely reported, either officially or unofficially. Therefore, we have conducted an annual, national audit study to monitor HfA facilities and subjects.

This study aims to clarify the current situation of HfA and to examine the changes in the contents of HfA from the past to now. We first present the data obtained in the 2013 survey, and then compare the results of the obtained data in 2007.

MATERIALS AND METHODS

2013 survey

We created two paper questionnaires (facility and case questionnaires) for psychiatrists working in psychiatric hospitals accepting HfA patients. Questionnaires were sent to 205 hospitals that were identified as accepting the HfA cases by the previous study, and responses were requested *via* mail. The survey was conducted between July 2013 and February 2014.

The facility questionnaire was designed to clarify the following specifications and characteristics of each facility: the facility organizer (public sector or private hospital), and the number of beds, psychiatrists, psychiatric nurses, occupational therapists, psychiatric social workers, psychotherapists, public health nurses, and patients treated through HfA during the survey period. The case questionnaire was then used to collect data of the patients under HfA based on the MTS Act who were discharged between July 1, 2012 and June 30, 2013. The following information was collected: article number for the case, gender, age, family members, marital history, occupational history, therapeutic history, issued offense, relationship to the victim, relationship to the owner of the property (exclusive in arson cases), whether psychiatric testimonies (committed examination and/or public trial examination) were conducted before the allegation, decision by the prosecutor or the court preceding the allegation, psychiatric diagnosis, dual diagnosis (if applicable), physical complications (if applicable), treatment during HfA (medication, psychotropic drug injections, long-acting injections (LAI), or electro-convulsive therapy), term of seclusion and restraint, whether the examiner psychiatrist belonged to the facility where the patient was hospitalized, and the verdict of the District Court panel.

Comparison analysis

Next, we compared those results with similar data obtained in 2007. The 2007 survey comprised data of HfA patients from July 15, 2005 (the date the MTS Act was enforced) to January 15, 2007. The following common contents were collected: gender, age, issued offense, whether psychiatric testimonies (committed examination and/or public trial examination) were conducted before the allegation, decision by the prosecutor or the court preceding the allegation, psychiatric diagnosis, treatment during HfA, term of seclusion, whether restraint was performed, whether the examiner psychiatrist belonged to the facility where the patient was hospitalized, and the verdict of the District Court panel. The components of each questionnaire are summarized in Table 1.

Statistical analysis

The collected data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY). Values of $P < 0.05$ were considered statistically significant in each analysis. We adopted either χ^2 test, Fischer's exact test, or Unpaired *t*-test, following each character of the data, for statistical evaluation. Data are expressed as mean ± SD unless otherwise stated. The statistical methods of this study were reviewed by Dr. Kensuke Yoshimura in Department of Mental Health/Psychiatric Nursing, Graduate School of Medicine, The University of Tokyo.

RESULTS

2013 survey

Response rate: We received responses from 134 facilities (response rate: 65.4%) covering 171 patient records. According to an official report, 388 cases were decided by court panels based on the MTS Act in 2012[15]. Estimating that all of these cases required HfA, the capture rate was approximately 44.1%.

Facility questionnaire responses: Of the facilities, 46 were national, prefectural, or semi-official hospitals, and 88 were private hospitals. The mean number

Table 1 Items on the questionnaires in the 2013 survey

Facility questionnaire	Case questionnaire
Facility organizer	Article number
Number of beds	Gender[1]
Psychiatric beds	Age[1]
Other types of beds	Family members
Number of staffs	Marital history
Psychiatrists	Occupational history
Psychiatric nurses	Therapeutic history
Occupational therapists	Issued offense[1]
Psychiatric social workers	The victim
Psychotherapists	The owner of the damaged property (if applicable)
Public health nurses	Psychiatric testimonies[1]
Number of the accepted HfA cases[1]	Preceding Decision by the prosecutor or the court[1]
	Psychiatric diagnosis[1]
	Dual diagnosis (if applicable)
	Physical complications (if applicable)
	Treatment during HfA
	Medication
	Psychotropic drug injections[1]
	Long-acting injections[1]
	Electro-convulsive therapy[1]
	Seclusion and restraint[1]
	Belonging of the examiner psychiatrist[1]
	Verdict of the District Court panel[1]

[1]Collected also in the 2007 survey.

Table 2 Characteristics of facilities in the 2013 survey

Item	Options	*n*
Organization	National, prefectural, or semi-official	46
	Private sector	88
Number of beds[1]	Psychiatric beds	284 ± 136
Other types of beds	Equipped	27
	Unequipped	107
Number of staffs[1]	Psychiatrist	10.4 ± 5.9
	Designated Physician	7.4 ± 3.9
	Judgment Physician	1.9 ± 2.0
	Psychiatric nurse	113.1 ± 51.3
	Occupational therapist	8.0 ± 5.1
	Psychiatric social worker	8.3 ± 5.5
	Candidate of Mental Health Advisor	0.6 ± 1.0
	Psychotherapist	3.8 ± 3.2
Experience of accepting HfA case	Yes	69
	No	64
	Unknown	1

[1]Data expressed as mean ± SD. HfA: Hospitalization for assessment.

of psychiatric beds was 284 ± 136, and 27 facilities were equipped with beds for non-psychiatric patients. The average staffing levels were as follows: 10.4 ± 5.9 psychiatrists (7.4 ± 3.9 designated physicians, 1.9 ± 2.0 judgment physicians), 113.1 ± 51.3 psychiatric nurses, 8.0 ± 5.1 occupational therapists, 8.3 ± 5.5 psychiatric social workers (0.6 ± 1.0 were mental health advisor candidates), and 3.8 ± 3.2 psychotherapists. Only 13 facilities employed public health nurses. Sixty-nine facilities (51.5%) accepted at least one HfA patient during the survey period (Table 2). The facilities that accepted HfA cases had higher proportions of judgment physicians (1.30 *vs* 0.48, df = 122, t = 3.4; P = 0.0009) and mental health advisor candidates (0.37 *vs* 0.17, df = 116, t = 2.3; P = 0.02) per 100 psychiatric beds compared with facilities that did not accept HfA cases (unpaired t-test).

Case questionnaire: Of the 171 cases, 168 were subject to HfA by Article 34 of the MTS Act (initial assessment), and 3 were subject to Article 60 (assessment for recall). In total, 123 were men and 48 were women, and the mean age was 46.6 ± 16.4 years; 125 patients lived with their family and 40 lived alone at the time of the offense (unknown = 6). Furthermore, 93 had never been married, 38 were currently married, 21 were divorced, and 5 were widowed (unknown = 14 cases). We also found that 97 had at least one prior job and 25 had no work experience (unknown = 49 cases). Regarding their therapeutic history, 35 patients had no experience of past psychiatric treatment until the issued offense, whereas 62 were being withdrawn from treatment, 63 were under ongoing outpatient care, and 7 were hospitalized (unknown = 4 cases); 100 patients had been hospitalization before the issued offense.

The issued offenses were: homicide (n = 24), attempted homicide (n = 34), arson (including attempted arson; n = 41), robbery (including attempted robbery and robbery with injury; n = 7), injury leading to death (n = 5), rape (including attempted rape; n = 1), injury (n = 64), sexual coercion (n = 2), "other" (n = 18). This distribution was no different from that in the official report[16]. The victims were family members (n = 71), friends (n = 13), strangers (n = 31), and "others" (n = 25). In the arson cases, the damaged property was owned by self (n = 37), family (n = 3), friend (n = 1), stranger (n = 1), and "other" (n = 8).

In 59 cases (34.5%), at least one psychiatric testimony (committed examination and/or public trial examination) occurred before the allegation. The decisions prior to the HfA submission were as follows: no prosecution by reason of insanity (prosecutor; n = 105), suspended prosecution by reason of diminished responsibility (prosecutor; n = 33), not guilty by reason of insanity (court; n = 3), suspended imprisonment with diminished responsibility (n = 16), and "other" (n = 14).

The main psychiatric diagnoses, categorized according to the International Classification of Disease, 10th edition, were F0 (Organic, including symptomatic, mental disorders) 18, F1 (Mental and behavioral disorders due to psychoactive substance use) 13, F2 (Schizophrenia, schizotypal and delusional disorders) 111, F3 [Mood (affective) disorders] 14, F4 (Neurotic, stress-related and somatoform disorders) 2, F5 (Behavioral syndromes associated with physiological disturbances and physical factors) 0, F6 (Disorders of adult personality and behavior) 2, F7 (Mental

retardation) 9, F8 (Disorders of psychological development) 2, and F9 (Behavioral and emotional disorders with onset usually occurring in childhood and adolescence) 0. Dual diagnoses were present in 32 cases (18.7%), and recorded as F0 1, F1 7, F2 1, F3 1, F4 2, F6 3, F7 14, and F8 3. During the HfA period, 9 patients required consultations with physicians from other hospitals, and 3 patients were transported to another hospital for the treatment of physical complications.

In terms of treatment strategies, 161 patients were prescribed medication and 10 received no medication. Five patients received a psychotropic injection, and one received LAI. No patient received electro-convulsive therapy. However, 116 patients were secluded for a mean of 32.2 ± 27.1 d (not secluded = 32; unknown = 23 cases), and 10 patients required physical restraint for periods from 3 to 67 d (no restraint = 148; unknown = 13).

In 142 cases, the examiner psychiatrist originated from the HfA facility, whereas a psychiatrist from another hospital took the role of the examiner psychiatrist in 20 cases (unknown = 9). The verdicts determined by the panel were hospitalization order (n = 120), community treatment order (n = 12), no treatment/release (n = 57), and allegation rejected or withdrawn (n = 6; unknown = 6).

Comparison to the results in the 2007 survey

Response rate: In the 2007 survey, we gathered data for 284 cases covering one-and-a-half years, from July 15, 2005 (the date of enforcement) to January 15, 2007. Based on the assumption that 388 cases of HfA occur annually, the capture rate was estimated to be 48.8%. No statistically significant differences existed in the capture rate between the two surveys (χ^2 = 2.09, df = 1, P = 0.15).

Demographic data: Of the 284 cases, 196 were men and 76 were women (unknown = 12), which did not significantly differ from the 2013 survey (χ^2 = 0.00087, df = 1, P = 0.98). The mean age of the patients was 43.2 ± 13.9, which was slightly lower than that of the 2013 survey (unpaired t-test without the assumption of equality of the variance, t = −2.22, df = 280.507, P = 0.027).

The issued offenses were homicide (n = 41), attempted homicide (n = 33), arson (including attempted arson; n = 74), robbery (including attempted robbery and robbery with injury; n = 14), injury leading to death (n = 6), rape (including attempted rape; n = 5), injury (n = 91), sexual coercion (n = 7), and unknown (n = 13). In 61 cases (21.5%), at least one psychiatric testimony was performed before the allegation, and this testimony was more likely to be conducted in 2013 (χ^2 = 8.56, df = 1, P = 0.004). The decisions prior to the HfA submission were as follows: no prosecution by reason of insanity (prosecutor; n = 220), suspended prosecution by reason of diminished responsibility (prosecutor; n = 10), not guilty by reason of insanity (court; n = 2), suspended imprisonment with diminished responsibility (n = 23), and "other" (n = 29).

For the 2007 data, the dominant psychiatric diagnoses were as follows: F0 17, F1 15, F2 204, F3 29, F4 4, F5 1, F6 3, F7 10, F8 1, and F9 0. 33 patients received psychotropic injections, 6 patients started LAI, and 2 patients received electro-convulsive therapy. Injections were less common during HfA in 2013 (χ^2 = 7.54, df = 1, P = 0.006). Some 194 patients were secluded for a mean of 37.1 ± 26.5 d and 57 were not secluded (unknown = 33), while 15 patients required physical restraint during HfA.

In 221 cases, the examiner psychiatrist was from the HfA facility to which the patient was hospitalized, whereas a psychiatrist from another hospital took up that role in 59 cases (unknown = 4 cases). The examiner psychiatrist was more likely to belong to the HfA facility to which the patient was hospitalized (χ^2 = 5.32, df = 1, P = 0.02). The panel verdicts were hospitalization order (n = 137), community treatment order (n = 57), no treatment/release (n = 44), allegation rejected or withdrawn (n = 7; unknown = 39). Hospitalization orders were more likely to be provided in the 2013 data than that in the 2007 data (χ^2 = 19.76, df = 3, P < 0.001). The results of the comparison are summarized in Table 3.

DISCUSSION

In this study, we attempted to clarify the current focus of HfA as well as the changes in its operation. We gathered data for almost half of all cases subject to HfA in 2012-2013 and compared it with the data in 2005-2007. This revealed several important considerations for the proper management of patients under HfA.

Approximately one-third of the facilities accepting HfA cases were administered by an official state organization. Considering that more than 90% of psychiatric hospital care is administered by the private sector in Japan, and that the majority of private hospitals accept official involuntary hospitalization cases[16], private hospitals appear reluctant to participate in HfA. Moreover, there tended to be higher staffing levels in facilities accepting the HfA cases; that is, only hospitals with adequate staff could cope with the offenders with mental disorders.

In our study, men were 2.5 times more likely to be subject to HfA than women. Men are known to commit crimes 5-10 times more often than women, particularly homicide[17,18], yet a higher proportion of women (19/76 = 25%) committed homicide in our study (21/196 = 10.7%) (χ^2 = 6.23, df = 1, P = 0.01). This may have been due to the considerable amount of infanticide cases by mothers, which is common in Japan[19,20].

The mean age of offenders in the 2013 survey was significantly higher than that in the 2007 survey.

Table 3 Comparison between the datasets obtained in 2007 and 2013

Year		2007	2013	*P* value
n		284	171	
Gender	Male	196	123	0.98[1]
	Female	76	48	
Mean age		43.2 ± 13.9	46.6 ± 16.4	0.027[2]
Psychiatric testimony	No	223	112	0.004[1]
	Yes	61	59	
Psychiatric diagnosis	F0	17	18	NA
(ICD-10)	F1	15	13	
	F2	204	111	
	F3	29	14	
	F4	4	1	
	F5	1	0	
	F6	3	2	
	F7	10	9	
	F8	1	2	
	F9	0	0	
Injection	No	251	166	0.006[1]
	Yes	33	5	
Depot	No	278	170	0.26[3]
	Yes	6	1	
Electroconvulsive therapy	No	282	171	0.53[3]
	Yes	2	0	
Seclusion	No	57	32	0.8[1]
	Yes	194	116	
	mean term (d)	37.1 ± 26.5	32.2 ± 27.1	0.12[2]
Restraint	No	269	148	0.83[1]
	Yes	15	10	
Examiner Psychiatrist	No	59	20	0.002[1]
belongs to the hospital where	Yes	221	142	
the patient was hospitalized				
Verdict	Hospitalization	137	120	< 0.001[1]
	Community treatment	57	12	
	No-treatment	44	57	
	Rejected or withdrawn	7	6	

[1]χ^2 test; [2]Unpaired *t*-test (data shown by mean ± SD); [3]Fischer's exact test. NA: Not available.

Considering that the mean age in Japan increased from 43.7 in 2007 to 45.5 in 2013[21], this difference may be consistent with societal trends. Furthermore, most offenders had no history of marriage, which is also consistent with a questionnaire survey of mental health care users in which just 13.0% (132/1016) of the participants lived with a spouse[22]. In contrast, 80% of the responders had an occupational history. In another survey of psychiatric outpatients, we reported that 40% of patients had no current occupation[23], while a survey of mental healthcare users revealed that one-fourth earned enough money for daily living[24]. Even after accepting the limitations of combining these findings, it appears that forensic patients have superior occupational performance to standard psychiatric outpatients. The relationship between executive function and offending in patients with mental disorders remains controversial[25], and further analyses with sophisticated datasets will be required to investigate the association between occupational history and serious offending.

Almost half of all offenders in these surveys were under ongoing psychiatric treatment, and relatively few were therapy naïve. This is much different from that reported in other countries[26]. It may therefore be essential to enrich the care for patients already attached to medical practitioners, rather than to introduce a new treatment pathway for patients without a therapeutic history. This approach could reduce serious crimes by patients with mental disorders in Japan.

The percentage of HfA cases implementing the use of psychiatric testimony increased between the survey periods, suggesting that prosecutors have come to consider the criminal responsibility of offenders deliberately. This tendency is consistent with the establishment of the Lay Judge Act (2009). According to this new legislation, in the case of serious crimes where the defendant can be subjected to the MTS Act, a lay judge system is used; since its enforcement, psychiatric testimony has been more common in Japan[27,28]. Prosecutors appear to require psychiatric testimony in any cases of questionable criminal responsibility, subject to the lay judge system, leading to a higher proportion of psychiatric testimony in HfA cases. This is advantageous in terms of clarifying diagnoses, but can delay medical treatment that tends to be withheld during psychiatric testimony, which may

cause the offender's mental state to deteriorate.

Most offenders subjected to the HfA in these surveys had schizophrenia or some other psychotic disorders. This is expected considering only those considered to be irresponsible or to have diminished responsibility were subject to HfA. In contrast, dual diagnoses were identified in approximately one-fifth of the cases, which is less than that previously reported in other countries[26,29]. It was reported that 23.3% of inpatients treated under the MTS Act in designated hospitals had dual diagnosis, including intellectual disability, developmental disorders, and substance misuse[30]. This discrepancy suggests that dual diagnoses were overlooked in some cases at the HfA stage. Deeper investigation is necessary to make a precise diagnosis during HfA to determine the best treatment strategy for the subjects.

The majority of the offenders were prescribed medication, which is rational considering the fact that most of them were diagnosed with schizophrenia. Facilities accepting HfA cases seem to be disciplined in prescribing medications for the offenders in the same way as they would for other patients with mental disorders, as recommended by expert consensus[9]. However, fewer offenders received injectable psychotropic drugs during HfA in the 2013 data than that in the 2007 data. This could suggest that recent offenders were adequately treated with oral medication and did not need injections. A solid knowledge base and sophisticated HfA procedures probably help in minimizing the reliance on invasive treatment. On the other hand, accumulating evidence suggest the efficacy of LAI of antipsychotics upon patients with psychosis[31,32]. It is highly estimated that offenders with psychotic disorders are adaptable to LAI in terms of maintaining compliance and stabilizing their mental state. However, the term of HfA is limited to 2 or 3 mo. Introduction of LAI at the initial stage of HfA has some difficulties, such as the risk of misdiagnosis and acquiring informed consent. Forced LAI induction is not recommended by experts in the HfA[9]. An appropriate strategy of using LAI in the HfA should be established.

Most offenders were secluded during the HfA process, although the precise term of seclusion varied. Therefore, the likelihood of seclusion was much higher than that in acute psychiatric units in the US[33]. In Japan, the standard management of patients with schizophrenia, and therefore risk for harm to others, tends to involve physical seclusion[34]. Our surveys revealed that the proportions of secluded offenders have not changed since the MTS Act was enforced. One of the reasons for frequent seclusion in Japan seems to be a small number of nursing staff, as experts recommended rich human resource in the HfA setting[9]. The fact that the seclusion rate per bed in a year is only 0.1-0.2 in designated inpatient facilities[35] is consistent with the estimation above. Although restraint was less frequent than seclusion, it continues to be used at similar rates in 2013. Reductions are necessary in both these areas, when possible.

While this is a controversial topic, it is recommended that the examiner psychiatrist should be selected from among the psychiatrists at the hospital where the offender is hospitalized because this brings practical advantages[36]. In almost 90% of respondents in the 2013 survey, the examiner psychiatrist met this criterion, which had increased from the 2007 data. This result suggests improved processes for selecting the examiner psychiatrist.

In terms of the panel decisions, hospitalization orders were more common in the 2013 data than in the 2007 data, and community treatment orders were less frequently adopted. We assume that the panel has become more defensive over recent years. In July 2007, the Supreme Court made a verdict that it is inappropriate to withhold treatment orders for offenders who need psychiatric care as part of the MTS Act simply because adequate care can be provided through the Mental Health and Welfare Act[37]. After this verdict, offenders requiring any inpatient care were to be hospitalized in designated inpatient hospitals under the MTS Act, regardless of the severity of their mental disorders. Another possible explanation is more practical; some years after the MTS Act was brought into law, several hospitals opened new wards to accept the cases of MTS act. It is possible that bed shortages initially suppressed the decision to hospitalize patients early after the introduction of the MTS Act.

In conclusion, the characteristics of offenders with mental disorders did not change between the two survey periods. In contrast, treatment and administration of subjects under the HfA has improved to some extent. Nevertheless, several challenges must still be overcome to ensure proper treatment in the HfA setting.

The main limitation of this study is its inherent selection bias. All respondents of our survey voluntarily returned the questionnaires we sent. Therefore, it is possible that only those facilities in which the staff was willing to participate in the HfA responded to our survey. Even after confirming that the proportion of cases was consistent with that in official reports, care should be taken when generalizing our results to the broader HfA landscape.

COMMENTS

Background

There had been broad controversy regarding the treatment of offenders with mental disorders. Some major associations around mental health practitioners were opposing to establishment of forensic mental health scheme, insisting such a policy would strengthen the discrimination against the patients with mental disorders. Even now some people including mental health experts are involved in the movement aiming the repeal of the Medical Treatment and Supervision (MTS) act. There was also a broad argument which were responsible for the administration of the hospitalization for assessment (HfA) scheme. Neither the Ministry of Justice, Ministry of Health, Labour and Welfare, or the Supreme Court are willing to handle the HfA management. The authors are strongly concerned about the risk that some patients are inappropriately treated in the HfA because their situation has not been clarified by the

authorities. It is the motive of conducting this study.

Research frontiers

There are several topics around the MTS act. Besides the HfA scheme, decision making for the patients with developmental disorder, substance misuse, and/or personality disorder are often discussed. Although inpatients treatment strategy has been established, outpatient care is still inadequate in terms of social resource. How to deal with the patients who hardly respond to the treatment is another issue, as the same in foreign countries.

Innovations and breakthroughs

This article is the first paper reported in English about the current situation and challenges of the HfA scheme in Japan, as far as we know. This scheme was started only eight years ago. Therefore, the authors considered the importance of recording the concurrent situation, perhaps valuable for further reference in the future.

Applications

Medical practitioners and lawyers engaging in the MTS act management should know the fact described in this article. This study itself is quite domestic, but the authors are planning to conduct some international comparison studies about this region, to improve the forensic mental health systems in each country.

Terminology

The authors have described some essential words to understand the MTS act in the main article.

Peer-review

One of the reviewers assessed this article as a paper aimed to investigate the components of HfA and the management changes from 2005 (when a new forensic mental health legislation has been introduced) to the present using mailing questionnaire surveys between 2005 and 2013. The authors are thankful for good understanding of our work to the reviewers.

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Systematic review of suicide in economic recession

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Abstract

AIM: To provide a systematic update of the evidence concerning the relationship between economic recession and suicide.

METHODS: A keyword search of Ovid Medline, Embase, Embase Classic, PsycINFO and PsycARTICLES was performed to identify studies that had investigated the association between economic recession and suicide.

RESULTS: Thirty-eight studies met predetermined selection criteria and 31 of them found a positive association between economic recession and increased suicide rates. Two studies reported a negative association, two articles failed to find such an association, and three studies were inconclusive.

CONCLUSION: Economic recession periods appear to increase overall suicide rates, although further research is warranted in this area, particularly in low income countries.

Key words: Economic recession; Suicide; Unemployment; Time series; Systematic review

Core tip: This review provides evidence for an association between economic recession and suicide at the ecological level. There is also evidence that the most recent recession is associated with an increase in suicide rates in high income countries such as Europe and North America. Methodological issues somewhat limit the comparability of some of the studies. High income countries were overrepresented in included studies, meaning that future studies in this area should focus their analyses on low and middle income countries wherever possible. More individual level analyses are also required in order to identify causal associations between economic recession and suicide.

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INTRODUCTION

In the aftermath of the deepest recession since the 1930s, which resulted in a global economic downturn and a subsequent loss of an estimated 30 million jobs worldwide[1], it is worth revisiting the academic literature on the public health effects of economic recession. Of particular interest is the effect of economic recession on suicide rates, as increased suicide rates can be understood as a manifestation of psychosocial stress in populations, which may increase in periods of recession. This area was a topic of interest for academics even in the preceding two centuries[2,3] and suicide has become an increasing public and global health problem, with a 60% increase in global suicide rates over the last 45 years[4].

An economic recession can be described as a sustained reduction in economic productivity which is often measured through indicators such as gross domestic product (GDP) and unemployment rates. An economic recession can also be placed within an economic (or business) cycle in which there are cyclical upturns and downturns in the performance of an economy; with economic recessions representing cyclical downturns[5]. Thus, the National Bureau of Economic Research in America defines economic recessions as "contractions that occur within an economic cycle"[6]. Suicide rate changes in relation to the economic cycle can be described as pro-cyclical if the rate increases as an economy experiences a cyclical upturn, or counter-cyclical if the rate increases during a cyclical downturn in the performance of an economy[5].

Previous studies have either reviewed the literature that has been published within a year[7], or have systematically examined all the literature published in the last few decades[8-10], or have analysed specific major recessions[11]. In this review we aim to critically examine the literature focused on the relationship between completed suicide rates and economic recession. Thus, this review adds to previous studies by also including literature published in the last few years, with a focus on the effects of the most recent economic recession, which commenced in 2007 and is known as The "Great Recession".

MATERIALS AND METHODS

The "Ovid SP" database search interface was used to search for articles published over the period from January 1992 to March 2014 pertaining to our research topic in the following databases: Ovid Medline (R), PsychINFO, Embase Classic, Embase and PsychARTICLES. The search strategy used the following keywords including cross-referencing: (econom*, financ*, cris*, cycl*, recessio*, depressio*, trend*decline, stagnation, contraction*, downturn*) and (suici*, mortality, mental health).

The search was limited to English language papers only. In addition, the world- wide web, google scholar and citation tracking were used to identify papers in the "grey" literature outside the above official databases.

The following inclusion criteria were applied to the abstracts or the full article as appropriate: (1) Studies published in peer-reviewed journals; (2) Only studies focused on the association between economic recession and suicide "completions" were included, *i.e.*, studies reporting on suicide attempts were not considered; (3) Economic indicators such as unemployment rate and GDP had to be reported in order to define a recession period or to act as a proxy for an economic recession; and (4) All age groups were considered.

Exclusion criteria were: (1) Qualitative studies, *i.e.*, with no quantitative data at all; and (2) Studies based solely on cities/neighbourhoods and not including national data or trends.

RESULTS

The literature search initially yielded 3086 references of which 93 were identified for full text review. Of these 93 studies, 38 were included in this review (Figure 1). Specifically, 31 studies found a positive association between economic recession and increased suicide rates following the onset of recession. Two studies reported a clear overall negative association between economic recession and suicide (*i.e.*, economic recession appearing to be a protective factor for suicide at the ecological level), two studies did not find an association and three studies were inconclusive in their findings (Tables 1 and 2). Tables 3 and 4 provide a short critique of every included study.

Positive association studies

Of the studies finding a positive association between economic recession and suicide, 29 were time-series studies (Table 1) and two were cohort studies[12,13]. Five of the positive association studies only used descriptive statistics to clarify the relationship between economic recession and suicide[14-18]. The remaining positive association studies generally utilised regression or correlation analyses (or both) to investigate this association. A subset of the positive association studies used similar study designs where regression analyses were performed on panel data[19-25]. In these studies, national and regional unemployment rates were used to proxy economic cycles consisting of recessions and booms. A few studies also used statistical techniques which provided estimates of excess mortality attributable to recession[23,24,26-28]. Most of the positive association studies were conducted in

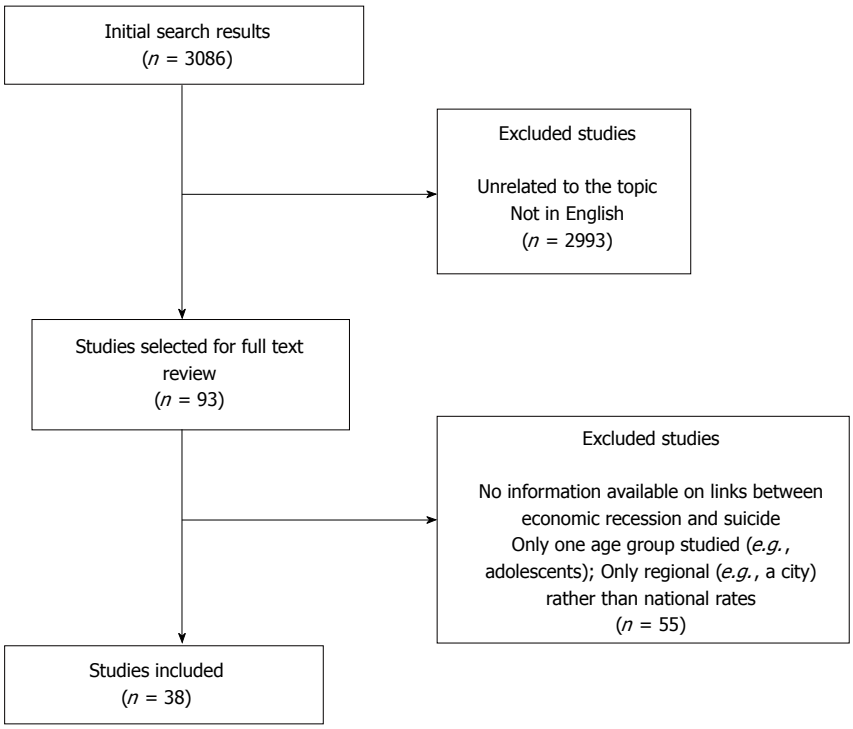

Figure 1 Flow chart of systematic literature search and review.

high income countries, particularly in the United States and Europe. A few studies were conducted in Asian countries[14,15,28-30], the Asian Financial Crisis in the late 1990s being the economic recession of interest for most of these studies[14,15,28]. In addition to the Asian Financial crisis other positive association studies investigated the "Great Recession", which began in 2007[17,23-27,30-34], the recession associated with the collapse of the Soviet Union in the early 1990s[16,21,35], and the Great Depression of the 1930s[18].

Negative association studies and inconclusive studies

Seven studies[35-41] either reported a clear negative association between economic recession and suicide, no association or were inconclusive. Of note, all these studies were time-series studies (Table 2) with the majority of them using panel data. Two of the studies in this category reported a clear overall negative association between economic recession and suicide[36,37]. Two studies failed to find an association between economic recession and suicide rates[39,41] and the results of three studies were inconclusive[35,38,40]. These studies were classified as "inconclusive" due to either reporting both positive and negative associations between economic recession and suicide across different countries[38], mixed results depending on the specific analysis[40]; or a lack of power to infer robust conclusions from the results[35].

Studies in this category either investigated the impact of multiple economic cycles on suicide rates[36,39,40], or the impact of specific recessions such as the Great Recession[38,41], the Post-Soviet economic collapse[35] and others[37]. Nearly all the study settings were European countries with the exception of one study conducted in Mexico[36].

DISCUSSION

This systematic review appears to show an association between economic recession and increased suicide rates. However, several methodological limitations must be considered when interpreting these results.

Methodological issues

The designs of the included studies varied widely, particularly the way in which economic recession was defined. This heterogeneity in study design and exposure measures limited comparisons across the studies. The main methodological difference concerning statistics across the selected studies was whether regression or correlation analyses were performed rather than only performing descriptive analyses on time-series data. There were also studies investigating the interaction between economic recession and suicide over multiple economic cycles which did not allow us to draw conclusions from specific recession periods within the study periods that were investigated[12,19,20,22,29,36,39,40,42-49]. These studies used regression analyses to analyse the impact of these economic cycles on suicide rates. Thus, domestic product or national and regional unemployment rates, were used as recession indicators where cyclical variations in unemployment rates or GDP represented booms (periods of high economic productivity) and recession periods. These studies were therefore difficult to compare with those using pre-defined

Table 1 Positive Association Studies

Ref.	Countries studied	Study design	Suicide data source	Recession period	Economic indicator(s) used	Findings
Yang[45]	United States	Time series study Multiple regression analysis	Hollinger P.C Violent Deaths in the United States New York: Guild 1987[63]	Not Specified	Gross National Product per capita Unemployment rate	Total suicide rates were significantly and positively associated with increases in gross national product per capita and unemployment rate ($P < 0.05$ for both) However, total suicide rates were significantly and negatively associated with increases in gross national product with a one year lag ($P < 0.05$)
Lester *et al*[47]	United States and Japan	Time series study Pearson correlation analyses and regression analyses	Annual volumes of Vital Statistics of the United States	Not Specified	Change in Gross National Product Unemployment Rate	Increase in unemployment was significantly and positively correlated with increase in suicide rates in both the United States and Japan ($P < 0.05$ for both). Regression analyses, however, only showed a positive and significant relationship between unemployment and suicide rates in Japan ($P < 0.05$)
Gavrilova[16]	Russia	Time series study Descriptive statistics	Gokomstat (Russian statistical committee)	1992-1993	Average real earning and consumer prices	Male suicide rate + 61% and Female Suicide Rate + 22% over 1991-1994 Male morality rate (per 100000) 1991: 47.7 1994: 76.9 Female Mortality Rate (per 100000) 1991: 11.6 1994: 13.2
Ruhm[19]	United States	Panel Study Regression analysis	US Census Bureau	Not Specified	Unemployment Rate	Suicide rate predicted to increase by 1.3% for every percentage point increase in unemployment rate ($P = 0.05$)
Brainerd[21]	22 former Soviet Bloc Countries	Panel study using regression analysis	World Health Organisation "Health For All" Database 2000	1990-1994	Gross national product per capita and employment to population ratio	A $100 increase in GNP per capita predicted a decrease in suicide rate by 0.14% ($P > 0.05$) to -0.20% ($P < 0.01$) in males A one percentage point increase in employment to population ratio predicted decreased suicide rates in males by 3% ($P < 0.01$)
Lester[42]	United States	Panel Study Regression analysis	Statistical Abstract of the United States	Not Specified	Gross state product per capita Female labour force participation	A one percent increase in gross state product per capita was associated with a 0.45% decrease in total state suicide rates and a 0.55% decrease for male suicide rates ($P < 0.05$ for both)
Kim *et al*[28]	South Korea	Time Series Study Descriptive statistics and regression analysis	1999 report on cause specific mortality by the South Korean Statistical office	1997-1999	Unemployment rates and GDP	Suicide cases increased for three months after the recession onset, but decreased after this point Estimated excess suicide mortality caused by recession = 5.1 in 1998 and 0.5 in 1999 ($P < 0.01$ for both estimates)
Gerdtham *et al*[12]	Sweden	Cohort Study using descriptive statistics and probit regression	Statistic Sweden's Survey of living conditions	Not specified	Advanced notification of job loss, changes in GDP, deviation from GDP trends unemployment rates, industry capacity utilisation, and industry confidence indicators	A one standard deviation increase in GDP decreased the risk of suicide by 22.7% ($P < 0.05$) A one standard deviation increase in the confidence indicator reduces suicide risk by 22.3% ($P < 0.05$). A one standard deviation decrease in the advanced notification of job loss rate, decreased suicide risk by 21.5% ($P < 0.05$)
Khang *et al*[15]	South Korea	Time-series Study Descriptive statistics	Death certificates from South Korean Statistical office	1997-2002	Unemployment rate and GDP per capita	Substantial increase in suicide rates post 1997 in males and females, and then a decline in the rate in both sexes until 2000 Age specific male and female suicide rates (per 100000) in 1996 and 1998: 1-14: MF = 0.8 (1996) and 0.8 (1998) 15-34: MF = 13.5 (1996) and 16.5 (1998) 34-65: M = 26.4 (1996) and 44.3 (1998) F = 8.9 (1996) and 11.9 (1998) 65-79: M = 42.4 (1996) and 58.5 (1998) F = 15.8 (1996) and 22.3 (1998)
Tapia Granados[44]	United States	Time series study Regression analysis	Historical Statistics of the United States	Not Specified	Unemployment rates	Suicide rates significantly associated with increases in the rate of change of unemployment rates from 1920-1944 ($P < 0.01$) and 1920-1996 ($P < 0.01$)
Granados[20]	Spain	Panel study Regression analysis	Instituto Nacional de Estadística. (National Statistics Institute)	Not specified	National and province level unemployment rates	Suicide rate predicted to increase by 1.28% for every percentage point increase in the unemployment rate ($P = 0.05$)

Chang *et al*[27]	27 European Countries 18 American Countries 8 Asian Countries One South African Country	Time series study	World Health Organisation Mortality Database and The Center for Disease Control Online Database (for the United States)	2008-2010	Gross Domestic Product and Unemployment	Overall suicide rates in men rose 3.3% (95%CI: 2.7-3.9) with a rate ratio of 1.033 (95%CI: 1.027-1.039) and an estimated excess mortality of 5124 (95%CI: 4219-6029) that could be attributed to the recession
Garcy *et al*[13]	Sweden	Time series study Cox regression	Swedish work and mortality database	1993-1996	Unemployment rates	No excess hazard of suicide mortality attributable to unemployment during the recession in men or women, although an excess hazard post-recession (1997-2002) in men (Hazard ratio = 1.43, 95%CI: 1.31-1.56) and women (Hazard ratio = 1.26, 95%CI: 1.04-1.54)
Chan *et al*[30]	South Korea	Time Series Study Regression analysis	National Statistical office of Korea	January 2009 to December 2010	Unemployment Rates	Between 2009 and 2010, there was a statistically significant positive association ($P < 0.001$ for most associations) between suicide rates and national unemployment rates in both the employed and unemployed except in employed men and women aged 50-59 and unemployed men aged 30-39
Madianos *et al*[32]	Greece	Time series study Descriptive statistics correlation and regression analyses	Vital Statistics Bureau of the Hellenic Statistical Authority	2008-2011	Unemployment Rates Debt as a percentage of Gross Domestic Product	Unemployment and debt as percentage of GDP were significantly and positively correlated with suicide rates $\rho = + 0.64$, $P < 0.001$ for unemployment, and $\rho = +0.47$, $P < 0.05$ for debt as a percentage of GDP In regression models, increases in unemployment and debt as percentage of GDP were significantly associated with increases in suicide rate ($P < 0.05$ for debt as a percentage of GDP and $P < 0.01$ for unemployment)
Phillips *et al*[25]	United States	Panel study Regression analysis	National Center for Health Statistics	2007-2009/2010	Unemployment Rates	Unemployment significantly ($P < 0.05$) and positively associated with changes in suicide rates but not in the elderly (65+) or young (15-24)
Pompili *et al*[33]	Italy	Time series analysis Joinpoint regression	Italian Mortality Database	2007-2010	Gross Domestic Product Unemployment rate	2006-2010: Age specific suicide rates increased in working age men (25-64) by 12% (RR = 1.12; 95%CI: 1.04-1.19), but not in older (65-85+) or younger age groups (1-24)
Reeves *et al*[26]	Europe and North America	Time series study	World Health Organisation Mortality Database and The Center for Disease Control Database	2008-2010 (Europe) 2008-2009 (Canada)	Unemployment rates	Using 2007 as a baseline, the excess suicide mortality attributable to the recession across the United States, Canada and Europe was 10000

recession periods and performing descriptive trend analyses on time series data[14-18,35], since the exposure measures differed so greatly. Since most of the included studies were ecological, inferences concerning individual suicide risk during times of recession should be made with caution. Only two studies[12,13] used a study design (cohort study) that allowed for individual level analyses and causality associations to be made.

Risk of bias

The main sources of bias in included studies are likely to come from deficiencies in mortality data. Omitted variables which influence suicide rates and are associated in some way with the onset of recession, are also a major source of bias. In the case of mortality data it is reasonable to assume that suicides are more likely to be underreported or misclassified rather than overreported since socio-cultural factors and the stigma associated with suicide, may potentially lead to underreporting. Indeed, one of the included studies[15] has raised concerns regarding the potential misclassification of suicides due to stigma. Because of this misclassification bias and the different ways in which suicides are classified and coded across countries, making international comparisons based on suicide data from different countries remains a contentious issue[34]. Since most of the studies in this review analysed populations in high income countries, with well-developed statistical authorities, it is unlikely that collected suicide statistics were grossly inaccurate and if a proportion were misclassified, the negative association between recession and suicide would be even more marked, meaning the findings of this review would underestimate the strength of the association.

Omitted variable bias may be a focus of concern in all selected studies, particularly those that did not conduct statistical analyses to take this potential bias into account. A number of panel studies attempted to mitigate the impact of omitted variable bias by using fixed effect regression analysis[12,19-22,24,25,40]. This kind of analysis

Table 2 Negative Association Studies and studies with inconclusive results

Ref.	Country studied	Study design	Suicide data source	Recession period	Economic indicators	Findings
Hintikka *et al*[37]	Finland	Time series Study Regression analyses	Causes of death statistics reported by Statistics Finland in 1996	1990-1995	Unemployment Rate and Gross Domestic Product	Female and Male Suicide rates positively associated with increases in GDP ($P < 0.05$)
Rancans *et al*[35]	Latvia	Time series study Descriptive statistics	Statistical Yearbooks of the Medical Statistics Bureau of the Latvian Ministry of Health and the Demographic Yearbooks of the Latvian Central Statistical Bureau	1990-1994	Gross Domestic Product and Unemployment rates	Rapid increase in suicide rates after 1989 reaching a maximum in 1993 (42.5 per 100000) The drop in GDP after 1990/1991 and the subsequent rise in unemployment did not correspond strictly with suicide rates changes
Neumayer[40]	Germany	Panel study using regression analyses	The German Federal Statistical Office	Not specified	Unemployment rates for initial analysis and gross domestic product for sensitivity analysis	A decrease in suicides for every percentage point increase in unemployment rate in males (0.98% decrease $P < 0.1$) and females (1.9% decrease $P < 0.05$) A decrease in suicides for every percentage point increase in unemployment rate in males (1.22% decrease NS) and females (1.97% decrease in females $P < 0.01$) Sensitivity analysis found that decreases in suicide rates were not associated with recession
Gonzalez *et al*[36]	Mexico	Panel study using regression analysis	Administrative records of death certificates	Not Specified	State Gross Domestic Product Per Capita	Decreases in state GDP per capita associated with decreases in the overall suicide rate across all states ($P < 0.01$)
Mackenbach *et al*[39]	25 European countries in Western and Eastern Europe	Time series study with regression analysis	International Mortality Data Base of the National Center for Health Statistics of the Centers for Disease Control	Not Specified	Gross Domestic Product	Changes in gross domestic product were not significantly associated with overall suicide rates across all countries in men and women
Saurina *et al*[41]	England and its sub-regions	Panel study using conditional and hierarchical mixed regression modelling	United Kingdom Office for National Statistics	2008-2010	Unemployment Rates	The increase in suicides between 2008 and 2010 was not statistically significant No significant association between unemployment rates and suicide at the national level, although at the regional level there were statistically significant negative and positive associations
Laanani *et al*[38]	Austria, Finland, France, Germany, the Netherlands, Spain, Sweden and the United Kingdom	Panel Study using regression analysis	Eurostat mortality database	2008-2010	Unemployment Rates	Overall 0.3% increase in suicide rates for every 10% increase in unemployment overall (95%CI: 0.1-0.5) Associations between unemployment and suicide within countries were inconsistent A positive significant association between unemployment and suicide in three countries: Netherlands, United Kingdom and France was found

NS: Non-significant; RR: Rate ratio; GDP: Gross domestic product.

reduces the effects of contextual differences that states or regions in a panel may have. This means that panel studies using fixed effects regression have the advantage of assessing the relationship between economic recession and suicide across many samples within a panel whilst also controlling for the effects exerted by unselected variables[19,25]. Other studies[36,37,39,42,45-47,49,50], which did not use panel data, attempted to reduce the effect of omitted variable bias by including variables that were anticipated to exert a confounding effect in regression models.

While a number of time-series analyses did not include potential confounders (such as alcohol consumption, divorce rates, public health expenditure or female labour force participation) in regression models, they attempted to make adjustments for trends within studied nation states that may have obscured the relationship between economic recession and suicide. Three of these analyses[28,30,41], attempted to adjust for autocorrelation within time series data; with seasonal variations in suicide rates being a manifestation of such autocorrelation. Studies using the aforementioned techniques to reduce the effects of omitted variable bias are less likely to have their

Table 3 Critique of Positive Association Studies

Ref.	
Yang[45]	This study uses aggregated population data and only investigates contemporaneous and very short term lagged effects of economic variables on suicide rates. This study supports the evidence of other studies based in the United States that economic recession can exert a short term impact on suicide rates; although the utility of this study in identifying causal associations is questionable
Lester *et al*[47]	No individual level evidence included in this study. Suicide rates by age category were not computed
Gavrilova[16]	Mortality data quality is questionable as is cause of death coding. Suicide data could have been inaccurately coded leading to underestimates of suicide mortality. No individual level evidence was included and only descriptive statistical analysis was performed
Ruhm[19]	No individual level data was included in the study. No information on suicide rates by gender was provided. The inclusion of 4 yr lags for unemployment lags, whilst an improvement on similar published studies only provides a short term insight into the interaction between fluctuations in unemployment and suicide rates
Brainerd[21]	Gross national product per capita and employment rates used in the study are likely to be underestimates. This means that regression estimates are more likely to identity regressors as not exerting an effect on suicide rates. The panel used in this study is biased by missing or incomplete data for a number of included countries. No individual-level data was included in the study
Lester[42]	Spatial analyses of suicide rates within states were not performed, thus providing no insight into any clustering of suicide mortality within states. Age specific suicide rates were not included although a breakdown of suicide mortality by ethnicity was. No individual level data was included in the study
Kim *et al*[28]	Mortality data was derived from death certificates which may not be fully accurate. The use of aggregated population data limits the ability to make causal inferences about the interaction between economic recession and suicide. An age breakdown of suicide rates was not provided
Gerdtham[12]	Unlike most other included studies, a large individual level dataset was collected using a prospective cohort study design. Numerous sensitivity analyses were performed to address potential flaws with the initial study design. However, the decrease in the male mortality rates is concentrated in the first few years of the study period meaning there may be an variable that has not been accounted for in the study that is causing this effect
Khang *et al*[15]	Concerns have been raised by this study about the quality of cause of death coding in South Korea which may have affected the accuracy of data in this study. Total suicides may have been underreported due to a miscoding of such deaths as being unintentional - as a result of stigma. Only descriptive analyses of suicide data were performed, meaning any omitted variable bias has not been corrected for
Tapia Granados[44]	This study benefits from analysing the impact of a number of economic cycles on suicide mortality over a long period of time. Data on suicide mortality and economic indicators were taken from a range of official statistical sources, to provide data for the century studied in the study. This study does not explore the effect of mediating factors which relate economic recession to suicide. By studying aggregated population data rather than individual level data, this study only provides evidence for an association between recession and suicide
Granados[20]	The study design used is very similar to the design used in Ruhm (2000)[19] and the finding that suicide rates increase during recessions is consistent with Ruhm's study. This study also expands on Ruhm's work by providing sex specific mortality rates. However like Ruhm's study, only short term effects of recession on suicide rates are explored; and the use of panel data can exacerbate attenuation bias resulting from underestimates of suicide mortality in official data. As with all ecological studies, the ability to make causal inferences between recession and suicide is impaired by a lack of individual level data
Berk *et al*[50]	Seasonality in suicide rates was not adjusted for in this study. No individual level data was included in this study either. Lagged effects of changes in included economic indicator were not computed
Granados[29]	Correlation and regression analyses were both performed in this study to elucidate the relationship between recession and suicide. The time series data in this study has also been detrended to make it more suitable for regression analysis. As the author suggests, the study would have been strengthened if a panel study design had been used as the association between economic recession and suicide could be tested across many sub-regions in Japan
Altinanahtar *et al*[49]	This study is notable for using auto regressive distributed lags which allow for the exploration of long run relationships between variables. This study's focus on Turkey is also notable as it is a middle income rather than a high income country and high income countries form the majority of countries studied by the literature. This study however does not study suicides according to age and gender and no individual level data has been included
Chang *et al*[14]	This study provides one of the first analyses of the effects of the 1998 Asian financial crisis on the main countries in the region who were affected. Of concern is the potential difference in the accuracy of suicide coding practices across studied countries as well as the completeness of suicide data. State specific effects such as political unrest (*e.g.*, in Hong Kong) were not fully controlled for in this study
Tapia Granados *et al*[18]	Regression analyses of the interaction between the depression and overall mortality were performed but not for suicide rates specifically. Only descriptive statistics were used to describe the interaction between suicide rates and the depression. A breakdown of suicide rates by age or gender was not provided
Stuckler *et al*[22]	Of note in this study is the analysis of the effect of social protection spending on the interaction between unemployment and suicide that this study performed. Using unemployment as a proxy for economic conditions, the effects of both smaller and larger increases in unemployment on suicide rates was tested as well. Other included studies tended to not perform the aforementioned analyses. This study only analysed the short term effects of recession and as with many of the included studies, this study was analysing the impact of recession on populations rather than individuals
Wu *et al*[46]	The authors of this study opted to detrend time series data in order to make it more suitable for regression analysis. The risk of omitted variable bias was well mitigated with the inclusion a range of potential confounders. The authors state that the results should be approached with caution due to data limitations, but these limitations were not specified
Ceccherini-Nelli *et al*[48]	Variations in suicide documentation across the four countries studied may vary which complicates comparisons made between these countries. The co-integration analyses performed in this study allow for the analysis of the long term interactions between economic variables proxying economic conditions and suicide rates; which is a major strength of this study. These analyses however only test for associations rather than causality

Luo *et al*[43]	The nonparametric analyses used in these studies did not allow for the analysis of the effect of recession severity or length on suicide rates, as all recessions were presumed to be of the same length and severity. Multiple regression analysis was not performed thus increasing the likelihood that omitted variables have biased the results
Stuckler *et al*[17]	This study represents a very preliminary analysis of suicide data from 2009. This means that any effects of the 2008 recession would not have arisen fully and any conclusions made based on data analysis may be premature
Barr *et al*[23]	The unemployment rate in this study is based upon the number of claimants of unemployment benefits which may underestimate the true unemployment rate. At the national level, the level of fiscal consolidation within England, does not seem to have been estimated or controlled. This is significant as this variable could influence both the unemployment and suicide rates, thus acting as a confounder. The sub-regions of England investigated in this study have different levels of deprivation and the unemployment rate may have differing impacts on the suicide rate in these regions, which are not expressed in the study itself. Only the immediate effects of economic recession have been investigated as the lagged effects have not been calculated
Reeves *et al*[24]	United States suicide data may underestimate the true suicide rate. The excess mortality estimates rely on short term extrapolations of pre-recession suicide trends
Lopez Bernal *et al*[31]	The use of interrupted time series analysis allowed for the controlling of seasonality in time series data. Unlike many other included studies, the extent of residual autocorrelation in the time series data was estimated and a control analysis was conducted; using mortality from accidental falls as an outcome measure rather than suicide mortality. Because of the low number of monthly suicide rates in some regions of Spain, regions within the country had to be combined in order to increase statistical power. This means there were less units of observation for the interaction between economic recession and suicide
Chang *et al*[27]	Differences in coding and classification of suicide may lead to an introduction of bias between countries, which may be exacerbated by the large number of countries studied (54 countries in this study). The sample of studied countries is also skewed by the presence of a large number of high income countries and an underrepresentation of low income countries; particularly from Sub-Saharan Africa. This means that overall excess mortality estimates may be more of a representation of the relationship between economic recession and suicide in high income countries than in low income countries
Garcy *et al*[13]	As in [12], this study analyses individual level evidence and the results seem to suggest a causal association. The great strength of this study is its very large sample size of individuals (more than 3 million) and the inclusion of a range of socioeconomic variables within the cox regression analyses that were conducted. As this study provided further analyses where individuals who had previously attempted suicide or had a previous mental health diagnosis were excluded, the relationship between unemployment and suicide in this study is less likely to be spurious; especially considering the fact that this study has been conducted at the individual level. However this study could not test whether mental health deteriorated as a result of unemployment meaning the behaviour of an important mediating factor has not been elucidated in this study
Chan *et al*[30]	Suicide data derived from death certificates may be more vulnerable to misreporting bias. This study attempts to focus the study of the South Korean population by stratifying by occupational status as well as gender; although the flaws associated with using aggregated population data remain. The inclusion of students and housewives in the "unemployed" label used by the S. Korean national statistical office, may distort the relationship between economic recession and suicide rates as these groups may respond to the onset of recession quite differently compared to those who lost their jobs as a result of recession
Madianos *et al*[32]	The study only explores the short term effects of economic recession on suicide rates. Monthly and regional suicide rates which may have provided a greater insight into the timing and spatial distribution of suicides were not included
Phillips *et al*[25]	This study performed age and sex stratified analyses of the association of between included economic variables and suicide rates. The authors acknowledge the potential impact of omitted variables such as gun ownership which were not included in analyses because of a lack of comprehensive data
Phillips *et al*[25]	This study only provides evidence of changes in suicide mortality during an economic recession. Data is provided up until 2010 but negative GDP growth only stopped in 2013 with a return to recession in 2014. Therefore this study does not capture the full extent of the suicide mortality response to recession conditions
Reeves *et al*[26]	The confidence intervals for the estimated excess European suicide mortality attributable to the recession are quite wide. The unadjusted difference between baseline suicide rates and recession suicide rates are compared to estimate suicide rates; meaning that the impact of confounders has not been adjusted for, nor has any seasonality in the time series data been controlled

results distorted by such a bias compared to those selected studies using only descriptive statistics[14-18,35].

Differences in the use of economic indicators

The use of different economic indicators in the included studies to proxy or define the occurrence of an economic recession may have affected the results. For instance, using GDP, which is one of the main economic indicators used to demarcate a recession period, might be to some extent distant from the experience of people living through recessions. Also, this is a measure which provides no insight into how wealth is distributed within countries. For instance, a country experiencing a recession in which there is a moderate contraction in GDP, could be more severely affected than another country that had a more equal distribution of wealth but a more severe contraction in GDP.

However, unemployment rates may be an insensitive indicator of recession as demonstrated by one of the selected studies[40]. The negative association found between economic recession and suicide in this analysis (with unemployment rates as an economic indicator) was not supported by a further sensitivity analysis performed within the study using GDP growth as an indicator[40]. Hence, this may indicate that certain markers are less effective indicators of economic conditions.

Unemployment rates also tend to be a lagging indicator of recession, so using unemployment rates alone may cause a different period of time to be specified as a recession period, rather than the actual recession period as defined by conventional GDP measures. Alternatively, studies including multiple economic indicators could more accurately proxy and define economic recession. In one study[12], only half of the economic indicators used were associated with changes in suicide rates. Therefore, it could be speculated that if only one indicator was used in this

Table 4 Critique of Negative Association and Inconclusive Studies

Ref.	
Hintikka *et al*[37]	Potential confounding variables such as state health expenditure were not included. Finnish suicide data seems to be highly reliable so incomplete data is less likely to be a major source of bias. The finding that rapid increases in unemployment were not associated with increases in suicide rates is interesting, but the lack of individual level evidence means that underlying explanations for this association cannot be arrived at from this study alone
Rancans *et al*[35]	Only a descriptive analysis of economic and suicide data was performed here meaning the effect of any confounding variables was not controlled for. This study only demonstrates a simple temporal association (or strict lack of it) between unemployment rates, gross domestic product, and suicide rates
Neumayer[40]	The panel study design used here is very similar to Ruhm, 2000[19]. Interestingly on sensitivity analysis using gross domestic product as the main proxy for economic fluctuations, variations in suicide mortality no longer behave pro-cyclically. As with the other included panel studies, attenuation bias may be a problem if suicide statistics underestimate suicide mortality
Gonzalez *et al*[36]	Age breakdowns for suicide mortality were not provided. No individual level analyses were performed in this study. This study takes great care in ensuring the quality of its mortality data; going as far as to test whether quality of death classification varies with the economic cycle
Mackenbach *et al*[39]	Differences in the accuracy and quality of cause of death coding and classification between countries and within countries over time may have biased the results of this study. The investigation into the relationship between income and mortality in this study implies a causal relationship between the two, although this is contentious
Saurina *et al*[41]	Using a different regression model to Barr *et al*, this study contradicts the findings of Barr *et al* despite the fact that the study location (England) and the study period are very similar. The authors of this paper argue that Barr *et al*'s methodology is incomplete and has probably produced a spurious relationship between recession and suicide due to not controlling for confounding variables; particularly those with a regional dimension. Despite claiming to improve upon Barr *et al*'s methodology, this study is still probably biased by the change in classification from ICD-9 to ICD-10 (although Barr *et al*'s study would be similarly affected). Furthermore the location of suicide (*e.g.*, rural or urban) may have a confounding effect; and this kind of spatial confounding may not have been adequately controlled for in this study
Laanani *et al*[38]	This study provides an interesting insight into the question of a causal link between recession and suicide. By performing a sensitivity analysis to check for confounding by a "crisis effect", this study found that such an effect varied between countries and the association between unemployment and suicide in studied countries was statistically significant, but fairly weak and variable. This however may be a reflection of the quality of unemployment as a proxy for economic conditions in studies that investigate multiple countries at once. This study also emphasises the inherent problem in trying to investigate causal associations between economic recession and suicide using ecological study designs

study, a spurious relationship between economic recession and suicide may have been found.

Study locations

Of relevance, the vast majority of the selected studies were conducted in either high or middle income countries. Hence, the relationship between economic recession and suicide in low income countries remains unclear and further research is therefore needed in this area.

The impact of high profile economic recessions in high and middle income countries, such as the Great Recession, the post-communist period in Russia (1991-1994) and the Asian Financial Crisis (1997-1998/9) have been the focus of recent research rather than recessions in low income countries, *e.g.*, 18 of 38 studies included in this review, reported on these recessions.

Mediating factors between economic recession and suicide

The effects of economic recession on suicide rates are multi-level; so its onset influences both the macro-socioeconomic and micro-socioeconomic environment of nation states. For instance, nearly all of the included studies investigated the impact of economic recession on the macro-socioeconomic environment, apart from the two studies that were performed at the individual level[12,13]. Generally, national unemployment rates and GDP acted as the main signifiers of the macro-socioeconomic environment within included studies (See "economic indicators used" column in Tables 1 and 2). As a major signifier of the macro-socioeconomic environment and a modifier of suicide rates, unemployment is arguably the main mediating factor that must be considered[51-57]. Another key factor may be indebtedness, which is related to unemployment since those who have become unemployed may take out loans to compensate for their loss of earnings[58]. Indebtedness has also been independently associated with suicide in certain studies[59,60], although this particular association may have been distorted due to the retrospective design of these studies. However, the interaction between recession, the macro-socioeconomic and micro-socioeconomic environments, may not have been sufficiently examined. For example, many of the studies in this review have explored the relationship between unemployment or GDP and aggregated suicide rates. However, these studies have not investigated the interaction between recession, individual level behaviours and the individual level environment-as signified by divorce rates, family structure, substance misuse and many other factors. This gap in the literature seems to be due to the lack of multi-level analyses in this area. These studies are indeed needed to gain a more in-depth understanding of the mediating factors at the individual level and the interactions between themselves.

In addition, the interaction between mediating

factors may also be liable to significant differences across cultures. For example, the role of employment and the subsequent potential mental health consequences in high income Western countries may not have the same effects in low income countries where unemployment could be more or less stigmatised. Such potential differences across countries highlight the complexity of the interaction between mediating factors with regard to the complex relationship between economic recession and suicide rates.

Mitigating the impact of economic recession on suicide

The role of unemployment and indebtedness in linking economic recession with suicide rates would provide some support for increased government spending on social protection (*e.g.*, unemployment benefits, healthcare and debt relief programmes) to act as a counterbalance against the increased financial stress which tends to occur in unemployed and heavily indebted populations during recessions. For example, one of the included studies identified a link between increased per capita spending on active labour market programmes[11] (which attempt to increase employment) and a reduction in suicide rates. This study also argued that the reason underlying suicide rates decreased in Sweden and Finland in the 1990s, when both countries suffered from economic recession, was their robust social protection programmes as well as active labour market programmes which assisted the unemployed in finding work. Such programmes may also explain why there was a clear overall negative association between economic recession and suicide in a study based in Finland[37].

Periods of economic recession may also highlight deficiencies in mental health services which may be put under extra strain during these periods. This could provide an opportunity to invest and improve mental health services, although this may be challenging in an environment where fiscal policies focused on reducing the overall size of the budget for health services are implemented. In other words, mental health services may face stiff competition for a declining pool of resources.

Social protection may potentially act as a buffer against the negative socioeconomic effects of recession. Therefore, developing social protection interventions would require a better understanding of the groups who are likely to be more exposed to the negative effects of an economic recession. For example, if increased unemployment was clearly demonstrated to mediate the relationship between economic recession and suicide rather than indebtedness, active return-to-work schemes may play a more relevant role in social protection spending than debt relief programmes.

Evidence for the effects of the great recession on suicide rates

Twelve studies investigated the impact of the Great Recession on suicide rates[17,23-27,30-33,38,41]. Ten studies[17,23-27,30-33] found evidence for an association between the recession and suicide rates, one study did not replicate such an association[41] and another study reported mixed results[38]. Europe and the United States were unsurprisingly the focus of this research effort and overall there does seem to be compelling country-level and international evidence from the studies included in this review that the Great Recession has had a significant impact on suicide rates in multiple countries. However, the findings from some studies have received different interpretations. For instance, the preliminary analysis of European suicide data by Stuckler *et al*[17] has been criticised for drawing premature spurious conclusions[61,62]. The results of Barr *et al*'s study from England[23] have been partially contradicted by another study on suicide trends in England after the Great Recession[41], which failed to find a statistically significant association between the onset of recession and suicide rates. These criticisms do not undermine the weight of the evidence in this area. Rather, they operate as a reminder that research in this area is highly complex and that the ecological study designs favoured by most of the included studies do not permit causal associations to be made.

In the light of this review, there are grounds to consider an association between economic recessions and increased suicide rates. However, various methodological differences between the study designs suggest caution in interpreting this finding. Moreover, the association between economic recession and suicide rates at a population level (as investigated by most of the included studies) provides little insight into the impact of economic recession on assessing suicide risk at an individual level. Since these studies have mostly been carried out in high and middle income Western and South-East Asian countries, future research in low income countries is needed, the recent 2007 recession period providing a good opportunity to conduct these studies. Also, multiple economic indicators should be used in order to better understand the underpinning of such a complex association. Overall, economic recession appears to lead to major socioeconomic changes at national levels which also may have an impact on suicide rates. In particular, these findings should become a focus of concern for researchers and policymakers in order to develop and implement specific suicide prevention strategies over these high-risk periods.

COMMENTS

Background

There exists a large body of literature that has investigated the relationship between economic recession and suicide across many different countries and time periods. Such studies have often proposed a sociological or economic framework for understanding how economic recession can influence suicide rates. In the years 2007 and 2008, the "Great Recession" occurred which was an economic recession of global proportions and was the most severe of its kind since the Great Depression of the 1930s. In light of this most recent recession, this review article seeks to provide a systematic update of the

research in this area as well as a more in-depth analysis of the strengths and limitations of individual articles.

Research frontiers

The current research hotspot is the synthesis of the academic literature concerning the interaction between the most recent recession of 2007 and suicide rates. This is an expanding area of inquiry. Future research frontiers will most likely include research into the interaction between economic recession and suicide in low and middle income countries, and individual level research into this interaction rather than population level. If more individual level analyses of the relationship between recession and suicide are produced, then future reviews will most likely focus on synthesising the results from these studies. If the heterogeneity across these studies is not an issue and these studies use similar designs and methodologies, it is at least conceivable that meta-analyses of individual level studies will be conducted; thus providing high level evidence of the individual experience of economic recession on suicide risk.

Innovations and breakthroughs

This review provides an up-to-date qualitative synthesis of the most recent published literature relating to the most recent recession as well as literature investigating past recessions. It is hoped that this will allow readers to compare the evidence from previous recessions to evidence pertaining to the most recent recession. The review is focused entirely upon suicide rather than on mental health or mortality more generally. A short critique of all included studies has been provided which highlight notable strengths and limitations as well as providing general insights. Issues concerning the measurement and definition of recession, the methodological issues that arise from this, and sources of bias are discussed in depth in this review. This review discusses the included studies in terms of broad study design categories whose relevance is explained. Crucially, this review surpasses previous reviews which have not taken account of the most recent evidence.

Applications

This review can be used to acquire a basic grounding in the research literature relating to the relationship between economic recession and suicide in the past few decades. It can also be used as a guide to specific published articles in this area as a short synopsis and critique is provided for each included study.

Terminology

Procyclical variations in suicide mortality refers to increases in suicide mortality as an economy grows. Countercyclical variance reflects an increase in suicide rate when economic recession occurs. Gross Domestic Product refers to the total market value of goods and services produced by a nation state or region. The consumer price index measures the change in value of a specified group or "basket" of goods commonly purchased by consumers. The "Great Recession" refers to the most recent global recession that began in 2007. Active labour market programmes are government programmes which attempt to actively intervene in labour markets to assist the unemployed in finding and acquiring work.

Peer-review

This is a very nice manuscript. There is a thoughtful review of the literature and a balanced overview of the conclusions. It might be useful to have a few short line of critique on each of the 11 individual articles as well.

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