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Contents

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EVIDENCE REVIEW

1167 Child abuse and psychopathy: Interplay, gender differences and biological correlates

di Giacomo E, Santorelli M, Pessina R, Rucco D, Placenti V, Aliberti F, Colmegna F, Clerici M

REVIEW

1177 Polyamines and polyamine-metabolizing enzymes in schizophrenia: Current knowledge and concepts of therapy

Bernstein HG, Keilhoff G, Laube G, Dobrowolny H, Steiner J

1191 Nuclear receptors modulate inflammasomes in the pathophysiology and treatment of major depressive disorder

Wang H, Kan WJ, Feng Y, Feng L, Yang Y, Chen P, Xu JJ, Si TM, Zhang L, Wang G, Du J

1206 Review of barriers and interventions to promote treatment engagement for pediatric attention deficit hyperactivity disorder care

Baweja R, Soutullo CA, Waxmonsky JG

MINIREVIEWS

1228 Newer antipsychotics: Brexpiprazole, cariprazine, and lumateperone: A pledge or another unkept promise?

Barman R, Majumder P, Doifode T, Kablinger A

1239 E-technology social support programs for autistic children: Can they work?

Wall NG, Smith O, Campbell LE, Loughland C, Wallis M, Henskens F, Schall U

1247 Factors related to compliance with the COVID-19 health regulations among young people

Jaureguizar J, Redondo I, Galende N, Ozamiz N

1259 Mechanism of olfactory deficit in neurotrauma and its related affective distress: A narrative review

Logan M, Kapoor S, Peterson L, Oliveira M, Han DY

1267 Physical activity and mental well-being during COVID-19 pandemic

Abdelbasset WK, Nambi G, Eid MM, Elkholi SM

ORIGINAL ARTICLE

Basic Study

1274 Differential aberrant connectivity of precuneus and anterior insula may underpin the diagnosis of schizophrenia and mood disorders

Aryutova K, Paunova R, Kandilarova S, Stoyanova K, Maes MH, Stoyanov D

World Journal of Psychiatry

Monthly Volume 11 Number 12 December 19, 2021

Contents

1288 Validity and reliability of the Dutch version of the displaced aggression questionnaire

Smeijers D, Denson TF, Bulten EH, Brazil IA

Case Control Study

1301 *BDNF* methylation and mRNA expression in brain and blood of completed suicides in Slovenia

Ropret S, Kouter K, Zupanc T, Videtic Paska A

1314 Developing a nomogram for predicting the depression of senior citizens living alone while focusing on perceived social support

Byeon H

Retrospective Study

1328 Affect regulation in psychoanalytic treatments of patients with a borderline personality disorder–psychoanalysis and psychodynamic psychotherapy–a comparison

Steinmair D, Wong G, Frantal S, Rohm C, Löffler-Stastka H

Observational Study

1346 Impact of lockdown relaxation and implementation of the face-covering policy on mental health: A United Kingdom COVID-19 study

Rathod S, Pallikadavath S, Graves E, Rahman MM, Brooks A, Soomro MG, Rathod P, Phiri P

SYSTEMATIC REVIEWS

1366 Autism spectrum disorder and personality disorders: Comorbidity and differential diagnosis

Rinaldi C, Attanasio M, Valenti M, Mazza M, Keller R

1387 Psychological impact of the COVID-19 pandemic on individuals with serious mental disorders: A systematic review of the literature

Fleischmann E, Dalkner N, Fellendorf FT, Reininghaus EZ

1407 Psychoeducation in bipolar disorder: A systematic review

Rabelo JL, Cruz BF, Ferreira JDR, Viana BM, Barbosa IG

Contents

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EVIDENCE REVIEW

Child abuse and psychopathy: Interplay, gender differences and biological correlates

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Abstract

Child abuse is an important source of mental and physical adverse consequences for victims, their family, and their community. The impact of violence during childhood on the development of the victim is a very sensitive theme. Other than internalizing symptoms, it is interesting to analyze the possibility that a victim may assume the role of persecutor. With this aim, we evaluate Literature and examine the interplay among different types of child abuse (emotional neglect, emotional abuse, physical neglect, physical abuse and sexual abuse) and the development of psychopathy. We consider the role of post-traumatic stress disorder and that of personal environment as potential mediators between abuse and psychopathy. Furthermore, an in-depth analysis on possible differences due to the victim's gender is performed. Finally, analysis focused on genetic variants, such as the polymorphism of 5HTT and MAO-A, or a biological alteration, like the difference in daily cortisol levels that could be related to the development of psychopathy after a trauma.

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Core Tip: Childhood trauma and psychopathy are strictly related; emotional abuse, emotional neglect and physical abuse show stronger association with the development of psychopathy. Even if sexual abuse is more frequent in females, most researches did not find a significant correlation between psychopathy and sexual abuse in both genders. Furthermore, trauma is the hallmark of secondary psychopathy causing, in a fragile mind, the uprising of mental illness.

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INTRODUCTION

Child abuse is a strong predictor of short and long term physical and mental illness. Five types of maltreatment are commonly recognized: Sexual, physical and emotional abuses (EAs) and physical and emotional neglect. Child sexual abuse is a serious concern with worldwide prevalence rates between 8%-31% for girls and 3%-17% for boys[1]. Every year, about 4%-16% of children are physically abused and one in ten is neglected or psychologically abused. During childhood, between 5% and 10% of girls and up to 5% of boys are exposed to penetrative sexual abuse, and up to three times higher numbers of children are exposed to any kind of sexual abuse[2].

Many research findings support the hypothesis that exposure to early life stress in the form of child abuse and/or neglect is associated with a huge increased vulnerability to major psychiatric and other medical disorders[3]. Research shows that children who have been physically or sexually abused have a greater risk of depression, suicidality, post-traumatic stress disorder, as well as antisocial personality disorder, psychopathic traits or psychopathy. Psychopathy is characterized by distinct interpersonal and affective traits (*e.g.*, manipulativeness, callousness), as well as a disinhibited, reckless lifestyle (*e.g.*, impulsivity, irresponsibility)[4].

The aim of the present narrative review is to evaluate the interplay between child abuse and psychopathy with special attention to gender differences and possible biological causes.

PRIMARY AND SECONDARY PSYCHOPATHY

An original theory differentiates the psychopathy in two subcategories: Primary psychopathy that have innate biological origins and could be characterized by low levels of anxiety and secondary psychopathy developed in response to adverse environmental experiences (Table 1). Primary psychopaths are incapable of emotions such as empathy and guilt, and so appear callous, cold, and lacking anxiety. In contrast, secondary psychopaths have a relatively normal capacity for emotional experience. Due to environmental stressors and trauma, however, they experience an excess of negative emotions and so exhibit high levels of anxiety and emotional distress, hostility, aggression, and impulsive behavior. Those differences would mirror the characteristics of the Psychopathy Checklist-Revised - PCL-R Factor 1 (F1; interpersonal and affective traits) and Factor 2 (F2; impulsive, antisocial, and chronically unstable lifestyle).

Dargis *et al*[5] studied the correlation between primary and secondary psychopathy (PCL:R) and trauma (Childhood Trauma Questionnaire-CTQ) in a sample of 110 psychopaths (PCL-R > 30) *vs* 112 inmates (PCL-R < 30). The psychopaths were split in 2 subgroups: Low negative affect (LN, n = 72) and high negative affect (HN, n = 38).

Table 1 Primary and secondary psychopathy

Ref.	Sample (women, %)	Tests	Significant association
Borja and Ostrosky[7], 2013	194 (0)	ETI - PCL-R	EA, SA (HP *vs* LP) and PA (HP, MP *vs* LP)
Craparo *et al*[13], 2013	22 (0)	TEC - PCL-R	Total score (early exposure)
Dargis *et al*[9], 2017	183 (0)	CTQ - PCL-R	Total score, EA, EN, PA and PN
Dargis *et al*[5], 2018	222 (0)	CTQ - PCL-R	Total score, EA, EN, PA, PN (HN); PA and PN (LH)
Gobin *et al*[11], 2015	88 (57.95)	CTQ - PPI	PA
Kolla *et al*[10], 2013	45 (0)	ETI - PCL-R	PA
Ometto *et al*[8], 2016	107 (43.92)	CTQ - PCL:YV	Total score, EN and PA
Poythress *et al*[15], 2006	615 (0)	CATS - PPI	Total score
Schimmenti *et al*[6], 2015	78 (0)	TEC - PCL-R	EA and PA (only to factor 2)
Schraft *et al*[14], 2013	170 (15.64)	CTQ - PCL:YV	Total score, EA, EN, PN
Woodfield *et al*[12], 2016	101 (0)	LEC-5 - SRP-SF	Total score

HN: High negative affect; LN: Low negative affect; LP: Low psychopathy levels; MP: Medium psychopathy level; HP: High psychopathy level; PA: Physical abuse; EN: Emotional neglect.

The HN subgroup scored significantly higher at the CTQ total score than the LN subgroup. In particular, the HN subgroup scored significantly higher in EA, PA, EN; while they did not differ for PN and SA. HN psychopaths scored higher than the other inmates at the CTQ total score and in all types of abuse except for SA. LN psychopaths significantly suffered more PA and PN than other inmates. The hallmark of the difference between secondary psychopathy (HN) and primary psychopathy (LN) was emotional neglect and EA that were significantly higher in HN compared to LN offenders suggesting that emotional maltreatment has specific associations with that subtype of psychopathy.

Schimmenti *et al*[6] evaluated the link between child abuse (CA) (measured with the Traumatic Experiences Checklist-TEC) and psychopathy (measured with Psychopathy Checklist-Revised - PCL-R) in 78 male prisoners. The EA was significantly related to the PCL-R total score, factor 1 (interpersonal/affective facets) and factor 2 (lifestyle/antisocial facets); while Physical abuse (PA) was linked only to factor 2. Furthermore PCL-R total scores were higher when EA occurred in childhood. As a consequence, the authors hypothesized a key role of EA in childhood; in fact, it was the best predictor of psychopathy scores and could distort the affective development of children, as implied in the construct of malignant narcissism, which has been theoretically proposed as a crucial dimension for understanding the inflated self-representation and lack of empathy among criminals.

Similarly, Borja *et al*[7] evaluated the relationship between several early traumatic events and psychopathy analyzing 194 male inmates with the PCL-R and the Early Trauma Inventory (ETI). They divided inmates in 3 subgroups: Those with low psychopathic levels (LP, n = 96, scoring 0-19 point at the PCL-R); inmates with medium psychopathy level (MP, n = 59, scoring from 20 to 29) and inmates with a high level of psychopathy (HP, n = 44, scores > 30). EA and SA were significantly higher in HP compared to LP group. Moreover PA was higher in MP *vs* LP and HP *vs* LP. After a regression analysis they found that early-life traumatic events and EA strongly influenced the PCL-R total score. Additionally HP and MP were exposed to more hostile environment than LP. Ometto and colleagues[8] underlined the relationship between abuse, detected through the CTQ, and the development of psychopathy (Psychopathy Checklist:Youth Version; PCL:YV) in 107 teenagers. The PCL:YV total score was positively correlated to the abuse and inversely correlated to the frequency of general social skill (measured with The Multidimensional Personality Questionnaire-Brief Form [MPQ-BF]). In the same study, Emotional neglect (EN) was positively related to the PCL:YV total factor and interpersonal, affective and lifestyle factors. PA was positively correlated to the PCL:YV total factor and affective, lifestyle and antisocial factors of the PCL:YV. Emotional and sexual abuse were not related to psychopathy. At a Multiple linear regression for the association of distinct types of maltreatment (CTQ) and social skills (Social Skills Inventory for Adolescents; SSIA) with psychopathic features (PCL: YV), EN was the only abuse related to psychopathy,

especially with the interpersonal Factor.

Dargis *et al*[9] examined psychopathy (PCL:R) and trauma (CTQ) in 183 inmates and discovered a significant correlation between the CTQ total score and Psychopathy, in particular PA, PN, EN and EA were significantly related to the PCL:R but no significant relation with SA was found. Factor 2 (lifestyle and antisocial features load) was related to the CTQ total score while EA, EN, PA and Factor 4 (antisocial features) were related to PA and CTQ total score; no link between factor 1 and trauma was detected. Dargis and colleagues evaluated Antisocial Personality Disorder (ASPD), trauma and Conduct Disorder (CD): PA was the only form of trauma related to ASPD while CD was related exclusively to SA. With the same aim, Kolla *et al*[10] evaluated the link among ASPD, psychopathy (PCL-R) and trauma in 45 subjects divided in 3 subgroups: 10 inmates with ASPD and psychopathy (PCL-R > 25), 15 ASPD without psychopathy (PCL-R < 25) and 15 non offenders. The first group reported greater physical abuse during childhood but no more sexual or EAs than those without psychopathy.

THE IMPACT OF POST TRAUMATIC STRESS DISORDER

Another important variable that deserves consideration is the role of PTSD in the interplay between trauma and psychopathy; the work of Gobin *et al*[11] analyzed this variable in 88 inmates (51 females and 37 males) evaluating ASPD (Structured Clinical Interview for DSM Axis II Personality Disorders; SCID-II), trauma (CTQ), psychopathy (Psychopathic personality inventory; PPI) and PTSD (PTSD checklist civilian version). Physical and crime-related trauma were associated with ASPD, while sexual abuse was not. Victims of PA were 5.04 times more likely to be diagnosed with ASPD than those without history of PA. Likewise, inmates with history of crime related trauma were 2.92 more likely to be diagnosed with ASPD than those without. PA was confirmed as the only type of trauma related to psychopathy, whereas the severity of PTSD symptoms was not related to the PPI or ASPD. The role of PTSD was also examined by Woodfield *et al*[12] They underlined a relation between psychopathy (Self-report psychopathy scale-short Form; SRP-SF), trauma (The life events checklist; LEC-5) and PTSD (The Posttraumatic Stress Disorder-checklist Version 5). The total LEC-5 score was significantly related to both primary and secondary factors, but the secondary had a stronger correlation with trauma. More importantly, only the secondary facet of psychopathy had a correlation with PTSD, showing a key role in moderating the effect of trauma on the development of PTSD. Specifically, trauma exposure was positively associated with increased PTSD symptoms in individuals with low levels of secondary psychopathy, and negatively associated with PTSD symptoms with those with high levels of secondary psychopathy. These findings contribute to the understanding of the nature of the relationships between PTSD, psychopathic facets, and trauma exposure, as the association between trauma exposure and PTSD is explained by secondary but not primary psychopathic traits.

Craparo *et al*[13] examined the role of age in mediating the effect of trauma on the development of psychopathy. They measured traumatic experiences (TEC) and traits of psychopathy (PCL-R) in 22 male subjects and suggested that an early exposure to relational trauma in childhood can play a relevant role in the development of more severe psychopathic traits. Indeed, subjects with higher PCL-R score experienced relational traumatic events earlier in life compared to the rest of participants. There was also a significant negative association between age at first relational trauma and psychopathy scores.

THE ROLE OF COMMUNITY VIOLENCE

Another variable that needs to be taken in consideration is the role of violence in the community in the relationship between trauma and psychopathy.

Schraft *et al*[14] highlighted the effect of community violence (Community Experience Questionnaire; CEQ) on trauma (CTQ) and psychopathy (PCL:YV) in their work on 170 detained adolescents (147 males, 23 females). The CTQ total score was positively correlated to the PCL:YV total score and scores of the PCL:YV behavioral and antisocial factors. The CEQ total score positively correlated to the PCL:YV total scores, as well as to scores of interpersonal, behavioral, and antisocial factors. EA, PN and EN were associated with higher levels of psychopathic traits. Higher levels of traumatic exposure within home and community were associated with higher levels of

psychopathic characteristics. Higher CEQ scores were related to higher scores in behavioral and antisocial facets of psychopathy.

PSYCHOPATHY, TRAUMA AND DISSOCIATION

Poythress *et al*[15] evaluated the role of Dissociative experiences (Dissociative experiences scale; DES) in the link between trauma (Child abuse and Trauma Scale; CATS) and psychopathy in 615 male inmates**.** Psychopathy, abuse, and dissociation scales were weakly but significantly associated one with another. Tests of correlation revealed that the lifestyle features of psychopathy were significantly more linked to abuse total scores than affective or interpersonal features. Furthermore, lifestyle feature of psychopathy was significantly more correlated to the DES total score than interpersonal features, but not to affective ones. Abuse was not related to interpersonal and affective features of psychopathy. In contrast, abuse exerted a direct effect on impulsive and irresponsible lifestyle, and that relationship was not mediated by dissociative experiences. Their research demonstrated that child abuse is positively linked, even if weakly, to psychopathy and moderately to the impulsive and irresponsible lifestyle of psychopaths without a significant mediation of dissociative symptoms.

BIOLOGICAL CORRELATES

Different studies analyzed the role of biological alterations that may link trauma and psychopathy (Table 2). Cima and colleagues[16] evaluated variations of salivary cortisol in 47 (24 psychopath and 21 non psychopath) inmates tested with the PPI scale for psychopathy, the CTQ for childhood trauma, compared to the group of non-psychopaths -control group (27 males). The salivary cortisol was analyzed four times a day at 8 am, 11am, 2pm and 4pm. Criminals, non-psychopathic as well as psychopathic, reported significantly more traumatic childhood experiences than the control group and the non-psychopathic criminals did not differ from psychopathic criminals except for PN, which difference was significant. Trauma and salivary cortisol were not related in the whole sample.

Nevertheless, they found a reduction on the Daily Average Cortisol (DAC) in psychopaths that was also significantly related to PA. Besides, the cortisol area under the curve (AUC) in that group was related to EA and EN, the diurnal cortisol slope was related to PN with a significant relation between the PPI total score and DAC. Traumatic experiences, in that group, was also positively related to impulsive nonplanfullness (fourth subscale of the PPI) and external blame attribution factor on the PPI, while there was a negative association between traumatic childhood experiences, cold-heartedness and stress immunity. The crucial finding of this study was the evidence of hypoarousal in psychopaths with a reduction of the diurnal cortisol compared to non-psychopaths. This finding fits with the notion that non-psychopathic offenders are more reactive, emotional delinquents, while psychopathic offenders are more instrumental and cold-blooded.

Two studies analyzed monoamine oxidase-A (MAO-A) and 5-hydroxyindoleacetic acid transporter (5HTT) alterations in connection to psychopathy and trauma. Sadeh *et al*[17] analyzed 237 inmates with the CTQ and the PCL:SV, and their genetic variations of 5HTT and MAO-A were detected from saliva samples. The PCL:SV factor 1 (interpersonal/affective facets) was higher in 5HTT long/Long allele *vs* short/short, but it was not found an etiological explanation linking trauma, psychopathy and genetic alterations. The PCL:SV factor 2 (lifestyle/antisocial facets) was higher in people with the MAO-A variant with low activity *vs* high activity moreover 5HTT long/Long have higher PCL:SV factor 2 than short/short. In particular MAO-A genotype was most consistently associated with the impulsive and irresponsible traits of the Lifestyle factor. Interestingly, no correlation was found between genetic alteration and the trauma-psychopathy link. Likewise, in the work of Hollebarch *et al* [18], which evaluated trauma (CTQ), psychopathy (Self-Reported Psychopathy scale) and the MAO-A uVNTR genotype in a sample of 2796 people, MAO-A uVNTR genotype was significantly associated to general psychopathy in women, meaning that women with the MAOA-L genotype had slightly higher levels of psychopathy compared to their MAOA-H counterparts, but they did not find the same in men. Childhood trauma was associated with psychopathic traits in adults, both in men and women. They did not find any interaction between MAOA uVNTR genotype and any

Table 2 Different studies analyzed the role of biological alterations that may link trauma and psychopathy

Ref.	Sample (women, %)	Tests	Significant association	Biological analysis
Cima *et al*[16], 2008	47 (0)	CTQ - PPI	PN (Psychopath *vs* inmates not psychopath)	DAC (related to PN) reduction in psychopath; AUC related to EA, EN
Hollerbach *et al*[18], 2018	2796 (45.24)	CTQ- SRPS	Total score	Total score in women (MAOA-L); MAOA-L in women related to EA, EN and PN
Sadeh *et al*[17], 2013	237 (0)	CTQ-PCL:SV	NS	F1 (5HTT long/long *vs* 5HTT short/short; F2 (MAOA-L *vs* MAOA-H)

DAC: Daily average cortisol; AUC: Cortisol area under curve; F1: Factor 1 of PCL:SV; F2: Factor 2 of PCL:SV; MAOA-L: MAO-A low activity; MAOA-H: MAO-A high activity.

traumatic factor on psychopathic traits. Their results suggest that psychopathy in general, and social deviance in particular, were associated with childhood trauma in men and women, and that psychopathic traits are subject to variation of the MAOA uVNTR genotype in women. Hollebarch and colleagues[18] discovered that the "childhood trauma" factor was not influenced by a variation of MAO-A in men, while women with MAOA-H genotype showed a slightly higher scores of PN, EN and EA. In general, no significant link that could explain the influence of trauma on psychopathy has been discovered yet. We could explain this result with the primary and secondary psychopathy theory, according to which the primary psychopathy has a genetic cause that determines the onset of the illness whereas the secondary psychopathy has traumatic and problematic environmental reasons as etiological causes. Further genetic study might explain the role of the genetic alterations that support the onset of psychopathy.

GENDER DIFFERENCES IN THE RELATIONSHIP BETWEEN TRAUMA AND PSYCHOPATHY

Watts *et al*[19] analyzed trauma (CTQ) and psychopathy (Levenson self-report psychopathy scale) in a non-forensic sample of 1169 subjects (73% female) (Table 3). They underlined two gender differences: the first one was the relation between boldness and childhood neglect that was negative or small to moderate in males but almost absent in females. The second was the relation between disinhibition, meanness and childhood maltreatment that was stronger for males than females. In their sample, men suffered more child abuse than women with the exception of sexual and EAs that were more frequent in females.

Thomson and colleagues[20] evaluated the role of sex differences in the association between the 4-facet model of psychopathy (PCL-SV) (interpersonal, affective, lifestyle, antisocial) and aggression (physical, verbal, and indirect), and LPA (Lifetime Physical Abuse) in a sample of 369 males and 204 females. The relation between physical aggression and affective facet of psychopathy was significant in both genders. High affective traits predicted physical aggression in women with a history of physical abuse but not in women without it. Instead, physical aggression was predicted by low affective traits in men with a history of physical abuse while lower levels of physical aggression were associated with low affective traits in men without a history of physical abuse. Moreover, verbal aggression was significantly related to the antisocial factor of psychopathy in women. Furthermore, high antisocial traits predicted verbal aggression exclusively in men who suffered from physical abuse.

Gender differences were also analyzed by Sevecke *et al*[21]. They studied 170 male and 171 female adolescent detainees using the CTQ, the PCL-YV and the Dimensional Assessment of Personality Pathology Basic Questionnaire (DAPP-BQ) for personality assessment. They found that gender was a strong predictor of the PCL:YV total score and all four psychopathy dimensions; incarcerated male adolescents had a significantly higher PCL:YV total score as well as all four psychopathy dimensions than incarcerated female adolescents. The PA was related to the antisocial facet of the PCL-YV in both males and females and it was also related to the interpersonal facet in males. No relation was found between SA and psychopathy in both genders. Interestingly, the subjects who did not suffer from PA had a stronger association

Table 3 Trauma and psychopathy in a non-forensic sample of 1169 subjects

Ref.	Sample (women, %)	Tests	Significant association in men	Significant association in women
Blonigen *et al*[25], 2012	226 (100)	PTE-PCL-R	/	Total score (AF)
Farina *et al*[24], 2018	976(19.98); P:253 (45); M:723 (13)	MAYSI-2+ CTQ- YPI +PPI-SF	PA, EA	PA, EA
Hicks *et al*[26], 2011	140 (100); 31 Pr, 39 Sc	I-PCL-R	/	PA (Sc); SA (Pr[19])
Krischer *et al*[23], 2008	283 (47.43)	CTQ- PCL:YV	PA (total score, AFC and AF); EA (AF)	EN (related with AF)
Lansing *et al*[22], 2018	107 (52.23)	CTQ- YPI	NS	EA
Sevecke *et al*[21], 2016	341(50.14)	CTQ - PCL:YV	PA (related to AF and IF)	PA (related to AF)
Thomson *et al*[20], 2019	573 (35.60)	LPA + AQ - PCL-SV	PAG (affective facet of psychopathy); LAT related to PAG in history of PA	PAG (related to AF); HAT related to PAG; in history of PA; VA[4] (related to ANF[5])
Watts *et al*[19], 2017	1169 (73)	CTQ - LPS	Child abuse (more frequent in male)	EA, SA (more frequent in female)

LPS: Levenson self-report psychopathy scale; HAT: High affective trait; PAG: Physical aggression; VA: Verbal aggression; ANF: Antisocial factor of psychopathy; LPA: Lifetime physical abuse; AQ: Aggression questionnaire; LAT: Low affective trait; AF: Antisocial factor of psychopathy; IF: Interpersonal factor of psychopathy; YPI: Youth Psychopathic Trait Inventory; AFC: Affective factor of psychopathy; MAYSI-2: Youth Screening Instrument Version 2 Traumatic Experiences Scale; PPI-SF: Psychopathic Personality Inventory-Short Form; P: Pennsylvania; M: Missouri; PTE: Potentially traumatic events; I: Interview, interview, prison file, and responses on the life events checklis; Pr: Primary psychopaths; Sc: Secondary psychopaths.

between emotional dysregulation and psychopathy than those who reported PA. Opposite to the study of Sveiche *et al* (no reference), Lansing *et al*[22] did not find any significant difference on the psychopathy scale in males compared to females. Women had higher frequencies of emotional and sexual abuse than men. In particular EA was the most frequent abuse for EOPD (Early onset persistent delinquent) girls while PA was the most common abuse among EOPD boys. Nearly half of the girls in their sample suffered from SA which was infrequently reported by boys. A significant correlation between psychopathy and abuse was documented only in women and it resulted particularly strong with EA. Lansing and colleagues supported a lack of significant relation between psychopathy and SA in men, and between PA and psychopathy in women. Kricher and colleagues[23] examined 185 adolescent inmates *vs* 98 students (control group) and discovered that abuse was more frequent among inmates than in the control group; women, in particular, reported significantly more emotional, sexual and physical abuses than men. Contrasting with previous studies, neither the PCL: YV total score, or any of its four factors significantly differed between abused and non-abused women except for the Factor 4 (antisocial psychopathy) that significantly correlated to Emotional Neglect in delinquent girls. Instead, boys that suffered PA had higher PCL-YV total scores as well as higher Affective and Antisocial Factors. Furthermore, they showed poorer Anger Control, more Irresponsibility and more Serious Criminal Behavior. Likewise, boys who reported EA were also characterized by significantly higher scores in the Antisocial Factor of the PCL-YV. Authors discovered a significant correlation between the Affective Factor 2 and Physical Abuse and between the Interpersonal Factor 1 of the PCL-YV and Emotional Neglect in male inmates. In contrast with Kricher *et al*[24], Farina and colleagues found a significant relation between trauma and psychopathy in both males and females. Their sample was recruited in 2 different penitentiaries: 253 inmates from Pennsylvania and 723 in Missouri, tested with the YPI and PPI-SF scale for psychopathy and the CTQ for trauma. In the Pennsylvania sample they found significantly more SA and EA in females than in males. Psychopathy was associated with physical and EAs in both male and female juvenile offenders with stronger association in girls. No correlation was found between SA and psychopathy in both genders. Another important variable they evaluated was the impact of PTSD in the relation between trauma and psychopathy in males and females. Blonigen *et al*[25] considered a sample of inmate women (26 of whom had a PCL-R > 30). Interpersonal and affective facets of psychopathy were unrelated to Potentially traumatic events (PET) or PTSD. Instead, they found a significant relation among antisocial facet and PET; furthermore, antisocial facet was uniquely associated with PTSD too. The lifestyle facet was prefer-

entially linked to abuse in adulthood and antisocial facet to abuse in childhood. Moreover, both PTE and PTSD were related to the factor 2 of psychopathy, known as the externalizing spectrum of psychopathy. The theory of primary and secondary psychopathy was also investigated in the study of Hicks *et al*[26] They evaluated psychopathy (PCL-R) with a different cut off (25), splitting the sample in 2 groups: 70 psychopaths and 70 controls. Out of 70 psychopaths, 31 were primary and 39 were secondary psychopaths. The secondary psychopaths had personality traits of negative emotionality and low behavioral constraint, more substance use disorder, more violent behavior and more mental health problems including symptoms of post-traumatic stress disorder and suicide attempts than primary psychopaths. The secondary psychopaths suffered more PA than controls prisoners or primary psychopaths. Instead, primary psychopaths experienced significantly more SA than controls. Moreover, secondary psychopaths reported significantly more PTSD symptoms, history of mental health treatments and suicidal attempts than control or primary psychopaths. An interesting finding was that primary psychopaths had lower rates of suicide attempts, though those rates did not differ significantly from that of control prisoners.

DISCUSSION

Child abuse is a serious public concern with adverse short and long term consequences. The aim of the present narrative review is the identification of the development of psychopathic traits in victims, with a special attention to gender differences and biological reasons.

Primary psychopaths, who are those characterized by a low level of anxiety and lack of emotions and sense of guilt, suffer less emotional maltreatments than secondary psychopaths, thus confirming the development of that subtype of psychopathy (secondary) in response to adverse experiences. In accordance, EA and neglect are related to affective facet with higher level of psychopathy at the PCL-R if EA occurs during childhood.

The severity of psychopathy is also linked to the moment of exposure to relational trauma with more serious traits in case of early exposure during childhood. Traumatic exposure to domestic violence or violence in the community is linked to higher degrees of psychopathy. Dissociative symptoms as well as post-traumatic stress disorder demonstrate weak association in the development of psychopathy after a childhood trauma. Similarly, biological correlates that could justify the development of psychopathy in response to traumatic experiences have not been demonstrated yet, even if women show a variation in the MAOA uVNTR genotype might be associated with psychopathic traits in victims of childhood trauma. Generally speaking, men show stronger psychopathic traits at the PCL-R and all psychopathic dimensions. A strong gender-oriented difference among several abuses and the development of psychopathy has not been highlighted yet. Sexual abuse has not been linked to higher levels of psychopathy, but it is the only type of abuse that shows higher frequency in primary psychopaths. This evidence is controversial because the severe adverse consequences of sexual abuse are well documented. It is feasible that sexual abuse might be less reported or disclosed, especially by men, due to stigmatization often linked to this type of abuse.

Although some kinds of abuse are associated with increased risk of developing psychopathy, with gender-oriented differences, the lack of biological explanations still limit knowledge on primary psychopathy.

CONCLUSION

Our work highlights a significant relation between trauma and psychopathy: EA, emotional neglect and physical abuse are the most frequent types of abuse related to psychopathy in males and females. Sexual abuse was the only kind of abuse that did not show a significant relation with psychopathy in most studies that we analyzed even if it was more frequent in women than men. A biological background, able to promote the onset of psychopathy is plausible and should be further investigated. Trauma is the key etiological factor of secondary psychopathy.

The most frequent limitations we detected were evaluations with self-reported scales since psychopaths have a high inclination to lie. Moreover, almost every study investigates inmates, a population with a more frequent history of trauma that could

biased the impact of trauma on psychopathy.

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REVIEW

Polyamines and polyamine-metabolizing enzymes in schizophrenia: Current knowledge and concepts of therapy

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Abstract

Polyamines play preeminent roles in a variety of cellular functions in the central nervous system and other organs. A large body of evidence suggests that the polyamine pathway is prominently involved in the etiology and pathology of schizophrenia. Alterations in the expression and activity of polyamine metabolizing enzymes, as well as changes in the levels of the individual polyamines, their precursors and derivatives, have been measured in schizophrenia and animal models of the disease. Additionally, neuroleptic treatment has been shown to influence polyamine concentrations in brain and blood of individuals with schizophrenia. Thus, the polyamine system may appear to be a promising target for neuropharmacological treatment of schizophrenia. However, for a number of practical reasons there is currently only limited hope for a polyamine-based schizophrenia therapy.

Key Words: Polyamines; Spermidine; Spermine; Schizophrenia; Animal models; Therapy

Core Tip: This review summarizes the advancements in research on the implications of polyamines and their metabolites for schizophrenia. Evidence from clinical and experimental studies show that some members of the polyamine regulatory system are altered in schizophrenia, but no polyamine-based therapy for schizophrenia is currently available.

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INTRODUCTION

Schizophrenia is one of the great scourges of humanity, affecting approximately 1% of the worldwide population. It is a devastating and debilitating mental illness, which appears to result from a complex interplay between genetic and environmental risk factors. Clinically, schizophrenia may be characterized by an array of positive, negative and cognitive symptoms, which include hallucinations, delusions, disorganized speech or executive function, impaired memory and reduced cognitive abilities[1]. Unfortunately, a large percentage of patients with schizophrenia suffer from treatment-resistance. Therefore, there is an urgent need for new treatment opportunity strategies.

Among putative therapeutic targets for schizophrenia treatment are polyamines (PAs), their precursors, derivatives and conversion enzymes. Aliphatic PAs constitute a small family of polycationic molecules derived from decarboxylation of ornithine[2], which play a crucial role in the developing and mature mammalian central nervous system (CNS). The initial suggestion that these were contributing factors to schizophrenia pathology dates back to the late 1950s, when it was shown that N,N-dimethyl-p-phenylenediamine oxidation rates were increased in sera of schizophrenia patients compared to non-psychotic individuals[3,4]. Since then, numerous papers have shown that the PAs, spermine, spermidine and putrescine, as well as their metabolites, are functionally linked with schizophrenia. The goal of this article is to review the current knowledge and insights about the role of the PA system in schizophrenia. Further, we attempt to assess the suitability of PA as targets for therapeutic intervention.

SEARCH STRATEGY

Using relevant search terms we searched published literature (including doctoral theses and patents) from 1 January 1955 to 21 January 2021 in PubMed and Google Scholar. Search terms were schizophrenia in combination with one or more of the following terms: polyamines, spermine, spermidine, putrescine, agmatine, S-adenosylmethionine, acrolein, L-ornithine decarboxylase, antizyme, antizyme inhibitor, spermine oxidase, spermidine synthase, spermidine/spermine N1-acetyltransferase, polyamine oxidase, S-adenosylmethionine decarboxylase, agmatinase and agmatinase-like protein. No language restrictions were applied.

THE PA PATHWAY IN THE HEALTHY CNS

Natural PAs, spermine and spermidine, and their precursor putrescine are present at relatively high concentrations in the mammalian brain. Because of the limited transport of PAs across the blood-brain barrier, their presence in the CNS should largely result from local synthesis (described previously in[5]). Brain PA content is tightly controlled through a complex network of biosynthetic and catabolic enzymes and a recently discovered transport system. However, while there are no doubts about the brain-borne origin of the largest fraction of cerebral PA, the precise cellular locus of PA biosynthesis has been a matter of contention for several years.

PAs are present at high concentrations both in glial cells (especially astroglia) and neurons[6-9]. Under normal conditions, neurons express L-ornithine decarboxylase (EC 4.1.1.17, ODC; Figure 1A), the rate-limiting enzyme of PA biosynthesis, which generates putrescine from ornithine[10,11]. This suggests that neurons are the primary source of newly synthesized PAs in the brain. Consequently, the observed strong astroglial immunostaining for spermidine and spermine would have to occur due to other reasons. Currently, it is certain that there is an efficient PA transport system involved in translocation of PAs from the site of synthesis in neurons to glial cells, a site of uptake, accumulation and release[9]. Indeed, various vesicular transporters for

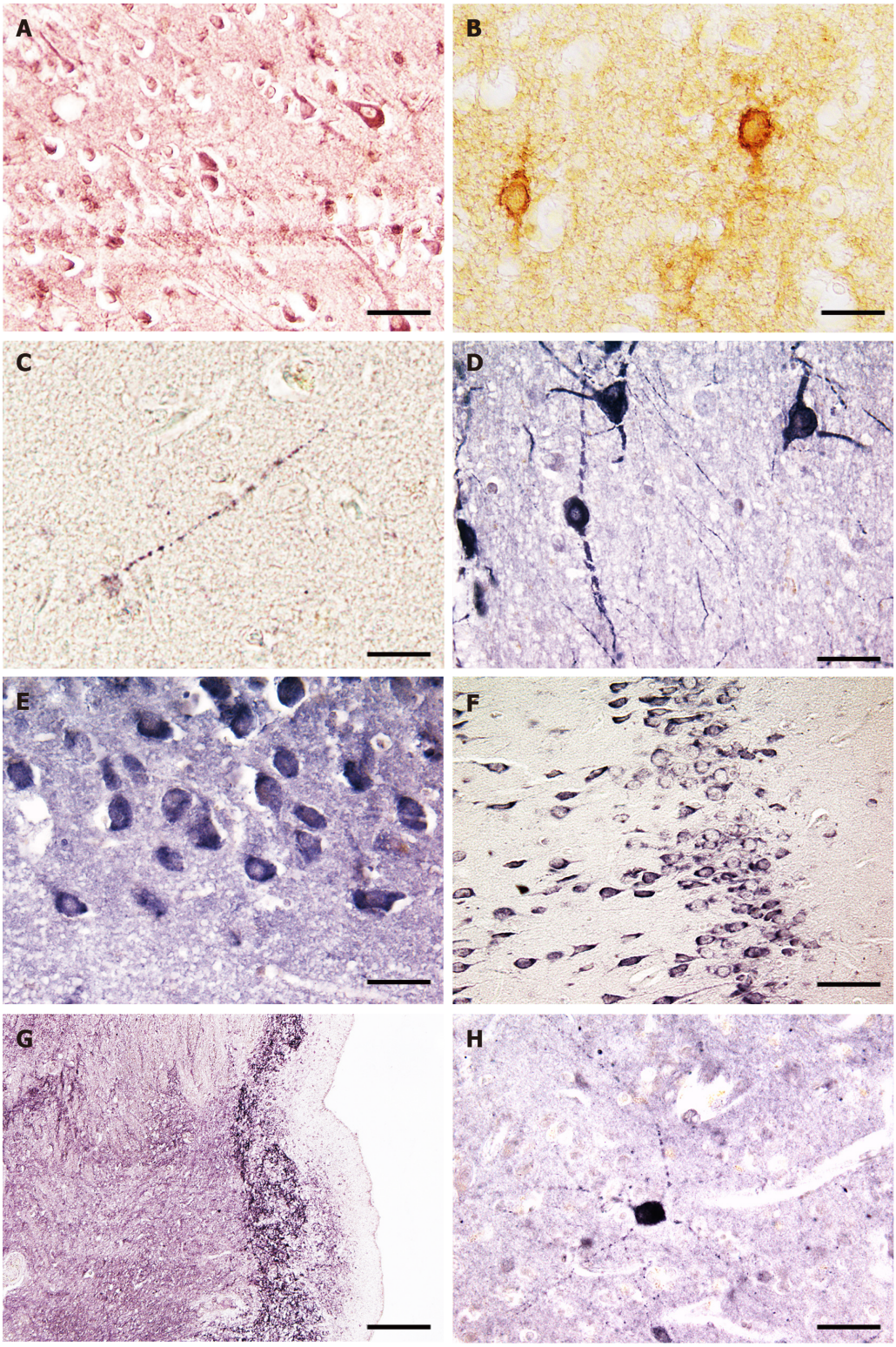

Figure 1 Cellular localization of polyamine-metabolizing enzymes and antizyme inhibitor 2 in human and rat brain with nickel-enhanced streptavidin-biotin immunocytochemistry. A: Ornithine decarboxylase immunoreactive neurons of the human prefrontal cortex. Bar = 70 μm; B: Antizyme inhibitor 2 expressing neurons in the human prefrontal cortex. Bar = 30 μm; C: Antizyme inhibitor 2 immunoreactive fiber in the human temporal cortex. Note the typical pearlchain-like structure as already described by others[18]. Bar = 20 μm; D: Strong spermine oxidase immunoreactive neurons in the human hypothalamus (interstitial nucleus). Bar = 30 μm; E: Multiple spermine oxidase expressing neurons in the CA2 region of the human hippocampus. Bar = 30 μm; F: Spermine oxidase expressing neurons in rat medial prefrontal cortex. Bar = 55 μm; G: Low power microphotograph of agmatinase immunoreactivity in human habenula. Bar = 140 μm; H: Single agmatinase immunopositive neuron in the human insular cortex. Bar = 30 μm.

PAs have been identified[12-15], and these may function bidirectionally[9].

Interestingly, other enzymes and enzyme regulators involved in the metabolism PAs are also predominantly or exclusively located in neurons. The ODC antizyme (which binds to ODC and thereby destabilizes and inactivates the enzyme) and

antizyme inhibitors 1 and 2 (AZINs, which both enhance ODC activity) have been found in neurons but not glia[16-18] (Figure 1B and C). Spermidine/spermine N1-acetyltransferase (EC 2.3.1.57, SAT1) is an enzyme responsible for PA interconversion. Its mRNA is widely distributed in neurons, with the highest concentrations found in the hippocampus and olfactory bulb[19]. The enzyme spermidine synthase (EC 2.5.1.22, which catalyzes the interconversion of S-adenosylmethionine to spermidine and 5'methylthioadenosine was localized to multiple rat brain neurons and neuropil of several brain regions [accumbens nucleus, hypothalamus, hippocampus (Figure 1E), cerebral cortex, striatum, cerebellum and others][20,21]. Spermine oxidase (EC 1.5.3.16, SMOX), which catalyzes the conversion of spermidine to spermine, is immunocytochemically detectable in many neurons of the cerebral cortex, hypothalamus, hippocampus, thalamus and cerebellum of human and rat brains (Figure 1D-F).

The neuromodulator agmatine, which is a precursor of putrescine, can be detected in synapses[22,23]. Agmatine is highly expressed in magnocellular hypothalamic neurons and many other nerve cell populations[23,24]. The agmatine-degrading enzyme, agmatinase (EC 3.5.3.11) was found in distinct interneurons of rat and human brain, located in cerebral cortex, hippocampus, habenula and cerebellum (Figure 1G and H)[25,26]. Interestingly, a second agmatine-metabolizing enzyme (called agmatinase-like protein) is present in rat brain neurons and astrocytes[27]. Finally, arginase (EC 3.5.3.1, ARG), which converts L-arginine into L-ornithine and urea, and arginine decarboxylase (EC 4.1.1.19, which catalyzes the conversion of L-arginine into agmatine and carbon dioxide) are widely expressed in rat brain neurons[28,29]. Thus, neurons harbor all PA synthesizing and degrading enzymes studied so far apart from the agmatinase-like protein, which is located mainly in astroglial cells[27]. However, the situation may be different in neonatal brains because recent evidence suggests that developing astroglial cells contain catalytically active ODC, synthesize PAs and release these[30]. The major reactions of the PA pathway are shown in Figure 2.

SOME CRITICAL FUNCTIONS OF PA IN THE CNS AT A GLANCE

The classical PAs, spermine, spermidine and putrescine are multifunctional chemical compounds, which serve a variety of important tasks in the CNS (for overviews see[5,9,10,30-32]). PA pathways play pivotal roles in the correct development of nervous tissue. There is experimental evidence to suggest that the replication of neurons and their precursor cells are dependent on the maintenance of certain region-and time-specific PA levels[32]. Depletion of PAs through inhibition of ODC arrests brain cell maturation, disrupts neuronal migration, disturbs the outgrowth of neurites and impairs the formation of synapses[11,31,32]. In addition, PAs are prominently involved in proliferation of neonatal astrocytes[30]. In both the pre- and postnatal CNS, PAs act as intracellular growth factors. By directly binding to DNA or the rough endoplasmic reticulum, spermine and spermidine increase the rate of cell growth and control protein synthesis of brain cells[11,33].

In the mammalian CNS PAs act as important endogenous modulators of glutamate receptors and are capable of altering the functioning of *N*-methyl-D-aspartate (NMDA) receptors. As NMDA receptor ligands, PAs exert both activator and inhibitor effects. On the one hand, PAs can enhance NMDA receptor currents by increasing the probability of channel opening. On the other hand, spermine is able to block NMDA channels in the open state, thereby reducing or blocking NMDA receptor currents by a voltage-dependent reduction of single-channel conductance[34,35]. Another inhibitory effect of spermine is to reduce the sensitivity to glutamate (or other glutamate site agonists) at NMDA receptors composed of NMDA receptor 1/NMDA receptor 2B subunits by reducing the affinity for glutamate[34]. PAs also contribute to alterations of membrane excitability by interacting with ionotropic kainate and AMPA glutamate receptors (discussed in detail in[36]). Modulation of glutamate signaling by PA influences a variety of functional processes in the brain, ranging from regulation of neuronal and glial excitability to memory and aging[37].

Another mechanism through which PAs exert influence on membrane excitability is the blockade of outward potassium currents through, consequently so-called, inwardly-rectifying potassium channels. Inwardly-rectifying potassium channels exhibit a sharp voltage dependence and crucially contribute to maintenance of the resting membrane potential. Thus, they are involved in the regulation of bioelectrical excitation of many cell types including neurons and glial cells[9,37-40]. The basic mechanism underlying this steep voltage dependence is the channel blockade by PA and magnesium. PAs are thought to enter the inwardly-rectifying potassium channel

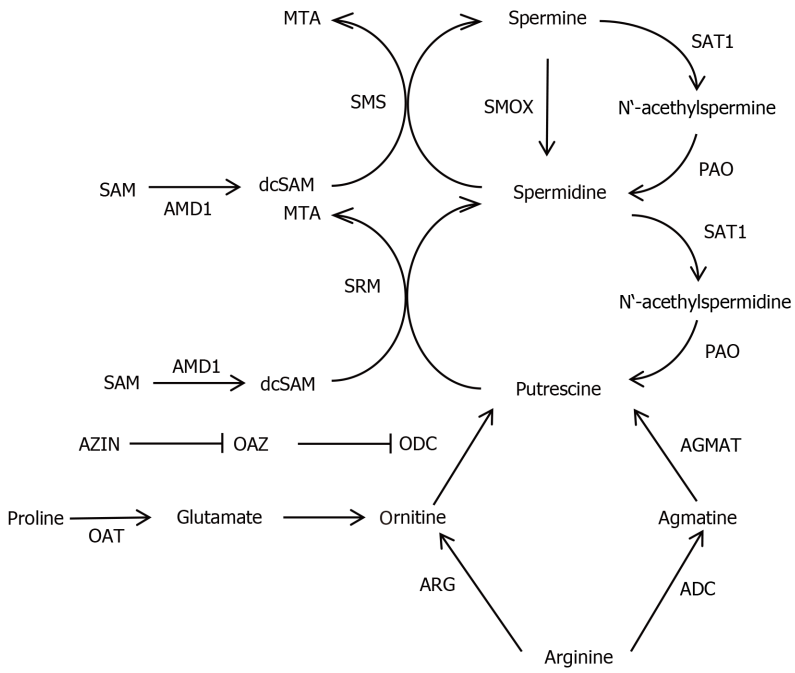

Figure 2 Major pathways of polyamines biosynthesis and interconversion (from Gross and Turecki[71]; scheme reproduced with permission of Bentham; modified). ADC: Arginine decarboxylase; AGMAT: Agmatinase; AMD: S-adenosylmethionine decarboxylase; ARG: Arginase; AZIN: Ornithine decarboxylase antizyme inhibitor; dcSAM: Decarboxylated S-adenosylmethionine; MTA: 5'-methylthioadenosine; OAT: Ornithine aminotransferase; OAZ: Ornithine decarboxylase antizyme; ODC: Ornithine decarboxylase; PAO: Polyamine oxidase; SAM: S-adenosylmethionine; SAT1: Spermidine/SpermineN1 acetyltransferase; SMS: Spermine synthase; SMOX: Spermine oxidase; SRM: Spermidine synthase.

pore *via* the intracellular side of the membrane and displace multiple ions during their stable binding site within the channel[40].

Lastly, PAs act as free radical scavengers and effective antioxidants. This role is unrelated to the activation of the NMDA receptor[41]. Of note, PA catabolism, which is upregulated after traumatic brain injury and other stressful situations, can be a source of toxic reactive oxygen species[41,42].

The PA agmatine, a decarboxylation product of arginine, is an endogenous ligand of imidazoline, α_2-adrenergic and glutamatergic NMDA receptors[43,44]. Agmatine is a neuromodulator and neurotransmitter, which significantly contributes to the regulation of various neurotransmitters and signaling pathways (reviewed in[43-47]). Several studies have demonstrated that agmatine is involved in cognitive processes [47-50]. In addition, it performs a neuroprotective function by reducing oxidative damage, neuroinflammation and proapoptotic signaling[43,51].

THE PA SYSTEM IN SCHIZOPHRENIA

In the early 1980s it was hypothesized that PA might play a central role in the etiology of schizophrenia[52]. Since then, numerous papers have appeared in support of this conjecture, while others call in question a significant role of PA in schizophrenia development and persistence.

GENETIC ASPECTS OF PA METABOLISM IN SCHIZOPHRENIA

Compared with psychically healthy individuals, tissue and body fluid concentrations of some PAs are altered in patients suffering from schizophrenia. Since single nucleotide polymorphisms in the intron region of *ODC* (+316 G>A) and the promoter region of the SAT1 encoding gene *SAT* (1415 T>C) genes are known to be associated with the expression levels of PAs[53], both gene polymorphisms might be potential genetic markers for susceptibility to schizophrenia. Only the *SAT 1* gene polymorphism has been studied so far. There were no significant differences in the distribution of the genotypes of the *SAT*-1415 T/C single nucleotide polymorphisms

between schizophrenia patients, non-psychotic psychiatric patients and healthy controls. However, a "mild association" between the C allele and psychopathology was found for the female group[54]. A translational convergent functional genomics study identified *AZIN 1*, the gene encoding antizyme inhibitor 1, as a candidate gene for schizophrenia (convergent functional genomics score 3.0[55]).

ALTERATIONS IN GENE EXPRESSION, ENZYME ACTIVITIES AND EPIGENETIC REGULATION OF PA-RELATED GENES IN SCHIZOPHRENIA

A comprehensive DNA microarray study revealed that the expression of *AZIN 1* was reduced in almost all samples from subjects with schizophrenia. In addition, reduced cellular expression of AZIN 1 was verified by *in situ* hybridization of postmortem brain samples of the same schizophrenia subjects. Of note, this reduction was not a consequence of long-term neuroleptic treatment of the patients since there was only a marginal reduction of AZIN 1 expression in haloperidol treated monkeys[56]. Ornithine aminotransferase (EC 2.6.1.13) is an enzyme that has been indirectly connected with PA metabolism through catalyzing the formation of glutamate or proline from ornithine[57]. This enzyme was found to be reduced in samples from schizophrenia patients[56]. However, other studies were unable to replicate these findings. Maycox *et al*[58] could not identify any differentially expressed genes implicated in PA metabolism in two large schizophrenia cohorts (with more than 30000 mRNA transcripts).

Numerous communications have dealt with altered expression and/or activity of PA-metabolizing enzymes in brain tissue or blood of schizophrenia patients. Conflicting findings exist regarding polyamine oxidase(PAO). Blood plasma PAO activity was reportedly lower in acute schizophrenia patients[59,60]. This decrease in activity was unrelated to the subtype of schizophrenia (paranoid *vs* non-paranoid), age of onset or neuroleptic treatment[60-62]. In contrast with these findings, Dahel *et al*[63] and Das *et al*[64] found increased PAO activity in blood sera from schizophrenic patients, which was reduced by electroconvulsive therapy[63]. On the other hand, ODC activity was found to be normal in prefrontal cortex and hippocampus autopsy samples from people who suffered from schizophrenia[65], and there were no differences with regard to the number of ODC immunoreactive entorhinal cortex neurons between schizophrenia patients and controls[5]. Another study that measured SMOX activity found increased activity in sera from schizophrenia patients compared to non-psychotic controls[66], whereas AMD and SAT1 activities were unaltered in prefrontal cortex and hippocampus tissue of schizophrenia patients[65].

The density of agmatinase-containing interneurons was lower in the hippocampus of schizophrenia patients in comparison with controls[43]. Significantly increased activity of ARG (a gate keeper enzyme of PA synthesis) was observed in the cerebrospinal fluid of schizophrenia patients[67]. Lastly, increased enzyme activity and ARG II protein expression were found in postmortem brain tissue specimen in schizophrenia[68], whereas plasma ARG activity was significantly lower in schizophrenia than in controls[69].

There is evidence that gene regulation *via* epigenetic modifications play a major role in schizophrenia pathophysiology. However, in contrast to other mental disorders and suicide, no such modifications for PA metabolizing genes in schizophrenia have been identified[70-72].

PA CONTENT IN TISSUES AND BODY FLUIDS IN SCHIZOPHRENIA

Several reports have targeted the levels of cerebral and peripheral PA in schizophrenia patients. Elevated blood concentrations of spermine and/or spermidine have been measured in treated schizophrenia patients[73,74] and in drug-naïve cases[75], whereby long-term neuroleptic treatment was shown to reduce spermine levels[75,76]. Also, increased concentrations of spermidine and total PA were detected in fibroblasts obtained from schizophrenia patients (reviewed in[11]). So far, little information is available regarding brain PA concentrations in schizophrenia. Gilad *et al*[65] could not find significant alterations of PA levels in postmortem brain tissue of schizophrenia persons compared with controls. However, a more recent paper described significantly elevated levels of spermine, spermidine and putrescine in many brain regions of psychotic individuals[77].

Significantly increased agmatine concentrations were measured in blood plasma and postmortem frontal cortex tissue of individuals with first episode and chronic schizophrenia[68,78-80], and antipsychotic treatment was found to decrease blood agmatine levels[77]. In contrast to the previously mentioned work, reduced blood agmatine levels were measured in early-onset schizophrenia[81]. The amino acid L-arginine is metabolized by ARG, which is the first step in PA synthesis. Increased blood plasma arginine levels were reported in medication-naïve, first episode patients. Medication had no influence on enhanced blood concentrations in schizophrenia patients[79]. Finally, two-fold increased concentrations of S-adenosylmethionine were found in prefrontal cortex samples of schizophrenia patients compared with controls. This drastically increased brain S-adenosylmethionine content was not affected by postmortem interval or medication[82]. The main findings regarding this are summarized in Table 1.

PA IN THE CNS OF SUICIDE COMPLETERS

Numerous studies have shown alterations of PA and PA-metabolizing enzymes in individuals who died by suicide (reviewed in[5,71,83]). However, a closer look at these studies reveals that they all provide findings from individuals who had suffered from major depression or from suicide victims with no specified psychiatric diagnosis but not from those with schizophrenia. Thus, it would be interesting to determine if schizophrenia patients who died by suicide would differ from non-suicide schizophrenia persons with regards to PA levels.

PA IN ANIMAL MODELS OF SCHIZOPHRENIA

A promising approach to identify and better understand diverse schizophrenia symptoms in humans has been to investigate behavioral phenotypes in animal models of the disease[84]. Although numerous animal models of schizophrenia have been introduced so far, only a few of these have accounted for the role of PAs and their metabolites. We studied the cellular expression of ODC in rats with neonatal lesions of the ventral hippocampus and found increased immunostaining in the prefrontal, perirhinal and entorhinal cortex[85]. In addition, we found an increased density of SMOX-immunoreactive medial prefrontal neurons (unpublished findings). Increased levels of putrescine, spermidine, spermine and arginine and decreased levels of agmatine were found in the prefrontal cortex and hippocampus of male and female rat offspring after maternal immune activation[86].

Prepulse inhibition of the startle reflex response is disturbed in schizophrenia, although there are conflicting findings regarding the influence of agmatine on this effect. In one study, agmatine was reported to disrupt prepulse inhibition in rats[87], whereas another investigation found that low doses of agmatine attenuated the disruptive effects of the psychotomimetic substance phencyclidine on this response [88]. Other studies showed that agmatine depressed conditioned avoidance response and enhanced the inhibitory effect of haloperidol and olanzapine on this readout. Furthermore, agmatine attenuated apomorphine induced climbing and diminished amphetamine or ketamine induced hyperlocomotor activity[89,90]. Injection of phencyclidine, which induces psychotic symptoms in healthy individuals, was shown to also alter arginine metabolism in the rat hippocampus and prefrontal cortex[90], and withdrawal from repeated phencyclidine administration has been found to alter ARG activity as well as the concentration of arginine metabolites in rat brain[68].

Interestingly, transgenic animals, which overexpress ODC and/or SAT1, show a variety of neuroanatomical, neurochemical and behavioral peculiarities but not schizophrenia-like behavior[91]. SMOX overexpression in the neocortex in Dach-SMOX mice leads to glutamate excitotoxicity[92], which is a characteristic feature of human schizophrenia[93-95]. The main findings regarding this are summarized in Table 2.

POSSIBLE IMPACT OF PA PATHWAY ABNORMALITIES ON SCHIZOPHRENIA PATHOLOGY

PAs and their metabolites are crucial factors in a variety of functions, which are disrupted in schizophrenia. These disease-related functional impairments range from

Table 1 Summary of polyamine-related findings in human schizophrenia studies

No significant differences in the distribution of the genotypes of the *SAT*-1415 T/C SNP between schizophrenia patients and healthy controls[54].
CFG study identified *AZIN 1* as a candidate gene for schizophrenia[55].
DNA microarray and *in situ* hybridization studies show decreased AZIN 1 expression in schizophrenia. No influence of neuroleptic treatment[56].
OAT expression is reduced in samples of schizophrenia individuals[56,57].
No differently expressed genes implicated in PA metabolism in two large schizophrenia cohorts[58].
PAO activity is lower in blood plasma of acute and chronic schizophrenia patients[59-62].
PAO activity increased in blood sera of schizophrenic patients[64,65], reduction by electroconvulsive therapy[62].
ODC activity and cellular expression is normal in brain autopsy samples from people who suffered from schizophrenia[65,66].
SMOX activity is markedly higher in sera of schizophrenic patients[67].
AMDI and SAT1 activities are unaltered in brain tissue of schizophrenia individuals[65].
Density of AGMAT-containing interneurons is reduced in the hippocampus of schizophrenia patients[43].
Increased ARG activity in the CSF of schizophrenia patients[67].
Increased ARGII activity and protein expression in postmortem brain tissue in schizophrenia[68].
ARG activity is lower in plasma of schizophrenia individuals[71].
Elevated blood concentrations of spermine and/or spermidine in drug-naïve and treated schizophrenia patients[73-75].
Long-term neuroleptic treatment reduces spermine levels[76,77].
Increased concentrations of spermidine and total PA in fibroblasts from schizophrenia patients (reviewed in[11]).
PA levels normal in postmortem brain tissue of schizophrenia persons[65].
Elevated levels of spermine, spermidine and putrescine in brains of psychotic individuals[77].
Increased agmatine concentrations in blood plasma and postmortem brains of individuals with first episode and chronic schizophrenia[68,78-80].
Antipsychotic treatment decreases blood agmatine levels[77].
Reduced blood agmatine concentrations in early-onset schizophrenia[81].
Increased concentrations of SAM in brain samples of schizophrenia patients[82].

SNP: Singlenucleotide polymorphism; OAT: Ornithine aminotransferase; ODC: Ornithine decarboxylase; SMOX: Spermine oxidase; AGMAT: Agmatinase; AMD: S-adenosylmethionine decarboxylase; ARG: Arginase; PA: Polyamines; CSF: Cerebrospinal fluid; CFG: Convergent functional genomics; SAM: S-adenosylmethionine; SAT1: Spermidine/Spermine N1 acetyltransferase; PAO: Polyamine oxidase; AZIN: Antizyme inhibitor.

abnormal prenatal CNS development (disrupted neuronal migration and other pathological processes), impaired glutamate receptor functioning, glia pathology and immune dysregulation, to serious cognition problems and bizarre behavior. Thus, it is conceivable that altered PA supply and/or action contribute to the initiation and further progression of these impairments. More specifically, since spermine and spermidine positively influence many of these disturbed cellular mechanisms (see our considerations about PA functions), one may expect deficits in brain PA content in schizophrenia. Curiously, the opposite is the case as either increased blood and brain levels[73-75] or normal concentrations[65] of PA and ODC[81,85,87] have been reported for schizophrenia and animal disease models. Moreover, increased PA levels are not the result of neuroleptic treatment since anti-psychotics decrease PA concentrations in tissues and blood[75,76]. Thus, it seems unlikely that increased concentrations of spermine or other PAs contribute to schizophrenia pathology. In particular, there is no evidence that a PA excess is involved in impaired NMDA receptor functioning as observed in schizophrenia[34].

The situation is less evident with agmatine, which shows beneficial effects on some of the functions disrupted in schizophrenia. Increased agmatine concentrations were determined in blood plasma and post-mortem brain of individuals with first episode and chronic schizophrenia[68,76-81]. In contrast, reduced levels were measured in brain tissue of rat offspring after maternal immune activation[86]. It cannot be excluded, however, that overproduction of PA in human schizophrenia represents an attempt to compensate for certain functional losses (for example, induction and promotion of autophagy[95-97], which is abnormally reduced in schizophrenia[96]).

Table 2 Summary of polyamine-related findings in studies of animal models

Neuronal expression of ODC increased in rats with neonatal lesion of the ventral hippocampus[85].
Neuronal expression of SMOX increased in rats with neonatal lesion of the ventral hippocampus (unpublished).
Increased brain levels of putrescine, spermidine, spermine and arginine but decreased levels of agmatine were measured in rat offspring after maternal immune activation[86].
Agmatine disrupts prepulse inhibition in rats[87].
Agmatine attenuates the disruptive effects of phencyclidine on prepulse inhibition[88,89].
Injection of phencyclidine alters arginine metabolism in rat brain[90].
Withdrawal from repeated phencyclidine administration alters ARG activity and the levels of arginine metabolites in rat brain tissue[91,92].
No schizophrenia-like behavior in transgenic animals that overexpress ODC and/or SAT1[91].
SMOX overexpression in mice leads to glutamate excitotoxicity[91,92], a characteristic feature of "human" schizophrenia.

ARG: Arginase; ODC: Ornithine decarboxylase; SAT1: Spermidine/SpermineN1 acetyltransferase; SMOX: Spermine oxidase.

In addition, the possibility cannot be excluded that there may be a PA deficit in the developing CNS of future schizophrenia patients, which would contribute to disturbed prenatal brain development[11,96]. However, the latter scenario is not likely since increased concentrations of PA have been determined in rat offspring after maternal immune activation, a suitable neurodevelopmental model of the disease[86].

While the findings showing that increased PA and agmatine levels would not serve as convincing arguments in support of their involvement in schizophrenia pathology, it is possible that increased expression and enzyme activity of SMOX is a contributing factor[66]. SMOX catalyzes the oxidation of spermine to produce spermidine, hydrogen peroxide (H_2O_2) and 3-aminopropanal, which may spontaneously be converted to acrolein[97]. Consequently, increased oxidative stress was identified in SMOX over-expressing Dach-SMOX mice[92] which resulted in glu, tamate excitotoxicity[92,95]. Both reactive oxygen species, hydrogen peroxide and acrolein, are highly cytotoxic, as these can lead to production of massive cellular damage and pathologies[98-101]. Interestingly, in major depression and schizophrenia patients, significantly increased concentrations of protein-conjugated acrolein were measured, which could be reduced by anti-psychotic medication[101]. There is ample evidence that oxidative stress is a core feature in schizophrenia (for recent comprehensive reviews, see[101-104]). Oxidative stress is thought to be one of the mediators of progressive changes in brain structure and function in schizophrenia, which take place as schizophrenia progresses. The pathophysiological consequences include gray matter loss, myelination deficits and subsequent cognitive and functional impairment [105].

The extent that increased SMOX activity contributes to the aberrantly activated immune[104] and inflammatory[106] processes in schizophrenia remains to be established.

THE PA PATHWAY – A TARGET FOR NEW THERAPIES?

In schizophrenia, the brain and blood levels of PAs are normal or even increased. Hence, higher dietary intake of spermine or spermidine[43,107] cannot be a suitable approach to remove or mitigate schizophrenia symptoms. A potentially more promising approach would be to reduce SMOX expression or activity in order to diminish the generation of hydrogen peroxide and acrolein. Indeed, it has been shown recently that targeting SMOX is neuroprotective in a model of ischemic brain damage [108]. In this context, however, two questions need to be answered: (1) How to depress SMOX activity; and (2) What would be the consequences of this? In general, there are only a few approaches for a potentially successful intervention in this pathway. One of these is the application of the SMOX inhibitor *N*-(3-{[3-(dimethylamino)propyl] amino}propyl)-8-quinolinecarboxamide, which is under consideration for anti-cancer therapy[107]. Another one is the irreversible inhibition of SMOX by use of the PAO inhibitor MDL72527 {N1,N4-(bis(2,3-butadienyl)-1,4-butanediamine)}[108]. However, the application of both enzyme inhibitors produces a number of serious side effects. Furthermore, SMOX has an essential role in normal brain PA homeostasis (for review,

see[101,107,108]), which might be disrupted by any kind of intervention. Thus, the use of these enzyme inhibitors for schizophrenia therapy does not appear to be viable. Hence, PA-based schizophrenia therapy will probably remain an unresolved issue in the foreseeable future.

CONCLUSION

The PA system plays an essential role in the brain and other organs. Over the past half century, numerous reports appeared that showed that PAs, their precursors and derivatives, as well as some PA-metabolizing enzymes, are altered in schizophrenia, thus giving rise to the possibility for new PA-based therapies. Unfortunately, there are currently no prospects for such a therapeutic intervention, given a number of currently insurmountable obstacles. Therefore, further studies are urgently needed to learn more about the relationship between the PA system and schizophrenia pathology.

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REVIEW

Nuclear receptors modulate inflammasomes in the pathophysiology and treatment of major depressive disorder

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Abstract

Major depressive disorder (MDD) is highly prevalent and is a significant cause of mortality and morbidity worldwide. Currently, conventional pharmacological treatments for MDD produce temporary remission in < 50% of patients; therefore, there is an urgent need for a wider spectrum of novel antidepressants to target newly discovered underlying disease mechanisms. Accumulated evidence has shown that immune inflammation, particularly inflammasome activity, plays an important role in the pathophysiology of MDD. In this review, we summarize the evidence on nuclear receptors (NRs), such as glucocorticoid receptor, mineralocorticoid receptor, estrogen receptor, aryl hydrocarbon receptor, and peroxisome proliferator-activated receptor, in modulating the inflammasome activity and depression-associated behaviors. This review provides evidence from an endocrine perspective to understand the role of activated NRs in the pathophysiology of MDD, and to provide insight for the discovery of antidepressants with novel mechanisms for this devastating disorder.

Key Words: Major depressive disorder; Immune inflammation; Inflammasome; Nuclear receptors

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Core Tip: We summarize the evidence on nuclear receptors (NRs), such as glucocorticoid receptor, mineralocorticoid receptor, estrogen receptor, aryl hydrocarbon receptor, and peroxisome proliferator-activated receptor, in modulating inflammasome activity and depression-associated behaviors. This review provides evidence from an endocrine perspective to understand the role of activated NRs in the pathophysiology and treatment of major depressive disorder. Hopefully, the modulation of NRs with hormones and metabolites may become one of the key endocrinologic mechanisms for the development of novel therapeutics to increase the likelihood of therapeutic efficacy.

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INTRODUCTION

Major depressive disorder (MDD) is common, has a high recurrence rate and disability rate, and affects approximately 300 million people worldwide[1]. However, the underlying pathophysiological mechanisms of MDD have yet to be completely understood. Although effective treatments are available, market-approved antidepressants have many problems, such as a single mechanism of action, delayed effect [2], and numerous side effects[3], and approximately one third of all patients fail to respond to conventional antidepressants[4]. Accordingly, there is an urgent need for new conceptual frameworks and perspectives to understand the occurrence and development of depression to develop better treatments. As another important hypothesis of depression, several lines of evidence have established an association between MDD and the neuroimmune pathway, although some psychiatrists have argued about the causal relationship between inflammation and depression[5-7]. In this review, we outline emerging data that point to nuclear receptors (NRs) as potentially important contributors to the pathophysiology of depression. We first review the current research on the inflammatory hypothesis of depression, and investigate the role of inflammasomes in the neuroimmune pathway of depression. The regulatory roles of NRs [including glucocorticoid receptor (GR), mineralocorticoid receptor (MR), estrogen receptor (ER), aryl hydrocarbon receptor (AHR), and peroxisome proliferator-activated receptor (PPAR)] in inflammasome activation and pathophysiology of depression are also investigated. Finally, these interactions are discussed as a foundation for new therapeutics that target the NRs to treat depression.

INFLAMMATION AND MDD

Inflammatory response is a survival mechanism in human self-protection, which is the defensive response of the body to various traumatic stimuli. Endogenous or exogenous pathogens and tissue damage are initially detected by pattern recognition receptors (PRRs), such as Toll-like receptors and nucleotide-binding oligomerization domain (NOD)-like receptors, mainly expressed by cells that participate in the innate immune response[8]. Following the activation of such receptors, signals are then transmitted to activate transcription factors. These factors regulate hundreds of genes that increase the initial inflammatory response. The brain has its own highly complex immune regulation system and is closely connected with the peripheral immune system[9]. Crosstalk between the immune system and the central nervous system (CNS) is very important for the establishment of appropriate immunity against infection and injury, the maintenance of mental health, and the influence of behavioral response[10].

The role of inflammation in the causation and exacerbation of MDD is supported by the findings from clinical studies that patients with chronic inflammation (*e.g.*, asthma [11,12] and meningitis[13,14]), tumors, and autoimmune diseases (*e.g.*, multiple

sclerosis[15,16], Guillain-Barre syndrome[17], and systemic lupus erythematosus[18,19]) are more likely to suffer from depression, the secretion of inflammation-activated cytokines [interleukin (IL)-1β, IL-6, tumor necrosis factor α (TNFα), and C-reactive protein] in the peripheral blood and cerebrospinal fluid of patients with depression is increased[20,21], microglial activation and neuro-inflammation were found in the brain of patients with depression examined post mortem[22], and both nonsteroidal anti-inflammatory drugs and cytokine inhibitors have an active therapeutic effect on depression[23-25]. Preclinical studies have demonstrated that repeated stress events cause neurobiological changes including synaptic plasticity deficits[26] and neurotransmitter system dysregulation[27,28], leading to depressive-like behavior. Apart from these neurobiological responses, exposure to stress also has physiological and immunological consequences such as increased expression of inflammatory cytokines (such as IL-1β, TNFα, and IL-6) in the blood and brain[29]. Although cumulative evidence supports that immune inflammation plays a very important role in the pathogenesis of depression, the exact mechanism remains unclear.

INFLAMMASOMES IN THE NEUROIMMUNE PATHWAY OF MDD

The term 'inflammasome' was first proposed by the Tschopp research group in 2002 [30]. Inflammasomes are multiprotein complexes (-700 KD) composed of intracellular PRRs, and are an important part of the innate immune system. They can recognize pathogen-associated molecular patterns (PAMPs, such as lipopolysaccharide and bacteria) or host-derived danger signaling molecular patterns [DAMPs, including adenosine triphosphate (ATP), heat shock proteins (Hsp), glucose, uric acid, high mobility group box 1, and molecules associated with oxidative stress], and can recruit and activate pro-caspase-1. Activated caspase-1 cleaves the precursors of IL-1β and IL-18 to produce corresponding mature cytokines[31]. Activated inflammasomes can also induce apoptosis. Over the past 18 years, extensive research in this area has illustrated the key components of inflammasome activation and its role in disease processes. To date, five receptor proteins have been found to assemble inflammasomes, consisting of the NOD, leucine rich repeat (LRR)-containing protein (NLR) family members NLRP1, NLRP3, and NLRC4, as well as the proteins absent in melanoma 2 and pyrin[32]. The existing evidence suggests that NLRP1 and NLRP3 inflammasomes, especially NLRP3, play an important role in the neuroimmune pathway of MDD[33].

NLRP1 inflammasome

NLRP1 is the first identified inflammasome sensor protein[31]. Humans only have one NLRP1 protein, containing PYD, NOD, and LRRs domains, a function-to-find domain, and a carboxy-terminal caspase-associated recruitment domain[31]. The NLRP1 inflammasome, mainly expressed in neurons, is predominantly implicated in pathologies of neuronal injury and cognitive impairment, which are core features of MDD[34,35]. Although no clinical studies have reported the NLRP1 inflammasome changes in the pathogenesis of MDD patients, animal studies suggest that the NLRP1 inflammasome may play an important regulatory role in depressive-like behavior. Li *et al*[36] found that inhibiting the product of NLRP1 inflammasome could eliminate the depression-like behaviors caused by a chronic constriction injury. Recent studies showed that chronic unpredictable mild stress (CUMS) increased the expression of NLRP1 inflammasome complexes and pro-inflammatory cytokines. Hippocampal *Nlrp1a* knockdown prevented the NLRP1 inflammasome-driven inflammatory response and improved CUMS-induced depressive-like behaviors[37]. The above results suggest that NLRP1 inflammasome may be a potential antidepressant target, and further mechanisms need to be clarified.

NLRP3 inflammasome

Unlike NLRP1, NLRP3, mostly expressed in microglia cells, is activated by the most diverse array of danger signals[33,34]. NLRP3 has been reported to participate in the pathophysiology of depression in animal models and MDD patients. Supporting the hidden role of the NLRP3 inflammasome in MDD patients are data demonstrating that NLRP3 activation is increased in peripheral blood mononuclear cells[38,39]. Preclinical evidence linking the NLRP3 inflammasome to depressive-like behaviors has been found in numerous animal models, including an acute model of systemic lipopolysaccharide administration[40], chronic stress models[33], and ovariectomy and estrogen-deficient mice. These models can lead to depressive-like behavior and up-regulation of NLRP3 expression in rodents. Down-regulation of the expression of NLRP3 by some

biological methods can reverse depression-like behavior[41]. NLRP3 inflammasome-driven pathways in depression have been widely reviewed[42]. In brief, psychological stress and danger substances can activate the NLRP3 inflammasome, which may lead to the release of pro-inflammatory cytokines and induction of depression. Next, we will focus on the role of NRs in the activation of inflammatory bodies in the following chapters.

ROLE OF NRS IN REGULATION OF INFLAMMASOMES AND DEPRESSION

The NR superfamily is a family of ligand-regulated transcription factors that are widely expressed throughout the body[43]. NRs are activated by steroid hormones, such as androgen, estrogen, and progesterone, and other lipid-soluble signals, including oxysterols, retinoic acid, and thyroid hormone, and regulate the expression of a wide range of genes linked to metabolism and inflammation. There are 49 known members in humans[43]. All NR superfamily members have a common architecture, containing a variable N-terminal domain, a central DNA binding domain (DBD), a hinge region, a carboxy-terminal ligand-binding domain (LBD), and a variable C-terminal domain[44]. Of these, the DBD and LBD are the two most highly conservative binding domains. The DBD contains two zinc-fingers, which act as a hook, that provide base-specific binding to sequences in the vicinity of target genes. The LBD of NRs consists of a three-layered, antiparallel, helical sandwich and is connected to the DBD by a flexible hinge domain. According to the key characteristics of dimerization, DNA binding motifs, and ligand binding, NRs can be broadly divided into four classes [steroid receptors, retinoid X receptor (RXR) heterodimers, homodimeric orphan receptors, and monomeric orphan receptors][45]. There are some obvious structural and functional differences between different classes, and the role of different NRs in the neuroimmune mechanism of MDD are described.

NRs in MDD

GR

GR is a member of the steroid receptors, and is activated by the endogenous steroid hormone cortisol[46]. Unliganded GR is predominantly localized within the cytoplasm [47]. Glucocorticoid (GC) binding causes conformational changes of the GR and activates multiple functional domains, including the hinge and LBD regions. After rapidly and efficiently being transported to the nucleus, the GR binds to the specific GC response elements of the genome to form a nuclear complex containing the GR and co-regulatory factors, which jointly activate or inhibit the transcription of GC responsive genes[48].

The participation of GR down-regulation in the pathophysiology of MDD has been demonstrated in clinical and preclinical studies. Drug-free MDD patients have reduced *GR* mRNA expression together with increased expression of the FK506 binding protein 5[49,50], which reduces GR function and promotes inflammation by coordinating with Hsp90. Kang *et al*[51] found an association between the methylation of GRs and depression later in life. A meta-analysis demonstrated that the *NR3C1* (GR) rs41423247 homozygous mutation may be a risk factor for MDD [odds ratio (OR): 0.77, 95% cumulative incidence (CI): 0.64-0.94, $P = 0.01$][52]. Studies on transgenic mice and a mouse stress model found that the down-regulation of GR expression is significantly related to depressive-like behavior[53]. Exogenous GC exacerbates depressive-like behavior, and down-regulates GR expression. In addition, accumulating evidence has illustrated that GR antagonists, such as mifepristone, ameliorate psychotic symptoms and cognitive deficits in MDD and bipolar disorder[54,55]. However, this seems to contradict the hypothesis of enhanced immune inflammatory response in MDD, as GC is one of the most effective anti-inflammatory hormones in the body.

It is also understandable that the effect of GR on the immune system and synapse is highly dependent on the time and dose. Mounting data indicate that innate immune cytokines cause insufficient GC signals by decreasing GR expression, blocking translocation of the GR from the cytoplasm to the nucleus, and disrupting GR-DNA binding through nuclear protein-protein interactions, which may be a reasonable explanation for this problem. Escoter-Torres *et al*[56] have reviewed the mechanisms of inflammatory gene regulation by the GR. Here, we will mainly explore the relationship between GR and inflammasomes in the pathophysiological mechanism of MDD.

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction was assumed to be due to aberrant adrenal GC secretion and disorderly hormone feedback loops in MDD patients[57]. GC-induced activation of the NLRP3 inflammasome may mediate the potentiated neuroinflammation[58]. However, whether the effects of inflammasome activation and the HPA axis are regulated through GR-related pathways is still unclear. Nevertheless, some evidence suggests that the GR is closely related to inflammasomes, which play an important regulatory role in some immune inflammatory diseases, such as MDD and acute-on-chronic hepatitis B liver failure[59]. In chronic obstructive pulmonary disease-induced depression, GR dysfunction mediates activation of the NLRP3 inflammasome. Preclinical evidence has shown that activation of the GR-NF-κB-NLRP3 pathway in microglia mediated chronic stress-induced neuroinflammation and depressive-like behavior[60]. Chronic corticosterone (CORT) treatment can increase Txnip and upregulate Txnip-NLRP3 binding, which activated the NLRP3 inflammasome, and induced the activation of caspase-1 and the release of IL-1β[61]. In addition, chronic GC exposure may increase neuroinflammation through NLRP1 inflammasome activation and induce neurodegeneration[62]. In conclusion, subsequent studies should be devoted to exploring how GR regulates the activation of inflammatory bodies and thus regulates the neuroimmune response.

MR

Negative feedback regulation of the HPA axis requires the participation of the dual-receptor system of MR and GR[63]. Similar to GR, MR is another member of steroid receptor and ligand-inducible transcription factors. In the brain, MR has approximately 10-fold higher affinity for CORT than the GR[64]. Due to the differences in affinity, CORT at the basal level largely occupies the MR, whereas higher hormone levels progressively occupy the GR after stress and circadian/ultradian peaks[65]. Early research results showed that brain MRs did not play an important role in the regulation of the stress response; however, subsequent studies demonstrated that MRs were essential for nongenomic regulation of glutamate transmission in the hippocampus by CORT. Based on this, considering that MRs are expressed abundantly in the limbic circuitry, a number of studies have focused on their regulatory role in depression and cognitive dysfunction[66].

The expression of MRs was decreased in the hippocampus, inferior frontal gyrus, and cingulate gyrus in depressed patients[67,68]. In addition, neuroendocrine studies also indicated abnormal MR function in MDD[63]. Otte C *et al*[69] found that the administration of an MR agonist (fludrocortisone) in drug-free patients with depression effectively reduced cortisol secretion and improved their verbal memory and executive function. In MDD patients treated with escitalopram, fludrocortisone accelerated the treatment response by 6 d. Furthermore, *MR* gene variants[70,71] and haplotypes[72,73] have been associated with depression symptoms and stress-induced reward-related learning deficits, and MR haplotypes may be potential biomarkers for a subgroup of patients with atypical depression[73]. In addition, MR malfunction and abnormal DNA methylation level have been demonstrated in treatment-resistant depression, depression during pregnancy, and in adolescence[74,75]. In preclinical studies, the role of the MR in the regulation of HPA-axis activity, executive function, and memory performance has been well demonstrated. In contrast to the effect of GR antagonists on long-term potentiation (LTP), MR antagonists inhibited the LTP process, suggesting that the MR and GR have opposite effects on the adjustment of synaptic plasticity after stress exposure[76]. The results from transgenic mice with forebrain knockout or overexpression of *MR* confirmed the role of MR in learning and memory[77]. After loss of the *MR* gene in the forebrain, mice displayed an aberrant basal and stress-induced CORT secretion and deficits in learning and memory[78]. In contrast, overexpression of MR in the forebrain improved spatial memory and behavior performance[79].

Research on the role of MR in the pathogenesis of depression is still in its infancy, and its possible mechanism has not been fully explained. Chen *et al*[80] reviewed the possible mechanism of MR in regulating depression, learning, and memory from different perspectives, such as HPA-axis activity, 5-HT transmitter system, adult-neurogenesis, and inflammation. Considering that MR can participate in the regulation of other and immune-related diseases by activating NLRP3 inflammasome[81,82], whether the role of MR in the pathogenesis of depression is involved in inflammasomes and modulation of inflammasomes will be important research directions in the future.

ER

Given that the prevalence of depression in women is 2-3 times higher than that in men and changes in mood are simultaneously associated with estrogen levels[83], a potential role for estrogen in the pathophysiology of depression has generated substantial interest. It is well documented that estrogen can regulate neurotransmission, enhance the levels of serotonin and noradrenaline, and plays a vital role in emotion processing, cognition regulation, and motivation triggers[84,85]. The data from clinical and preclinical research show that estrogen is involved in modulation of depression and anxiety. For example, cumulative clinical studies found that menopausal declines in estrogen levels were associated with an increase in mood disturbances in women[86,87]. Moreover, premenopausal women with depression had lower levels of 17β-estradiol (E_2) than non-depressed women[88]. In rodents, ovariectomy, resulting in estrogen deficiency, induced an increase in depression and anxiety-like behavior[89] which was improved by E_2 replacement[90].

Estrogen plays its biological role mainly through activating ERs. The ERs including ERα (ESR1) and ERβ (ESR2) are members of a superfamily of hormone-regulated transcription factors, and regulate the gene transcription of estrogen by binding to specific DNA sequences[91]. Genetic variation in ERs may therefore modify estrogen signaling, such as altering binding efficiency and disrupting normal gene regulation, thus increasing susceptibility to developing depression in women. Ryan J *et al*[87] carried out a detailed review and pointed out that there was a significant correlation between *ESR1* gene polymorphism and severe depression in women. Preclinical research has demonstrated that ERα and ERβ agonists can reverse stress-induced depressive behavior and cognitive deficits[92]. However, the specific mechanism of ER in stress-induced depression remains unclear. Some studies have found that NLRP3 inflammasome activation mediates estrogen deficiency-induced depressive-like behavior and neuroinflammation in the hippocampus of mice[93]. In other inflammation-related diseases, such as endometriosis and breast cancer, the ER regulates the activation of NLRP3, which leads to inflammation[94,95].

AHR

AHR is a ligand-activated transcription factor which was first identified as a contaminant of the chemical herbicide Agent Orange[96]. However, AHR has been proved to be a crucial modulator of host-environment interactions in recent years, espe-cially for immune and inflammatory responses. As an NR, AHR is bound by co-chaperones Hsp90 and XAP that maintain its localization in the cytoplasm. After ligand binding, AHR is released from its co-chaperones and is transferred to the nucleus, where it forms a heterodimer with AHR nuclear translocator (ARNT) and binds to DNA to regulate target gene expression[97]. AHR can bind to many diverse ligands, including exogenous synthetic aromatic hydrocarbons [*e.g.*, benzo (a) pyrene], exogenous natural chemicals [*e.g.*, tryptophan (Trp) and norisoboldine], and endogenous ligands (*e.g.*, tryptamine and kynurenine)[98]. Specifically, compounds from the Trp metabolic pathway, especially the kynurenine pathway (~95% of Trp metabolism), provide many ligands for the AHR and play an important role in the regulation of immune and inflammatory responses. A large body of studies have shown that the AHR is associated with many diseases driven by immune/inflammatory processes, including MDD, asthma, multiple sclerosis, rheumatoid arthritis, and allergic reactions[97].

Increased kynurenine (KYN) production from Trp metabolism, mediated by indoleamine 2,3-dioxygenase (IDO), is a biomarker of immune dysregulation in depression [99]. Clinical and preclinical data have consistently shown an elevated KYN level with depressive behavior after immune disturbance. The activation of AHR signaling may play an important role in immune regulation. Preclinical evidence has shown that blocking the AHR can reverse KYN-induced monocyte trafficking, neuroimmune disorder, and depression-like behavior in mice[99]. Recent clinical studies have also confirmed that the AHR is related to the individual difference in plasma KYN concentration in MDD patients[100]. The AHR regulates the expression of Trp-2,3-dioxygenase 2 (TDO2) and IDO1/2, and downstream enzymes kynurenase and kynurene 3-monooxygenase (KMO). The results of *in vitro* cell culture showed that AHR knockdown resulted in a decrease of KYN concentration in the cell culture medium, which may be due to the increase in quinolinic acid, a downstream metabolite of KYN[97]. Quinolinic acid is a neurotoxic NMDA receptor agonist and contributes to MDD symptoms[100]. Although cumulative data have confirmed the regulatory role of AHR in depression-like behavior induced by an abnormal KYN metabolic pathway, the specific mechanism has not been clearly elucidated. A

significant result showed that AHR can regulate the activity of NLRP3 inflammasome by inhibiting the transcription of *NLRP3*[101]. The proposed model is as follows: Following engagement by AHR cognate ligands, it forms a heterodimer with ARNT in the nucleus, binds to the xenobiotic response element (XRE) regions located at the NF-κB site in the promoter of *NLRP3* and then inhibits NF-κB transcription activity, finally decreasing *NLRP3* transcription and subsequent inflammasome activation[101]. In view of the role of NLRP3 in the neuroimmune mechanism of depression, this may be the potential mechanism of AHR in regulating depressive episodes. In addition, the AHR acts as a potential crosstalk mediator between the adaptive immune system in the gut and gut microbiota-derived metabolites. Whether AHR has a certain role in the brain-gut axis dysfunction of MDD should be investigated in subsequent research.

PPARs

PPARs are ligand-activated transcription factors and members of the NR receptor superfamily. Three isotypes of PPARs have been identified, namely, PPARα, PPARβ/δ, and PPARγ[102]. Despite the three PPAR isoforms having a high degree of structural homology, they have distinct tissue distribution, ligand-binding properties, and functional roles. Endogenous and natural ligands of PPARs mainly include fatty acids and fatty-acid derivatives. PPARs translocate into the nucleus upon ligand binding, where they form heterodimers with the RXR and then bind to peroxisome proliferator response elements to regulate transcriptional target genes. The physiological characteristics of PPARα, β/δ, and γ and their role in other diseases have been extensively reviewed[103,104], and will not be elaborated here. Next, we will discuss the role of PPARs in depression.

PPARα

PPARα is distributed in many peripheral tissues which catabolize high amounts of fatty acids. In the CNS, PPARα is highly expressed in the basal ganglia, prefrontal cortex, thalamic nuclei, hippocampus, and ventral and tegmental areas[105]. In these regions, the distribution of PPARα in neurons is higher than that in glial cells. Recent research found that PPARα modulates the stress response, neurotransmission, neuroinflammation, and neurogenesis and plays an important regulatory role in some neuropsychiatric diseases, such as depression, post-traumatic stress disorder, and neurodegenerative diseases[106]. Preclinical studies found that knockout or overexpression of PPARα in rodent brain could imitate or reverse the depressive-like behavior induced by chronic stress. In addition, PPARα selective agonists (WY14643 and fenofibrate) have been associated with antidepressant effects in stress-induced depression models[107,108]. Some antidepressants, such as venlafaxine and fluoxetine, need PPARα to play an antidepressant role[109]. The antidepressant effect may be mediated by acting on the cAMP response element-binding (CREB)-mediated biosynthesis of brain-derived neurotrophic factor (BDNF)[109-111]. Some studies have also indicated that PPARα can modulate mesolimbic dopamine transmission and improve depression-related behavior[112]. Furthermore, N-palmitoylethanolamine, which stimulates PPARα, induced a dose-dependent antidepressant effect by engaging neurosteroid biosynthesis[113]. In summary, PPARα may play an important role in the pathogenesis of MDD and the effects of antidepressant medications, and it may be a new target for developing novel antidepressants.

PPARβ/δ

PPARβ/δ is the most widely expressed isoform in the brain, with particularly high levels in the hippocampus, entorhinal cortex, and hypothalamus[105]. Compared with the other two subtypes, PPARβ/δ showed a higher expression level in neurons, and had neuroprotective effects in some CNS disease models[114]. Recent studies have found that overexpression of PPARβ/δ in the hippocampus can inhibit depressive-like behavior induced by chronic stress in rats, which corresponds to a significant down-regulation of PPARβ/δ expression in the hippocampus when rats experience chronic unpredictable stress[115]. Subsequent studies have found that when PPARβ/δ is knocked down, rats show depressive-like behavior[116]. Similar to the antidepressant effect of PPARα, the CREB-BDNF pathway may also be involved in the antidepressant effect of PPARβ/δ. Furthermore, chronic stress can increase the expression of TWIST1, which will lead to mitochondrial damage and ATP deficiency by down-regulating PPARβ/δ expression, and eventually leads to depression-like behavior in mice[116]. How overexpression of PPARβ/δ and its agonists play an antidepressant role is still unclear.

PPARγ

PPARγ is highly expressed in the amygdala, dental gyrus, prefrontal cortex, ventral tegmental area, and basal ganglia[105]. Under normal physiological conditions, PPARγ can co-localize with neurons and astrocytes in human and mouse brain, but not with microglia. However, PPARγ can also be expressed in microglia when the functional status of microglia changes. PPARγ agonists have been synthesized for the treatment of metabolic diseases, especially dyslipidemia and type 2 diabetes mellitus, as well as non-metabolic diseases including neurodegenerative diseases, cancer, and inflammatory diseases due to their important metabolic regulation and excellent druggability[117,118]. Compared with the above two subtypes, the relationship between PPARγ and depression has been more widely recognized, and clinical trials on the antidepressant effects of PPARγ agonists are in full swing. Some gratifying results have been found and were well reviewed[117].

In conclusion, all isotypes of PPAR may participate in the pathophysiology of depression, and even antidepressants based on PPAR agonists have been developed. However, how PPARs play an antidepressant role seems unclear, although some studies have shown that this occurs by regulating the biosynthesis of BDNF and regulating the 5-HT neurotransmitter system. Activation of PPARs inhibits the activation of inflammasomes (in particular NLRP3) and the release of inflammatory cytokines, which is similar to the changes in patients with depression and in depressive models[119,120]. Therefore, whether and how PPARs play an antidepressant role by regulating the inflammatory response will be an important future research direction. In fact, some studies have found a link between them. Liu *et al*[121] found that oridonin, mediated through the PPARγ receptor signaling pathway, modulated excitatory alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the prefrontal cortex, and showed fast and significant antidepressant efficacy. In addition, Song *et al*[122] found that, astragaloside IV, which exhibited PPARγ agonist activity, ameliorated stress and neuroinflammation-induced depressive-like behaviors *via* the PPARγ/NF-κB/NLRP3 inflammasome axis in mice. Apigenin exhibits antidepressant-like effects by inhibiting NLRP3 inflammasome activation through the upregulation of PPARγ in rats with CUMS[123]. Moreover, in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease, PPARβ/δ agonist alleviates NLRP3 inflammasome-mediated neuroinflammation[120].

CONCLUSION

Given the relatively low overall response rates and the wide range of 'adverse' events associated with current antidepressants, there is an urgent need for novel therapeutics to treat specific underlying disease mechanisms that are not addressed by the antidepressants targeting the serotonergic and/or noradrenergic system. Hopefully, the modulation of NRs with hormones and metabolites may become one of the key endocrinologic mechanisms for the development of novel therapeutics to increase the likelihood of therapeutic efficacy. Here, we reviewed the regulatory role of NRs (including the GC, MR, ER, AHR, and PPAR) in inflammasome activation and the pathophysiology of depression (Figure 1). Indeed, a major breakthrough in the pathophysiology of depression was the discovery that DAMPs and PAMPs activate inflammasomes, which enhance caspase-1 activity, and subsequently inhibit excitatory AMPA receptor synaptic plasticity in the brain circuitry to change mood-associated behaviors[124,125]. Cumulative studies have shown that activation of the NRs may directly change the activity of inflammasomes to modulate the levels of mature forms of caspase-1 and IL-1β. Caspase-1-mediated programmed cell death and surface stability of the AMPA receptor in the hippocampus, are essential for depression-like behavior[125]. Current data suggest that direct modulation of NRs may offer new opportunities to mitigate depressive disorders. However, several directions are warranted for future studies: (1) To identify more NR activators for the treatment of MDD; (2) To address the detailed mechanism of how NRs modulate inflammasomes; and (3) To perform clinical trials to prove the role of NR modulators in the treatment of MDD. These NR modulators can be safely used in combination with currently available antidepressants to simultaneously target multiple disease mechanisms and increase the likelihood of therapeutic success.

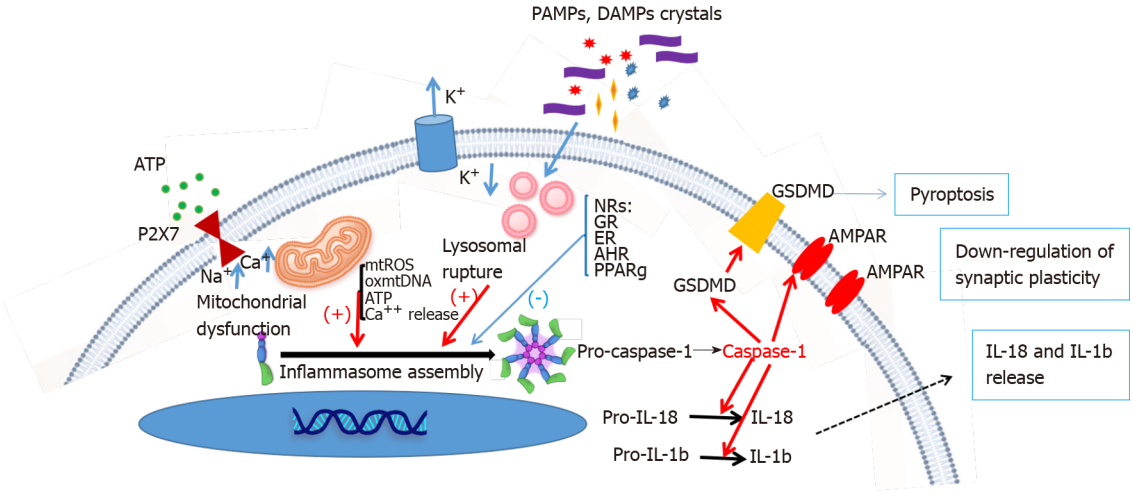

Figure 1 Inflammasome activation in the pathophysiology of major depressive disorder - roles of the nuclear receptors. NLRP3 inflammasome activation, which includes canonical and noncanonical activation pathways, is induced by a number of pathogen-associated molecular patterns and danger signaling molecules patterns. The canonical activation pathway involves stimulation-mediated activation signals such as ion fluxes, lysosomal rupture, mitochondrial dysfunction, and so on. Mitochondrial dysfunction leads to the production of mitochondrial reactive oxygen species, damaged mitochondrial DNA, and calcium release from the mitochondria, and all these changes facilitate the assembly of inflammasomes. Activation of the inflammasome causes caspase-1 activation, leading to the maturation and release of interleukin (IL)-1/IL-18 and pyroptosis. In addition, caspase-1 modulates the membrane stability of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which leads to the down-regulation of AMPA receptors at the synapses. Nuclear receptors inhibit the assembly of NLRP3 inflammasome, which will finally protect the excitatory AMPA receptor synaptic activity and contribute to the antidepressant mechanism of the nuclear receptor activators. ROS: Reactive oxygen species; PAMPS: Pathogen-associated molecular patterns; DAMPS: Danger associated molecular patterns; GSDMD: Gasdermin D; AMPAR: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; IL: Interleukin; NRs: Nuclear receptors; GR: Glucocorticoid receptor; ER: Estrogen receptor; AHR: Aryl hydrocarbon receptor; PPAR: Peroxisome proliferator-activated receptor; ATP: Adenosine triphosphate.

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REVIEW

Review of barriers and interventions to promote treatment engagement for pediatric attention deficit hyperactivity disorder care

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a common and impairing behavioral health disorder, impacting over 5% of children worldwide. There are multiple evidence-based pharmacological and psychosocial treatments for ADHD, and greater service utilization is associated with improved acute and long-term outcomes. However, long-term outcomes are suboptimal as multimodal treatments are often not accessed and most care ends prematurely. This narrative review discusses barriers to engagement for children and adolescents with ADHD and their families as well as interventions to overcome these barriers. Families face a variety of structural and attitudinal barriers, ranging from cost and access to stigma and low self-efficacy to successfully implement change. There are multiple interventions that may enhance engagement with ADHD care including psychoeducation, integration of behavioral services in general medical settings, telehealth as well as specific adaptations to existing ADHD treatments, such as the use of motivational interviewing or shared decision making. Integration of behavioral health into general medical settings and telehealth have been found in controlled studies to increase access by reducing both structural and attitudinal barriers. Adding motivational interviewing, shared decision making and other engagement interventions to evidence-based ADHD treatments has been found to reduce attitudinal barriers that translates into improved participation and satisfaction while enhancing outcomes. However, little is known about how to promote extended engagement with ADHD services even though a chronic care model for ADHD is recommended.

Key Words: Attention deficit hyperactivity disorder; Treatment engagement; Barriers; Interventions; Children; Adolescents

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Core Tip: Assessment of families' motivation for care at treatment initiation and recurrently over the course of treatment, especially during times of increasing stress and declining functioning, is essential to promote sustained engagement. Aspects of motivation that predict sustained engagement include desire and readiness for care, treatment preferences, self-efficacy to access and implement the selected treatment and perceived barriers to the treatment. Integrating services into trusted medical settings to reduce stigma, telehealth to reduce the burden of care, shared decision making to promote autonomy, psychoeducation about treatment options and how attention deficit hyperactivity disorder impacts current functioning and motivational interviewing can be employed to promote engagement.

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common and impairing behavioral health (BH) disorder, impacting over 5% of children worldwide[1]. Impairment often persists into adulthood leading to recommendation to treat ADHD with a chronic care model[2,3]. Multiple evidence-based pharmacological and psychosocial interventions exist for ADHD[3-5]. In the United States, most children diagnosed with ADHD receive some treatment for it with 5% of school-aged children prescribed ADHD medication. In other countries rates of ADHD medication use in children are often below the reported prevalence rates, varying from 3% (France, Japan) to 5% (Iceland)[6]. Across countries, multimodal treatment and rates of any counseling services rates under 50%, even in countries where treatment guidelines prioritize initial treatment with behavioral interventions[7-11]. In the United States, most care starts in primary care, with primary care clinicians (PCCs) being the most common provider of ADHD services[12]. However, a number of specialty medical providers treat ADHD and schools offer a variety of therapeutic supports[7,12].

Most countries in the European Union and the United Kingdom have universal access, National Health Systems, funded by the State *via* taxpayer deduction on the worker´s paychecks. These systems usually also cover the rest of the family, including children, even if the parents are not working at the time. There are different levels of coverage within the European Union especially for medication and counseling services leading to appreciable variations in ADHD care across national boundaries. Access to specialists varies widely across countries, as do the administrative requirements to get to specialty care. Initial assessment and diagnosis can start in general or specialty settings[13,14]. For example, in the United Kingdom, patients with possible ADHD are referred to a Child Psychiatry and Psychology Evaluation Unit that performs a comprehensive medical, psychiatric, psychological, school and social evaluation that may take several months to be completed. In Italy, there are less than 10 Pediatric Neuropsychiatry Outpatients Units that are allowed to prescribe methylphenidate, creating substantial waits for a country with a population of 60 million. In Spain, Child and Adolescent Psychiatry is not recognized as a specialty yet. Pediatricians can start medication, and can refer to either Pediatric Neurology (usually younger children and those with medical comorbidity as epilepsy or neurodevelopmental delays) or Child Psychiatry Units usually staffed by general psychiatrists with variable levels of expertise.

CARE OUTCOMES

Despite well-established assessments and evidence-based and available treatments,

long-term outcomes are suboptimal across countries[2,15,16]. One major challenge to achieving optimal long-term outcome is treatment engagement. Initiating care can be a challenge as many referred families fail to access any care[17]. When initiated, care is often interrupted or quickly discontinued. In both primary care and specialty care settings, utilization rapidly declines over the first year of treatment[18-20]. In the United States, care for nearly 60% of publically insured youth does not meet federal guidelines for frequency of reassessment[21]. Similarly, low rates have been found in Australia, with only 28% children diagnosed with ADHD receiving any services in the past 6 mo[22] and sizable percentage of children with ADHD in United Kingdom are not receiving treatment[23]. When stopping care, most patients still exhibit appreciable impairment[21] and many who experience interrupted care never return[24].

Numerous studies have shown rapid declines in ADHD medication usage over time. In both Europe and the United States, over half of children stop medication within 6 mo[25,26]. Rates of treatment utilization for CNS stimulants continue to decline after year one[27]. By the end of adolescence, only 10% of youth with ADHD are using medication even half of the time[2]. Even short-term medication adherence is challenging as over one month, only about 40% of children take every dose of medication prescribed[28].

Engagement with counseling services face similar if not greater challenges to those for medication treatments. In the United States, many families never access counseling, as these services are less likely to be available in general medical settings than medication treatments[29,30]. Up to half of referrals for counseling services for ADHD fail to translate to any treatment[31] as families often stop care when referred to external BH providers[18]. For those who do connect, care often ends prematurely[20, 32]. In a review of insurance claims data in the United States from 2008-2014, under half of families with a child diagnosed with ADHD accessed any billable psychosocial services. Among families accessing any treatment, only half attended 4+ sessions over any 12-month period[10]. Other reports from the United States[33], other western Countries and across the globe[34,35] show similarly low rates. Multimodal treatment is recommended for children[3,5], most desired by caretakers[36] and is most likely to optimize functioning especially for low-income youth[4,37,38]. However, combined treatment is particularly challenging to establish and maintain, with only 20%-33% youth accessing both counseling and medication in the same year[10,39].

While challenging to achieve, greater service utilization is associated with improved acute and long-term outcomes[16,20,40], especially in primary care where treatment usage rates are particularly low[31,41,42]. Therefore, efforts to promote sustained utilization may be one means to enhance long-term outcome. Current ADHD guidelines[3,5] recommend engagement efforts that begin when care starts. They advise measuring progress towards personal goals along with symptoms using scheduled assessments, while promoting families to be informed advocates in their child's care. This review will discuss identified barriers to engagement with pediatric ADHD care and interventions to overcome these barriers (Figure 1).

Existing literature was ascertained in the English language, published until March 2021, using searches of MEDLINE and PsycInfo for the following categories: ADHD, children, adolescence, engagement, adherence, methylphenidate, amphetamine, pharmacotherapy, drugs, CNS stimulants, nonstimulants, medication, psychotherapy, psychosocial intervention, counseling, parent training, behavioral therapy, and multimodal treatment. References from identified articles were reviewed to ensure that all relevant papers were included.

BARRIERS OF TREATMENT ENGAGEMENT

Numerous barriers have been identified to sustained engagement with pediatric mental health services. These can be classified as structural such as long waiting lists, limited hours of operation or cost and attitudinal, which encompass a variety of perceptions about mental health and its treatment. These include beliefs that mental health disorders do not exist or cannot be improved, to stigma about receiving a diagnosis or treatment for it.

Structural barriers

A variety of physical, geographical, financial and access barriers have all been found to impede ADHD care in over half of families of a child with the disorder[19,43]. Geographical barriers such as distance to a provider have been found to be particularly relevant to BH care, especially in rural areas where there are few specialty

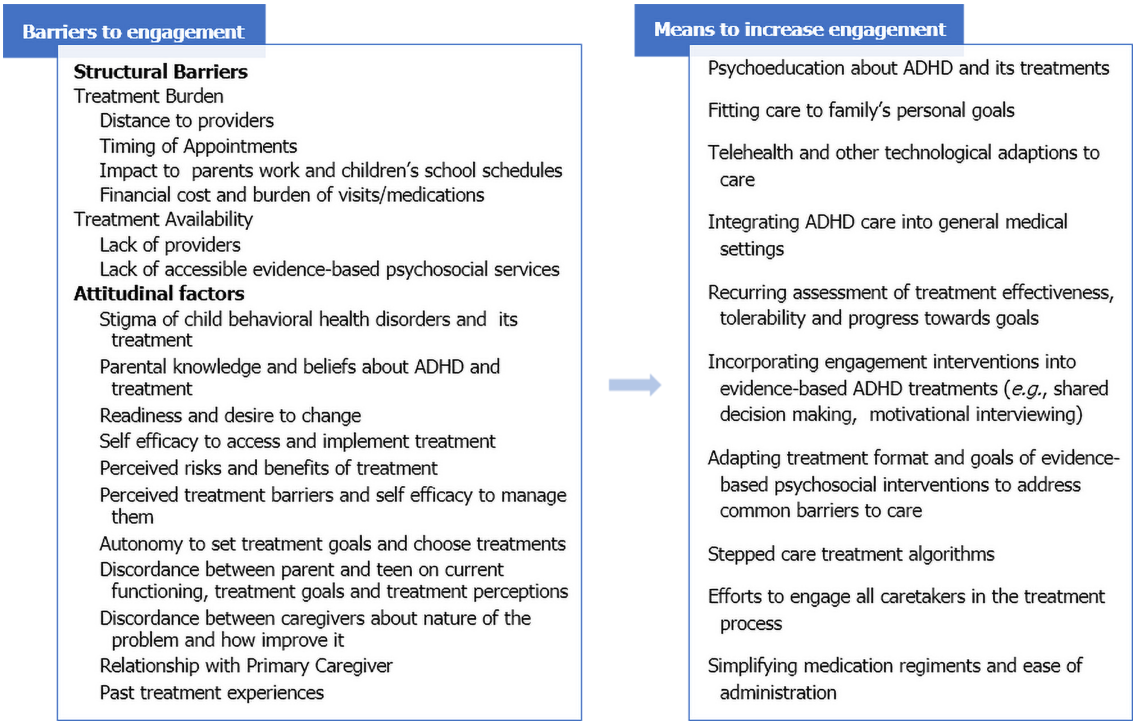

Figure 1 Barriers and interventions to promote treatment engagement for attention deficit hyperactivity disorder. ADHD: Attention deficit hyperactivity disorder.

treatment options[44,45]. These structural barriers exist to varying degrees in different healthcare models. Despite having a Universal National Health System in the European Union and the United Kingdom, there are still structural barriers to ADHD care. In a study from Taiwan, families who are able to access specialty care appear more likely to stay in care than those getting care in general medical settings[46]. Mostly problematic is the limited availability of Child Psychiatrist and Child Psychology providers. That lack of availability generates sizable travel times, long waiting lists and suboptimal reassessment schedules.

Financial cost is a commonly cited structural barrier to the treatment for ADHD[22,47,48]. In the United States, treatment coverage can vary widely by insurance plan, creating substantive financial barriers even for those with health insurance. For example, behavioral interventions for children are not covered as an essential benefit under the Affordable Care Act[49]. Bussing *et al*[50] reported that 38% families reported cost as a main reason for not to pursue treatment, while rates of medication usage are positively correlated with income[51]. Lowering costs has been found to improve treatment adherence for ADHD care[52]. In Europe, ADHD care is not universally covered by public insurance[53]. Even in countries with universal healthcare coverage that encompasses ADHD services, the long wait times have created a private healthcare market where cost of services can be an appreciable barrier. ADHD significantly increases a family's medical cost, more than many other chronic medical conditions. ADHD in children can also reduce parents' capacity to attend work. Parents of ADHD youth are more likely to have ADHD themselves[54], which is associated with reduced educational achievement and earning potential[55]. Parental psychopathology may also impact the ability to engage with and implement BH services for their children[56,57].

When socio-economic status (SES) has been formally examined as a treatment barrier, the data is mixed. Lower SES is associated with less likely to engage and adhere to ADHD treatment[20,50]. In the United States, public *vs* private insurance is associated with higher rates of counseling services[7,10,12]. In the Multimodal Treatment of ADHD study (MTA), SES moderated adherence to behavioral and combined treatment, but not medication[19]. Other analysis has observed that SES is inversely associated with medication adherence[58]. In the United States, differences in treatment utilization across race/ethnicity are diminished when sociodemographic variables are taken into consideration[59].

Taking ADHD medication several times per day can be an appreciable challenge[28,48,60,61]. Extended-release versions that only require once daily dosing are associated

with improved adherence[25], but even youth using extended-release preparations struggle with adherence[40]. Furthermore, extended-release medications often come with higher costs forcing families and prescribers to balance between finances and convenience[62]. More than 40% stimulants medication prescription for ADHD require prior-authorization in countries where they have managed care[63] creating additional barriers to more convenient and palatable care. In other countries, office visits are required to adjust the dose and the long waits between appointments can create a sizable impediment to timely dose optimization.

Attitudinal factors

Uptake of care can be low even when it is readily accessible[38,42,64,65]. Attitudinal barriers[66] more strongly predict BH utilization than treatment type or provider, especially for low-income families[38]. Parents are the main agent of change for a child's BH, making parental attitudes, perceptions and preferences important variables to assess when trying to promote engagement[67]. Parental knowledge and beliefs regarding ADHD and its treatment affect decisions to both initiate and continue with care[68]. Parents who feel that they have little influence over their child's behavior or that their child is choosing to misbehave are less likely to engage in counseling interventions for ADHD[69,70]. Parental attributions for a child's behavioral problems appear to be particularly robust predictors for fathers who are more likely to engage in care when they feel they can influence their child's behavior[71].

Parental views on ADHD medication vary widely, ranging from unacceptable to the preferred treatment[27,72]. Parents who view their child's symptoms as a medical disorder are more likely to initiate medication[72]. In contrast parents who view ADHD as age normative fluctuations in behavior[48,73] are less likely to use medication. Parental knowledge about ADHD and medication treatment is predictive of medication acceptance and usage[19,34,74]. While having more knowledge may increase willingness of parents to initiate medication, it does not reliably predict medication adherence or long-term usage and may reduce interest in evidence-based psychosocial treatments[34,75]. The degree of symptom reduction also does not predict adherence. Rather parents appear to weigh the perceived risks of medication usage *vs* its perceived benefits while deciding how often and for how long to use medication[24]. Pretreatment preferences for treatment modality do not reliably predict uptake of counseling services as most adults rate psychosocial treatments as palatable[76]. Initial treatment decisions also impact future care. Past medication use is one the most robust predictors for future medication use for ADHD, while use of medication appears to lower motivation for future counseling services even when impairment persists, both in clinical trials offering free care[77] and in routine care[10].

There are meaningful differences in treatment utilization across racial/ethnic groups. Black children are less likely than White children to use medication, but more likely to utilize counseling. Hispanic families are less likely than White non-Hispanic families to utilize counseling and medication. However, rates of medication are increasing over time amongst families of different races and ethnicities, particularly for Hispanic families[78,79]. Parental health beliefs about ADHD also appear to be influenced by race and ethnicity. Non-Hispanic White families are more likely to report greater knowledge about ADHD, more likely to view it as a medical disorder and more likely to view medication as safe than Black or Hispanic families. Moreover, Black and Hispanic families are more likely to report side effect concerns regarding ADHD medication and expect less benefit from medication[80-84]. In contrast to White Non-Hispanic families, increasing parental knowledge about ADHD in Hispanic families is associated with increased odds to utilize counseling but not medication[75].

Parents' perception about the impact of the child behaviors on parental and family functioning influences decision to pursue, accept and persist with treatment for ADHD[19,22]. For example, parents who perceive their child's behavior to be negatively affecting their career, are more likely to seek treatment[19]. The child's level of current functioning as well as the impact of treatment on their functioning appears to be particularly relevant for decisions regarding when to use medication for Hispanic families[75]. While increased parental stress may drive treatment seeking, persistently stressed parents are prone to disengage care[84]. Similarly, children with comorbid disorders, especially other externalizing behavioral disorders, may be more apt to present for treatment but experience higher rates of premature dropout[19].

Stigma related to child mental health and specifically to ADHD have been identified as sizable barriers to initiating treatment[81,85]. Unfortunately, there is continuous to be an appreciable stigma regarding having a child with ADHD and surrounding treatment for ADHD[74]. In the MTA study, stigma was a common reason for discontinuing medication[24]. However, failure to treat also increases the risk of being

stigmatized as Singh *et al*[86] observed youth are more likely to experience stigma due to their symptomatic behaviors than to disclosing medication use. Parental perceptions of their relationship with their child's healthcare provider influences decisions to initiate ADHD medication and can counteract stigma concerns, especially when the primary care provider is also managing ADHD[72]. However, providers do not always talk with families about their goals and preferences for the treatment for the ADHD[87]. Opinions of others also impact care decisions as parents are most likely to engage in a treatment when medical advice meshes with feedback from family and friends[88].

Attitudinal factors may also influence national healthcare policy. The acceptance of biological psychiatry may be a barrier to both diagnosis and treatment. For example, in France (population 65 million), where there is still a strong psychoanalytic tradition and the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases nomenclatures are not widely accepted, there are only a few approved ADHD medications and very limited specialty treatment centers[89,90]. Spain (population 47 million), where Child and Adolescent Psychiatry is still not a recognized medical specialty, has just one child psychiatry fellowship program at the University of Navarra[91].

Patients and families value treatment choices and typically will access more preferred treatments. Treatment goals have also been found to predict which type of ADHD intervention is used. Parents prioritizing academic goals are more likely to use medication, while those with behavioral goals lean towards psychosocial treatments [65]. However, for ADHD, it does not appear that families access only preferred treatments. Most treatment seeking families rate psychosocial treatments as most palatable but medication is more commonly used in the United States, even in young children[7,10,12,76]. Using easily accessible but unpalatable treatments has been identified as one cause for poor sustained utilization of ADHD services[40]. However, even caretakers preferring psychosocial treatments often fail to persist with treatments [76] suggesting using preferred treatments is insufficient to produce sustained engagement.

Perceptions about the burden and safety of treatment also predict utilization. Many parents report hesitancy to use ADHD medications due to side effect concerns[92,93]. Side effects are also one of the most common reasons for discontinuing ADHD medication reported by parents and adolescents[24,93]. The most common side effect concerns related to changes in sleep, appetite, mood and perceived risk of addiction [94]. For counseling services, the perceived intensity and burden of care are relevant factors as parental motivation for care is one of the most robust predictors of counseling dropout and treatment response[20,95-97].

Self-efficacy is another variable impacting engagement with ADHD care, especially for counseling where parents are the primary agents of change for their child. Parents of children with ADHD report increased parental stress and reduced self-efficacy[64, 98]. In fact, parental self-efficacy mediates the relationship between parental ADHD and increased parenting stress[99]. Low self-efficacy in mothers and fathers predict poor treatment outcome in children with ADHD. In the MTA study, parents with low self-efficacy had difficulties in implementing behavioral plans, consistently administering medications, and reported more stress[100].

Engaging all caretakers improves treatment utilization and durability[101]. Engaging fathers can be particularly challenging as ADHD is associated with higher rates of divorce, single parenting and separated households and fathers are less likely to present for office-based care[102,103]. Perceived criticism by the other parent is a major risk factor for dropout for fathers[104], so parental conflict can present a major barrier to sustained care. Single parent families also face unique challenges to accessing, persisting and implementing ADHD treatments including higher rates of parental psychopathology and smaller social support networks[19,102].

For adolescents to initiate and persist with a treatment, the patient and parent must recognize and agree on a problem, desire better functioning and believe that the treatment is an acceptable means to achieve a goal that they all feel capable of implementing and accessing. Adolescents prioritize autonomy to set their own goals and the freedom to pick treatments that match their goals[105,106]. All these aspects of motivation have been found to predict utilization of pharmacological and counseling services for ADHD[40,74,107]. Self-awareness about functioning is often poor in adolescents with ADHD and has been found to correlate with medication adherence [108,109]. Adolescents' limited insight of their current impairments often leads to parents and teens disagreeing about the need for treatment, and the level of discordance predicts treatment persistence[24,107]. Higher trait antagonism in adolescents also predicts reduced treatment uptake[110]. Not surprisingly, treatment

adherence, especially for medication, declines rapidly over adolescence. Across countries, medication use drops significantly during adolescents[2,111]. Typically, the decision to stop is driven by the adolescent with the most common reason for discontinuation being the adolescent felt medication was not needed anymore. However, parents and teachers continue to report high rates of impairment in adolescents stopping medication. Therefore, it appears that adolescents' limited self-awareness is an appreciable barrier to both starting and continuing with ADHD care[24,107,108]. Side effect concerns, followed by stigma are the next most common reason reported by adolescents for stopping medication[24,110].

INTERVENTIONS TO PROMOTE TREATMENT ENGAGEMENT

Psychoeducation

As parental knowledge and perceptions of ADHD influence decisions to start ADHD care, psychoeducation has been explored as a means to improve treatment uptake. For example, more extended ADHD assessments are associated with increased parental willingness to start medication[112]. The largest study assessing this issue was set in the United States and examined the efficacy of a neuro-educational intervention in 658 families of children with ADHD whose parents had either discontinued or declined medication for their children following their initial diagnosis of ADHD. At study entry, lack of direct testing of their child's attention span and side effect concerns were the most commonly reported barriers to treatment. The study intervention consisted of a semi-structured diagnostic interview supplemented with two objective measures of attention and impulse control over 3 sessions with last session dedicated to a systematic review of findings with the family along with psychoeducation about ADHD and its treatment. This visit was run using a manualized format which included information about the causes of ADHD, rationale for medication use, strategies for reducing side effects, tips for improving sleep and diets, importance of school support and accommodation and practical strategies to address common behavioral, emotional and social problems during early phase of medication treatment. Following this brief diagnostic and educational intervention, over 70% of parents started medication for their children with treatment rates increasing to over 95% by month 6. At the 2-year follow-up, 95% were still taking medication for ADHD [113]. However, other studies have not observed associations between psychoeducation and persistent treatment engagement[34,75,114], and a systematic review found that patient education alone has limited impact on medication adherence in youth [115]. In a small study set in Spain, adding a brief nurse run psychoeducation intervention to medication treatment led to lower mean doses with no loss of efficacy *vs* medication alone[116]. Therefore, psychoeducation may also be a means to improve treatment tolerability.

Integrated care

Families report greater comfort in primary care settings *vs* BH settings[117,118]. However, specialty care is associated with increased contact and more frequent medication adjustments. Integration of BH services into primary care is one means to accomplish increased contact with patients that predicts greater service utilization[41], especially in countries where generalists provide much of the ADHD care[7,119]. Most models employ two main techniques: Embedding specialty BH providers in primary care to offer counseling services and training primary care providers to employ systematic medication pathways for ADHD supported by remote child psychiatrists.

One of the first randomized trials of an integrated care ADHD intervention was published by Kolko *et al*[120], where 163 children were randomly assigned to nurse-administered intervention or to enhanced usual care (diagnostic assessment, recommendations, and facilitated referral to a specialty mental health provider in the community). The nurses completed an extensive training period and received ongoing supervision from specialists for the study duration. The core components of the intervention were: in office application of a menu of evidence-based counseling interventions, school consultation, case coordination and crisis management. The intervention arm was more likely to receive and complete mental health services, reported fewer barriers for services, more satisfaction, and were more likely to meet personalized treatment goals even though symptoms levels did not differ between groups[120]. A second similarly sized randomized controlled trial (RCT) of the intervention across 4 primary care sites using masters level care managers produced similar findings as well as greater overall improvement on the Clinical Global

Impressions Scale[121]. A more recent larger RCT of over 300 youth from 8 practices *vs* enhanced usual care (psychoeducation and care coordination services) found that the intervention led to greater rates of treatment initiation and completion, as well as larger changes in internalizing and externalizing symptoms, parental stress and satisfaction and primary care provider ADHD care competencies[122].

In a randomized comparative effectiveness trial, families of children being evaluated in primary care for ADHD (N: 156, ages 6-12), received care management with decision support using a collaborative care model and were randomized to enhanced care *vs* basic care. All treatment occurred in the primary care setting using care managers without a formal BH background, and families were recruited from low-income neighborhoods. Care managers in the enhanced care arm were trained in both motivational interviewing (MI) and parent management techniques to help parents identify and initiate ADHD care, address their own mental health concerns and improve their child's behaviors. In the enhanced arm, half of the families attended the primary care-based parenting intervention and 72% initiated medication for ADHD in their children. For the entire sample, there was no difference between basic and enhanced arm on means changes in scores for inattention, hyperactivity/impulsivity, oppositionality and social skills at both 6 mo and 12 mo of follow-up. However, after 12 mo, the enhanced arm experienced greater improvement among children with ADHD consistent presentations, with moderate to large effect sizes (0.57 for hyperactivity/impulsivity, 0.55 for oppositionality, and 0.69 for social skills)[42].

In a quasi-experimental design, Power *et al*[123] compared a multimodal primary care-based intervention to treatment as usual enhanced by a psychoeducation intervention. The Partnering to Achieve School Success (PASS) included family engagement strategies, behavioral therapy targeting the whole family, school consultation using principles of trauma-informed care. It was compared to treatment as usual supplemented with parent education and support groups. PASS was associated with greater changes in objectively measured negative parenting behaviors (ES = 30) and larger changes in child impairment (ES = 35) but not symptom scores [123].

Use of technology to promote engagement

Technology has also been used to enhance ADHD care through creation of specialized databases that prompt providers when and how to collect critical information such as parent and teacher ratings of ADHD symptoms and side effects[41]. Other technological advancements such as text message reminders from electronic medical records for when to take medication have increased adherence in adults with the disorder [124]. A recent review on telemedicine in the management of ADHD concluded that telemedicine is well accepted and valued by clinicians, caregivers, and educators. Use of telemedicine was also associated with improved outcomes although the results were limited by the small number of studies, most of which did not employ a control arm[125].

Telehealth services have also been used to reduce the structural barriers to integrating BH into pediatric primary care. The Children's ADHD Telemental Health Treatment Study randomized families of children with ADHD to one of two different telehealth delivery models in a predominantly rural area[126]. In the direct care telehealth intervention arm, participating families received 6 medication sessions over 22 wk by child psychiatrists *via* telehealth and parent behavior training, provided in person by community therapists who were supervised remotely. The Control arm received treatment from PCCs augmented with a telepsychiatry consultation from study psychiatrists. Children in both service models improved but those in the direct care telehealth arm experienced greater reductions in symptom scores and impairment [127].

A European study examined the efficacy of a behavioral parent training administered *via* telehealth in children already treated with CNS stimulants. The RCT compared the telephone-assisted self-help (TASH) intervention to routine clinical care. TASH did not separate on the primary outcome of parent rated impairment but group differences were seen on externalizing symptoms and negative parenting behaviors. Parents also expressed high satisfaction with the program, but completion rates were higher for families with a greater educational level and fewer additional stressors[128].

Interventions specifically targeting engagement

Several evidence-based psychosocial interventions for ADHD have incorporated formal engagement interventions to promote treatment uptake. For pediatric BH, engagement interventions have greater impact than those only addressing structural barriers[129]. These interventions target multiple aspects of motivation, including

desire and readiness for care, self-efficacy, treatment goals and preferences and planning for potential care barriers that all predict counseling and medication use and efficacy[65,74] and treatment persistence[20,24,95]. MI is the most commonly employed engagement intervention in pediatric ADHD treatments. It is a collaborative conversation designed to strengthen a patient's desire to change[130,131]. MI has been applied in medical and BH settings with moderate effects for improving a range of outcomes[132,133]. The other common components of these engagement interventions are a family interview to identify goals, a strengths-based assessment to promote self-efficacy, identify areas of need and a feedback session emphasizing discrepancies between current and desired functioning. These programs are often tailored to a specific population prone to greater challenges engaging with ADHD care, such as adolescents, fathers or single mothers.

In a study among single mothers of children with ADHD, participants were randomly assigned to an enhanced behavioral parent training program-the Strategies to Enhance Positive Parenting (STEPP) program or a traditional behavioral parent training program. The STEPP program (nine 21/2 h session) focused on enhancements to the format, delivery, and content of traditional parent training programs including: (1) An enhanced intake procedure to addresses practical barriers for participation in treatment, define realistic expectations from treatment, and identify attributions related children's behavior that promote parental efficacy; (2) Programming to improve social support for parents; and (3) A systematic problem-solving skill. Both arms led to improvements in child behavior but STEPP resulted in better attendance, participation and satisfaction[102]. COACHES (Coaching Our Acting-out Children: Heightening Essential Skills) is a behavioral parenting program designed for fathers that packages evidenced based techniques into a youth sporting event. During the first hours, fathers learn how to implement effective parenting strategies, while children practice soccer skills combined with a contingency management approach for appropriate behavior. During the second hour, the parent and child groups join for a soccer game, where fathers practice learned parenting strategies and get live feedback from therapists. COACHES was associated with better attendance and greater change in parenting behaviors and children's problem behaviors than standard behavioral parent training[134].

The STAND (Supporting Teens' Academic Needs Daily) program was designed to promote adolescents and parents in partnering to improve the teen's academic and home functioning. The first two sessions employ MI to aide parents and teens in identifying mutually agreeable goals and therapeutic techniques they will use prior to starting any specific treatments. STAND has been found to significantly improve adolescent functioning under randomized conditions, with parents and adolescents reporting high satisfaction, credibility and therapeutic engagement[108]. STAND has also been administered *via* videoconferencing with acceptable therapeutic alliance, treatment fidelity and effects[135]. When applied by community therapists, STAND led to increased parent participation and satisfaction *vs* treatment as usual. No differences in adolescent attendance or satisfaction were seen but STAND was associated with increased rates of starting or restarting ADHD medication *vs* treatment as usual[136].

Hamrin *et al*[137] used MI to improve medication adherence in 48 adolescents with mood disorders. The trial was set in specialty offices with psychiatrists applying MI with good fidelity during medication management visits. There was significant improvement in objectively measured medication adherence over a 30-d period (d = 0.65). While this trial did not require ADHD for entry, half of the sample had comorbid ADHD, and there was no evidence of reduced efficacy in those with ADHD *vs* those without it.

In Europe, where treatment of ADHD largely occurs in specialty settings[14], standardized care pathways have been developed for these settings. One example is the Dundee ADHD Clinical Care Pathway in Scotland[138]. It has standardized protocols for four stages derived from the NICE guidelines[5]: Referral and pre-assessment, assessment, initiating treatment and continuing care. Patients are referred to the program with initial screening conducted by nurse specialists who gather structured parent and teacher ratings prior to direct assessment, which focuses on functional impairments in the child and the level of family functioning. The Schedule for Affective Disorders and Schizophrenia for School-Aged Children for DSM-IV--Present and Lifetime (KSADS-PL) is used for diagnostic determination. The assessment concludes with the family meeting with a senior clinician to review results. Initial treatment offerings are stratified by patient age with families of children under 6 referred to evidence-based behavioral parent training programs and those over 6 offered medication. A 4-wk dose optimization protocol is used for medication, prefer-

encing methylphenidate products. It consists of 3 to 4 visits that can be remote or in person with structured rating scales from parents and teachers used to titrate to optimal effect. Standardized definitions of meaningful response are used to determine if the initial treatment choice should be maintained or switched. Once optimized, nurse visits occur every 6 mo that measure adherence, stigma, other care barriers and functioning at home, school and with peers. Behavioral interventions are offered targeting identified impairments. The creators of the model report high rates of initial medication use, large reductions in ADHD symptoms and maintenance of effects over time. However, there are no randomized trials of this care pathway to date.

One limitation of these programs is that they were set in either university-based or other specialty BH settings that families had to be referred to or discover on their own. In addition, they employ trained BH staff, which may not be available outside of specialty settings. While some of the same principles have been applied in general pediatric settings as part of an integrated care model, there has been limited formal examination of their capacity to promote ADHD treatment in these settings. Silverstein *et al*[42] addressed this limitation by comparing the efficacy of an enhanced ADHD care management system *vs* a basic collaborative care intervention in urban primary care pediatric practices predominantly serving low-income families. All families referred by their primary care providers for an ADHD assessment were eligible with 40% of participating children found to have presentations consistent with ADHD. Nonclinical care managers in the enhanced arm were trained in an evidence-based parenting intervention and used preset MI scripts that focused on the benefits of medication usage. The two arms did not differ in levels of observed improvement over 12 mo with both groups showing reduced symptoms and improved social functioning over time. When analyses were limited only to the 40% of the sample with ADHD consistent presentations, significant differences in symptoms of ADHD and ODD as well as social skills were observed. Enhanced care was also associated with increased medication usage but had little impact on externally referred ADHD services[42]. Moreover, the specific impact of the use of MI was not able to be assessed apart from the larger treatment package.

Brinkman *et al*[139] completed a smaller study set in pediatric primary care designed to assess the capacity of a brief shared decision-making intervention to improve treatment uptake. The intervention offers psychoeducation about ADHD and its treatments while eliciting parental goals and treatment preferences. It was added to the initial treatment discussion with pediatrician for their child with ADHD (age range 6-10 years). This shared decision-making intervention was found to be feasible and well received by parents without increasing the duration of the visits. It improved parental knowledge of ADHD and increased initial interest in ADHD treatment. However, it had no impact on office contacts/visits or medication adherence over the next 90 d.

DISCUSSION

There are multiple evidence-based pharmacological and psychosocial treatments for ADHD, and greater service utilization is associated with improved acute and long-term outcomes[16,20]. However, long-term outcomes are suboptimal across countries and a major identified challenge to achieving optimal long-term outcome is sustained engagement with care. There are both structural and attitudinal barriers to care that serve as appreciable impediments to sustained engagement for many families of children with ADHD. Over the past two decades there has been increasing research identifying these barriers and developing interventions to overcome them. Many structural barriers are hard to modify such as geography and SES[12,19,20]. However, frequency of contact whether in person or remote improves treatment persistence[41,140]. Modifications to how and where pediatric BH care is administered have been effectively employed to increase contact and overcome other structural barriers. These interventions also broach attitudinal barriers by embedding care in less stigmatizing settings than specialty BH clinics. Engagement strategies have also been developed that directly address attitudinal barriers that can be applied wherever ADHD care occurs. These interventions include psychoeducation, MI or shared decision making. Other treatments, such as stepped care models, hold promise but their impact on engagement has not been systematically examined.

Integration of ADHD services into primary care

Integrated care for pediatric behavior problems have shown to be feasible and

effective across several studies. Integrating BH into primary care has enhanced outcomes, largely through increased service utilization of both medication and on-site counseling services[31,42,127]. Integration has been able to address both structural and attitudinal barriers by locating BH services in accessible primary care settings and building on families established relationships with their primary care providers[72]. Models employing full integration *vs* colocation of services have led to greater impact on the frequency of appointments for ADHD management[141]. Most models employ care managers who serve as the family's primary point of contact and guide them through the multiple aspects of care to reduce the burden of managing a chronic disease. Nurses and other primary care staff with little formal BH experience can be remotely trained and supported to accomplish these roles. Integrated models have also proved feasible and effective in populations with increased barriers to care[142]. However, integrated models require sizable effort and financial investment and are only beginning to become common occurrences in the United States[143]. Child Psychiatry access programs where primary care providers can access child psychiatrists when an acute need arises have become increasingly popular in the United States as they allow a single specialist to impact a broad geographic area. Many of these programs also offer care coordination services to families to help them connect to care. These programs have been effective at improving access to care and promoting evidence-based BH treatments for ADHD and other BH disorders in primary care[29,144].

Even when integration occurs, it is often not feasible to embed a full range of BH services into primary care. Therefore, referrals to external BH providers remain a common occurrence, and is a point in the care pathway where dropout often occurs [145]. Integrated models do not address the challenges of accessing referred care, which have proved particularly challenging to overcome[146]. Moreover, a sizable subset of families fails to engage integrated ADHD therapy services[42] in part because some stressed families do not inform PCCs about their child's struggles even when they view care as accessible[111]. Efforts to streamline and personalize the BH referral process that leverages the family's established relationship with their PCCs have been found to improve access to externally referred care[147].

Telehealth

For ADHD, increasing visits may promote engagement[140], but adding visits is challenging in primary care as stressed families are unlikely to come more frequently and long waits often preclude more frequent office visits with specialists. Rating scales and remote contact with families have proved as effective as office visits for improving ADHD outcomes[41,140], with less burden to staff and families than sole reliance on face-to-face interactions[148]. Therefore, collection of rating scales, communication through a patient portal or other forms of asynchronous or synchronous remote contact can be used to build engagement, especially in areas with long travel distances to care.

Telehealth has been recommended as an effective means to increase access and improve engagement for pediatric BH services[149,150]. In children with ADHD, meaningful changes in functioning have been captured through telehealth interventions[125-127], and several evidence-based psychosocial interventions for pediatric behavioral problem have been adapted for telehealth application[151]. There is an emerging evidence base to support both direct patient care and peer-to-peer consultation models using telehealth[29,126,127]. These tele-methods are effective for underserved families and have found to be palatable across race and ethnicity[126,127]. The effectiveness of these techniques for the chronic care of ADHD has not been studied as published studies have not extended beyond 6 mo[152].

Tele methods have become increasingly common during the coronavirus pandemic [153-155] given the multiple barriers to face-to-face contact. Treatment guidelines for ADHD telecare during the pandemic are being developed[154,155] and rules requiring a face-to-face visit for prescription of controlled substances medications have been loosed during the pandemic in the United States. European ADHD Guidelines report it is reasonable to start ADHD medications during the pandemic for patients who did not have a baseline, face-to face cardiovascular assessment if they meet following 3 criteria: (1) No personal history of cardiac symptoms; (2) No family history of early (< 40 years) sudden death in a first degree relative; and (3) Patient must have baseline measurement of blood pressure and heart rate by a family member or another person remotely on three separate occasions. If the first two conditions are not satisfied, a referral to a pediatric cardiologist should be made before starting the medication for the ADHD[155].

Assessing and enhancing motivation for ADHD care

Chronic care models assessing functioning and motivation starting when care begins are recommended[156]. Failure to synchronize treatment intensity for a chronic disorder like ADHD to the motivational state of the family can lead to feelings of defeat and disengagement[157]. Families of ADHD youth have higher rates of parental ADHD, depression, divorce and exposure to adverse childhood experiences, which all impair motivation[20,158]. Initial evaluations should assess for a wide range of psychosocial stressors impacting the patient and the family as well as assessing parent-child and family relationships[64]. Initially, stress may promote change as it can lead to treatment seeking efforts[19]. However, chronically worsening stress impedes change, as stressed families are more apt to decide the current state is unmodifiable, especially when there are financial barriers to care[38]. Waiting too long to assess motivation risks families dropping out of care[84]. The combination of waning motivation and reports of increasing impairment or family strain indicate increased risk for dropout.

The success of any initial treatment is always contingent on the family's motivation to make a change in their child's behavior, whether this is through giving medication or attending a counseling visit. According to the transtheoretical model, change is a process, progressing from recognizing an undesirable behavior, to contemplating change, to intending to act, to modifying the behavior and then to maintaining the desired state[130,159]. Goal achievement is most likely when progression is sequential and the motivational stage is used to inform treatment decisions. Therefore, efforts to improve motivation should be a fluid process tailored to the status of the patient and family at the current time. Current ADHD guidelines recommend repeatedly measuring motivation and using results to tailor an individualized care plan[3,5].

Cunningham has applied the transtheoretical model of change to ADHD care[160]. Contacting the PCCs is the most common first step in the ADHD care pathway[119]. Parents presenting to a care provider with concerns about their child's ADHD are likely at the preparation stage[159] as they have achieved an awareness of their child's struggles and have a goal to improve them. However, adolescents are often not at the same stage as their parents, and direct assessment of their motivation for care is critical. To move towards action, a palatable treatment option that parents and adolescents feel they can access and successfully implement to achieve their goal must be identified[161]. Psychoeducation may be help for more receptive families towards starting treatment[113] but simply providing information about treatment options is unlikely to move many parents and teens from preparation to action to maintenance of changes[34,113,114]. Some families presenting for assessment are not ready for active treatment even if their child is appreciably impaired. For example, external forces such as schools may drive people into the office who are only in the contemplation stage. For them, it may be critical to address motivation for care prior to directly promoting treatment.

MI is widely used to help patients down to age 12 to clarify goals, explore the benefits and risks of engaging in treatment[130,162,163], address stigma and other attitudinal barriers and promote self-efficacy to benefit from treatment seeking efforts [132]. Simple single item motivation rulers can be employed to measure each of these core aspects of motivation (readiness and desire to change, self-efficacy to implement change, treatment preferences and overcoming perceive barriers) as they have been found to predict health behaviors in adults[164] and adolescents[165].

Initial change behaviors can be nurtured by expressing an interest in family's views about the sources of their child's problems while rolling with their resistance to change. Minimizing their concerns or attempting to solve problems for them may reduce self-efficacy and threaten autonomy. Empathetically providing patients with objective feedback on differences between current *vs* desired functioning can be used to generate change talk to enhance readiness and desire to change. Recognizing areas where the child is doing well and instances where parents have successfully achieved past goals for their child promotes self-efficacy to move forward with identified changes. Once parents have identified a specific goal that they feel motivated to and capable of achieving, they may be most receptive to discussing specific treatments. Shared decision-making can then be used to identify a treatment that matches their goals, while also crafting realistic treatment expectations to increase the chances that families will initiate new services for ADHD. To engage adolescents, it is essential that treatment centers around their goals *vs* parental or provider goals to create engagement[139]. Clinicians may need to aide parents and teens in identifying a mutually acceptable treatment goal. Parental input on ways to incentivize the adolescent working towards their goal (making curfews or screen time contingent on making visible effort to achieve a goal) can be elicited. To foster sustained engagement,

providers should empathically affirm treatment seeking behaviors by parents and adolescents, aide in finding supports and reinforcers to sustain ongoing change behavior and offer to help them plan to overcome identified barriers[159,166].

These techniques of MI have been integrated with high fidelity into several counseling interventions for ADHD[102,123,135]. They have also been used to increase medication adherence in general medical and specialty settings[42,136,137]. Modifying the format of existing counseling interventions to increase interest (*e.g.*, Fabiano's COACHES for fathers) or supplementing the content to address specific barriers for populations with multiple impediments to engagement (Chacko's STEPP for single mothers or Sibley's STAND for adolescents with academic struggles) have also been employed. Modifying content could potentially reduce efficacy for primary outcomes or increase dropout if new content is added; however, controlled results support that these adaptations increase attendance, participation and satisfaction with some producing better outcomes than the unmodified interventions[108,134].

Other modifiable factors for promoting engagement

Medication issues: Parents' most frequently cited reasons for discontinuing ADHD medication is lack of efficacy or intolerable adverse effects. Health care providers should closely monitor patients during the dose optimization phase using structured measures of efficacy and tolerability. Once dose is optimized, monitoring should assess functioning, adherence, tolerability and ongoing need for medication. For adolescents, it is also important to directly assess their perceptions of the need for medication and ensure that medication addresses a goal that is relevant to them. Reducing the number of doses per day by switching to long-acting preparations has been found to increase compliance with medications for ADHD[25,26,28,167]. Formulation alterations, such as liquids, patches or chew tabs can also be an option, for children either who have difficulties in swallowing pills.

Involvement of all caregivers: Caretakers may have differing views on the severity and cause of the child's behavioral struggles. They may also be at different stages of change in regards to treatment seeking efforts, especially when they reside apart[3,168]. Therefore, efforts should be made to contact all custodial caretakers to assess their personal views. It has been found identifying parental attributions for the child's problem behaviors that emphasize the capacity of the parent to promote positive change has been found to increase engagement for fathers not residing full time with the child[71]. Strengthening support networks enhances service initiation and persistence with care, while fathers' participation in care improves maintenance of treatment effects[169]. Therefore, engaging all caretakers can be a means to increase the amount and the impact of utilized services. Telehealth may be a particularly useful tool to engage fathers, as they are less likely to present for office-based care[20]. It can also be used to separately engage caretakers prone to disagree with each other. Reducing conflict between parents may be another means to engage fathers as perceived criticism from the mother is a major risk for their dropout from treatment [104].

Stepped care*:* The appreciable commitments required of parents for intensive counseling interventions may be one reason why stressed families receive less benefit from these programs[170]. Stepped care reduces burden without sacrificing impact, as low intensity treatments are initiated for all, followed by incrementally more intensive services if impairment persists. Combining stepped care with tailoring approaches to individualize subsequent care further minimizes burden and is recommended for treating childhood behavior problems[152].

There is evidence of efficacy of stepped care for ADHD in controlled settings, with the sequence of behavior therapy followed by medication leading to the greatest enhancements in functioning at a lower cost than starting with medication[62,77]. Stepped care models for ADHD have not been examined outside the confines of research studies. However, there is evidence that medication usage reduces parental motivation for psychosocial services both in controlled and naturalistic settings[10,77]. For multiply stressed families, lower intensity counseling programs have been found to be less costly and not inferior in efficacy to more intensive programs such as Parent Child Interaction[152]. They may be the preferred initial intervention especially for families with multiple barriers to high intensity care.

Limitation

Most studies assessing barriers to care are drawn from Western Europe and the United States while the vast majority of the trials of interventions designed to promote

engagement were run in the United States. Integrated models for pediatric BH care have not been well studied outside of the United States, possibly in part due to national policies regarding the payment and provision of BH care that are separate from the those for the rest of medicine. Cultural perceptions of ADHD and health care policy varies widely across the globe, limiting the generalizability of these findings. While behavioral parenting interventions are efficacious in countries beyond their origin[171], the impact of engagement barriers and interventions for them could variably appreciably given the impact of culture on perceptions of pediatric BH[43]. It was encouraging to see that several studies recruited racially and ethnically diverse families[42,123] with a focus on populations that are less likely to access BH care[102, 134]. Furthermore, there are only a few RCT specifically designed to measure engagement and even less that track engagement for more than 6 mo. Additionally, most interventions were multi-pronged, so it is hard to determine the impact of any single engagement technique. The heterogeneity of the interventions and assessment methods used to measure and promote engagement further inhibited the ability to draw conclusions from the collective literature base. Only a limited number of studies have examined how to improve uptake of externally referred services, which remain a common form of treatment[146].

CONCLUSION

Despite a number of evidence-based treatments, long-term outcomes for youth with ADHD remain suboptimal. ADHD care often ends quickly even when high levels of impairment persist. Families face a variety of structural and attitudinal barriers to engagement, ranging from cost and access to stigma and low self-efficacy to successfully implement change. Integration of BH into general medical settings and telehealth have been found in controlled studies to increase access by reducing both structural and attitudinal barriers. Adding MI, shared decision-making and other engagement interventions to evidence-based ADHD treatments reduces altitudinal barriers that translates to improved participation and satisfaction with care while enhancing outcomes. However, improving uptake of externally referred BH services remains a challenge and little is known about how to enhance long-term engagement with ADHD services even though a chronic care model for ADHD is recommended.

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MINIREVIEWS

Newer antipsychotics: Brexpiprazole, cariprazine, and lumateperone: A pledge or another unkept promise?

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Abstract

Antipsychotic agents are used for various indications in the treatment of psychiatric disorders. Despite their proven roles in multiple conditions, the treatment-emergent side effects of antipsychotic medications, such as metabolic side effects, are often the limiting factor for their long-term and short-term uses. Moreover, antipsychotic medications are often criticized for being less effective in treating different disabling symptoms such as negative symptoms of schizophrenia. As a result, the search for safer and more efficacious antipsychotic agents is ongoing. Newer antipsychotic agents are gaining attention related to emerging efficacy and tolerability data in treating neuropsychiatric conditions. In this review, we attempt to appraise the scientific data on psychopharmacology, safety profile, and efficacy of the newer additions to the list of second-generation antipsychotics, namely brexpiprazole, cariprazine, and lumateperone. We conducted a selective review utilizing PubMed, clinicaltrials.gov, and Cochrane databases to gather appropriate publications, keeping broad inclusion criteria. There were no restrictions on the age of the study population or the year of publication. We also cross-referenced articles and references to capture all existing studies. Our review of the current literature indicates that all three antipsychotic agents appear to be promising based on their short-term studies, while long-term studies remain limited. There is also a need for a head to head comparison between the newer antipsychotics with the other antipsychotic agents to ascertain if the newer agents are any better than the others.

Key Words: Antipsychotic agent; Brexpiprazole; Cariprazine; Lumateperone; Psychopharmacology; Schizophrenia

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Core Tip: In this review article we attempted to appraise the scientific literature on three newer antipsychotics such as brexpiprazole, cariprazine and lumateperone and presented their safety and efficacy data. Our aim was to investigate the status of these antipsychotic agents in treating various psychiatric disorders.

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INTRODUCTION

Antipsychotics have revolutionized the treatment of psychiatric disorders in the last few decades[1]. Despite advances in psychopharmacology, the quest for more effective and safer antipsychotic medications is not yet over. Schizophrenia remains one of the most chronic, debilitating psychiatric disorders whose optimal treatment approach is still a matter of research. In a global burden of disease study involving more than 30000 respondents from four European countries, schizophrenia was found to have the highest functional burden across hundreds of physical and mental health issues[2]. Second-generation antipsychotics (SGAs) are commonly used to treat schizophrenia and other conditions, including bipolar disorder[3-5]. Despite their proven efficacy, existing antipsychotic medications are limited by treatment-emergent side effects and their ability to address a limited collection of symptoms of schizophrenia such as delusions, hallucinations, disorganized thoughts, and bizarre behavior[6]. The lack of efficacy of medications to treat negative symptoms of schizophrenia, poor quality of life, and medication non-adherence remain a challenge[7,8]. Clozapine, which was introduced in 1971, remains the most efficacious antipsychotic medication despite potentially dangerous side effects[9]. This review aims to appraise the scientific data on psychopharmacology, safety profile, and efficacy of the newer additions to the list of SGAs, including brexpiprazole, cariprazine, and lumateperone.

LITERATURE SEARCH

We conducted a selective review utilizing PubMed, clinicaltrials.gov, and Cochrane databases to gather appropriate publications. The search was carried out between December 2020 to January 2021, keeping broad inclusion criteria to ensure the incorporation of relevant articles. There were no restrictions on the age of the study population or the year of publication. The authors cross-referenced articles and references to capture all existing studies. Authors PM, RB, and TD performed the literature search with author AK as a consultant. PM, RB, and TD wrote the initial draft and AK provided feedback and elaboration on the manuscript. All authors approved the final version.

BREXPIPRAZOLE

Brexpiprazole, a novel serotonin-dopamine activity modulator, a partial agonist of the dopamine D2 receptors and is structurally similar to its predecessor, aripiprazole. Brexpiprazole is also a partial agonist at serotonin 1A (5-HT1A) receptors and a potent antagonist at 5-HT2A, α1B, and α2C adrenergic receptors[10]. This newer antipsychotic has less intrinsic agonist activity at the D2 receptor compared to aripiprazole and, as a result, may be less activating (as manifested by agitation and restlessness) than aripiprazole[11]. Antagonism of 5-HT2A and α1B receptors and agonism of 5-HT1A receptors decrease side effects related to D2 receptor blockade in the striatum including akathisia and other extrapyramidal side effects (EPS) due to an increased

release of dopamine downstream[11,12]. Compared to aripiprazole, brexpiprazole has increased potency at these three receptors, namely, 5-HT2A, 5-HT1A, and α1B leading to fewer potential treatment-emergent movement effects. Brexpiprazole also has lower antihistamine activity at the H1 receptor, and as a result, may be associated with less sedation and weight gain than aripiprazole[11]. Brexpiprazole has no apparent anticholinergic side-effects given its minimal activity and affinity for the muscarinic acetylcholine receptors[12]. CYP3A4 and CYP2D6 primarily metabolize brexpiprazole to DM-3411, an inactive metabolite; has about 95% bioavailability after oral administration, and achieves peak plasma concentration 4 h after administration, and a steady-state concentration is reached within 10-12 d of daily administration[13].

Safety and efficacy data of brexpiprazole in schizophrenia research

On July 10, 2015, the United States Food and Drug Administration (FDA) approved brexpiprazole for the maintenance treatment of schizophrenia and as an adjunct treatment to antidepressants for the treatment of major depressive disorder (MDD) in adults[14]. However, brexpiprazole continues to be examined in clinical trials for possible use in attention deficit hyperactivity disorder, autism, conduct disorder, oppositional defiant disorder, Bipolar disorder, and agitation in Alzheimer's disease [15,16].

VECTOR[17] and BEACON[18] trials are the two major studies establishing the efficacy of brexpiprazole in schizophrenia treatment. These two, 6-wk, phase 3, randomized, placebo-controlled clinical trials used fixed doses of brexpiprazole *vs* placebo in patients with acute schizophrenia. Brexpiprazole demonstrated statistically significant improvement in the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions-Severity (CGI-S) in both studies. In the VECTOR trial, Correll *et al*[19] demonstrated a statistically significant reduction in PANSS scores with both 2 and 4 mg brexpiprazole compared to placebo[19]. On the other hand, in the BEACON trial, Kane *et al*[20] found a statistically significant decrease in PANSS scores with the 4 mg brexpiprazole dose group only, not with 1 or 2 mg doses, compared to placebo[20]. However, both VECTOR and BEACON trials lacked active comparators and were short term trials. Few studies have established the long-term efficacy of brexpiprazole as maintenance therapy for schizophrenia. In a phase 3, randomized, double-blind, placebo-controlled trial, Fleischhacker *et al*[21] demonstrated that patients taking brexpiprazole had significantly longer time to impending relapse and a lower rate of relapse (13.5% *vs* 38.5%) as compared to placebo[21,22]. ZENITH trial [23], a 52-wk, open-label brexpiprazole study, reported that the PANSS total score improved on average by 12.2 points in patients receiving brexpiprazole. There was an improvement in mean CGI-S score of 0.6 and Personal and Social Performance scale total score of 7.7 points in patients taking brexpiprazole[24]. A recent randomized, double-blind, functional magnetic resonance imaging (fMRI) study[25] evaluating the effects of brexpiprazole on brain regions that control impulsive behavior in patients with stable schizophrenia reported that this medication decreased right ventrolateral prefrontal cortex (VLPFC) activation and decreased stop-signal reaction time (SSRT). The stop-signal task was a task associated with inhibition/control of impulsivity. Thus, this study concluded that brexpiprazole might be exerting benefits on inhibition-related brain activation and behavior in patients with schizophrenia[26]. Brexpiprazole was well-tolerated in schizophrenia trials with akathisia, headache, somnolence, tremor, weight gain as commonly reported side effects[13].

Safety and efficacy data of brexpiprazole in MDD research

PYXIS[27] and POLARIS[28] phase 3 trials led to the FDA approval of brexpiprazole as an adjunctive treatment for MDD. Both of these studies were six weeks, randomized, double-blind, and placebo-controlled, and evaluated the efficacy of brexpiprazole as an adjunctive treatment in MDD by comparing changes in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score. The participants were adult patients with MDD with an inadequate response to 1-3 previous antidepressant trials. Both studies had an 8-wk single-blind prospective treatment phase where subjects received a standard antidepressant; those with inadequate responses were included in the study. In the POLARIS trial, 3 mg brexpiprazole demonstrated a statistically significant improvement in MADRS score as compared to placebo. However, brexpiprazole 1 mg did not reach statistical significance[29]. Similarly, the PYXIS trial, which used 2 mg brexpiprazole dosing, also reported a reduced mean MADRS total score compared to placebo corroborating its efficacy as an adjuvant treatment in MDD[30].

Data from short- and long-term trials of brexpiprazole as a treatment adjunct in MDD reported minimal changes in prolactin levels, low rates of post-baseline prolactin elevation, low rates of prolactin-related side effects, and a moderate improvement in

sexual functioning[31]. Akathisia, headache, somnolence, tremor, and weight gain were reported as common side effects[13].

CARIPRAZINE

Cariprazine is a SGA approved by the United States FDA in 2015 for the maintenance treatment of schizophrenia[32]. While most atypical antipsychotics are D2 antagonists, cariprazine is a dopamine D3/D2 receptor partial agonist with a 10-fold higher affinity for D3 receptors than D2 receptors[33,34]. Cariprazine differs from two other dopamine receptor partial agonists, aripiprazole and brexpiprazole, by its distinct receptor-binding characteristics not only at dopamine D2/D3 receptors but also at serotonin 5HT1A, 5HT2B, 5HT2A, 5HT2C, and histamine H1 receptors[35]. Structurally, cariprazine is an antagonist at the dopamine D3 receptor but functionally acts as a partial agonist with 70% intrinsic agonism[34]. Dopamine D3 receptors in the prefrontal cortex regulate cognition, mood, and negative symptoms and are also distributed in other brain regions, including the nucleus accumbens that controls reward and motivation. Cariprazine, as an antagonist of the dopamine D3 autoreceptors, is hypothesized to play a role in motivation, depression, and reward by increasing dopamine release in the prefrontal cortex[36].

The pharmacokinetic characteristics of cariprazine are also distinct from other antipsychotics. Cariprazine is highly plasma protein bound, time to peak concentration is 3-6 h[37] and it is primarily metabolized by CYP 3A4, and by CYP 2D6, to a lesser extent. It has two major active metabolites, desmethyl cariprazine, and didesmethyl cariprazine. Didesmethyl-cariprazine (DDCAR) has a long half-life of 1-3 wk[38]. A longer half-life might protect against the rapid onset of relapse following non-adherence in patients with schizophrenia.

Safety and efficacy data of cariprazine in schizophrenia research

Among the four major randomized, placebo-controlled pivotal trials, one trial of cariprazine in the treatment of schizophrenia failed as the placebo response was much higher than the cariprazine group[39]. In the other three trials, all tested cariprazine dosages of 1.5, 3, 4.5, 6, 3-6, and 6-9 mg/d, were superior to placebo in reducing the PANSS and CGI-S scores[40-42]. A significant improvement in the hostility item of the PANSS was observed in these three studies. In two metanalyses, both higher and lower dosages of cariprazine demonstrated superior efficacy as compared to placebo in acute schizophrenia[43,44].

Safety data collected from these four trials reported a lower discontinuation rate in the patients who received cariprazine 1.5-6 mg/d compared to patients on placebo [35]. Pooled data on adverse effects noted a higher likelihood of weight gain, hypertension, akathisia, and EPS that led the FDA to recommend the lower dose range of 1.5 to 6 mg/d in schizophrenia[45,46]. In the pooled data, mean changes in metabolic parameters and hypotension were no different from the placebo group; there were also no differences in syncope, prolactin level, or Qtc > 500 ms[46,47]. As *per* the product label, the most common side effects are EPS and akathisia[45]. In a study among 586 patients with schizophrenia[48], the most common adverse effect was akathisia (16%), followed by headache, insomnia, and weight gain. However, the discontinuation rate from akathisia was < 1% in comparison to 12.5 % from all other adverse events. Among the D2 partial agonist antipsychotics, the risk of weight gain and somnolence is much lower with cariprazine, but akathisia is higher than with aripiprazole and brexpiprazole[47]. In placebo-controlled studies, observed relapse rates were much higher in the placebo group than the patients on cariprazine 47.5% *vs* 24.8%[49]. Because of longer half-life, relapse at 4 wk following discontinuation of cariprazine was 2-7 times lower than in other relapse prevention studies[50].

Safety and efficacy data of cariprazine in mood & anxiety disorders research

Cariprazine is also approved in the United States for mania and mixed episodes related to bipolar mood disorder type I in adults[51]. In bipolar mania, more cariprazine treated patients had improved CGI-S scores than patients on placebo; that is, more cariprazine-treated patients shifted from the severely ill to the mildly ill or better category as compared to the placebo-treated patients (55% *vs* 36%, odds ratio = 2.1)[51]. Post hoc analyses of three randomized, double-blind, placebo-controlled clinical studies showed that a significantly higher proportion of patients with cariprazine achieved response and remission in bipolar mania on all evaluated measures when compared with the placebo-treated group[52]. Most importantly,

improvement in manic symptoms did not precipitate depressive symptoms. Subsequent research on the role of cariprazine in bipolar I depression and MDD are being studied.

In animal studies, cariprazine has demonstrated antidepressant-like activity and has reduced anhedonia-like behavior[53], comparable to aripiprazole and the tricyclic antidepressant imipramine[54]. In the same study by Duric *et al*[54], the anxiolytic-like action of cariprazine has also been elicited in mice. Theoretically, cariprazine may improve depressive symptoms because of its unique D3 preferring dopamine D3/D2 receptor partial agonism along with serotonin 5HT1A receptor partial agonism. However, in a randomized, double-blind, placebo-controlled phase 3 trial, cariprazine did not show significant benefit as an augmenting agent in MDD, though it was well-tolerated with no significant differences in side effects compared to placebo[55].

On the contrary, in a study by Earley *et al*[56], cariprazine at 1.5-3 mg/d was safe and effective in reducing the depressive symptoms in bipolar I depression[56]. In a recent placebo-controlled study, cariprazine 1.5 mg/d significantly reduced depressive symptoms but not cariprazine 3 mg/d[57]. Clearly, the efficacy of cariprazine in bipolar I depression is not yet fully established.

Additional studies of cariprazine

In a case series described by Sanders and Miller[58], three cases of type I bipolar mood disorder with co-morbid substance abuse elicited an abrupt decrease in craving and use of the substances concomitant with improved mood symptoms after initiating cariprazine with their existing medication regimen. Findings in animal studies demonstrate that cariprazine improves cognition, improves pro-social behavior, and decreases the rewarding effect of cocaine[59]. Interestingly, cariprazine can resensitize resistant cancer cells to mitoxantrone by modulating ABCG2 (breast cancer resistance protein) and *via* several other distinct mechanisms[60].

LUMATEPERONE

Lumateperone[7], received United States FDA approval to treat schizophrenia in adults in December 2019[61]. Lumateperone possesses unique pharmacologic actions on the serotonin, glutamine, and dopamine systems. It is a presynaptic partial agonist and postsynaptic antagonist at D_2 receptors, an antagonist at serotonin 5-HT_{2A} receptors, and a glutamate modulator[7,8,62]. The presynaptic partial agonism and postsynaptic antagonism at dopamine D_2 receptors allow a lowered presynaptic release of dopamine and postsynaptic blockade of dopamine, leading to a more efficient reduction of dopaminergic signaling than other antipsychotic medications [63]. At the same time, it has negligible binding potential to other receptors such as histaminic or muscarinic receptors, which are associated with sedation, cognitive and metabolic side-effects[63]. One of the critical components of lumateperone is the 60-fold separation between its affinity for 5-HT_{2A} receptors and D_2 receptors. At a lower dose, lumateperone antagonizes the 5-HT2A receptor and promotes sleep and reduces aggression, but at a higher dose, antipsychotic and antidepressant effects emerge[63,64]. It also indirectly modulates the glutamatergic phosphoprotein associated with D1-dependent augmentation of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) activity *via* the mammalian target of the rapamycin (mTOR) pathway, which could contribute to a potent and rapid antidepressant action[65]. Additional actions such as serotonin transporter inhibition and stimulation of phosphorylation of glutamatergic NMDA $GluN_{2B}$ receptors[8] are unique to lumateperone. The steady-state concentration is reached in approximately five days and is metabolized by several enzymes, including but not limited to uridine 5'- diphospho-glucuronosyltransferases (UDP-glucuronosyltransferase, UGT) 1A1, 1A4, and 2B15, aldoketoreductase (AKR)1C1, 1B10, and 1C4, and cytochrome P450 (CYP) 3A4, 2C8, and 1A2[66]. The half-life of lumateperone and its metabolites ranges from 13 to 21 h which allows a once a day dosing regimen[8].

Safety and efficacy data of lumateperone in schizophrenia research

Three industry-sponsored placebo-controlled trials among patients with an acute exacerbation of schizophrenia have investigated the role of lumateperone in the treatment of schizophrenia[67-70]. Correll *et al*[71], in a four-week-long, three-armed placebo-controlled, randomized phase 3 clinical trial[71], involving 450 patients aged 18-60, with acute exacerbation of schizophrenia, demonstrated that 42 mg of lumateperone (equivalent to 60 mg of lumateperone tosylate), brought significant improve-

ment as compared to placebo from baseline to day 28 on the PANSS total score and the CGI-S[71]. There was no statistically significant difference between 28 mg of lumateperone (equivalent to 40 mg of lumateperone tosylate), as compared to placebo. A previous phase 2 multi-site randomized, double-blind, placebo-controlled, and active-controlled trial (risperidone) involving 335 acutely psychotic patients with schizophrenia also demonstrated antipsychotic efficacy at 42 mg (equivalent to 60 mg of lumateperone tosylate), but not at the 84 mg dose (equivalent to 120 mg of lumateperone tosylate)[72]. A subgroup analysis revealed that the forty-two mg also significantly reduced the total PANSS and the Calgary Depression Scale for Schizophrenia (CDSS) score with an effect size much larger than risperidone (effects sizes for PANSS and CDSS approximated 1 for lumateperone, and 0.60 and -0.48, respectively for risperidone). The improvement in negative symptoms with lumateperone 42 mg did not reach statistical significance. The authors concluded that the lack of a significant difference was due to relatively low negative symptoms at baseline[72]. In another phase 3 randomized clinical trial[73], involving 696 subjects, 60 mg, and 20 mg lumateperone tosylate were compared with risperidone 4 mg and placebo for six weeks, but lumateperone (at either dose) was not significantly different from the placebo on the primary endpoint in the intent-to-treat population[74]. Such results may be related to an unusually high placebo response rate at specific sites, which affected the overall results. In a position emission tomography study[75] in patients with schizophrenia, the mean peak dorsal striatal D2 receptor blockade was 39% attained after an hour of taking 60 mg lumateperone tosylate. Higher D2 receptor occupancy is associated with a higher risk of EPS and hyperprolactinemia, indicating lumateperone may be associated with less risk of EPS and hyperprolactinemia[76].

All studies indicate a favorable side-effect profile of lumateperone. Lumateperone was also favorable to risperidone in terms of safety and tolerability, including a lower risk of hyperprolactinemia, hyperglycemia, hyperlipidemia, and weight gain. The most commonly reported adverse effects with lumateperone are mild sedation and somnolence. The most common side effect reported by Correll *et al*[71] was sedation (9.3%-12.7%), followed by fatigue (4.7%-5.3%), and constipation (4%-6.7%) among lumateperone- treated patients. In the same study, two patients discontinued treatment due to severe, treatment-emergent adverse- effects: One developed orthostatic hypotension and the other one developed convulsions with preexisting risk factors. There was no increase in suicidal ideation or behavioral or EPS[71]. In the other trial, by Lieberman *et al*[72], no severe adverse reaction occurred in the lumateperone group[72]. In the same study, two patients discontinued treatment in the lumateperone group- one for dryness of mouth and another for worsening schizophrenia whereas, three patients stopped treatment in the risperidone group due to akathisia and increased creatine phosphokinase level; 17% developed somnolence. There was no difference in the median weight gain between lumateperone and placebo groups; interestingly, the median weight gain was less than the patients on risperidone experienced (2.5 kg *vs* 1 kg), and no EPS were reported[72]. In an open-label safety switching trial, 301 patients with stable symptoms of schizophrenia were switched from previous antipsychotic medication to a daily dose of 60 mg lumateperone tosylate for six weeks and then switched back to the previous or another antipsychotic and reassessed after two additional weeks[77]. The study demonstrated a statistically significant improvement in total cholesterol, low-density lipoprotein cholesterol, body weight, and prolactin with switching to lumateperone. The progress was reversed as the treatment was changed back to the previous antipsychotic medication[77]. The most commonly reported side effects were mild to moderate and comprised of somnolence (6.6%), headache (5.3%), and dry mouth (5.3%), EPA (1.0%)[77]. Part 2 of the open-label study[78], is currently evaluating the safety and efficacy of switching to 60 mg lumateperone from the previous antipsychotic medication. In another study, one hundred seven patients experienced a mean reduction of 1.82 kg weight by day 175 and 3.16 kg by day 350. Almost 24% had at least 7% weight loss. The most common side effects were somnolence (20%), dryness of the mouth (7%), headache (7%), diarrhea (7%), and EPS (0.8%). The rate of somnolence decreased with night administration[79].

Summary of comparisons between newer FDA approved antipsychotics and the other SGAs

Although there is a lack of head-to-head comparisons among the newer antipsychotic medications, there is some evidence showing possible differences. In three 26-wk randomized clinical trials in Europe, higher efficacy of cariprazine over risperidone for negative symptoms has been established[40,80,81]. In a recent retrospective chart

Table 1 Characteristics and indications of brexpiprazole, cariprazine, and lumateperone

Name	Characteristics	Dose	Common adverse reactions	FDA indications
Brexpiprazole	Partial agonist of dopamine D2 receptor, a partial agonist of serotonin 1A (5-HT1A) receptors, and a potent antagonist at 5-HT2A, α1B, and α2C adrenergic receptors	2-4 mg/d for schizophrenia; 2 mg/d for MDD	Akathisia, headache, somnolence, tremor, and weight gain	Maintenance treatment of schizophrenia Adjunctive treatment for major depressive disorder in adults
Cariprazine	Dopamine D3/D2 receptor partial agonist with 10-fold higher affinity for D3 receptors than D2 receptors, antagonism at serotonin $5HT_{2A}$, $5HT_{2B}$ with moderate to high binding affinity	1.5 mg/d-6 mg/d for schizophrenia; 3-6 mg/d for bipolar mania	Akathisia, EPS, headaches, weight gain, headache, insomnia, and extrapyramidal side effects	Maintenance treatment of schizophrenia. Mania and mixed episodes related to bipolar mood disorder type I in adults
Lumateperone	Presynaptic partial agonist and postsynaptic antagonist at D_2 receptors, an antagonist at serotonin 5-HT_{2A} receptors, and a glutamate modulator	42 mg for schizophrenia	Sedation, somnolence, headache, dryness of mouth, extrapyramidal side effects	Schizophrenia in adults

FDA: Food and Drug Administration; MDD: Major depressive disorder; EPS: Extrapyramidal side effects.

review, the metabolic parameters of patients treated with brexpiprazole, lurasidone, asenapine, cariprazine, or iloperidone were assessed at six weeks, 12 wk, and up to 12 mo. Olanzapine was used as a comparator. Although all the newer antipsychotics had significantly favorable metabolic characteristics compared to olanzapine, the risk of weight gain and increased body mass index was more with brexpiprazole and iloperidone among the newer antipsychotics. In contrast, a minimal increase in weight was reported with cariprazine and asenapine[64]. Among the three dopamine partial agonists (aripiprazole, brexpiprazole, and cariprazine), patients on aripiprazole had the most significant reduction of PANSS scores in schizophrenia, cariprazine had the most potent effects on Young Mania Rating Scale scores in mania, and brexpiprazole significantly reduced the MADRS score as an adjunctive treatment of MDD[35]. However, a recent systematic review and network meta-analysis concluded that there was no difference in the safety and efficacy between aripiprazole and brexpiprazole in the treatment of schizophrenia[82].

CONCLUSION

Brexpiprazole, cariprazine, and lumateperone have demonstrated efficacy in treating schizophrenia in the short term. Longer-term studies are limited in number. Based on short-term studies, all three newer antipsychotics appear to be promising, specifically due to fewer metabolic side effects and possible efficacy on negative symptoms in schizophrenia (Table 1). Further research focusing on comparative effectiveness will aid in identifying whether brexpiprazole, cariprazine, and lumateperone are truly better than their precursors. Future studies should compare the safety and efficacy of these newer antipsychotics with older antipsychotic medications to provide patterns or predictors with respect to efficacy in particular patient groups.

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MINIREVIEWS

E-technology social support programs for autistic children: Can they work?

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Abstract

Autism is a neurodevelopmental condition with associated difficulties that present differently across individuals. One such difficulty is recognizing basic and complex facial expressions. Research has previously found that there are many evidence-based support programs available for building non-verbal communication skills. These programs are frequently administered with a therapist or in a group setting, making them inflexible in nature. Programs hosted on e-technology are becoming increasingly popular, with many parents supportive of them. Applications (apps) that are hosted on technology such as iPads or mobile phones allow users to engage in building skills in real-time social settings and own what they are learning. These technologies are frequently used by autistic children, with apps typically focusing on identifying facial features. Yet at this current time, there are mixed reviews of how to design such programs and what their theoretical backing is, with many studies using a mix of observation and psychological assessments as outcome measures. Eye-tracking and electroencephalography are established methodologies that measure neural processing and gaze behaviors while viewing faces. To better support the field moving forward, objective measures such as these are a way to measure outcomes of apps that are designed for helping children on the spectrum build skills in understanding facial expressions.

Key Words: Autism; Facial expression recognition; Technology; Eye-tracking; Electroen-

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Core Tip: Social support programs hosted on interactive technologies are becoming increasingly popular in the field of autism research. There are varied methods by which researchers determine the effectiveness of these programs. The review aims to address the current field by providing recommendations for assessing evidence-based tablet applications that support social skill development.

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INTRODUCTION

Defining characteristics of autism

The core features of autism spectrum disorder are difficulties with social communication and restricted and repetitive behaviours[1]. However, it is commonly associated with atypical cognitive profiles, executive dysfunction, atypical perceptual and information processing, all of which vary across individuals[2]. Although the diagnostic term for autism is "Autism Spectrum Disorder", many autistic people prefer identity first language rather than person first language (*e.g.*, autistic person rather than person with autism)[3-6]. Hence, the review will use identity first language hereafter.

In Australia, approximately one in 150 people are diagnosed with autism[7]. Changes in reporting practices over time and increased awareness contribute to the increased rates of diagnosis in many cases[8-10]. Strengths and difficulties vary between individuals with autism being clinically categorised by the type of supports needed[1]. In 2018, school-aged (aged 5-20) autistic people reported the greatest difficulty they faced was fitting in socially[7]. Non-verbal communication skills account for more than 60% of overall communication ability, and has been identified as an especially important issue due to the key role these skills play in the way people socialise[11]. Studies have found that difficulties with non-verbal social skills in autistic people vary widely and include understanding facial expressions, using conversational gestures and joint attention[12-15]. Understanding these subtleties in communication plays a critical role in building trusting friendships and relationships with others, especially during school years.

UNDERSTANDING FACIAL EXPRESSIONS

Understanding and processing facial expressions is considered some of the most important non-verbal communication skills as they are often the first feature we notice when meeting other people. Faces convey important social information about our mood and intentions to those around us. An inability to understand expressions has been linked to greater difficulties in social situations[16,17]. Autistic people are observed to have significant difficulties in recognising facial expressions, and these difficulties have been found to increase over time[17-19]. Although difficulties are experienced with all six basic emotions (happy, sad, fear, disgust, angry and surprise), autistic people are observed to have specific difficulties with more complex emotions such as anger, fear and surprise.

ALEXITHYMIA IN THE AUTISTIC POPULATION

Alexithymia is a trait that occurs in approximately 5% of the neurotypical population and in an estimated 50% of the autistic population[20]. It is defined by difficulties identifying and describing one's own emotions and a lack of awareness related to physical sensations from emotions[17]. This trait is found to play an important role in interpreting facial expressions. It has been theorized that the facial expression recognition difficulties autistic people experience may actually be due to alexithymia, and not social communication difficulties[17]. However, regardless of the potential cause, the ability to interpret and respond appropriately to the facial expressions of others is important to support social connectedness for autistic people.

CURRENT SOCIAL SUPPORT PROGRAMS

Numerous support programs have been developed for children on the autism spectrum that target skill building in social-cognitive, sensory-integration and relationship-based domains[20]. In fact, many evidence-based practices for working with people on the spectrum are focused on helping social communication, play and joint attention[21]. In clinical practice, there are typically two types of programs, the first being a comprehensive treatment model such as Early Intensive Behaviour Intervention which is often organised around a conceptual framework and overarching model[22]. Such programs often require the child to participate in settings outside of their norm (*e.g.*, a clinic) and requires a minimum (20-h) time commitment by family as well as the participant. In addition, the maintenance and generalisation effects of such programs are observed to be significantly lower compared to when participation occurs in a child's typical setting[13]. The second type of support programs are those aimed at gaining a new skill or overcoming a specific behaviour; these are typically shorter programs (*e.g.*, 10–20 fortnightly sessions) until the goal is achieved. These can be manual or technology-based and include video modelling. Many video modelling programs were developed to focus on specific social-communication behaviours such as social initiation, compliment giving and conversations[23], and are seen as highly effective in helping build these skills[24].

Technology-based support programs have been organised into eight categories: computers and internet, videos, mobile technologies (mobile phones and tablet computers), shared active surfaces, virtual and augmented reality, wearables, robotics and natural use interfaces[25]. Programs delivered *via* these technologies is growing across skill areas, as they allow for on-the-go use and can complement current therapies children and adolescents may be engaged in[26-28]. In fact, van der Meer *et al*[28] suggested how portable technology such as iPads and iPhones are viable technology aids for people in areas such as communication and transitioning skills. A recent example of this technology introduced the concept of animal filters on a mobile device to understand how the idea of mind-blindness or emotion recognition can vary in contexts[29]. Other software applications or "apps" allow the user to take a photo or video while attaching specific emotions to them, which aides in recognising the emotion in the future[29].

Although there is generally no theoretical backing for the use and design of such technologies, acceptability of e-technology is high across both children and parents, with many children using iPhones and iPads almost daily[30]. Parents reportedly like the idea of tablet-based therapy, especially when it comes with in-built instructions. This is not surprising when we consider that many parents work long hours, are time poor, and struggle with the costs of taking children to regular therapy sessions[31]. Although an appetite clearly exists among parents for support programs delivered on mobile devices, a meta-analysis by Hong *et al*[32], found that there were only 14 studies with a combined 36 participants that examined tablet-mediated support programs focusing on social and communication related skills delivery. Further research has also identified that many allied health professionals do not regularly use tablet computers within their sessions[33]. This means a significant gap exists between what is currently available and what health care consumers would like to be able to access. There is a clear need for further e-technology development and research, with larger sample sizes, and targeted delivery of therapies using a variety of devices, such as tablets and virtual reality, to provide learning and simulation in naturalistic settings to lessen this translational gap.

There have been some developments in designing programs for better interpretation of facial expressions. One early development by Baron-Cohen *et al*[34]

used video modelling. The Transporters DVD targeted expression recognition by adding human faces to animated trains and to engage children in social interactions. Over time, video modelling has proven to be a viable method for helping people on the spectrum learn social skills[34]. Developments in other e-technology are still progressing. Clark *et al*[35] point out that 15 e-technology therapy-based studies were conducted between 2000 and 2016. A review identified that many tablet applications (apps) are designed as support tools with a strong focus on social skills[36]. Apps can provide flexibility of delivery of therapies using a game-based environment to be played in real-time social settings, decreasing anxiety and supporting skill development[36,37]. However, the generalisation effects for these programs were mixed, due mostly to a lack of follow up and observation outside the research setting [38,39]. A way forward would be evaluating the therapeutic benefits of e-technology support programs by objectively measuring changes in behaviour and underlying brain function that is associated with facial information processing.

TECHNIQUES FOR DESIGNING SOCIAL SUPPORT PROGRAMS

Eye-tracking

An important part of social communication is the ability to interpret social signals such as those displayed through facial expressions. Displays of emotion are generally processed by looking at the eye and mouth regions of the face, then linking the information cognitively to a social context or verbal cue. Eye-tracking technology provides a real-time objective measure of face perception and feature processing. Fixation frequency and saccadic velocity (speed of synchronised eye movements) can be mapped to provide a scan path recording. Scan path recordings in the general population show an 'upside down' triangular pattern of performance focused on the eye regions and mouth (Figure 1). Comparatively, scan path patterns for autistic people tend to show more inconsistent viewing of the facial features, with fixations mostly falling on non-salient facial regions such as the chin, ear and hairline[40]. Findings from eye-tracking technology provided important insight to why autistic people may experience difficulties interpreting facial emotions and social situations.

Findings from a number of studies report eye avoidance in autistic people and conclude a general consensus that autistic people scan faces differently when compared to non-autistic people[40,41]. Avoiding the eye area, as observed in autistic people, suggests that facial information is encoded and processed differently to their non-autistic peers[42-44]. In a meta-analysis on eye-tracking and social attention, autistic people spent less time giving attention to social stimuli compared to non-autistic people overall[45]. The research reported that this occurred more frequently when there were more people shown in the content, such as a social scene rather than a singular person. Further evidence suggests that when the facial information is coded in such a way, the greater likelihood of difficulties with social skills[46].

Specific emotions also appear to impact face processing performance. Eye avoidance (with predominant focus on the mouth region) is more frequent in autistic adolescents when specifically viewing negative emotions[47]. In a study examining angry faces, Black *et al*[44] showed that autistic children were more likely to avoid viewing angry faces and scored higher on the social communication difficulties subset measure of the Gilliam Autism Rating Scale-3 (GARS-3)[48]. Greater attention to the mouth region when viewing face images is also associated with higher rates of social anxiety[46,49-51]. Innovations in e-technology-based support programs provide a mechanism to deliver targeted supports which assist with facial expression recognition and processing difficulties, particularly those to improve eye-tracking of the most salient facial feature areas such as the eyes and mouth regions. Eye-tracking technology also allows a more objective measure of behavioural changes in face processing.

Event related potentials

Another method to explore social communication is to use electroencephalography (EEG). EEG is an electrophysiological monitoring method to measure the electrical activation in the brain in real time. This measurement is highly sensitive and can measure brain responses to the millisecond (ms) and is therefore complimentary for eye tracking researchers. It is common for these brain responses to be labelled by their polarity; either positive (P) or negative (N) due to their electrical deflection, combined with the time after stimulus onset. Additionally, these brain responses are known as event related potentials (ERPs) and are defined "as the direct result of a specific sensory, cognitive or motor event"[52]. For example, a common ERP used in emotional

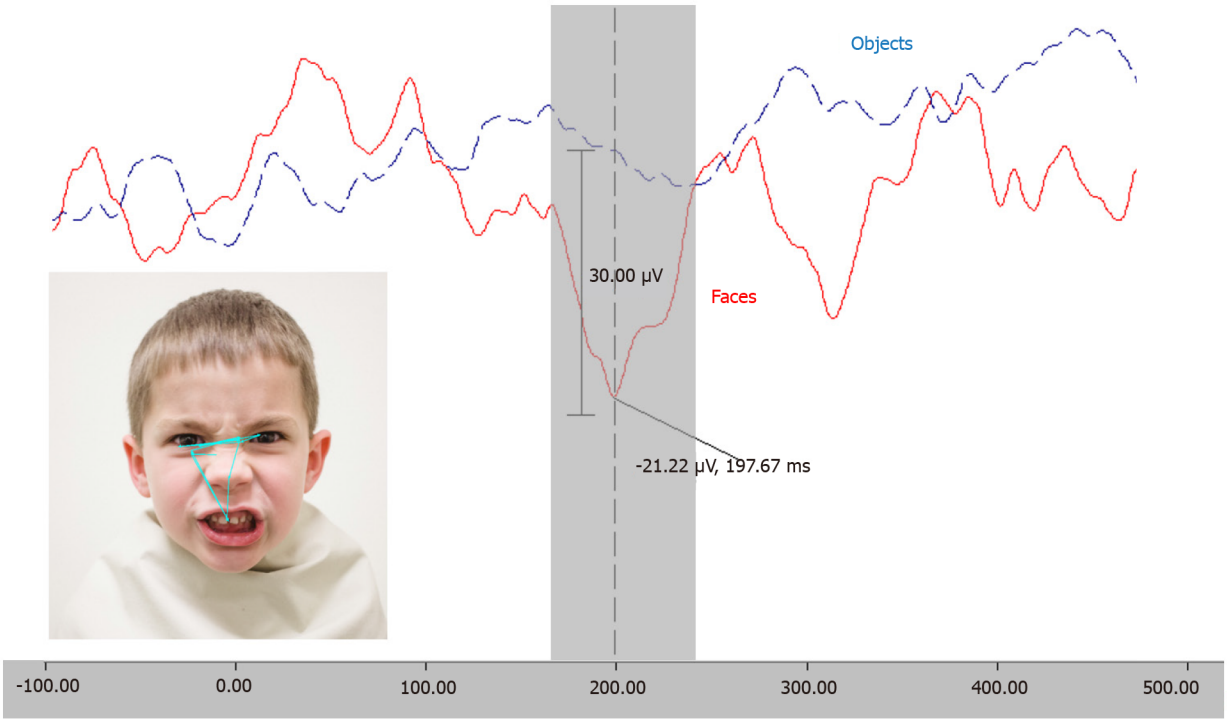

Figure 1 Event-related potentials in response to face (red) and (blue) object images of a non-autistic child. The grey area marks the face-specific event-related potential referred to as N170. Insert shows a normal scan path covering the eye and mouth region of a non-autistic child when viewing a face image.

recognition or social communication research is named the N170. The N170 ERP is observed as a significant amplitude deflection in a negative direction 170 ms after stimulus onset. Figure 1 shows the N170 in response to a face in a non-autistic child.

The N170 is a robust and reliable measure of facial recognition and has been confirmed by spatial functional magnetic resonance imaging, which demonstrates the response is generated from an area of the brain specific for facial recognition known as the fusiform gyrus. This brain region also encodes other complex visual stimuli but is most responsive when processing facial features[41]. Research has found that the N170 is not different in response to angry, fearful or neutral faces between non-autistic or autistic participants[16,41,43]. This means that the identification of a face as such is very fast, but the identification of a specific emotion expression takes longer as it requires a more detailed evaluation of the facial features and is captured by subsequent ERPs (*i.e.*, N200/P300)[53].

Autistic people usually have a slower processing time than non-autistic people when looking at facial stimuli; with slower processing times being associated with less face processing expertise[41,42,54]. Further research confirmed that there is a link between scanning the eye-region and a faster N170 response[41]. Moreover, a smaller N170 is also associated with less developed socials skills and more atypical social behaviours as is more common in autistic people[55].

CONCLUSION

Recording eye-tracking and ERPs are well suited and established methodologies that allow for a more objective assessment of support program benefits at the behavioural (eye-tracking) and neural (ERPs) level. They are less intrusive and demanding than other methods, such as functional brain imaging. As the general idea, e-technology should support these basic processes which are fundamentally involved in facial stimuli processing. The *FaceTile* task[56] is a good example of how this can be achieved, for instance, as a game-like app for autistic children. The game would ask children to recognise emotions in photographs of same-aged children. The photographs are initially covered by tiles, with the goal to remove as few tiles as possible to make a decision on the expressed emotion. The children would learn to remove tiles over the eye and mouth area to maximise their chances in doing well,

with the number of tiles over the photo increasing and becoming smaller on each level up. The aforementioned evaluation methods could then be used to test the autistic children's eye-tracking performance before and after playing the *FaceTile* game (*i.e.*, until reaching the desired game performance level). If the *FaceTile* game actually improves the face viewing strategy (*i.e.*, spending more time in the eye and mouth region) the face-specific neural processes should also improve as indexed by a larger N170 ERP compared to the pre-support program level. These measures could be further used to test possibly improved social comprehension more generally, for instance, employing tests such as the NEPSY-II[57], Cambridge Face Memory Test–Children[58], or the Social Communication Questionnaire–Current[59] before and after playing the *FaceTile* game. As such, the behavioural and cognitive measures of the application would make it a well-rounded, evidence-based program to help support autistic children to build skills in understanding facial expressions.

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MINIREVIEWS

Factors related to compliance with the COVID-19 health regulations among young people

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Abstract

The coronavirus pandemic has affected all facets of our lives and all ages and social strata worldwide. Measures have been taken to protect against the spread of the virus, such as more rigorous hand hygiene, the use of face masks and social distancing. However, the focus has often been on young people, who have been seen as a group lacking sufficient respect for government-imposed measures. This review outlines the preventive measures that have been taken in different countries and discusses their specific impact on young people and adolescents, taking into account the developmental stage and concrete needs of this age group. It summarizes those studies that have provided information on compliance with preventive measures by young people and adolescents, concluding that although compliance levels among this age group are lower than among older adults, the general view of youths as non-compliant is not consistent with real, objective data. The review also summarizes different views regarding the possible reasons for this lower level of compliance, taking into account both social (gender and age) and personal factors (personality, empathy, prosociality, self-control, cognitive styles and motivations), and discusses the practical implications of these findings for the future.

Key Words: COVID-19; Health regulations; Compliance; Young people; Adolescents

Core Tip: The effects of health regulations designed to prevent the spread of the coronavirus disease 2019 virus may be much more intense and pernicious among young people than adults. Social and personal factors, as well as the level of information to which one is exposed, peer influence and the number of elderly people one knows are factors that may help us understand why it is more challenging for

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young people to comply with the established measures. This greater insight may help us design more effective preventive strategies and awareness raising campaigns, so that we can be better prepared for future crises.

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INTRODUCTION

Coronavirus disease 2019 and health regulations

In December 2019, there was an outbreak of the coronavirus disease 2019 (COVID-19) in Wuhan (Hubei, China). At the beginning of 2020, the disease began to spread throughout China, with the rapid increase of confirmed cases and deaths soon starting to spread around the world. On January 31, 2020, the World Health Organization declared the COVID-19 outbreak a Public Health Emergency of International Concern [1].

Each country took its own measures to protect the health and safety of its citizens, contain the progression of the disease and strengthen the public health system. South Korea became the world leader in containing the virus, focusing strongly on mass testing, early contact tracking and quarantine[2]. In other parts of the world, such as China, Spain, Italy and the United States, the increase in the number of daily cases prompted governments to implement mitigation measures[3] such as stricter hand hygiene, travel restrictions, school closures and social distancing.

At the beginning of the pandemic, at least 186 countries instigated varying degrees of restrictions on population movements to curb the spread of COVID-19 and prevent health systems from being overwhelmed[4]. The first measure taken in many countries was a home lockdown and the establishment of restrictions such as allowing people to circulate on public roads only for essential tasks such as buying food, commuting to work or caring for dependents[4]. Moreover, in many countries, face-to-face educational activities were suspended in all schools and at all stages, cycles, grades, courses and levels of education, with this being one of the most widely-used measures to help maintain social distancing and decrease the contagion rate[5].

Following these restrictions, and after the incidence of the disease had started to abate, governments began to create exit strategies to unblock and re-establish "normality" in their respective countries, always in accordance with public health principles and population indicators[6]. The restrictive measures caused major economic and social disruption around the world, and governments were forced to try different exit strategies[7]. In the absence of a treatment or vaccine, some countries took measures to limit the density of gatherings. In addition to banning large concentrations of people, on a smaller scale, workplaces were obliged to establish schedules to limit crowding in offices, and healthcare facilities were forced to reduce opening hours, space out waiting rooms and offer weekend and evening appointments to accommodate and care for the most at-risk patients. Commercial establishments limited the number of people allowed in their store, and bars and restaurants reduced their capacity and even closed down during the most critical moments of the pandemic[3].

In terms of individual responsibility, behaviors in response to COVID-19 were similar to the health behaviors described by Bish and Michie[8] in relation to pandemics in general. These behaviors fall into one of three categories: preventive behaviors, which include hand washing, the use of face masks, coughing into one's sleeve and getting vaccinated; avoidance behaviors, which include social distancing; and quarantine and illness management behaviors, which refer to actions taken once a person believes they have been infected and in the case of COVID-19 includes self-quarantine[9].

In addition to being a simple and low-cost intervention, hand washing for the control of infectious diseases has the advantage of offering easy compliance as well as great health benefits. Indeed, several studies have shown that hand washing reduces

the risk of virus transmission by 55%[10].

As for the use of face masks, despite several debates about their effectiveness, in most parts of the world they have been declared mandatory in public places to prevent the spread of the virus. The use of face masks is one of the non-pharmaceutical intervention measures that can be implemented effectively without drastically altering social practices[11]. Their use in the community may also be beneficial for healthy individuals, as transmission may be presymptomatic.

Another of the measures implemented is social distancing, with scientific evidence confirming that a physical distance of at least 1 meter significantly reduces infection, and that distances of 2 meters may be even more effective. It has been demonstrated that social distancing measures prevent the transmission of the virus, thereby reducing the spread of the infection[12].

Another individual area of responsibility in the context of the current pandemic is self-quarantine. People who have been infected with the virus need to isolate themselves in order to prevent the spread of the disease. However, those who have been exposed to COVID-19 should also be isolated in order to monitor whether or not they develop the disease over time[13].

Many different health regulation measures have been implemented since the start of the pandemic. In most countries, the measures were more restrictive at the beginning and have since varied in accordance with incidence rates and hospital saturation. However, those that have remained clear and constant in many countries and have been maintained throughout the pandemic include the use of face masks, social distancing, self-quarantine and the avoidance of large gatherings of people.

The health regulation measures currently in place are therefore the main strategies used to prevent the transmission of the COVID-19 virus[14], and these measures have an important differential impact on people in accordance with variables such as age.

THE IMPACT OF HEALTH REGULATIONS ON YOUNG PEOPLE

Studies about the COVID-19 and previous pandemics have identified the fear of contamination and restricted social contact as the main risk factors for increased mental health problems[15,16]. Indeed, Orben *et al*[16] assert that "it is possible that the effects of such deprivation of social contact will extend beyond the period of physical distancing and might affect the population for years to come" (p. 634).

Social distancing may be especially challenging for adolescents and young people. Social contact is essential for developing cognition, emotions, attachment and relationships and contributes to the physiological regulation of the body's responses to acute stressors[17,18]. It is well known that peer relationships are central across the different areas of psychosocial development during adolescence and youth. As children grow older, peers become the referents around which leisure time is structured and provide emotional support and guidance in the process of growing up [19]. However, adolescence is also an especially vulnerable stage of life and is associated with strong risks for the development of mental health problems, such as anxiety and depression[20]. Moreover, the multiple hormonal and neurobiological changes that take place during this period have been linked to heightened emotional reactivity, which in turn leads to a constant need to adjust coping and stress regulation strategies[21]. Conversely, high-quality peer relationships seem to protect against mental health problems and to strengthen adolescent resilience[22].

Therefore, if we accept that young people and adolescents are at greater risk of emotional problems and that their peers are an important source of social and emotional support, it is logical to assume that the situation engendered by the pandemic may be particularly critical for them. Alivernini *et al*[23] concluded that a pandemic is a stressful life event that can have a major impact on adolescent development, especially affecting their mental health and increasing their levels of anxiety and psychological distress. Moreover, emotion regulation skills may fail when exposed to a global, ongoing stressor such as the COVID-19 pandemic, or it may be impossible to implement such skills due to pandemic-related restrictions[24].

Research has found elevated mental health concerns during the COVID-19 pandemic in comparison with time points prior to its onset[25,26]. In the specific case of adolescents, Alivernini *et al*[23] explored the positive and negative emotions of a sample of Italian adolescents before and after the start of the COVID-19 pandemic, finding an increase in adolescents' levels of negative affect following the national lockdown and a decrease in their levels of positive affect. These results are consistent with those found by Rogers *et al*[27] among United States adolescents, with the authors

arguing that the pandemic may have challenged the psychological and coping resources of adolescents and young people, leading to fluctuations in underlying mood states and rendering them more vulnerable to mental health problems.

A qualitative study carried out in the United Kingdom, which explored public perceptions and experiences of social distancing and social isolation related to the COVID-19 pandemic, found that frustration or anxiety over loss of social interaction and fears over the duration of social distancing and isolation measures were all major worries[28]. A similar study also identified participants' concerns about not being able to socialize face-to-face with their peers as well as their willingness to participate in the response and recovery process as a means to make their voices heard[29].

In response to this lack of face-to-face interactions with peers and the decrease in leisure time spent in large groups with friends, young people and adolescents have increased the time they spend on social media and the internet. The use of screens has increased considerably, not only because it is a way of interacting with peers but also because it has been the means of communication to which many schools and universities have had to resort. Some studies have asserted that adolescent use of digital technologies and social media might mitigate some of the negative effects of physical distancing[16]. In contrast, however, previous studies have identified certain risks linked to the excessive use of screens, such as poor sleep, higher accumulated time spent sedentarily and exacerbated risk for mental health problems[30]. Indeed, the study by Larcher *et al*[29] mentioned above identified some concerns among young people about the significant amount of screen time to which they are now exposed during the pandemic. In this respect, Orben *et al*[16] suggested that the types of technology used by young people should be taken into account since engaging in direct communication may increase wellbeing[31] and help maintain personal relationships[32], whereas passive use of social media has been related to negative effects (social comparison, envy, *etc.*)[33]. Moreover, the effect information and communication technology use at all levels of education has had on pupils' academic and holistic development remains to be seen.

On a more optimistic note, increased family time may be one of the positives that can be taken from the critical situation to which the pandemic has brought us. The fact that young people and adolescents have spent more time with their families may have mitigated the effects of the drop in social face-to-face interactions with peers. In particular, adolescents who have positive relationships with their parents or caregivers may be less affected by physical distancing than those who do not or who are living alone[16].

COMPLIANCE WITH HEALTH REGULATIONS AMONG YOUNG PEOPLE

Compliance rates

Adolescents and young adults are internationally considered to be the potentially least compliant age group in relation to the measures established by different governments, especially those involving social distancing[34].

This had already been found prior to the pandemic in relation to other health-related behaviors[35,36]. In contrast to the younger population, a study conducted in May 2020 found that the older population was the one that engaged most in protective health behaviors[9].

But let us examine the compliance rates reported to date. For example, in a study conducted with 683 adolescents (13-18 years) from the United States, Oosterhoff *et al* [37] found that most youths were engaging in social distancing a lot (26.9%) or a great deal (56.6%), with fewer engaging in social distancing somewhat (13.0%) or a little (3.5%).

Similarly, a longitudinal study that was already collecting data in Zurich prior to the pandemic (in this case with 737 young adults) found that non-compliance was somewhat higher for hygiene-related measures than for social distancing, but even so, non-compliance levels were low[34].

In another study, also carried out in Switzerland but in this case in another canton [38], the authors observed high self-reported adherence to rules (85%), which increased significantly with age and level of worry.

In Oslo (Norway), 12686 secondary school students were found to have high percentages of compliance with the regulations. Most of them exceeded 70% compliance, with hand washing (84%) being the rule most frequently complied with. However, the compliance rate for physical distance (50%) was considerably lower[39]. In other words, although it is true that most adolescents comply with the established

rules, the greatest difficulty seems to be in maintaining social distances, something which, as has already been pointed out in previous sections, is especially difficult during a developmental stage such as adolescence. Nevertheless, Rieger[40] found high levels of compliance with even social distancing among 250 university students in Germany.

In light of the findings outlined above, it seems that the prevalent pessimistic view of young people's compliance rates is inconsistent with real, objective data. This is similar to what Raude *et al*[41] observed about France. Underlying this may be the fact that everyone feels they are complying much more than everyone else with the established regulations. In this sense, it is worth noting the study by Shelby *et al*[38] which observed a discrepancy between respondents' perceptions of their own compliance (85%) and their perceptions of others' compliance (65%).

Nevertheless, even if non-compliance is not always as high as is often perceived, it may be interesting to determine the factors behind both compliance and non-compliance with the aforementioned measures.

Explanatory factors

At this point, it may be worth mentioning both more immediate factors that explain why people do not comply with the measures and not so immediate previous risk factors, which at both a personal and social level may be influencing this lack of compliance. Regarding the former, variables such as the perception of risk, the search for information, trust in the government and the perception of compliance with these measures as a moral obligation are related to a higher level of respect for them (see studies cited by Nivette *et al*[34]).

In their own study, Nivette *et al*[34] distinguished between internal (such as wanting to protect oneself and others) and external factors (such as having social events cancelled) for social distancing compliance. Likewise, they identify a series of barriers that can lead to non-compliance with this measure, including feelings of sadness derived from loneliness or the inability to work remotely. Fortunately, aspects such as misconceptions and/or conspiracy theories yielded practically residual data (1%-3%), suggesting that despite the attention these issues sometimes receive in the media, they do not really seem to be a major reason for failing to comply with the recommended health measures.

Among the variables mentioned above, the one that seems to stand out from the others is trust in the government, which largely determines the population's compliance with the different preventive measures in countries such as France[41] and Japan, to cite only two.

In relation to the not so immediate pre-existing aspects, which can be considered more long-term risk or protective factors, two types can be distinguished: social factors and personal factors.

The most widely studied social factors have been gender and age. For example, it has been found that women generally comply more than men with the established public health measures[34]. This was also found in Spain in a study carried out during the weeks of severe lockdown[42] as well as in France where it was found that men, as well as young adults, were less likely to follow the guidelines established to curb the spread of the virus[41]. This second finding is also linked to the other psychosocial variable mentioned above, namely age.

Numerous studies highlight age as a key variable for compliance with preventive measures; in some cases, even after controlling for the effect of other factors[43]. Nivette *et al*[34] found that people over 45 years of age were significantly more compliant with social distancing than those aged 18-24. These results are consistent with those reported in Spain during the severe lockdown by Gutiérrez *et al*[42]. These authors found that the age groups most likely to break the rules were those between 20-30-years-old and under 20-years-old, which had non-compliance percentages of 32.7% and 23.3%, respectively. Similarly, Margraf *et al*[44] point out that there are countries, including Spain, in which younger people show less adherence to norms than other age groups.

With respect to personal variables, one of the factors that has been studied regarding non-compliance with health measures among the adult population in general is personality, specifically aspects such as high levels of the so-called dark triad traits (machiavellianism, narcissism and psychopathy) or low levels of agreeableness[45]. These are known as antisocial traits and have been studied by Miguel *et al*[46] in a large sample of Brazilian adults (n = 1578), with the results indicating (as expected) that people with an antisocial pattern profile found it more difficult to comply with the measures than those with an empathy pattern.

The same can be said for people who avoid risk and are more prone to health/safety behaviors. In times of the pandemic, these people tend to adopt measures such as social distancing and mask wearing[46,47] or tend to reduce their mobility[48,49] to a greater extent than those with a risk attitude.

Coroiu *et al*[14] discuss the role of empathy and prosocial behavior as well as the barriers and facilitators of compliance. Moreover, a series of studies conducted with 3718 people from Germany, the United States and the United Kingdom has found that fostering empathy for those most vulnerable to the virus encourages adherence to prevention measures[50].

Likewise, level of self-control also seems to have a significant influence on compliance with the established preventive measures. People with higher levels of self-control comply to a greater extent with rules such as social distancing or the use of face masks, and the weight of this factor remains significant even after controlling for other factors such as political ideology or demographic variables[47].

Xu and Cheng[47] also identify another personal variable, in this case of a cognitive type, which influences compliance with preventive measures: need for cognition, understood as a tendency to seek information and engage in systematic thinking that increases decision-making competence. This variable has previously been associated with other healthy behaviors, such as being informed about AIDS or adopting a positive attitude towards condom use[51]. In the context of the current pandemic, need for cognition is understood as a personal variable associated with a higher level of compliance with measures such as social distancing and face mask wearing.

Another psychological factor that may influence compliance is the time perspective [52], defined by Sobol *et al*[53] as "a cognitive style involving a tendency to focus on a particular segment of time: past, present or future" (p.2). The "carpe diem" perspective (focused on the here and now, in the sense of being aware that what one does at this moment has an influence on the future situation) has been found to be the best predictor of compliance.

All the factors described so far refer to the population in general, but what can be said about the younger generations in particular? Is there any factor that explains the level of compliance with preventive measures among this segment of the population?

One of the variables that has been studied in relation to both youths and the general population is gender, although the conclusions are as yet unclear. For example, in a study carried out with young adults in Switzerland, a higher level of non-compliance was found among men in terms of total scores on the hygiene, social distancing and general non-compliance measures. However, a more detailed examination of the results revealed no differences between men and women in many of the specific aspects of each measure[34].

Oosterhoff *et al*[37] analyzed motives for respecting social distancing norms in a sample of 683 American adolescents aged between 13 and 18 years from the perspective of Self-Determination Theory[54]. According to this theory, the motives that prompt a person to act in a certain way may be externally controlled (*e.g.*, obeying imposed rules) or autonomous (volition-based). A priori, autonomous motivations are more closely associated with prosocial behaviors than controlled motivations[55] as well as entailing greater benefits in terms of mental health for the person who puts them into practice[56]. These reasons were the ones most commonly reported by the participants in the study. Specifically, "youths most commonly referenced prosocial motivations, including social responsibility (78.1%) and not wanting others to get sick (77.9%), to engage in social distancing"[37], although controlled motivations were also common. Similar results were found by Alivernini *et al*[23] in a longitudinal study with Italian adolescents.

In relation to those rules with which we are often obliged to comply, prior to the pandemic it was found that young people with characteristics of the so-called antisocial potential[57] are more likely to break the rules, and the scientific evidence gathered in times of the pandemic also seems to be consistent with this. For example, impulsivity and certain personality traits such as amorality, egoism and psychopathy are associated with greater non-compliance with health measures[58]. For their part, Alivernini *et al*[23] report that of the personality-related aspects they analyzed, only one, openness to experiences, was found to have a statistically significant relationship with physical distancing behavior. Specifically, the results indicated that adolescents who were more non-compliant with the social distancing norm were those who were more attracted to risk, although this association was weak.

Another variable that has been identified is peer influence, which is particularly important (both negatively and positively) during this vital developmental stage[59] and may be an aspect to take into account in the future when attempting to design campaigns that really manage to convince this age group of the importance of

complying with health measures.

For their part, Sobkow *et al*[60] focused on risk perception and the cognitive and emotional factors that may influence it, studying the impact of variables such as affect, mental imagery, controllability, self-efficacy and numeracy.

In a study carried out with 2130 Chinese adults (university students), Guo *et al*[61] analyzed the individual and environmental factors that may be behind compliance with social distancing rules. The individual factors identified included variables such as gender, depressive symptoms and psychological distress, whereas the influence of social media was the principal environmental factor found, with people who spend less time informing themselves online being more vulnerable due to their limited knowledge of the measures required to stay safe.

Finally, another factor that seems to influence the younger population's compliance with health measures such as social distancing is the number of elderly people they know personally[40]. This may be relevant when designing and implementing prevention programs aimed at this segment of the population.

Table 1 summarizes the main findings on factors related to the level of compliance with COVID-19 prevention measures.

CONCLUSION

The emergence of the COVID-19 pandemic at the beginning of 2020 plunged the world into an unprecedented situation, with implications in all spheres of people's lives. In order to cope with this crisis and curb the spread of the virus, governments in different countries took measures, which were generally stricter at the beginning of the pandemic (*e.g.*, lockdown) and have since been relaxed as contagion and death rates and pressure on healthcare systems have decreased[6]. Nevertheless, some restrictions, such as the use of face masks, hand washing and social distancing remain in force in many countries, and until vaccines and treatments begin to have a clear impact, compliance with these rules will continue to be key elements in the struggle to keep the situation under control.

In this regard, it should be noted that adolescents and young people have been internationally identified as the age group least committed to compliance with these measures[34,42,44]. However, it is important to understand that given the characteristics of their developmental stage (*e.g.*, need for greater contact with peers for their cognitive, social and emotional development), compliance is particularly difficult for them. Moreover, it should not be forgotten that adolescents and young people are more vulnerable to mental health problems[20], and limitations on social contact put them at even higher risk[22]. One way or another, what is certain is that it is not yet possible to anticipate how long physical distancing measures will remain in place and how they will affect adolescents' and young people's development and mental health in the longer term. Although social distancing measures are temporary, several months of physical distancing represent a large proportion of a young person's life during a sensitive period of development, and in this sense, the effects may be much more intense and pernicious than among adults. Furthermore, we still do not know how other stressors stemming from this crisis will influence adolescents and young people in the future (economic pressure, uncertainty, cancellation of public events marking key life stages and rites of passage, *etc.*)[16]. Finally, although technological devices enable relationships to be maintained at a distance and bring people closer to their peers, their excessive use also has negative consequences[30], and they should not, therefore, be viewed as the only alternative.

As for the factors that influence compliance or non-compliance with established measures, the few studies that have been published to date point to a wide range of different elements that still require further research and in-depth study. For the moment though, it seems that lower compliance is associated with factors such as being male and being young as well as with having an antisocial personality pattern, a low level of empathy, a low level of self-control or a certain tendency to engage in risky behaviors. The level of information to which one is exposed, the influence of peers and the number of elderly people one knows also seem to play a role. Although explanations of the influence of these factors are still tentative, they point the way for further research. Moreover, it is interesting to consider these factors as possible foci for interventions in the long term. Indeed, many of the factors identified can be modified or improved: for example, self-control can be strengthened with practices such as delayed gratification[62,63]; news report and message framing may affect how people evaluate the risk of an incident or situation[64,65] and may therefore be useful for

Table 1 Explanatory factors for compliance/adherence to coronavirus disease 2019 measures

Factor types	Factor sub-types	Specific aspect	Adherence/compliance	
Immediate factors		Trust in the government	Higher level of trust	Higher compliance
		Perception of risk	Higher perception of risk	
		Search for information	More search of information	
		Perception of compliance with rules	Perceiving compliance as a moral obligation	
Previous risk-factors	Social factors	Gender	Women	Higher compliance
		Age	Older people	
	Personal factors	Personality traits	Machiavellism	Lower compliance
			Narcissism	
			Psychopathy	
			Antisocial traits	
		Risk taking	More risk taking	
		Empathy and prosocial behavior	Higher empathy and prosocial behavior: higher compliance	
		Self-control	More self-control: Higher compliance	
		Need for cognition	Tendency to seek information and to follow a systematic thinking	Higher compliance
		Time-perspective	"Carpe diem" perspective	
		Motivation	Autonomous motivation	
		Influence of peers	Depending on peers' attitudes	
		Number of elderly people one knows	Higher number	

addressing risky attitudes[40]; and emphasizing relations with the elderly may help raise awareness and enhance empathy towards this population group.

However, although the contribution of these individual factors is of great interest, when thinking about preventive strategies or awareness raising campaigns, it is important to include interventions that will impact a large number of people since individual variables are usually difficult to modify, even more so in such a short period of time as that required to curb the spread of a virus. It is particularly important to continue with an exhaustive study of all the factors that facilitate or hinder compliance with social distancing measures ("stay-at-home" or "shelter-in-place" orders), given that these may potentially be required for months or even years[14] and involve significant lifestyle changes. One possible strategy for encouraging these behaviors would be to provide the population with real data on those who do not comply with the measures, of whom there are far fewer than generally believed[41]. This would perhaps encourage people to consider non-complaint behaviors as isolated and non-representative events, which would in turn decrease the general frustration felt by those who make the effort to comply as well as increasing social criticism of these attitudes.

In relation to the specific ways in which preventive or intervention campaigns can be implemented, some authors highlight the need to identify which groups are at greater risk of non-compliance with the rules in order to design social marketing strategies or policies that are customized and adapted to their specific characteristics [66]. The basic argument is that if we want standards to be effective, we cannot simply direct them at the entire population and expect everyone to comply. Rather, an effort should be made to adjust them to different social groups and their particularities.

To facilitate this last point, and given that adolescents and young people are one of those groups with a lower level of compliance, many authors and studies have already pointed out the importance of giving youths a voice and involving them in strategic plans for restructuring the policies, systems, workflows and communities affected by COVID-19. The idea is that they should not perceive the measures as something

imposed by adults or institutions, and therefore far removed from their own world, but rather as something worth getting involved in. It is therefore advisable to give adolescents and young people the autonomy to develop and deliver their own campaigns through social media, for example, supported by influencers and/or people who are relevant to them[60]. We should validate the passion felt by youths to regain normalcy while at the same time encouraging, empowering, and engaging them in forming creative solutions for a new normal.

Finally, it is important to note that although the future of the coronavirus crisis looks brighter every day, the reality is that we will continue to have to live with these measures for some time yet to come. It is therefore essential to apply the knowledge we are gaining to the way in which we deal with this pandemic, until it finally comes to an end, and to take advantage of all these ideas and resources to prepare for other social and health crises that may occur in the future.

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MINIREVIEWS

Mechanism of olfactory deficit in neurotrauma and its related affective distress: A narrative review

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Abstract

Traumatic brain injury (TBI) is among the leading causes of death and disability all over the globe. TBI is also commonly associated with clinical sequelae of posttraumatic depression, and reports of other subsequent affective distress are common. Similarly, posttraumatic changes in chemoreceptive sensory functions, primarily due to coup-contrecoup injury induced shearing of the olfactory nerve fibers, leading to anosmia and ageusia are also well documented in the literature. However, the current literature is limited in addressing the intersections between said variables. The aim of this study was to provide a focused narrative review of the literature, to address these intersections found in clinical sequelae of TBI. As chemoreceptive sensory deficits are also linked to significant affective distress of their own, this review addresses the bidirectionality between sensory deficit and affective distress. Prevalence, demographics, mechanisms, and clinical implications are presented. Previous research is presented and discussed, in an effort to highlight the importance of consideration for all factors in TBI patient care and future research.

Key Words: Brain injuries; Brain injuries, traumatic; Anosmia; Depression; Affective symptoms; Smell

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Core Tip: In neurotrauma, coup-contrecoup injury induced shearing of olfactory fibers commonly leads to bilateral anosmia or severe hyposmia, and related ageusia. Post-traumatic sensory loss and depression are common in patients. All three variables' intersections in traumatic brain injury's clinical sequelae are discussed.

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INTRODUCTION

Traumatic brain injury (TBI) has been consistently connected to a broad spectrum of pathologies including post-injury cognitive and sensory deficits[1]. According to the Centers for Disease Control and Prevention's (CDC) most recent statistics, TBI is responsible for approximately 2.9 million hospitalizations, emergency department (ED) visits, and deaths in the United States alone[2,3]. Within those 2.9 million cases, nearly 1 million of them were in children[2]. TBI related ED visits rose 53% from early 2000's to mid-2010's, and most signs point to these numbers continuing their annual rise in the future with only minor fluctuations[2,3]. The age group with the highest rates for TBI are ages 75 and older[2]. Additionally, the leading cause of TBI related deaths change for each age bracket. For ages 0 to 4, the leading cause for TBI related death was homicide. For ages 15-24, 25-34, and greater than 75 years, the leading cause was motor vehicle accidents. The leading cause for 45-64 years old is intentional self-harm. Finally, falls accounted for the highest rate of TBI related death for age 65-74[2].

TBI can range from mild effects, such as transient mental status changes, to lasting deficits in motor skills, sensory perception, and cognitive ability[1,2,4]. Because of the wide range in severity of TBI symptoms, there is an extensive amount of literature and research within the scientific community into the etiology, pathophysiology, symptoms, and treatment options for TBI. However, an often-overlooked side effect which can be attributed to TBI is olfactory disturbance (OD). Due to the mechanism and the biophysics of acutely rapid acceleration immediately followed by deceleration associated with TBI (coup-contrecoup injury), the olfactory bulbs and the olfactory epithelium are at high risk for damage *via* exogenous trauma induced shearing[5,6]; as the severity of the TBI increases, so does the risk of OD. Recent literature shows OD incidence rates (specifically anosmia) of 9.5% for mild TBI, 20% for moderate TBI, and 43.5% for severe TBI[5].

When attempting to understand the cause-and-effect relationship of TBI's direct association with OD, it is important to discern the role of head trauma as one of the main origins[7,8]. As noted in the extent literature, there are varying degrees of dysfunction encompassed by the TBI diagnosis, many of which depend on the localization of injury[9]. This has been found to be the case with OD as well, given that not all parts of the brain known to play a role in the process of olfaction are isolated to one specific area[8,10]. In instances of cerebral neurotrauma, there is a greater chance of damage to the olfactory bulb and other anterior structures, such as the olfactory cortex (OFC)[11,12]. If the trauma is more severe and diffuse in nature, there is a greater chance of disruption to sensory integration pathways, located in more posterior sections of the brain[13]. A common result of damage to the olfactory integration chain often manifests as parosmia, a dysfunction in the specificity of smell detection[14]. The replacement of normal, appetizing food aromas with repugnant odors, more associated with malodorous substances[14], is an applicable example. There is no one exclusive type of impairment or location of damage across all TBI patients[15]. Given the strong association of OD with TBI, we can conclude that multiple variants of OD can exist, particularly when considering the effects of coup-contrecoup injury[7,11,14,16].

The types of dysfunction classified as OD can range from a simple difficulty in recognizing aromas, to further disruptive forms of parosmia, and even complete anosmia or absence of olfactory perception[7,14,16]. There are multiple mechanisms for post-traumatic OD. The most common etiology, however, is related to the

"anterior-posterior movement" of the brain in relation to the interior of the skull itself, from prior mentioned coup-contrecoup injury[7,11].

OD's severity can vary greatly, typically categorized as either total loss of smell (anosmia), decreased smell sensitivity (hyposmia), or altered sense of smell (dysosmia/parosmia). OD is a prevalent condition in the United States, with an estimated rate of 10%-15% in adults over the age of 40 having disrupted smell in any given year[5,17]. When there is a sensory disturbance as prevalent as OD, we must also assess other potential subsequent problems that can come secondary to OD. A significant association to OD is depression and related disorders. Both depression and OD have neuroanatomical structures that contain common layers[18]. However, the similarities between these anatomical substrates lead to more complications in clinical differentials. Not only can depression be secondary to OD, but the inverse can also be true. In addition to developing depression post-OD, olfactory functioning can also be negatively impacted by depressive states[18], rendering this "chicken or the egg" phenomenon a challenge in accurate clinical differentials.

TBI is also associated with an increased risk of depressive symptoms. Depression has been a well-known clinical sequelae of TBI and the literature on this topic has been established for decades[19]. Additional literature also has been illustrating how clinicians can improve their diagnostic clarity for major depressive disorder (MDD), as well as how much loss of consciousness (LOC) can play a role in the severity of MDD symptoms and overall cognitive functioning[20,21]. While the estimated rate of depression in TBI patients does vary greatly (anywhere from 6%-76%), the literature has established that the incidence of MDD within the TBI population is significantly higher than the general population[21-23]. Nonetheless, given the wide range of current prevalence estimates, continued pursuit of controlled studies to address said variance is needed.

TBI AND SENSORY LOSS

As supported by the literature, the volume, or amount of gray matter and associated neurological connections within the olfactory bulb, has been associated with varying levels of functionality[9]. In patients with a decreased olfactory bulb volume, there is a strong correlation with decreased olfactory function, as evidenced by poor performance on various multi-modal examinations[14,24]. This trend of decreased olfactory capacity is augmented by the presence of TBI, or more specifically, its location and severity[14,15]. As noted previously, in patients with more diffuse neurocognitive injury, there is an increased chance of greater complexity in OD, relative to frontal lobe damage and resulting anosmia[14].

Incidence rates for complete anosmia after TBI range from 9.5%-43.5% and are highly correlated with the severity of the TBI[5]. This is compared to the approximately 20 million adults over age forty in the United States who suffer from OD[25].

In considering TBI as a primary source of OD[7,8], it is estimated that an approximate one-year recovery period exists, where the patient has the potential to gradually regain any function that was otherwise lost or impaired by their TBI. This is however, also often followed by a plateau of functional re-acquisition[15]. Similar to the global phenomenon witnessed in TBI patients, individuals with OD, specifically, may gradually regain their olfactory functionality[26,27]. This has been hypothesized to be related to the synaptogenesis of nerve cells connected to the areas damaged by the TBI, such as the olfactory bulb or OFC[28].

The olfactory system is a complex network of systems that make up one of the oldest sensory modalities of mammals[29]. The olfactory epithelium is found on the superior medial vertical lamellae of the superior turbinates, and is made up of three different types of cells: Basal, supporting, and olfactory receptor[29,30]. The olfactory system experiences consistent turnover and regeneration of its adult neurons[29]. A key part of the olfactory mechanism is the olfactory bulb, which receives the signals from the olfactory epithelial cells and continues the communication process for olfaction to be executed[30,31]. As mentioned prior, when the nerve fibers of the olfactory receptor cells are sheared or stretched from the coup-contrecoup injury, they are no longer connected to the olfactory bulb[30,31]. This leads to the disruption of sensory signals within the olfactory pathway, resulting in anosmia[5,25,30].

The epithelial cells present within the olfactory system are the only known neuron group that possess the ability to regenerate when damaged, contingent to the integrity of the olfactory bulbs[25,29]. Costanzo[31] states that "the olfactory epithelium retains its capacity to undergo neurogenesis long after development", and that the degree of

neuronal recovery varies with the severity of the injury. There are multiple barriers to effective regeneration, including spatial challenges from disruption of axon sheath alignments, fibrosis over the olfactory bulb, and/or broken synaptic sites[31]. With multiple challenges, it becomes exponentially complex for the neurons to reconnect to the olfactory bulbs. This likely explains a correlation between the severity of the TBI and the difficulty of functional recovery of olfactory senses (Figure 1).

Currently, many modalities and tools exist to identify the various forms of neurological disruption. Psychophysical and electrophysiological assessments, in addition to neuroimaging techniques, are among the tools used to diagnose OD[32-35]. In recent years, however, a more advanced form of imaging has garnered interest for its ability to scan restricted areas of the brain with more precision[32]. Known as diffusion tensor imaging (DTI), has already demonstrated itself to be a useful tool, capable of providing enhanced insight into the etiopathogenesis of the neurological disruption associated with OD[13].

DTI employs fractional anisotropy, the indices of the diffusion of water molecules across white matter tracts in the brain[13,32], in comparison to more established, de facto neuroimaging. This technique provides a more detailed, *in vivo* quantification of nerve fila and white matter microstructure, down to the individual nerve fibers[36,37]. In terms of its relevance to OD, medical professionals now possess the ability to illustrate the severance of nerve fibers from the olfactory bulb or other essential areas that play a role in the sensory integration of olfaction[12,13,32]. This enables the visualization of minute or gradual regrowth that is often missed by other forms of neuroimaging[13].

A 2017 study by Bonanno *et al*[13] focused on the role that DTI may play in the treatment of TBI and related OD; more specifically, the discrepancy between MRI and DTI were highlighted[13]. Both of the imaging techniques were performed within the same time period, first at baseline shortly after the TBI and then again, at 1-year status/post[13]. MRI demonstrated the presence of encephalomalacia, while the DTI scan was remarkably able to reveal significant axonal regrowth in both the left and right hemispheres[13,38]. This was demonstrated by as much as a 142% increase in average length of fiber tracts within the right hemisphere alone, relative to a baseline scan performed shortly after the TBI[13]. A 112% increase in the overall number of fiber tracts was also observed[13]. While DTI may be an effective tool in tracking white matter changes in the brain, additional studies utilizing the imaging technique for the examination of OD, in particular, are needed[13].

SENSORY LOSS AND DEPRESSION

Depression is common in the population, with estimates that 8%-12% of individuals in the United States will be affected by depression at least once in their lifetime[39]. The 2017 study published by the National Survey on Drug Use and Health revealed that the prevalence of a major depressive episode in adult females (8.7%) was significantly higher than adult males (5.3%) when accounting for sex, and that the 18-25 age bracket is home to the highest prevalence rate (13.1%) when accounting for age. In addition, individuals who reported two or more races had the highest rates (11.3%) when accounting for race[40]. In 2017 alone, 4.5% of the United States adult population experienced at least one major depressive episode with severe impairment, which also made up approximately 64% of major depressive episodes[40]. These statistical trends continue when looking at adolescents, but all of the prevalence rates are increased[40]. This shows that depression is still a prevalent issue in society and most people who are experiencing depressive episodes have severe impairment.

The literature also illustrate links between sensory loss, specifically olfactory functioning, and various mental health conditions including schizophrenia[17,39]. Deems *et al*[41] studied the relationship between depression scores and OD patients revealed that sensory dysfunction influences quality of life[41]. Subsequent studies have been conducted to explore the relationship between depression and OD. However, most of these studies have shown mixed results, which is likely related to inconsistency within the study populations[17,39,42]. While some studies focused on people reporting primary olfactory loss, others included patients with primary depression.

Despite the need for ongoing research to clarify the exact relationship between OD and depression, we can still deduce many things from this relationship. We know that when the olfactory bulb suffers from reduced input, there is a clear negative relationship with neurotransmitter concentration, leading to the potential disturbance

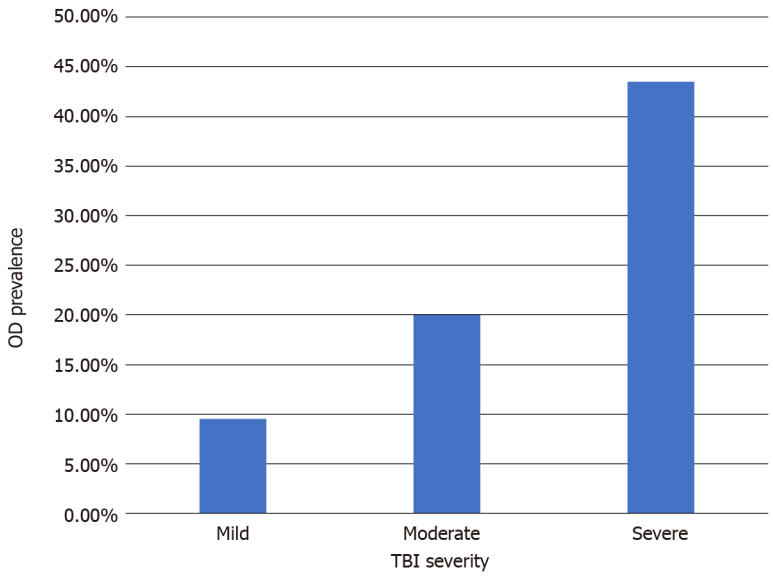

Figure 1 Olfactory disturbance prevalence by traumatic brain injury severity. OD: Olfactory disturbance; TBI: Traumatic brain injury.

of emotional functioning[18]. Additionally, olfactory functions are highly involved in emotion and memory due to signal exchanges from the olfactory bulb to the hippocampus and amygdala[39]. There is also a correlation between OD and depression symptoms that is mediated by the severity of the loss of smell[17]. Based on longitudinal studies, there is a predictive relationship between one month follow up parosmia scores and six month follow up depression and anxiety scores[42]. It has also been demonstrated that treatment for OD can lead to a decrease in depression scores, even if more replication is needed to increase confidence in that claim[39]. There is also evidence for clinicians to include both affective and olfactory assessments in TBI cases, as it can aid in the prediction of affective outcomes[42]. In summary, there is a bidirectional relationship between sensory loss and depression.

In addition, the recent coronavirus disease 2019 (COVID-19) pandemic has led to some further development in research, especially in the context of sensory loss. It is well known to most that sensory loss, primarily smell and taste, is among the more prevalent symptoms of COVID-19[43]. Other neurological injuries can also occur following COVID-19 infection, including strokes, that can impair affective and sensory functioning[44]. While researches on reinfection rates, mortality predictors, and electrocardiogram readings are still being investigated, there are affective concerns that should continue to be addressed[45-47]. Within the context of affective distress with known COVID-19 related symptoms including anosmia, self-care remains critical prior to regain of function back to baseline[48]. It is worth investigating whether this COVID-19 related sensory loss will hold the same link between olfactory sensory loss and long-term affective distress as discussed above.

TBI AND DEPRESSION

TBI accounted for nearly 3 million ED visits in 2014, which was up from 1.2 million in 2006, and has been experiencing steady increases in its annual death rate and hospitalization rates[1,9]. Recent estimates show that the annual financial cost of TBI associated problems is more than 56 billion dollars[22]. In addition to this great financial cost, there is also a high risk of developing symptoms of depression, impaired life satisfaction, and various chronic disabilities[2,19-23,49]. Once the age bracket where TBI is most common (age 75+) is compared to the prevalence rates of depression (ages 18-25), it is easy to see these risky age groups tend not to overlap[2,23,40]. Despite this, we are seeing an increase in depressive rates within TBI patients which tend to be significantly different than the general population rates. Depression also negatively impacts proper recovery trajectory after a TBI[19].

Within TBI patients, some experience a LOC and others do not lose consciousness, with the odds of experiencing a TBI with LOC increasing based on several factors, including TBI severity and various biological and social factors[20,22,50]. One study that analyzed the 2014 data from the Ohio Behavioral Risk Factor Surveillance System

showed that 21% of adults reported to have at least one TBI with LOC in their lifetime [50]. That same study showed that various factors associated with an increased reporting of TBI with LOC included lower income, being male, age, and unemployment status[50]. Additional studies have shown that TBI (both with and without LOC) contributes to increased depressive symptoms, lower cognitive functioning, and risk for lifelong neuropsychiatric concerns[20].

It is critical for clinicians to better understand the relationship between TBI and MDD in order to better serve their patients and assist the patients on their road to recovery. Even though many physicians are aware of the link between these two diagnoses, the diagnosis of MDD when a patient is experiencing disturbed mood after a TBI remains a more complex concern. Due to the additional diagnostic criteria of MDD and the differential diagnosis between MDD and the other depressive disorders, many physicians can easily misdiagnose a TBI patient's affective concerns[21]. More research is needed in this area to show how to qualitatively and quantitatively improve the accuracy of mood disturbance diagnoses within TBI patient population.

CONCLUSION

As one of the world's leading causes of death and disability, TBI is a highly complex clinical phenomenon. With the bidirectionality of sensory loss and depression, as they are among some of the more common clinical sequelae of TBI, these clinical presentations themselves further complicate posttraumatic prognosis and related treatment planning. In milder injuries, said symptoms can be assessed to assist in differentials, prognostic implications, and guidance for acute therapeutic regimen. In more moderate and severe injuries with permanent injury sequelae, said symptom assessments can also assist with long term care planning, along with guided therapeutics for quality of life improvement. As the literature continues its pursuit in the study of TBI mechanisms, it remains imperative that direct and peripheral symptoms like olfaction and related gustation, affective distress, and their bidirectional implications are continuously investigated, beyond the traditional pathophysiological mechanisms. As this study was formatted as a focused topic narrative review to investigate TBI related sequelae, the study is limited in the quantity of systematically reviewing the TBI variables highlighted in this study. Recommendations for future studies include systematic analyses and review of the literature, meta-analyses, and controlled studies to further assess the bidirectionality of sensory loss and affective distress in TBI.

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MINIREVIEWS

Physical activity and mental well-being during COVID-19 pandemic

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Abstract

The corona virus disease 2019 (COVID-19) pandemic has resulted in most nations deciding upon self-isolation and social distancing policies for their citizens to control the pandemic and reduce hospital admission. This review aimed at evaluating the effect of physical activity on mental well-being during the COVID-19 pandemic. It was concluded that the COVID-19 pandemic may lead to augmented levels of angiotensin-converting enzyme (ACE)-2 that led to cardiovascular and neurological disorders associated with highly inflammatory effects of viral infection affecting the brain tissues leading to damage of the nervous system and resulting in cognition dysfunction, insulin sensitivity reduction, and behavioral impairments. Anxiety and depression may lead to negative effects on various quality of life domains, such as being physically inactive. Regular physical activities may reduce inflammatory responses, improve ACE-2 responses, and improve mental well-being during self-isolation and social distancing policies related to the COVID-19 pandemic. Further studies should be conducted to assess the different intensities of physical activities on cardiovascular function, and mental well-being during the COVID-19 pandemic.

Key Words: COVID-19; Physical activity; Mental well-being; Pandemic; Angiotensin-converting enzyme-2

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Core Tip: The corona virus disease 2019 (COVID-19) pandemic has resulted in most nations deciding upon self-isolation and social distancing policies for their citizens to control the pandemic and reduce hospital admission. This review aimed at evaluating the effect of physical activity on mental well-being during the COVID-19 pandemic. COVID-19 may lead to cardiovascular and neurological disorders associated with inflammatory effects of viral infection affecting brain tissues, leading to nervous system damage and cognitive dysfunction, insulin sensitivity reduction, and behavioral impairments. Regular physical activities may reduce inflammatory responses, improve angiotensin-converting enzyme-2 responses, and mental well-being during self-isolation and social distancing.

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INTRODUCTION

The corona virus disease 2019 (COVID-19) pandemic caused by the novel coronavirus SARS-CoV-2 appeared in China in 2019[1]. The infection probably resulted from a usual assortment of animal hosts prior to zoonotic spread that affected populations worldwide and caused thousands of deaths[2]. Through a cellular membrane receptor known as angiotensin-converting enzyme-2, SARS-COV-2 influences host cells, affects lungs with insufficient oxygen supply, and accordingly may affect cardiac and brain tissues[3]. With the rapid progress of COVID-19, most nations decided upon self-isolation and social distancing policies for their citizens and residents to control the pandemic and reduce hospital admission, with a recommendation of self-isolation and social distancing to successfully control the pandemic outbreak[4].

At this time, it is important for all populations to understand the local characteristics of COVID-19 transmission and social distancing policy as the transmission of COVID-19 is predicted to occur up to 2024, and intermittent or extended social distancing may be continued to 2022 and will cause major lifestyle changes among people worldwide[5]. Therefore, it is doubtful during these policies that individuals can continue their sedentary behaviors to maintain their healthy condition[6]. Government policies of social isolation and distancing during the COVID-19 pandemic can increase disturbance of mental health, including anxiety and depression[7]. Figure 1 presents the negative effects of the COVID-19 pandemic on physical activity and mental health.

Nutritional deprivation may affect cognitive status and lead to mood disorders[8]. Poor physical activity levels during COVID-19 quarantine can also lead to sedentary behaviors that could lead to the development of chronic cardiovascular, metabolic and mood disorders[9,10]. Several studies have reported that regular physical activity and exercise training are considered effective nonpharmacological interventions in several chronic disorders[9].

MENTAL HEALTH AND COMMUNITY

Generally, the development and prevalence of mental health impairments are associated with social and physical determinants[11]. Community service integration may promote awareness of mental well-being, reduce discrimination and stigma, support social recovery, and prevent mental dysfunction[12,13].

International guidelines accentuate community care for mental well-being and the World Health Organization also has suggested stipulations of integrated and comprehensive social care for mental well-being, including prevention and interventional protocols in the community incorporating the perceptions of families and service providers[14]. It is reported that individuals with psychological impairment should be encouraged to live without assistance among populations[15].

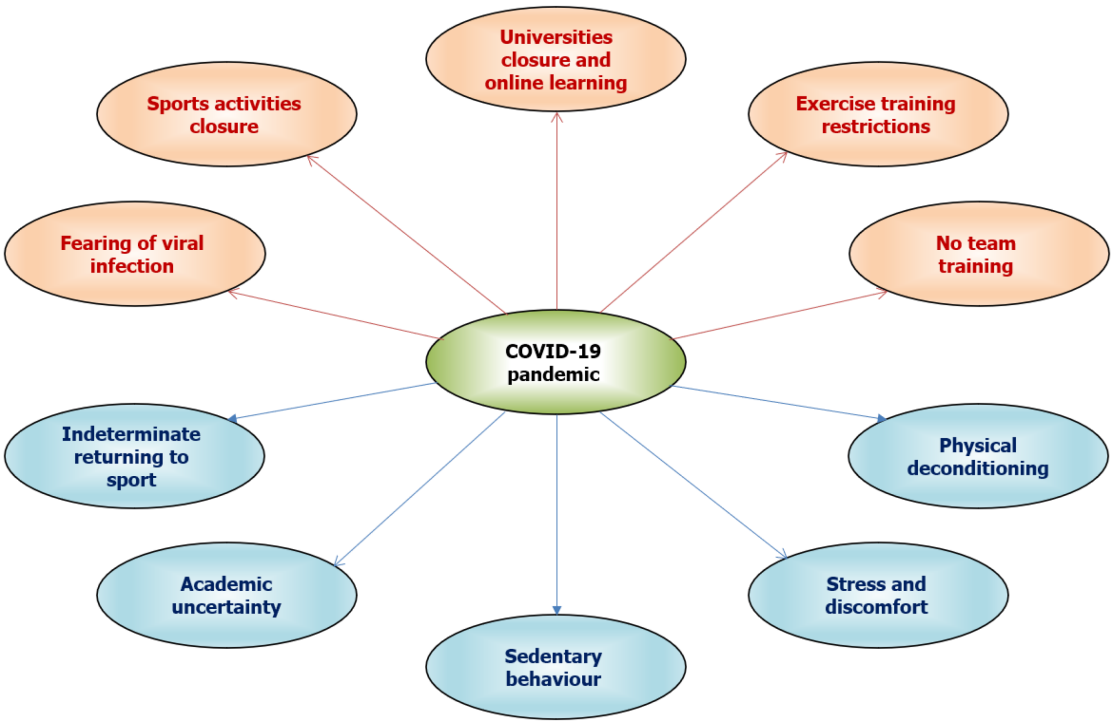

Figure 1 Negative effects of COVID-19 pandemic on physical and mental well-being.

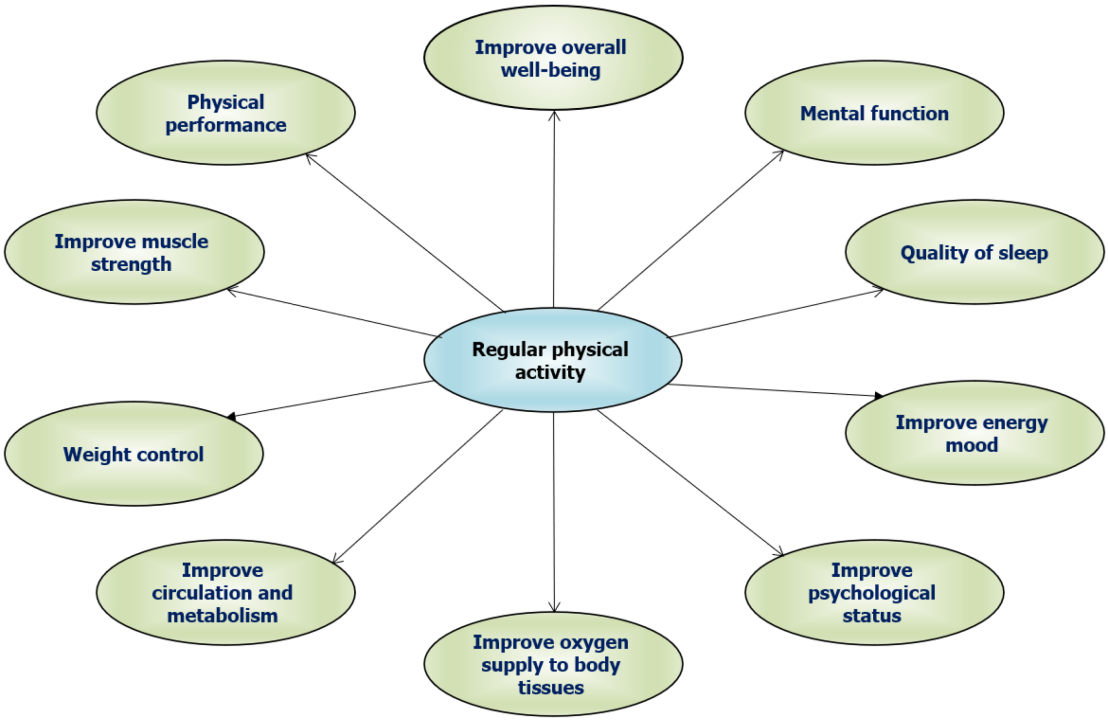

Figure 2 Positive effects of regular physical activity on physical and mental well-being.

NEUROLOGICAL MANIFESTATIONS RELATED TO COVID-19

Brain tissues may be affected by viral infection due to infected nerve cells through infected vascular endothelium, or leukocyte migration into the brain circulation[16]. Although headache and anosmia are the major prevalent neurological disorders related to COVID-19, neurophysiological impairments have been documented, including encephalopathy, seizures, consciousness impairment, and stroke[17,18].

Table 1 Physical activity and mental health during COVID-19 pandemic

Refs	Measures	Findings and recommendations
Wright *et al* [32], 2021	Incidence of fear, physical activity, and mental well-being indicators questionnaires	Physical activity may improve mental well-being and protect against the undesirable impacts of COVID-19. Regular physical activities should be encouraged to improve mental well-being during COVID-19 pandemic.
Xiao *et al* [33], 2021	Lifestyle and home environment, physical and mental well-being, and occupational environment questionnaires	Significant reduction in physical and mental well-being including impaired physical activity, increased junk food intake, and absence of coworker communications
Faulkner *et al* [34], 2021	Short form of IPAQ, WHO-5 well-being index, and depression, anxiety and stress scale-9	Negative changes in physical activity before COVID-19 containment policies presented poor mental well-being, while positive physical activity behavior showed better mental well-being
Meyer *et al* [35], 2020	Self-reported physical activity, anxiety and depression status, social connection, loneliness, and stress	Adherence to physical activity contributions and restrictive screening time during unexpected societal alterations may alleviate the consequences of mental well-being
Carriedo *et al* [36], 2020	International Physical activity questionnaire (IPAQ), 6-item self-report scale of depression symptoms, Connor-Davidson CD-RISC resilience scale, and positive and negative affect schedule	Regular moderate or vigorous physical activity provide positive resilience and reduce depression symptoms during COVID-19 quarantine
Maugeri *et al* [37], 2020	IPAQ and psychological general well-being index	Reduced physical activity have a greatly undesirable effects on psychological status and mental well-being. Adherence to a regular physical activity program is the main approach for improving physical and mental well-being during COVID-19 confinement.
López-Bueno *et al*[38], 2020	Short form of physical activity vital sign and single-item question for mood and anxiety	Adherence to regular physical activities associated with better mood and lower anxiety with WHO recommendations during COVID-19 quarantine
Duncan *et al* [39], 2020	Online survey on perceived changes in physical activity due to COVID-19 mitigation and mental well-being using 10-item perceived stress scale and 6-item anxiety subscale	COVID-19 mitigation policies may affect physical activity and mental well-being. Participants with reduced physical activity levels showed higher anxiety and stress levels.
Jacob *et al* [40], 2020	Self-reported physical activity questionnaire, Beck anxiety and depression inventories, and 7-item short Warwick-Edinburgh mental well-being scale	During COVID-19 social distancing, participants adherent to vigorous and moderate physical activity showed better mental well-being

COVID-19: Corona virus disease 2019.

It was reported that approximately 36% of COVID-19 patients suffered from neurological symptoms such as impaired consciousness and cerebrovascular disorders associated with inflammatory effects of viral infection[19]. This inflammation may affect the brain tissues leading to damage of the nervous system and cognitive dysfunction, insulin sensitivity reduction, and behavioral impairments[20]. Also, these inflammatory reactions associated with viral infection may develop primitive neurological manifestations[21].

Due to impaired neural plasticity, the initial fatality of nerve cells, and disturbed neurotransmitter production, psychoses, impaired memory, and post-traumatic stress disorders may occur with COVID-19[22]. In addition, angiotensin-converting enzyme (ACE)-2 is expressed with COVID-19 in several brain areas, such as the olfactory system, striatum, and cortex, and on various types of nerve cells such as astrocytes, microglia, neurons, and oligodendrocytes[23]. The primary projected mechanism that affects the function of the nervous system is ACE-2 activation associated with COVID-19 through augmentation of inflammatory responses[20,23].

PHYSICAL ACTIVITY AND MENTAL HEALTH

A recent cross-sectional study found that individuals who conducted a regular physical exercise for one month had good life satisfaction during quarantine, while the individuals who stayed at home and without physical exercise suffered from poor health conditions[24]. It was also reported that isolation and social distancing related to COVID-19 led to a greater incidence of anxiety and depression[25]. Accordingly, these reports suggest that individuals who conducted physical exercise during COVID-19 should be regularly observed as they may be particularly irritated by self-isolation. Therefore, exercise training for a long time does not indicate good mental well-being, but it may be a predictor of developing mood disorders[25].

It can be assumed that overtraining or prolonged exercise training may lead to pessimistic health conditions such as mood disorders[20]. The quarantine associated with COVID-19 may increase the development of a sedentary lifestyle among different populations including adolescents[26]. Regular exercise training improves immune function, lowers the severity of symptoms, and reduces the mortality rate in individuals exposed to viral infection[10]. Conducting physical activity or sports during the COVID-19 pandemic may provide a complementary and alternative treatment to develop mental well-being[27].

It is documented that COVID-19 may be associated with neurotropism, neuroinvasion, and neuroinflammation that could clearly affect the outcomes of mental well-being including acute myelitis, cerebrovascular disorders, encephalitis, and encephalopathy[28]. Several exercise training programs and different laboratory investigations should be conducted to assess the influence of exercise training on COVID-19 and how it prevents disturbances of mental well-being. Regrettably, studies that suggest or explain the ideal exercise protocol conducted during the COVID-19 pandemic and its influence on mental and cardiovascular well-being are limited, and therefore the relationship between exercise training, cardiovascular function, and mental well-being should be investigated.

Anxiety and depression are the most frequent mental disorders, with varied incidence rates among different ages, including adults, adolescents, children, and particularly aged individuals[29]. It is reported that anxiety and depression may lead to negative effects on various quality of life domains, such as being physically inactive [30]. The pathophysiology of anxiety and depression is still not clearly explained, and an abundance of biomarkers have been recommended to identify the sequences and development of mental disorders[30,31].

Recent studies have proved that adherence to physical activities and exercise training programs during COVID-19 quarantine is associated with better mental health and lower anxiety and depression levels. However, poor physical activity levels are associated with higher levels of anxiety and depression in addition to poor mental health and well-being[32-40] (Table 1).

Exercise training and physical activity have been suggested as nonpharmacological interventions to eliminate the complications associated with self-isolation and social distancing during the COVID-19 pandemic [27]. The effects of different exercise programs are not being clearly investigated during the COVID-19 pandemic. Physical activity may improve mental well-being and protect against the undesirable impacts of COVID-19. Regular physical activities should be encouraged to improve mental well-being during the COVID-19 pandemic[32-40]. Figure 2 shows the positive effects of regular physical activity on physical and mental well-being.

CONCLUSION

The COVID-19 pandemic may lead to augmented levels of ACE-2 that led to cardiovascular and neurological disorders associated with inflammatory effects of viral infection, affecting the brain tissues and leading to damage to the nervous system and cognitive dysfunction, insulin sensitivity reduction, and behavioral impairments. Anxiety and depression may lead to negative effects on various quality of life domains, such as being physically inactive. Regular physical activities may reduce inflammatory responses, improve ACE-2 responses and mental well-being during self-isolation and social distancing related to the COVID-19 pandemic. Further studies should be conducted to assess the different intensities of physical activities on cardiovascular function, and mental well-being during the COVID-19 pandemic.

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ORIGINAL ARTICLE

Basic Study

Differential aberrant connectivity of precuneus and anterior insula may underpin the diagnosis of schizophrenia and mood disorders

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Abstract

BACKGROUND

Over the past decade, resting-state functional magnetic resonance imaging (rs-fMRI) has concentrated on brain networks such as the default mode network (DMN), the salience network (SN), and the central executive network (CEN), allowing for a better understanding of cognitive deficits observed in mental disorders, as well as other characteristic psychopathological phenomena such as thought and behavior disorganization.

AIM

To investigate differential patterns of effective connectivity across distributed brain networks involved in schizophrenia (SCH) and mood disorders.

METHODS

The sample comprised 58 patients with either paranoid syndrome in the context of SCH (n = 26) or depressive syndrome (Ds) (n = 32), in the context of major depressive disorder or bipolar disorder. The methods used include rs-fMRI and subsequent dynamic causal modeling to determine the direction and strength of connections to and from various nodes in the DMN, SN and CEN.

RESULTS

A significant excitatory connection from the dorsal anterior cingulate cortex to the anterior insula (aI) was observed in the SCH patient group, whereas inhibitory connections from the precuneus to the ventrolateral prefrontal cortex and from the aI to the precuneus were observed in the Ds group.

CONCLUSION

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The results delineate specific patterns associated with SCH and Ds and offer a better explanation of the underlying mechanisms of these disorders, and inform differential diagnosis and precise treatment targeting.

Key Words: Schizophrenia; Major depressive disorder; Bipolar disorder; Resting-state functional magnetic resonance imaging; effective connectivity; precuneus; insula; default mode network; salience network

Core Tip: The present study reports a significant excitatory connection from the anterior cingulate cortex to the anterior insula (aI) that was observed in the schizophrenia patient group, whereas inhibitory connections from the precuneus (Pc) to the ventrolateral prefrontal cortex and from aI to Pc were observed in the major depressive episode group. The results delineate specific aberration patterns which correspond to the clinical presentations of the nosological units and can further contribute to a better explanation of the underlying mechanisms of these disorders as well as to inform differential diagnosis and precise treatment targeting.

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INTRODUCTION

Schizophrenia (SCH) is one of the most devastating and socially important diseases, as well as one of the most poorly understood mental conditions that affects people typically in late adolescence/early adulthood and leads to a functional decline in the personal, social and economic aspects of those affected[1]. Although psychotic symptoms, such as delusions and hallucinations, are the most commonly associated behavioral manifestations of SCH, it is primarily a cognitive disorder[2] with an established specific disability profile in terms of cognition and psychosocial dysfunction, and some authors recommend using that as a special differential diagnostic criterion in existing diagnostic instruments[3-5]. However, mood disorders are also often accompanied by serious cognitive deficits[6,7] and these deficits often persist well after symptomatic relief. Furthermore, the most severe cognitive deficits in patients with depressive syndrome (Ds) have been identified in the same cognitive domains as those seen in SCH spectrum disorders, including concentration, memory and executive functions[7-9].

Unlike other diseases, mental illnesses are classified into diagnostic categories based on top-down, phenomenologically derived criteria. The clinical manifestations of psychiatric disorders are not only multifaceted but also characterized by a high incidence of symptom overlap[10]. As a result of their poor biological validity concerning their etiology due to the limited knowledge about the exact pathological processes, the assessment methods in psychiatry exist outside of the traditional medical framework[11,12]. The contemporary gold standard, represented by the Diagnostic and Statistical Manual of Mental Disorders 5th edition[13] and the International Classification of Diseases X division[14] taxonomies, appears to have a lot of inconsistencies[12]. Thus, the use of those manuals leads to the conclusion that mental illnesses often have high rates of comorbidity, heterogeneity, and presence of intermediate cases[12]. For example, studies show that around half of the SCH cases exhibit symptoms that can be fitted into the category of a Ds[15,16]. In contrast to the presence of a single mental disorder, the presence of two or more mental illnesses is related to increased severity, inadequate pharmacological treatment response, and a substantial suicide risk[17]. This, along with a lack of comprehensive knowledge about the neural and molecular mechanisms that underpin behavioral deviations, explains the therapeutic failures in SCH and mood disorders. All the above-mentioned

inconsistencies highlight the imperative need to identify diagnostic biomarkers in psychiatry.

Functional magnetic resonance imaging (fMRI) in psychiatric research is often used to collect signals from brain regions indicating blood oxygen level dependent changes in response to cognitive tasks [task-related fMRI (tr-fMRI)]. Those kinds of studies suggest impaired brain activity during cognitive load involving language, memory, and concentration in patients with mental illness[18-21].

In contrast, resting-state fMRI (rs-fMRI) is a popular instrument for macroscale functional connectomics that can localize low-frequency differences in random brain functions representing interindividual variations in brain activity and mind–brain interactions found in different psychiatric disorders[22]. Over the past decade, rs-fMRI has concentrated on brain networks such as the default mode network (DMN), the salience network (SN), and the central executive network (CEN), allowing for a better understanding of cognitive deficits observed in SCH and mood disorders, as well as other characteristic SCH phenomena such as thought and behavior disorganization [23].

In a previous study[24], we investigated the rs-fMRI effective connectivity in SCH patients with paranoid syndrome and patients with mood disorders with Ds. In addition, in the same sample, we performed tr-fMRI of the von Zerssen's Paranoid-Depressive Self-Assessment Scale[25], which consists of paranoid-specific, depressive-specific and neutral items. An example of a paranoid-specific item on the scale is "Other people constantly follow and control me", and an example of a depressive-specific item is "I often feel simply miserable". The results from tr-fMRI show that the areas that are activated in SCH patients during paranoid-specific items, including the precuneus (Pc) and the posterior cingulate cortex are parts of the DMN, whereas the results for the Ds sample in the same study did not yield any significant clusters of activations. The results from the resting state effective connectivity, however, informed an inhibitory connection from the prefrontal cortex (PFC) to the anterior insula (aI) in the SCH group, which was completely absent in the Ds group. These data led us to assume that disrupted connectivity from the PFC⇒aI at rest may contribute to impaired cognitive functions, behavioral disorganization, and functional disability in people suffering from SCH[26]. Furthermore, the observed DMN activation during the task might be indirect evidence of the inhibitory connection from the PFC⇒aI at rest, which could interfere with the balancing function of the SN as a dynamic switch between the DMN and CEN[24,27].

As the Pc is an integrated element in the DMN and the aI is a central hub in the SN, we hypothesize that functional disruptions in those regions are linked to behavioral abnormalities and cognitive deficits in psychotic disorders. The DMN is characterized by a high baseline firing rate at rest and deactivation at cognitive tasks onset[28]. As the DMN is described as a network that normally activates at rest[29], little is known about the exact mechanisms by which the DMN is activated in SCH patients during the performance of a task. Therefore, our goal was to identify specific patterns in the resting-state effective connectivity of the SN and DMN in the SCH and Ds groups that could explain the behavioral deficits observed in both the paranoid and Ds groups, as well as to test whether these deficits share common or distinct neuropatho-physiological patterns.

We decided to test whether at rest, when patients are instructed not to think about anything specific, there was altered connectivity between the components of the SN and DMN, comparing two disease units – SCH (paranoid syndrome) *versus* mood disorders (Ds).

Hence, the present study was conducted to delineate the effective connectivity patterns at rest with a prior hypothesis that the SN in SCH must have a fundamentally impaired connectivity, which prevents the switching between DMN and CEN, thereby interfering with their basic functions. Our motivation to conduct such a comparative study came from the aforementioned discrepancies, which arise from the lack of biological validity of available diagnostic tools, which ultimately leads to inaccurate diagnosis or high comorbidity in psychotic and affective disorders. By proving neurobiological markers to distinguish the two disorders, we aimed to expand knowledge about their etiology and incorporate it into clinical practice, ultimately optimizing diagnosis and prognosis, and thus choosing the right treatment for these severe mental illnesses.

MATERIALS AND METHODS

Participants

For the current study, we recruited 58 patients, namely 26 with a paranoid syndrome –in the context of SCH (mean age 39.2 ± 13.2 years, 13 male) and 32 with Ds (mean age 42.9 ± 11.7 years, 10 male) – in the context of major depressive disorder (MDD) (n = 14, mean age 42.4 ± 12 years, 5 male), or bipolar disorder (BD) (n = 18, mean age 43.3 ± 11.8 years, 5 male) – according to the diagnostic criteria of DSM IV Text Revision[30]. The assessment of the participants was performed by experienced psychiatrists (DS, SK and KA) using the general clinical interview[31], the structured Mini-International Neuropsychiatric Interview (M.I.N.I. 6.0)[32], and clinical global impression scale[33]. The positive and negative syndrome scale[34] was chosen for the assessment of the SCH group. A minimum rating of 3 on P1 (delusions) and/or P6 (suspiciousness) was set to secure a reasonable severity of the episode. The severity of the depressive episode was assessed using the Montgomery–Åsberg Depression Rating Scale[35]. A cut-off value of 20 was chosen, which is considered to constitute a DS of moderate severity. Both clinical groups were on stable medication for at least 14 d.

The requirements for participation were the following: age > 18 and < 65 years; lack of metal implants (*e.g.*, pacemaker); absence of comorbidity with other psychiatric disorders (substance use disorders, anxiety disorders, *etc.*); and absence of severe neurological disorders or traumatic brain injury with loss of consciousness. Psychiatric history was further considered as a source of information to supplement the exclusion criteria. Each of the patients provided a written informed consent complying with the Declaration of Helsinki. The protocol of the study was approved by the University's Ethics Committee (ID: P-369/29.05.2015).

Image acquisition

Subjects were scanned on a 3T MRI system (GE Discovery 750w) and the protocol included the following sequences: (1) high-resolution structural scan (Sag 3D T1 FSPGR, slice thickness 1 mm, matrix 256 × 256, relaxation time (TR) 7.2 ms, echo time (TE) 2.3 ms, flip angle 12; and (2) resting-state functional scan-2D echo planar imaging (EPI), with slice thickness 3 mm, matrix 64 × 64, TR 2000 ms, TE 30 ms, 36 slices, flip angle 90, a total of 192 volumes. Before the EPI sequence, subjects were instructed to remain as still as possible with eyes closed and not to think of anything.

Resting-state data analysis

The SPM 12 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/) software running on MATLAB R2020b for Windows was used to perform data analysis. During the preprocessing of the EP images, they were realigned, co-registered with the structural scans, normalized to Montreal Neurological Institute (MNI) space, and smoothed with a 6-mm full-width-at-half-maximum Gaussian kernel.

First-level resting-state analysis was conducted using a general linear model applied to the time series. Regions of interest (ROIs) were predefined based on their involvement in the SN and the DNM with 6-mm radius spheres. The ROIs with their MNI coordinates are presented in Table 1.

These five ROIs were subjected to spectral dynamic causal modeling (spDCM). We used a completely connected model, which meant that each node was linked to the others. A spectral DCM, in contrast to a stochastic DCM, measures effective connectivity from the cross spectra of changes in neuronal states rather than directly from their time courses[36]. Furthermore, using the parametric empirical bayes method introduced in SPM12, the individual spDCM models were jointly estimated. Finally, the estimated spDCM models were used to extract connectivity strengths (A-matrix) for further statistical analysis in SPSS.

Statistical analysis

Statistical analysis of the demographic and clinical characteristics of the participants, as well as of the connectivity strengths of the spDCM model were performed using SPSS for Windows 22.0. The level of significance was set to $P < 0.05$, two-tailed, for all tests. Student's t test was used for continuous variables and the χ^2 test for categorical variables. The normality of distribution of the coupling values was tested with the Shapiro–Wilk test and the significance of all tests was set at 0.05.

Table 1 Regions of interest with their Montreal Neurological Institute coordinates

Region of interest	X	Y	Z	Brodmann area
DLPFC (left)	-28	46	26	46
VLPFC–opercular part of the IFG (left)	-41	19	41	44
dACC (left)	0	32	26	24
aI (left)	-36	14	-4	48
Pc (left)	-10	-54	30	23

DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; IFG: Inferior frontal gyrus; dACC: Dorsal Anterior cingulate cortex; AI: Anterior insula; Pc: Precuneus; X, Y, Z: Montreal Neurological Institute coordinates.

RESULTS

Demographic and clinical characteristics

There were no significant differences in age, sex, age of onset, episode duration, and education level between SCH and Ds patients. The clinical characteristics of the whole patient sample are given in detail in Table 2. The two subgroups of Ds (bipolar and unipolar) did not differ significantly in their demographic or clinical variables (Table 3).

Resting-state results

We performed the analysis as described above and received various connections between the ROIs. The significant connections are described below within the different groups of patients and between them.

Resting-state effective connectivity in patients with Ds: The coupling connectivity strengths that significantly differed from zero in the group of patients with Ds are presented in Table 4 and Figure 1. There were 15 significant both inhibitory and excitatory connections mainly engaging the prefrontal and parietal regions.

Resting-state effective connectivity in SCH patients: The results from the one-sample *t* test in the SCH group yielded seven connections that were significantly different from zero. These connections were presented mostly by SN regions and the Pc, as well as self-inhibition of the dorsal anterior cingulate cortex (dACC). The ventrolateral prefrontal cortex (VLPFC) did not present in any of the significant connections. A detailed description of the results is given in Table 5 and Figure 2.

Differences in the resting-state effective connectivity between SCH and Ds patients: To explore the differences between the two groups, independent samples *t* tests comparing the mean connectivity strengths were performed. The coupling strengths of the connection from the Pc to VLPFC and from the aI to the Pc, both inhibitory connections, were present in the Ds group but absent in the SCH group. In the SCH patients, a significant excitatory connection from the dACC to aI was present that was absent in the Ds group (Figure 3).

The findings of this study suggest that physicians treating patients with SCH and Ds should communicate with their patients that their illness is characterized by alterations in brain connectome data, which in part may explain their symptoms.

DISCUSSION

Our analysis of the rs-fMRI data demonstrated that, in the patients with Ds, significant excitatory influence was exerted dorsolateral prefrontal cortex (DLPFC)⇒Pc, DLPFC⇒dACC, dACC⇒Pc, dACC⇒DLPFC and VLPFC⇒Pc, while inhibitory influences were exerted Pc⇒dACC, Pc⇒VLPFC, Pc⇒DLPFC, aI⇒Pc, aI⇒VLPFC, and VLPFC⇒dACC and self-inhibition of the VLPFC, dACC and aI.

In the SCH patients, significant effective connectivity, that is, causal interaction in terms of excitatory influence, was exerted dACC⇒aI, dACC⇒DLPFC and DLPFC⇒aI, whereas inhibitory influences were exerted Pc⇒dACC, Pc⇒DLPFC and aI⇒dACC, and self-inhibitory influence of the dACC. The VLPFC in the SCH group did not participate in any interactions with the other ROIs.

Table 2 Demographic and clinical characteristics of all participants

	SCH patients (*n* = 26)	Ds patients (*n* = 32)	*P* value
Age (mean ± SD)	39.2 ± 13.2	42.9 ± 11.7	0.448[1]
Sex (M/F)	13/13	10/22	0.115[2]
Education (years)	13.6 ± 3.1	13.5 ± 3.2	0.871[1]
Age at onset (years)	25.8 ± 8	32.1 ± 11.8	0.060[1]
Episode duration (weeks)	19.6 ± 28	13.7 ± 16.8	0.159[1]

[1]Independent samples *t* test.
[2]χ^2 test, $P < 0.05$.
SCH: Schizophrenia; Ds: Depressive syndrome; SD: Standard deviation.

Table 3 Demographic and clinical characteristics of the two depressive syndrome subgroups

	MDD patients (*n* = 14)	BD patients (*n* = 18)	*P* value
Age (mean ± SD)	42.4 ± 12	43.3 ± 11.8	0.286[1]
Sex (M/F)	5/9	5/13	0.712[2]
Education (years ± SD)	14.6 ± 3.8	12.8 ± 2.6	0.197[1]
Age at onset (years)	30 ± 12	31.5 ± 12	0.734[1]
Episode duration (weeks)	8.8 ± 9.3	17 ± 20	0.197[1]

[1]Independent samples *t* test.
[2]χ^2 test, $P < 0.05$.
MDD: Major depressive disorder; BD: Bipolar disorder; SD: Standard deviation.

However, the main findings from the comparison between the two groups can be summarized as follows: (1) In the Ds group, during rs-fMRI, there was strong involvement of the Pc, which is the central hub of the DMN. There was an inhibitory connection from the aI to the Pc and from the Pc to the PFC; and (2) In the SCH group, during rs-fMRI, there was no DMN activity but instead, there was an excitatory connection from the anterior cingulate cortex to the aI regions that compose the SN.

Concerning the significant deviations observed in the patients with Ds, the following can be discussed. The Pc is a central node of the DMN[37] that becomes more involved during rest when the mind is in a task-free state[38] and its altered function has long been thought to be a neuronal substrate for depression[39]. It plays an important role in the integration of mental processing through its participation in cognitive control functions including visual imagery, episodic memory, and self-directed processes. The observed inhibitory influence from Pc⇒PFC could be related to increased internal ruminating thoughts that are a characteristic trait in patients suffering from Ds[40].

The VLPFC is a component of the PFC that is situated on the inferior frontal gyrus (IFG) that belongs to Brodmann's field 44, which we included as an ROI in our study. Our results demonstrate that, in the Ds group, the DMN exerted an inhibitory influence upon the PFC (particularly the IFG). Studies on the therapeutic effect of ketamine, which is one of the most effective known treatments in the management of suicidality and self-injurious behavior[41,42], show that ketamine normalizes alterations in this area, namely on its opercular part (which was examined in the current study – Broadman's field 44)[43].

The rapid effect of ketamine, which is most likely due to its action on the IFG, conjoined with the lack of consistency in the improvement of the condition, indicates that the disturbances in the IFG might be secondary. Our results suggest a model in which the Pc is the primary component responsible for the secondary deficiencies in the IFG function. We hypothesize that the effect of ketamine may be prolonged by combining it with a therapeutic method that acts directly on the Pc, which would ultimately lead to a normalization of the altered effective connectivity (inhibition of Pc ⇒IFG) and thus an improvement in IFG function. Such a suitable therapeutic tool could be the repetitive transcranial magnetic stimulation (rTMS)[10], whose effects can

Table 4 Connections significantly different from zero in the depressive syndrome group

Connections	Mean	*P* value
dACC→DLPFC	0.146	0.029[a]
Pc→DLPFC	-0.239	0.002[b]
VLPFC⊃	-0.185	0.002[b]
dACC→VLPFC	0.180	0[c]
aI→VLPFC	-0.250	0.002[b]
Pc→VLPFC	-0.177	0.007[b]
DLPFC→dACC	0.212	0.004[b]
VLPFC→dACC	-0.181	0.02[a]
dACC⊃	-0.160	0.007[b]
Pc→dACC	-0.228	0.006[b]
aI⊃	-0.216	0.003[b]
DLPFC→Pc	0.090	0.047[a]
VLPFC→Pc	0.133	0.029[a]
dACC→Pc	0.090	0.049[a]
aI→Pc	-0.284	0[c]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
⊃: Self-inhibitory connection; DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; IFG: Inferior frontal gyrus; dACC: Dorsal anterior cingulate cortex; AI: Anterior insula; Pc: Precuneus.

Table 5 Connections significantly different from zero in the schizophrenia group

Connections	Mean	*P* value
dACC→DLPFC	0.172	0.004[b]
Pc→DLPFC	-0.384	0.001[b]
dACC⊃	-0.189	0.009[b]
aI→dACC	-0.303	0.013[a]
Pc→dACC	-0.366	0.001[b]
DLPFC→aI	0.110	0.039[a]
dACC→aI	0.126	0.026[a]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
⊃: Self inhibitory connection; DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; dACC: Dorsal Anterior cingulate cortex; aI: Anterior insula; Pc: Precuneus.

be detected not only in the targeted stimulation area but also in other distant areas of the brain that are functionally relevant and occur on existing neural networks[44].

In individuals with Ds, cognitive and emotional aspects linked to the insula are impaired, suggesting that the insula dysfunction may be at the core of the disease's clinical manifestations[45]. Activity in both the IFG and the aI is often dismissed as being relevant only to motor inhibition or orienting responses and therefore not functionally significant or cognitive. Tops and Boksem[46], however, demonstrated that IFG/aI is involved in dynamic attentional and working memory processing. The IFG/aI is also one of the regions that commonly demonstrates elevated activity related to anxiety and distress[47], which are typical features of the Ds. In addition, antide-

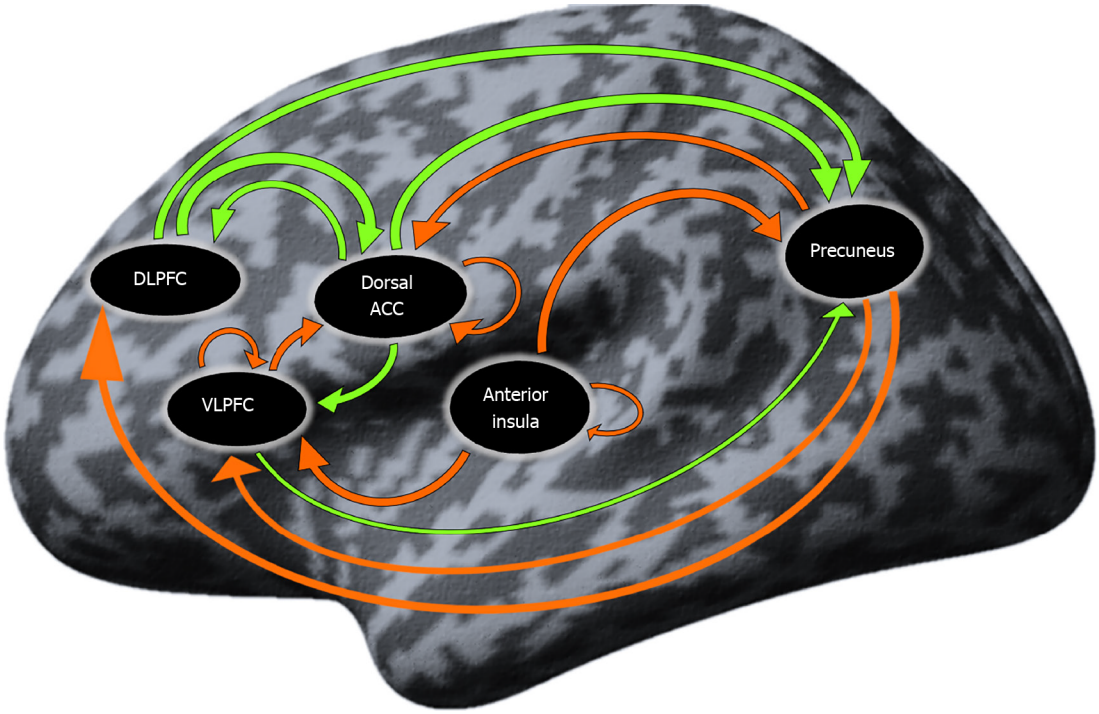

Figure 1 Connections significantly different from zero ($P < 0.05$) in the depressive syndrome group. Orange arrow: Inhibitory influence; green arrow: Excitatory influence. DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; Dorsal ACC: Dorsal anterior cingulate cortex.

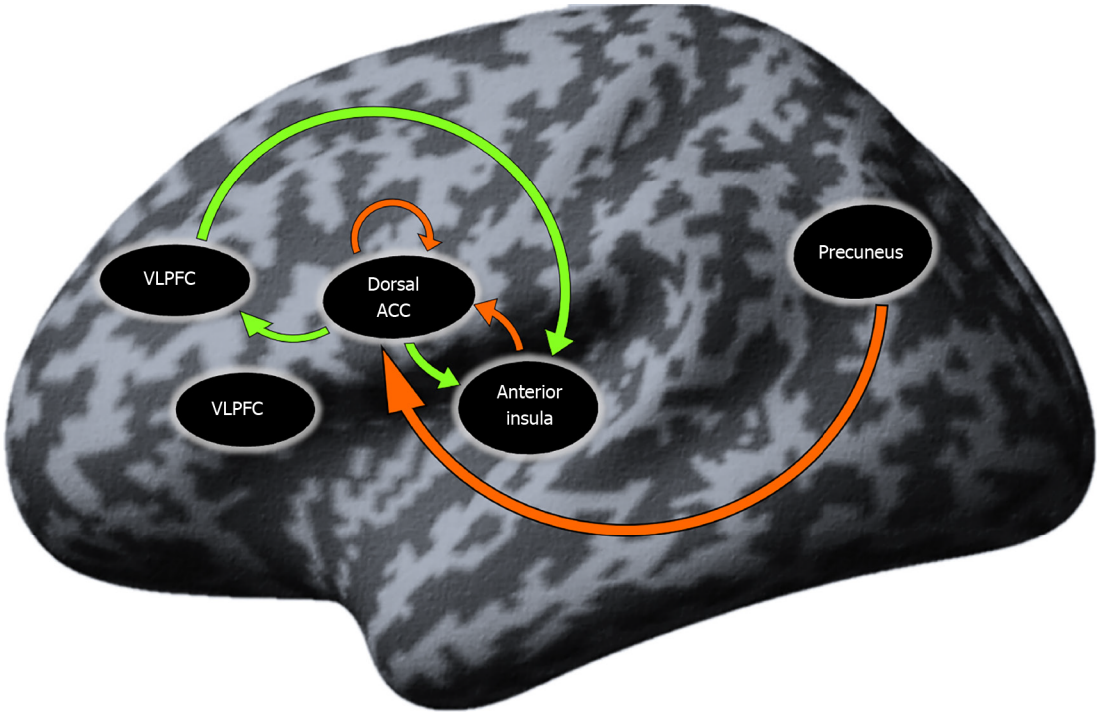

Figure 2 Connections significantly different from zero ($P < 0.05$) in the schizophrenia group. Orange arrow: Inhibitory influence; green arrow: Excitatory influence; DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; Dorsal ACC: Dorsal anterior cingulate cortex.

pressant treatment and sleep deprivation are attributed to a change in activation from the IFG/aI to the DLPFC[48]. This may be due to Ds patients' difficulty disengaging from issues and rumination, which decreases optimistic prospective and retrospective memory[49].

Analyzing our findings on patients in a depressive episode, we suggest that future research should focus deeper on examining the impaired effective connectivity between important brain regions, most notably the PFC, insula and Pc, relying on the

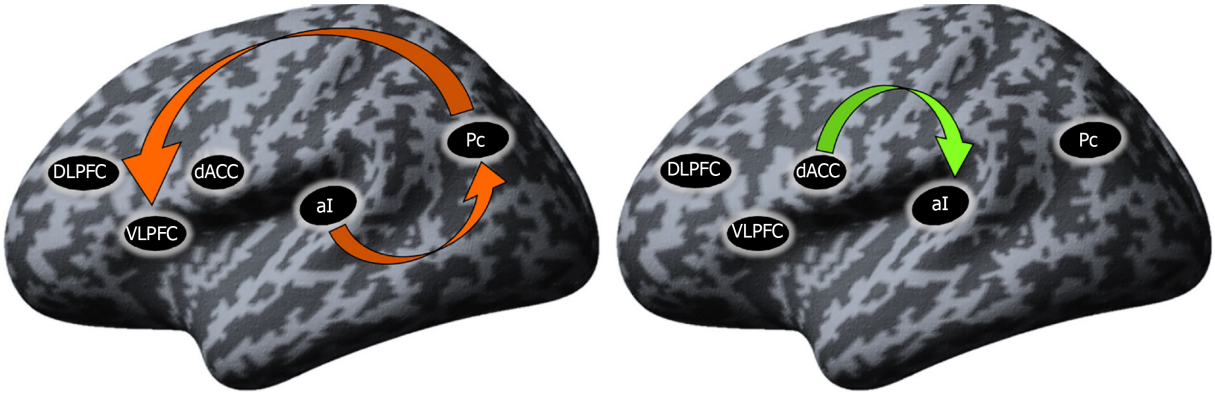

Figure 3 Connections significantly different from zero ($P < 0.05$) between the two groups. Red arrow: Inhibitory influence; green arrow: Excitatory influence; DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; dACC: Dorsal Anterior cingulate cortex; aI: Anterior insula; Pc: Precuneus.

translational approach in neuroscience aimed at incorporating the gained knowledge into clinical practice for more successful treatment options for the Ds. We hypothesize that our findings may serve in this process by combining the psychopharmacological approach, using ketamine, which is known to modulate the function of the IFG, together with a biomedical instrumental method rTMS, targeting the Pc and PFC. Such a translational therapeutic approach could lead to a lasting improvement in the condition and ultimately optimize the prognosis of the disease.

Concerning the significant deviation (excitatory connection from the dACC⇒aI) observed in the SCH group, the following findings can be discussed: The dACC is a key region involved in cognitive and emotional processing[50,51]. Brodmann's area 24 (dACC, which we examined) was associated in the past with abnormal behavioral manifestations which laid the foundation for bilateral cingulotomy psychosurgery. In such cases, neuropsychological follow-up revealed cognitive deficiency, especially in the executive functions[52]. Heilbronner and Hayden[53] suggested that the dACC is a structure specialized for representing task-state conditions that influence actions and that dACC neurons link context with strategies by combining a variety of task-relevant information to construct a representation of abstract control over decisions and actions.

The aI is an integral center for mediating dynamic interactions between large-scale brain networks engaged in externally oriented attention and self-cognition. This brain structure performs numerous cognitive, affective, and regulatory processes, including interception, emotional reactions, and empathy. The roles delegated to the insula can be conceptualized through a few simple mechanisms: bottom-up identification of salient events; shifting between other large-scale networks to promote access to attention and working memory capacity when a salient event is registered; involvement of the anterior and posterior parts to adjust the autonomic response to salient stimuli; and strong functional connectivity with the ACC[54]. The perception of both visual and auditory emotional information, pain, and subjective projections of the self are all insula-related functions that are disrupted in SCH[55]. The processing of self-representations is important for distinguishing between self-generated and external information, meaning that insula dysfunction could lead to perceptual disturbances, a prevalent symptom of SCH.

The dACC and aI are the two major components constituting the SN. In healthy individuals, the activation of SN is normally observed through a variety of cognitive tasks[54]. Its primary function is to facilitate the switching of brain connectivity between the default mode and the task-related states[56]. Disrupted synchronization between the anti-correlated networks of DMN and CEN that underlie default modes and task-related activity has been postulated as a key pathophysiological characteristic of SCH[57]. Previous research has reported reduced SN connectivity during information processing and reward prediction in SCH[58,59]. Since those are cognitively charged tasks, and in SCH the SN has reduced activity in the performance of these tasks, both the DMN and CEN may exhibit disrupted activity.

These assumptions were confirmed in our previous study[24], where we observed altered resting-state connectivity from the PFC⇒aI and task-related activations in the Pc in patients with SCH, indicative of the involvement of neural networks such as the SN and the DMN and their abnormal interactions with each other in SCH etiopathogenesis. Other neuroimaging studies in SCH also reported evidence of reduced

inhibition of the DMN during task-related paradigms[60]. We suggested that the inhibitory frontoinsular connection at rest leads to disruption of the salience processing due to the insular dysfunction as a result of its failure as a dynamic switch between the DMN and CEN. As a result, the DMN stays active during tasks and the CEN does not manage to activate at all, which could explain the cognitive deficits observed in SCH individuals reflecting as a serious impact on their functioning in professional and social aspects.

The current data support this hypothesis, as the resting-state excitatory connection observed between SN's main components – dACC⇒aI – leads to hyperactivity of the SN and ultimately to a salient perception of reality through excessive engagement with indifferent stimuli, which explains the abnormal self-referential thinking that is a characteristic trait of SCH. It appears that inaccurate evaluation of stimuli that would usually be deemed irrelevant seems to be the source of abnormal salience processing in individuals with SCH psychoses. As a result, subthreshold stimuli become excessively attention-getting, which is referred to as aberrant salience by Kapur[61] and proximal salience by Palaniyappan and Liddle[55].

According to Kapur, the central hyperdopaminergic activity causes unwarranted salience to events that would not typically be considered as relevant, resulting in a pathologically exaggerated feeling of the significance of ordinary experiences, perceptual distortions, and delusional causal conclusions. Palaniyappan broadened Kapur's idea of aberrant salience by introducing the concept of proximal salience, with a hypothesis regarding the role of the aI in salience processing to include not just hallucinations and delusions associated with psychosis, but also the debilitating disturbances of cognition and volition associated with chronic SCH. With our current study, we manage to confirm this hypothesis as our finding (excitatory influence of dACC⇒aI) suggests that schizophrenic patients stay in a resting state of aberrant salience. This process may be relevant for the onset of psychotic symptoms, whereby hallucinations are a direct consequence of the aberrant salience[61] of internal representations, and delusions are a cognitive attempt to make sense of these aberrantly salient perceptions and further with the progression of the illness the incorrectly assigned proximal salience[55] produces not only the perceptual and cognitive disturbances of acute psychosis but also the symptoms of behavioral disorganization, *via* disturbed information processing and goalsetting.

In summary, the results of our study help to understand SCH as a behavioral disorder caused by disintegration across the key brain networks. The abnormal hyperconnectivity of the SN during rest, interfering with its dynamic switch function could explain the inability of the DMN's components to activate during rest and to deactivate during cognitive load[24]. Our prior hypothesis that the SN in SCH must have a fundamentally impaired connectivity, which prevents the switching between DMN and CEN, thereby interfering with their basic functions, was confirmed by the present study. We suggest that our findings could help both in the biological understanding of the etiology of SCH and in the development and improvement of the therapeutic approach. We visualize a future where translational neuroscience would ultimately integrate psychopathology, psychopharmacology, instrumental methods, and even neurosurgical techniques to restore the brain imbalances by modulating the altered connectivity in the brains of people suffering from SCH[10].

There were several limitations to our study, which need to be considered. First, our study sample was small and there was diagnostic heterogeneity in the Ds group consisting of both patients with MDD and BD, since our comparison is on a syndrome, not a categorical level. Moreover, all the patients were undergoing psychopharmacological treatment, which may be a confounding factor for the determined intraconnectome signatures. An important future aspect in this area may be a study of the longitudinal supervenience between the pretherapeutic and post-therapeutic resting-state signatures across the whole syndromic spectrum including depression–mania–psychosis.

Therefore, even though our data confirm previous studies of dysconnectivity in schizophrenic psychosis, such a model requires additional testing with a larger sample of patients using various imaging tools. Furthermore, the interdisciplinary translational approach in neuroscience can be applied by combining different scientific disciplines such as psychopharmacology, psychopathology, and functional neuroimaging. A suitable tool seems to be the pharmaco-fMRI, which could provide additional insights about the complex mechanisms of interactions between the key brain networks by studying the distribution of various molecules in and between nodes that compose the SN, DMN and CEN.

CONCLUSION

We managed to deliver evidence that despite the clinical overlaps, there are objective neuroimaging signatures of disease that can fundamentally distinguish SCH and mood disorders. We propose a model in which the behavioral deviations observed in the Ds group are due to abnormal inhibitory connections in the resting state between nodes of the DMN and SN with the PFC, while in the SCH group there is a hyperconnectivity of the SN, leading to the perception of indifferent internal stimuli as particularly significant. The resting state of aberrant salience observed in the SCH group has the potential to explain the psychotic symptoms, where hallucinations are an attempt to comprehend the abnormal internal salient stimuli, and delusions are a secondary cognitive phenomenon through which the patient explains these abnormal perceptions. In addition, the inclusion of the concept of proximal salience helps to understand the etiology of the persistent and chronic psychoses and the role of the SN and in particular, the insula in the formation of the complex SCH symptoms, such as speech, thought and behavioral disorganization.

ARTICLE HIGHLIGHTS

Research background

The present resting-state functional magnetic resonance imaging (rs-fMRI) study was conducted in two groups of patients – schizophrenia (SCH) and individuals with mood disorders with the depressive syndrome (Ds) – to delineate the effective connectivity patterns at rest with the prior hypothesis that the salience network (SN) in SCH must have a fundamentally impaired connectivity, which prevents the switching between anticorrelated default mode network (DMN) and central executive network (CEN), thereby interfering with their basic functions and that this disruption may serve as neuroimaging biomarker to distinguish between the two groups of patients.

Research motivation

Our motivation to conduct such a comparative study comes from the lack of biological validity of available diagnostic tools, which ultimately leads to inaccurate diagnosis or high rates of comorbidity, and therefore an inadequate choice of treatment for psychotic and affective disorders.

Research objectives

By proving neurobiological markers to distinguish between SCH and mood disorders, we aimed to expand knowledge about their etiology and incorporate it into clinical practice, ultimately optimizing diagnosis and prognosis, and thus choosing the right treatment for these severe mental illnesses.

Research methods

The methods used include rs-fMRI and subsequent dynamic causal modeling (spDCM) to determine the direction and strength of connections to and from various nodes in the DMN, SN and CEN. The positive and negative syndrome scale was chosen for the assessment of the SCH group, and the severity of the Ds was assessed using the Montgomery–Åsberg Depression Rating Scale. The SPM 12 software running on MATLAB R2020b for Windows was used to perform data analysis. First level resting-state analysis was conducted using a general linear model. Regions of interest were predefined based on their involvement in the SN and the DNM. Furthermore, using the parametric empirical bayes method introduced in SPM12, the individual spDCM models were jointly estimated. Finally, the estimated spDCM models were used to extract connectivity strengths (A-matrix) for further statistical analysis in SPSS.

Research results

The coupling strengths of the connection from the precuneus (Pc) to the prefrontal cortex and from the anterior insula (aI) to the Pc, both inhibitory connections were present in the Ds group but absent in the SCH group. In the SCH patients, a significant excitatory connection from the dorsal part of the anterior cingulate cortex to the aI was present which was absent in the Ds study group.

Research conclusions

We managed to deliver evidence that despite the clinical overlaps, there are objective neuroimaging signatures of disease that can fundamentally distinguish SCH from mood disorders. The resting state of aberrant salience and proximal salience observed in the schizophrenic group has the potential to explain not only the psychotic symptoms, such as hallucinations and delusions, but also gives insight into the formation of the unique for SCH behavioral and thought disorganization.

Research perspectives

We suggest that our findings could help both in the biological understanding of the etiology of SCH and mood disorders in the development and improvement of the therapeutic approach. We visualize a future where translational neuroscience would ultimately integrate psychopathology, psychopharmacology, instrumental methods, and even neurosurgical techniques to restore brain imbalances by modulating the altered connectivity in the brains of people suffering from SCH and mood disorders.

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ORIGINAL ARTICLE

Basic Study

Validity and reliability of the Dutch version of the displaced aggression questionnaire

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Author contributions: Smeijers D and Brazil IA translated the original DAQ to Dutch; The back-translation was evaluated by Denson TF; Smeijers D wrote the first draft of the manuscript; Brazil IA and Denson TF contributed significantly to the next versions of the manuscript; Bulten EH reviewed the manuscript; all authors approved its publication.

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Abstract

BACKGROUND

Displaced aggression occurs when a person encounters a provoking situation, is unable or unwilling to retaliate against the original provocateur, and subsequently aggresses against a target that is not the source of the initial provocation. The displaced aggression questionnaire (DAQ) was developed to measure individual differences in the tendency to displace aggression.

AIM

To develop a Dutch version of the DAQ and examine relationships between the DAQ and novel individual differences.

METHODS

The Dutch version of the DAQ was created using a back-translation procedure. Undergraduate students (n = 413) participated in the current study. The questionnaires were administered online.

RESULTS

The results confirmed the original three-factor structure and showed good reliability and validity. We also found differential relationships between trait displaced aggression, social anxiety and cognitive distortions.

CONCLUSION

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The results may indicate that distinct patterns exist in the development of the different dimensions of trait displaced aggression. This study adds to the growing cross-cultural literature showing the robustness of trait displaced aggression in several different cultures.

Key Words: Displaced aggression questionnaire; Displaced aggression; Questionnaire; Dutch translation; Psychometric properties

Core Tip: The current study confirmed the original three-factor structure of the Displaced Aggression Questionnaire in a Dutch sample. We also found differential relationships between trait displaced aggression, social anxiety and cognitive distortions. The results may indicate that distinct patterns exist in the development of the different dimensions of trait displaced aggression. This study adds to the growing cross-cultural literature showing the robustness of trait displaced aggression in several different cultures.

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INTRODUCTION

Everyone experiences aggressive urges once in a while, but people are generally not very likely to "take these feelings out" on innocent others. Aggression is usually directed towards the source of provocation[1]. However, some factors can force us to displace our aggressive urges onto underserving others: When the source of frustration or the provocateur are not present and/or when someone is unable, unwilling or afraid to retaliate against the original provocateur[1-4]. Under any of these circumstances, aggression is redirected toward/displaced onto less powerful, easily available or seemingly innocent targets. The tendency to displace aggression is considered to be a stable trait that differs between individuals[5]. People with high inclinations towards displacing aggression seem more likely to aggress against undeserving others, such as coworkers, family members, or fellow drivers[5,6]. Also, individuals with the antisocial, borderline, and narcissistic personality disorder are thought to be more likely to exhibit trait displaced aggression, which highlights the clinical relevance of this phenomenon[7].

Trait displaced aggression consists of three dimensions: angry rumination (affective dimension), revenge planning (cognitive dimension) and behavioral displaced aggression (behavioral dimension)[5]. Angry rumination refers to perseverative thinking about a personally meaningful anger-inducing event[8]. Revenge planning is defined as engaging in thoughts about retaliation for a prior provocation[9]. Displaced aggression as a behavioral dimension is conceptualized as the tendency to act aggressively towards people other than the original source of a provocation[5]. It is thought that individuals high in trait displaced aggression use anger rumination to cope with life's provocations. Furthermore, individuals who take it out on others may be more likely to ruminate about the initial provocation[7], and are more likely to focus on their angry mood and to plan retaliation. Therefore, it is thought that ruminative activity maintains aggression-related affect, cognition, and arousal, through which negative emotional reactions toward those they subsequently encounter increase[5].

To assess individual differences in trait displaced aggression, Denson *et al*[5] developed the Displaced Aggression Questionnaire (DAQ). The DAQ consists of 31-items sub-divided in three subscales: angry rumination (*e.g.*, "I often find myself thinking over and over about things that have made me angry"), revenge planning (*e.g.*, "if somebody harms me, I am not at peace until I can retaliate") and behavioral displaced aggression (*e.g.*, "when angry, I have taken it out on people close to me").

All items are rated on a 7-point scale (1 = extremely uncharacteristic of me, 7 = extremely characteristic of me). The DAQ has high levels of internal consistency (Angry rumination α = 0.92; Revenge planning α = 0.91; Behavioral displaced aggression α = 0.91; total scale α = 0.95), exhibits good test-retest reliability at an interval of 4-wk (ranging from 0.75-0.80) and 11-wk (ranging from 0.78-0.89), and has good discriminant (*e.g.*, impulsivity, extroversion) and convergent validity (*e.g.*, physical and verbal aggression, anger coping styles). Finally, the DAQ predicted displaced aggression in a laboratory paradigm, domestic abuse, and road rage[5].

The DAQ has previously been translated into Romanian and Spanish. Both these adaptations confirmed the three-factor structure of the original questionnaire and showed good psychometric properties[10,11]. Both translations also confirmed positive associations with criterion measures (*e.g.*, trait anger, trait aggression, impulsivity, and big five personality traits), but did not explore any associations with other clinically relevant characteristics. For instance, Denson *et al*[5] suggested a potential association with fear or anxiety as their results showed an association between trait displaced aggression and behavioral inhibition. The authors reasoned that individuals high in trait displaced aggression are more likely to initially inhibit retaliatory responses when confronted with provocations. Subsequently, they withdraw from the provocation and continue to experience anger and conspire revenge. This association with behavioral inhibition and social withdrawal might also indicate that individuals high in trait displaced aggression experience elevated levels of withdrawal-related affect, such as anxiety and fear. Moreover, self-focused rumination is not only thought to generate and maintain anger, but also social anxiety (for review see[8,12]). It has also been suggested that anger rumination is associated with blame externalization and self-centeredness[8], also referred to as cognitive distortions. Cognitive distortions are defined as inaccurate thoughts, attitudes, or beliefs regarding own or others' behavior[13]. Previous studies have shown a strong association between such cognitive distortions and aggressive behavior[14-17]. However, the association with rumination and displaced aggression remains understudied. Elucidating the association between trait displaced aggression, social anxiety, and cognitive distortions will further increase our understanding of the mechanism of trait displaced aggression.

The current study sought to create and examine the validity and reliability of a Dutch version of the DAQ. The original three-factor structure was verified, and the convergent and discriminant validity were examined by investigating the association between the Dutch version of the DAQ and state and trait anger, physical aggression, verbal aggression, anger disposition, hostility, impulsivity and extraversion. Additionally, the association with social anxiety and cognitive distortions was examined. It was hypothesized that impulsivity, hostility, anger, and aggression were positively associated with displaced aggression. A negative association with extraversion was expected. Finally, a positive association was hypothesized between anger rumination and social anxiety, and between anger rumination and cognitive distortions related to blame externalization and self-centeredness.

MATERIALS AND METHODS

Participants

413 undergraduate students (82.6% female; 17.4% male) from Radboud University, Nijmegen participated in the current study. The mean age of the participants was 20.04 years (SD = 3.18) and the majority were undergraduates enrolled in social sciences (n = 310; 75%).

Materials

DAQ: The DAQ[5] consists of 31-items which assess trait displaced aggression and consists of three facets: Angry rumination (*e.g.*, "I keep thinking about events that angered me for a long time"), revenge planning (*e.g.*, "When someone makes me angry, I can't stop thinking about how to get back at this person") and behavioral displaced aggression (*e.g.*, "I take my anger out on innocent others"). The Dutch version of the DAQ was created in the current study (see Supplementary material).

Aggression questionnaire: The aggression questionnaire (AQ)[18] is a self-report questionnaire to assess an overall trait of aggression. It consists of 29 items which are divided into four subscales: physical aggression, verbal aggression, anger and hostility. The items are scored on a 5-point Likert scale (1 = extremely unlike me to 5 =

extremely like me). The Dutch translation has acceptable/good psychometric properties (Cronbach's α ranging from 0.51 to 0.86)[19]. In the present study, the internal consistency was acceptable to good (Cronbach's α ranging from 0.69 to 0.81).

How I think questionnaire: The How I think questionnaire (HIT)[13] is a 54-item self-report questionnaire to assess self-serving cognitive distortions. The items are divided into four cognitive distortion subscales (self-centered, blaming others, minimizing/labeling, assuming the worst) and four behavioral referent categories (physical aggression, opposition-defiance, lying, stealing). The cognitive distortion subscales refer to the actual distortions, whereas the behavioral referent categories concern the types of cognitive distortions that are related to antisocial behavior. Items have to be answered on a 6-point Likert scale (1 = totally agree to 6 = totally disagree). The Dutch translation has good reliability (Cronbach's α ranging from 0.90 to 0.94) and validity (all *R's* > 0.20)[20]. In the current study the internal consistency varied from acceptable to good (Cronbach's α ranging from 0.75 to 0.87).

State-Trait Anger Scale: The State-Trait Anger Scale (STAS)[21] has been designed to measure state and trait anger. It is a self-report questionnaire of 20 items subdivided into two subscales that capture state (10 items) and trait anger (10 items), respectively. State anger refers to an emotional condition of a patient, which is consciously experienced and fluctuates over time. Trait anger refers to the disposition to become angry, and is thought to be a stable personality quality and to differ greatly across individuals[22]. The Dutch translation has good reliability for trait anger (Cronbach's α = 0.78)[23]. The internal consistency was excellent in the current study (Cronbach's α for state anger = 0.91, trait anger = 0.87).

Novaco Anger Scale-Provocation Inventory: The Novaco Anger Scale-Provocation Inventory (NAS-PI)[24,25] consists of two parts: the NAS and the PI. The NAS assesses anger. It consists of 48 items that quantify things that people sometimes think, feel, and do. The items are subdivided in three subscales: Cognition, arousal and behavior, which are rated on a 3-point scale (1 = never true, 2 = sometimes true, 3 = always true). The PI consists of 25 items that refer to anger-eliciting situations that need to be rated on a 4-point scale (1 = not at all angry, 4 = very angry). The Dutch translation has excellent psychometric properties (Cronbach's α ranging from 0.92 to 0.95)[24]. The internal consistency was good in the current study (Cronbach's α ranging from 0.75 to 0.89).

Barratt Impulsivity Scale: The Barratt Impulsivity Scale (BIS-11)[26] is a 30-item self-report questionnaire that assesses individual differences in impulsivity. The BIS-11 measures 3 types of impulsivity defined as attentional impulsiveness, motor impulsiveness and non-planning impulsiveness. Items are rated on a 4-point scale ranging from 1 (rarely/never) to 4 (almost always/always). The Dutch translation has good psychometric properties (Cronbach's α = 0.81)[27]. Because we employed the BIS-11 as a measure for overall impulsivity, only the total score was used. In the current study the internal consistency was good (Cronbach's α = 0.81).

Ten-Item Personality Inventory: The Ten-Item Personality Inventory (TIPI)[28] is a 10-item self-report questionnaire to assess Big-Five personality dimensions. The TIPI consists of five subscales: extraversion, openness to experiences, emotional stability, conscientiousness and agreeableness. Items are rated on a 7-point scale (1 = strongly disagree, 7 = strongly agree). The Dutch translation has good convergent and discriminant validity (all *R's* > 0.20)[29]. In the current study, only the subscale extraversion showed good internal consistency (Cronbach's α = 0.72) and was, therefore, the only subscale of the TIPI used for the validation. For the other subscales Cronbach's α ranged from 0.28 to 0.59, indicating that these scales did not measure the target construct reliably.

Liebowitz Social Anxiety Scale: The Liebowitz Social Anxiety Scale (LSAS)[30,31] is a 24-item self-report questionnaire to assess social anxiety and avoidance. Each item is rated for level of fear (ranging from 0 = none to 3 = severe) and avoidance (ranging from 0 = none to 3 = almost always) it triggered in the past week. Both the original and the Dutch version have stable psychometric properties. In the current study the internal consistency was excellent (Cronbach's α = anxiety: 0.93, avoidance: 0.89).

Procedure

The Dutch version of the DAQ was created using a back-translation procedure. First, the original DAQ was translated to Dutch by Smeijers D and Brazil IA. Then, the first

Dutch version was translated back to English by a native English speaker. Finally, the back-translation was evaluated by Denson TF, who developed the original DAQ[5]. No content edits were made to the DAQ during the translation process.

The current study had a cross-sectional design. The questionnaires were administered online and were completed individually, with all the required information and instructions provided in writing. After receiving information about the nature of the study, participants signed a consent form. In total, it took participants approximately 60 min to complete the questionnaires. All participants received course credits for their participation. The current study was approved by the institutional review board (ECSW2017-2306-520).

Statistical analyses

First, the means, standard deviations, mean inter-item correlations, skewness and kurtosis statistics for the DAQ total and the individual subscale scores were calculated. Next, the internal reliability of the DAQ Dutch version in the current sample was investigated using Cronbach's α. Subsequently, a confirmatory factor analysis (CFA) was used to verify the three-factor model of the DAQ[5] and to test whether the three factors loaded on a general latent variable represented trait displaced aggression. The analysis was conducted with a WLSMV estimator in Mplus version 7[32]. The DAQ items are rated on a 7-point Likert scale, and thus yields ordinal data. Therefore, the WLSMV estimator was favored because it is specifically designed for categorical (*e.g.*, binary or ordinal) observed data (*e.g.*,[33]). Each item was constrained to load on one factor (*i.e.*, the original factor identified by Denson *et al*[5], 2006). Model fit was evaluated using absolute and conventional fit indices; the Chi-square statistic, the Tucker-Lewis index (TLI), and the comparative fit index (CFI), the root mean square error of approximation (RMSEA) model fit was considered to be good for CFI and TLI values greater than 0.90 and a non-significant Chi-square test ($P > 0.05$)[34-36]. For RSMEA, a value less than 0.06 was considered to be good, and a value between 0.05 and 0.10 was considered an acceptable fit[37]. A factor loading ≥ 0.4 was considered strong[38].

The convergent and discriminant validity were examined using correlation analyses. A bootstrapping procedure (5000 iterations) was used to determine 95%CI and to test the significance of the correlations. By bootstrapping, one is able to simulate the population distribution of the correlation and to provide confidence intervals for the correlation coefficients[39]. This approach yields more accurate estimates compared to estimates obtained without resampling, as would be the case in traditional parametric correlation analysis[40].

Finally, the relationships between the DAQ and social anxiety and cognitive distortions were explored in more detail. Specifically, unique patterns of social anxiety and cognitive distortions on anger rumination, revenge planning, and behavioral displaced aggression were examined. Bayesian path analyses were conducted using Mplus version 7[32]. Social anxiety and avoidance, and the cognitive distortions related to self-centeredness, blaming others, minimizing/mislabeling, and assuming the worst served as independent variables, while anger rumination, revenge planning, and behavioral displaced aggression served as dependent variables. Instead of the DAQ items, the DAQ subscales were now used. The subscales consisted of the mean of the corresponding items and were, therefore, on a continuous instead of an ordinal scale. In order to be able to compare the estimates, these variables were standardized by computing z-scores. All variables were treated as continuous, observed, variables. Path analysis was conducted with a Bayesian estimator (using the default Gibbs sampler PX1), 4 Markov Chain Monte Carlo chains and 100.000 iterations (of which the first 50.000 were used as burn-in trials) (see [16]). This analysis was exploratory in nature. Therefore, a Bayesian estimator was favored because it is data driven and, furthermore, avoids statistical assumptions about the distribution of the test statistics (*e.g.*,[41]).

In this study, a model was considered to show good fit if convergence was achieved with a proportional scale reduction ≤ 1.05[42]. Furthermore, the posterior predictive *P* value, a measure of similarity between observed and simulated data generated by the model being examined, should ideally be close to 0.5, which means that the model's predictions are consistent with the observed data[43]. Finally, the Chi-Square test to conduct Posterior Predictive Checking (with a 95% credibility interval; 95%CI) should include the value 0[42]. Significance of the regression weights were determined based on the 95%CIs of the Bayesian posterior distribution. The 95%CIs of the regression weights that did not contain the value 0 were considered significant.

RESULTS

Descriptive statistics and internal consistency

Descriptive statistics are displayed in Table 1. The internal consistency and mean inter-item correlations were found to vary from good to excellent for all subscales and the scale as a whole. Finally, all subscale scores correlated positively with each other (see Table 2).

Factor analysis

A CFA was conducted to verify the original three-factor solution of the DAQ. The CFA showed an acceptable fit: χ^2 (431) = 2034.65, $P < 0.001$; CFI = 0.92; TLI = 0.91; and RMSEA = 0.09. The items demonstrated good factor loadings (see Supplementary material). Additionally, the three factors loaded significantly (all *P's* < 0.001) on the superordinate latent variable for trait displaced aggression, and demonstrated high factor loadings (anger rumination = 0.792; revenge planning = 0.810; behavioral displaced aggression = 0.734), see Figure 1.

Construct validity

Anger rumination, revenge planning and behavioral displaced aggression were significantly positively correlated with the STAS state and trait anger, LSAS anxiety and avoidance, BIS-11, and all subscales of the AQ, HIT and the NAS and negatively with the TIPI extraversion subscale (see Table 2).

Path analysis

Social anxiety and avoidance, the four types of cognitive distortions, and anger rumination, revenge planning, and behavioral displaced aggression were included in the model. The path model is displayed in Figure 2, only significant results are displayed. The results revealed that social anxiety had a direct positive effect on anger rumination and behavioral displaced aggression (see Table 3). Cognitive distortions related to Blaming Others had a direct positive effect on behavioral displaced aggression, whereas cognitive distortions related to minimizing/mislabeling had a direct effect on revenge planning. The 95% credibility interval for the difference between the observed and the replicated Chi-square values is -20.76 to 21.43. Posterior predictive *P* value = 0.49, indicating an excellent model fit.

DISCUSSION

The current study examined the validity and reliability of the Dutch version of the DAQ. The results showed that the descriptive characteristics for the subscales of the Dutch DAQ were consistent with previous findings[5,11]. Furthermore, all subscales exhibited excellent reliability, and the inter-item correlations were good. Also, the original three-factor structure was confirmed in the current sample. However, the Chi-square value did not indicate a good fit, but this finding is in line with previous research[10,11]. It is important to note that this statistic is sensitive to sample size and often rejects the model when large samples are used[34]. In combination with the good values for CFI and TLI, the acceptable value for RMSEA, and the good factor loadings, the model showed acceptable fit. Finally, the three factors loaded significantly on a general latent variable. This finding provides support for the notion that anger rumination, revenge planning, and behavioral displaced aggression reflect dimensions of the general construct of trait displaced aggression. The current findings indicate that the proposed three-factor structure for the DAQ scales extends to the Dutch version and showed the robustness of trait displaced aggression cross-culturally.

Furthermore, all subscales correlated in the expected directions with the criterion measures; positive associations were found with hostility, impulsivity, and several forms of anger and aggression and a negative association was found with extraversion, which is in line with previous studies[5,10,11]. Additionally, a positive association was found with two other clinically relevant characteristics; social anxiety and several forms of cognitive distortions. Specifically, it was found that a high score on all three dimensions of trait displaced aggression were associated with high social anxiety and the tendency to avoid social situations. Denson *et al*[5] suggested a possible relation between trait displaced aggression and fear and anxiety. The current findings provide support for this notion. Based on the confidence intervals and effect sizes, it seemed that the association was the strongest with anger rumination. This may suggest that anxious individuals are more internally focused, which is also supported

Table 1 Descriptive characteristics of the Dutch displaced aggression questionnaire

	α	*r*	mean ± SD	Skewness	SE	Kurtosis	SE
Anger rumination	0.924	0.552	3.36 ± 1.32	0.474	0.12	-0.437	0.24
Behavioral displaced aggression	0.925	0.558	2.43 ± 1.13	0.909	0.12	0.545	0.24
Revenge planning	0.921	0.556	1.89 ± 0.97	2.138	0.12	5.376	0.24
Total	0.95	0.392	2.56 ± 0.94	0.992	0.12	1.498	0.24

r: Inter-item correlations; SD: Standard deviation; SE: Standard error.

by the aforementioned negative association with extraversion.

Additionally, the results of the path analysis showed that social anxiety indeed had the strongest relation with anger rumination but also with behavioral displaced aggression. It can be speculated that anxious individuals may act out their anger less easily and withdraw from provoking situations. Consequently, they seem to be more likely to ruminate about anger-provoking events, which in turn could increase the risk of behavioral displaced aggression[5]. Social anxiety is characterized by the fear that your behavior/performance will be evaluated as humiliating or embarrassing[44]. This fear may inhibit any form of acting out towards the original (less familiar) provocateur. However, among close others, social anxious individuals may not experience this intense fear[45], because they probably have learned that close others will support them regardless of their performance. This may induce a sense of safety. When feeling safe, it might be easier to vent (suppressed) feelings. Individuals high in trait anger and aggression and with high levels of social anxiety may avoid acting out their anger in provoking situations, but displace aggression towards close others. This combination of characteristics might play a role in the mechanism behind, for instance, domestic violence.

Also, the correlations with cognitive distortions may provide some additional evidence for an internal focus in individuals high in trait displaced aggression. Specifically, when comparing the confidence intervals and effect sizes, it seemed that all cognitive distortions showed a stronger association with revenge planning, which was contrary to our hypothesis. The findings of the path analysis showed that cognitive distortions related to minimizing/mislabeling had the strongest relation with revenge planning. Cognitive distortions of this type refer to depicting antisocial behavior as being acceptable, causing no real harm, or referring to others with a dehumanizing label[13]. It may be that such cognitive distortions have a reinforcing effect on revenge planning by easily justifying antisocial behavior in general and possibly retaliation in specific.

Additionally, cognitive distortions related to Blaming Others were most strongly related to behavioral displaced aggression. Distortions of this type refer to the misattribution of blame to outside sources or misattributing misfortune to innocent others [13]. Such distortions might increase the risk of displaced aggression as believing that others are the ones to blame probably easily justifies acting out anger or aggression. Contrary to our hypothesis, the path analysis did not indicate an association between trait displaced aggression and cognitive distortions related to self-centeredness. Cognitive distortions of this type refer to acquiring status to one's own needs, views, expectations, and desires to such a degree that the legitimate views of others are scarcely considered or even disregarded[13]. These types of distortions might play a role in the emergence of an aggressive conflict. However, it also may be suggested that due to such distortions the focus is too much on the self that it might even limit or distract from any angry feelings causing no rumination or displaced aggression. Also, a different view of another might not even induce anger as someone else's opinion will be disregarded.

Generally, cognitive distortions are thought to be strongly related to externalizing behaviors (for a meta-analysis see[46]). Cognitive distortions might play a role in neutralizing feelings of blame and preserving a positive self-image. If the individual has learned that this can be achieved through inappropriate use of aggression and/or antisocial behavior, cognitive distortions may strengthen or maintain such maladaptive tendencies to protect the self-image[14,47]. Also, the more persistent such distortions are, the more difficult adjusting maladaptive tendencies will be (see[48]). The current findings are also in line with other studies showing different patterns of associations between distinct types of cognitive distortions and subtypes of aggression.

Table 2 Correlations between the displaced aggression questionnaire and the State-Trait Anger Scale, Liebowitz Social Anxiety Scale, Barratt Impulsivity Scale, Ten-Item Personality Inventory extraversion, Aggression questionnaire, How I think questionnaire, and the Novaco Anger Scale

	Anger rumination	Behavioral displaced aggression	Revenge planning
Anger rumination	-	r = 0.529[c], 95%CI = 0.452-0.599	r = 570[c], 95%CI = 0.499-0.631
Behavioral displaced aggression	r = 0.529[c], 95%CI = 0.452-0.599	-	r = 0.510[c], 95%CI = 0.406-0.602
Revenge planning	r = 0.570[c], 95%CI = 0.499-0.631	r = 0.510[c], 95%CI = 0.406-0.602	-
STAS state	r = 0.317[c], 95%CI = 0.233-0.398	r = 0.290[c], 95%CI = 0.204-0.385	r = 0.465[b], 95%CI = 0.323-0.597
STAS trait	r = 0.475[c], 95%CI = 0.389-0.556	r = 0.515[c], 95%CI = 0.415-0.605	r = 0.546[b], 95%CI = 0.420-0.665
LSAS anxiety	r = 0.320[c], 95%CI = 0.230-0.408	r = 0.267[c], 95%CI = 0.159-0.371	r = 0.253[b], 95%CI = 0.123-0.381
LSAS avoidance	r = 0.308[c], 95%CI = 0.214-0.404	r = 0.236[c], 95%CI = 0.133-0.337	r = 0.263[b], 95%CI = 0.156-0.376
BIS-11 total	r = 0.185[c], 95%CI = 0.088-0.274	r = 0.200[c], 95%CI = 0.105-0.288	r = 0.379[c], 95%CI = 0.283-0.469
TIPI extraversion	r = -0.099[a], 95%CI = -0.181-0.000	r = -0.034, 95%CI = -0.127-0.064	r = -0.111[a], 95%CI = -0.198--0.014
AQ physical	r = 0.311[c], 95%CI = 0.215-0.399	r = 0.332[c], 95%CI = 0.232-0.425	r = 0.611[b], 95%CI = 0.516-0.698
AQ verbal	r = 0.250[c], 95%CI = 0.161-0.346	r = 0.259[c], 95%CI = 0.173-0.351	r = 0.321[b], 95%CI = 0.236-0.409
AQ anger	r = 0.511[c], 95%CI = 0.429-0.587	r = 0.581[c], 95%CI = 0.491-0.664	r = 0.497[b], 95%CI = 0.382-0.597
AQ hostility	r = 0.502[c], 95%CI = 0.419-0.581	r = 0.411[c], 95%CI = 0.320-0.501	r = 0.481[b], 95%CI = 0.381-0.571
HIT self-centered	r = 0.215[c], 95%CI = 0.123-0.307	r = 0.325[c], 95%CI = 0.225-0.416	r = 0.517[b], 95%CI = 0.412-0.612
HIT blaming others	r = 0.275[c], 95%CI = 0.193-0.349	r = 0.370[c], 95%CI = 0.283-0.452	r = 0.557[b], 95%CI = 0.459-0.652
HIT minimizing/mislabeling	r = 0.267[c], 95%CI = 0.178-0.349	r = 0.321[c], 95%CI = 0.220-0.411	r = 0.588[b], 95%CI = 0.494-0.674
HIT assuming the worst	r = 0.278[c], 95%CI = 0.201-0.351	r = 0.329[c], 95%CI = 0.232-0.422	r = 0.542[b], 95%CI = 0.428-0.643
HIT opposition defiance	r = 0.312[c], 95%CI = 0.222-0.397	r = 0.387[c], 95%CI = 0.295-0.473	r = 0.586[b], 95%CI = 0.488-0.676
HIT physical aggression	r = 0.286[c], 95%CI = 0.200-0.364	r = 0.360[c], 95%CI = 0.272-0.445	r = 0.617[b], 95%CI = 0.518-0.705
HIT lying	r = 0.278[c], 95%CI = 0.186-0.368	r = 0.298[c], 95%CI = 0.218-0.388	r = 0.461[c], 95%CI = 0.369-0.554
HIT stealing	r = 0.122[a], 95%CI = 0.042-0.204	r = 0.239[c], 95%CI = 0.144-0.336	r = 0.432[c], 95%CI = 0.309-0.543
NAS cognition	r = 0.572[c], 95%CI = 0.487-0.649	r = 0.441[c], 95%CI = 0.336-0.530	r = 0.539[c], 95%CI = 0.420-0.635
NAS arousal	r = 0.638[c], 95%CI = 0.566-0.704	r = 0.542[c], 95%CI = 0.442-0.622	r = 0.534[c], 95%CI = 0.420-0.636
NAS behavior	r = 0.417[c], 95%CI = 0.329-0.501	r = 0.504[c], 95%CI = 0.411-0.588	r = 0.640[c], 95%CI = 0.528-0.734
NAS PI	r = 0.417[c], 95%CI = 0.325-0.505	r = 0.434[c], 95%CI = 0.347-0.516	r = 0.412[c], 95%CI = 0.329-0.503

[a]P < 0.05.
[b]P < 0.02.
[c]P < 0.001. CI: Confidence interval; STAS: State-Trait Anger Scale; LSAS: Liebowitz Social Anxiety Scale; BIS-11: Barratt Impulsivity Scale; TIPI: Ten-Item Personality Inventory; AQ: Aggression questionnaire; HIT: How I think questionnaire; NAS: Novaco Anger Scale; PI: Provocation Inventory.

For instance, it has been found that cognitive distortions related to physical aggression were associated with the actual disposition to use physical aggression. Another example is that verbal aggressive behavior was most strongly associated with cognitive distortions related to opposition-defiance (*i.e.*, disrespecting rules, laws, and authority and external reasons for deviant behavior)[14,16]. Another novel finding was that social anxiety and cognitive distortions were differentially related to the subscales of the DAQ. This might suggest that distinct patterns exist in the development of the different dimensions of trait displaced aggression. However, it is important to note that some of the estimated effect sizes in the path analysis were rather low (*e.g.*, β 0.171 and β 0.184). Also, the cross-sectional design of the current study does not allow for strong claims concerning causality. Thus, the results have to be interpreted with caution. Prospective research is needed to elucidate the role of social anxiety and cognitive distortions in further detail, but also to elucidate potential distinct patterns in the development of trait displaced aggression.

Table 3 Standardized results of Bayesian path analysis with 95% credibility intervals

Dependent variable	Parameter	Estimate (β)	95%CI (lower 2.5%-upper 2.5%)
Anger rumination	Social anxiety	**0.171**	(0.003, 0.335[1])
	Social avoidance	0.095	(-0.072, 0.26)
	Cognitive distortions SC	-0.069	(-0.237-0.102)
	Cognitive distortions BO	0.05	(-0.155, 0.253)
	Cognitive distortions MM	0.091	(-0.103, 0.283)
	Cognitive distortions AW	0.132	(-0.075, 0.335)
Revenge planning	Social anxiety	0.042	(-0.103, 0.185)
	Social avoidance	0.048	(-0.097, 0.192)
	Cognitive distortions SC	0.037	(-0.11, 0.183)
	Cognitive distortions BO	0.157	(-0.02, 0.331)
	Cognitive distortions MM	**0.357**	(0.189, 0.519[1])
	Cognitive distortions AW	0.042	(-0.137, 0.219)
Behavioral displaced aggression	Social anxiety	**0.184**	(0.017, 0.346[1])
	Social avoidance	-0.018	(-0.183, 0.148)
	Cognitive distortions SC	0.114	(-0.055, 0.281)
	Cognitive distortions BO	**0.259**	(0.057, 0.455[1])
	Cognitive distortions MM	-0.015	(-0.207, 0.176)
	Cognitive distortions AW	-0.03	(-0.232, 0.175)

[1]Statistically significant predictors are flagged. CI: Credibility intervals; SC: Self-centered; BO: Blaming others; MM: Minimizing/labeling; AW: Assuming the worst.

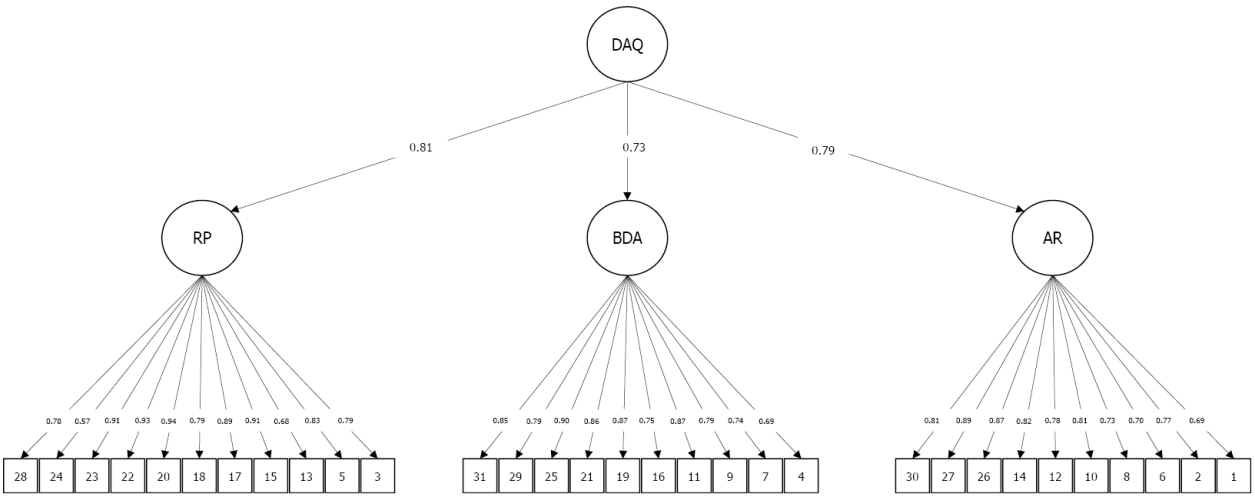

Figure 1 Factor structure of the Dutch displaced aggression questionnaire. Standardized factor loadings are displayed. DAQ: Displaced aggression questionnaire; RP: Revenge planning; BDA: Behavioral displaced aggression; AR: Anger rumination.

The present research allowed us to test aspects of the multiple system models of angry rumination[8]. According to the model, following a provocation, some people are more likely to ruminate than other people. Trait displaced aggression is one such individual difference that increases the likelihood of rumination following provocation. The influence of trait displaced aggression on actual aggressive behavior is subsequently moderated by the cognitive features of the rumination itself (called the "cognitive level" in the model). Because we know little of the cognitive content of the rumination associated with trait displaced aggression, in the present research, we

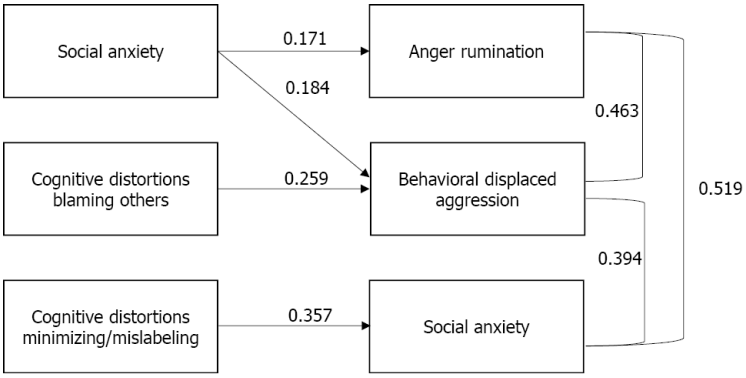

Figure 2 Standardized regression weights in the Bayesian path model. Only significant results are displayed in order to maintain readability.

assessed various aggression-related cognitive distortions. This allowed us to investigate the extent to which these cognitive distortions characterize individual differences in trait displaced aggression. Doing so may expand the multiple system models by providing novel information on the content of angry rumination among people high in trait displaced aggression.

Trait displaced aggression is thought to be an important contributor to the development of aggression. It is considered to be a personality characteristic, which means that through the repeated use of aggression individuals high in trait displaced aggression have developed aggressive schemas and knowledge structures[5]. Consequently, they have acquired strong associations between provocations and aggressive affect, arousal, and cognition. These internal processes are highly likely to contain anger rumination and revenge planning and presumably linger for a longer period of time[5]. This in turn increases the likelihood of engaging in aggressive acts. Therefore, trait displaced aggression is of great importance in understanding and explaining aggression, such as in the context of domestic violence and road-rage. More insight in distinct developmental patterns could determine which dimension of trait displaced aggression will be most prominent in a specific individual. In particular, this is important for clinical practice as this would foster the development of targeted interventions that fit the needs of individual patients.

One potential limitation of the present study is that the sample consisted primarily of female participants. The results might therefore not be generalizable to men. This gender disbalance is in line with previous studies[5,10]. Moreover, these studies found no or only small gender differences on DAQ scores. This may suggest that males and females are relatively similar in trait displaced aggression. Future research has to elucidate possible gender differences in further detail in samples consisting of an equal quantity of males/females. Second, the current sample consisted of undergraduate students not typified by clinical levels of aggression. Even though everyone experiences aggressive urges once in a while, the majority often does not have difficulties in controlling their aggressive impulses. Severe problems in regulating aggressive impulses might be strongly related to acting out on innocent others. Such behavior is often seen in cases of domestic violence, victims of bullying and traumatized individuals. Future research should include a sample of individuals displaying severe levels of aggression to elucidate the reliability and validity of the DAQ in aggressive samples. Including clinical samples could also reveal similarities and/or differences between the mechanism behind displaced aggression in different contexts. Third, criterion validity and test-retest reliability were not examined in the current study. Future research should elucidate whether the Dutch version of the DAQ can also be used for repeated measurements.

CONCLUSION

Notwithstanding the limitations, the results encourage the use of the Dutch version of the DAQ to measure individual differences in trait displaced aggression. This study adds to the growing cross-cultural literature showing the robustness of trait displaced aggression in several different cultures. The measurement of individual differences in trait displaced aggression might be a starting point for reducing for instance domestic violence, workplace aggression, and road rage[5]. Once the current findings are

confirmed in aggressive samples, an important next step would be to investigate whether currently used general aggression interventions (*e.g.*, Aggression Replacement Training)[49] also reduce anger rumination, revenge planning, and behavioral displaced aggression. If these interventions do not suffice, specific interventions need to be developed to treat the different dimensions of trait displaced aggression. The DAQ is likely to be a valuable instrument to assess trait displaced aggression in clinical settings.

ARTICLE HIGHLIGHTS

Research background

Displaced aggression occurs when a person encounters a provoking situation, is unable or unwilling to retaliate against the original provocateur, and subsequently aggresses against a target that is not the source of the initial provocation. Trait displaced aggression consists of three dimensions: Angry rumination, revenge planning, and behavioral displaced aggression. The displaced aggression questionnaire (DAQ) was developed to measure individual differences in the tendency to displace aggression. Previous studies, however, did not explore any associations with other clinically relevant characteristics.

Research motivation

Elucidating the association between trait displaced aggression, social anxiety, and cognitive distortions will further increase our understanding of the mechanism of trait displaced aggression.

Research objectives

The current study developed a Dutch version of the DAQ and examined relationships between the DAQ and novel individual differences.

Research methods

A sample of undergraduate students (n = 413) participated in the current study. The DAQ was translated using a back-translation procedure. Subsequently, the Dutch DAQ, aggression questionnaire, How I think questionnaire, State-Trait Anger Scale, Novaco Anger Scale-Provocation Inventory, Barratt Impulsivity Scale, Ten-Item Personality Inventory, and the Liebowitz Social Anxiety Scale were administered in an online survey.

Research results

The results confirmed the original three-factor structure and showed good reliability and validity. We also found differential relationships between trait displaced aggression, social anxiety and cognitive distortions.

Research conclusions

The results encourage the use of the Dutch version of the DAQ to measure individual differences in trait displaced aggression. The results might indicate that distinct patterns exist in the development of the different dimensions of trait displaced aggression. This study adds to the growing cross-cultural literature showing the robustness of trait displaced aggression in several different cultures.

Research perspectives

Once the current findings are confirmed in aggressive samples, an important next step would be to investigate whether currently used general aggression interventions also reduce anger rumination, revenge planning, and behavioral displaced aggression.

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ORIGINAL ARTICLE

Case Control Study

BDNF methylation and mRNA expression in brain and blood of completed suicides in Slovenia

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Author contributions: Videtic Paska A and Ropret S designed the study and the experiments; Zupanc T collected patient data, brain tissue, and blood samples; Ropret S performed the majority of experiments, analyzed the data, and wrote the manuscript; Kouter K performed DNA extraction, bisulfite conversion of DNA, and helped with RNA extraction; Videtic Paska A corrected the manuscript; all the authors approved the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Medicinal Ethics Committee of the Republic of Slovenia, No. 47/12/12.

Informed consent statement: The samples included in the study are post mortem samples collected during the course of autopsy at the Institute of Forensic Medicine, University of Ljubljana. The collected samples were used for routine analyses associated with the autopsy as well as for the

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Abstract

BACKGROUND

Suicide is a major public health problem. Worldwide, around 800000 people die by suicide every year. Suicide is a multifactorial disorder, with numerous environmental and genetic risk factors involved. Among the candidate genes, changes in the *BDNF* locus at the gene, epigenetic, mRNA, and protein expression levels have been implicated in psychiatric disorders, including suicidal behavior and completed suicides.

AIM

To investigate changes in *BDNF* methylation and expression of four alternative *BDNF* transcripts for association with completed suicide.

METHODS

This case-control study included 42 unrelated male Caucasian subjects, where 20 were control subjects who died following acute cardiac arrest, and 22 were suicide victims who died by hanging. DNA and RNA were extracted from brain tissue (Brodmann area 9 and hippocampus) and from blood. DNA methylation and mRNA expression levels were determined by targeted bisulfite next-generation sequencing and reverse-transcription quantitative PCR. Statistical analysis was done by use of two-tailed Student's *t* tests for two independent samples, and the Benjamini-Hochberg procedure was implemented for correction for multiple comparisons.

RESULTS

In DNA from brain tissue, there were no significant differences in *BDNF* methylation between the study groups. However, data showed significantly reduced DNA methylation of the *BDNF* region upstream of exon I in blood

molecular-genetic analyses. In Slovenia use of post mortem samples does not include use of informed consent, but the collection and use of the samples has to be approved by the Medicinal Ethics Committee of the Republic of Slovenia. For the collected samples the approval of the Medicinal Ethics Committee is attached.

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Grade B (Very good): B, B
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Grade D (Fair): 0
Grade E (Poor): 0

samples of suicide victims compared to the controls (5.67 ± 0.57 *vs* 6.83 ± 0.64, P_{corr} = 0.01). In Brodmann area 9 of the brain of the suicide victims but not in their hippocampus, there was higher expression of *BDNF* transcript I-IX (NM_170731.4) compared to the controls (0.077 ± 0.024 *vs* 0.05 ± 0.013, P = 0.042). In blood, expression analysis for the *BDNF* transcripts was not feasible due to extensive RNA degradation.

CONCLUSION

Despite the limitations of the study, the obtained data further support a role for BDNF in suicidality. However, it should be noted that suicidal behavior is a multifactorial disorder with numerous environmental and genetic risk factors involved.

Key Words: Suicidal behavior; Epigenetics; Next-generation sequencing; Brain; Blood; Caucasian

Core Tip: *BDNF* methylation analysis of brain tissues did not show differences between control subjects and suicide victims, although there was higher expression of *BDNF* transcript I-IX in Brodmann area 9 of the suicide victims. Furthermore, the data obtained from blood were interesting, especially in terms of the direction of the effects. Although due to the extensively degraded RNA in the blood, we were not able to confirm these effects on mRNA expression. Although suicide is a multifactorial disorder, our data overall further support the previously implicated role of BDNF in suicidality.

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INTRODUCTION

Suicide is a major public health problem. Globally, around 700000 people die by suicide every year. Indications are that for every completed suicide, there will have been more than 20 'unsuccessful' suicide attempts[1]. Suicide is the final and extreme act in the continuum of intentional self-destruction by a suicidal subject. Suicidal behaviors are complex and heterogeneous, and they result from interactions between numerous environmental and genetic risk factors[2,3]. Indeed, part of the genetic component of suicide risk is determined by epigenetic factors. These are heritable and can be modified under environmental influences, which can result in altered gene expression without any changes to the DNA nucleotide sequence[3-5].

A number of candidate genes have already been shown to have associations with psychiatric disorders, including suicide and other related behaviors. Among these is a member of the neurotrophin family encoding *BDNF*[6,7]. BDNF is a nerve growth factor that has an important role in the development of the central nervous system as well as in the regulation of structural, synaptic, and morphological plasticity in adults [8]. BDNF acts through its binding to two distinct receptors: Neurotrophic tyrosine receptor kinase 2 and nerve growth factor receptor (also known as p75 neurotrophin receptor)[9].

BDNF is a secreted protein that is synthesized as a pre-proBDNF precursor. After removal of the signal peptide, proBDNF is proteolytically cleaved into the pro-peptide and the mature BDNF. However, not only the mature BDNF but also proBDNF and the released BDNF pro-peptide are functionally active. A role for the pro-peptide itself has only recently been acknowledged[9,10].

The human *BDNF* locus spans approximately 70 kb of chromosome 11 and has a complex structure. It includes 11 exons (I-V, Vh, VI-VIII, VIIIh, IX), of which 9 have

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functional promotors and 4 contain alternative splice sites. The sequence that encodes the BDNF precursor form (*i.e.* pre-proBDNF) is located within exon IX[11], while the other exons are not translated. The complexity of the *BDNF* locus enables specific and precise temporal and tissue regulation of *BDNF* expression as well as regulation of its expression in response to the environment[11,12].

Given the roles of BDNF during development of the nervous system and regulation of brain plasticity in adults, it is not surprising that BDNF is emerging as one of the key factors in the development of mental disorders. Indeed, genetic[13] and epigenetic changes in the *BDNF* locus[14] and changes in *BDNF* mRNA and/or protein expression levels[14-18] have already been implicated in suicide.

Numerous studies[19-26] have defined links between epigenetic processes and mental disorders, including for nonfatal suicidal behavior, with DNA methylation established as the most studied mammalian epigenetic mechanism. These studies have shown that *BDNF* methylation in blood of subjects with mental disorders is usually higher than for that of control subjects. However, studies on *BDNF* methylation specifically in completed suicides are rare. Targeted and whole-genome methylation analyses were used in two studies that showed higher *BDNF* methylation in the brains of suicide victims compared to controls[14,27]. Interestingly, a recent study from our group where we also used a whole-genome methylation approach did not show the *BDNF* locus as differentially methylated in the brains of suicide victims when compared to controls[28].

In contrast to these few studies that have explored *BDNF* methylation in completed suicides, studies that have examined the expression of *BDNF* in suicide victims are more abundant. Some of these studies involved subjects who had been diagnosed with psychiatric disorders prior to dying by suicide. Nonetheless, the prevailing majority of these studies has shown that *BDNF* expression at the mRNA and/or protein levels is downregulated in several brain regions of suicide victims[14-18,29-31]. Keller *et al*[14] demonstrated a correlation between *BDNF* methylation and its expression at the mRNA level.

In terms of *BDNF* expression at the mRNA level, the vast majority of studies have examined total *BDNF* mRNA levels. Two studies, however, explored *BDNF* expression with regards to alternative mRNAs transcribed from the *BDNF* locus[30,31]. Wong *et al*[30] investigated the four most abundant and best characterized *BDNF* alternate transcripts (*i.e.* I-IX, II-IX, IV-IX, VI-IX) and showed significant upregulation of *BDNF* transcript I-IX (5'-exon = exon I) in patients with schizophrenia who died by suicide. They also reported similar trends for *BDNF* transcripts II-IX and IV-IX[30]. Reinhart *et al*[31] instead examined total *BDNF* mRNA levels and the levels of alternative mRNAs transcribed from the *BDNF* locus in several brain regions of patients with major depression disorder, bipolar disorder, and schizophrenia. Among all of these patients, about 37 % had died by suicide. The total *BDNF* mRNA levels did not differ from the controls across these brain regions and disease states. However, interestingly, they showed differences in expression of the alternative *BDNF* mRNAs[31,32].

To date, the studies that have explored methylation and/or expression of the *BDNF* locus for association with suicide at different levels have been performed with brain tissue only, with no similar approaches applied to blood. However, these data have shown that despite the multifactorial and polygenic nature of suicide and related behaviors, disturbances in the *BDNF* locus might make important contributions to the development of psychiatric disorders, including suicide and related behaviors. Therefore, further studies are needed to understand its role better.

Slovenia is a small European country that has a disproportionately high suicide rate. According to the latest suicide figures available from the World Health Organization in 2016, Slovenia ranked 13th highest globally and 9th highest in Europe. Despite the previous decline in the suicide rate in Slovenia from 2007, suicide still remains a serious public health problem. Combined with previous studies from our and other research groups, this encouraged us to investigate methylation of the *BDNF* gene and its expression levels in both brain tissue and blood from suicide victims and control subjects in the Slovenian population.

MATERIALS AND METHODS

Study subjects

This study included 42 unrelated male Caucasian subjects, where 20 were control subjects who died following acute cardiac arrest, and 22 were suicide victims who died by hanging. The patient data, brain tissue samples, and blood samples were collected

during regular autopsy procedures in 2014 and 2015 at the Institute of Forensic Medicine, Faculty of Medicine, University of Ljubljana (Ljubljana, Slovenia). The samples were stored at –80 °C prior to being processed.

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (Approval N° 47/12/12).

Experimental procedures

***BDNF* methylation**: For the samples from both the control subjects and the suicide victims, the differences in methylation levels of five *BDNF* regions of interest (ROIs) in or near the CpG islands (regions with high frequency of CpG) were studied by next-generation sequencing (NGS) of bisulfite-converted DNA. The ROIs for methylation of *BDNF* were I1, I2, II, IV, and VI, as shown in Supplementary Figure 1, relative to the positions of the *BDNF* CpG islands and exons. The chromosomal coordinates and further details for the nucleotide sequences are given in Supplementary Figure 2.

Genomic DNA was extracted from 25 mg to 30 mg liquid nitrogen pulverized brain tissue from Brodmann area 9 (BA9) and hippocampus and from 200 µL blood from the right femoral vein. The DNA was extracted (QIAmp DNA mini kits; Qiagen, United States), according to the manufacturer's instructions, with the quantities and qualities of the DNA determined spectrophotometrically using a microplate reader (Synergy H4 Hybrid; BioTek, United States).

The DNA (1.0 µg) was subjected to sodium bisulfite conversion (EpiTect bisulfite kits; Qiagen, United States), according to the manufacturer's instructions. Then 20 ng to 40 ng of the bisulfite-converted DNA was used as templates for amplicon preparation for library construction. Amplicons were prepared by two rounds of PCR, according to the universal tailed experimental design and in such a way that sequencing was bidirectional (Guidelines for Amplicon Experimental Design, Roche, April 2014). In the first round of PCR, the *BDNF* ROIs were amplified with simultaneous addition of universal sequences. The specific parts of the fusion primers were designed using the Methyl Primer Express v1.0 software (Applied Biosystems, United States) and are listed in Supplementary Table 1. The universal sequences of the products from the first round of PCR were targeted in the second round of PCR by fusion primers that were labeled by the NGS system (454 Junior; Roche, Germany) adaptor and Multiplex Identifier sequences for sample identification. The reaction mixtures and cycling conditions for first and second rounds of PCR are given in Supplementary Tables 2 and 3, respectively. After each round, the samples were checked for the correct length of the amplicons on 2% agarose gels.

The amplicons from the second round of PCR were purified (Agencourt AMPure XP PCR purification system; Beckman Coulter, United States), with the purities determined on 2% agarose gels. The purified amplicons were precisely quantified using dsDNA assay kits (Quant-iT PicoGreen; Thermo Fisher Scientific, United States). The procedures for the purification and quantification of the amplicons was according to the Amplicon Library Preparation Manual (Roche, April 2014). Each amplicon solution was diluted to 10^9 amplicon molecules/µL. The amplicon library was prepared by pooling equal volumes of these diluted amplicon solutions. Then the library was diluted to the final concentration of 10^6 amplicon molecules/µL, with RNA/DNA quantification on a bioanalyzer (High Sensitivity DNA kits; Agilent Technologies, United States). The library was prepared and quantified according to Amplicon Library Preparation Manual (Roche, April 2014). The library was clonally amplified by emulsion PCR (emPCR Amplification Manual Lib-A; GS Junior and GS Junior+ Series; Roche, April 2014).

The libraries prepared from brain tissue (*i.e.* BA9, hippocampus) and from blood were sequenced in two separate runs on an NGS system (454 Junior; Roche, Germany), according to Sequencing Manual (GS Junior Titanium Series; Roche, January 2013).

***BDNF* mRNA expression:** The expression levels of *BDNF* transcripts NM_170731.4, NM_170732.4, NM_170733.3, and NM_170735 were determined by reverse transcription-quantitative PCR for the samples from the control subjects and the suicide victims.

Total RNA was extracted from 10 mg to 15 mg liquid nitrogen pulverized tissue from the BA9 and hippocampus brain regions and from 4 mL to 7 mL of blood from the right femoral vein using TRI Reagent solution (Sigma-Aldrich, Germany), according to the manufacturer instructions. RNA quantity and quality were determined spectrophotometrically (NanoDrop ND-1000; Thermo Scientific, United States) and by determination of the RNA Integrity Number on a bioanalyzer (Agilent) using kits (RNA 6000 nano kits; Agilent Technologies, United States).

Then, 3 μg total RNA (in 20 μL) from BA9, hippocampus, and blood of each subject were treated with DNase I and then reverse transcribed. The DNase I reaction mixture (total volume, 25 μL) also included 2.5 μL 10× buffer (Cat. #04 716 728 001; Roche, Germany), 0.2 μL DNase I (Cat. #04 716 728 001; Roche, Germany), and 2.3 μL double-distilled water. The treatment (thermocycler: GenAmp 2700; Applied Biosystems, United States) was for 10 min at 30 °C for DNA degradation, followed by 10 min at 75 °C for DNase I inactivation. The reverse transcription (Transcriptor Universal cDNA Master; Roche, Germany) reaction mixture (final volume, 40 μL) contained 25 μL DNase I treated RNA solution, plus 8 μL 5× buffer (Cat. #05 893 151 001; Roche, Germany), 2 μL 20× reverse transcriptase (Cat. #05 893 151 001; Roche, Germany), and 5 μL double-distilled water. The temperature profile for the reverse transcription reaction (thermocycler: GenAmp 2700; Applied Biosystems, United States) was: primer annealing, 5 min at 25 °C; reverse transcription, 10 min at 55 °C; inactivation, 5 min at 85 °C; with cooling to 4 °C.

The primers used for the reverse transcription-quantitative PCR were either designed using an online tool (Primer-BLAST; NCBI) or predesigned primers (Assay Design Centre, Roche, Germany). The primer sequences, efficiencies, and product lengths are given in Supplementary Table 4. Among the tested candidate reference genes, those encoding beclin1 and dynactin subunit 2 showed the greatest expression stability in these samples and were used for normalization. The primer efficiencies were calculated based on validation experiments on two-fold and five-fold serial dilutions of cDNA derived from a mix of RNA from 10 suicide victims and 10 control subjects.

Quantitative PCR reactions were performed in 5 μL volumes in triplicate (ViiA7 real-time PCR system; Applied Biosystems, United States), as 0.75 μL cDNA sample, 1.15 μL double-distilled water, 2.5 μL SYBR Select Master Mix (Applied Biosystems, United States), and 0.6 μL of each forward and reverse primer (2.5 mM stock). The conditions were the same for all of the quantitative PCR cycling, except for annealing and extension. For the reference genes and for the *BDNF* transcripts, this followed: UDG activation, 2 min at 50 °C; polymerase activation, 10 min at 95 °C; denaturation, 15 s at 95 °C; with 40 cycles of annealing and extension for 1 min at 60 °C (beclin1, dynactin subunit 2, I-IX, IIc-IX) or 59 °C (IV-IX), or 40 cycles of annealing for 15 s at 59 °C with extension for 1 min at 72 °C (IXabcd); with all followed by the melting curve for 15 s at 95 °C, 1 min at 60 °C, and 15 s at 95 °C; and finally cooling to 4 °C.

Data analysis

BDNF methylation: After processing the raw sequencing data, quality filtering was applied. Due to an abundance of stretches of long homopolymeric regions, which are characteristic of bisulfite-converted DNA, the reads were quality filtered using bisulfite sequencing adjusted filter settings (Customer Support; Roche, Mannheim, Germany). In the read clean-up, adapter sequences were removed using the Cutadapt v1.11 software[33]. The reads were demultiplexed according to the study subjects (*i.e.* Multiplex Identifier_Forward#_ Multiplex Identifier_Reverse# combination) using the SFF tools and according to the *BDNF* ROIs, using the Cutadapt v1.11 software[33]. For sequence alignment, the FASTA format read files together with a file containing the bisulfite unconverted reference sequences were loaded into BiQ Analyzer HT[34] with the following settings: Minimal sequence identity, 0.80; minimal conversion rate, 0.85; and maximal fraction of unrecognized sites, 0.15. The results of the alignment were exported to MS Excel 2010, as the files containing numbers of loaded, filtered out, and exported reads. For each of the *BDNF* ROIs of each study, the following were determined: Subject mean conversion rate, mean methylation rate, and methylation status of individual CpGs in each read. Where the number of exported reads for a *BDNF* ROI of a subject was ≤ 20, the reads for the particular *BDNF* ROIs of this subject were excluded from any further analysis.

After testing for normal distributions of the data, the differences in the mean methylation levels of the *BDNF* ROIs, and the differences in the methylation frequencies of the individual CpGs for the ROIs between the suicide victims and the controls were determined using two-tailed Student's *t* tests for two independent samples. Statistical analysis and figure construction were carried out using the GraphPad Prism v6.0 software (GraphPad Software, United States). The Benjamini-Hochberg procedure[35] was implemented for correction for multiple comparisons, using a calculation file obtained online: BenjaminiHochberg.xlsx (https://github.com/abbiepopa/DPTB_RTOverallEG).

***BDNF* mRNA expression:** The expression of the *BDNF* transcripts was determined by the relative quantification method. The threshold cycle values were transformed into

mRNA quantities, taking efficiency into account. For each sample, the means of the triplicate measurements were calculated. Where the standard error within a triplicate was ≥ 20%, the replicate contributing the most to the standard error was excluded, and only the duplicate was considered for further analyses. Samples with standard errors within the triplicates of ≥ 40% were automatically excluded from further analyses. The experimental data were normalized to the geometric means of the quantities of beclin1 and dynactin subunit 2 mRNAs[36].

After testing the values obtained for normality of distribution, differences in *BDNF* transcript expression between control subjects and suicide victims were determined using two-tailed Student's *t* tests for two independent samples. The analyses were carried out using MS Excel 2010 and the GraphPad Prism v6.0 software (GraphPad Software, United States).

RESULTS

Study subjects

The ages and full background clinical data for the individual control subjects and suicide victims are given in Supplementary Table 5. Two-tailed Student *t* tests for independent samples showed significant differences in mean ages (± standard deviation) between the controls (54.6 ± 7.7 years) and suicide victims (44.0 ± 12.3 years), with the controls about 10 years older on average (P = 0.002). There were no significant differences in post-mortem intervals between these two study groups (28.2 ± 23.0 h *vs* 27.7 ± 13.8 h, P = 0.935).

The psychiatric diagnosis (where applicable) and post-mortem toxicology were obtained for each subject of both of the study groups. Among the control subjects, one had been previously diagnosed with schizophrenia and tested positive for psychoactive drugs and ethanol. One control subject without psychiatric diagnosis was also positive for psychoactive drugs, and six were positive for ethanol exclusively (Supplementary Table 5). Six suicide victims were previously diagnosed with one or more psychiatric disorders or symptoms, including: Schizophrenia, previous suicide attempt, depression disorder, bipolar disorder, adjustment disorder, anxiety, and alcohol dependence syndrome. Five of these suicide victims tested positive for psychoactive drugs, and two of them were positive for ethanol. The suicide victim with alcohol dependence syndrome was positive for ethanol. One suicide victim without psychiatric diagnosis was positive for psychoactive drugs. Eleven suicide victims were positive for ethanol exclusively.

BDNF methylation

The DNA methylation levels of the five *BDNF* regions for BA9, hippocampus, and blood of the control subjects and suicide victims were analyzed by targeted NGS of bisulfite-converted DNA. The mean bisulfite conversion rates and number of study subjects with sufficient numbers of reads in each of the studied tissues for each of the *BDNF* regions are given in Supplementary Table 6. Additionally, the number of reads for the post-filtration steps of each of the tissues studied are given in Supplementary Table 7.

Comparison of the control subjects and the suicide victims showed no significant differences in the methylation levels of the *BDNF* ROI (*i.e.* I1, I2, II, IV, VI) for both BA9 (Supplementary Figure 3) and hippocampus (Supplementary Figure 4, Table 1, and Supplementary Tables 8 and 9). In contrast, for blood of suicide victims compared to controls, there were significantly lower mean methylation levels for *BDNF* region I2 [t(40) = 2.832, P_{corr} = 0.01] (Figure 1 and Table 1). Closer inspection of the methylation within *BDNF* region I2 revealed significant differences for the methylation levels between the study groups for four of the CpGs. Compared to the controls, the suicide victims showed lower methylation of CpG 2 [t(40) = 3.044, P_{corr} = 0.011], CpG 6 [t(40) = 3.662, P_{corr} = 0.007], CpG 11 [t(40) = 2.923, P_{corr} = 0.014], and CpG 12 [t(40) = 3.921, P_{corr} = 0.004] (Figure 2 and Supplementary Table 10). However, there were no significant differences in the methylation levels for *BDNF* regions I1, II, IV, and VI in the blood of the controls and suicide victims (Supplementary Table 10).

BDNF mRNA expression

Expression levels of four transcripts from the *BDNF* locus in BA9, hippocampus, and blood were examined in control subjects and suicide victims by reverse transcription-quantitative PCR. The quality of the isolated RNA and mean quantification cycle

Table 1 Comparisons of the methylation levels across the *BDNF* regions in the control subjects and suicide victims

Tissue	Study group	*BDNF* region (% methylated)				
		I1	I2	II	IV	VI
Brain-BA9	C	4.55 ± 0.45	4.43 ± 0.39	8.48 ± 0.91	3.81 ± 0.32	3.37 ± 0.30
	SV	4.15 ± 0.56	4.28 ± 0.32	8.78 ± 1.09	4.03 ± 0.46	3.05 ± 0.23
	P value	0.260	0.557	0.667	0.418	0.090
Brain-Hippocampus	C	4.76 ± 0.48	4.16 ± 0.44	10.19 ± 0.51	3.74 ± 0.46	3.46 ± 0.34
	SV	4.40 ± 0.39	4.60 ± 0.43	10.30 ± 1.10	3.66 ± 0.37	3.52 ± 0.31
	P value	0.222	0.147	0.851	0.772	0.774
Blood	C	7.81 ± 1.03	6.83 ± 0.64	15.95 ± 1.36	5.71 ± 0.39	5.38 ± 0.95
	SV	7.00 ± 0.80	5.67 ± 0.57	14.26 ± 1.2	5.54 ± 0.38	4.80 ± 0.46
	P value	0.198	0.007[a]	0.067	0.521	0.245

[a]*P*corr < 0.05 (Benjamini–Hochberg method). The studied regions are labelled with Roman numerals (I, II, IV, and VI) according to the vicinity of the exons 1, 2, 4, or 6. The region preceding the first exon (I) is divided into two parts, I1 and I2 due to technical reason of maximum amplicon length recommendation for 454 GS Junior sequencing system (400 bp/region, including 454 GS Junior sequencing primers). Data are means ± 95% confidence interval. C: Controls; SV: Suicide victims. BA9: Brodmann area 9.

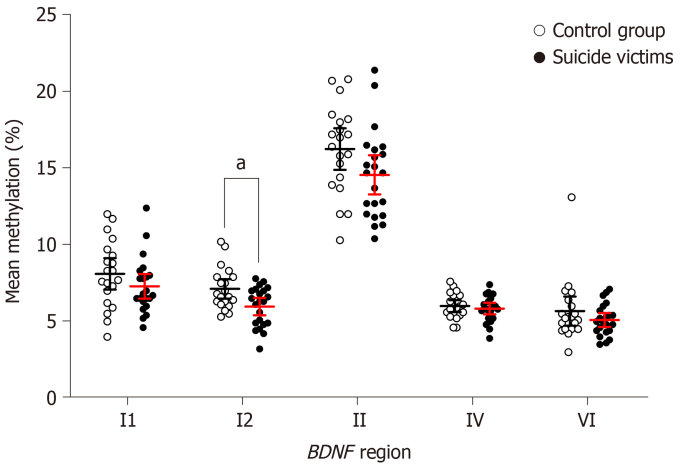

Figure 1 Methylation levels across the five studied *BDNF* regions in the blood from the control subjects and suicide victims. The studied regions are labelled with Roman numerals (I, II, IV, and VI) according to the vicinity of the exons 1, 2, 4, or 6. The region preceding the first exon (I) is divided into two parts, I1 and I2 due to technical reason of maximum amplicon length recommendation for 454 GS Junior sequencing system (400 bp/region, including 454 GS Junior sequencing primers). Each circle symbol represents an individual study subject. Data are medians (horizontal bars) of the mean methylation levels for the *BDNF* regions ± 95% confidence interval (red, suicide victims). [a]*P* < 0.05 (two-tailed Student's *t* test for two independent samples) between groups.

values for each condition are given in Supplementary Tables 11 and 12. In blood *BDNF* transcript expression analysis was not feasible due to extensive degradation of the RNA.

When compared to control subjects, the analysis for the brain region BA9 of the suicide victims showed slightly, but significantly, higher expression of the *BDNF* transcript NM_170731.4 [t(30) = 2.130, *P* = 0.042; 95% confidence interval: 0.001–0.054] (Figure 3 and Table 2). The analysis of the expression of other *BDNF* transcripts (*i.e.* NM_170732, NM_170733.3, NM_170735) in region BA9 showed no significant differences between study groups (Figure 3 and Table 2). In the hippocampus, none of the *BDNF* transcripts was significantly differentially expressed between the study groups (Supplementary Figure 5 and Table 2).

Table 2 *BDNF* alternative transcript expression in brain Brodmann area 9 and hippocampus in controls and suicide victims

Tissue	*BDNF* transcript	Total	Subjects				*P* value	95%CI
		Analyzed	Controls		Suicide victims			
		n (%)	*n* (%)	Relative expression	*n* (%)	Relative expression		
BA9	NM_170731.4	30	15	0.050 ± 0.013	15	0.077 ± 0.024	0.042[a]	0.001–0.054
	NM_170732.4	35	19	0.139 ± 0.026	16	0.154 ± 0.036	0.451	-0.026–0.058
	NM_170733.3	38	20	0.162 ± 0.027	18	0.188 ± 0.044	0.270	-0.022–0.075
	NM_170735	30	15	0.103 ± 0.019	15	0.095 ± 0.019	0.553	-0.033–0.018
Hippocampus	NM_170731.4	36	16	0.342 ± 0.117	20	0.312 ± 0.069	0.630	-0.154–0.094
	NM_170732.4	35	17	0.420 ± 0.120	18	0.369 ± 0.067	0.428	-0.181–0.079
	NM_170733.3	37	18	0.466 ± 0.111	19	0.475 ± 0.061	0.878	-0.111–0.129
	NM_170735	36	18	0.399 ± 0.092	18	0.341 ± 0.073	0.308	-0.171–0.056

[a]Nominal statistically significant difference ($P < 0.05$) two-tailed Student's *t* test for two independent samples. CI: Confidence interval. BA9: Brodmann area 9.

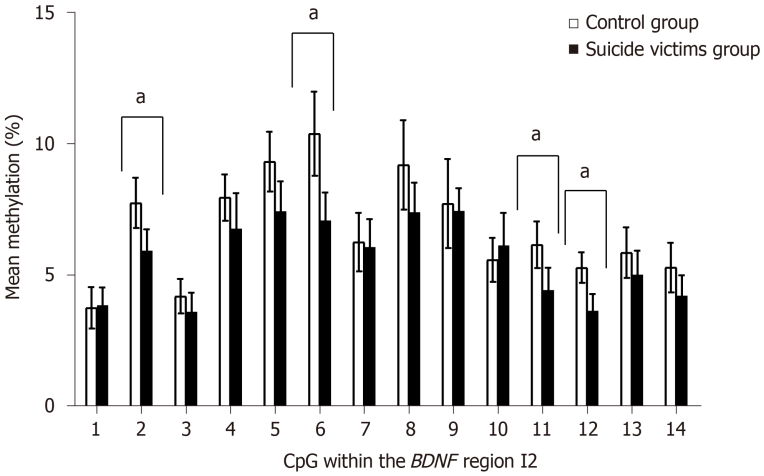

Figure 2 Methylation levels of individual CpGs within the *BDNF* I2 region in the blood from the control subjects and suicide victims. Data are means ± 95% confidence interval; [a]$P < 0.05$ (two-tailed Student's *t* test for two independent samples) between groups.

DISCUSSION

In this study, we examined *BDNF* methylation and the expression levels of *BDNF* transcripts in brain (*i.e.* BA9, hippocampus) and blood from control subjects and suicide victims from the Slovenian population, which is known to have a high risk of suicidality. Despite the decrease in Slovenian suicide rates in the past decade (SI-STAT Data Portal; Supplementary Figure 6), the number of deaths due to suicide still remains concerning. In Slovenia, roughly 80% of suicide victims are men, and the most commonly used suicide method is suffocation by hanging[37].

Study subjects

To maximize the homogeneity of our study groups, tissue samples were collected only from male controls who died by acute cardiac arrest (age range: 33-64 years) and from male suicide victims who died by hanging (age range: 29-60 years). The difference in the mean ages between the study groups was not unexpected (controls were 10.6 years older), as the control group was represented by subjects who passed away due to a reason more commonly associated with an older population. Due to the small sample size, the suicide victims were not subgrouped in terms of their comorbidities and/or medications.

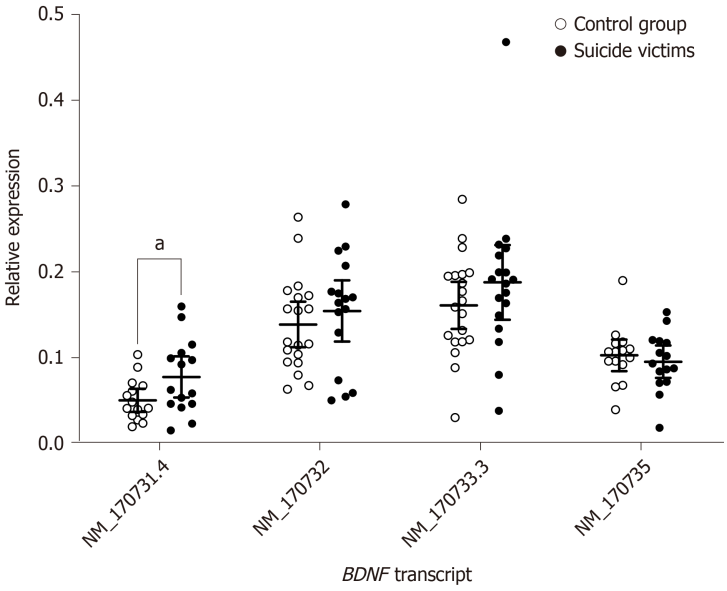

Figure 3 Relative expression levels of alternative *BDNF* transcripts in the Brodmann area 9 brain region of the control subjects and suicide victims. Each circle symbol represents an individual study subject. Data are medians (horizontal bars) of the mean methylation levels for the *BDNF* regions ± 95% confidence interval (black, suicide victims). [a]*P* < 0.05 (two-tailed Student's *t* test for two independent samples) between groups.

BDNF methylation

NGS of bisulfite-converted DNA was used to determine the methylation rates across the five *BDNF* regions, plus the methylation rates of individual CpGs within these regions. Methylation was assayed for the BA9 of the prefrontal cortex, the hippocampus, and blood and compared between controls and suicide victims.

For BA9 and hippocampus, the present study did not show any significant differences in *BDNF* methylation between the controls and suicide victims. Our previous whole-genome methylation study showed several differentially methylated CpGs in BA9 and hippocampus of suicide victims compared to controls[28]. However, none of these differentially methylated CpGs was located within or in the vicinity of the *BDNF* locus, which is in agreement with the present study. In contrast, other studies have shown increased *BDNF* locus methylation in brains of suicide victims[14,27], although they explored different brain areas, which would explain these discrepancies.

Comparison of the *BDNF* locus methylation for blood of the controls and suicide victims instead showed *BDNF* I2 (upstream of exon I) with significantly reduced methylation for suicide victims. Also, more specifically within *BDNF* I2, 4 of the 14 CpGs examined were significantly hypomethylated in blood of these suicide victims. We have been unable to find similar studies to date that have the *BDNF* methylation of DNA from blood in completed suicides. Previous studies on blood from elderly people and patients with psychiatric or other conditions who also showed suicidal behavior (*i.e.* suicide ideation, suicide attempts) have reported increased *BDNF* methylation over the controls[21-25]. To the best of our knowledge, there are only two studies to date that have reported decreased *BDNF* methylation in blood of psychiatric patients compared to controls. However, in these two studies, none of the subjects showed suicidal behavior[19,26].

BDNF mRNA expression

Quantitative PCR was used to determine the expression levels of four alternative *BDNF* transcripts in brain tissue (BA9, hippocampus) and blood of these controls and suicide victims: NM_170731.4, NM_170732, NM_170733.3, and NM_170735.

In BA9, relative to the controls, the *BDNF* transcript NM_170731.4 (5′-exon = exon I) showed slightly, but significantly, higher expression in the suicide victims. With regard to psychiatric disorders, there are only two studies to date that have examined expression of some of the individual *BDNF* mRNA transcripts[30,31]. Wong *et al*[30] showed higher expression of *BDNF* transcript I-IX (5′-exon = exon I) compared to control subjects in dorsolateral prefrontal cortex in patients with schizophrenia who died by suicide. However, as almost half of their schizophrenia suicide victims tested positive for antidepressants, the authors could not rule out effects of the drugs on the

experimental outcome[30]. Reinhart *et al*[31] revealed higher expression over controls for transcript IIc-IX (5'-exon = exon IIc) in striatum of subjects with major depressive disorder. Their patient groups (*i.e.* schizophrenia, bipolar disorder, major depressive disorder) also included subjects who died by suicide (approximately 40 %). Interestingly, the total *BDNF* mRNA levels did not differ in any of these disease states compared to controls in any of the brain regions they studied (*i.e.* dorsolateral prefrontal cortex, striatum, hippocampus)[31].

In the present study, determination of the expression of these *BDNF* transcripts in blood could not be carried out. As shown in Supplementary Table 11, blood RNA was significantly degraded as reflected in the low RNA integrity numbers. Low quality RNA was further indicated by high quantification cycles for the reference genes in comparison to the brain tissue (Supplementary Table 12). It should be noted that the brain and blood tissue samples were frozen at -80 °C, and the nucleic acids were not immediately extracted from the tissues. Freezing and thawing of blood samples causes extensive cell lysis, which leads to poor RNA recovery, while brain tissue can be frozen and thawed without significant effects on RNA recovery[38].

Nonetheless, a number of past studies that explored total *BDNF* mRNA levels have shown decreased expression in the postmortem brain of suicide victims and in blood of psychiatric patients that attempted suicide[14,15,17,18,39].

Limitations

Several limitations of this study can be noted. First, the sample size was relatively small (n = 42), which limits the power of the study. Moreover, only tissue samples from males were collected. Therefore, the results might not be generalizable to the wider (female) population. Further, for the group of suicide victims, the lack of subgrouping, the exclusion of subjects with comorbid psychiatric disorders, and the use of psychoactive drugs might represent confounding factors.

A hypothesis-driven approach was used here, which focused on one candidate gene. Psychiatric disorders, and also suicide and related behaviors, are multifactorial disorders with numerous interacting genetic and environmental risk factors involved. However, the choice to study the *BDNF* gene was based on previous studies that had implicated its involvement in the pathogenesis of psychiatric disorders, including suicide.

Considering the DNA methylation approach used, despite preservation of the methylation patterns during bisulfite treatment of DNA, this reaction does not discriminate between methylation and hydroxymethylation of cytosines. Indeed, recent studies that have used oxidative bisulfite NGS have shown altered gene hydroxymethylation patterns in the brain of depressed patients who died by suicide [40,41]. DNA methylation and gene expression are not only tissue specific but also cell type specific. Thus, for the brain analysis, the tissue here included several cell types of particular brain regions (*i.e.* within BA9 and hippocampus). Hence, the data obtained from the brain tissues represent *BDNF* methylation and *BDNF* mRNA expression across all cell types from these brain regions. We also did not explore total *BDNF* mRNA expression in the present study sample. Finally, due to substantial RNA degradation, we were not able to obtain data on *BDNF* transcript expression in blood of these control subjects and suicide victims.

CONCLUSION

To the best of our knowledge, this is the first study that aimed at exploring *BDNF* locus methylation and the expression of four *BDNF* transcripts in brain and peripheral blood in the same cohorts. This was also carried out in a population with a high suicide rate. Despite this, *BDNF* methylation analysis of the brain tissues did not show differences between the study groups. The higher observed expression of *BDNF* transcript I-IX in BA9 of the suicide victims should be taken with caution, as this barely reached statistical significance. However, the data obtained from blood are interesting, especially in terms of the direction of the effects, although due to the extensively degraded blood RNA we were not able to confirm these effects on mRNA expression. Finally, although the present study and data from a number of other studies implicate *BDNF* in suicidality, it must be kept in mind that suicide is a multifactorial disorder with numerous environmental and genetic risk factors involved.

ARTICLE HIGHLIGHTS

Research background

Suicidal behavior is a complex behavior with multifactorial etiology. Despite the large body of work, the full mechanism of suicidal behavior is not known. There are however strong indicators that changes in epigenetic mechanisms, specifically DNA methylation, can be an important factor.

Research motivation

Brain derived neurotrophic factor, *BDNF*, plays an important role in brain plasticity, and therefore it could be involved in modulation of suicidal behavior. Molecular-genetic data from a population with a high suicide rate could contribute to deeper understanding of the biological background of suicide.

Research objectives

The objective of our study was to investigate *BDNF* at two levels: DNA methylation and gene expression. As DNA methylation and gene expression can be highly tissue specific, we included two different brain regions and also blood as a peripheral tissue that is more easily accessible.

Research methods

Altogether, 42 subjects were included in the study (20 control subjects and 22 suicide victims). Samples of brain (hippocampus and Brodmann area 9) and blood were obtained during routine autopsy. We used targeted bisulfite sequencing to assess the DNA methylation level of five *BDNF* regions of interest (I1, I2, II, IV, and VI), and quantitative PCR to determine gene expression of four *BDNF* transcripts.

Research results

When comparing suicide victims and control group, we observed no significant changes in *BDNF* DNA methylation level in the brain. Changes were observed in blood, where suicide victims exhibited lower mean DNA methylation level of *BDNF* region I2 compared to the control group. In gene expression analysis, one *BDNF* transcript (NM_170731.4.) was upregulated in Brodmann area 9 of suicide victims compared to the control group.

Research conclusions

Due to tissue associated limitation, a complete insight into *BDNF* changes was not possible, namely inspection of blood *BDNF* expression level. Still, we observed changes both in DNA methylation level in blood and gene expression in brain, indicating the possible association of *BDNF* with suicidal behavior.

Research perspectives

Data from this study was obtained from a Slovenian population, which has a high suicide risk. The findings are thus an important contribution to a better understanding of the biological basis of suicidal behavior and the involvement of neurotrophic factors such as *BDNF*.

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ORIGINAL ARTICLE

Case Control Study

Developing a nomogram for predicting the depression of senior citizens living alone while focusing on perceived social support

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Abstract

BACKGROUND

Although the number of senior citizens living alone is increasing, only a few studies have identified factors related to the depression characteristics of senior citizens living alone by using epidemiological survey data that can represent a population group.

AIM

To evaluate prediction performance by building models for predicting the depression of senior citizens living alone that included subjective social isolation and perceived social support as well as personal characteristics such as age and drinking.

METHODS

This study analyzed 1558 senior citizens (695 males and 863 females) who were 60 years or older and completed an epidemiological survey representing the South Korean population. Depression, an outcome variable, was measured using the short form of the Korean version CES-D (short form of CES-D).

RESULTS

The prevalence of depression among the senior citizens living alone was 7.7%. The results of multiple logistic regression analysis showed that the experience of suicidal urge over the past year, subjective satisfaction with help from neighbors, subjective loneliness, age, and self-esteem were significantly related to the depression of senior citizens living alone ($P < 0.05$). The results of 10-fold cross validation showed that the area under the curve of the nomogram was 0.96, and the F1 score of it was 0.97.

CONCLUSION

It is necessary to strengthen the social network of senior citizens living alone with friends and neighbors based on the results of this study to protect them from

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depression.

Key Words: Senior citizens living alone; Nomogram; Depression; Risk factor; Perceived social support; Subjective social isolation

Core Tip: In this study, the significant predictors of depression of the senior citizens living alone were the experiences of suicidal urge over the past year, dissatisfaction with help from neighbors, subjective loneliness, age, and low self-esteem. The results of this study implied that it is necessary to develop a support system customized for subjects to strengthen the relation network for preventing depression in senior citizens living alone so that they can receive actual support (reinforced qualitative network) from acquaintances such as neighbors rather than the frequency of physical contact (reinforced quantitative network).

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INTRODUCTION

The incidence of diseases involving senile dementia is rapidly increasing globally due to a rapid increase in the aging population[1]. One of the outcomes of these diseases, depression, is an important and frequent psychiatric disorder in the senile stage, and it is predicted to become the second most important factor in the global disease burden [1]. Since depression can be treated through drug and psychosocial therapy, it is very important to diagnose and treat it as soon as possible. Nevertheless, it is difficult to diagnose depression in the senile stage in good time because it is often erroneously confused with physical symptoms (*e.g.*, a headache, dizziness, *etc.*) by other family members (senior citizens complain about these more often than younger people), while cognitive decline due to depression is often obscured by the normal aging process[2,3]. Thus, it tends to be neglected without receiving appropriate attention, diagnosis, and/or treatment[2,3]. Hence, many senior citizens living in the community may be suffering from depression even if they have not been clinically diagnosed with it by medical personnel[4].

Although detecting depression in good time is an important requirement for the aged, depression tends to be discovered late or not treated adequately due to various reasons, such as a lack of awareness of one's depression, the complex manifestation of depression, and a decrease in the interest of close acquaintances and family members. However, if geriatric depression is neglected without being properly treated, the individual will suffer from unnecessary mental and social pain, which can lead to serious outcomes such as suicidal ideation[5,6]. Consequently, it is very important to accurately diagnose and detect geriatric depression when treating diseases involving senility[5,6].

The proportion of the elderly population who are living with and/or supported by their children continues to decrease in South Korea in concert with a rapid increase in the number of elderly people living alone[7]. As of 2015, the number of senior citizens living alone in South Korea was 1379000, which is a 1.8-fold increase (777000 people) compared to 2005[7], and is expected to increase to 3.43 million by 2035[7]. Moreover, the proportion of senior citizens living alone is expected to increase to 23.2% in 2035 from 17.8% in 2020. Senior citizens living alone must handle everything that arises in their daily lives, and they exist in poorer environments than those supported by their children not only from economic (income and consumption) and welfare perspectives but also concerning their mental health. The findings from the Survey of Living Conditions and Welfare Needs of Korean Older Persons[7] show that senior citizens living alone are usually old and poorly educated, while the proportion of female senior

citizens living alone is five times higher than those living with their families. Pogŏn Sahoe Yŏn'gu[8] reported that senior citizens living alone had poorer subjective health and were more likely to suffer from a disease such as depression than those living with their families. Thus, the mental health of senior citizens living alone is poorer than those living with their families and the causes of depression in the former are many rather than singular[8,9].

Although the number of senior citizens living alone is increasing, few researchers have identified factors related to the characteristics of depression in these individuals by using epidemiological survey data representative of this population group. Although epidemiological surveys on the prevalence of depression in the senile stage have been actively conducted in many countries[10-13], the prevalence of depression varied between them due to differences in the survey sampling methods, depression testing tools, and evaluation methodology. Researchers usually use two-phase designs in psychiatric epidemiological studies to classify subjects into a depression-positive group and a depression-negative group quickly and economically by using a simple standardized screening test in the first phase followed by conducting a robust diagnostic test in the second phase to save on the labor and economic burden[14]. There-fore, in the first phase, we used the Center for Epidemiological Studies Depression Scale (CES-D)[15], a widely used standardized screening test, to identify the prevalence of depression in senior citizens living alone. Second, we evaluated the prediction performance [area under the curve (AUC) for the receiver operating characteristic, general accuracy, balanced accuracy, F1 score, sensitivity, and specificity] by building models for predicting depression in senior citizens living alone, which included subjective social isolation and perceived social support as well as personal characteristics such as age and alcohol consumption. Last, we developed a nomogram that allows practitioners to check multiple risk factors for depression in senior citizens living alone using visual graphs and to calculate the prevalence of depression while considering the personal characteristics of the subjects based on these results.

MATERIALS AND METHODS

Data source

This study is a secondary data based on the Korean Psychosocial Anxiety (KPA) survey, an epidemiological survey representing the South Korean population. KPA-survey was conducted from August to September 2015 by the Korea Institute for Health and Social Affairs. The study stratified the population, obtained from the Residence Registration Data (complete enumeration) conducted by the Ministry of Security and Public Administration as of June 2015, into 17 cities and provinces (*i.e.*, Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, Ulsan, Sejong, Gyeonggi-do, Gangwon-do, Chungcheongbuk-do, Chungcheongnam-do, Jeollabuk-do, Jeollanam-do, Gyeongsangbuk-do, Gyeongsangnam-do, and Jeju-do). Afterward, this study extracted samples using the quota sampling method with considering the gender, age, and residential area ratios. This study selected 200 eups, myeons, and dongs from 3552 eups, myeons, and dongs in South Korea using the probabilities proportional to size (PPS) method. In order to secure randomness when extracting sampling sites, the PPS was applied after sorting the districts in the order of city, county, and district based on the administrative district code. After selecting 200 sampling sites, the 5th household from the Community Service Center of each selected eup, myeon, or dong was chosen as the sampling household by visiting the selected sampling site, and finally, 7000 adults (19 years or older) were surveyed. This study conducted an in-person survey by having trained surveyors who received survey training visit the sample households using the computer assisted personal interview method. This study was approved by H University's Clinical Research Ethics Committee (No. 20180042). This study analyzed 1558 senior citizens (695 males and 863 females) who were 60 years or older and completed the KPA-survey.

Measurement

Depression, an outcome variable, was measured using the short form of the Korean version CES-D (short form of CES-D)[16]. CES-D[15] is a standardized self-report depression test that is used most commonly in the world and can measure depression in healthy people easily. This test was developed by the National Institute of Mental Health for investigating the epidemiological status of depression in a community and has been widely used in many countries in various languages as a screening instrument for depression[16]. Many previous studies have proven the high internal

consistency and validity of CES-D[17,18]. More recently, the scale of short form of CES-D, which has secured good reliability and validity, has also been developed and used for subjects who have difficulties in responding to the 20 items of the original CES-D (*e.g.*, senior citizens, those with dyslexia, or illiterates)[19-23]. Short form of CES-D has been continuously used in epidemiological surveys because it reduces the response burden of the participants and it has the advantage that it can be easily used for the elderly who suffer from many physical symptoms and have difficulties in answering a long item due to a decrease in concentration[24]. The KPA-survey, the data source of this study, used standardized short form CES-D consisting of 11 items. This test classified depression into four levels based on the frequency of depression symptoms experienced by the subject over the past week. Moreover, the severity of symptoms was classified into four classes using a Likert scale (0 points = rare or 1 d or fewer per week; 1 point = occasional or 1 to 2 d per week; 2 points = often or 3 to 4 d per week; and 3 points = mostly or 5 d or more per week). A higher total score means more depression symptoms. This study defined the threshold of depression as 16 points based on the previous study[22] on the elderly in South Korea.

Explanatory variables were age (continuous variable), alcohol consumption (abstainers or normal drinkers, high-risk drinkers, and those with alcohol use disorder), self-esteem, suicidal ideation over the past year (yes or no), subjective social isolation (rarely, occasionally, often, or usually lonely), frequency of communication with other family members (a 10-point scale with a higher score infers more frequent communication), interaction with neighbors and friends [regular club activities (yes or no), perceived social support (a 10-point scale), trust neighbors (yes or no), and satisfied with help (support) from neighbors (yes or no)], satisfaction with the neighborhood environment (yes or no), satisfaction with the safety level of the neighborhood (yes or no), and satisfaction with the medical services in the region (yes or no) [25]. The self-esteem item was measured by using the Self-Esteem Scale (SES) comprising 10 items (a total score of 40 points)[26]: A low score (15 or less) indicates poor self-esteem. The Alcohol Use Disorders Identification Test (AUDIT)[27] developed by the World Health Organization for the preliminarily screening of high-risk drinkers comprises 10 items with a total score of 40 points: 0-15 points identify abstainers and normal drinkers, 16-19 points identify high-risk drinkers, and ≥ 20 points identify individuals with alcohol use disorder.

Developing a model to predict the depression of senior citizens living alone

The general characteristics and depression prevalence of the subjects were presented/present in percentages. The effects of depression were examined by Chi-square test. This study built a depression prediction model using logistic regression analysis to find out the effect of each variable on depression. This study selected variables using step-forward regression analysis. Moreover, this study presented an unadjusted crude model, which was not adjusted with confounding factors, and an adjusted model, which was adjusted with confounding factors.

The developed depression prediction model contained a nomogram to make it possible for clinicians to interpret the prediction results (prediction probability) easily. The nomogram was composed of 4 elements. The first was a point line. It was the line located at the top of the monogram to indicate the score corresponding to the risk range of a factor. In the case of a logistic nomogram, it ranged from 0 to 100 points. The second was a risk factor line. This line indicates the score range of a risk factor influencing the occurrence of an event. The number of risk factor lines was equal to the number of risk factors. The third was a probability line. The probability line was the sum of finally calculated nomogram scores and it was placed at the bottom of the nomogram to derive the probability (risk) of depression. The fourth is a total point line. It was constructed by calculating it based on a statistical model.

Evaluating the prediction performance of a model for predicting the depression of senior citizens living alone

The sample size of this study was small (n = 1558). Therefore, when the prediction performance of the model is validated using a held-out validation method (*i.e.*, a validation method that divides the dataset into a training dataset and a validation dataset at a 7:3 ratio), it poses a risk of overfitting. Consequently, it is more likely to decrease the reliability of prediction results. As a result, this study used 10-fold cross-validation to validate the prediction performance of the developed depression prediction model (nomogram). AUC, general accuracy, balanced accuracy, F1 score, sensitivity, specificity and calibration plot were presented. The calibration plot is a graph for visually confirming the degree of agreement (y, Calibration curve and x,

predicted probability) between the predicted probability and the observed probability. Sensitivity indicates the ratio of true positives: The ratio of the developed model to predict the senior citizen living alone with depression as depression. Specificity indicates the ratio of true negatives: The ratio of the developed model to predict the senior citizen living alone without depression as no-depression accurately. R version 4.0.3 (Foundation for Statistical Computing, Vienna, Austria) was used for analyses and significance level was 0.05 in two-tailed test.

RESULTS

General characteristics of subjects

General characteristics of all subjects (1558 subjects) are presented in Table 1. The mean age was 67.9 ± 5.5 years old: 55.4% of them were women and 44.6% of them were men. The results of the AUDIT showed that most of the subjects were normal (52.4%), no suicidal urge over the past one year (91.0%), very rare subjective loneliness (44.1%), and homemaker (35.5%). The prevalence of depression among the senior citizens living alone in the community, measured by short form of CES-D was 7.7%.

Characteristics of the subject according to the prevalence of depression

The characteristics of the subjects according to the prevalence of depression are presented in Table 2. The results of chi-square test showed that depression was significantly ($P < 0.05$) affected by age, self-esteem, subjective frequency of communication with other family members, alcohol use disorder, the experience of suicidal urge over the past year, subjective trust satisfaction with neighbors, subjective satisfaction with help (support) from neighbors, subjective satisfaction of the safety level of the neighborhood, subjective satisfaction of the medical service of the region, regular club activities, and subjective loneliness.

Developing a model for predicting depression of senior citizens living alone

Table 3 shows a model for predicting the depression of senior citizens living alone. The results of univariate logistic regression analysis (crude model) showed that all variables (age, self-esteem, alcohol use disorder, the experience of suicidal urge over the past year, subjective trust satisfaction with neighbors, subjective satisfaction of the living environment of the neighborhood, subjective satisfaction of the safety level of the neighborhood, subjective satisfaction of the medical service of the region, regular club activities, subjective loneliness, subjective frequency of communication with other family members, and subjective frequency of communication with neighbors/friends) were significantly ($P < 0.05$) related to the depression of senior citizens living alone. However, the results of the adjusted model revealed that the depression of senior citizens living alone was independently associated only with the experience of suicidal urge over the past year [odds ratio (OR): 3.57, 95% cumulative incidence (CI): 1.55-8.22], subjective satisfaction with help (support) from neighbors (OR: 0.29, 95%CI: 0.13-0.66), subjective loneliness (occasionally lonely: OR: 5.04, 95%CI: 1.00-4.65; often lonely: OR: 187.19, 95%CI: 23.17-1512.13; mostly lonely: OR: 758.12, 95%CI: 56.44-10183.32), age (OR: 1.17, 95%CI: 1.07-1.26), and self-esteem (OR: 0.81, 95%CI: 0.72-0.91).

Developing a nomogram to predict the depression of senior citizens living alone based on multiple risk factors

A nomogram for predicting the depression of elderly living alone based on multiple risk factors is presented in Figure 1. Among the risk factors of depression of senior citizens living alone, subjective loneliness had the greatest influence, and the senior citizens living alone who responded that they felt lonely showed the highest risk of depression. For example, the nomogram for predicting depression predicted that the depression risk of senior citizens who had suicidal urge over the past year, were not satisfied with subjective help (support) with neighbors, thought that they were mostly lonely, had 15 points in Rosenburg SES scale (self-esteem), and were 80 years or older was 99.8% (Figure 2).

Validating a nomogram for predicting the depression of senior citizens living alone

The developed nomogram for predicting the depression of senior citizens living alone was validated by using AUC, general accuracy, balanced accuracy, F1 score, sensitivity, and specificity (Table 4). The results of 10-fold cross validation showed that the AUC of the nomogram was 0.96, the general accuracy of it was 0.95, the balanced

Table 1 General characteristics of subjects

Characteristics	*n* (%)
Age, mean ± SD	67.9 ± 5.5
Gender	
Male	695 (44.6)
Female	863 (55.4)
Occupation (ISCO)	
Managers	20 (1.3)
Professional	12 (0.8)
Clerical support workers	6 (0.4)
Service workers	97 (6.2)
Sales workers	166 (10.7)
Skilled agricultural, forestry and fishery workers	88 (5.6)
Craft and related trades workers	77 (4.9)
Plant and machine operators, and assemblers	9 (0.6)
Elementary occupations	130 (8.3)
Housewives	553 (35.5)
Unemployed persons	399 (25.6)
Alcohol use disorder (AUDIT)	
Normal drinker	817 (52.4)
High-risk drinker	278 (17.8)
Alcohol use disorder	13 (0.8)
Self-esteem, the experience of suicidal urge over the past year	
No	1418 (91.0)
Yes	140 (9.0)
Subjective loneliness	
Very rare	687 (44.1)
Occasionally lonely	639 (41.0)
Often lonely	210 (13.5)
Mostly lonely	22 (1.4)
Self-esteem scale, mean ± SD	28.7 ± 3.4
Depression	
No	1438 (92.3)
Yes	120 (7.7)

ISCO: International Standard Classification of Occupations; ADUIT: Alcohol Use Disorders Identification Test.

accuracy of it was 0.80, the sensitivity of it was 0.98, the specificity of it was 0.62, and the F1 score of it was 0.97. The equation of the calibration plot was drawn along the ideal line; coefficient of determination (R squre) was 0.853 (Figure 3). The AUC of the developed nomogram for predicting the depression of senior citizens living alone is presented in Figure 4.

Table 2 The characteristics of the subjects according to the prevalence of depression, *n* (%)

Variables	Depression		*P*
	No (*n* = 1438)	Yes (*n* = 120)	
Age, mean ± SD	67.75 ± 5.53	70.95 ± 4.99	< 0.0001
Self-esteem scale, mean ± SD	29.06 ± 3.26	25.01 ± 3.43	< 0.0001
Subjective frequency of communication with other family members, mean ± SD	2.54 ± 0.95	2.05 ± 0.94	< 0.0001
Subjective frequency of communication with neighbors and friends, mean ± SD	2.25 ± 1.05	2.05 ± 1.11	0.05
Alcohol use disorder			< 0.001
Normal drinker	766 (93.8)	51 (6.2)	
High-risk drinker	258 (92.8)	20 (7.2)	
Alcohol use disorder	6 (46.2)	7 (53.8)	
Self-esteem, the experience of suicidal urge over the past year			< 0.001
No	1349 (95.1)	69 (4.9)	
Yes	89 (63.6)	51 (36.4)	
Subjective trust satisfaction with neighbors			< 0.001
No	163 (76.9)	49 (23.1)	
Yes	1275 (94.7)	71 (5.3)	
Subjective satisfaction with help from neighbors			< 0.001
No	420 (85.7)	70 (14.3)	
Yes	1018 (95.3)	50 (4.7)	
Subjective satisfaction of the living environment of the neighborhood			0.08
No	245 (89.7)	28 (10.3)	
Yes	1193 (92.8)	92 (7.2)	
Subjective satisfaction of the safety level of the neighborhood			< 0.001
No	230 (84.3)	43 (15.7)	
Yes	1208(94.0)	77 (6.0)	
Subjective satisfaction of the medical service of the region			< 0.001
No	386 (88.5)	50 (11.5)	
Yes	1,438 (92.3)	120(7.7)	
Regular club activities			< 0.001
No	975 (90.5)	103(9.5)	
Yes	463 (96.5)	17(3.5)	
Subjective loneliness			< 0.001
Very rare	685 (99.7)	2 (0.3)	
Occasionally lonely	617 (96.6)	22 (3.44)	
Often lonely	131 (62.4)	79(37.6)	
Mostly lonely	5 (22.7)	17(77.3)	

DISCUSSION

The prevalence of depression in senior citizens living alone in the community measured using the short form of the CES-D was 7.7%, which is 2-4 times higher than reported in previous studies (1%-4%)[28-31]. In particular, after combining the results from 16 studies, Beekman *et al*[32] reported that the weighted mean prevalence of depression in the elderly living alone in the community was 1.77%. In contrast, Park *et al*[33] identified the prevalence of depression in 6018 senior citizens who participated

Table 3 A model for predicting the depression of senior citizens living alone: Odds ratio and 95% confidence interval

Variables	Crude model	Adjusted model	VIF
Alcohol use disorder			
Normal drinker	1.00	1.00	
High-risk drinker	1.16 (0.68, 1.99)	1.08 (0.45, 2.59)	1.14
Alcohol use disorder	17.52 (5.67, 54.06)[a]	1.54 (0.16, 14.80)	1.20
Self-esteem, the experience of suicidal urge over the past year			
No (Ref)			
Yes	12.83 (7.74, 21.26)[a]	3.57 (1.55, 8.22)[a]	1.27
Subjective trust satisfaction with neighbors			
No (Ref)	1.00	1.00	
Yes	0.20 (0.12, 0.32)[a]	1.02 (0.43, 2.40)	1.37
Subjective satisfaction with help from neighbors			
No (Ref)	1.00	1.00	
Yes	0.24 (0.15, 0.39)[a]	0.29 (0.13, 0.66)[a]	1.40
Subjective satisfaction of the living environment of the neighborhood			
No (Ref)	1.00	1.00	
Yes	0.41 (0.25, 0.66)[a]	0.51 (0.23, 1.10)	1.19
Subjective satisfaction of the safety level of the neighborhood			
No (Ref)	1.00	1.00	
Yes	0.32 (0.20, 0.53)[a]	0.46 (0.21, 1.04)	1.19
Subjective satisfaction of the medical service of the region			
No (Ref)	1.00	1.00	
Yes	0.46 (0.28, 0.73)[a]	0.56 (0.26, 1.20)	1.19
Regular club activities			
No (Ref)	1.00	1.00	
Yes	0.38 (0.20, 0.70)[a]	2.04 (0.81, 5.15)	1.31
Subjective loneliness			
Very rare (Ref)	1.00	1.00	
Occasionally lonely	12.21 (2.86, 52.14)[a]	5.04 (0.58, 43.39)	6.87
Often lonely	206.54 (50.13, 850.86)[a]	187.19 (23.17, 1512.13)[a]	7.89
Mostly lonely	1164.50 (210.83, 6431.88)[a]	758.12 (56.44, 10183.32)[a]	3.10
Subjective frequency of communication with other family members	0.55 (0.49, 0.61)[a]	0.95 (0.71, 1.27)	2.16
Subjective frequency of communication with neighbors and friends	0.59 (0.53, 0.66)[a]	1.10 (0.81, 1.48)	2.12
Age	0.89 (0.85, 0.93)[a]	1.17 (1.07, 1.26)[a]	1.42
Self-esteem scale	0.70 (0.65, 0.74)[a]	0.81 (0.72, 0.91)[a]	1.33

[a]$P < 0.05$.
VIF: Variance Inflation Factor.

in the Nationwide survey on dementia in Korea that was 17.5% higher than in the present study. The differences in the reported prevalence of depression suggest that the number of senior citizens at a high risk of depression (even if not yet clinically diagnosed) may actually be higher than the reported number. Therefore, the development of a customized prediction model that can screen this high risk of de-pression group based on the results of the present study is needed.

Table 4 Validating a nomogram for predicting the depression of senior citizens living alone

Measure	Description	Value
TP		1012
TN		49
FP		29
FN		18
AUC		0.96
Accuracy	(TP + TN)/(TP + TN + FP + FN)	0.95
Balanced accuracy	[TP/(TP + FN) + TN/(TN + FP)]/2	0.80
Sens	TP/(TP + FN)	0.98
Spec	TN/(TN + FP)	0.62
FPR	FP/(TN + FP)	0.37
FNR	FN/(TP + FN)	0.01
F1 score	2/(1/Sens + 1/PPV)	0.97

TP: True positive; TN: True negative; FP: False positive; FN: False negative; AUC: Area under the curve; FPR: False positive rate; FNR: False negative rate; PPV: Potential path volume; Sens: Sensitivity; Spec: Specificity.

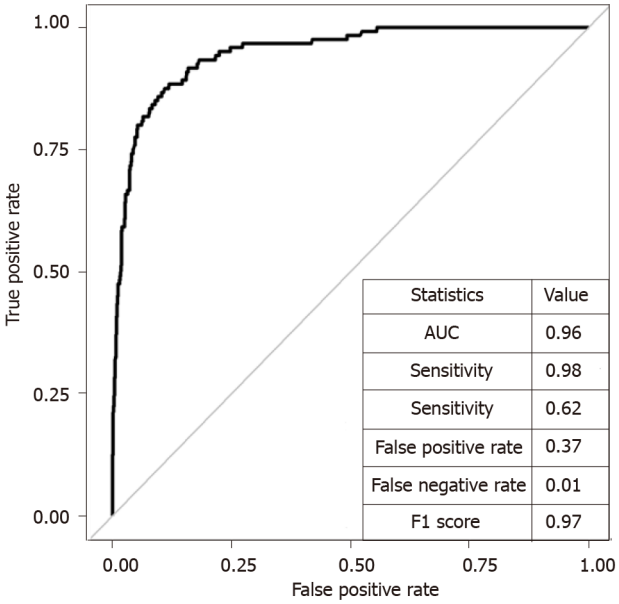

Figure 1 The area under the curve of the developed nomogram for predicting the depression of senior citizens living alone. AUC: Area under the curve.

In the present study, the significant predictors of depression in senior citizens living alone were suicidal ideation over the past year, dissatisfaction with help (support) from neighbors, subjective loneliness, age, and low self-esteem. It is known that the prevalence of depression in the elderly increases with age[34,35] and low self-esteem [36,37]. Many studies have reported that old people show a high risk of depression regardless of gender because they are more likely to lose their spouses, become physically weaker, have fewer opportunities to participate in social activities, become more susceptible to disease, and suffer from physical dysfunction[38,39]. Nevertheless, researchers have mainly tried to identify individual risk factors for depression using regression analysis[40-43], which negates discovering multiple risk factors for depression. In the present epidemiologic study, multiple risk factors for depression in senior citizens living alone were identified based on a nomogram. Moreover, the risk of depression in senior citizens living alone who had experienced suicidal ideation

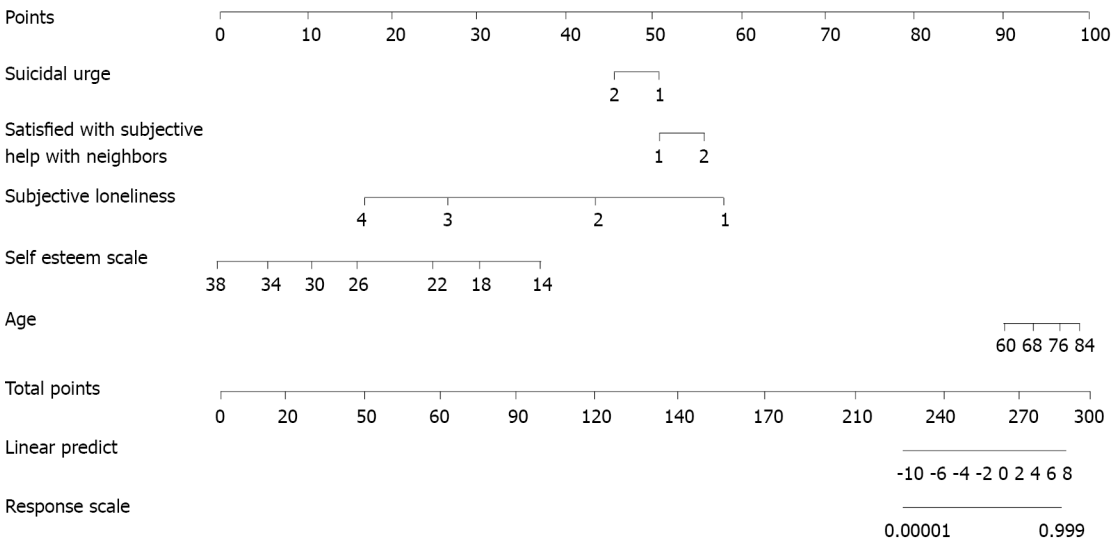

Figure 2 A nomogram for predicting the depression of elderly living alone.

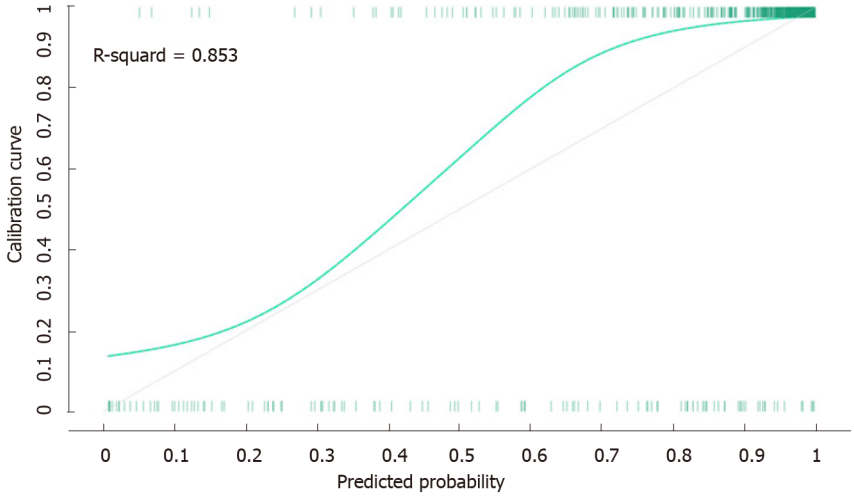

Figure 3 Calibration plot for nomogram model.

over the past year, were not satisfied with help (support) from neighbors, felt lonely, had low self-esteem (≤ 15 on the Rosenburg SES scale), and were ≥ 80 years old was 99.8%, which is very high. Therefore, screening this high-risk group for multiple risk factors and continuously monitoring them from a community perspective to prevent depression in the senile stage is urgently required.

Another finding of this study was that poor perceived social support or a weakened social network (social bonds and meaningful social contact[44]) was identified as a risk factor for depression in senior citizens living alone. A social network is a multidimensional concept that encompasses social relationships and factors such as the frequency of contact with family members, friends, and spouses; the degree of mutual assistance; and satisfaction with social relationships can be used to measure it[45]. Previously, several research groups have also reported that the lack of a social network is a major risk factor for depression in the elderly[41,43], which is in agreement with our results.

It has been reported that the reinforcement of a social network (such as support from acquaintances) can alleviate depression (*i.e.*, it is a preventative factor)[46]. In the case of senior citizens living alone, support from acquaintances such as neighbors can complement a lack of support from immediate family members and/or relatives. Senior citizens living alone and interacting with neighbors on equal terms is considered to be a very important element in their social networks. Park[47] reported that senior citizens who frequently met friends or neighbors had a significantly lower risk of depression and explained that this was because they received more social support when they met acquaintances more frequently. However, the results of the present

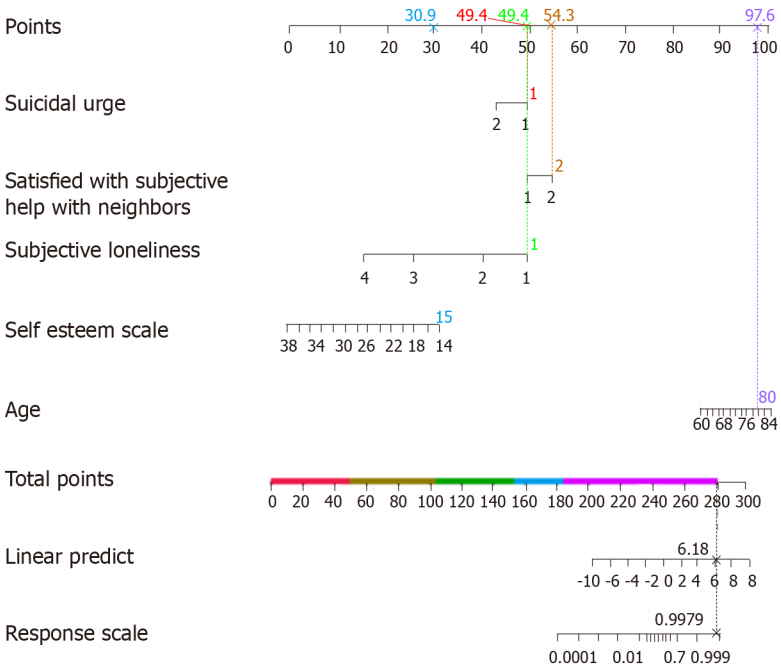

Figure 4 Application example of depression prediction nomogram for elderly living alone: Senior citizens who had suicidal urge over the past year, were not satisfied with subjective help with neighbors, thought that they were mostly lonely, had 15 points in the Self-Esteem Scale, and were 80 years or older.

study show that the frequency of contact with friends and neighbors (a quantitative factor) did not significantly affect the relationships in the social network whereas actual help (a qualitative factor) did significantly. Thus, this qualitative aspect of support that positively supported the emotional or economic problems of senior citizens living alone was more important than the number of meetings in the social network.

In summary, the results of the present study reveal that living alone due to the loss of a spouse and/or breakdown of the family network are more likely to cause emotional disorders such as depression. Moreover, strengthening qualitative aspects such as direct support from neighbors could more effectively lower the risk of depression than quantitative aspects such as the frequency of communication with family members or neighbors.

We identified factors related to depression in the elderly living alone using representative epidemiologic data and developed a nomogram that can help clinicians visually and conveniently identify the risk factors of depression, including social networks as well as demographic factors, which are the advantages of the study.

The limitations of this study are as follows: (1) We could not identify the severity of depression because we only analyzed the prevalence of depression in senior citizens living alone using a depression screening test, further studies are required to prove the risk factors of depression by identifying the severity of depression based on medical diagnosis; (2) We only used a self-report survey on the social isolation or social network of senior citizens living alone; a self-report survey poses the risk of recall bias, so in future studies, we will mitigate this by using interviews with social workers who regularly visit the homes of the senior citizens living alone and collecting data by using the Internet of Things; and (3) Since this is a cross-sectional study, it is impossible to determine causal relationships between the risk factors for depression in senior citizens living alone, and thus, a longitudinal study should be conducted in the future to achieve this.

CONCLUSION

The results of the present study imply that it is necessary to develop a support system customized for each senior citizen living along by strengthening his/her relationship network for preventing depression. Actual support from acquaintances such as neighbors (reinforcement of the qualitative aspect of the network) rather than the

frequency of physical contact (reinforcement of the quantitative aspect of the network) is key for protecting them from depression. Furthermore, establishing an improved mental health policy that identifies and continually manages groups of senior citizens living alone with a high risk of developing depression based on multiple risk factors is needed.

ARTICLE HIGHLIGHTS

Research background

Senile diseases are rapidly increasing globally due to the rapid aging of the population. Among these diseases, depression is an important and frequent psychia-tric disorder in the senile stage, and it is predicted to be the second major factor in the global burden of disease.

Research motivation

Although the number of senior citizens living alone is increasing, only a few studies have identified factors related to the depression characteristics of senior citizens living alone by using epidemiological survey data that can represent a population group.

Research objectives

This study developed a nomogram that allows physicians to check the multiple risk factors of depression of senior citizens living alone using visual graphs and to calculate the prevalence probability of depression while considering the personal characteristics of a subject based on these results.

Research methods

This study analyzed 1558 senior citizens (695 males and 863 females) who were 60 years or older. Depression, an outcome variable, was measured using the short form of the Korean version CES-D (short form of CES-D). This study built a depression prediction model using logistic regression analysis to find out the effect of each variable on depression. The developed depression prediction model contained a nomogram to make it possible for clinicians to interpret the prediction results easily.

Research results

In this study, the significant predictors of depression of the senior citizens living alone were the experiences of suicidal urge over the past year, dissatisfaction with help (support) from neighbors, subjective loneliness, age, and low self-esteem.

Research conclusions

The results of this study implied that it is necessary to develop a support system customized for subjects to strengthen the relation network for preventing depression in senior citizens living alone so that they can receive actual support from acquaintances such as neighbors rather than the frequency of physical contact.

Research perspectives

It is needed to establish an improved mental health policy that identifies high depression risk groups among senior citizens living alone based on multiple risk factors and continuously manages them.

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ORIGINAL ARTICLE

Retrospective Study

Affect regulation in psychoanalytic treatments of patients with a borderline personality disorder–psychoanalysis and psychodynamic psychotherapy–a comparison

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Abstract

BACKGROUND

A recent meta-analysis has confirmed that the effects of psychotherapy on patients with borderline personality disorders (BPD) are still insufficiently understood. Evidence of differences between different types of therapies has been questioned.

AIM

To study repetitive interaction patterns in patients with BPD undergoing either psychoanalysis or psychodynamic therapy.

METHODS

Psychoanalysis (PSA) or psychodynamic psychotherapy (PDT) was administered to 10 patients each, the two groups were matched. Therapy regimens were applied according to care as usual/manualized including quality control and supervision as usual. Randomization to one of the groups was done after baseline assessment. During classical PSA (n = 10) and PDT (n = 10), semiannually, recordings (audio or video) of five consecutive therapy sessions were taken over three years for an ex-post analysis. The patients' characteristics, such as affect parameters [Affect regulation and experience Q-sort (AREQ)], quality of object

study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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relations (quality of object relations scale) and personality traits [Shedler-Westen Assessment Procedure (SWAP-200)] were analyzed retrospectively by independent raters. Therapeutic action (psychotherapy process Q-sort) and affective (re)actions of the patients (AREQ) were then analyzed in relation to changes found in the patients' characteristics.

RESULTS

During the first year of therapy (PSA: n = 10; PDT: n = 9), the therapeutic method PSA was associated with significant improvements in the variable "SWAP Borderline", while in PDT change was not significantly different to baseline (PSA: P = 0.04; PDT: P = 0.33). Long-term results and follow up was available for seven participants in PSA and for five in PDT after three years; change in SWAP borderline for the whole sample was not significant at this time point when confronting to baseline (P = 0.545). However, differences between PSA and PDT were significant when analyzing the "mean change" in the SWAP Borderline variable after one year of therapy (P = 0.024): PSA led to slightly increased BPD symptoms, while PDT to a decrease; for the long run, variance of observed change was higher in PSA than in PDT (SD_{PSA} ± 9.29 *vs* SD_{PDT} ± 7.94). Our assumption that transference interpretations, closely followed by affective changes in the patient, could be useful modes of interaction was reproducible in our findings, especially when looking at the descriptive findings in the long-term data. The analysis of repetitive interaction structures demonstrated a very specific "time-lag" between therapeutic intervention and a corresponding increase in positive affect in successful therapy cases.

CONCLUSION

Exploring the change processes in the patients' characteristics and linking these changes to specific treatment strategies is of clinical importance when starting treatment and for its long-term progress.

Key Words: Psychoanalysis; Psychodynamic psychotherapy; Borderline personality disorder; Affect regulation; Affect regulation and experience Q-sort; Transference

Core Tip: This is a retrospective study to evaluate similarities and differences between psychoanalysis (PSA) and psychodynamic psychotherapy (PDT) in patients with borderline personality disorder. Both treatments were adequately effective. However, interactional aspects varied between PSA and PDT, requiring further investigation and consideration in therapy.

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INTRODUCTION

In treatment research and outcome studies, the specific factors within the therapeutic process which lead to clinically significant progress are often not as apparent as one might hope. This applies to classical psychoanalysis (PSA)[1] as well as to psychoanalytically oriented psychotherapy/psychodynamic psychotherapy (PDT)[2]. There is a lack of empirical data, particularly studies regarding psychoanalytic techniques, demonstrating the need for further research in this field[3]. Studies examining factors at work in the psychoanalytic process which determine outcome measures are rare[4, 5]. A major objective in psychoanalytic process research is the identification and validation of factors that lead to structural change and changes in maladaptive emotional patterns[6]. Intended for evaluating treatment progress, by examining

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process factors in connection to outcome measures, the following variables were of importance for the present study.

Outcome measures–patient characteristics and influencing factors

One important point is that experiences that are affectively meaningful[7] and/or affects that are difficult to tolerate represent the essential catalysts for change. Several treatment studies have examined or even verified this hypothesis[8-10]. Affective instability and impulsivity due to impaired affect perception and regulation leading to intra- and interpersonal dysfunction are key features in patients with borderline personality disorder (BPD). Clinical researchers have suggested that attention be paid to affective experience, for it determines positive outcomes[11] (see also[12-14]). In this matter, one should attempt to specify which affective state in connection with a particular personality pathology (*e.g.*, quality of object relation[5]) should be dealt with, in order to achieve satisfying treatment outcomes. The next logical step would then be to identify to what extent therapeutic action during the analytic process is responsible for the observed therapeutic results[15].

Therapeutic action–active elements and mediators

Psychoanalytic treatment studies investigating therapeutic interventions, which are mainly based on psychoanalytic models of mental functioning[16], are quite rare. However, Jones and Ablon[17] and Jones[18] conceptualized the mode of therapeutic action, describing it as a "repetitive interaction structure"[17,18]. This empirically derived conceptualization, of the therapist-patient interaction, covers both therapeutic actions [*e.g.*, clarification, confrontation, (transference) interpretation] and the patient's (re)actions. Depending on the perspective, a patient's (re)action may be seen as a reflection of his/her own psychic structure, object representation, compromise formation or impulse-defence configuration. A similar concept is known as the "transference-countertransference-process"[4]. Kantrowitz[4] and Jones[18] were one of the first to claim that dynamic aspects in patient-therapist interactions, being resonant or dissonant, are essential to therapy results[4,18]. The "two-person-process" should therefore be explored, to widen our knowledge of patient characteristics, particularly of influencing factors (such as affect parameters, transference patterns, or object relations patterns), and most notably regarding the agents of therapeutic action. The role these influencing factors play in therapy outcomes is currently quite well researched (see the quality of object relations[5]). The mediating function of the quality of the therapeutic relationship between patient and therapist, which is configured early on in therapy (in general as early as in the 2nd session), has already been described by Blatt and Zuroff[19] (2005) as being extremely important for the therapeutic process[19].

Hence, questions arise of how therapeutic interaction styles during psychoanalytic treatments come about, how they are displayed and explored and how these modes of interaction can create a foundation for treatment progress and the change process in general. In the current study, affect parameters and character traits (item constellations), which have already shown predictive power for therapy outcomes in other samples[20], were compared to differentiate types of interaction styles. Our investigation was applied to PSA and PDT of BPD patients in a retrospective study: By analyzing recordings of sets of consecutive sessions of two matched groups of BPD patients. The hypothesis was that changes during the treatment process would only occur if specific therapist-patient interactions emerge. The therapist-patient interaction was hypothetically defined as being effective when therapeutic action was met, after a particular time interval, with an affective (re)action (meaning an increase in positive affects) in the patient.

Based on the hypothesis, that significant therapeutic interactions occur in both treatment forms, the objective of the study was to explore the differences between "classical psychoanalysis–PSA" and "psychodynamic psychotherapy–PDT". By employing therapy concomitant evaluations, first treatment outcomes and second interaction styles of the repetitive interaction structure were examined for differences.

MATERIALS AND METHODS

Therapeutic methods and therapists

Our study group took audio/videotapes of PSA sessions and PDT sessions semiannually. All participants and the therapists involved gave their informed consent.

PSA: Ten patients were treated at four sessions a week with PSA. Each patient was treated by a different therapist. The analysts had a minimum of five years of clinical experience in conducting psychoanalytic treatment and had completed their training at the Vienna Psychoanalytic Society [German: Wiener Psychoanalytische Vereinigung (WPV)/IPA]. Weekly supervisions, based on a modern, object-relational Kleinian model[21,22] and additionally two external supervisions, each performed every three months by two training analysts from the British Psychoanalytic Society (Segal H and Daniel P), verify the analytic quality of and therapy adherence to the therapeutic model.

PDT: Ten further patients were treated at two sessions a week with PDT. In this group also, each patient was treated by a different therapist. The therapists had completed their psychotherapeutic training according to the manual for PDT[14]. Supervisions, ensuring the quality of therapy and therapy adherence, were performed weekly by an experienced training analyst and PDT supervisor.

Psychoanalysis: In psychoanalytic treatment, non-directive listening is carried out with a neutral attitude, aiming to overcome sources of resistance, with the method of free association at the heart of the technique. Thus, although the analyst must get involved with the patient, he remains "equidistant" from the id, ego, and superego, as well as with respect to conflicts in the relationship and within the therapist himself [23]. Key psychoanalytic concepts (the unconscious, drives, defenses, object relations, Oedipus complex, transference) have a direct impact upon concepts for treatment technique (countertransference, interpretation, resistance)[24]. The analyst's focus is on the patient's mind during the therapy session rather than on the patient's existence in "external reality". The treatment goal is the development of ability for self-reflection and analysis, symbolizing and engaging in object relations.

Unlike in psychoanalytic oriented therapy, the higher frequency of the sessions provides a suitable framework for the analysis of hitherto abstract fears, wishes, and unconscious conflicts. However, as distinguished from PDT, the indication for PSA is sometimes limited due to lacking reflective functioning skills, ego-integration, and externalizing defense processes.

Therapists' adherence to the method taught by the Vienna Psychoanalytic Society (WPV/IPA) was ensured by supervision carried out on a regular basis, as described above.

PDT in patients with a borderline personality: For a more thorough description of the applied method, see the textbook of Burian and Grossmann-Garger[25]. Psychodynamic or "psychoanalytic-oriented" psychotherapy is derived from psychoanalysis, but it differs from it not only by the frequency of sessions, but also by the lack of the use of a couch[26]. The therapeutic activity is defined, rather, by a clear problem statement and by work on the alleviation of symptoms or on identity integration. This method emphasizes the importance of the patient's actual external reality, and emphasis is brought to the here and now[25]. Transference interpretation and analysis of the transference relationship aims for modification of internalized patterns regarding object relations, behavior, and affect perception and regulation. Treatment goals often imply work on a sense of consistency about who oneself and others are across time and different contexts[26].

In contrast with psychoanalysis, neutrality frequently has to be sacrificed because of danger arising from possibly destructive enactment, when patients seem unable to contain their inner psychic conflicts. Supportive interventions are sometimes necessary.

Adherence of the therapists to the manual[14] was ensured by the supervision carried out at a regular basis mentioned above.

Participant population

We applied a hot spot recruiting strategy that allowed for a matched pair design. The patient recruitment timeframe was four years. All patients willing to participate in the study, and fulfilling the inclusion criteria were included in the study. Participants treated with PSA and PDT were matched according to age, gender, DSM-IV-TR diagnosis[27] (Diagnostic and Statistical Manual of Mental Disorders, DSM, American Psychiatric Association 2000), pathological personality traits, assessed using Shedler-Westen Assessment Procedure-200 (SWAP-200)[28], and Kernberg[29]'s structural diagnosis. The audio/videotape analysis of recorded sessions and comparing the two therapeutic methods applied was carried out only after the completion of three years of psychotherapy. Thus the analysis's findings did not influence the therapeutic interventions. All patients showed the structural diagnosis of a BPD[29]. All

participants underwent Structured Clinical Interview for the DSM-IV-TR Disorders and an examination by a psychiatrist (*i.e.*, care and quality control as usual). Only participants fulfilling the DSM-IV diagnosis of BPD were included in the study. The participants had the following DSM-IV diagnosis of axis 1 comorbidities: Major depression, dysthymia, depression, anxiety disorder, eating disorder (22%: 296.00, 17%: 300.4, 10%: 311, 39%: 300.0, 12%: 307.0). The study included 20 patients, with an average age of 31 years (± 9). Patients were randomly assigned to therapists, often depending on the availability of a therapist.

The sample consisted of four (20%) male and 16 (80%) female patients with a relatively high level of education: While three patients (15%) only finished compulsory school, 14 patients (70%) were high school graduates and three (15%) had a university degree. Most of the patients (17) were single (85%); however, two (10%) were married, and one (5%) was divorced. One patient from the PDT group was excluded from the analysis since only baseline data were collected for the patient, and no further data on therapy development during the follow-ups were available. In Table 1, further descriptive analysis of the patient population, including mean SWAP profile scores, for both therapy groups (PSA *vs* PDT) is presented.

Ethic: Approval from the ethics committee of the City of Vienna and the Medical University of Vienna was given; EK Nr.: 2169/2013. This study was done in accordance with the terms set forth in the Declaration of Helsinki. Written informed consent was given.

Design

After obtaining informed consent for this observational study, treatment sessions of twenty patients were recorded semiannually over a period of three years. In the case of PSA, treatment sessions were assessed using verbatim transcripts and audio recordings of the peer-supervisions as well as external supervisions, while in the case of PDT, sessions were assessed using video recordings.

From the beginning of therapy, in an interval of six months, recordings (audio or video) of five consecutive therapy sessions were analyzed for patient characteristics and interactions, using the following instruments.

Instruments analyzing patient characteristics

SWAP-200: Character traits were determined using the SWAP-200[24,26], assessed by two independent external raters, both of whom were medical students, each having at least six years of experience with the instrument; with adequate training, they regularly underwent assessments of inter-rater reliability. Their inter-rater reliability showed a constant κ_{mean} = 0.69. The SWAP-200 is a personality assessment instrument for use by clinically experienced mental health professionals requiring a professional assessment (*e.g.*, during an ongoing therapeutic engagement) or a systematic clinical research interview. Test-retest reliability for the instrument is r = 0.85 for the SWAP's trait and personality disorder dimensions. The mean reliability when comparing to DSM-IV personality disorders was 0.90 for SWAP scales. Multiple research groups in multiple samples have provided strong evidence, qualifying SWAP-200 as a reliable and valid measure independent from applied methods[30]. The SWAP is based on the Q-sort method, and thus it uses a fixed score distribution, with items being rated as more or less descriptive of a person, with the possibility of detecting even fine nuances.

Based on the SWAP-200 scoring systems, personality score profiles are generated. The scores are standardized scores (T-scores) based on norms established in a clinical sample[28]. Scores indicate the match between a patient and a diagnostic prototype derived either from DSM-IV diagnostic categories (which include the personality disorders in DSM-IV as well as depressive personality disorder) and/or an alternative set of personality syndromes derived empirically (*via* Q-factor analysis, see SWAP manual). Thus, a high degree of overlap with the SWAP-profile "dysregulated/borderline" *(i.e.*, variable SWAP-borderline") indicates that the degree of resemblance between the actual patients with the diagnostic prototype representing the personality disorder is also very high. The "Borderline/Emotionally Dysregulated" personality is described as overlapping with the DSM-IV construct. Patients with this profile lack affect-regulation (intense and volatile affect) and show states of desperation and despair with a tendency to self-harm[31].

Affect experience and affect regulation Q-sort (AREQ): Affective experience and affect regulation were assessed using the affect regulation and experience Q-sort AREQ[32,33]. The AREQ is an expert-rating, 98-item Q-sort test, exploring affective functioning using an interview. Sufficient convergent and discriminant validity have

Table 1 Descriptive analysis of the patients in the therapy groups psychoanalysis and psychodynamic psychotherapy

	PSA (*n* = 10)	PDT (*n* = 9)	*P* value[1]
Mean age (yr)	30.4 ± 7.5	31.9 ± 10.2	0.719
Sex	8 f, 2 m	7 f, 2 m	0.912
Therapeutic dose (mean)	390 sessions	124 sessions	0.001
DSM IV axis II diagnosis	Borderline personality disorder		
Structural diagnosis	Borderline personality organization		
SWAP diagnosis			
Paranoid	49.37	48.85	0.871
Schizoid	49.65	54.79	0.201
Schizotypal	51.27	53.72	0.475
Antisocial	49.22	45.62	0.132
Borderline	52.97	48.62	0.289
Histrionic	53.92	46.37	0.127
Narcissistic	50.86	46.56	0.249
Avoidant	47.78	54.18	0.037
Dependent	49.29	52.01	0.233
Obsessive-compulsive	47.65	52.51	0.245

[1]*P* value calculated using ANOVA. PSA: Psychoanalysis; PDT: Psychodynamic psychotherapy (*i.e.*, psychoanalytically oriented psychotherapy); SWAP: Shedler-Westen Assessment Procedure.

been shown. Affect experience includes the following three factors: Socialized negative affect, positive and intense negative affect, and affect experience, the latter of which itself includes reality focused response, externalizing defense, and avoidant defense [32]. The inter-rater reliability of two independent raters, both having an average of six years of experience with the instrument, showed an average $\kappa = 0.70$. They were both medical students, undergoing regular training and quality assessment.

Quality of object relations scale (QORS): The quality of object relations was evaluated by two independent external raters, using the QORS[33,34], and showed an inter-rater reliability of $\kappa_{mean} = 0.69$. The raters were both medical students, undergoing regular training and quality assessment. The QORS is an interview-based expert-measure with adequate criterion-related, construct validity[35]. The QORS assesses personality pathology with respect to object-relational maturity. Object relations are intrapsychic representations of self- and objects which arise out of emotionally important early relationships. The level of object relations is a known factor related to the outcome of psychotherapy. The interview scale consists of five levels of object-relational patterns with the manual giving explicit criteria for each of them and a description of prototypical cases. The rater distributes a total of 100 points, allocating them to five object-relational levels: Primitive, searching, triangular, controlling, and mature (for a thorough description of the method see[35]). According to Lindfors and colleagues, low quality of object relations is characterized by discontinuity and devaluation in relationships, with poor self-confidence and major separations in childhood identified as predictors of low-QOR[35].

Instruments analyzing processes occurring during therapy

Psychotherapy relationship questionnaire (PRQ): The quality of the psychotherapeutic relationship was assessed using the German version[36] of the PRQ[37]. With the help of 90 items, five dimensions of transference relationship patterns (hostile, narcissistic, anxious/preoccupied, avoidant/counter dependent, and sexualized) as well as a positive working alliance (secure/engaged) can be differentiated. The dimension "positive working alliance" is of particular interest to the current study, and as Bradley *et al*[37] and Tanzilli *et al*[38] have already shown, it acts as an indicator for the quality of the working relationship between patient and therapist, which in turn, strongly predicts treatment outcome in psychotherapy[39].

Psychotherapy process Q-sort (PQS): Patient-therapist interrelation variables were assessed using the PQS[40,41]. For this study, in order to analyze the process occurring during therapy, only items related to therapeutic action were utilized[41] (Table 2). From a psychoanalytic perspective, these items specifically covered transference interpretations considering the "total situation" described by Joseph/Astor[42]. The goal was to evaluate dyad-specific interaction structures, which are recurrent, mutually influencing patterns of interrelation between therapist and patient, whose experience, recognition, and understanding are fundamental elements of therapeutic action[17,34]. Therapeutic action was evaluated by two independent raters (κ_{mean} = 0.84) using the items presented in Table 2.

The raters were medical students, undergoing regular training, interrater assessments, and quality control.

Statistics

The statistical methods of this study were performed and reviewed by a biomedical statistician, Sophie Frantal, from the Medical University of Vienna before submission.

To begin with, a descriptive analysis (mean, standard deviation, minimum and maximum) of the variables of interest was created. However, due to the rather small sample-size, also ranges were used to characterize the sample. Next, the differences between the two groups (PSA and PDT), based on pre-post comparison of the main factor "SWAP Borderline"[28], were examined. For this purpose, the scores at the beginning of therapy (*t1*), after one year of therapy (*t3*) and after three years of therapy (*t7*), were evaluated. Also, additional factors possibly influencing outcome, such as age, gender, education, family status and gender of the therapist, were included in the analysis. Missing values, detected after data documentation, were excluded from the analysis. To answer the question dealing with the differences between the two therapeutic methods in concern to the changes observed in the variable "SWAP Borderline", all variables of interest were tested in univariate analysis (linear regression or variance analyses). Only variables that showed statistically significant p-values in the univariate analysis were subsequently tested in a multivariate linear model (ANOVA or ANCOVA). Furthermore, effect size was also calculated for groups PSA and PDT.

In the following step, differences between the two therapy groups concerning the factors "positive affect" (AREQ), "QORS-total score", "therapeutic action" (PQS), and "positive working alliance" (PRQ) were assessed. These factors were explored in the same manner as the factor "SWAP Borderline". Similarly, in the cases, where the variable of interest "therapeutic method" did not show any statistically significant effects, no further risk factors were analyzed. The number of therapy sessions ("therapeutic dose"), defined as the mean number of sessions in which each therapeutic method (PSA *vs* PDT) was applied, was also tested as a factor possibly having influence on the variable "Borderline".

Analyses were performed using the "freeware" program R.2.8.0[43] and SPSS Statistics version 17.0. $P < 0.05$ were considered to be statistically significant.

RESULTS

Progress results

The differences between the two therapeutic methods, PSA and PDT, with regards to the main variable "SWAP Borderline", are presented in Table 3. Even though the differences are not significant, a simple comparison between the mean values shows that borderline pathology, in the case of PSA, continuously decreases. However, in the PDT group, it primarily increases, particularly in the first year. This observation is also reflected in the effect size: d = 0.79 after one year of PSA, d = 0.88 after three years of PSA, d = 0.04 between first and third year of PSA; d = |0.40| after one year of PDT, d = 0.04 after three years of PDT, d = 0.33 between first and third year of PDT. After three years of PDT, the main variable "Borderline" improves considerably compared to the values measured after the first year of PDT, whereupon the therapeutic method PSA shows less change in the same time span. This, however, must be interpreted with caution, due to the fewer number of patients after three years of therapy (three dropouts in PSA, four dropouts in PDT after three years). Even tough, the dropout rate is not surprising, as it might be related to the frequent alliance ruptures typical for borderline pathology, and the naturalistic design must be considered before generalizing this finding. However, looking beyond the main variable and more at individual items in detail, in both groups, patients who dropped out were charac-

Table 2 Items from the psychotherapy process Q-sort–that were applied to assess therapeutic action in the present study

Item	Description
2	Therapist draws attention to patient's non-verbal behavior, *e.g.*, body posture, gestures
22	Therapist focuses on patient's feelings of guilt
28	Therapist accurately perceives the therapeutic process
36	Therapist points out patient's use of defensive maneuvers, *e.g.*, undoing, denial
40	Therapist makes interpretations referring to actual people in the patient's life
50	Therapist draws attention to feelings regarded by the patient as unacceptable (*e.g.*, anger, envy, excitement)
62	Therapist identifies a recurrent theme in the patient's experience or conduct
65	Therapist clarifies, restates, or rephrases patient's communication
67	Therapist interprets warded-off or unconscious wishes, feelings, or ideas
79	Therapist comments on changes in patient's mood or affect
80	Therapist presents an experience or event in a different perspective
82	The patient's behavior during the hour is reformulated by the therapist in a way not explicitly recognized previously
93	Therapist is neutral
98	The therapy relationship is a focus of discussion
100	Therapist draws connections between the therapeutic relationship and other relationships

Table 3 Differences in the variable "Shedler-Westen Assessment Procedure Borderline" measured at baseline (*t1*), after 1 yr of therapy (*t3*) and after 3 yr of therapy (*t7*) (mean ± SD)

		n (%)			Min	Max	*P* value[1]	*dt3*[2]	*dt7*[2]
Baseline (*t1*)	PSA	10	52.97	8.73	42.69	71.88		0.79	0.88
	PDT	9	48.62	8.56	40.23	67.63		|0.40|	0.04
	Total	19	50.90	8.70	40.23	71.88	0.289	0.24	0.45
After 1 yr of therapy (*t3*)	PSA	10	46.26	8.21	29.99	60.21			0.04
	PDT	9	51.80	7.49	40.26	65.30			0.33
	Total	19	48.88	8.17	29.99	65.30	0.145		0.20
After 3 yr of therapy (*t7*)	PSA	7	45.96	6.75	37.63	56.78			
	PDT	5	49.01	10.20	38.90	61.33			
	Total	12	47.23	8.07	37.63	61.33	0.545		

[1]*P* value calculated using ANOVA.
[2]*d* = Cohen's. *d*: Represents effect size measured after 1 yr (*t3*) and after 3 yr (*t7*) of therapy.
PSA: Psychoanalysis; PDT: Psychodynamic psychotherapy; SWAP: Shedler-Westen Assessment Procedure; SWAP-borderline: SWAP personality syndrome "dysregulated/borderline".

terized by an increase of projective mechanisms (projection, projective identification) as displayed in SWAP-Item 076 and Item 116. This was observed mainly during the first year (Figure 1), but generally persisted until the moment a patient dropped out of therapy. Additionally, it was observed that these patients and their therapists showed low scores in the PQS-Item 36, 50 (displaying therapists' work on defensive mechanisms) and PQS-Item 28 (therapists' accurate perception of the therapy process) (Table 2). These ratings might display a lack of ability to perceive, contain and work through the projective mechanisms in the therapeutic relationship (Figure 1), which was also observed and discussed in the supervision group. Interestingly, drop-out patients' pressure and usage of projective mechanisms were low at the beginning of both forms of therapy compared to continuing and finishing patients, who presented higher amounts of projective identification at the beginning of therapy. Also, PQS Items 36, 50, and 28 (Table 2) were higher in cases where therapy reached completion.

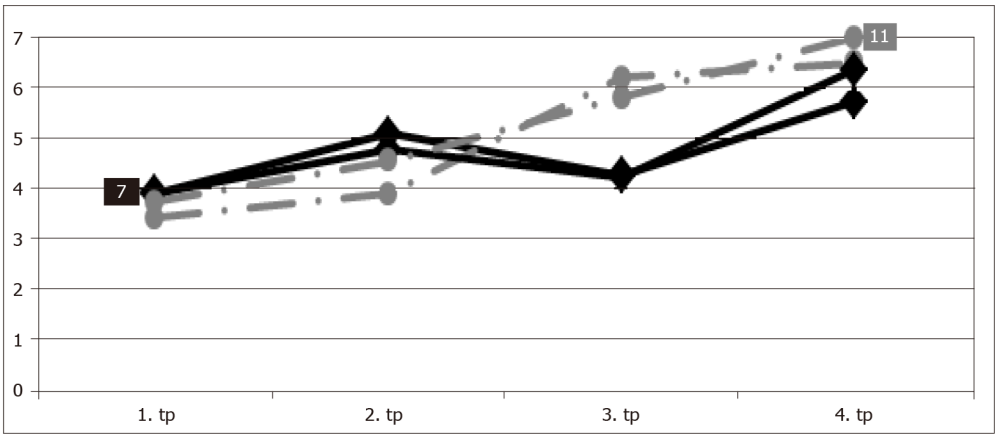

Figure 1 Course of Shedler-Westen Assessment Procedure-items 76 and 116. Course of sensible Shedler-Westen Assessment Procedure-Items 076 ('7', black) and 116 ('11', grey) both assessing "projective identification" (Item 076: "Manages to elicit in others feelings similar to those he or she is experiencing" (*e.g.*, when angry, acts in such a way as to provoke anger in others; when anxious, acts in such a way as to induce anxiety in others); Item 116: "Tends to see own unacceptable feelings or impulses in other people instead of in him/herself."). Disrupted line: Broken off treatment, continuous line: Completed treatment; *tp*: Half-yearly measurements showed a significant effect of time ($P = 0.004$). SWAP: Shedler-Westen Assessment Procedure.

As far as the drop-out patients could be reached, they reported no increase in self-harming behavior; one was referred to supportive therapy by the therapist due to the development of psychotic transference.

First year of therapy–outcome variables

Considering the patients' characteristics, changes in borderline pathology and, simultaneously, improvements in the quality of object relations were observed, when both forms of therapy were taken into account. With regard to the patient, an increase in the ability to recognize positive affects was observed during PSA, while a decrease in the same category was seen during PDT. However, an increase in therapeutic action was observed during PDT, while therapeutic action during PSA treatment stayed constant. Concerning the working alliance, a reduction in the positive working relationship between therapist and patient was noted during PSA treatment, whereas an increase in the same category was observed during PDT. The descriptive analysis of the pre-post variables (SWAP-Borderline, AREQ-positive affect, QORS-total score, PRQ-positive working alliance and PQS-therapeutic action), defined as the difference between the values of each variable at beginning of therapy (*t1*) and after one year of therapy (*t3*,) is presented in Table 4 ("SWAP-borderline" = SWAP personality syndrome "dysregulated/borderline"). All means were close to zero (with the exception of "SWAP-Borderline"), showing little to no difference between baseline and follow up (after one year) measurements (Table 4: "mean"). Only the variable "SWAP-Borderline" showed a negative response during the first year of PDT treatment (*i.e.*, less BPD symptoms), and a positive value in the PSA treatment (*i.e.*, more BPD symptoms) however, the standard deviation was in this case somewhat higher than in the other variables (mean SWAP Borderline PSA = 6.71; SD ± 9.29; mean SWAP Borderline PDT = -3.18; SD ± 7.94).

In univariate analysis, the difference between the two therapeutic methods in concern to changes in the variable "SWAP Borderline" was examined and was shown to be significantly different (PDT: Estimate 4.07; T = 2.19; SD ± 1.73; $P = 0.402$; Table 5). The age of the patients was found to not be significantly different, with a $P = 0.087$, however it still displayed a strong trend, with younger patients showing better results (Table 5). Thus, it is evident that during the first year of therapy, the therapeutic method PSA led to a higher decrease regarding the symptom profiles reproduced in the variable "SWAP Borderline" than the therapeutic approach PDT (Table 3). Nevertheless, a higher variance of individual therapy results after the first year occurred in PSA (Table 3). Thus, when looking at the mean change in the variable "SWAP Borderline" after one year, PDT showed a significantly more pronounced improvement (Table 4). Sex, education, and family status of the patient as well as the sex of the therapist were not found to be significant. A multivariate analysis, regarding the risk factors therapeutic method and patient age, was also performed and the following results were found: In both cases, the levels of significance did not change and the therapeutic method remained significant (PDT: Estimate 4.01; T = 2.33 ± 1.73; *P*

Table 4 Changes in patient characteristics, borderline pathology, and object relations after one year of therapy (mean ± SD)

				Min	Max	*P* value
SWAP Borderline	PSA	6.71	9.29	-1.58	29.58	0.024[a]
	PDT	-3.18	7.94	-10.61	15.22	
	Total	2.02	9.85	-10.61	29.58	
AREQ positive affect	PSA	-0.11	0.98	-1.57	1.86	0.513
	PDT	0.19	0.86	-0.94	1.43	
	Total	0.03	0.91	-1.57	1.86	
QORS total score	PSA	-0.20	0.73	-1.60	0.90	0.726
	PDT	-0.34	0.75	-1.70	0.50	
	Total	-0.26	0.72	-1.70	0.90	
PRQ positive working alliance	PSA	0.15	0.35	-0.33	0.50	0.339
	PDT	-0.27	0.73	-1.08	0.50	
	Total	-0.08	0.60	-1.08	0.50	
PQS therapeutic action	PSA	-0.00	0.60	-0.73	1.00	0.318
	PDT	-0.28	0.45	-1.07	0.47	
	Total	-0.14	0.53	-1.07	1.00	

[a]*P* < 0.05. Mean differences ("mean") regarding the mean scores of the relevant variables ("Shedler-Westen Assessment Procedure-borderline", "Affect experience and affect regulation Q-sort-positive affect", "Quality of object relations scale total score", "Psychotherapy relationship questionnaire-positive working alliance", "Psychotherapy process Q-sort therapeutic action") between the score at baseline *vs* the score after the first year of therapy (t1 minus t3, where t1 represents measurements taken at baseline and t3 after 1 yr of therapy). PSA: Psychoanalysis; PDT: Psychodynamic psychotherapy; SWAP: Shedler-Westen Assessment Procedure; AREQ: Affect experience and affect regulation Q-sort; QORS: Quality of object relations scale; PRQ: Psychotherapy relationship questionnaire; PQS: Psychotherapy process Q-sort.

Table 5 Univariate analysis of the variable "Shedler-Westen Assessment Procedure Borderline" (mean ± SD)

Patient characteristics	Estimate		T value	*P* value
PDT group	4.07	1.86	2.19	0.042[a]
Sex of patient	2.89	5.18	0.56	0.584
Sex of therapist	7.15	4.24	1.68	0.109
Education: Apprenticeship	12.21	10.49	1.16	0.261
Education: Vocational school	3.15	8.29	0.38	0.709
Education: High school	-2.80	5.78	-0.48	0.635
Married	-1.03	7.19	-0.14	0.888
Divorced	-0.39	9.90	-0.04	0.969
Age	0.41	0.22	1.81	0.087

[a]*P* < 0.05. SWAP-borderline: Shedler-Westen Assessment Procedure personality syndrome "dysregulated/borderline"; PDT: Psychodynamic psychotheray.

= 0.033), while patient age continued to not reach the fixed significance level (Age: Estimate 0.40; T = 1.98 ± 0.20; *P* = 0.064).

Secondary variables

Examining the four secondary variables during the first year of therapy, no statistically significant differences could be found between the two types of therapeutic methods (PSA *vs* PDT): AREQ-positive affect (estimate -0.31; T = -1.70 ± 0.18; *P* = 0.117), QORS-total score (estimate 0.08; T = 0.38 ± 0.20; *P* = 0.714), PRQ-positive working alliance (estimate 0.00; T = 0.01 ± 0.26; *P*= 0.993) and PQS-therapeutic action (estimate 0.14; T = 1.01 ± 0.14; *P* = 0.333). Consequently, no further calculations and analyses were

performed, regarding the secondary variables. Similarly, no significant changes were found in the variable "therapeutic dosage" (P = 0.298). However, the changes observed after time-point *t5*, *i.e.*, after 2.5 years of PDT, resulting in a constant decrease in borderline pathology, is quite interesting (difference in "SWAP Borderline", in the 175th session mean was -9.08; in the 245th session mean was 15.22). In the therapeutic method PSA, a constant decrease in borderline pathology is seen from the start.

"Repetitive interaction structures," which are defined as responses of the patient towards therapeutic action with an increase in positive effects, are depicted in Figure 2. The graph illustrates a sequence of five consecutive sessions measured on a semi-annual basis. However, it is essential to mention that Figure 2 is merely a graphic presentation of the data since therapeutic action had no significant influence on the variable "SWAP Borderline". The main finding is depicted in Figure 2: The time-lag of the repetitive "interaction structures" in PSA is shorter (approximately two/three sessions) than the time-lag observed during PDT (about five sessions). Thus, the descriptive analysis showed patterns quite distinct for each method.

Qualitative analysis of interactive patterns, example

With respect to PSA, a qualitative analysis of character traits with the SWAP showed repetitive patterns of trait fluctuations over the course of three years. The interpretation of the object-relationship dyad in transference with patient-, therapist-, and interaction-variables carried out with the PQS showed repetitive patterns of interaction when treatment was successful. PQS patient items and interaction items showed a rise in patient items when "interaction structure" items were rated as low and vice versa (Figure 3). In unsuccessful therapy attempts, in neither the SWAP nor in the PQS/AREQ ratings did similar patterns manifest, with a relatively constant course over time (not shown). When looking at a set of five consecutive sessions, positive affective response (measured with the AREQ) increased following therapeutic interventions, with a time-lag phenomenon manifestly present (Figure 4). Qualitative analysis revealed shorter time-lag for the positive affective response of the patient towards the therapists' interaction in PSA in contrast to PDT (Figure 2; PSA two/three sessions, PDT five sessions).

DISCUSSION

The combined analyses of repetitive patient-therapist interaction structures (AREQ, PQS) and patient characteristics (SWAP-200, AREQ, QORS) performed in this study have met the demands for therapy concomitant evaluations, which were briefly mentioned in the introduction and have also been described in the literature[10]. By means of such therapy concomitant evaluations, where the assessment of therapeutic techniques and changes in patient characteristics are combined, the possibility of specifying specific therapeutic methods is opened up.

Changes in patient characteristics

Our results have shown that patients, who were treated with PDT in the same time frame as patients treated with psychoanalysis proper, showed similar changes in the quality of object relations and affect parameters, albeit, however, with considerably distinct changes in personality pathology.

The increase in borderline pathology at the beginning of the PSA treatment is quite noticeable (mean change in SWAP borderline: PSA +6.71, PDT -3.18) with a higher variance of observed changes in the PSA group especially in the first year of therapy (Table 4). However, after one and after three years of therapy, mean “SWAP borderline” score was lower in the PSA group, while in the PDT group this score was even slightly increased.

These results indicate that indications for the two different methods must be assigned wisely, as they are not interchangeable.

Although all patients were diagnosed with BPD at the beginning of treatment, the two groups differed in the first six months of therapy. Considerably more patients in the PDT group were affected by social inhibitions (avoidant/self-conscious traits) and discomfort in social (schizoid traits) and close relationships (schizotypal traits). Borderline patients with schizoid personality pathology, treated with PDT, showed improvements, especially after the first year of therapy, while corresponding patients in the parallel group, treated with PSA, showed positive changes right from the start. Similar results have been reported in the Anna Freud Center study[44], where the psychoanalytic treatment of young patients with borderline and narcissistic

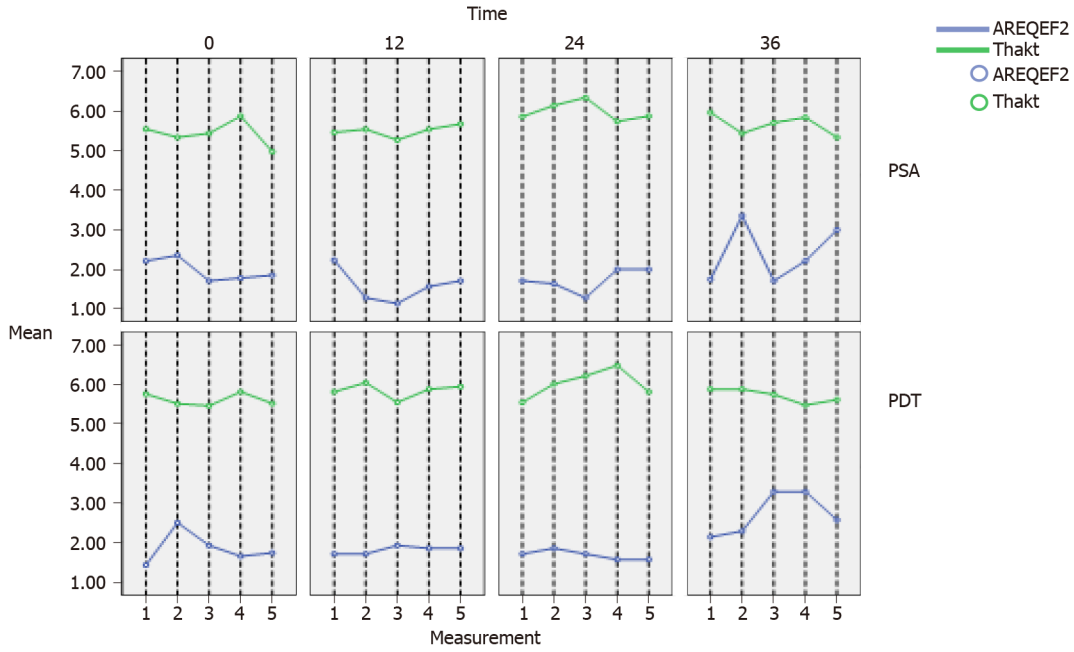

Figure 2 Therapeutic action and positive affect. The evaluation of therapeutic action ('thakt', *i.e.*, psychotherapy process Q-sort-therapeutic action) and positive affects in patients ['Affect experience and affect regulation Q-sort (AREQ)-EF2', *i.e.*, AREQ-positive affect] was performed semi-annually in five consecutive therapy sessions (measurement 1-5). The results of the annual measurements (baseline, 12, 24 and 36 mo) of thakt and AREQ-EF2 (mean) are presented in the figure for the psychoanalysis and for the psychodynamic therapy group. PSA: Psychoanalysis; PDT: Psychodynamic psychotherapy.

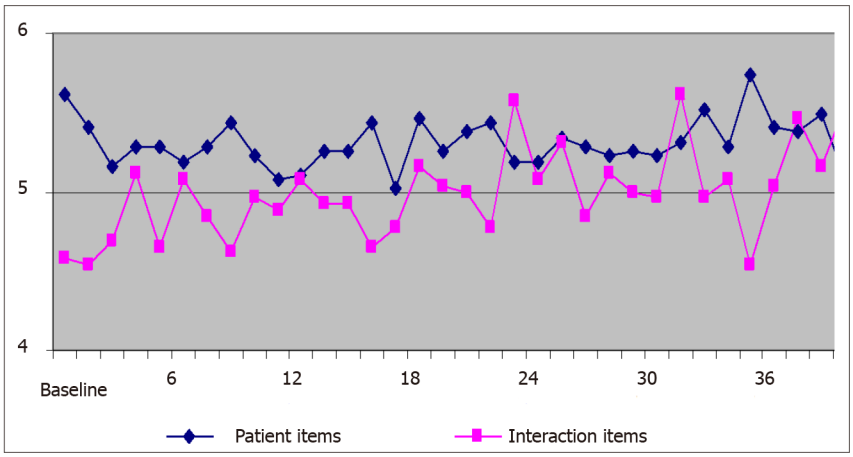

Figure 3 Patient-therapist interactions. Object-relation dyad measured with psychotherapy process Q-sort. Patient items are shown in blue, "interaction structure items" are shown in magenta. The follow-up was > 36 mo.

personality disorders was performed at different frequencies (five times *vs* once *per* week) and then ultimately compared. The problems encountered with narcissistic personalities of not being able to accept interpretations[45] or creating transference configurations, where the analyst becomes a shut-out observer[46], are more likely to be solved during PSA.

In the descriptive analysis of the secondary moderating and mediating variables, it appeared that in higher-frequency therapeutic methods, such as PDT, therapeutic action increased during the first year of therapy. This observation could possibly be related to the therapists' more vigorous focus on the working alliance (see an increase in a positive working relationship). But, one can only speculate here, since the secondary variables did not show any statistically significant differences between the two therapeutic methods. The therapeutic dose, interestingly, also did not show any statistical significance, by which closer observation of the interaction process becomes more relevant.

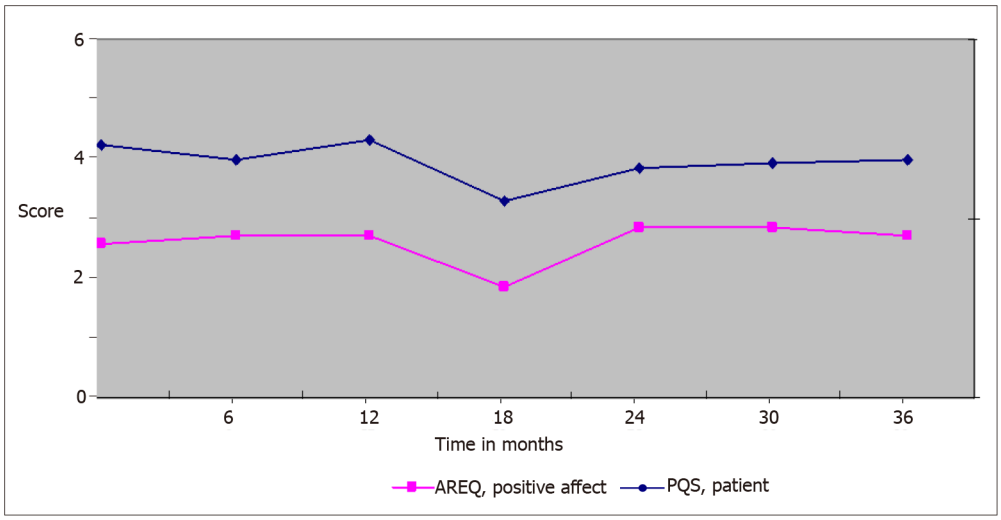

Figure 4 Affective response and psychotherapy process: Case example. Affective response (Affect experience and affect regulation Q-sort: Positive affect, shown in magenta) and therapeutic interaction structures (Psychotherapy process Q-sort: Shown in blue) over the course of 36 mo. PQS: Psychotherapy process Q-sort; AREQ: Affect experience and affect regulation Q-sort.

Interaction process

Psychoanalyses, with quick interactions (meaning that a therapeutic action is followed by an increase in positive affects in the patient within the next two to three sessions, *i.e.*, within two or three days), show a continuous decrease in the borderline pathology. Transference interpretations[42,47], closely followed by affective changes in the patient, present the most effective interaction styles in PSA. Strachey[48] described, taking into consideration Melanie Klein's theory, the role of projection and introjection in the analytic situation: The patient projects impulses and aspects of his/her inner world onto the analyst and then reacts upon these (projected aspects) as if these elements were part of the analyst[21,48]. Strachey[48] stressed, that changes in one's psyche are possible, when the previously described phenomena are analyzed step by step (*e.g.*, by analyst-centered interpretations), as it is often done in psychoanalysis[47-49]. Interactional micro-processes occurring during psychotherapeutic treatment (*i.e.*, body language, facial expressions and facial micro expressions, expression in words and ideas) provide cues about unconscious fears, wishes and conflicts. These enactments lead to a countertransference reaction in the therapist often outside of awareness at first. By getting to know patients' affect perception, processing, and expressions, therapists can provide interpretations and analysis.

Clarification and confrontation, as well as the interpretation and working through of the external reality of the patient, play a large role in higher-frequency therapeutic methods such as PDT[50]. Patterns in social interaction and ways of problem-solving are enacted in the patient-therapist setting, a thorough observation of such enactments (manifesting in language, gesture, facial expression, and micro-expression) is crucial for the detection of unconscious and preconscious material. This interactivity in the learning environment provided by the therapeutic setting leads to improved problem-solving and achievement of new perspectives.

The interaction styles in the PDT group of our study were slower; therapeutic actions and respective positive affective reactions of the patients were often observed to extend over three or four sessions (*i.e.*, two weeks). This difference, observed in the descriptive analysis, could possibly be due to different session frequencies, setting, or therapeutic techniques. Meltzer[12] and Etechegoyen[51] have pointed out, that at the beginning of treatment mostly externalizing, projective mechanisms can be observed [12,51]. If these projective mechanisms are not understood and treated promptly and sufficiently, unsatisfactory therapy outcomes will be then more likely. The worsening of the borderline pathology could hypothetically be associated with the therapists' focus mainly on external reality and working alliance, without employing transference (optionally analyst-centered) interpretations.

Limitation

While assigning patients to the two therapy groups, PSA and PDT, despite the known heterogeneity of BPD patients[52], we attempted to match patients who were comparable to one another, as far as their personality structure was concerned;

however, differences in the patients' personality traits were found in both therapy groups. The fact that the assigning of patients to therapy groups depended on the availability of a therapist may be seen as a legitimate point of criticism. These differences, however, were only found to be significant in patients with avoidant traits and may therefore be seen as having an only minor influence on the total outcome. As for the "therapeutic dosage", it would be of further scientific interest, to systematically research the relationship between the number of treatment sessions and therapy outcome. This study showed no significant differences in this matter.

Treatment of patients with the borderline disorder has traditionally been limited due to high drop- out rates already within the first months of treatment in outpatient settings (by the six-month point only 34% to 57% of BPD outpatients remain in treatment[53,54]). Although BPD has a known positive trajectory over time, comorbidities[55] are frequent and long-term functional recovery is difficult, with short-term therapies often not addressing the underlying problematic personality traits[56]. Thus, in our clinical understanding, the analysis of the characteristics of early patient-therapist interactions is essential due to known difficulties in collaboration with BPD[53,54]. One strength of this study is that complete long-term follow-up data (three years) were available for a majority of the participants (*i.e.*, PSA: 70%, PDT: 50%). Future research should investigate the specific drop-out process in BPD and further investigate factors that may improve long-term outcome, like repairing alliance ruptures.

Our research was carried out in a naturalistic manner, conducting on-site assessments. Thus, the observed phenomena resemble the 'real world'. Hypothesis-generating clinical research does not replace hypothesis-testing, but it can facilitate the development of a specific hypothesis that can be tested by the application of an experiment. The retrospective design limits the level of evidence. Our findings have descriptive value and contributed to the foundation of clinical-relevant hypotheses that might be further investigated in an experimental study design. Emotional reactivity in patients with borderline personality disorder (BPD) due to dysfunctional processes is still a concept being developed[52,57]. We agree that a larger sample size would have been favorable. With a small sample we are limited to detecting big differences or big "effects" and our data need replication[58]. Further research should choose a larger sample size, to ensure sufficient power for extrapolating the results of any statistical analysis to the overall patient population. Of course, the design of an observational study with hot-spot recruitment should be replicated, which is currently under progress in our department. Replication seems not only necessary, but interesting, as other centers had found similar findings[59] especially concerning the dose-efficacy question and differences in high- and low-frequent settings: The more sessions took place with psychoanalytic technique, the better psycho-structural change could be achieved[59].

Very restricted resources often limit availability of psychotherapy in outpatient settings, despite the relevance of mental health problems. However, psychotherapy should be available for everyone with psychological strains and in need of treatment. In the outpatient clinic where this study took place, therapy places for borderline patients also with limited resources were available. Unfortunately, this might not be the usual terms.

CONCLUSION

Exploring the changes in patient characteristics and linking these changes to specific treatment strategies is of clinical importance not only when starting treatment but also for its long-term progress. The quality and accurate timing of patient-therapist interactions seem to be essential to change processes than the number of such interactions. During psychoanalytic treatments, therapy concomitant evaluations should be used to identify aspects of the therapy, that can either be promising for or preventive to a positive outcome and so that the therapist can accordingly adjust his/her intervention techniques. In therapy concomitant evaluations, the observation of repetitive interaction structures in connection to changes in patient characteristics should be a focus. By assessing the capability of therapists to interpret transferences appropriately, this instrument of a treatment concomitant evaluation could be used to assure the quality of psychoanalytic treatments. However, high-level evidence from meta-analysis regarding effects of psychological therapies for people with borderline personalities is still scant but benefits over TAU have been shown[60-63].

ARTICLE HIGHLIGHTS

Research background

Emotional reactivity in patients with borderline personality disorder (BPD) due to dysfunctional processes is still a concept being developed. Specifically designed psychotherapies for BPD have significant, modest benefits over TAU. The effects of psychotherapy on BPD are still insufficiently understood. Substantial heterogeneity of processes and populations studied contributes to varying research results when investigating the effects of different treatment methods, and whether they differ from each other.

Research motivation

The question was whether similarities and differences between psychoanalysis (PSA) and psychodynamic psychotherapy (PDT) in BPD would be detectable, especially in terms of emotional reactivity in the patient-therapist interaction.

Research objectives

We aimed to study repetitive interaction patterns in patients with BPD undergoing either psychoanalysis or psychodynamic therapy.

Research methods

Within a retrospective study framework, we compared matched PSA (n = 10) and PDT (n = 10) BPD patients' treatment sessions. Five consecutive sessions were recorded and analyzed, with evaluation of effects compared to baseline over three years. Patient characteristics (including affect regulation and personality traits), quality of object relations, as well as related therapeutic actions, were analyzed (micro-process analysis).

Research results

Differences between PSA and PDT were significant when analyzing the "mean change" in the Shedler-Westen Assessment Procedure Borderline variable after one year of therapy (P = 0.024). Variance of observed change was higher in PSA than in PDT (SD_{PSA} ± 9.29 *vs* SD_{PDT} ± 7.94). Transference interpretations are followed closely by affective changes in the patient, and were useful modes of interaction.

Research conclusions

PSA and PDT were both effective in BPD. Interactional aspects differed between the two treatments.

Research perspectives

As BPD patients are a very heterogeneous population, further research should focus on investigating optimal matching of BPD patients to specific modes of affect regulation, as well as which specific level of personality functioning would benefit from a given therapy modality.

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ORIGINAL ARTICLE

Observational Study

Impact of lockdown relaxation and implementation of the face-covering policy on mental health: A United Kingdom COVID-19 study

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Author contributions: Rathod S, Rathod P and Phiri P developed the study protocol and questionnaire; Rathod S, Phiri P, Soomro MG, and Rahman MM contributed to the manuscript development; Rahman MM conducted the analysis; all authors reviewed and approved the final version of the manuscript.

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Abstract

BACKGROUND

Pandemic mitigation policies, such as lockdown, are known to impact on mental health of individuals. Compulsory face covering under relaxed lockdown restrictions gives assurance of less transmission of airborne infection and has the potential to improve mental health of individuals affected by restrictions.

AIM

To examine the association of the lockdown relaxation and the implementation of the face covering policy on the mental health of the general population and sub-groups in the United Kingdom using interrupted time series model.

METHODS

Using a web-based cross-sectional survey of 28890 United Kingdom adults carried out during May 1, 2020 to July 31, 2020, changes in mental health status using

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generalised anxiety disorder (GAD-7), and impact of events scale-revised (IES-R) scales are examined, at the dates of the first lockdown relaxation (July 4, 2020) and the subsequent introduction of face covering (July 24, 2020) in United Kingdom. A sharp regression discontinuity design is used to check discontinuities in mental health outcomes at policy-change dates.

RESULTS
Average GAD-7 scores of participants were 5.6, 5.6 and 4.3 during the lockdown period, the lockdown relaxation phase and the phase of compulsory face covering, respectively, with lower scores indicating lower anxiety levels. Corresponding scores for IES-R were 17.3, 16.8 and 13.4, with lower scores indicating less distress. Easing lockdown measures and subsequent introduction of face covering, on average, reduced GAD-7 by 0.513 (95%CI: 0.913-0.112) and 1.148 (95%CI: 1.800-0.496), respectively. Corresponding reductions in IES-R were 2.620 (95%CI: 4.279-0.961) and 3.449 (95%CI: 5.725-1.172). These imply that both lockdown relaxation and compulsory face-covering have a positive association with mental health scores (GAD-7 and IES-R).

CONCLUSION
The differential impact of lockdown and relaxation on the mental health of population sub-groups is evident in this study with future implications for policy. Introduction of face covering in public places had a stronger positive association with mental health than lockdown relaxation.

Key Words: COVID-19; Psychological impact; Lockdown; Face-covering; Mental health; Anxiety

Core Tip: Positive association of lockdown relaxation and face-covering policies on the mental health (MH) of various population sub-groups is reported. Professional groups and health workers had lower generalised anxiety disorder (GAD-7) scores than other workers. During the compulsory face-covering phase, all professional groups improved on GAD-7 and impact of events scale-revised (IES-R) scores. Significant improvements in MH scores were found among non-key workers. Gender was associated with different MH outcomes during the lockdown, with females scoring higher on the GAD-7 and IES-R scales than males. However, both groups showed a significant improvement in MH status during the period of face-covering, with slightly higher improvements noted in males.

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INTRODUCTION

Restriction of people's movements and interactions following wide-spread transmission of coronavirus disease 2019 (COVID-19) has been experienced by the global community. Several countries in the world have implemented lockdown measures to contain the spread of infection and/or delay the spread of infection in order to reduce mortality and morbidity.

The United Kingdom government implemented national lockdown in England on March 23, 2020. The restrictions imposed by the lockdown impacted on the health, economic and social welfare of individuals, households and society[1]. Lockdown reduced educational performance and nutrition of United Kingdom children caused by junk food intake[2]. Although it improved roadside air quality in the United

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Kingdom because of the reduction of vehicles[3], there was £370 billion loss to the United Kingdom economy[4] in addition to the loss of human lives and health[5].

The lockdown measures were first relaxed on July 4, 2020 and further changes, primarily the compulsory use of face covering in shops, were introduced on July 24, 2020. Table 1 summarises relaxation measures and face covering policy introduced following lockdown on March 23, 2020. Policy makers and mental health care providers need to know the reliable estimates of such effects to target policies and services to mitigate the mental health impact of restrictive measures due to COVID-19.

Globally, there is evidence of mental health decline among the general population during the COVID-19 pandemic. China, Spain, Italy, Iran, the United States, Turkey, Nepal, and Denmark, reported relatively higher rates of symptoms of anxiety (6.33% to 50.9%), depression (14.6% to 48.3%), post-traumatic stress disorder (7% to 53.8%), psychological distress (34.43% to 38%), and stress (8.1% to 81.9%) among the general population[6]. Stay-at-home orders, greater reduction of social contacts and perceived changes in everyday life were the primary pathways to increased mental health problems[7].

In the United Kingdom, there is evidence of minor psychiatric disorders during the first month of lockdown. For example, generalized health questionnaire (GHQ-12) reported an increase of 0.48 (95%CI: 0.07–0.90) from 2018-19 to April, 2020[1]. Daly *et al* [8] also found a similar increase in GHQ-12 in the United Kingdom. The highest increases of GHQ-12 are seen among 18–24 years old (2.69 points, 95%CI: 1.89–3.48), 25–34 years old (1.57, 95%CI: 0.96–2.18), women (0.92, 95%CI: 0.50–1.35), and people living with young children (1.45, 95%CI: 0.79–2.12). The mental health of United Kingdom adults was slightly better at the early stages of lockdown than at the end of lockdown[9]. Suicidal thoughts increased during lockdown, especially among young United Kingdom adults[10]. However, the mental health effects of COVID-19 on United Kingdom healthcare professionals are ambiguous[11], and some studies found a positive impact of the pandemic on the mental health of this specific group in the United Kingdom[12,13]. A key limitation of these studies is that they did not undertake causal analyses, which is key for policy and programming. Further, there is a need to evaluate the impact of face covering policy on the mental health of different population sub-groups.

Altschul *et al*[14] captured associations of face-covering with the mental health of United Kingdom adults using the logit model and concluded that wearing face coverings more often does not negatively impact mental health. Mental health impact of face covering may be due to the confidence people felt, particularly those vulnerable, with regard to the protection it might offer from infection. Face covering was promoted with medical narrative[15] and hence its use was primarily seen as a medical intervention. It is important to understand whether such intervention provides mental health improvements. This paper addresses the research gap by trying to capture any associations of COVID-19 restrictions and their easing with key policies on the mental health of United Kingdom adults with special focus on population sub-groups. The authors used sharp regression discontinuity design (RDD) to analyse discontinuities in mental health outcomes at key policy-change dates. We also tested the key identification condition, the local randomization. If the factors affecting mental health outcomes were not found discontinuous at those cut-off dates, discontinuities in mental health outcomes were likely to be causal given other identification conditions (*e.g.*, unconfoundedness) hold[16]. There is no formal way of testing them, but this can be checked informally through falsification tests (*e.g.*, checking discontinuities in mental health outcomes at any false dates, checking false outcomes at lockdown policy changing dates). In this study, we consider the informal test through visual inspection of figures.

MATERIALS AND METHODS

Data

A cross-sectional online international survey of adults, 16 years and above, was carried out during May 1, 2020 to July 31, 2020 yielding a sample size of 28890 in England. Further details of the methodology are documented in an earlier publication by the group[13]. Of the total sample, 20174 completed the online questionnaire during lockdown; 4550 during the first phase of relaxation and 4145 during the face covering policy period.

Table 1 Lockdown relaxations in the United Kingdom

Date	Policy changes
July 4, 2020	2-metre distance rule was dropped
	Members of two different households have been able to drink or dine together
	Households will be able to host visitors, including overnight, and to meet with members of different households, on different occasions – including in a pub, restaurant or hotel, for example
	To reopen pubs, campsites, hairdressers, and churches. All these venues will be expected to collect and keep the contact details of visitors, so they can be traced in the event of a local outbreak of the virus
	Theatres and concert halls will also be able to reopen but they cannot host live performances because of concerns including the risk that singing can transmit the virus
July 24, 2020	Face mask has become compulsory in shops

Southern Health National Health Service (NHS) Foundation Trust co-ordinated the online survey with support from 50 NHS Trusts, Universities, and The Centre for Applied Research and Evaluation International Foundation. These organisations advertised the survey to their staff, patients and the general public with a weblink to the survey platform. Overall, more than 100 organizations were involved in sending the survey links to potential participants *via* professional routes and social media (Figure 1).

Study design

To study the impact of easing lockdown and introduction of face covering on mental health, both control and experimental groups are required. However, as the first United Kingdom lockdown was implemented at national level, there was no control group (*i.e.* areas without lockdown) available naturally within the nation to identify the impact of easing lockdown measures on mental health. In the absence of such control population, the RDD model is the most suitable method to address the objectives. As the United Kingdom lockdown and face covering policy had clear implementation protocols, including exact date and time, it was easier to identify cut-off points for policy change required for the chosen method. As far as we know there was no other policy announcement that might affect the mental health of the population to contaminate the effect. The two cut-off points (date of first lockdown easing and introduction of face covering) were July 4, 2020 and July 24, 2020, respectively. The RDD methodology allows for the creation of control and experimental groups by identifying populations with the same characteristics just before and after each cut-off date (*i.e.* July 4, 2020 and July 24, 2020). The population before the cut-off date serves as the control group and the after the cut-off date will be the experimental group. This creates two sets of control and experimental groups, one set at each cut-off date generating a quasi-experimental design.

The study received ethics and HRA approval. IRAS project ID: 282858; REC reference: 20/HRA/1934 from London-Westminster Research Ethics Committee on 27 April 2020.

Diagnostics

To test whether the data qualifies for RDD, predicted values of generalised anxiety disorder (GAD-7) and impact of events scale-revised (IES-R) are plotted against the interview end date (Figures 2 and 3). Vertical lines indicate cut-off dates. As data are highly scattered, figures without vertical lines (at the cut-off dates) and fitted lines will cause difficulty in understanding discontinuities at the cut-off dates. Predicted values are generated from regressions of these indices on the trend variable allowing discontinuities and changes in slopes. These predicted values pass through scatter points, which are daily averages of these indices. The interview end date is the date of completing the survey questionnaire by an individual. Interview end dates are used to make the trend variable (*e.g.*, 1 for first date, 2 for second date, *etc.*), and this gives the appropriate assignment variable. The two mental health measures show clear negative discontinuities at the first and second cut-off dates, implying that easing lockdown restrictions and introduction of face covering improved mental health.

Visual inspection of the two figures indicates slope changes after the first cut-off date. In survey data, such slope changes can be difficult to interpret. The analysis captures intercept discontinuities (steps) after also controlling for slope changes, as

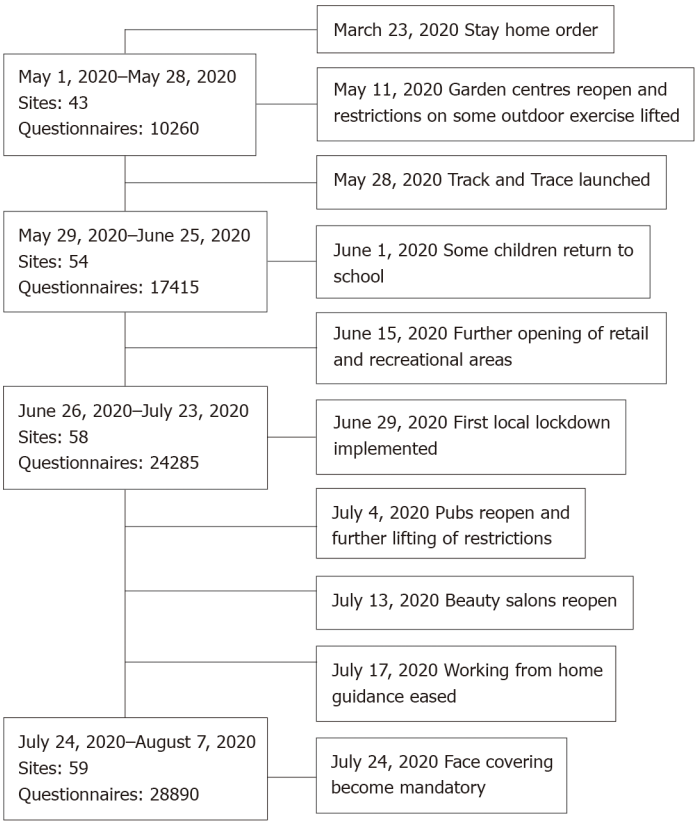

Figure 1 Survey recruitment and significant lockdown dates.

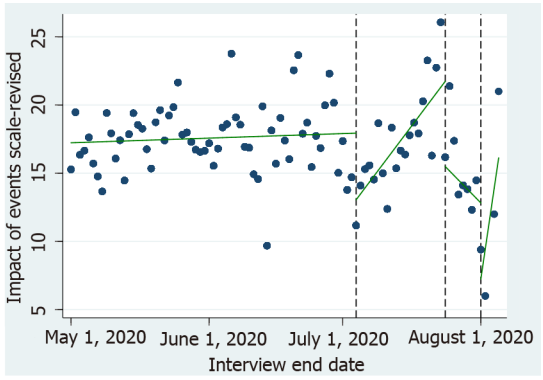

Figure 2 Discontinuities in impact of event scale-revised scale at two cut-off dates.

suggested by Angrist and Pischke[17] in RDD.

Modelling

The unit of analysis is an adult aged 16 years or over. The outcome of interest, mental health outcome measured using GAD-7 and IES-R, is denoted by Y, which varies across different groups of individuals (*e.g.*, health *vs* non-health workers, male *vs* female, *etc.*) by date. For purposes of regression, date is used as the trend variable, which contains 1 for the first date, 2 for the second date, and so on. Individual and time are indicated by i and t, respectively. As mental health conditions change around the cut-off time, the following RDD type of interrupted time series model was used:

$$Y_{it} = \alpha + \beta_1 d_{t1} + \beta_2 d_{t2} + \beta_3 d_{t1}(Trend_t\text{-}c_1) + \beta_4 d_{t2}(Trend_t\text{-}c_2) + \beta_5(Trend_t\text{-}c_1) + X_{it}\theta + \epsilon_{it}$$

where α is the constant term, d_{t1} = *1{Interview end date* ≥ 4^{th} *of July}*, and d_{t2} = *1{Interview end date* ≥ 24^{th} *of July}* are discontinuity dummies, c_1 = *Value of trend for the date of* 4^{th} *of July* and c_1 = *Value of trend for the date of* 24^{th} *of July* the two cut-off points, X_{it} is the row vector of control variables (listed in Tables 2 and 3) and θ is the column vector of their coefficients, and $\in_{it}$ is the error term. β_1 and β_2 are parameters of discon-

Table 2 Sampling distribution of mental health outcomes, demographics, lifestyle changes, and pre-existing health conditions by lockdown periods

Time by lockdown easing policy	May 1, 2020-July 3, 2020 (Lockdown phase)		July 4-23, 2020 (Lockdown relaxation phase)		July 24-31, 2020 (Face-covering phase)		Total		
Outcome and control variables	No.	%	No.	%	No.	%	No.	%	*P* value
Total sample	20173	100	4550	100	4145	100	28890	100	
Mental health outcomes/scores									
GAD-7									
Total	15634	100	3379	100	3153	100	22166	100	
Missing	4539		1171		992		6711		
IES-R									
Total	14516	100	3141	100	2961	100	20618	100	
Missing	5657		1409		1184		8260		
Demographics, lifestyle changes, and pre-existing health conditions									
Key worker									
No	5400	29.7	1260	31.4	1778	48.8	8438	32.6	
Yes (health)	9205	50.6	1961	48.9	1161	31.8	12327	47.7	
Yes (non-health)	3595	19.8	793	19.8	708	19.4	5096	19.7	
Total	18200	100	4014	100	3647	100	25861	100	< 0.001
Missing	1973		536		498		3014		
Gender									
Female	15324	84.2	3331	83.4	2701	75.2	21356	82.8	
Male	2872	15.8	662	16.6	891	24.8	4425	17.2	
Total	18196	100	3993	100	3592	100	25781	100	< 0.001
Missing	1977		557		553		3094		
Age category or group									
Under 21	332	1.8	90	2.2	81	2.2	503	1.9	
21-24	828	4.5	163	4	100	2.7	1091	4.2	
25-34	3627	19.8	709	17.5	566	15.4	4902	18.8	
35-44	4076	22.2	794	19.5	712	19.4	5582	21.4	
45-54	4676	25.5	1008	24.8	851	23.2	6535	25.1	
55-64	3462	18.9	882	21.7	795	21.6	5139	19.7	
65 and over	1319	7.2	416	10.2	568	15.5	2303	8.8	
Total	18320	100	4062	100	3673	100	26055	100	< 0.001
Missing	1853		488		472		2820		
Ethnicity									
Non-white British	1649	9	362	8.9	351	9.5	2362	9.1	
White British	16703	91	3698	91.1	3325	90.5	23726	90.9	
Total	18352	100	4060	100	3676	100	26088	100	< 0.001
Missing	1821		490		469		2787		
Religion									
Non-Christian	9794	54.1	2140	54.3	1905	53.8	13839	54.1	
Christian	8306	45.9	1798	45.7	1633	46.2	11737	45.9	

Total	18100	100	3938	100	3538	100	25576	100	0.911
Missing	2073		612		607		3300		
Age left education									
≤ 18 (A-level or less)	5967	33	1557	38.9	1249	34.4	8773	34.1	
> 18 (Higher degree)	12118	67	2442	61.1	2381	65.6	16941	65.9	
Total	18085	100	3999	100	3630	100	25714	100	
Missing	2088		551		515		3161		
Accommodation									
Rented home	5030	27.5	1163	28.7	847	23	7040	27	
Own home	13288	72.5	2891	71.3	2834	77	19013	73	
Total	18318	100	4054	100	3681	100	26053	100	< 0.001
Missing	1855		496		464		2822		
Vulnerable according to government category									
No	13735	80.6	2938	78.5	2610	77.7	19283	79.8	
Yes (do not require shielding)	2005	11.8	503	13.4	494	14.7	3002	12.4	
Yes (require shielding)	1307	7.7	303	8.1	257	7.6	1867	7.7	
Total	17047	100	3744	100	3361	100	24152	100	< 0.001
Missing	3126		806		784		4725		
Experienced coronavirus									
No	4354	24.9	1016	26.3	971	27.8	6341	25.5	
Yes	13152	75.1	2843	73.7	2518	72.2	18513	74.5	
Total	17506	100	3859	100	3489	100	24854	100	0.001
Missing	2667		691		656		4022		
Pre-existing mental health condition									
No	10685	62.6	2288	60.8	2404	70.1	15377	63.3	
Yes	6395	37.4	1476	39.2	1026	29.9	8897	36.7	
Total	17080	100	3764	100	3430	100	24274	100	< 0.001
Missing	3093		786		715		4604		
Drinking alcohol									
Never	2611	14.6	540	13.7	492	13.8	3643	14.4	
Monthly or less	3954	22.2	944	24	692	19.4	5590	22.1	
2-4 times a month	3909	21.9	930	23.6	824	23	5663	22.3	
2-3 times a week	4873	27.3	1007	25.6	999	27.9	6879	27.1	
4 times or more a week	2479	13.9	520	13.2	569	15.9	3568	14.1	
Total	17826	100	3941	100	3576	100	25343	100	< 0.001
Missing	2347		609		569		3532		
Taking drug									
No	17354	97.9	3810	97.3	3465	97.3	24629	97.7	
Yes	369	2.1	107	2.7	95	2.7	571	2.3	
Total	17723	100	3917	100	3560	100	25200	100	< 0.001
Missing	2450		633		585		3675		
Suicidal thoughts									

No	12015	68.3	2591	66.7	2521	71.5	17127	68.5	
Yes	5572	31.7	1292	33.3	1005	28.5	7869	31.5	
Total	17587	100	3883	100	3526	100	24996	100	< 0.001
Missing	2586		667		619		3879		

GAD-7: Generalised anxiety disorder-7; IES-R: Impact of events scale-revised.

tinuities at two respective cut-off dates, and β_3 and β_4, are parameters of kinks (slope changes) at two respective cut-off dates. Parameters of interest in this paper are discontinuity parameters, β_1 and β_2, which give changes in mental health scores at the two cut-off dates.

The control variables included in the analysis are socio-demographic characteristics (*e.g.*, profession, age, ethnicity, religion, gender, education, accommodation, *etc.*), lifestyle characteristics (*e.g.*, experiencing coronavirus, drug use, drinking alcohol, *etc.*), and pre-existing health conditions (*e.g.*, vulnerability, suicidal thoughts, mental health conditions). The outcome variable of interest is mental health status. Two widely used standardized measures have been used to measure levels of anxiety (GAD-7)[18], and subjective distress (IES–R)[19]. The GAD-7 ranges from 0 to 21, and it categorizes as minimal (0-4), mild (5-9), moderate (10-14), and severe (15-21). The IES-R ranges from 0 to 88, and it categorizes as minimal (0-23), post-traumatic stress disorder (PTSD) may be a concern (24-32), probable PTSD diagnosis (33-38), and high PTSD (39-88). A total of 22,166 respondents completed the GAD-7 questionnaire. Of those 15634 were completed during lockdown, 3379 during the first phase of lockdown relaxation, and 3153 during the face covering phase. A total of 20618 respondents completed the IES-R questionnaire, 14516 respondents completed this during lockdown, 3141 during the first phase and 2961 during the second phase of lockdown relaxation.

Table 2 presents percentage distribution of control variables used in the regressions according to lockdown, lockdown relaxation, and face covering implementation period. It suggests that the proportions of control variables in the three time periods follow a similar pattern. However, there are higher proportions of health workers (31.8%-50.6%) and females (75.2%-84.2%) in the sample. The table shows that (P < 0.001) percentages of control variables vary significantly during each of the time periods. Such discrepancies in demographic characteristics of respondents will not violate identification conditions as discrepancies of those covariates do not exist around the cut-off dates in most cases (*e.g.*, the existence of local randomization available in supplementary material). The table also shows missing values, which are unlikely to make any serious impact on the results of regressions as the individuals are distributed based on comparable characteristics before and after the cut-off dates.

RESULTS

Mental health outcomes by background characteristics

Table 3 provides average scores of the two mental health measures for three time periods: During lockdown; during relaxation and the face covering period. Comparisons of the average scores between these time periods gives us raw estimates of the effects of the lockdown relaxation and the compulsory face covering policies. The average scores of GAD-7 and IES-R at the three time periods suggest that the mental health of the respondents was worse during lockdown but has improved after the lockdown easing and during the period of face covering. For example, the overall mean GAD-7 scores were 5.6 each for the lockdown period and the first phase of lockdown relaxation, compared to 4.4 during the period of face covering. For the IES-R, the average scores were 17.3, 16.8 and 13.4 for the periods of lockdown, lockdown relaxation, and face covering, respectively, suggesting a reduction in anxiety and distress during the first relaxation, but significant reductions were noticed during the period of face-covering.

There were notable differences in the associations of lockdown relaxation and compulsory face covering policies on mental health of various population sub-groups. Among the professional groups, health workers had the lowest GAD-7 score (5.1) compared to other key workers (6.3) and non-key workers (5.8) during the lockdown period. Similar findings were observed for the IES-R, 18.5 for non-key workers, 15.9 for health workers and 19.0 for other key workers. During the compulsory face covering

Table 3 Means of mental health conditions by lockdown easing periods, demographics, lifestyle changes, and pre-existing health conditions

Control variables	Means of GAD-7 (*n* = 18948) (95%CI)			Means of IES-R (*n* = 17739) (95%CI)		
	May 1, 2020-July 3, 2020 (Lockdown)	July 4-23, 2020 (Lockdown relax)	July 24-31, 2020 (Face-covering)	May 1, 2020-July 3, 2020 (Lockdown)	July 4-23, 2020 (Lockdown relax)	July 24-31, 2020 (Face-covering)
Total study population	5.6 (5.5-5.7)	5.6 (5.3-5.8)	4.4 (4.2-4.6)	17.3 (16.9-17.6)	16.8 (16.0-17.6)	13.4 (12.7-14.2)
Key worker						
Not a key worker	5.8 (5.6-6.0)	6.2 (5.7-6.7)	4.1 (3.8-4.4)	18.5 (17.8-19.2)	19.9 (18.2-21.5)	13.1 (12.1-14.2)
Health	5.1 (5.0-5.3)	5 (4.7-5.3)	4.3 (3.9-4.6)	15.9 (15.4-16.3)	14.4 (13.4-15.4)	12.2 (11.0-13.5)
Not in health	6.3 (6.1-6.6)	6.1 (5.5-6.6)	5.3 (4.8-5.9)	19 (18.2-19.8)	18.5 (16.8-20.3)	16.1 (14.4-17.9)
Gender						
Female	5.8 (5.7-5.9)	5.7 (5.5-6.0)	4.8 (4.5-5.1)	18 (17.6-18.4)	17.3 (16.4-18.2)	14.4 (13.5-15.2)
Male	4.3 (4.0-4.5)	4.8 (4.1-5.4)	3.2 (2.8-3.7)	13.3 (12.4-14.1)	14.1 (12.2-16.1)	10.7 (9.4-12.1)
Age group						
Under 21	7.7 (6.8-8.5)	9.3 (6.7-11.9)	8.6 (6.4-10.9)	24 (20.9-27.1)	30.8 (20.8-40.8)	28.8 (20.2-37.3)
21-24	7.9 (7.4-8.5)	7.8 (6.3-9.2)	6.7 (5.0-8.4)	22.6 (20.8-24.3)	21.4 (17.0-25.7)	19.2 (13.9-24.5)
25-34	6.8 (6.5-7.0)	7.5 (7.0-8.1)	5.7 (5.1-6.4)	19 (18.2-19.8)	21.3 (19.4-23.2)	15.4 (13.3-17.4)
35-44	6.1 (5.9-6.3)	6.1 (5.6-6.6)	5.2 (4.7-5.7)	18.3 (17.5-19.0)	17.8 (16.1-19.5)	14.4 (12.8-15.9)
45-54	4.9 (4.7-5.1)	4.8 (4.4-5.3)	4.5 (4.0-5.0)	16.2 (15.6-16.9)	14.5 (13.0-16.0)	13.2 (11.8-14.7)
55-64	4.6 (4.4-4.8)	4.8 (4.3-5.3)	3.7 (3.3-4.1)	15.7 (15.0-16.5)	14.8 (13.2-16.4)	12.6 (11.2-14.0)
65 and over	3.1 (2.8-3.4)	3.1 (2.5-3.7)	1.9 (1.4-2.3)	10.8 (9.7-11.8)	12.2 (9.7-14.6)	8.1 (6.5-9.7)
Ethnicity						
Non-white	4.9 (4.5-5.2)	5.9 (5.1-6.8)	4.9 (4.1-5.7)	15.9 (14.7-17.1)	19.2 (16.3-22.0)	14.4 (12.0-16.8)
White	5.6 (5.5-5.7)	5.5 (5.3-5.8)	4.4 (4.1-4.6)	17.4 (17.0-17.7)	16.6 (15.7-17.4)	13.3 (12.5-14.1)
Religion						
Non-Christian	5.7 (5.6-5.9)	6.0 (5.6-6.3)	4.6 (4.3-4.9)	17.6 (17.2-18.1)	17.6 (16.5-18.7)	13.8 (12.8-14.8)
Christian	5.4 (5.2-5.5)	5.1 (4.8-5.5)	4.2 (3.9-4.5)	16.8 (16.3-17.3)	15.8 (14.6-17.0)	12.9 (11.9-14.0)
Education						
A-level or less	6.2 (6.0-6.4)	6.1 (5.7-6.6)	4.5 (4.1-4.9)	19.1 (18.4-19.8)	19.1 (17.6-20.5)	14.3 (12.9-15.7)
Higher degree	5.3 (5.2-5.4)	5.2 (4.9-5.5)	4.4 (4.1-4.6)	16.4 (16.0-16.8)	15.5 (14.6-16.4)	13 (12.2-13.9)
Type of accommodation						
Rented	7.1 (6.9-7.3)	7.8 (7.3-8.3)	6.7 (6.1-7.3)	21.6 (20.9-22.3)	23.1 (21.4-24.8)	19.7 (17.8-21.6)
Own	5 (4.9-5.1) 4	4.7 (4.5-5.0)	3.8 (3.5-4.0)	15.7 (15.3-16.0)	14.4 (13.5-15.3)	11.7 (10.9-12.4)
Shielding status (government)						
Shielding not required	5.5 (5.4-5.6)	5.5 (5.2-5.8)	4.4 (4.1-4.6)	16.8 (16.5-17.2)	16.2 (15.3-17.1)	12.9 (12.1-13.7)
Shielding required (but not Shielding)	5.5 (5.2-5.9)	5.1 (4.5-5.8)	4 (3.4-4.6)	17.6 (16.5-18.6)	16.6 (14.5-18.8)	13 (11.0-14.9)
Shielding required (shielding)	6.6 (6.2-7.0)	7.4 (6.4-8.5)	5.5 (4.6-6.5)	21.2 (19.8-22.6)	23.9 (20.7-27.2)	19.3 (16.2-22.3)
Experience of COVID-19						
No such experience	5.1 (4.9-5.3)	5.1 (4.6-5.6)	3.9 (3.5-4.4)	15.5 (14.8-16.2)	16.3 (14.7-18.0)	12.1 (10.7-13.5)
Yes	5.7 (5.6-5.8)	5.7 (5.4-6.0)	4.6 (4.3-4.9)	17.8 (17.4-18.2)	17 (16.1-17.9) 1	3.9 (13.1-14.8)
Pre-existing mental health						

No	4.1 (4.0-4.2)	3.7 (3.5-3.9)	3.2 (2.9-3.4)	13 (12.6-13.3)	11.5 (10.7-12.3)	9.7 (9.0-10.4)
Yes	8.2 (8.0-8.4)	8.7 (8.3-9.2)	7.6 (7.1-8.1)	24.9 (24.3-25.6)	25.9 (24.5-27.4)	23 (21.3-24.7)
Drinking alcohol						
Never	6.3 (6.0-6.6)	6.2 (5.5-6.9)	5.7 (4.9-6.4)	19.7 (18.6-20.7)	17.9 (15.6-20.2)	16.2 (13.8-18.6)
Monthly or less	6.2 (6.0-6.5)	6.6 (6.0-7.1)	5 (4.4-5.5)	18.8 (18.0-19.6)	19.5 (17.6-21.3)	15.2 (13.4-17.0)
2-4 times a month	5.4 (5.2-5.6)	5.3 (4.8-5.8)	4.3 (3.8-4.7)	16.7 (15.9-17.4)	17 (15.4-18.5)	13 (11.5-14.5)
2-3 times a week	5 (4.9-5.2) 5	5.2 (4.7-5.6)	3.9 (3.5-4.4)	15.5 (14.9-16.1)	15.2 (13.7-16.7)	12.2 (10.9-13.5)
4 times or more a week	5.1 (4.8-5.3)	4.3 (3.7-5.0)	3.8 (3.2-4.4)	16.9 (16.0-17.9)	13.4 (11.6-15.3)	12 (10.3-13.7)
Drug use						
Never	5.5 (5.4-5.6)	5.5 (5.2-5.7)	4.3 (4.1-4.6)	17.1 (16.8-17.5)	16.6 (15.8-17.4)	13.1 (12.4-13.9)
Ever	7.7 (6.8-8.6)	9.6 (7.9-11.4)	7.3 (5.5-9.1)	23.8 (20.9-26.8)	25.5 (19.9-31.1)	24.2 (18.3-30.0)
Suicidal thoughts ever						
No	4.5 (4.4-4.6)	4.4 (4.1-4.7)	3.4 (3.2-3.7)	13.9 (13.5-14.3)	13.2 (12.3-14.0)	10.3 (9.6-11.0)
Yes	7.8 (7.6-8.0)	8 (7.6-8.5)	6.9 (6.4-7.4)	24.3 (23.7-25.0)	24.4 (22.8-25.9)	21.6 (19.9-23.3)

CI: Confidence intervals; COVID-19: Coronavirus disease 2019; GAD-7: Generalised anxiety disorder-7; IES-R: Impact of events scale-revised.

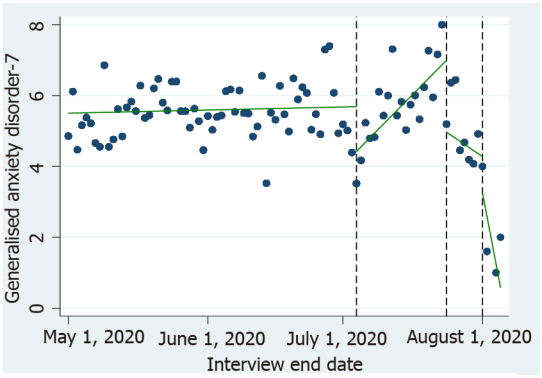

Figure 3 Discontinuities in generalised anxiety disorder-7 scale at two cut-off dates.

phase, there were improvements (mean reductions) in both mean scores for all three professional groups; the GAD-7 and IES-R scores were 4.1 and 13.1 for non-key workers, 4.3 and 12.2 for health workers, and 5.3 and 16.1 for non-health workers during the period of face covering, respectively. These imply that greater improvements in mental health are found among non-key workers than key workers, meaning that non-key workers were affected more by COVID-19. However, the regression results give a better indication.

In this study, gender was associated with mental health outcomes. During the lockdown, females had higher GAD-7 mean scores (5.8) compared to males (4.3). A similar pattern was observed for the IES-R (18.00 for females and 13.3 males). Both groups have shown significant improvements in anxiety and distress during the period of face covering, but slightly higher improvements are seen among males compared to females.

Table 3 further shows that both GAD-7 and IES-R were higher among younger age groups. For example, during lockdown, GAD-7 score was 7.7 for the under 21 years age group compared to 3.1 for the 65+ age group. The IES-R was 24.00 for the below 21 years age group compared to 10.8 for the 65+ age group. Both the scores of all age groups have declined during the face covering period. Compared to the middle age groups (*e.g.*, 35-44, 45-54), higher reductions (at least in terms of percentage) are seen among the lower and higher age groups.

Ethnic variations in mental health were also noted in this study. White ethnic population had higher GAD-7 (5.6) and IES-R (17.4) scores during the lockdown period compared to non-white (GAD-7, 4.9; IES-R, 15.9) ethnic group. Both ethnic groups showed notable improvements in average GAD-7 and IES-R scores at the face covering period, but not during the lockdown relaxation period. The white group shows greater improvements in mental health than the non-white group. Among non-Christians, both GAD-7 (5.7) and IES-R (17.6) scores were higher compared to Christians (GAD-7, 5.4; IES-R, 16.8). Similar to ethnicity, notable improvements in the average anxiety and distress scores of the two measures were noted in the face covering period, but not for the lockdown relaxation period. Slightly greater improvements in mental health are seen among Christians (who are mainly white ethnic population) than non-Christians.

Educational differences in mental health status by lockdown status and face covering were found in this study. During lockdown, average mental health scores for the two measures were higher for those with A-level or less (GAD-7, 6.2; IES-R, 19.1) compared to those with degree qualification (GAD-7, 5.3; IES-R, 16.4). Although there were some improvements in the mental health scores during the first lockdown relaxation, larger improvements were noted in the face covering period. In the face covering period, larger falls in both scores are seen among lower educated groups, implying that this group of educated people that includes lower-skilled workers was possibly hit more by COVID-19. Those who lived in rental accommodation during lockdown experienced more distress, with higher scores for both GAD-7 (7.1) and IES-R (21.6) compared to those living in their own homes (GAD-7, 5.0; IES-R, 15.7). Notable improvements in both GAD-7 and IES-R scores were found in the face covering period, and greater improvements are seen for those who live in their own houses.

During the lockdown period, those who shielded as *per* government advice had higher mental health scores for the two measures (GAD-7 = 6.6; IES-R = 21.2) compared to those who did not shield although they were advised to shield (GAD-7 = 5.5; IES-R = 17.6). Again, improvements in mental health of both groups are seen during the face covering period, but greater improvements are seen among those who shielded. Those who have experienced some COVID-19 related unpleasant experiences, had higher anxiety and distress scores (GAD-7 = 5.7; IES-R = 17.8 during the lockdown phase) compared to those who did not experience such situations (GAD-7 = 5.1; IES-R = 15.5 during the lockdown phase). Their mental health status improved significantly when the face covering policy was introduced. Greater improvement is seen among individuals who experienced coronavirus in IES–R scores. Similarly, those who had pre-existing mental health problems had higher mental health scores in both GAD-7 and IES-R in all three phases. Again, they experienced lower mental health problems after the face covering policy was introduced, but individuals without pre-existing mental health conditions experienced greater mental health improvements during the face covering phase.

In all three phases, those who never drank alcohol had higher anxiety and distress scores compared to those who reported alcohol consumption four or more times a week. Implementation of the face covering policy improved mental health scores of all groups of alcohol users. Users of drugs had higher anxiety and distress scores compared to 'never' users, but never users of drugs showed higher improvements in mental health scores during the face covering phase. Those who ever experienced suicidal thoughts had higher anxiety and distress scores compared to those who never had such thoughts. As with all other factors, improvements were noted when the face covering policy was introduced, but again, greater improvements are seen among the non-vulnerable group, those who never experienced suicidal thoughts.

Results from regression models

Table 4 shows the changes in mental health outcomes measured using GAD-7 and IES-R by two policy changes dates (July 4 and 24, 2020), and demographics, pre-existing health conditions, and lifestyles. For every group of demographics, pre-existing health conditions, and lifestyles, changes in anxiety and distress scores at two dates were estimated by running a simple OLS regression, which followed the specification of the interrupted time series model equation. The coefficients of two discontinuity dummies for two policy changes dates, which are estimates of changes in anxiety and distress scores at two dates, are shown in the Table 4. In each regression, linear function of trend variable (time) was considered, as Figures 2 and 3 did not suggest any non-linearity. To note that, in the regression of a group, all other covariates except one corresponding to that group were used. For example, in the regression of the male group, the only male dummy was dropped, but all other covariates defined by all

Table 4 Changes in mental health indices by cut-off dates, control variables from regression discontinuity design regression models

Policy change dates in 2020	Population sub-groups	GAD-7, changes (95%CI)	*P* value	IESR, changes (95%CI)	*P* value
July 4, 2020 (Lockdown relaxation date)	Total sample	-0.513 (-0.913, -0.112)	0.081	-2.620 (-4.279, -0. 961)	0.464
July 24, 2020 (Face-covering start date)	Total sample	-1.148 (-1.800, -0.496)		-3.449 (-5.725, -1.172)	
	Key worker				
July 4, 2020 (Lockdown relaxation date)	Not a key worker	-0.910 (-1.810, -0.011)	0.062	-3.546 (-6.235, -0.857)	0.708
	Health	0.017 (-0.602, 0.637)		-1.643 (-3.914, 0.628)	
	Non-health	-0.756 (-1.877, 0.365)		-1.704 (-5.115, 1.708)	
July 24, 2020 (Face-covering start date)	Not a key worker	-1.191 (-2.259, -0.123)	0.064	-3.877 (-7.410, -0.343)	0.843
	Health	-0.986 (-1.584, -0.387)		-1.693 (-4.376, 0.991)	
	Non-health	-1.421 (-3.454, 0.613)		-5.458 (-9.144, -1.772)	
	Gender				
July 4, 2020 (Lockdown relaxation date)	Female	-0.496 (-0.983, -0.010)	0.817	-2.606 (-4.445, -0.767)	0.936
	Male	-0.622 (-1.652, 0.409)		-2.461 (-5.929, 1.007)	
July 24, 2020 (Face-covering start date)	Female	-1.013 (-1.778, -0.248)	0.382	-3.369 (-5.789, -0.948)	0.926
	Male	-1.739 (-2.993, -0.485)		-3.112 (-6.985, 0.762)	
	Age group				
July 4, 2020 (Lockdown relaxation date)	Under 21	-5.482 (-9.526, -1.437)	0.029	-19.319 (-41.541, 2.902)	0.260
	21-24	-0.103 (-1.975, 1.770)		-3.715 (-8.350, 0.920)	
	25-34	-0.314 (-1.346, 0.717)		-2.653 (-4.900, -0.406)	
	35-44	-0.640 (-1.646, 0.366)		0.545 (-2.309, 3.399)	
	45-54	0.179 (-0.663, 1.021)		-1.871 (-4.785, 1.043)	
	55-64	-0.911 (-2.117, 0.294)		-5.390 (-9.419, -1.361)	
	65 and over	-0.923 (-2.330, 0.484)		-2.633 (-8.466, 3.199)	
July 24, 2020 (Face-covering start date)	Under 21	-0.983 (-5.502, 3.536)		-3.941 (-23.634, 15.753)	
	21-24	-0.830 (-6.322, 4.661)		-2.354 (-14.469, 9.761)	
	25-34	-1.928 (-3.272, -0.584)		-7.306 (-11.582, -3.029)	
	35-44	-0.722 (-2.406, 0.962)		-0.469 (-5.717, 4.780)	
	45-54	-0.641 (-1.940, 0.658)		-2.386 (-5.752, 0.980)	
	55-64	-0.997 (-1.971, -0.023)		-1.930 (-5.331, 1.472)	
	65 and over	-1.447 (-2.952, 0.057)	0.995	-4.192 (-9.646, 1.261)	0.795
	Ethnicity				
July 4, 2020 (Lockdown relaxation date)	Non-white	1.302 (0.085, 2.518)		3.185 (-2.139, 8.510)	
	White	-0.657 (-1.129, -0.185)	0.018	-3.044 (-4.830, -1.259)	0.035
July 24, 2020 (Face-covering start date)	Non-white	-0.104 (-1.715, 1.506)		-0.380 (-6.308, 5.548)	
	White	-1.243 (-1.957, -0.529)	0.348	-3.567 (-5.888, -1.246)	0.410
	Religion				

July 4, 2020 (Lockdown relaxation date)	Non-Christian	-0.369 (-0.934, 0.195)	0.522	-2.500 (-4.563, -0.437)	0.904
	Christian	-0.652 (-1.298, -0.006)		-2.679 (-4.909, -0.449)	
July 24, 2020 (Face-covering start date)	Non-Christian	-1.298 (-2.290, -0.306)	0.578	-3.473 (-6.483, -0.464)	0.957
	Christian	-0.928 (-1.630, -0.226)		-3.354 (-6.289, -0.420)	
	Education				
July 4, 2020 (Lockdown relaxation date)	A-level or less	-1.363 (-1.929, -0.797)	0.007	-3.958 (-6.641, -1.275)	0.221
	Higher degree	-0.080 (-0.512, 0.352)		-1.955 (-3.408, -0.502)	
July 24, 2020 (Face-covering start date)	A-level or less	-1.421 (-2.058, -0.783)	0.460	-4.109 (-6.780, -1.438)	0.561
	Higher degree	-0.876 (-1.712, -0.041)		-2.667 (-5.356, 0.022)	
	Accommodation				
July 4, 2020 (Lockdown relaxation date)	Rented	-0.369 (-1.449, 0.712)	0.796	-1.933 (-5.935, 2.068)	0.675
	Own	-0.517 (-0.919, -0.114)		-2.719 (-4.784, -0.653)	
July 24, 2020 (Face-covering start date)	Rented	-1.837 (-3.056, -0.618)	0.197	-4.387 (-9.165, 0.391)	0.571
	Own	-0.782 (-1.419, -0.144)		-2.820 (-4.892, -0.748)	
	Require shielding by government				
July 4, 2020 (Lockdown relaxation date)	Not required	-0.322 (-0.750, 0.107)	0.241	-2.212 (-3.717, -0.706)	0.560
	Required shielding, but not shielding	-1.243 (-2.295, -0.191)		-4.136 (-8.303, 0.032)	
	Required shielding and shielding	-0.655 (-2.023, 0.713)		-3.447 (-8.512, 1.619)	
July 24, 2020 (Face-covering start date)	Not required	-0.978 (-1.721, -0.234)	0.393	-3.175 (-5.683, -0.668)	0.956
	Require shielding, but not shielding	-1.045 (-2.351, 0.261)		-3.730 (-10.106, 2.647)	
	Require shielding and shielding	-3.064 (-4.686, -1.442)		-4.742 (-10.111, 0.628)	
	Experience of COVID-19				
July 4, 2020 (Lockdown relaxation date)	No	-0.559 (-1.279, 0.161)	0.892	-1.999 (-4.771, 0.774)	0.657
	Yes	-0.490 (-0.961, -0.018)		-2.795 (-4.666, -0.924)	
July 24, 2020 (Face-covering start date)	No	-1.927 (-2.904, -0.951)	0.156	-6.223 (-10.542, -1.905)	0.131
	Yes	-0.875 (-1.621, -0.129)		-2.462 (-4.509, -0.416)	
	Pre-existing mental health condition				
July 4, 2020 (Lockdown relaxation date)	No	-0.343 (-0.729, 0.043)	0.551	-2.308 (-3.782, -0.834)	0.788
	Yes	-0.649 (-1.582, 0.284)		-2.772 (-6.246, 0.702)	
July 24, 2020 (Face-covering start date)	No	-0.687 (-1.194, -0.181)	0.239	-1.407 (-3.154, 0.340)	0.056
	Yes	-1.576 (-3.163, 0.012)		-6.239 (-10.192, -2.286)	
	Drinking alcohol				
July 4, 2020 (Lockdown relaxation date)	Never	-1.025 (-2.463, 0.412)		-3.091 (-7.778, 1.596)	
	Monthly or less	-0.582 (-1.779, 0.615)		-3.020 (-6.621, 0.581)	

	2-4 times a month	-0.243 (-0.901, 0.415)		-2.017 (-4.434, 0.401)	
	2-3 times a week	-0.050 (-0.543, 0.443)		-1.782 (-3.882, 0.319)	
	4 times or more a week	-1.165 (-2.178, -0.151)	0.401	-3.784 (-7.229, -0.340)	0.828
July 24, 2020 (Face-covering start date)	Never	-1.309 (-3.955, 1.337)	0.835	2.636 (-2.839, 8.111)	0.607
	Monthly or less	-1.240 (-2.787, 0.306)		-2.619 (-5.693, 0.455)	
	2-4 times a month	-1.251 (-2.243, -0.259)		-6.981 (-10.394, -3.568)	
	2-3 times a week	-1.140 (-1.694, -0.587)		-4.444 (-7.173, -1.715)	
	4 times or more a week	-0.601 (-2.269, 1.067)		-1.616 (-6.815, 3.583)	
	Taking drugs				
July 4, 2020 (Lockdown relaxation date)	No	-0.504 (-0.890, -0.118)	0.542	-2.522 (-4.160, -0.883)	0.955
	Yes	0.631 (-3.023, 4.286)		-2.827 (-12.067, 6.412)	
July 24, 2020 (Face-covering start date)	No	-1.114 (-1.669, -0.558)	0.875	-3.571 (-5.538, -1.604)	0.222
	Yes	-1.470 (-6.338, 3.398)		5.805 (-11.429, 23.039)	
	Suicidal thoughts ever				
July 4, 2020 (Lockdown relaxation date)	No	-0.173 (-0.599, 0.252)	0.039	-0.941 (-2.482, 0.600)	0.003
	Yes	-1.232 (-1.983, -0.481)		-5.938 (-8.759, -3.118)	
July 24, 2020 (Face-covering start date)	No	-0.831 (-1.343, -0.319)	0.337	-2.520 (-4.065, -0.975)	0.511
	Yes	-1.588 (-3.487, 0.310)		-4.256 (-9.486, 0.974)	

Note: To capture the effects of lockdown easing and compulsory face-covering on different groups, separate OLS regressions were run for all demographics, lifestyle change type, and pre-existing health condition (listed above) using the Regression Discontinuity Design model. Cluster/date/trend adjusted 95% confidence intervals are in parentheses. *P* values are shown to indicate whether changes in mental health scores are different among those listed groups. CI: Confidence intervals; COVID-19: Coronavirus disease 2019; GAD-7: Generalised anxiety disorder-7; IES-R: Impact of events scale-revised.

other groups are used.

Compared to discontinuities seen in Figures 2 and 3, the smaller discontinuities in outcomes are due to controlling for the effects of a large set of individual risk factors. This should be obvious as the regressions control for individual risk factors. We have focused on mental health changes at the cut-off dates only, not the differences in the entire time span. Therefore, we do not rely on the results shown in Tables 2 and 3.

Overall, the coefficients suggest a statistically significant fall in both anxiety and distress scores at the two policy changes dates. The fall in GAD-7 score at the first and second cut-off dates was -0.513 (95%CI: -0.913, -0.112) and -1.148 (95%CI: -1.800, -0.496), respectively. The corresponding figures for IES-R were -2.620 (95%CI: -4.279, -0.961) and -3.449 (95%CI: -5.725, -1.172), respectively. These figures suggest that both anxiety and distress reduced when the lockdown relaxation and the face covering measures were introduced. The reductions in mental health scores were higher when the face covering policy was introduced compared to the start of the lockdown relaxation.

There was no statistically significant reduction in the GAD-7 (0.017, 95%CI: -0.602, 0.673) and IES-R scores (-1.643, 95%CI: -3.914, 0.628) for health workers and other key workers (GAD-7: -0.756, 95%CI: -1.877, 0.365; IES-R: -1.704, 95%CI: -5.115, 1.708) at the first cut-off date. However, for health workers, when face covering was introduced the GAD-7 score reduced significantly, although there was no significant change in their IES-R score. At the second cut-off date, other key workers had a significant reduction in IES-R (-5.458, 95%CI: -9.144, -1.772) but no statistically significant change in GAD-7 score (-1.421, 95%CI: -3.454, 0.613).

Anxiety and distress scores significantly reduced for both females (GAD-7: -0.496, 95%CI: -0.983, -0.010; IES-R: -2.606, 95%CI: -4.445, -0.767) and males (GAD-7: -0.622, 95%CI: -1.653, 0.409; IES-R: 2.461, 95%CI: -5.929, 1.007) at the first cut-off date and also at the second cut-off date (females: GAD-7: -1.013, 95%CI: -1.778, -0.248; IES-R: -3.369, 95%CI: -5.789, -0.948) (males: GAD-7: -1739, 95%CI: -2.993, -0.485; IES-R: -3.112, 95%CI:

-6.985, -0.762). At both dates, the fall in GAD-7 were higher among males compared to females. IES-R shows the opposite picture. Those below 21 years of age showed a statistically significant decline in GAD-7 (-5.482: 95%CI: -9.526, -1.437) at the first cut-off date compared to all other age groups. However, the reductions in mental health scores were not statistically significant in the below 21 years group when the face covering policy was introduced (GAD-7: -0.983, 95%CI: -5.502, 3.536).

People from white ethnic background had a significant reduction in GAD-7 (-0.657, 95%CI: -1.129, -0.185 at the first cut-off date; and -1.243, 95%CI: -1.957, -0.529 at the second cut-off date) and IES-R (-3.044, 95%CI: -4.830, -1.259 at the first cut-off date; -3.567, 95%CI: -5.888, -1.246 at the second cut-off date). There was no statistically significant change in the mental health status of non-white ethic population in the study.

Christians had a statistically significant fall in GAD-7 (-0.652, 95%CI: -1.298, -0.006 at the first cut-off date; -0.928, 95%CI: -1.630, -0.226 at the second cut-off date) and IES-R (-2.679, 95%CI: -4.909, -0.449 at the first cut-off date; -3.354, 95%CI: -6.289, -0.420 at the second cut-off date). At the first cut-off date, non-Christians had a significant decrease only in IES-R (-3.473, 95%CI: -6.483, -0.464). At the second cut-off date, non-Christians had a significant reduction in GAD-7 (-1.298, 95%CI: -2.290, -0.306) and IES-R: (-3.473, 95%CI: -6.483, -0.464).

There were significant reductions in the anxiety and distress scores of people with A-level or below and higher degree at both cut-off points. However, for higher degree holders, the improvements in mental health were seen only in IES-R (-1.955, 95%CI: -3.408, -0.502) at the first cut-off date and GAD-7 at the second cut-off date (-0.876, 95%CI: -1.712, -0.041). The lower educated group had a greater improvement in mental health at both cut-off dates.

People living in rented accommodation did not report improvements in their mental health at the first cut-off date (GAD-7: -0.369, 95%CI: -1.449, 0.712; IES-R: -1.933, 95%CI: -5.935, 2.068), but did report an improvement at the second cut-off date for GAD-7 only (-1.837, 95%CI: -3.056, -0.618). Those living in their own accommodation had statistically significant improvements in both GAD-7 and IES-R at both cut-off dates.

Those who were shielding did not report any improvements in their mental health at the first cut-off date (GAD-7: -0.655, 95%CI: -2.023, 0.713 and IES-R: -3.447, 95%CI: -8.512, 1.619). There was improvement in GAD-7 at the second cut-off date for this group. Those who were not shielding had no improvement in mental health, except for GAD-7 at the first cut-off date (-1.243, 95%CI: -2.295, -0.191).

Those who experienced COVID-19 illness reported an improvement in their mental health status at the first (GAD-7: -0.490, 95%CI: -0.961, -0.018) and second (GAD-7: -0.875, 95%CI: -1.621, -0.129) cut-off dates. Those who did not experience any such problems reported an improvement in their mental health at the second cut-off date only.

People who had previous mental health conditions did not experience statistically significant improvements in their mental health at the first cut-off date (GAD-7: -0.649 95%CI: -1.582, 0.284; IES-R: -2.772, 95%CI: -6.246, 0.702). At the second cut-off date, there was improvement for this group in IES-R (-6.239, 95%CI: -10.192, -2.286), but not in GAD-7. For those with no mental health issues, improvement in GAD-7 was noted at the second cut-off date.

Statistically significant improvement in mental health was seen at the first cut-off date among respondents who drank alcohol 4 or more times in a week (GAD-7: -1.165, 95%CI: -2.178, -0.151; IES-R: -3.784, 95%CI: -7.229, -0.340). At the second cut-off date, those who drank alcohol moderately had statistically significant improvement in the measured mental health indices. Those who were taking drugs did not experience an improvement in their mental health scores at the first (GAD-7: 0.631, 95%CI: -3.023, 4.286; IES-R: -2.827, 95%CI: -12.067, 6.412) or second cut-off dates (GAD-7: -1.470, 95%CI: -6.338, 3.398; IES-R: 5.805, 95%CI: -11.429, 23.039). However, at both cut-off dates, there were significant improvements in the mental health of those who did not take drugs.

Those who reported suicidal thoughts ever in their life showed improvements in their mental health at the first cut-off date (GAD-7: -1.232, 95%CI: -1.983, -0.481; IES-R: -5.938, 95%CI: -8.759, -3.118), but not at the second cut-off date (GAD-7: -1.588, 95%CI: -3.487, 0.310; IES-R: -4.256, 95%CI: -9.486, 0.974). However, those who had no suicidal thoughts had no improvements in their mental health at the first cut-off date (GAD-7: -0.173, 95%CI: -0.599, 0.252; IES-R: -0.941, 95%CI: -2.482, 0.600), but did improve at the second cut-off date (GAD-7: -0.831, 95%CI: -1.343, -0.319; IES-R: -2.520, 95%CI: -4.065, -0.975).

Robustness check

These results would be robust if the local randomization exists around the cut-off (policy changing) dates, meaning that individuals are randomly distributed around the cut-offs. If it can be shown that all control variables (*e.g.*, demographics, pre-existing health conditions, and lifestyles, which are dummy variables) are insignificantly discontinuous at those cut-off dates, it can be said that the local randomization exists around those cut-offs. In other words, insignificant discontinuities in control variables will guarantee that significant discontinuities in mental health scores (GAD-7 and IES-R) happen due only to policy changes (relaxation of lockdown and face-covering), not due to changes in the control variables, which also affect those mental health scores.

Separate OLS regressions of every control dummy following the same RDD specification in equation were run. The outcome variable was just replaced with the control dummy. Every dummy has a base category, for which the dummy variable is not needed; otherwise, there would be a dummy trap. For that reason, when the male dummy is used, for example, the female dummy is not needed, and Supplementary Table 1 does not show results for that reason. The coefficients of the discontinuity dummies for two cut-off dates, with 95%CI, are shown in Supplementary Table 1 in Supplementary material. As both GAD-7 and IES-R had different sizes of samples, two groups of such regressions of control variables were run using two different common samples of GAD-7 and IES-R. Common samples come from the regressions of those mental health scores. Results in Supplementary Table 1 imply that most of the control dummies are insignificantly discontinuous, implying that the main results in Table 4 are mostly robust.

Other biases (caused by unobserved factors', changes or any other policy changes that affect mental health outcomes) can be captured by checking discontinuities in the density of the assignment/trend variable. We found this was statistically insignificant (not shown). There were no other national policy changes at exactly those cut-off dates. From the visual inspection of Figures 2 and 3, there were no clear discontinuities in mental health outcomes at any other dates. If discontinuities in mental health outcomes at the policy changing cutoff dates were random events, there would have been such discontinuities at other dates. This informal falsification test also implies that our results capture mostly causal effects.

Limitations

A key limitation of this study is a high number of missing cases and non-random selection of participants. However, the methodology used in this study mitigates against this limitation by comparing matching cases before and after each policy intervention. Identification tests imply that local randomization exists around the cut-off dates, implying that the findings are robust.

Another limitation is the non-probability sample design and time limited survey which means longitudinal changes were not possible to elicit. Similarly, pre pandemic data was not available, although this was not possible for this survey which was not designed pre pandemic. However, the results from phase one will be compared to phase two of the survey that was conducted from November 20, 2020 to February 2021.

DISCUSSION

This paper examined the association of the lockdown relaxation and the implementation of the face covering policy on the mental health of the general population and sub-groups in the United Kingdom using interrupted time series model. Mental health status was measured using two standardised mental health measures, GAD-7 and IES-R.

This study in the United Kingdom reports a casual association of lockdown on mental health of the participants. The findings compare with similar research carried out in the United Kingdom which showed "minimal" impact of lockdown on the mental health of the general population[1,8,9]. One of the reasons for "mild" anxiety and distress in the United Kingdom during lockdown may be because of several economic and welfare government policies.

This study confirms improvements in anxiety and distress levels following lockdown relaxations. Relaxation of lockdown started on July 4, 2020 in the United Kingdom and showed significant improvements in the population's mental health conditions. However, much greater improvement in anxiety and distress was observed

when face covering in public places was enforced on July 24, 2020. It appears that face covering provided confidence in protection from the virus while visiting friends, public places, clinics, shops and other such places. It may be noted here that when lockdown relaxations were implemented on July 4, 2020, face covering use in the United Kingdom was very limited. Face covering implementation in public places had a significant positive association with mental health on all population sub-groups, suggesting wider benefit of the face covering policy on mental health.

This study identified significantly higher levels of anxiety and distress among people with pre-existing mental health issues, those who were shielding, those who reported suicidal thoughts, drug and alcohol use, and experience of episodes of COVID-19 illness. These population sub-groups benefited by both lockdown relaxation and face covering policy. However, face covering had a greater association with improvement in anxiety and distress than lockdown relaxation.

Higher levels of anxiety and distress among females and younger age groups were noted in this study, which is similar to the emerging global evidence[20]. The findings also compare to other studies that have reported differential impact of COVID-19 Lockdown restrictions on mental health by predisposing health conditions and socio-demographic characteristics. An international study carried out by CARE in 40 countries showed that 27% of women reported an increase in challenges associated with mental illness compared to only 10% of men[20]. A study carried out in Tunisia showed anxiety, depressive symptoms, and stress were found in about 85% of women [21]. Other studies also reported experience of higher mental health problems among females compared to males[6]. A meta-analysis of 206 studies showed minimal differences in the prevalence of mental health issues such as anxiety, depression, and PTSD among healthcare professionals and the public during the pandemic. A new development in this study was that there appears to be higher prevalence of suicidal thoughts/ideation or self-harm (11% *vs* 5.8%) and lower prevalence of wellbeing (28.2% *vs* 52.6%) among the public compared to healthcare professionals which had previously not been reported[22]. Globally there is evidence of domestic violence and more workload for women than men during lockdown[23-26]. There is evidence of lower participation of women in COVID-19 related policy committees[27].

Similar to findings from this study, there is evidence from various studies that the younger age groups had higher levels of mental health problems during lockdown restrictions compared to older age groups[6]. However, older adults have shown lower sleeping quality during the pandemic period compared to the pre-pandemic period[28].

Health workers, particularly frontline staff, played an important role during the pandemic. At the beginning of the pandemic, there is evidence of increased mental health impact on health workers. For example, at the time of COVID-19 in China and Japan, depression, anxiety, insomnia and resilience were higher among frontline health workers than the general population[29,30]. The prevalence of depression, anxiety, and stress has been shown to have remained elevated even after the restrictions were lifted in a study in Malaysia[31]. In this study, anxiety and stress levels of health workers were lower than other key workers. The reason for low levels of anxiety and stress among health workers is currently less understood and a probable reason could be their professional attitude and support from the general public for the important work they do for the country. One can also hypothesise that the health workers learned self-help stress-management and mindfulness that they prescribed to their patients[32]. Studies have also reported increased mental health problems in those who had chronic/psychiatric illnesses, unemployment, student status, and frequent exposure to social media/news concerning COVID-19, compared to their counterparts[6,33]. Living alone during the lockdown, a longer duration of illness, and smoking habits had higher associations with COVID-19 related distress [34]. Detachment, pre-existing mental health problems, fewer coping strategies and childlessness were associated with higher levels of depression and stress[35]. Our study shows similar findings, thereby endorsing the evidence base of the impact of the pandemic.

CONCLUSION

In conclusion, evidence is building on the differential psychological impact of the pandemic, resultant restrictions and policies, based on socio-demographic variables, pre-existing vulnerabilities and health care worker status that will help future planning and policies. Such evidence when used collectively should inform future

planning for pandemics and develop collective and individual physical and mental resilience.

ARTICLE HIGHLIGHTS

Research background

The global pandemic caused by coronavirus disease 2019 has led to wide spread changes in people's day to day lives.

Research motivation

The changes in people's lives and livelihoods due to the global pandemic, associated lockdowns and government guidance is anticipated to have a great impact on people's emotional and social wellbeing.

Research objectives

Positive association of lockdown relaxation and face covering policies on the Mental Health of various population sub-groups is reported.

Research methods

A regression discontinuity design was used to analyse data gathered on people's health and wellbeing during different time periods and restrictions *via* online survey platform.

Research results

In comparison to other key workers and non-key workers during lock down, professional groups and health workers had lower generalised anxiety disorder (GAD-7) scores indicating lower anxiety levels. Similar findings were noted for the impact of events scale-revised (IES-R) scores with health workers, indicating lower levels of distress. During the compulsory face covering phase, there were improvements in mental health scores for all three professional groups assessed by GAD-7 and IES-R. Greater improvements in mental health scores were found among non-key workers than key workers. Gender was associated with different mental health outcomes during the lockdown, with females scoring higher on the GAD-7 and IES-R scales in comparison to males. However, both groups showed a significant improvement in mental health status during the period of face covering, with slightly higher improvements noted in males.

Research conclusions

An impact on people's wellbeing was found, with anxiety and depression levels improving when relaxations in restrictions happened.

Research perspectives

Further investigation into pandemic preparedness for those with pre-existing conditions such as anxiety, depression or obsessive-compulsive disorders and modifying psychological interventions in this population is warranted.

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SYSTEMATIC REVIEWS

Autism spectrum disorder and personality disorders: Comorbidity and differential diagnosis

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Abstract

BACKGROUND

Differential diagnosis, comorbidities and overlaps with other psychiatric disorders are common among adults with autism spectrum disorder (ASD), but clinical assessments often omit screening for personality disorders (PD), which are especially common in individuals with high-functioning ASD where there is less need for support.

AIM

To summarize the research findings on PD in adults with ASD and without intellectual disability, focusing on comorbidity and differential diagnosis.

METHODS

PubMed searches were performed using the key words "Asperger's Syndrome", "Autism", "Personality", "Personality disorder" and "comorbidity" in order to identify relevant articles published in English. Grey literature was identified through searching Google Scholar. The literature reviews and reference sections of selected papers were also examined for additional potential studies. The search was restricted to studies published up to April 2020. This review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses method.

RESULTS

The search found 22 studies carried out on ASD adults without intellectual disability that met the inclusion criteria: 16 evaluated personality profiles or PD in ASD (comorbidity), five compared ASD and PD (differential diagnosis) and one performed both tasks. There were significant differences in the methodological

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approaches, including the ASD diagnostic instruments and personality measures. Cluster A and cluster C PD are the most frequent co-occurring PD, but overlapping features should be considered. Data on differential diagnosis were only found with cluster A and cluster B PD.

CONCLUSION
ASD in high-functioning adults is associated with a distinct personality profile even if variability exists. Further studies are needed to explore the complex relationship between ASD and PD.

Key Words: Autism spectrum disorder; Asperger's Syndrome; Personality disorder; Adulthood; Comorbidity; Differential diagnosis

Core Tip: Differential diagnosis, comorbidities and overlaps with other psychiatric disorders are common among adults with autism spectrum disorder (ASD). Findings of most studies support that ASD in high-functioning adults is associated with a distinct personality profile even if variability exists. Cluster A and cluster C personality disorders (PD) are the most frequent co-occurring PD in ASD, but overlapping features should be considered.

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with an early onset and a genetic component. ASD is characterized by deficits in socio-emotional reciprocity, by impaired verbal and non-verbal communication skills, and by an inability to develop and maintain adequate social relationships with peers, and is associated with the presence of repetitive verbal and motor behaviours, restricted patterns of interest, the need for an unchanging (or at least predictable and stable) environment and *hypo- or hypersensitivity* to *sensory* inputs. The onset of clinical symptoms occurs during the early years of life[1].

The severity of ASD symptoms, intellectual functioning, age at diagnosis and psychiatric comorbidity have been shown to account for heterogeneity in clinical presentation, functioning and outcome[2-4].

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition[1], classifies three levels of ASD functioning. Level 1, which requires support, is the best functioning and includes the previous definitions of high-functioning ASD (a term commonly used in clinical practice) and Asperger's syndrome (AS), the closest to neurotypical functioning[1]. ASD level 1 may not have been diagnosed in adulthood and may also have been misdiagnosed as a psychiatric disorder[5,6]. Late-diagnosed individuals show higher levels of co-occurring psychiatric conditions, potentially related to the long-term stress in adaptation to daily life in society[7].

The most common coexisting psychiatric disorders in subjects with ASD include attention deficit hyperactivity disorder (ADHD)[8], obsessive–compulsive disorder[9,10], psychosis[11-13] and mood and anxiety disorders[14-16]. It is possible that adults with ASD level 1 are vulnerable to such disorders[17], in part because of their greater insight into their deficits[18] and greater sensitivity to discrimination[19].

The high frequency of co-occurring disorders and the development of learnt or camouflaging strategies[20] make it difficult to diagnose ASD in adults, especially in women[21,22]. Misdiagnosis, differential diagnoses, comorbidities and overlapping behaviour with other psychiatric diagnoses, as well as personality disorders (PD), should be considered[23]. While these patients are usually screened for the presence of

Axis I disorders, Axis II comorbidities are less often evaluated in this sample of patients[15]. However, in a recent survey Keller *et al*[24] found a PD comorbidity in ASD in 24% of the sample.

PD are enduring and pervasive patterns of inner experience and behaviour that deviate markedly from the expectations of the individual's culture, resulting in distress and impairment[1]. Both PD and ASD are life-long and egosyntonic disorders.

There is a growing interest in exploring the complex relationship between ASD and PD, because a better understanding of this topic may enhance the diagnostic process and also inform targeted interventions.

The purpose of this review is to summarize the research findings on PD in adults with ASD, focusing on comorbidity and differential diagnosis.

MATERIALS AND METHODS

The present review adhered to the standards set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[25]. A systematic review of the literature was performed through PubMed, using combinations of the following search terms: Asperger's Syndrome or/Autism + Personality/Personality disorder or + comorbidity. The search was restricted to studies published up to April 2020. Grey literature was identified through searching Google Scholar. The literature reviews and reference sections of selected papers were also examined for additional potential studies. All records that remained following the removal of duplicates were screened for the inclusion criteria.

Studies were included in this review if they examined PD (as a comorbid or differential diagnosis) in ASD samples. Only studies published in the English language and performed on adults without intellectual disability were selected. In studies for which IQ data were not reported, the participants had to be diagnosed with AS or high-functioning autism (HFA)/ASD level 1. Investigations carried out on non-clinical samples were excluded. Studies evaluating autistic traits in PD patients were also excluded. There were no restrictions made for the geographical region or setting of the study.

RESULTS

Figure 1 shows a PRISMA flow diagram of the systematic research process. The database search yielded a total of 6936 articles. Three additional records were identified through other techniques (ancestry method, grey literature searches and expert consultation). Following the removal of duplicates, 5808 articles remained for screening.

Upon screening of the records, a further 5735 articles were excluded for a variety of reasons, including a focus on different research topics or a failure to satisfy the inclusion criteria. Thus, the full texts of 74 articles were assessed, 22 of which qualified for inclusion.

In order to perform a better analysis, the studies were grouped into two main classes: Those examining personality or PD in ASD adults using categorical and dimensional models (comorbidity); and those comparing ASD with PD on personality traits or psychological functioning (differential diagnosis). In addition, one study[26] performed both tasks.

The characteristics of the studies included in this review are summarized in Table 1.

Seven reviews on psychiatric comorbidity/differential diagnosis of adults with ASD that also referred to PD were found[5,27-32], but only two papers were specifically focused on PD[33,34].

Personality disorders as comorbid diagnosis

Among studies exploring personality features in ASD, only a few assessed PD as a categorical diagnosis using the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II)[35,36] or the International Personality Disorder Examination (IPDE)[37] (see Table 2). As autistic traits overlap with aspects of several PD, dimensional measures were preferred to assess personality in adults with ASD.

Structured Clinical Interview for DSM-IV

A study[14] carried out on 117 patients with ASD found that 62% of the sample met

Table 1 Description of the studies included in the systematic review

Ref.	Setting	Aim	Statistical methods	Limitations
Soderstrom *et al* [50], 2002	NeuropsychiatricClinic in Sweden	To study the personality characteristics of adults with AS	One sample *t*-test	Small sample size
Anckarsäter *et al* [47], 2006	Neuropsychiatric Clinic in Sweden	To describe PD in relations to ADHD and ASD symptoms	One sample *t* - test	Non-specific symptoms may be overselected
Ketelaars *et al* [43], 2008	Center of Expertise for Autism in Netherlands	To explore difference between patients with mild ASD and patients without ASD in term of AQ scores and psychiatric comorbidity	X^2 test	Small sample size
Rydén and Bejerot[40], 2008	Psychiatric setting (tertiary unit) in Sweden	To characterize psychiatric patients with ASD in regard to demographical factors, psychiatric comorbidity and personality traits and compare the ASD group with a psychiatric control group; to compare differences of personality traits between females and males in the ASD group.	Fisher exact test; *t*-test; Kruskal-Wallis test	Not ADOS/ADI-R for assessing ASD; A naturalistic study
Hofvander *et al* [14], 2009	Neuropsychiatric Hospital in France NeuropsychiatricClinic in Sweden	To describe the clinical presentation and psychosocial outcome of a group of normal intelligence adults with ASD	X^2 test	Lack of comparison group; Two studies sites; Prevalence of comorbid psychiatric conditions may be overestimated
Sizoo *et al*[49], 2009	Two diagnostic centers specialized for adult patients with developmental disorders in Netherlands	To test whether adults with ASD or ADHD have distinct personality profiles, to assess how personality profiles in these groups differed by SUD status	One sample *t*-test	The clinically based diagnostic procedures; The absence of a psychiatric control group; All participants were diagnosed in adulthood
Geurts and Jansen[44], 2011	Tertiary psychiatric unit from diagnosing ASD in Netherlands	To draw the pathway to a diagnosis for adults referred to ASD assessment	Mann-Whitney *U* tests; Kruskal-Wallis tests; X^2 test	Retrospective chart study; Not standardized clinical interviews for assessing axis I and axis II diagnosis
Kanai *et al*[59], 2011	University Hospital in Japan	To examine the clinical characteristics of adults with AS	Spearman's rank correlation coefficient	Small sample size
Kanai *et al*[67], 2011	University Hospital in Japan	To examine the clinical characteristics of adults with AS	Mann-Whitney *U* test	Small sample size
Lugnegård *et al* [38], 2012	Neuropsychiatric clinics in Sweden	To explore the presence of PD in young adults with AS	X^2 test	Small sample size
Schriber *et al* [55], 2014	Local recruitment by physicians, psychologists, speech and language pathologists, occupational therapists, advocacy groups, regional centers, ASD support groups in United States	To compare self-reports of Big Five personality traits in adults with ASD to those of typically developing adults.	Independent sample *t* -test	Small sample size
Hesselmark *et al* [62], 2015	Tertiary psychiatric unit for diagnosing ASD; a community based facility for ASD; a website for ASD	To test validity and reliability of self-report data using the NEO-PI-R in adults with ASD	Independent sample *t* -test	Small sample size
Strunz *et al*[26], 2015	Department of Psychiatry at a University Hospital in Germany	To identify personality traits in adults with ASD and to differentiate them from patients with NPD, BPD and NCC	MANOVA	Selection bias (BPD and NPD were inpatients, while ASD were outpatients)
Helles *et al*[52], 2016	Neuropsychiatric Centre in Sweden	To examine temperament and character in males who were diagnosed with AS in childhood and followed prospectively over almost two decades	*t*-test; Kruskal-Wallis H testDunn's post hoc test	Only men with AS

Schwartzman *et al*[56], 2016	On line recruitment United States	To assess and compare personality traits of adults with and without elevated ASD traits using; the Five Factor Model of personality	Independent sample *t* -test	Online administration of self-report questionnaires; Sample was not representative of adult population with ASD
Vuijk *et al*[51], 2018	Expertise Centre for Autism in Netherland	To investigated temperament and character dimensions of men with ASD by individual case matching to a comparison group.	*t*-test	Only men with ASD
Ozonoff *et al* [65], 2005	University Child and Adolescent specialized clinic in United States	To explore personality and psychopathology in adult with ASD	Independent sample *t*-test	Small sample size
López-Pérez *et al* [95], 2017	Four different mental health institutions in Spain	To examine use of different interpersonal ER strategies in BPD and AS compared to normative control participants	ANOVA	Self-reports of interpersonal ER; ToM was not assessed
Dudas *et al*[92], 2017	CARD, online responders to a website	To compare ASC, BPD, and comorbid patients in terms of autistic traits, empathy, and systemizing	ANOVA	Diagnosis was based on self-report of patients
Murphy[100], 2006	High security psychiatric care in UK	To compare the ToM performance of three forensic patient groups (AS, Schizophrenia and PD patients)	Kruskal-Wallis H test	No control for the potential influence of medication on cognitive functioning
Stanfield *et al* [87], 2017	Clinical and support services in Scotland; Nonpsychotic people who had previously participated in the EHRS of schizophrenia	To compare Social Cognition in ASD and SPD using functional magnetic resonance imaging (fMRI).	Kruskal- Wallis tests	Small sample size
Booules-Katri *et al*[84], 2019	Patients and relatives of schizophrenia patients attending psychiatric service at a hospital in Spain; Public advertisements	To compare the ToM performance of a group of HFA and SSPD with a matched HC group	*t*-test	SSPD sample consisted of non-clinical individuals

ADHD: Attention deficit hyperactivity disorder; ADI-R: Autism diagnostic interview - revised; ADOS: Autism diagnostic observation schedule-generic; AQ: Autism quotient; AS: Asperger Syndrome; ASC: Autism spectrum condition; ASD: Autism spectrum disorder; BPD: Borderline personality disorder; Er: emotion regulation; HC: Health control; HFA: High-functioning autism; NCC: Non-clinical controls; NEO-PI-R: NEO personality inventory revised; NPD: Narcissistic personality disorder; PD: Personality disorder; SPD: Schizotypal personality disorder; SSPD: Schizotypal-schizoid personality disorder; SUD: Substance use disorder; ToM: Theory of mind.

the criteria for at least one PD: primarily obsessive–compulsive (32%), avoidant (25%) and schizoid PD (21%). Concerning cluster B PD, rates of comorbidity were low, but antisocial disorder was common in the pervasive developmental disorder subgroup. A high number of patients (35%) had more than two PD. The prevalence of PD did not differ between genders, with the exception of schizoid PD, which was significantly more common among women.

Lugnegård *et al*[38] reported that 48% of a sample of 54 young adults with AS fulfilled the criteria for a cluster A or cluster C PD diagnosis. This evidence was in line with Gillberg and Billstedt's review[27] reporting no cluster B PD comorbidity in this sample of patients. It is surprising that paranoid and dependent PD diagnoses were not found. There was a significant difference in PD prevalence between genders: 65% in males versus 32% in females. Patients with AS and a concomitant PD showed more marked autistic features according to the autism spectrum quotient (AQ)[39].

Similarly, no cluster B PD comorbidity was found by Strunz *et al*[26]. In research examining personality pathology in ASD compared to specific PD, 45% of ASD patients met the criteria for an Axis II PD diagnosis. In particular, 36% of ASD patients

Table 2 Summary of included studies exploring comorbid personality disorders diagnosis (according to DSM-IV) in autism spectrum disorder patients

Ref.	Participants	Measures	PD assessment instrument	PD Prevalence (at least one PD)
Ketelaars *et al*[43], 2008	*n* = 15 (4 AS, 10 PDD-NOS, 1 HFA)	AQ, SCAN-2.1	IPDE	> 50%
Rydén and Bejerot[40], 2008	*n* = 84 (5 autistic disorder, 51 AS, 28 PDD-NOS); 37% comorbid ADHD	SCID-I, WAIS III, ASSQ, ASDI, ASRS, MADRS,Y-BOCS, GAF, CGI-S, WRAADDS	SCID-II screen; SPP	> 40%
Hofvander *et al*[14], 2009	*n* = 117 (5 autistic disorder, 62 AS, 50 PDD-NOS)	WAIS-R or WAIS-IIISCID-I, ASDI	SCID-II	62%
Lugnegård *et al*[38], 2012	*n* = 54 (AS)	WAIS-III, DISCOS-11AQ	SCID-II or a structured DSM-IV-based clinical interview	48%
Strunz *et al*[26], 2015	*n* = 59 (49 AS, 10 HFA)	ADOS, ADI-R, MINI, SCID-I, DAPP-BQ,NEO-PI-R	SCID-II	45%
Geurts and Jansen[44], 2011	*n* = 105 (27 autistic disorder, 28 AS, 50 PDD- NOS); 34% of sample with intellectual disability	Former DSM-IV Axis I diagnosis reported	Former DSM-IV Axis II diagnosis reported	15%
Anckarsäter *et al*[47], 2006	*n* = 174 subjects with childhood onset neuropsychiatric disorder (47 ASD, 27 ASD+ADHD, 81 ADHD, 19 other diagnosis)	SCID-I, ASDI, Y-BOCS; ASHFAQ, TCI	SCID- II	75%

ADHD: Attention deficit hyperactivity disorder; ADI-R: Autism Diagnostic interview-revised; ADOS: Autism diagnostic observation schedule-generic; AS: Asperger syndrome; ASD: Autism spectrum disorder; ASDI: Asperger syndrome diagnostic interview; ASHFAQ: Asperger syndrome and high-functioning autism screening questionnaire; ASRS: Adult ADHD self-report scale; ASSQ: Autism spectrum disorder in adults screening questionnaire; ASDI: Asperger syndrome diagnostic interview; AQ: Autism spectrum quotient; CGI-S: Clinical global impression severity of illness; DAPP-BQ: Dimensional assessment of personality pathology; DISCOS-11: Diagnostic interview for social an communication disorder; GAF: Global assessment of functioning; HFA: High-functioning autism; IPDE: International personality disorder examination; MADRS: Montgomery asberg depression rating scale; MINI: Mini international neuropsychiatric interview; NEO-PI-R: Neo personality inventory revised; PDD-NOS: Pervasive developmental disorder not otherwise specified; SCAN-2.1: Schedules for clinical assessment in neuropsychiatry; SCID-I: Structured clinical interview for DSM-IV axis I disorders; SCID-II: Structured clinical interview for DSM-IV personality disorders; SPP: Swedish universities scales of personality; TCI: Temperament and character inventory; Y-BOCS: Yale -brown obsessive compulsive scale; WAIS-R: Wechsler adult intelligence scale-revised; WAIS-III: Wechsler adult intelligence scale-III; WRAADDS: Wender-reimherr adult attention deficit disorder scale.

met the criteria for schizoid PD, 17% for obsessive–compulsive PD and 2% for avoidant and paranoid PD diagnoses.

These findings are in line with those reported by Rydén and Bejerot[40]. They assessed adults with ASD having no intellectual disability using the structured clinical interview for DSM-IV (SCID-II) screen[41] and the Swedish Universities Scales of Personality[42]. Avoidant and schizotypal personality traits were more common in patients with ASD compared to the control group (patients without ASD). Patients with ASD scored higher on detachment and stress susceptibility and had a median of four PD compared to two in the control group. More than 40% of the ASD group reached the cut-off score for avoidant, borderline and obsessive–compulsive PD, more than a third had depressive, schizotypal, schizoid and narcissistic PD and at least 25% reached the cut-off for paranoid and passive-aggressive PD. Females with ASD scored significantly higher than males on borderline and passive-aggressive traits.

In a pilot study on adults with mild ASD, Ketelaars *et al*[43] found partial or complete PD, assessed by the IPDE[37], in more than half of the sample. Schizoid and avoidance were the most frequent PD. There were no significant differences in the pattern of Axis II comorbidity between the ASD and the non-ASD patients.

Instead, in a retrospective chart study[44] on adults screened for ASD, only 15% of ASD patients had a lifetime PD diagnosis. This lower comorbidity is probably due to the fact that one third of the patient group had an intellectual disability. People with autism and an intellectual disability were less likely to receive a diagnosis of PD[45, 46].

In a study on Temperament Character Inventory (TCI) profiles in ASD and ADHD [47], the presence of PD was assessed with the SCID-II in a subgroup of patients with childhood onset of a neuropsychiatric disorder: 75% of the sample met the criteria for at least one PD. Specific PD prevalences are presented in Table 3.

Table 3 Specific personality disorders (Structured clinical interview for DSM-IV axis II diagnosis) prevalence in autism spectrum disorder samples

PD	Lugnegård *et al*[38], 2012	Hofvander *et al*[14], 2009	Anckarsäter *et al*[47], 2006	Strunz *et al*[26], 2015
Paranoid	0%	19%	25.5 % ASD; 25.9% ASD + ADHD	2%
Schizoid	26%	13%	31.9% ASD; 22.2% ASD + ADHD	36%
Schizotypal	2%	21%	23.4% ASD; 11.1% ASD + ADHD	0%
Antisocial	0%	3%	0% ASD; 18.5% ASD + ADHD	0%
Histrionic	0%	0%	0%	0%
Borderline	0%	9%	10.6% ASD; 14.8% ASD + ADHD	0%
Narcissistic	0%	3%	6.4%ASD; 3.7% ASD + ADHD	0%
Avoidant	13%	25%	34% ASD; 11.1% ASD + ADHD	2%
Obsessive-compulsive	19%	32%	42.6% ASD; 29.6% ASD + ADHD	17%
Dependent	0%	5%	8.5% ASD; 22.2% ASD + ADHD	0%

PD: Personality disorders; ASD: Autism spectrum disorder; ADHD: Attention deficit hyperactivity disorder.

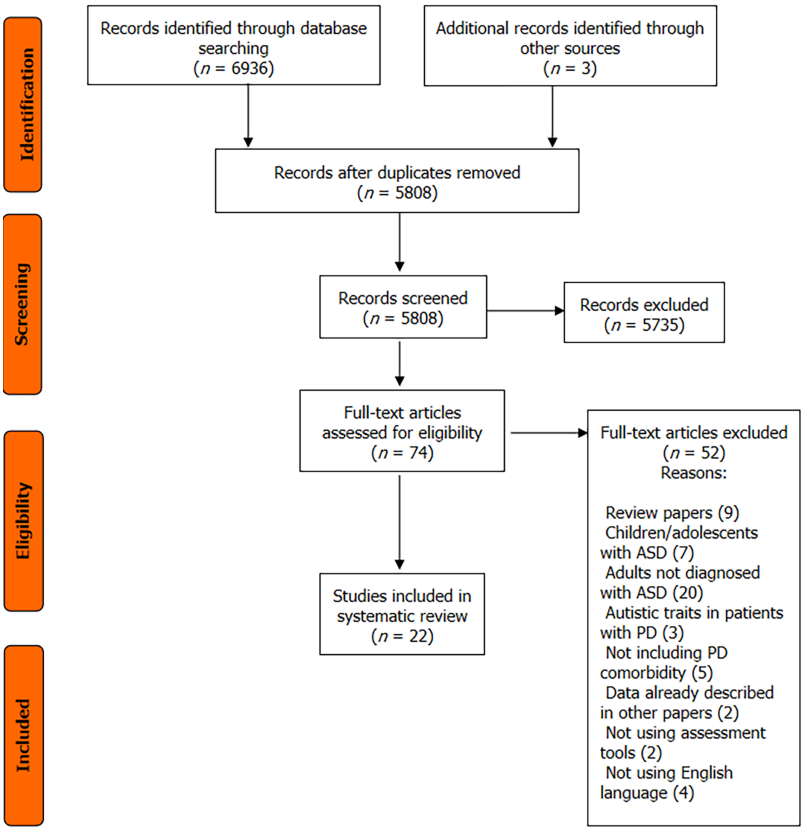

Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram of the systematic research process.

Temperament and character inventory

Studies using the temperament and character inventory (TCI) to evaluate personality in patients with ASD are presented in Table 4[48]. Four TCI studies on adults with ASD[47,49-51] found low scores on the character dimensions of self-directedness and cooperativeness. Moreover, ASD was associated with high harm avoidance, low reward dependence, low novelty seeking and high self-transcendence. The high level of rare answer scores also reflects the oddity and social insensitivity inherent in the self-descriptions of subjects with ASD[50,52]. Cluster A and cluster C PD were more common in patients with ASD assessed with the TCI and confirmed with the SCID-II

Table 4 Summary of studies using temperament character inventory to evaluate personality in adults with autism spectrum disorder

Ref.	Participants	Comparison group	Measures	Personality measures	Results
Anckarsäter *et al*[47], 2006	*n* = 113 (6 autistic disorder, 46 AS, 66 Atypical Autism); 47ASD+ADHD 66 ASD	Age and sex matched group	SCID-I; ASDI; Y-BOCS; ASHFAQ; TCI	TCI; SCID-II	Lower NS, RD, SD, C; Higher HA; Cluster A and Cluster C PD were common
Soderstrom *et al*[50], 2002	*n* = 31 AS	Age and sex matched group	WAIS-III	TCI	Higher HA ST; Lower NS, RD, SD, C
Sizoo *et al*[49], 2009	*n* = 75 (53 without SUD, 8 with past SUD, 14 with current SUD)	*n* = 657 NC	ADI-R; ADOS; DSM-IV criteria checklists; WAIS-III	VTCI	Higher HA, ST; Lower RD, SD, C; Lower NS and RD for ASD without SUD; Higher P for subgroups with current or past SUD
Vuijk *et al*[51], 2018	*n* = 66 (15 ASD, 25 AS, 26 PDD-NOS)	Matched comparison group (age, education, marital status)		TCI	Higher HA, lower NS, RD, SD, C
Helles *et al* [52], 2016	*n* = 40 AS	Within comparison group (no longer ASD/ASD pure/ASD plus)	GAFWAIS-IIIASDI; BDI; ASRS	TCI	Higher RD in no longer ASD; Higher HA, lower NS in ASD pure; Higher HA, lower C, SD in ASD plus

C: Cooperativeness; HA: Harm avoidance; NC: Neurotypical controls; NS: Novelty Seeking; P: Persistence; RD: Reward dependence; SD: Self-directedness; ST: Self-transcendence; SUD: Substance use disorder; SUD: No history of SUD; VTCI: Short version of temperament character inventory.

[47].

In the sample of AS patients included in another TCI study[50], the obsessional type of PD was the most frequent, followed by the passive-dependent, explosive and passive-aggressive types.

The TCI profiles differed somewhat when ASD was combined with a comorbid disorder such as ADHD[47] or substance abuse[49]. When ASD was comorbid with ADHD this was associated with higher levels of novelty seeking, whereas when ASD was comorbid with substance abuse this was associated with a higher degree of persistence and a lower degree of self-directedness compared to ASD patients without the comorbidity.

There was also some evidence indicating an association between temperament and character dimensions and long-term ASD diagnostic stability and psychiatric comorbidity. In a longitudinal cohort study by Helles *et al*[52], the TCI was used to assess 40 males who were diagnosed with AS in childhood and followed prospectively over almost two decades. Three distinct temperament and character profiles emerged. Those no longer meeting the criteria for ASD had high reward dependence. It is also interesting to note that in another study[50] 35.5% of the sample had reward dependence scores above the general population mean, suggesting that a subgroup of individuals with AS desire closer social interaction than they are able to establish. The participants with a stable ASD diagnosis and no current psychiatric comorbidity ('ASD pure group') were characterized by lower novelty seeking and higher harm avoidance compared with normative data; however, compared to the other groups harm avoidance was lower than for the 'ASD plus group' (those with a stable ASD diagnosis and psychiatric comorbidity), which showed elevated harm avoidance and low self-directedness and cooperativeness. In the ASD plus group, comorbidity disorders were depression, anxiety disorder and/or ADHD.

Vuijk *et al*[51] performed a re-analysis of scores on the TCI administered to a sample of 66 ASD men by individual case matching. Compared to the general population, patients with ASD scored significantly higher on the scale for harm avoidance, and lower on novelty seeking, reward dependence, self-directedness, and cooperativeness. These findings confirmed the results emerging from their previous research published in Dutch[53].

Big five personality traits

In Table 5 a summary of studies measuring the Big Five personality traits[54] in ASD patients is presented.

Schriber *et al*[55] investigated personality differences between ASD adults and neurotypical control adults using self-reports of the Big Five personality traits. Individuals with ASD were more neurotic, and less extraverted, agreeable, conscientious and open to experience, than neurotypical controls. The same

Table 5 Summary of studies measuring big five personality traits in adults with autism spectrum disorder

Ref.	Partecipants	Comparison group	Measures	Personality trait measures	Results
Schwartzman *et al*[56], 2016	*n* = 364 adults with elevated ASD traits	*n* = 464 adults with lower ASD traits	RAADS-R	IPIP-NEO-120	Neuroticism was positively correlated with ASD symptomatology; Extraversion, openness to experience, conscientiousness, and agreeableness were negatively correlated with ASD; About 70% of the variance in RAADS-R scores accounted for by the IPIP-NEO-120 facets. A great variability in personality traits emerged in the elevated ASD traits group with four distinct clusters of FFM personality types
Schriber *et al*[55], 2014	*n* = 37 ASD (29% HFA, 57% AS, 14% PDD-NOS)	*n* = 42 NC	WAIS; ADOS G	BFI	Higher Neuroticism Lower Openness to experience, Conscientiousness, Extraversion, Agreeableness
Kanai *et al*[67], 2011	*n* = 64 AS	*n* = 65 NC	AQ; HADS; L-SAS	NEO-FFI	AQ, HADS, and L-SAS were significantly higher in AS than in control. Higher Neuroticism, Lower Extraversion, Agreeableness, Conscientiousness AQ correlated with the subscale scores of HADS and NEO-FFI in AS
Strunz *et al*[26], 2015	*n* = 59 ASD(83% AS, 17% HFA)	*n* = 62 NPD,80 BPD, 106 NC	SCID-I/MINI	NEO-PI-R; DAPP BQ; SCID-II	On the NEO-PI-R: Conscientiousness: NCC = ASD > BPD and NPD Neuroticism: NCC < ASD = NPD < BPD; Extraversion: ASD < BPD, NPD, NCCOpenness for experience: ASD < NCC, BPD, NPDAgreeableness: ASD = BPD and NPD > NCCOn the DAPP-BQ: Inhibitedness: ASD = BPD > NCC and NPD Dissocial Behaviour: NCC = ASD < BPD and NPD; Emotional dysregulation: NCC < ASD = NPD < BPD Compulsivity: ASD > BPD, NPD, NCC
Hesselmark *et al*[62], 2015	*n* = 48 ASD	*n* = 53 NC	MINI	NEOPI-R	Satisfactory internal consistency of the NEOPI-R. Neuroticism correlated with psychiatric comorbidity in ASD group

BFI: Big five inventory; L-SAS: Liebowitz social anxiety scale; HADS: Hospital anxiety and depression scale; IPIP-NEO-120: International personality item pool representation of the NEO-PI-R; NEO-PI-R: Neo personality inventory revised.

personality differences were confirmed when controlling for age, gender and self- and parent reports. The findings indicated that the personality profile distinguished between ASD and neurotypical controls but did not significantly distinguish severity symptoms between individuals with ASD.

In another study, Schwartzman *et al*[56] compared adults with and without ASD using the International Personality Item Pool Representation of the NEO-PI-R (IPIP-NEO-120) as a trait measure. The IPIP-NEO-120, following the full-length version of the NEO[57,58], consists of 24 items per factor and 4 items per facet for a total of 120 items. The Big Five facets accounted for 70% of the variance in autism trait scores measured with the Ritvo Autism Asperger's Diagnostic Scale Revised (RAADS-R)[59]. Neuroticism correlated positively with autism symptom severity, whereas extraversion, openness to experience, agreeableness and conscientiousness correlated negatively with autism symptom severity.

The clinical characteristics of AS adults, including depression, anxiety and personality (NEO Five-Factor Inventory, NEO-FFI)[57], were examined by Kanai *et al*[59]. The AQ[39], Hospital Anxiety and Depression Scale (HADS)[60], Liebowitz Social Anxiety Scale (L-SAS)[61] and neuroticism scores were significantly higher in adults with AS than in controls, whereas the extraversion, agreeableness and conscientiousness scores were significantly lower. The total score of the AQ correlated with the anxiety subscale score of the HADS and the extraversion, openness and conscien-

tiousness subscale scores of the NEO-FFI in adults with AS, but not in the controls.

Strunz *et al*[26] assessed personality traits using the NEO-PI-R[62] and personality pathology using the Dimensional Assessment of Personality Pathology (DAPP-BQ)[63, 64] in four samples of adults: ASD, narcissistic PD, borderline PD and non-clinical controls. Personality traits and personality pathology specific to ASD could be identified: ASD individuals, when compared to non-clinical controls, showed significantly higher scores on the NEO-PI-R neuroticism and DAPP-BQ emotional dysregulation dimensions and lower agreeableness scores; ASD individuals had significantly lower scores on the NEO-PI-R extraversion and openness to experience scales and significantly higher scores on the DAPP-BQ inhibitedness and compulsivity scales, relative to all other groups.

Moreover, individuals with ASD scored significantly higher than all other groups on the NEO-PI-R straightforwardness (frankness in expression) subscale. The results of the comparison with PD will be described later as differential diagnosis features.

Minnesota multiphasic personality inventory

Table 6 shows a summary of studies using other assessment measures to evaluate personality in ASD.

Only one study[65] explored personality in HFA by administering the minnesota multiphasic personality inventory (MMPI-2)[66]. The ASD sample had higher scores on the L (Lie) validity scale, Clinical Scale Depression (D) and Social Introversion (Si), Content Scale Social Discomfort (SOD), Supplementary Scale Repression (R) and Personality Psychopathology Five (PSY-5) Introversion (INTR) scales than a matched sample of college students.

In ASD, sample comorbidity conditions were major depression, anxiety disorder and ADHD. The MMPI-2 profile reflected social isolation, interpersonal difficulties, depressed mood and coping deficits. This study also found medium-sized group differences from the control sample and elevations in 30%-40% of the ASD group on Scale 8 (Schizophrenia). These results could be related to psychotic symptoms but also to social alienation and general maladjustment. A high rate of elevation (30%) on the L scale reflects a desire to present a favourable impression and is quite unusual in this sample of patients.

Eysenck personality questionnaire

Kanai *et al*[67] examined 112 adults with AS using the eysenck personality questionnaire (EPQ)[68] and the Schizotypal Personality Questionnaire (SPQ)[69]. Patients scored higher than controls on the SPQ, higher on the neuroticism and psychoticism scores of the EPQ and lower on the extraversion and lie scores of the EPQ. The SPQ subscale scores (unusual perceptual experiences, odd behaviour and suspiciousness) were correlated with the total scores of the AQ in AS.

Personality disorders as differential diagnosis

In the literature investigating the relationship between PD and ASD, differential diagnosis is less explored than comorbidity. Studies comparing individuals with ASD or PD on different assessment measures are shown in Table 7, and each PD cluster is described in terms of differential diagnosis with ASD.

Cluster A personality disorders

Autism and schizophrenia spectrum disorders are classified separately in the DSM-5, but empirical findings suggest that these two disorders share overlapping features[70-72]. In clinical practice the most common difficulties are in the differential diagnosis of adults with ASD from those suffering from schizoid or schizotypal PD[29,73]. It is suggested that attention should be paid to the developmental history of the person, the prodrome and onset of the condition, its course and the absence of positive symptoms [74].

Social cognition (SC) deficits are points of overlap between ASD and schizophrenia spectrum disorders. SC includes cognitive mechanisms involved in the processing and interpretation of the social world[75-79]. Most studies on this topic directly examined patients with autism and schizophrenia[80-83] rather than schizoid or schizotypal patients. Only two studies meeting the inclusion criteria were found.

Booules-Katri *et al*[84] investigated differences in Theory of Mind (ToM), a main component of SC, which refers to the ability to understand the emotional and mental states of other people[75,78,79,85,86]. They used three advanced ToM tests in 35 patients with HFA, 30 patients with schizotypal-schizoid PD (SSPD) and 36 healthy controls: individuals with HFA showed worse performance and no dissociation

Table 6 Summary of studies using different assessment measures to evaluate personality in adults with autism spectrum disorder

Ref.	Participants	Comparison group	Measures	Personality measures	Results
Ozonoff *et al*[65], 2005	*n* = 20 HFA	24 NC (age, intelligence and gender matched college students)	WAIS-R	MMPI-2	Higher Depression, Social Introversion, Social Discomfort, Repression and PSY-5 scale Introversion
Kanai *et al* [59], 2011	*n* = 55 AS	57 NC	WAIS-R	SPQEPQ	SPQ: AS>NC; SPQ subscale scores (unusual perceptual experiences, odd behaviour, and suspiciousness) were correlated with total scores of the AQ in the AS group; Higher 'Neuroticism' and 'Psychoticism'; Lower 'Extraversion' and 'Lie'

EPQ: Eysenck personality questionnaire; MMPI-2: Minnesota multiphasic personality inventory; SPQ: Schizotypal personality questionnaire.

between affective and cognitive ToM components when compared with the SSPD patients; and the SSPD individuals scored significantly lower on cognitive than affective ToM tasks.

Stanfield *et al*[87] compared SC in ASD and schizotypal PD (SPD) using functional magnetic resonance imaging (fMRI). In the Ekman 60-Faces Test and the social judgement task there were no significant differences between the ASD, the SPD and the comorbid groups on any measure. All groups had similar patterns of impairment in the SC tests and few differences in clinical symptoms, but clear differences were seen between the ASD and SPD groups using fMRI during the social judgement task. Hyperactivation in SPD compared to ASD was found in the amygdala and the cerebellum. The fMRI findings for the comorbid group showed differences compared to the ASD group and similarities with the SPD group. The findings supported the hypo- and hyper-mentalizing theory of ASD and schizophrenia, highlighting the difficulty and importance of considering SPD as a differential diagnosis for ASD.

Cluster B personality disorders

In recent years there has been a growing interest in investigating deficits in SC, given the symptomatic overlap between autistic spectrum conditions and borderline PD (BPD)[88-91].

An investigation[92] into the difference and overlap between ASD and BPD was performed by evaluating autistic traits and empathizing and systemizing abilities in four samples: ASD, BPD, comorbid ASD+BPD and controls.

Similar to BPD, ASD patients scored higher than controls on the AQ[39] and the Systemizing Quotient-Revised (SQ-R)[93] but had lower empathizing abilities measured with the Empathy Quotient (EQ)[94]. The major limitations of this study were that diagnosis was based on the patients' self-reports, and that there was a preponderance of females in the BPD and control samples. The results support the view that some females with BPD have undiagnosed ASD.

In another study[95], 30 BPD, 30 AS and 60 matched control participants were compared on interpersonal emotion regulation strategies. Both patients with AS and those with BPD engaged less than the controls in interpersonal affect improvement. No differences were found for affect worsening. Individuals with AS did not differ in affect improvement and worsening, tending to generally engage less in interpersonal emotion regulation. Instead, individuals with AS reported using less adaptive (attention deployment, cognitive change) and more maladaptive (expressive suppression) interpersonal emotion regulation strategies compared to individuals with BPD and controls.

Differential diagnosis between ASD and narcissistic PD (NPD) may also be difficult. NPD was found to be one of the most prevalent PD in a help-seeking population of adults with suspicion of autism without intellectual disability in whom autism could be excluded[96]. Attwood[97] suggested that individuals with ASD, especially those with superior intellectual abilities, may overcompensate for feelings of inadequacy in social situations by becoming arrogant and egocentric.

Strunz *et al*[26] compared BPD, NPD and ASD on personality traits (NEO-PI-R) and personality pathology (DAPP-BQ), reporting different profiles. Adults with ASD had significantly higher scores on the NEO-PI-R conscientiousness dimension and significantly lower scores on the DAPP-BQ dissocial behaviour dimension than BPD and NPD patients. On the corresponding DAPP-BQ compulsivity scale, adults with ASD had significantly higher scores than all other groups.

Table 7 Studies comparing autism spectrum disorder patients with personality disorders patients on different assessment measures

Ref.	Participants	Comparison group	Measures	Results
Strunz *et al* [26], 2015	59 ASD (83% AS, 17% HFA)	62 NPD, 80 BPD, 106 NC	NEO-PI-R; DAPP BQ; SCID-I/MINI; SCID-II	On the NEO-PI-R: Conscientiousness: NCC = ASD > BPD and NPD; Neuroticism: NCC < ASD = NPD < BPD; Extraversion: ASD < BPD, NPD, NCC; Openness for experience: ASD < NCC, BPD, NPD; Agreeableness: ASD = BPD and NPD > NCC; on the DAPP-BQ; Inhibitedness: ASD = BPD > NCC and NPD; Dissocial Behaviour: NCC = ASD < BPD and NPD; Emotional dysregulation: NCC < ASD = NPD < BPD; Compulsivity: ASD > BPD, NPD, NCC
López-Pérez *et al*[95], 2017	30 AS	30 BPD60 matched NC	SCID-ISCID-IIEmotion regulation of others and self (two scales: extrinsic affect improvement, extrinsic affect worsening)Interpersonal emotion management	Affect improvement: BPD = AS < NNC; Affect worsening: BPD = AS = NNC; Affect improvement > affect worsening in BPD e NCC; Affect improvement = affect worsening in ASD; Adaptive interpersonal strategies (attention deployment, cognitive change) ASD < BPD and NNC; Maladaptive interpersonal strategies (expressive suppression) ASD > BPD and control.
Dudas *et al* [92], 2017	624 ASD	23 BPD; 16 ASD+ BPD; 2081 NC	AQ; EQ; SQR; SCID-II	AQ: NC < BPD = ASC < ASC+BPD; EQ:NC = BPD > ASC = ASC+BPD; SQR NC < BPD = ASC = ASC+BPD
Murphy [100]2006	39 AS; Male forensic patients detained in high security psychiatric care	39 PD (antisocial and/or borderline)39 SC with positive symptoms detained in high security psychiatric care	WAIS-R; ToM measures	IQ PD = AS > SC; AS and SC performed worse on two ToM measures (the Revised Eyes Task and the second order mental representation stories)
Stanfield *et al*[87], 2017	28 ASD	21 SPD; 10 CM; 33 NC	ADOS-G; SCID-II; PANSS; WAISsocial judgment taskEkmann 60 facies task; fRMI task of social judgement	SPD = CM = ASD < controls on social judgment task and Ekman 60-Faces Test; on positive symptoms: ASD < SPD = CM; on negative symptoms ASD = SPD > CM; fRMI: hyperactivation in SPD and CM group compared to ASD was found in the amygdala and the cerebellum
Booules-Katri *et al* [84], 2019	35 HFA	SSPD (n = 30) and a NC (n = 36)	O-LIFE questionnaire; SCID-I; SCID-II; ADI-R; ADOS; WAIS-III; ToM test	HFA showed greater impairment and no dissociation between affective and cognitive ToM components; SSPD scored significantly lower on cognitive than affective ToM test

BPD: Borderline personality disorder; CM: Comorbid group (SPD+ASD); EQ: Empathy quotient; NPD: Narcissistic personality disorder; O-LIFE questionnaire: Short version of the Oxford-Liverpool Inventory of Feelings and Experiences questionnaire; PANSS: Positive and negative syndrome scale; NC: Non clinical control group; SQR: Systemizing quotient revised; SSPD: Schizotypal-schizoid personality disorder; ToM: Theory of mind.

In BPD, higher levels of neuroticism, extraversion and openness for experience but less conscientiousness and the same level of agreeableness were found on the NEO-PI-R scores. The study also found, using the DAPP-BQ, more emotional dysregulation and dissocial behaviour and less inhibition and compulsivity in BPD patients compared with ASD patients. On the three inhibitedness subscales, no differences were reported. Even if the underlying causes social avoidance differed between BPD and ASD (social skill deficit in ASD versus fear of rejection in BPD), ASD individuals scored lower on the NEO-PI-R openness to experience dimension but significantly higher on the ideas (intellectual curiosity) subscale than BPD patients.

In relation to the difference between autism and narcissism, ASD patients' scores on the NEO-PI-R modesty and compliance subscales were comparable to non-clinical control subjects. Moreover, patients with ASD and non-clinical controls had similar scores on the DAPP-BQ narcissism subscale.

With regard to differential diagnosis with antisocial PD, different empathic dysfunctions in psychopathy and autism have been found[98,99]. Only one study[100] compared the ToM performances of forensic AS, schizophrenia and PD patients. In the PD group there were individuals with dissocial PD and/or BPD, diagnosed by expert clinicians. Patients were male and detained in high security psychiatric care. The results suggested that the AS and SC groups performed worse than the PD patients on the revised eyes task[101] and the second-order mental representation stories. The AS and PD groups did not differ on the Wechsler Adult Intelligence Scale full-scale IQ but both scored more highly than the SC group.

Cluster C personality disorders

It is well known that the phenomenology of obsessive–compulsive PD shows similarities to that of ASD[102], so misdiagnosis of ASD as anankastic PD is possible. It is suggested to consider first whether an individual has an underlying autism spectrum condition before diagnosing obsessive-compulsive PD[103]. In ASD, repetitive patterns of behaviour, in particular the pursuit of circumscribed interests, are often associated with pleasure and mastery rather than egodystonicity. Gadelkarim *et al*[104] suggested that in obsessive–compulsive patients the presence of obsessive–compulsive PD should alert one to the possible recognition of ASD.

No studies comparing ASD patients with cluster C PD patients met the inclusion criteria.

DISCUSSION

Examining personality in adults with ASD has only become the focus of research in recent years. The current review provides a literature summary of how personality and PD have been studied in high-functioning adults with ASD, focusing on two clinical issues.

The first issue for clinicians evaluating personality in ASD adult patients is to determine whether personality traits are part of the same autistic phenomenology or rather represent different categorical factors (comorbidity). The findings of studies focused on PD comorbidity suggested that approximately 50% of individuals with ASD fulfilled the diagnostic criteria for at least one PD.

The prevalence of PD comorbidity seemed to vary, increasing in samples of patients with other Axis I disorders, especially ADHD, and decreasing in mixed samples with intellectual disabilities. The most common comorbid PD belong to cluster A or cluster C (schizoid, schizotypal, obsessive–compulsive and avoidance PD). High rates of patients with more than one PD were found using the SCID-II. This suggests the utility of completing an assessment with other instruments to answer the question: 'True comorbidity or overlapping features?'[5]. Phenotypic similarities between high-functioning ASD and both schizoid/schizotypal and obsessive–compulsive PD have been noted, but the available data are sparse, so this could be a diagnostic challenge for clinicians[105,106]. An additional PD to an ASD diagnosis could be considered 'true comorbidity' if it gives relevant information for understanding patient functioning and for developing more specific treatments.

In most of the studies reviewed, the personality of adults with ASD was assessed in order to identify a specific profile differing from that of neurotypical controls. Big Five personality traits and the TCI dimensions are the most commonly used taxonomy for measuring personality in adults with ASD. The findings of these studies support the hypothesis that ASD in adults is associated with a distinct personality profile that is not equivalent to an ASD diagnosis or to a specific PD.

Regarding the Big Five traits, these patients have been shown in all the studies reviewed to be higher in neuroticism and lower in extraversion and agreeableness, and also in most of the studies to be lower in openness to experience and conscientiousness. At the same time, ASD characteristics are statistically independent of the Big Five personality traits in clinical samples.

Adults with ASD have repeatedly been shown to have a distinct temperament and character compared to neurotypical controls. Concerning the TCI dimensions, lower scores on the character dimensions of self-directedness and cooperativeness indicated a possible personality psychopathology[107,108]. Moreover, ASD was associated with high harm avoidance, low reward dependence, low novelty seeking and high self-transcendence. High harm avoidance reflects pessimism and shyness, and also state-dependent anxiety. Low reward dependence indicates impairments in social sensitivity, attachment capacity and adaptability. In individuals with an immature

character structure, high self-transcendence may lead to disregard for the basic realities of human interaction and social responsibilities.

As regards other personality measures, such as the EPQ and MMPI-2, the emerging profile reflected social isolation, interpersonal difficulties and psychotic-like symptoms.

In summary, the overall profile of personality traits and dimensions in ASD puts individuals at risk for other psychiatric disorders and lower functioning, even if variability exists.

Individuals with autism that are not diagnosed in childhood may have a high level of stress in trying to find a lifestyle to survive in a world that is difficult to understand; thus, building their personality with this level of chronic stress could be a trigger for creating a PD. Nevertheless, the neuropsychiatric dysfunctions associated with ASD permit considerable variation in personality. It has been suggested that personality mediates the relationship between autistic symptoms and well-being[109,110]. Exploring personality could provide a more comprehensive picture of adults with ASD, characterizing them through their individual strengths and weaknesses. It could advance the understanding of heterogeneity within patients and help in the development of more specific interventions. Treatment of PD comorbidity in adults with ASD is still in its infancy, but specific programmes have started to be developed [111].

The second critical issue is differentiating ASD patients from PD patients in clinical samples when searching for an ASD diagnosis. High-functioning ASD patients are frequently misdiagnosed with PD, and few studies were found on differential diagnosis between ASD and PD.

SC deficits could be useful for distinguishing ASD from PD, especially borderline and antisocial PD[112]. Gender could cause specific patterns of PD comorbidity and increase the risk of misdiagnosis, especially in women[14,113]; it has been suggested that some women with BPD have undiagnosed ASD.

Concerning the difference between autism and narcissism, individuals with ASD may appear egocentric because of a limited awareness of when it is appropriate to compliment oneself and when it is not. Nevertheless, ASD patients were found to be comparable to non-clinical controls on scales measuring narcissism in the only available investigation on this topic[26].

Differences in ToM abilities between ASD and cluster A PD have also been found, but functional neuroimaging may be better than SC testing for discriminating between autism and schizophrenia spectrum disorders[87].

Findings on differential diagnosis should be replicated and investigations should be extended to compare ASD patients with cluster C PD patients too.

Differential diagnosis should be based on clinical examination and a very careful history investigation of the first years of development, the first social relationships with other children and adolescents, changes of lifestyle during development and clinical symptoms of ASD in the first years of life.

Interviews such as the Autism Diagnostic Interview–Revised (ADI-R)[114] could help the clinician to collect the first symptoms of ASD. Personality assessment could help in confirming the diagnosis, but has to be used carefully by an expert clinician who knows the ASD cognitive style in order to avoid misunderstandings.

The findings of all the studies included in this review were based on self-reporting questionnaires or structured interviews that collected information only from the patients. This raises concerns about how a person with autism can read and understand the complex questions in a self-report test: individuals with autism could have difficulties in understanding the real meaning because of their literal way of reading a text. Nevertheless, studies have supported the validity of self-report in adults with ASD without intellectual disability[55,62].

CONCLUSION

This review provides a summary of the main findings in the literature regarding PD in adults with high-functioning ASD without intellectual disability. The aim of the review is to improve knowledge of the complex relationship between ASD and PD. Among the limitations of this review is the exclusion of studies looking for autistic traits in patients with PD or in non-clinical populations, which may be informative for giving a better understanding of overlapping features, as the question of commonality as opposed to comorbidity is not yet resolved. Furthermore, our research was conducted extensively on PubMed only. Future works should be conducted by

optimizing retrieval strategies and also including studies concerning adolescents. Another area little examined is the role of age in modulating the relationship between PD and ASD[115,116]. Longitudinal research on personality and ASD may clarify whether the relationship between personality and ASD increases in adulthood, as has been suggested[55].

ARTICLE HIGHLIGHTS

Research background

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction, as well as restricted, repetitive and stereotyped patterns of behaviour. Individuals with high-functioning ASD are more likely to be diagnosed in adulthood, probably due to the development of learnt or camouflaging strategies that make it much harder to identify the underlying difficulties. Late-diagnosed individuals report higher levels of co-occurring psychiatric disorders or misdiagnosis, because some features of ASD can overlap with symptoms of other psychiatric conditions as well as personality disorders (PD). In recent years there has been a growing interest in exploring the complex relationship between ASD and PD, especially for features that overlap with cluster A and cluster C PD.

Research motivation

Consideration of the relationship between PD and ASD, with a focus on differential diagnosis and comorbidity, can lead to a better understanding of this complex topic and can improve the diagnostic process as well as supporting the creation of targeted interventions.

Research objectives

To summarize the research findings on ASD and PD in adulthood, focusing on comorbidity and differential diagnosis.

Research methods

The guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) were followed in the present review. A comprehensive literature search was performed through PubMed, including only studies published in the English language and performed on adults without intellectual disability. The research included studies published up to April 2020.

Research results

The current review provides a literature summary of how personality and PD have been studied in high-functioning adults with ASD. The findings show that approximately 50% of individuals with ASD fulfilled the diagnostic criteria for at least one PD. The most common comorbid PD belong to cluster A or cluster C (schizoid, schizotypal, obsessive–compulsive and avoidance PD). High-functioning ASD patients are frequently misdiagnosed with PD, but only a few studies have been conducted on differential diagnosis. Furthermore, there were significant differences in methodological approaches, including ASD diagnostic instruments and personality measures.

Research conclusions

ASD in high-functioning adults is associated with a distinct personality profile even if variability exists. Cluster A and cluster C PD are the most frequent co-occurring PD, but overlapping features should be considered. Exploring personality could provide greater understanding of adults with ASD by identifying strengths and weaknesses, and could give relevant information for the development of specific and individual treatments.

Research perspectives

Further studies are needed to explore the relationship between ASD and PD, especially on differential diagnosis. It would be useful to explore the relationship between PD and ASD from a longitudinal perspective, take in account individual's life and development history.

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SYSTEMATIC REVIEWS

Psychological impact of the COVID-19 pandemic on individuals with serious mental disorders: A systematic review of the literature

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Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic is having a great impact on individuals from all over the world, particularly on individuals with mental disorders. Several studies found more pronounced psychiatric symptoms, notably symptoms of depression and anxiety.

AIM

To assess the situation of patients with serious mental illness (SMI: Affective disorders and schizophrenia) regarding their mental health outcome during the pandemic.

METHODS

A systematic search using the databases PubMed and MEDLINE was conducted, employing the key words "COVID-19", "SARS-CoV-2", "psychiatric/mental disorder/illness", "affective/mood disorder", "bipolar disorder", "(major) depression", "schizoaffective disorder", and "schizophrenia". Studies that had been published up until January 9, 2021 were included. Information of studies in languages other than English and German was mostly taken from their English abstracts.

RESULTS

The literature search concluded in the finding of 36 studies containing relevant clinical data. A general impairment of the mental health of individuals with SMI could be detected, particularly in individuals with affective disorders, as compared to those with schizophrenia. Compared to healthy controls, symptoms of anxiety, depression, and stress were more pronounced in individuals with SMI. Relevant factors found that impacted their mental health were age, resilience, and socioeconomic environment, especially the shortage of mental health services, lack of social support, and inadequate information about COVID-19.

CONCLUSION

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

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In light of these results, mental health services should be reinforced, notably the use of telemental health services. Furthermore, supplying individuals with SMI with adequate information about the COVID-19 pandemic and increasing their resilience is important. When researching the impact of the COVID-19 pandemic on individuals with SMI, standardization as well as follow-up studies are needed to enable better comparability and understanding.

Key Words: COVID-19 pandemic; Serious mental illness; Affective disorders; Bipolar disorder; Major depressive disorder; Schizophrenia

Core Tip: A greater deterioration was found in individuals with affective disorders, compared to individuals with schizophrenia. Factors influencing the impact on mental health were age, resilience, and socioeconomic circumstances. Consequently, the strengthening of mental health services, including the use of telemental health services with a focus on strengthening resilience, is necessary. Additionally, psychiatric patients should be supplied with appropriate information about the pandemic. In research, follow-up studies and standardization are required.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), is an infectious airborne disease. Initially detected in Wuhan, China[1], in December 2019, it subsequently spread throughout the world and reached the status of a pandemic on March 11, 2020[2]. In order to stop the propagation of the virus, lockdowns comprising measures of physical distancing, travel restrictions, and closure of public facilities were implemented in numerous countries worldwide[3].

The mental condition of both healthy and mentally ill individuals has been affected by the COVID-19 pandemic and its reverberations: Anxiety, distress[4,5], fear of the disease[5], loneliness[6], post-traumatic stress symptoms[7], and the prevalence of depression, anxiety, and suicidality[4,8,9] have been found to be higher in the general population as a consequence of COVID-19. In particular, the prevalence of depression has increased drastically[5,10,11], affecting up to a quarter of the population[12,13], compared to a prevalence of 6.8%-8.5% before the pandemic[10,14]. This is comparable to previous pandemics: During the SARS epidemic in 2003[15] and the West Africa Ebola virus disease pandemic from 2013 to 2016[16], similar effects were observed. Furthermore, economic growth has been stunted, resulting in a rising percentage of unemployment, and thus adding additional distress[17]. The individual condition during the COVID-19 pandemic might have been influenced by personality, resilience [18,19], coping strategies, and socioeconomic environment[20]. In summary, the pandemic in its entirety has led to restrictions of personal rights, heightened emotional distress, and fear of an uncertain future, and may advance the development of mental health problems[17,21].

Individuals already suffering from psychiatric disorders face additional issues that may influence their mental health: Limited resources for medical and psychotherapeutic treatment[22,23] and misinformation[22] have been an additional strain. Furthermore, an increase in social isolation and negative feelings might lead to a worsening of psychiatric symptoms and even illness exacerbation[24-26]. Literature shows conflicting results concerning the impact of the pandemic on the mental health of individuals with psychiatric disorders. On the one hand, symptoms of different mental disorders have been reported to be significantly higher in the wake of the

pandemic[27-31]. On the other hand, there was little to no change in symptomatology found in other studies[25,32-34], showing that more research in this area of interest is necessary.

Individuals with serious mental illness (SMI), which comprise bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SZ), are an especially vulnerable group due to several risk factors[35], such as severe psychiatric illness episodes, hospitalization[36], a lower level of education[37], and cognitive deficits[38-40]. Furthermore, problems when interacting with healthcare services, for instance difficulties adapting to the clinical environment[41], might lead to a worsening of well-being. Post-traumatic stress symptoms have been on the rise in both individuals with mental illness[42-44] as well as the general population[45,46], thus we focused on these symptoms in the course of our search as well. The need for increased support of this particular group of individuals has been highlighted by numerous mental health researchers[26,41,47].

The impact of COVID-19 on individuals with SMI has already been reviewed in June 2020, emphasizing the vulnerability of individuals with SMI and advocating for an increased focus on support for them[35]. Another review by Zhand and Joober[48] included 47 studies with the final search being completed in July 2020, however, the authors focused mainly on SZ spectrum disorders, not mentioning BD and MDD.

Furthermore, a systematic review by Barber *et al*[49], from June 2020, was found. The search yielded four studies, which found that individuals with SMI might show a decline of mental health due to COVID-19-related governmental measures. Furthermore, they experienced increased psychological distress during the crisis.

In comparison with already existing reviews, the current one focuses on the mental health outcome of individuals with SMI in general, encompassing solely papers providing scientific data and including studies that were published at a later time.

The aim of this review is to further broaden the understanding of these complex disorders and thereby provide insight in how to support individuals with SMI during a global crisis. The following questions will be answered: How are individuals with SMI affected by the pandemic in comparison to healthy controls (HC) and what are the main psychiatric symptoms they are displaying? What are risk and protective factors that influence the severity of psychiatric symptoms and who is particularly vulnerable to these factors? How does symptomatology and frequency of illness episodes change during the course of the pandemic?

MATERIALS AND METHODS

We conducted a review of literature for studies about COVID-19 and its impact on SMI in the databases PubMed and MEDLINE (Medical Literature Analysis and Retrieval System Online). The final search was conducted on January 9, 2021.

Inclusion criteria

The main criterion was whether the studies analyzed samples of adults with pre-existing psychiatric disorders (including BD, MDD, and SZ) regarding the impact of COVID-19 on their mental health. Primary outcome variables were those assessing psychological symptoms related to the pandemic.

The following Medical Subject Headings (MESH) search terms were applied in the database PubMed: "COVID-19" OR "SARS-CoV-2" [Title/Abstract] AND "psychiatric/mental disorder/illness" [Title/Abstract] OR "affective/mood disorder" [Title/Abstract] OR "bipolar disorder" [Title/Abstract] OR "(major) depression" [Title/Abstract] OR "schizoaffective disorder" [Title/Abstract] OR "schizophrenia" [Title/Abstract]. The relevance of the studies was determined by inspecting both the title and abstract of each study and the full text of several studies.

The following MESH search terms were applied in the database MEDLINE: "(covid19 or (covid(w)(2019 or 19)) or (corona(w)virus(w)disease(w)2019 or 19)) and (depression? or schizophren? or ptsd or (post(w)traumatic(w)stress))/ti" AND "(covid19 or (covid(w)(2019 or 19)) or (corona(w)virus(w)disease(w)2019 or 19)) and ((mental? or bipolar? or affectiv? or mood? or schizoaffect?)(w)(disorder? or illness?))/ti".

All languages were considered, with an emphasis on English and German literature. The relevance of the studies was determined by firstly inspecting the title of each study, then the abstract of a considerable portion of studies, and finally the full text of several studies.

Exclusion criteria

Scientific studies that were not accessible on publication sites or did not meet the defined criteria were not included: They were not original articles, did not contain scientific data about a sample of patients with SMI (BD, MDD, or SZ) or were not empirical studies, only reported about a single case, or, if they additionally encompassed other mental disorders, did not explicitly mention SMIs.

RESULTS

The results are displayed in Table 1, which encompasses an overview of the 37 analyzed studies. In summary, the following numbers of studies investigating SMI were found either alone or in combination with other disorders: 19 (SMI in general), 9 (affective disorders), 3 (BD), 16 (MDD), and 6 (SZ). The studies included participants from mainly 19 different countries and areas in North America (Canada, United States), Asia (China, India, Taiwan, Turkey), Australia, and Europe (Austria, Czech Republic, Denmark, France, Germany, Hungary, Italy, Netherlands, Norway, Romania, Spain, United Kingdom). Most of them were conducted in the time period from February to June 2020 during periods of physical distancing, thus evaluating mainly the first response to and short-term consequences of the crisis. One study was conducted in January 2020, and another in August and September 2020. The found studies were very heterogenous in samples and study design. Furthermore, not all trials investigated and defined intervention with comparable targets.

Limitations frequently encountered by scientists were small sample sizes, the inability to draw causal conclusions due to cross-sectional sample design, self-reported mental illness without clinical evaluation due to online surveys, possible selection bias, problems of generalization, and the lack of questionnaires measuring pandemic-related variables with the subsequent need to create questionnaires themselves.

How are individuals with SMI affected by the pandemic in comparison to HC and what are the main psychiatric symptoms they are displaying?

Most individuals with SMI had a positive stance regarding measures for preventing COVID-19[50,51], which was related to marriage and a higher level of education[51]. However, they were on average not as knowledgeable about COVID-19 and measures of prevention as HC[52,53]. This reduced knowledge was associated with a low socioeconomic status, little education, and insufficient social support[52]. A higher belief in self-obtained COVID-19 information was related to both more[54,55] and less [50] fear of the disease.

Compared with HC, individuals with SMI showed both more weight gain and frequent changes of sleep patterns[56], however, duration of sleep was found to remain stable over time[57]. An increase in the number of substances used was detected[49,52]. On average, individuals with SMI had fewer social contacts and did not go grocery shopping as often as before the pandemic[58].

Individuals with SMI experienced more symptoms of depression, anxiety[56,59,60], and stress[58-62], partly due to loneliness and isolation[63]. Additional symptoms were elevated feelings of paranoia[59] and isolation[64], self-harm, and suicidal ideation[65]. Fatigue was more prominent in those with a lower quality of life, which was related to severe depressive symptoms, insomnia, and pain[66]. While the majority of subjects with SMI reported to not be worried to get infected[52], they were on average more worried and fearful of contracting COVID-19[58] and made less use of coping strategies than HC[56]. Individuals with SMI were generally more concerned about their financial situation than their own health, although this was found in a study conducted in August and September 2020 and not at the beginning of the pandemic[63].

Individuals with affective disorders displayed both more voluntary self-isolation as well as stress related to it than in HC[67]. Among different disorders, levels of both perceived stress and related somatic complaints, as well as the latter's negative correlation with Clinical Global Impression (CGI), were highest in affective disorders [68]. Psychosocial distress was related to somatization, heightened alertness, psychic anxiety, and bad mood[69]. Other psychiatric manifestations included more symptoms of PTSD in patients with affective disorders than in HC[67], elevated feelings of vulnerability[63], and sleeping problems[61]. Fear about consequences on health[8] and socioeconomic status[67] was heightened in individuals with affective disorders as compared to HC, particularly in younger persons[69].

Table 1 Results of the database search concerning the mental health outcomes of individuals with serious mental illness

Ref.	Country or area, time	Psychiatric disorders	Methods; relevant questionnaires and COVID-19-related variables	Results	Limitations
Asmundson *et al*[67]	Canada and United States, March 21–April 1, 2020 (during the lockdown)	Affective disorders (BD and MDD) and anxiety-related disorders	Cross-sectional case-control online survey of 700 individuals with anxiety-related disorders, 368 individuals with affective disorders and 500 HC; PHQ-4, CSS, self-constructed questionnaires to measure self-isolation distress and coping strategies	Individuals with anxiety-related disorders experienced more COVID-19-related stress, fear, and PTSD symptoms than individuals with affective disorders and HC. Individuals with affective disorders had more PTSD symptoms and fear of socioeconomic consequences than HC. Patients with both BD and MDD exhibited more voluntary self-isolation and stress related to it. Individuals with psychiatric disorders and HC did not differ in the perceived effectiveness of their coping behaviour.	Self-report and not clinical evaluation of mental health, data about comorbidities was not gathered
Burrai *et al*[76]	Italy, April–May, 2020 (during the lockdown)	SZ and other psychotic disorders	Cross-sectional online survey of 77 patients with psychotic disorders and 100 HC; DASS-21, BRCS, COVID-19: Risk Perception (2 items based on Cho and Lee, 2015, and Liao, 2014), self-constructed questionnaire measuring worry	Patients with psychotic disorders were less stressed, more anxious, more worried about the current situation, and perceived the risk of being infected with COVID-19 as higher than HC. Participants with psychotic disorders living in communal residencies were supported by both their cohabitants and mental health professionals, remained adherent to their medication treatment, and possessed knowledge about the consequences of COVID-19.	Significant group differences in gender and education level, geographical limitations, observational design does not allow the determination of causality
Carmassi *et al*[42]	Italy, April 1-30, 2020(during the lockdown)	BD	Telepsychiatry-based cross-sectional clinical interviews and self-reports per e-mail of 100 patients with BD regarding post-traumatic stress symptoms (PTSS); IES-r, GAD-7, HAMD, YMRS	Acute PTSS were experienced by 17% of participants, which was related to COVID-19-related work/financial difficulties as well as anxiety, reported by 26% of participants. Acute symptoms of mania seemed to be protective. Furthermore, 17% of participants reported depressive symptoms.	Small sample size, self-report instruments were less accurate than an assessment by a clinician, not all COVID-19-related stress factors were considered, there was no control group
Chang *et al*[54]	Taiwan, March 23– April 23, 2020 (during the lockdown)	SMI and other disorders	Cross-sectional survey of 400 individuals with mental illness (242 with SZ, 67 with BD, 28 with MDD, and 63 with others); DASS-21, FCV-19S, BCIS, PCIBS	Participants who believed more strongly in the obtained COVID-19 information from newspapers, television, and online sources were more fearful of the disease. A higher level of fear was associated with more symptoms of depression, anxiety, stress, and less frequent behaviour concerning prevention.	Newly constructed questionnaires by using simple measures (BCIS, PCIBS), lack of examination of test-retest reliability (BCIS, SCIBS, FCV-19S) self-reported data, cross-sectional design does not allow the determination of causality
Chang *et al*[55]	Taiwan, March 23– June 30, 2020 (during the lockdown)	SMI, anxiety disorder, and substance use disorder	Cross-sectional survey of 414 patients with psychiatric disorders (197 with SZ, 141 with substance use disorder, 35 with BD, 34 with MDD, and 7 with anxiety disorder); DASS-21, SSS-S, FCV-19S, BCIS, PCIBS	Preventive behaviours recommended by the World Health Organisation could be explained by both COVID-19-related fear and trust in sources of information concerning this disease in individuals with SMI. COVID-19-related fear could be explained by trust in sources of information and self-stigma.	Cross-sectional design does not allow the determination of causality, self-report, bias (common variance, recall, social desirability), stable conditions do not allow generalizability, geographic limitations
Chen *et al*[74]	Taiwan, January–May, 2020 (during the lockdown)	MDD	Long-term follow-up study (structured interviews, at least three follow-ups over a period of three years) of a cohort of 116 patients with treatment-resistant MDD; structured interview about COVID-19-related changes and impact on participants' lives (physical, psychological, and social)	Patients with depression had confidence in the COVID-19-related prevention strategies of the government. They felt distressed about pandemic-related news reports. Patients with MDD have been found to be at a higher risk for suicidality, although the pandemic had a positive impact on some patients as well.	Time limit on interviews and therefore not sufficient collection of variables

Costa *et al*[64]	United States, last week of March 2020 (during the lockdown)	SMI, anxiety disorder, PTSD, OCD, borderline personality disorder, and other disorders	Cross-sectional online survey of 193 individuals with psychiatric disorder (162 with anxiety disorder, 103 with MDD, 78 with BD, 77 with PTSD, 25 with OCD, 24 with BPD, 3 with SZ, and 29 with other disorders; COVID-19-related variables: Self-constructed questionnaires to measure fear, concerns, and social situation	Most of the participants had concerns about their illness and the pandemic. Notably, they were concerned about COVID-19-related service disruption. especially individuals with MDD, who feared a shortage of medication. The diagnosis of MDD was associated with the fear of getting sick. Not coping well was related to feeling socially isolated and worry about not receiving mental health care as well as experience worse psychiatric symptoms. Staying in touch with others by using social media and text messages were seemingly the best communication methods for individuals with coping difficulties related to COVID-19.	Self-constructed questionnaires, self-reported mental illness
Di Nicola *et al*[73]	Italy, April 27-29, 2020 (directly after seven weeks of strict lockdown)	Affective disorders (BD and MDD)	Cross-sectional online survey of 59 remitted patients with MDD and 53 euthymic individuals with BD; K10, medical records, COVID-19-related variables: Lockdown conditions (living alone, changes in work routines, and working on the frontline)	In the sample, 25.9% of subjects experienced no likelihood of distress, 31.2% experienced mild and 42.9% moderate-to-severe likelihood of distress. Severe distress was predicted by low vitamin D levels and MDD diagnosis. Higher levels of distress were more frequently found in individuals who had a longer duration of psychiatric illness, were living by themselves during the lockdown, and had the habit of smoking.	Lack of longitudinal follow-up, self-constructed questionnaires, not all confounding variables for the relation between vitamin D levels and distress were included
Franchini *et al*[69]	Italy, March 9– April 9, 2020 (during the lockdown)	Affective disorders (BD and MDD)	Telephone-based, non-standardized survey of 101 euthymic patients with affective disorders; self-constructed questionnaires measuring emotional stressors and unpleasant lockdown experiences	The most frequently reported stress factor was frustration, which was significantly associated with unemployment, affecting two third of participants. Somatization, heightened alertness, psychic anxiety, and bad mood were related to unemployment as well. Associations between young age and anxiety, increased alertness, and monetary concerns could be found. The participants were satisfied with both the received supplies and information about the pandemic.	Non-standardized survey and therefore problems with generalization
Frank *et al*[61]	Germany, 2nd, and 3rd week of March 2020 (during the lockdown)	SMI, addictive disorders, and others	Cross-sectional, standardized interviews with 196 individuals with mental illness (121 with AD, 41 with SZ, 21 with addictive disorder, and 13 with others); CGI	More than half of participants were feeling more distressed than before the pandemic. Among individuals with affective disorders, 25% had sleeping problems.	Not mentioned
González-Blanco *et al*[62]	Spain, March 19-26, 2020 (during the lockdown, 5 d after the beginning)	SMI: Severe mental disorder (SMD: SZ and BD), and common mental disorder (CMD: MDD and anxiety)	Cross-sectional online survey of 125 individuals with SMD (65 with BD and 60 with psychotic disorders), 250 with CMD (125 with depression and 125 with anxiety), and 250 HC; DASS-21, IES, lifestyle variables	Individuals with SMD reported higher levels of anxiety, depression, and stress than HC, but lower levels than individuals with CMD. After confounding variables were controlled, HC had less anxiety than individuals with SMD with no other differences in psychological factors. In individuals with SMD, anxiety was related to being single, suffering from COVID-19 symptoms, and increased stress levels. Many individuals with SMD (87.2%) could relish free time, however the percentage of HC who could, was higher (94%).	Selection bias and limited representativeness through selective access to digital resources, self-reported diagnoses and psychiatric symptoms, binary scales instead of Likert-type scales to assess behaviour
Hamm *et al*[77]	United States, April 1-23, 2020 (during the lockdown)	MDD	Semi-structured qualitative interviews with 73 older adults (age > 60) with MDD, comparison with pre-pandemic data; PHQ-9, PROMIS anxiety scale	Patients with MDD had a lower quality of life during the pandemic than before, but did not differ in depression, anxiety, and suicidal ideation symptoms. They were resilient and mostly socially connected, worried about both contracting the virus and their mental health, and were not satisfied with governmental measures.	Patients participating may have been too distressed to do so: thus, the survey did not include MDD patients with severe symptoms, distorting results; sample was not ethnically diverse
Hao *et al*[72]	China, February 19-22, 2020 (during the	MDD and anxiety disorder	Cross-sectional online survey of 67 psychiatric patients (45 with mixed anxiety and depression,	Psychiatric patients showed more symptoms of depression, anxiety, stress, PTSD, and insomnia than HC. Additionally,	Generalisation not possible, no biological samples were obtained, low

	lockdown)		19 with other anxiety disorders, and 12 with MDD) and 109 HC; IES-R, DASS-21, ISI	they had more concerns about their physical health and higher levels of anger, impulsivity, and suicidal ideation than HC. The diagnostic criteria for PTSD were possibly fulfilled by more than 30% of participants with mental illness. More than 25% of them had moderate to severe insomnia.	response rate due to online recruitment, geographical limitation, cross-sectional study
Hölzle *et al*[68]	Germany, middle of May 2020 (during the lockdown with loosened restrictions)	SMI, psychotropic dependence, and other disorders	Cross-sectional assessment of 139 psychiatric inpatients (89 with affective disorders, 26 with SZ, 17 with psychotropic substance abuse, and 7 others); CGI, PSS, SRS	The disorders lead to differences in the CGI-score (M = 4.9, SD = 1.0), however, women had higher scores than men. Individuals with AD had the highest levels of both perceived stress and related somatic complaints. Higher CGI-scores were not associated with stress, but with stress-related somatic problems. These correlations were especially high in individuals with AD, and non-existent in individuals with SZ.	Not mentioned
Iasevoli *et al*[59]	Italy, April 13-17, 2020 (during the lockdown, one month after the beginning)	SMI	Telephone-based cross-sectional case-control study of 205 patients with SMI, 51 first-degree relatives, and 205 HC; PSS, GAD-7, PHQ-9, SPEQ	Individuals with SMI were of lower economic status and had more concordant diseases than HC. They experienced more symptoms of anxiety, depression, stress, and paranoia than HC. COVID-19-related stress was an important predictor for anxiety. Comorbidities had an independent influence on anxiety, depression, and stress. Caregivers showed more depressive symptoms than HC.	Not mentioned
Korsnes *et al*[50]	Norway, March–June, 2020 (during and after the lockdown)	SMI, anxiety, and other disorders	Cross-sectional online survey of 19 older (age > 65) psychiatric outpatients (15 with MDD, 2 with cognitive deficit/dementia, 1 with anxiety, and 3 with other diagnoses), 14 inpatients (12 with MDD, 6 with anxiety, 2 with BD, 2 with psychosis, and 1 with another diagnosis), and 46 employees working with them; COVID-19-related variables: Self-constructed questions about fear, prevention measures, risk, and consequences	The majority of patients approved of the strict prevention measures, were not afraid of being infected with COVID-19, and did not think that they would die in case of an infection. Psychiatric patients were generally less concerned about the repercussions of COVID-19 on their health than healthcare employees. Few were very worried, did not welcome the governmental measures, thought the infection risk to be increased the clinic, and/or saw a negative impact on their daily life.	Small sample size, generalisation not possible, self-constructed questionnaires, different times of response (similar measures, but different medial climate)
Liu X. *et al*[82]	China, January 30-February 21, 2020 (during the lockdown)	SZ	Retrospective double centre study of hospitalized SZ patients: 21 suspected to have COVID-19 (11 confirmed), and 30 without suspected COVID-19 infection; PANSS, PSS, HAMA, HAMD, PSQI, COVID-19-related variables: Treatment, symptoms	Schizophrenic patients with suspected COVID-19 had higher levels of stress, depression, and anxiety, and a worse quality of sleep, even after the adjustment for the use of benzodiazepines	Retrospective study: Longitudinal studies and follow-up are needed, assessments for the groups were performed by different doctors
Liu *et al*[70]	United States, April 13–May 19, 2020 (during and after the lockdown)	MDD, anxiety disorder, post-traumatic stress disorder, attention deficit hyperactivity disorder, insomnia, and others	Cross-sectional online survey of 898 young adults: 44.6% with mental illness: 38.2% with treatment and 6.2% without treatment (31.7% with depression, 29.0% with anxiety, 8.0% with PTSD, 6.9% with ADHD, 6.7% with insomnia, and 17.7% with others), 23.4% with a suspected mental illness, and 32.2% HC; PHQ-8, GAD-7, PCL-C, MOS-SS, HRQoL, COVID-19-related variables: Self-constructed questionnaires to measure worry and grief	Individuals with a diagnosed (treated or untreated) or suspected psychiatric illness were more likely to have symptoms of depression, anxiety, and PTSD than HC. Individuals who were diagnosed with or suspected to have a psychiatric illness experienced more worries connected to COVID-19, more sleeping problems, and a lower health-related quality of life.	No generalizability due to sample from possible COVID-19 "hotspots", variability in circumstances concerning the time of receiving treatment and/or diagnosis, no diagnosis in suspected cases, no information about treatment and adherence to it, no baseline data for comparison
Ma *et al*[81]	China, January 10–April 30, 2020(before, during, and after the lockdown)	SZ	Case-control assessment of 30 SZ inpatients who were isolated for 14 d and 30 who were not, with a longitudinal comparison of isolated patients	The isolation group experienced more stress, anxiety, and depression than the non-isolation group. After isolation, patients with SZ exhibited higher levels of stress and C-reactive	Small sample size, short observation period, several inflammatory markers were not sufficiently researched with

			before and after isolation; CPSS, PANSS, HAMD, HAMA, PSQI	protein and had a lower quality of sleep.	regard to their impact on social isolation and their correlation with the mental health
Matei *et al*[53]	Romania, March 16–May 14, 2020 (during the lockdown)	SMI and severe AUD	Cross-sectional survey of 115 male psychiatric inpatients (65 with SMI and 50 with severe AUD) and 57 HC; self-constructed questionnaires to measure general knowledge about COVID-19, prevention, and the ability to identify false statements about COVID-19	Patients with SMI were less informed about general knowledge as well as prevention of COVID-19 than HC. Additionally, they were less able to single out false information about COVID-19. Apart from patients with severe AUD being as informed about prevention measures as HC and therefore more informed than patients with SMI, there was no difference between these two groups.	Small sample size, all-male sample, potential selection bias due to the method of selecting HC from residential areas and shopping centres, not representative of all psychiatric illnesses
Muruganandam *et al*[52]	India, at the end of April 2020 (during the lockdown, one month after the beginning)	SMI	Telephone-based cross-sectional survey of 132 patients with SMI and their caregivers; self-constructed interview about COVID-19: Knowledge, perceived social support and aggression, psychiatric symptoms, somatic status	Among the participants, 8.3% did not know about the current pandemic and 75% were neither worried about being infected nor knowledgeable about the symptoms. Additionally, 66% possessed little knowledge about prevention and 20% did not know about the way of transmission. A lack of knowledge was associated with low socioeconomic status, little education, and meager social support. A third exhibited symptoms indicative of a recurrence of their illness.	Small sample size, lack of longitudinal follow-up, lack of healthy control group, self-constructed interview, assessment was not structured, dependence on caregivers' reports on patients' situations
Mutlu and Anıl Yağcıoğlu[36]	Turkey, March 23–April 13, 2020 (before and during the lockdown)	SMI	Telephone-based cross-sectional interviews of 155 individuals with SMI (131 with SZ and 24 with BD) and retrospective data analysis; collection of data about clinical characteristics, medication adherence, and relapse	The total relapse rate in the first trimester of the pandemic was 11% (n = 15 with SZ, n = 2 with BD), with the most frequently related influence being the interruption of antipsychotic medication (59%). However, the relapse rate did not differ from the rate in 2019. Individuals suffering from a relapse had been hospitalized at a more recent date than the individuals who remained stable. Very few patients (n = 2) attempted suicide or had suicidal thoughts during the pandemic.	Not mentioned
Orhan *et al*[77]	Netherlands, January 1, 2018– December 31, 2018 and April 2020 (during the lockdown)	BD	Baseline interviews and cross-sectional survey of 81 older (age ≥ 50) patients with BD; YMRS, CES-D, BAI, SPS, LS, PMS, UC, NEO-FFI, COVID-19-related variables: Fear, mental health impact, positive coping (see Pan *et al*, 2020)	Older patients with BD experienced less psychiatric symptoms during the pandemic compared to the baseline. Loneliness, not having children, passive coping style, low mastery, and neuroticism were associated with more psychiatric symptoms.	Large interval between the collection of baseline data and the interviews during COVID-19 pandemic, only short-time impact, relatively small sample
Pan *et al*[25]	Netherlands, 2006–2016 and April 1–May 13, 2020 (during and after the lockdown)	MDD, anxiety disorder, OCD	Three longitudinal studies with several follow-ups and a cross-sectional online survey of 1181 individuals with psychiatric disorders (1051 with MDD or anxiety and 130 with OCD) and 336 HC during the pandemic; QIDS, BAI, PSWQ, DJGLS	Participants with psychiatric disorders had higher symptoms of depression, anxiety, worry, and loneliness than HC. This was the case before as well as during the pandemic, however, the severity of symptomatology did not increase over time, even showing a slight decrease during the lockdown. In comparison, HC experienced a greater decrease of their mental health than individuals with mental illness.	Different modes of collecting data during face-to-face interviews compared to online surveys during the pandemic, low response rate, no standardised assessment for mental disorders, symptom severity was measured by number of diseases
Pellegrina *et al*[71]	France, during the first wave of the pandemic (during the lockdown)	MDD and anxiety disorder	Retrospective survey of 85 individuals with MDD or anxiety disorder; STAY-YA, Beck BDI-II, COVID-19-related variables: Perception, psychological resources, life conditions	Some participants experienced a worsening of their mood during the lockdown. More pronounced symptoms of both anxiety and depression, sleep disorders and addiction could be found.	Retrospective study: Longitudinal studies and follow-up are needed,
Pinkham *et al*[57]	United States, December 4, 2018–now (still ongoing) and April 3–June 4, 2020 (during and after the lockdown)	SMI	Baseline interviews, online surveys administered three times a day during a 10- or 30-d period before pandemic EMA, and ID-5 (psychosis module), PANa telephone-based cross-sectional survey during the pandemic of 148 patients with	Both affective and psychotic symptoms as well as the duration of sleep remained stable over time. An increase in the number of substances used and psychological well-being was reported, the latter of which was related to female gender and more time spent with other people. The two disorders did not differ in	Data was collected early; longer longitudinal studies should be conducted

			SMI (92 with SZ or schizoaffective disorder and 56 with affective disorder); baseline: MINI, SCSS, YMRS, MADRS, SUMD; EMA: Questionnaires about social life, mood, psychiatric symptoms, substance use well-being, and sleep; phone survey was a combination of baseline and EMA	patterns concerning stability or change.	
Pogany *et al*[63]	Hungary, August 1–September 15, 2020 (after the lockdown)	SMI, anxiety disorder, personality disorder, and others	Retrospective survey of 438 psychiatric patients (39.4% with SZ, 34.6% with affective disorder, 25.0% with anxiety disorder, 0.9% with personality disorder, and 2.7% with others); COVID-19-related variables: "Problem Evaluation Scale" to measure fear, isolation, and healthcare	A third of psychiatric patients felt a worsening of their condition during the time of governmental physical distancing measures, with 12% of them not believing it was related to these measures. Half of patients were feeling distressed because of loneliness and isolation, notably more woman than men. The percentage of individuals with psychiatric disorders who were concerned about their financial situation was higher that the percentage of those who were concerned about own health. Younger patients (age < 50 yr) experienced on average worsened health, were feeling more fearful, and had more difficulties adapting than older patients. In comparison to patients with psychotic disorders, patients with affective disorders were feeling more vulnerable. Patients with SZ had the least problems with a lack of information about COVID-19.	Not mentioned
Quittkat *et al*[58]	Germany, April 2-May 6, 2020(during the lockdown)	MDD, SZ, SP, OCD, GAD, SAD, IA, ED, panic disorder and PA, and BDD	Cross-sectional online survey and retrospective data assessment of 1207 individuals with psychiatric disorders (586 with depression, 135 with GAD, 86 with SAD, 83 with PA, 62 with ED, 47 with OCD, 30 with IA, 16 with BDD, 6 with SP, and 135 others) and 1026 HC; BDSI, CAHSA, DASS-21 (depression subscale), EDE-Q – 2nd ed., PHQ (Panic Model and Stress Subscale), PSWQ-d, SIAS, SPhS, WI, Y-BOCS	All participants had on average fewer social contacts and did not go grocery shopping as often as before the pandemic. All individuals reported augmented levels of psychosocial stress, worried more about COVID-19, and were more fearful of contracting this illness than HC. Among individuals with depression, a quarter perceived an improvement, whereas 57.51% experienced a decrease of their mental health and 45.9% felt the need for more therapeutic support. Individuals with SZ reported mostly no or only slight changes in their mental health and did not find further therapeutic support to be necessary.	Small sample sizes of some groups, retrospective data assessment, self-identification of mental disorders, individuals with mental illness and HC were not matched, possible gender bias, selection bias through method of recruitment, online assessment
Riblet *et al*[78]	United States, October 2019–March 2020 and April 23–May 4 (before and during the lockdown)	SMI	Longitudinal interviews of 11 veterans with SMI (5 with MDD, 5 with BD, and 1 with psychotic disorder), with three in-person interviews conducted before the stay-at-home order (baseline, 1- and 3-mo follow-up) and one telephone-based interview during the lockdown; baseline: MINI; later additions: Hopelessness, social connections, treatment engagement, and suicidal ideation	There were no relevant changes concerning psychiatric symptoms during the pandemic compared to before. Few participants, who were significantly older (M = 71.7 yr) experienced an increase in symptomatology.	Small sample size, geographical limitation: low infection rate in Northern New England, participants consisted solely of veterans with possibly easier treatment access, participants had been hospitalized because of their illness, no long-term follow-up
Rohde *et al*[60]	Denmark, February 1–March 23, 2020 (before and during the lockdown)	SMI, stress-related and adjustment disorders, personality disorders, autism, ED, hyperkinetic disorder, and others	Analysis of clinical notes of 14561 psychiatric inpatients, with 918 of them being further analyzed (198 with SZ, 130 with MDD, 68 with BD, and 522 others); screening of clinical notes for COVID-19-related psychiatric symptoms	The final number of patients with notes describing pandemic-related psychopathology was 918, with two thirds of them being female. Most notes contained symptoms related to logistical problems. The most common symptoms were anxiety (n = 539), stress (n = 174), delusions (n = 149), depression (n = 146), suicidality (n = 102), and obsessive-compulsive symptoms (n = 85).	Lack of systematic assessment for COVID-19-related psychopathology
Solé *et al*[56]	Spain, May 14–June 8, 2020 (during the lockdown)	SMI (SZ or BD and MDD and/or anxiety)	Cross-sectional online survey of 206 individuals with psychiatric illness (148 with BD or SZ and 50 with MDD or anxiety) and 413 HC; self-	In comparison to HC, individuals with psychiatric disorders reported less use of coping strategies, such as having a routine, social interactions, and a healthy lifestyle. Furthermore, they	Lack of generalizability, self-reported mental illness, different restrictions at different times when conducting the

			constructed questionnaires for psychological distress (inspired by GAD-7 and PHQ-9), trauma experiences (inspired by EGS-R), psychotic-like experiences (adapted from CAPE-42), resilience (derived from BRS and RS-14), affective temperament (inspired by TEMPS-A), perceived family environment (inspired by FES), cognitive reserve (based on CRASH), physical aggressiveness (derived AQ); lifestyle	experienced more symptoms of depression and anxiety during the lockdown. They showed more frequently changes of sleep patterns, weight gain, and tobacco consumption than HC. Individuals with depression and/or anxiety were more distressed and concerned about the future, suffered from more sleeping problems, and exercised more than individuals with SZ or BD.	survey, lack of longitudinal follow-up, possible gender bias, questionnaires were only based on validated scales and not these scales themselves were used
Somer *et al*[80]	Mostly in the United States, Italy, Turkey, UK, and Canada, mid-April–mid-May 2020 (during the lockdown)	MDD, anxiety disorder, MD	Cross-sectional online survey of 326 individuals with MD and 546 HC (417 with anxiety disorders, 226 with MDD, and 189 with others in both groups); MDS-16, COVID-19-related variables: Questions about changes in daydreaming and psychosocial functioning	Individuals with depression and anxiety, who were suspected to have MD, were feeling an elevated urge to daydream during the pandemic and had more problems controlling it than individuals with MD and none of these disorders.	No generalizability due to sampling limitations, cross-sectional design does not allow the determination of causality, low effect size, no clinical diagnosis of MD
Van Rheenen *et al*[75]	Australia, April 1-4, 2020 (during the lockdown)	Affective disorders (BD and MDD)	Cross-sectional online survey of 1292 participants with a self-reported affective disorder and 3167 HC; DASS-21, PANAS, COVID-related variables: Questionnaires about primary concerns, changes in personal situation, perceptions, or behaviour	Individuals with affective disorders reported higher psychological distress than HC. Individuals with BD experienced more stress and depressive symptoms compared to individuals with depression; men with BD had more symptoms of distress and depression than women. Both groups did not differ in their mild symptoms of anxiety. Individuals with BD showed more pronounced financial concerns than individuals with depressive disorder and HC.	Self-selection and potentially selection bias, cross-sectional design led to a retrospective self-analysis of changes by the participants with no validation by the authors, self-reported affective disorders, mood disorder group was not balanced regarding gender distribution, no baseline measures of mood and lifestyle
Winkler *et al*[8]	Czech Republic, November 2017 and May 6– 20, 2020 (during and shortly after the lockdown)	Affective disorders (BD and MDD), anxiety disorders, and AUD	Two cross-sectional interviews of 3306 participants in 2017 (10.84% with AUD, 7.79% with anxiety disorders, and 6.57% with affective disorder) and 3,021 in 2020 (18.58% with affective disorder, 12.84% with anxiety disorders, and 9.88% with AUD); MINI, COVID-19-related variables: Lifestyle, worries, seeking of mental professional help, psychiatric symptoms	In 2020, 29.63% of individuals in Czech Republic suffered from mental illness in comparison to 20.02% in 2017. The prevalence of MDD tripled and there was no difference in the prevalence of alcohol use disorder, however, more individuals exhibited binge drinking behavior (4.07% *vs* 6.39%). The suicide risk rose from 3.88% to 11.88% in 2020. Having a mental disorder was associated with more worryies about COVID-19-related impacts on health and economy.	No cohort study and therefore no assessment of the development of mental illness in previously health individuals, lack of face-to-face interviews, relaxation of MINI criterion, data collection after loosening of strictest COVID-19-related measures
Zhu *et al*[51]	China, 28 February-6 March, 2020 (during the lockdown)	SMI	Cross-sectional online survey of 925 inpatients with SMI (657 with SZ and 268 with affective disorder) in economically less developed geographic regions; clinical characteristics, COVID-19-related variables: Self-constructed questions about prevention, knowledge, information sources	The majority of participants (84.4%) had a positive stance regarding measures for preventing COVID-19, which was related to marriage and a higher level of education. The latter was additionally associated with more knowledge about the pandemic. The main sources of information were public media and individuals' attending physicians.	Lack of an outpatient control group, lack of examination of variables associated with attitude and knowledge pertaining COVID-19
Zou *et al*[66]	China, May 22-July 15, 2020 (during and after the lockdown)	SMI, organic mental disorders, and others	Cross-sectional online survey of 1063 older (age ≥ 50 yr) psychiatric patients (485 with MDD, and 578 with BD, SZ, organic mental disorders, and others); Patient Health Questionnaire (PHQ-9), ISI, NPRS, WHOQOL-BREF, self-constructed questionnaires to measure fatigue, COVID-19-related variables: Access to psychiatric services, treatment adherence, concerns	Nearly half of participants were feeling fatigue (47.1%), which was associated with a lower quality of life. A higher level of fatigue was related to more severe symptoms of depression, insomnia, and pain.	Results cannot be generalized, as the patients were of older age, cross-sectional design does not allow the determination of causality, several factors of importance were not researched due to logistical reasons

BD: Bipolar disorder; HC: Healthy controls; MDD: Major depressive disorder; OCD: Obsessive-compulsive disorder; PTSD: Post-traumatic stress disorder; SMI: Serious mental illness; questionnaires: AQ: Aggression Questionnaire; ASRM: Altman Self-Rating Mania Scale; BAI: Beck Anxiety Inventory; BCIS: Believing COVID-19 Information Scale; BDI-II: Beck Depression Inventory II; BDSI: Body Dysmorphic Symptoms Inventory; BRCS: Brief Resilient Coping Scale; BRS: Brief Resilience Scale; CAHSA: Continuum of Auditory Hallucinations-State Assessment; CAPE-42: Community Assessment Psychic Experiences; CES-D: Center for Epidemiologic Studies Depression Scale; CGI: Clinical Global Impression; CPSS: Chinese Perceived Stress Scale; CRASH: Cognitive Reserve Assessment Scale in Health; CSS: COVID Stress Scales; DASS-21: Depression; Anxiety; and Stress Scale-21 Items; DJGLS: De Jong Gierveld Loneliness Scale; EDE-Q: Eating Disorder Examination-Questionnaire – 2nd Ed.; EGS-R: Posttraumatic Stress Disorder Symptom Severity Scale-Revised; FCV-19S: Fear of COVID-19 Scale; FES: Family Environment Scale; GAD-7: Generalized Anxiety Disorder-7; HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale; IES(-r): Impact of Event Scale(-revised); HRQoL: Health-related quality of life; ISI: Insomnia Severity Index; K10: Kessler 10 Psychological Distress Scale; LS: Loneliness Scale; MADRS: Montgomery-Asberg Depression Rating Scale; MDS-16: Maladaptive Daydreaming Scale; MINI: Mini International Diagnostic Interview; MOS-SS: Medical Outcomes Study Sleep; NEO-FFI: NEO-Five Factor Inventory; NPRS: Numeric Pain Rating Scale; PANSS: Positive and Negative Syndrome Scale; PCIBS: Preventive COVID-19 Infection Behaviours Scale; PCL-C: PTSD Checklist – Civilian Version; PHQ-4/8/9: Patient Health Questionnaire-4/8/9; PMS: Pearlin Mastery Scale; PSQI: Pittsburgh Sleep Quality Index; PSS: Perceived Stress Scale; PSWQ: Penn State Worry Questionnaire; QIDS: Quick Inventory of Depressive Symptoms; RS-14: Resilience Scale; SCID-5: Structured Clinical Interview for DSM-5; SIAS: Social Interaction Anxiety Scale; SPEQ: Specific Psychotic Experience Questionnaire; SPS: Social participation scale; SPhS: Social Phobia Scale; SRS: Stress-Related Somatic complaints; SSS-S: Self-Stigma Scale-Short; STAY-YA: Spielberger's anxiety questionnaire (French: L'échelle d'anxiété état de Spielberger); SUMD: Scale to Assess Unawareness of Mental Disorder; TEMPS-A: Temperament evaluation of Memphis, Pisa, Paris, and San Diego-autoquestionnaire; UC: Utrechtse Copinglijst; WHOQOL-BREF: World Health Organization Quality of Life-brief version; WI: Whitely Index; Y-BOCS: Yale-Brown Obsessive Compulsive Scale – Symptom Checklist; YMRS: Young Mania Rating Scale.

Individuals with MDD were worried about their health and felt the need for more therapeutic support[58]. Numerous studies found more symptoms of depression[25,42,62,70,71], anxiety[42,62,70,72], PTSD[42,70,72], problems of sleep[70-72], stress[62,72], suicidality, anger, impulsivity[72], worry, loneliness[25], and elevated substance consumption[71] in patients with MDD compared to either HC or measured symptoms before the pandemic. MDD was a predictor of severe distress[73], which was connected to pandemic-related news[74]. Individuals with BD experienced more stress and depressive symptoms than those with MDD, with men having more severe depressive symptoms than women[75].

Individuals with SZ reported to be less stressed during the COVID-19 pandemic than HC[76] and had the least amount of problems with a lack of information about COVID-19 in comparison to other psychiatric disorders[63]. However, they were apparently both more anxious and worried about the current situation and perceived the risk of being infected with COVID-19 as higher than HC[76].

In comparison to individuals with SZ, patients with affective disorders were experiencing more feelings of vulnerability[63]. Furthermore, correlations between high CGI scores and stress-related somatic problems were especially increased in individuals with affective disorders, but could not be found in individuals with SZ[68]. Compared with BD and SZ, individuals with MDD were more worried about contracting the virus[64,77] and had more concerns about service disruption[64]. Furthermore, they were more concerned about the future, suffered from more sleep problems, and exercised more[56].

What are risk and protective factors that influence the severity of psychiatric symptoms and who is particularly vulnerable to these factors?

Regarding SMI in general, it was found that participants experiencing a worsening of psychiatric symptomatology were mainly elderly individuals[78] or had been hospitalized at a more recent date than the individuals who remained stable[36]. Nearly half

of them were experiencing fatigue, which was related to a lower quality of life[66]. However, most of elderly individuals with SMI experienced less psychiatric symptoms [79], approved of the strict governmental measures, and were not afraid of being infected with COVID-19. A higher level of fear was associated with more symptoms of depression, anxiety, stress, and less frequent behavior concerning prevention in older patients with SMI[50]. One study investigating elderly individuals with MDD found a lower quality of life, but not increased symptoms of depression and anxiety[77]. On average, younger patients experienced worse overall health, were feeling more fearful, and had more difficulties adapting than older patients[63]. Additionally, young age was related to increased anxiety and financial concerns in individuals with affective disorders[69].

Stress and distress in individuals with affective disorders were related to a longer duration of psychiatric illness, living alone during the lockdown, the habit of smoking, and frustration, which was associated with unemployment[69]. Especially younger individuals were concerned about pandemic-related consequences regarding their health[8] and socioeconomic status[67,69].

Concerning BD, symptoms of posttraumatic stress were related to anxiety and both work and financial difficulties in the wake of the pandemic. Acute manic symptoms seemed to be protective[42]. Loneliness, not having children, a passive coping style, low mastery, and neuroticism were associated with more psychiatric symptoms[79]. One study found that men had depressive symptoms to a greater extent than women [75]. Individuals with MDD and maladaptive daydreaming were feeling an elevated urge to daydream during the pandemic and had more problems controlling it[80].

Individuals with SZ living in isolation due to a suspected COVID-19 infection were more stressed, anxious, depressed[81], and had a worse quality of sleep than individuals with SZ who were not quarantined[82]. After the quarantine, this symptomatology continued[81]. When living in communal residencies, they were supported by both their cohabitants and mental health professionals, remained adherent to their treatment, and possessed knowledge about the consequences of COVID-19[74].

How does symptomatology and frequency of illness episodes change during the course of the pandemic?

On the one hand, two studies found that psychiatric symptoms remained stable over time in individuals with SMI[57,78], while another one found that the relapse rate did not significantly increase during the pandemic[36]. On the other hand, several studies showed a third of individuals with SMI to exhibit symptoms indicative of a recurrence of their illness or a worsening of symptomatology[52,63].

Pinkham *et al*[57] found that affective symptoms remained stable over time. In contrast, other studies showed that individuals with affective disorders apparently displayed a high likelihood of psychological distress[73,75]. In line with the latter finding, individuals with BD reported to have more psychiatric symptoms compared to the time before the pandemic in one study[75].

The research on MDD was contradictory: On the one hand, few studies showed that individuals with MDD were resilient, mostly socially connected, and did not experience increased symptoms of depression, anxiety, and suicidal ideation[77], with a quarter of them even perceiving an improvement of their mental health during the pandemic in one study[58]. On the other hand, the majority of studies found that individuals with MDD reported both a lower quality of life[70,72,77] and a decrease in mental health compared to the time before the pandemic[58].

Individuals with SZ reported mostly no or only slight changes in their mental health [57,58], and did not find further therapeutic support to be necessary[58].

DISCUSSION

This review is about the impact of COVID-19 on the mental health situation of individuals with BD, MDD, and SZ, gaining data from 19 different countries and areas. In the first months of the crisis, individuals with mental disorders experienced, on average, more pronounced psychiatric symptoms. Nevertheless, some studies showing a reduction of psychiatric symptomatology were found as well. Individuals with affective disorders showed an impairment in mental health, while those with SZ seemed to be mostly unaffected by the pandemic on a mental level. Overall, older patients experienced fewer decline in mental health than younger patients.

First and foremost, contradictory results about the impact of the pandemic on individuals with mental illness in general were found, showing both an increase and a decrease in psychiatric symptoms during the pandemic. The latter was reported more often, showing most commonly symptoms of depression, anxiety[56,59,60], and stress [58-62]. Notwithstanding, these results suggest that individuals with SMI were less affected by the pandemic than HC[25]. This observation was made by numerous authors researching not only individuals with SMI but mental illness in general[27,83] and might be applicable to this specific subgroup as well. The reason for this might be that individuals with mental disorders may be more used to periods of physical distancing and emotional upheaval due to disorder episodes, as Pan *et al*[25] similarly described. For HC, the pandemic has been a more drastic experience, severely influencing their daily lives and therefore leading to more pronounced symptoms of mental illness and a "normal"[25] reaction to this crisis. However, these results only feature the beginning of the COVID-19 pandemic, and the long-term effects on both HC and individuals with mental disorders require continued research.

While individuals with MDD were generally more worried about the pandemic and practiced more preventive behavior[62,77], those with BD seemed to suffer from more depressive symptoms without being as proactive about changing their situation[75]. Factors associated with higher levels of distress were largely connected to lifestyle[73] and socioeconomic environment[69], emphasizing the influence of these factors as well as the importance of outside help and a stable social network[35]. Unemployment was a particularly important factor, as it was related to frustration, anxiety, and bad mood [69], possibly leading to heightened fear about socioeconomic consequences[67]. Individuals with affective disorders are known to have a lower socioeconomic status and higher rates of unemployment than HC[84], making them more vulnerable for mental health degeneration in times of financial instability. In this context, the concept of resilience and strengthening it in individuals with psychiatric disorders, especially in individuals with BD, should be kept in mind for future interventions[85].

Although those diagnosed with SZ were more worried and anxious than HC[76], they seemed to be least affected by the crisis on a mental level among individuals with SMI, as the majority of SZ patients reported only little or no changes in their mental health[57,58,68]. This was explained by both a small sample size[58] and a disregard for "mundane worldly business"[68]. Possibly, they were indeed more preoccupied with their inner world, not focusing particularly on what happened during the pandemic. This coincides with the results about their apparent acceptance of a lack of information about COVID-19[63]. In addition, individuals with SZ reported support from their social network[76], helping them to lessen the mental burden in the wake of the pandemic.

Interestingly, more case reports were found about the exacerbation of SZ than of affective disorders, but these were not included in this review. This could be indicative either of a particular interest in such cases or an increased frequency of them. The latter may be explained by the diathesis-stress model[86], according to which environmental triggers can influence psychiatric symptoms of SZ. Amongst other factors, stress and the subsequent increase in cortisol levels lead to an increased release of dopamine[86,87]. Moreover, exacerbation might be associated with COVID-19 infection. Some patients who were infected were taking clozapine[87-89], which supports the hypothesis of this widely used drug increasing the risk for infection with COVID-19[90,91]. Likewise, stress, depression, and anxiety occurring in SZ patients with COVID-19 might advance an exacerbation[81,82]. COVID-19 itself might cause delirium as well[92]. In conclusion, individuals with SZ may not have been profoundly affected, however, they are vulnerable, especially in case of an infection, which could lead to an exacerbation.

Young age seems to be a risk factor for developing more severe psychiatric symptoms during the pandemic. Younger individuals with SMI had worse mental health and more feelings of fear[63] and anxiety[69] than older individuals, who were mostly reported to remain stable[77,79]. A connection of young age to financial concerns could be found[69], which might be related to unemployment, an important factor for the development of mental health problems during the pandemic. Moreover, social relations played an important part in maintaining the mental health of older adults (age > 60 years)[77]. Many of them were perhaps retired, making the measures of physical distancing a less severe change to their lives. After all, unlike younger adults, they did not have to adjust to the abrupt change of working from home instead of daily meeting their co-workers and thereby connecting socially. Additionally, they did not have the burden of caring for their children staying at home as well. Furthermore, resilience, a protective factor, was found to be high in older adults with SMI[77,79]. Resilience is known to rise with age[93], making it a possible reason for the

better coping ability of older individuals with SMI, which indicates the need for increased resilience once again, especially in younger individuals with SMI.

An increased belief in pandemic-related news was found to be associated with both increased[55] and decreased[50] fear in individuals with SMI, which may be related to the nature of information. Regardless of whether these individuals were more or less [53] informed about COVID-19 and its prevention than HC, they were generally more fearful and worried about the pandemic[58,76,77]. This is concerning if it is related to less prevention behavior[50], because individuals with SMI show more vulnerability to infection with COVID-19 than HC[94,95] and should therefore practice strict measures of prevention. Notably, COVID-19 patients with SZ featured a higher in-hospital mortality rate than HC[96,97]. Consequently, it is important for individuals with SMI to be supplied with information about the pandemic of adequate quality, which would lead to decreased fear and encourage them to protect both themselves and others.

Regarding the situation, increased treatment options for individuals with SMI are integral: Recommendations to use telepsychiatry have been made[98-100] and reports about its effectiveness have been given by several authors[101]. This kind of therapy seems to be well suited to face the situation of physical distancing, at least when it comes to patients without acute exacerbation of their condition requiring immediate medical intervention. In the light of elevated concerns about COVID-19-related healthcare shortages in individuals with mental illness[60,64], telepsychiatry gains in significance for easing the worries of these patients and helping them from afar.

Inconsistent results were found across different studies researching whether the mental health situation of individuals with SMI increased or decreased, although the latter was reported more often. These conflicting outcomes could be explained by cultural, social, and economic background, the pandemic-related situation of different countries, as well as factors pertaining to the implementation of the studies, such as the use of non-standardized questionnaires. Nevertheless, this shows that generalizing the results might not be possible in some cases and should be taken into consideration, as many authors mentioned in their studies. Additionally, these discrepancies highlight the need for measuring individuals' socioeconomic situation and other variables influencing their mental health situation. This was done by several authors; however, it would be important to not only report these results, but also use the aforementioned variables as covariates to facilitate international comparison. Further limitations implicate more aspects to be taken into account for future research: The sample should be of adequate size, follow-up studies are needed to research causality and observe long-term effects, and standardized questionnaires about COVID-19-related variables, such as those proposed by Chang *et al*[54], should be used to enable better comparability. Additionally, the conduction of a meta-analysis would be ideal to better evaluate the impact of the pandemic on individuals with SMI.

CONCLUSION

The pandemic and its consequences have been leading to a decrease in the mental health situation of individuals with SMI across the world, especially those with affective disorders. Increasing symptoms of anxiety, depression, and stress were most frequent and higher in comparison to HC. Along with age and resilience, the main contributing factors seem to be of socioeconomic nature, with the shortage of treatment options, fear, adequate information, and social support being particularly important. This precarious situation necessitates a reinforcement of mental health services, first and foremost the usage of telepsychiatry. Moreover, it is paramount to supply patients with adequate information about COVID-19 and its prevention and to increase their resilience. Respecting scientific research about psychiatric disorders, both standardizations to enable generalization of results and the conduction of long-term follow-up studies are integral to further investigate SMI.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) is greatly influencing the mental state of individuals from all walks of life. Individuals with serious mental illness (SMI: bipolar disorder, major depressive disorder, and schizophrenia) are especially vulnerable to the reverberations of such a crisis, leading among other symptoms to an increase of

depression and anxiety. The pandemic is an excellent opportunity to broaden the understanding of these disorders and improve methods of treatment.

Research motivation

Individuals with SMI having been researched in the course of several studies calls for a coherent analysis of all findings to gain an insight in the mind of these individuals, making their support more efficient. At the time of the search, no other review focusing on solely the clinical characteristics of individuals with SMI had been published in the searched databases.

Research objectives

This review aimed to assess the situation of individuals with SMI and their mental state during the COVID-19 crisis. The following questions were answered: (1) How are individuals with SMI affected by the pandemic in comparison to healthy controls (HC) and what are the main psychiatric symptoms they are displaying? (2) What are risk and protective factors that influence the severity of psychiatric symptoms and who is particularly vulnerable to these factors? And (3) How does symptomatology and frequency of illness episodes change during the course of the pandemic?

Research methods

We systematically searched MEDLINE and PubMed (day of the final search: January 9, 2021), including terms related to the impact of the COVID-19 pandemic on the mental health of individuals with bipolar disorder, major depressive disorder, and schizophrenia. Only studies providing original data were included.

Research results

The search yielded 36 studies. The impact of the COVID-19 pandemic generally affected the mental health of individuals with SMI in a negative way, with individuals with affective disorders being more impacted than those with schizophrenia. The most common symptoms were those of depression, anxiety, and stress. Mental health was mainly influenced by age, resilience, and socioeconomic circumstances, particularly the shortage of mental health services, lack of social support, and inadequate information about COVID-19.

Research conclusions

Mental health services, particularly telemental health services, should be reinforced to better support individuals with SMI and strengthen their resilience. Moreover, individuals with SMI should be supplied with information about the pandemic and the employment of protection measures.

Research perspectives

Future research requires follow-up studies to determine causality and long-term effects, greater sample sizes, and standardization.

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SYSTEMATIC REVIEWS

Psychoeducation in bipolar disorder: A systematic review

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Abstract

BACKGROUND

Bipolar disorder (BD) is a severe psychiatric disorder characterized by mood swings. Psychosocial interventions, such as psychoeducation, play an essential role in promoting social rehabilitation and improving pharmacological treatment.

AIM

To investigate the role of psychoeducation in BD.

METHODS

A systematic review of original studies regarding psychoeducation interventions in patients with BD and their relatives was developed. A systematic literature search was performed using the Medline, Scopus, and Lilacs databases. No review articles or qualitative studies were included in the analysis. There were no date restriction criteria, and studies published up to April 2021 were included.

RESULTS

A total of forty-seven studies were selected for this review. Thirty-eight studies included patients, and nine included family members. Psychoeducation of patients and family members was associated with a lower number of new mood episodes and a reduction in number and length of stay of hospitalizations. Psychoeducational interventions with patients are associated with improved adherence to drug treatment. The strategies studied in patients and family members do not interfere with the severity of symptoms of mania or depression or with the patient's quality of life or functionality. Psychoeducational interven-

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tions with family members do not alter patients' adherence to pharmacotherapy.

CONCLUSION
Psychoeducation as an adjunct strategy to pharmacotherapy in the treatment of BD leads to a reduction in the frequency of new mood episodes, length of hospital stay and adherence to drug therapy.

Key Words: Bipolar disorder; Mood disorders; Psychoeducation; Adherence; Mania; Depression

Core Tip: Bipolar disorder (BD) is a severe and chronic psychiatric disorder that requires intense treatment usually based on pharmacotherapy. Treatment applying psychotherapy adjunctive treatment is usually prescribed, although with inconsistent data. We aimed to perform a systematic review evaluating the evidence of psychoeducation in BD patients and their family members. Evidence suggests that psychoeducation of patients and family members is associated with a lower number of new mood episodes and a reduction in number and length of stay of hospitalizations. Psychoeducational interventions with patients are associated with improved adherence to drug treatment. Psychoeducation is a good interventional strategy for BD treatment.

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INTRODUCTION

Bipolar disorder (BD) is a chronic mental health illness characterized by mood swings [1]. It is estimated that more than 1% of the world population is affected by BD[2,3]. The prevalence rates for each BD subtype, I and II, in community-based samples are 0.6% and 1.4%, respectively, and the mean age of onset of the disease is approximately 20 years[2,3]. Poor treatment adherence is associated with mood swings, social stigmatization, and lower social support in BD[4]. Psychosocial interventions might play an essential role in promoting social rehabilitation and improving pharmacotherapy adherence. Studies have demonstrated that non-pharmacological interventions, such as psychoeducation and cognitive-behavioral and interpersonal therapy, promote effects in the treatment of acute mood episodes and maintenance treatment in BD[5]. These actions favors the early recognition of warning signs of mood instability and promote the development of healthier lifestyles[4].

Psychoeducation is an intervention strategy based on providing patients and/or relatives with information about the disorder to enhance their understanding and enable early identification of warning signs and mood changes, improving treatment adherence[5-7]. Psychoeducational strategies in BD might promote the frequency of new mood episodes and medication adherence[8]. The Barcelona Psychoeducation Program was associated with an almost ninefold decrease ratios regarding new mood episodes and reduced the number of symptomatic days, as well as the hospitalization's length of stay (LOS)[9]. Family psychoeducation intervention has been correlated with mood episode reduction in patients with BD[7]. When family members acquire better knowledge about the disorder, they contribute to the early detection of the first symptoms of changes in mood[10,11].

This systematic review aims to investigate the role of psychoeducation in BD in patients and in their family members.

MATERIALS AND METHODS

Search strategies and selection criteria

The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist. A systematic literature search was performed through the Medline (Medical Literature Analysis and Retrieval System Online/PubMed), Scopus and Lilacs databases. Studies published up to April 2021 were included. The key terms used were "bipolar disorder" and "psychoeducation". Studies in Portuguese and English were selected. Two independent reviewers (J.L.R. and I.G.B) analyzed the titles and abstracts; afterward, texts that fulfilled the requirements were included. The inclusion criteria were as follows: (1) Original psychoeducation intervention studies; (2) Placebo-controlled studies; and (3) Interventions aimed at adult patients with BD. The exclusion criteria were as follows: (1) Review, case series, and case report; (2) Interventions aimed at groups of patients with other mental or behavioral disorders; (3) Book chapters or reviews, systematic reviews or meta-analyses; (4) Studies written in languages other than English or Portuguese; (5) Low-quality studies according to the Newcastle–Ottawa scale (NOS) scale; and (6) Interventions aimed at children or adolescent patients with BD. Only original studies with a control group or baseline data for psychoeducation interventions in patients with BD and their relatives were included.

Data extraction and quality assessment

The systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42020168910.

We developed a data extraction table based on a Cochrane model[12]. One of the revisors (J.L.R.) extracted data and another (I.G.B) verified them. To reduce selection bias, two revisors (J.L.R. and I.G.B.) assessed the methodological quality of all the studies according to the NOS criteria[13]. The NOS is a "star system"-based scale, which scores a maximum of 4 stars corresponding to selecting studying groups, 3 stars for the ascertainment of either the exposure or outcome of interest, and 2 for the comparability of the groups; thus, the total NOS maximum score is 9. In the present study, we considered a minimum score of 5 on the NOS scale sufficient to be included [13]. In the circumstances of any disagreement between those 2 revisors, a third revisor was consulted (B.F.C) for consensus.

All extracted data included information about publication (including author name and year of publication), some group characteristics (sample size, gender, mean age, mood state and subtype of BD), methods (psychoeducation protocols; number of sessions; instruments that were applied, and who had performed them; kind of study, either a blinded or a randomized one) and their main outcomes.

RESULTS

Description of studies

Six hundred sixty-seven publications were identified from the literature search (PubMed: Five hundred and eighty-four; Scopus: Sixty-one and Lilacs: Twenty-four). Duplicated studies were excluded (n = 34). Five hundred thirty-nine were excluded after title and abstract screening. Twenty studies were included from manual extraction. Seventy-two studies were excluded: Four of these were article reviews; thirty-seven did not include psychoeducation treatment; four were about intervention strategies in patients under 18 years of age; five studies were qualitative studies; one study was about a protocol; and thirteen studies were duplicated. Eight studies were classified as low quality according to the NOS scale (*i.e.*, scored less than or equal to five stars) and were excluded from the present manuscript. A total of forty-seven publications were selected for this review, of which thirty-eight studies included patients with BD and nine studies included relatives of patients with BD (Figure 1).

Characterization of included studies

Studies in patients with BD: Thirty-eight clinical studies were included. Thirty-eight studies[6,8,11-46] scored five or more stars according to the NOS scale[12] (Table 1). There were thirty-three randomized studies[6,8,11-18,20-26,28-32,34-36,39-47] and five nonrandomized studies[19,27,33,37,38]. Eighteen studies included euthymic or remitted patients[6,8,11,16-21,25,26,28,33,35,37,41-43]. Two studies included patients with depressed mood[31,32]. Sixteen publications did not evaluate the mood episodes

Table 1 Newcastle–Ottawa scale evaluation for studies that assessed psychoeducation in bipolar disorder patients

Ref.	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total
Zhang *et al*[14], 2019	1	1	1	1	2	1	1	1	9
Wiener *et al*[15], 2017	1	1	1	1	1	1	1	1	8
Cardoso *et al*[16], 2015	1	1	1	1	1	1	1	1	8
Cardoso *et al*[17], 2014	1	1	1	1	1	1	1	1	8
Faria *et al*[18], 2014	1	1	1	1	2	1	1	1	9
Kurdal *et al*[19], 2014	1	1	1	1	1	1	1	1	8
Javadpour *et al* [20], 2013	1	1	1	1	2	1	1	1	9
de Barros Pellegrinelli *et al* [21], 2013	1	1	1	1	2	1	1	1	9
Candini *et al*[22], 2013	1	1	1	1	1	1	1	1	8
Colom *et al*[11], 2009	1	1	1	1	2	0	1	1	8
Colom *et al*[23], 2003	1	1	1	1	2	1	1	2	10
Colom *et al*[24], 2003	1	1	1	1	2	1	1	1	9
Dalum *et al*[25], 2018	1	1	1	0	1	0	1	1	6
Depp *et al*[26], 2015	1	1	1	1	1	1	1	1	8
Lauder *et al*[27], 2015	1	1	1	1	1	1	1	1	8
Torrent *et al*[28],	1	1	1	1	2	1	1	1	9

2013									
Smith *et al*[29], 2011	1	1	1	1	2	1	1	1	9
Sylvia *et al*[30], 2011	0	1	1	1	2	1	1	0	6
D'Souza *et al*[31], 2010	1	1	1	1	2	1	1	1	9
Castle *et al*[32], 2010	1	1	1	1	2	0	1	1	8
So *et al*[46], 2021	1	1	1	1	1	0	1	1	7
Sajatovic *et al*[33], 2009	1	1	1	1	2	1	1	1	9
Miklowitz *et al* [34], 2007	1	1	1	1	2	0	1	0	7
Miklowitz *et al* [35], 2007	1	1	1	1	2	1	1	1	9
González Isasi *et al* [36], 2014	1	1	1	1	1	1	1	1	8
Parikh *et al*[37], 2012	1	1	1	1	2	1	1	1	9
Zaretsky *et al*[38], 2008	1	1	1	1	1	1	1	1	8
Proudfoot *et al* [39], 2012	1	1	1	1	1	1	1	1	8
Aubry *et al*[40], 2012	1	1	1	1	1	0	1	0	6
Gonzalez *et al*[41], 2007	0	1	1	1	2	1	1	1	8
Miklowitz *et al* [42], 2003	1	1	1	1	1	1	1	1	8
Petzold *et al*[45], 2019	1	1	1	1	1	1	1	1	8
Pakpour *et al*[43], 2017	1	1	1	1	1	1	1	1	8
Morris *et al*[7], 2016	1	1	1	1	1	1	1	1	8

Kessing *et al*[44], 2014	1	1	1	1	1	1	1	1	8
Gumus *et al*[47], 2015	1	1	1	1	1	1	1	1	8
Eker *et al*[48], 2012	1	1	1	0	1	0	1	1	6
Perry *et al*[49], 1999	1	1	1	1	2	1	1	1	9

of the patients[12-15,22-24,27,29,30,34,36,38-40,44].

The DSM-IV diagnostic criteria for BD were applied in twenty-nine studies[6,8,11,12,15,16,18-21,23-26,29-35,37,40,42,43,46,47]. The DSM-III was applied in four studies [13,27,39,44], and the ICD-10 criteria were applied in two studies[22,41]. One study did not state its diagnostic criteria for BD diagnosis[17].

A total of 2721 patients with BD and 1107 controls were included. Patients were classified as having type I or II BD in twenty-four studies[6,8,11,17-20,23-27,29-32,34,35,37,38,40,42,46,47]. Six studies evaluated BD type I patients[21,28,33,39,41,45], and only one study assessed BD type II patients[15].

Psychoeducation programs in patients with BD: Psychoeducation interventions and outcomes are summarized in Table 2. Eleven studies[11,15-24] assessed the psychoeducation manual for BD (PMBD)[6]. Patients in the PMBP group presented a lower incidence of new mood episodes, fewer hospitalizations[11,23,24], and reduced LOS[11,21,24]. Patients in the PMBD group had a reduction in the number of depressive episodes[17,18,23]. No difference was observed in the number of mood episodes in four studies[15,16,18,21]. PMBD was associated with a higher adherence to pharmacological treatment and a higher quality of life in one study[20]. PMDB did not result in better functional parameters[19,21].

Eight studies evaluated Group psychoeducation (GP)[45-51]. BD included in the GP compared to controls exhibited a longer interval between mood episodes[44], higher adherence to pharmacological treatment[45,46], and lower rates of hospital admissions [44]. GP interventions were not associated with functional, social or family improvements[46].

Intensive psychosocial intervention was not associated with functional state improvement[35], mood episode frequency[33], or new mood episodes (Hamilton depression rating scale). One study showed a reduction in the number of hospitalizations and mean hospitalization time[37].

Other psychoeducational techniques were applied in eleven studies[11,22-24,26-29,36,38,39]. Illness Management and Recovery program (IMR)[22]; Family-focused treatment (FFT)[42]; Systematic Illness Management Skills Enhancement Programme BD (SIMSEP-BD)[31] and MoodSwings-Plus (MS-PLUS)[27] were associated with increased adherence to pharmacological treatment. Nutrition/weight loss, exercise, and wellness treatment (NEW Tx)[30] and Personalized Real-Time Intervention for

Table 2 Extracted data from studies that evaluated psychoeducation in patients with bipolar disorder

Ref.	BD	Sample size, N (P × C)	Age in years (P × C)	Female frequency (%) (P × C)	Intervention	Applied scales/parameters	Results
Zhang *et al*[14], 2019	I e II	35 × 39	34.2 × 34.6	57.1 × 46.2	SCIT	YMRS	$P = 0.21$
						HDRS	$P = 0.11$
						FAST	$P < 0.001$
						TMTA	$P = 0.77$
						SDMT	$P = 0.09$
						HVLT-R	$P = 0.09$
						SCWT	$P = 0.054$
Wiener *et al*[15], 2017	ND	32 × 29	24 × 23.81	83.3 × 76.2	PMBD	HDRS	$P = 0.028$
						YMRS	$P = 0.879$
Cardoso *et al*[16], 2015	ND	32 × 29	24.09 × 24.03	65.6 × 72.4	PMBD	BRIAN	$P = 0.88$
						HARS	$P = 0.175$
						YMRS	$P = 0.576$
						HDRS	$P = 0.074$
Cardodo *et al*[17], 2014	ND	32 × 29	24.09 × 24.03	65.6 × 72.4	PMBD	HDRS	$P = 0.001$
						YMRS	$P = 0.102$
Faria *et al*[18], 2014	II	32 × 29	24.09 × 24.03	72.4 × 65.6	PMBD	BRIAN	$P = 0.01$
						Depressive symptoms	$P = 0.001$
Kurdal *et al*[19], 2014	ND	40 × 40	37.17 × 33.9	35 × 40	PMBD	BDFQ	$P > 0.005$
Javadpour *et al*[20], 2013	I e II	45 × 41	24.4/23.2	23 × 21	PMBD	WHOQOL-BREF	$P < 0.001$
						MARS	$P = 0.008$
						Hospitalizations	$P < 0.001$
de Barros Pellegrinelli *et al*[21], 2013	I e II	32 × 23	43.43 × 43.74	23 × 15	PMBD	HDRS	$P = 0.820$
						YMRS	$P = 0.716$
						SAS	$P = 0.114$
						GAF	$P = 0.586$
						CGI	$P = 0.026$
Candini *et al*[22], 2013	I e II	57 × 45	41.5 × 44.8	52.6 × 48.9	PMBD	Hospitalizations	$P = 0.001$
						Number of days of hospitalization	$P = 0.001$
Colom *et al*[11], 2009	I e II	60 × 60	34.03 × 34.26	63.3 × 63.3	PMBD	New mood episode	$P = 0.002$
						Hospitalizations	$P = 0.023$
						Number of days of hospitalization	$P = 0.047$
Colom *et al*[23], 2003	I	25 × 25	35.36 × 34.48	64 × 60	PMBD	Mood episodes in the treatment phase	$P = 0.003$
						Mood episodes after 2 yr	$P = 0.008$
						Depressive episodes	$P = 0.004$
						Hospitalizations	$P = 0.001$
Colom *et al*[24], 2003	I e II	60 × 60	23.25 × 22.26	63.3 × 63.3	PMBD	New mood episode	$P = 0.001$
						Hospitalizations	$P = 0.05$

						Number of days of hospitalization	$P = 0.05$
Dalum *et al*[25], 2018	ND	23 × 24	41 × 45	46 × 44	IMR	IMRS-P	$P = 0.14$
						IMRS-S	$P = 0.76$
Depp *et al*[26], 2015	I e II	51 × 63	46.9 × 48.1	53.7 × 63.4	PRISM	YMRS	$P = 0.004$
						MADRS	$P = 0.036$
						IIS	$P = 0.636$
Lauder *et al*[27], 2015	I e II	71 × 59	39.87 × 41.35	73 × 76	MS–PLUS	ASRMS	$P = 0.02$
						MADRS	$P = 0.003$
						MOS-SSS	$P = 0.003$
						MARS	$P = 0.001$
						GPF	$P = 0.003$
Torrent *et al*[28], 2013	I e II	159 × 80	40.59 × 40.47	57.1 × 57.5	FR	FAST	$P = 0.002$
						HDRS	$P > 0.05$
						YMRS	$P > 0.05$
						Hospitalizations	$P > 0.05$
Smith *et al*[29], 2011	I e II	24 × 26	42.7 × 44.7	54.2 × 69.2	BBO	FAST	$P = 0.15$
						GAF	$P = 0.21$
						SAI	$P = 0.44$
						WHOQOL-BREF	$P = 0.25$
Sylvia *et al*[30], 2011	I e II	4 × 6	60 × 50.2	75 × 33	NEW TX	MADRS	$P = 0.10$
						LIFE-RIFT	$P = 0.014$
D'Souza *et al*[31], 2010	I	27 × 31	40.7 × 39.5	51.85 × 51.61	SIMSEP-BD	ARS	$P = 0.001$
						New mood episode	$P = 0.015$
						Time between mood episodes	$P = 0.001$
Castle *et al*[32], 2010	I e II	42 × 42	41.6 × 42.6	79 × 26	MAPS	Mood episode	$P = 0.003$
						Depressive symptoms	$P = 0.003$
						Knowledge about illness	$P > 0.05$
						ESM-PA	$P = 0.024$
						ESM-NA	$P = 0.001$
So et *et al*[46], 2021	I e II	38 × 26	35.8 × 43.1	78.9 × 73.1	LGP	Medication adherence	$P > 0.05$
Sajatovic *et al*[33], 2009	I e II	80 × 80	41.13 × 40	73.75 × 87.5	LGP	DAI	$P = 0.366$
						SRTAB	$P = 0.577$
						GAS	$P = 0.382$
Miklowitz *et al* [34], 2007	I e II	163 × 130	40.1 × 40	ND	IPI	Remission of symptoms 1 yr	$P = 0.001$
Miklowitz *et al* [35], 2007	I e II	84 × 68	ND	59 × 59	IPI	LIFE-RIFT	$P = 0.006$
González Isasi *et al* [36], 2014	I	20 × 20	43.35 × 39.25	45 × 50	CBT	STAI-S	$P = 0.062$
						YMRS	$P = 0.009$
						BDI	$P = 0.131$
						IS	$P = 0.001$
Parikh *et al*[37], 2012	I e II	109 × 95	40.9 × 40.9	53.2 × 63.2	CBT	LIFE	$P > 0.05$
						CARS-M	$P = 0.089$

						HDRS	$P = 0.089$
Zaretsky *et al*[38], 2008	I e II	40 × 39	ND	ND	CBT	CARS-M	$P = 0.001$
						HDRS	$P = 0.001$
Proudfoot *et al* [39], 2012	ND	139 × 134	35.3 × 40.9	66.9 × 69.4	BEP	GADS	$P > 0.05$
						WSAS	$P > 0.05$
						SWLS	$P > 0.05$
						BRIEF IPQ	$P = 0.001$
Aubry *et al*[40], 2012	I e II	50 × 35	46 × 52	66 × 62.9	LGP	Hospitalizations	$P = 0.001$
						Number of hospitalizations	$P = 0.009$
Gonzalez *et al*[41], 2007	I e II	11 × 11	40.5 × 41.0	45.45 × 45.45	IOM	GAF	$P = 0.65$
						CGI-BD	$P = 0.06$
						Depressive symptoms	$P = 0.005$
Miklowitz *et al* [42], 2003	I	31 × 70	35.6 × 36.6	58 × 66	FFT	SADS-C	$P = 0.001$
						New mood episode	$P = 0.001$
						MTS	$P = 0.001$
Pakpour *et al*[43], 2017	I e II	134 × 136	41.8 × 41.2	55.2 × 50.7	GP	MARS	$P = 0.001$
						YMRS	$P = 0.001$
						CGI	$P = 0.001$
						QoL.BD	$P = 0.001$
Petzold *et al*[45], 2019	I e II	39 × 34	44.32 × 42.69	43.6 × 47.1	GP	New mood episode	$P = 0.175$
						YMRS	$P = 0.241$
						HDRS	$P = 0.58$
						SF-36	$P = 0.359$
Morriss *et al*[7], 2016	I e II	153 × 151	44.2 × 46 ·5	60 × 56	GP	Time between mood episodes	$P = 0.012$
						SOFAS	$P > 0.05$
						SAS	$P > 0.05$
Kessing *et al*[44], 2014	I	72 × 86	64.1 × 63	61.1 × 48.8	GP	Time between mood episodes	$P = 0.014$
						Hospitalizations	$P = 0.064$
Gumus *et al*[47], 2015	I e II	41 × 41	38.7 × 40.05	40.5 × 56.1	GP	Number of mood episodes	$P = 0.208$
Eker *et al*[48], 2012	ND	35 × 36	34.57 × 36.54	54.3 × 52.8	GP	ANT	$P < 0.005$
						MARS	$P < 0.005$
Perry *et al*[49], 1999	I	34 × 35	44.1 × 45	68 × 69	GP	Time between manic episodes	$P = 0.008$
						Time between depressive episodes	$P = 0.19$

ANT: Attitudes towards neuroleptic treatment; ASRMS: Altman self-rating mania scale; ARS: Medication adherence scale; B: Baseline; BBO: Beating bipolar online; BD: Bipolar disorder; BDG: Bipolar disorder group; BDI: Beck depression inventory; BDFQ: Bipolar Disorder Functioning Questionnaire; BEP: Bipolar Education Program; BDNF: Brain-Derived Neurotrophic Factor; BRIAN: Biological Rhythm Interview of Assessment in Neuropsychiatry; BRIEF IPQ: The Brief Illness Perception Questionnaire; C: Controls; CARS-M: Clinician-Administered Rating Scale for Mania; CBT: Cognitive-behavioral therapy; CC: Collaborative care; CGI-BD: Clinical Global Impression Scale for Bipolar Disorder; DAI: Drug Attitude Inventory; EDM: Education about Disorders and Medications; ESM-PA: With in person positive affect as measured by using Experience Sampling Method; ESM-NA: Within-person negative affect as measured by using Experience Sampling Method; FAST: Functional Assessment Test; FFT: Family-focused treatment; FR: Functional remediation; GADS: The Goldberg Anxiety and Depression Scale; GAF: Global Assessment of Functioning; GAS: Global Assessment Scale; HVLT-R: Hopkins Verbal Learning Tests-Revised; GDNF: Glial cell line-derived neurotrophic factor; GPF: Global Measure of Psychosocial Functioning; GP: Group Psychoeducation; HARS: Hamilton Anxiety Rating Scale; HDRS: Hamilton Depression Rating Scale; IOM: Integrative Outpatient Model; IMR: Illness Management and

Recovery program; IMRS–P: Illness Management and Recovery Scale–participants' version; IMRS–S: Illness Management and Recovery Scale–staffs; IPI: Intensive Psychosocial Intervention; IS: Maladjustment scale; IRSRT: Interpersonal and social rhythm therapy; LGP: Life Goals Program; LIFE: Longitudinal Interval Follow-up Evaluation; LIFE-RIFT: The Range of Impaired Functioning Tool; MADRS: Montgomery–Asberg Depression Rating Scale; MOSSF-36: Medical Outcomes Survey Short-form General Health Survey; MTS: Maintenance Treatment Scale; MARS: Medication Adherence Rating Scale; MAPS: Monitoring mood and activities (M), assessing prodromes (A), preventing relapse (P) and setting Specific, Measurable, Achievable, Realistic, Time-framed (SMART) goals (S); MARS: Medication adherence rating scale; MS-PLUS: MoodSwings-Plus; MOS-SSS: Medical Outcomes Study Social Support Survey; ND: Not described; NEW TX-Program: Nutrition/weight loss, Exercise, and Wellness Treatment; NGF: Nerve growth factor; P: Patients; PMBD: Psychoeducation Manual For Bipolar Disorder; PRISM: Personalized Real-Time Intervention for Stabilizing Mood , QoL.BD: Quality of Life in Bipolar Disorder scale; SAI: Schedule for Assessment of Insight; SADS-C: Schedule for Affective Disorders and Schizophrenia, Change Version; SAS: Social Adjustment Scale; SCIT: Social cognition and Interaction Training; SCWT: Stroop Color-Word Test; SDMT: Symbol Digit Modalities Test; SIMSEP-BD: Systematic Illness Management Skills Enhancement Program Bipolar Disorder; SF-36: 36-Item Short Form Survey; SOFAS: Social and Occupational Functioning Assessment Scale; SRTAB: Self-reported treatment adherence behaviours; STAI-S: State Trait Anxiety Inventory; SWLS: The Satisfaction with Life Scale; TMTA: Trail Making Test-A; WHOQOL–BREF: World Health Organization Quality of Life, Brief version; WSAS: The Work and Social Adjustment Scale; YMRS: Young Mania Rating Scale.

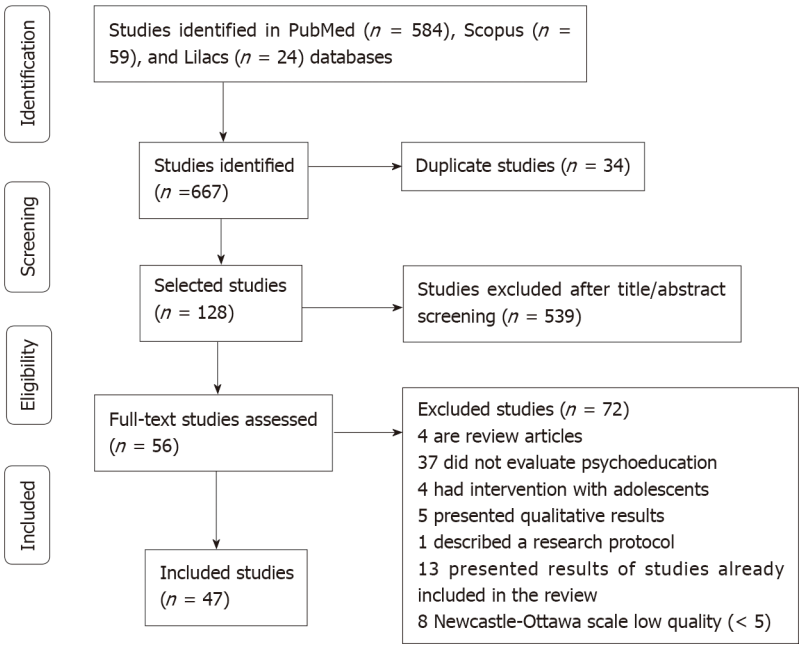

Figure 1 PRISMA flow diagram for studies evaluating psychoeducation in bipolar disorder.

Stabilizing Mood (PRISM)[25] were associated with a reduction in severity of mania symptoms. Depressive symptoms were less severe in patients submitted to MAPS-monitoring mood and activities (M), assessing prodromes (A), preventing relapse (P) and setting Specific, Measurable, Achievable, Realistic, Time-framed (SMART) goals (S)[32], integrative outpatient model (IOM)[38], and PRISM[25] interventions, when compared to control intervention. The online bipolar education program (BEP) was associated with a reduction in anxiety symptoms[39]. There was a reduction in the frequency of mood episodes in patients submitted to IMR[26] and MAPS[33]. Functional remediation (FR) was associated with improvement in functional status [28]. Social cognition and interaction training (SCIT)[14], FR[28], FFT[41], SIMSEP-BD [31], MAPS[32] and MS-PLUS[27] were not associated with changes in the severity of mood symptoms. FR did not influence the number of hospital admissions[28]. BEP [39], Beating bipolar online[29], and IOM[41] did not influence functional status. BEP was not associated with improvement in the quality of life or increased insight[29].

Studies with relatives of patients with BD: Nine clinical studies were included. Nine studies scored five or more stars[50-58] according to the NOS scale[13] (Table 3). There were seven randomized[50-52,54,58] and two nonrandomized studies[53,57]. Two studies evaluated euthymic patients[51,53]. Information regarding mood episodes was not available in seven studies[50-52,55-58].

Four studies diagnosed patients according to the DSM-III criteria[49,51-53], and four studies applied the DSM-IV[46-48,50]. One study did not state the BD diagnostic criteria[50]. Two studies assessed BD type I and BD type II patients[48,50]; three studies included exclusively BD type I patients[46,49,52]. Four studies did not specify

Table 3 Newcastle–Ottawa scale evaluation for studies that evaluated psychoeducation in relatives of patients with bipolar disorder

Ref.	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total
Hubbard *et al* [50], 2016	1	1	1	1	1	1	0	1	7
Fiorillo *et al* [51], 2015	1	1	1	1	1	1	1	0	7
Madigan *et al* [52], 2012	1	1	1	1	1	1	1	1	8
Reinares *et al* [53], 2008	1	1	1	1	1	1	1	1	8
Solomon *et al* [54], 2008	1	1	1	1	1	0	1	0	6
Reinares *et al* [55], 2004	1	1	1	1	1	1	1	0	7
Van Gent *et al* [56], 1991	1	1	1	1	1	0	1	0	6
Miklowitz *et al*[57], 2000	1	1	1	1	1	0	1	1	7
Simoneau *et al* [58], 1999	1	1	1	1	1	0	1	0	6

the BD type[45,47,51,53].

One hundred thirteen relatives were included in psychoeducation programs: one hundred and six were couples; twelve were sons/daughters; and ten were brothers/sisters. Fifty-four parents were included in the control groups, eighty-nine were couples, two were sons/daughters, six were brothers/sisters, and two were friends.

Psychoeducation programs aimed at family members of patients with BD: Psychoeducation interventions and outcomes are summarized in Table 4. Two studies[52,53] compared the program of pharmacotherapy and FFT and Crisis management with naturalistic follow-up (CMNF). There was no difference in the severity of mood symptoms after a one-year follow-up[52]. There was a reduction in the frequency of mood episodes in the FFT compared to the CMNF[52].

Three studies assessed the psychoeducational family intervention (PFI) strategy compared to a nonintervention control group[51,53,54]. There were no improvements in the frequency of mood episodes[50], adherence to treatment[53], or caregiver burden[55]. The group submitted to PFI showed a significant improvement in relation

Table 4 Extracted data from studies that evaluated psychoeducation in relatives of patients with bipolar disorder

Ref.	BD	Psychoeducation group			Group control			Applied scales/parameters	Results
		Psychoeducation strategy	*n* (%)		Intervention strategy	*n* (%)			
Hubbard *et al*[50], 2016	ND	GCPBD	18	8 Partner; 10 Parents	WL	14	3 Partner; 8 Parents; 1 Sibling; 2 Friend	DASS- 21	$P = 0.52$
								BAS	$P = 0.91$
								KBDS	$P > 0.05$
								BDSS	$P > 0.05$
Fiorillo *et al* [51], 2015	BD I	PFI	85	21 Parents; 44 Partner; 10 Son; 9 Sibling; 1 Other	WI	70	23 Parents; 31 Partner; 11 Son; 3 Sibling; 2 Other	Subjective burden	$P = 0.001$
								Professional help	$P = 0.001$
								Help in emergencies	$P = 0.01$
Madigan *et al*[52], 2012	ND	MFGP; SFGP	18; 19	ND	WI	10	ND	Caregiver knowledge	$P = 0.404$
								IEQ	$P = 0.795$
								GHQ12	$P = 0.723$
								WHOQOL Bref	$P = 0.355$
								GAF	$P = 0.617$
Reinares *et al*[53], 2008	BD I e II	PFI	57	35 Parents; 20 Partner; 2 Offspring/siblings	WI	56	27 Parents; 25 Partner; 4 Offspring/siblings	Amount of daily contact between the patient and the caregiver	$P = 0.757$
								Manic/hypomanic recurrence time	$P = 0.015$
								Medication adherence	$P = 0.611$
Solomon *et al*[54], 2008	BD I	MFGP; IFT	21; 16	ND	WI	16	ND	New mood episode	$P = 0.47$
								Hospitalization frequency	$P = 0.04$
								BRMS	$P = 0.44$
								HAM-D	$P = 0.12$
Reinares *et al*[55], 2004	BD I e II	PFI	30	17 Parents; 12 Partner; 1 Sibiling	WI	15	6 Parents; 6 Partner; 2 Son; 1 Sibiling	HAM–D	$P > 0.05$
								YMRS	$P > 0.05$
								Subjective burden of the caregiver	$P = 0.48$
								FES	$P = 0.22$
								Knowledge about the disorder	$P = 0.001$
Van Gent *et al*[56], 1991	ND	GT	14	14 Partner	WI	12	12 Partner	IPSQ	$P > 0.05$
								IPP	$P > 0.05$
								SCL-90	$P > 0.05$
Miklowitz *et al*[57], 2000	BD I	FFT	31	ND	CMNF	70	ND	New mood episode	$P = 0.042$
								Depressive symptoms	$P = 0.06$
								Manic symptoms	$P = 0.59$
Simoneau *et al*[58], 1999	ND	FFT	22	ND	CMNF	22	ND	KPI	$P > 0.05$

BAS: Burden assessment scale; BD: Bipolar disorder; BDSS: Bipolar disorder self-efficacy scale; BPRS: Brief psychiatric rating scale; BRMS: Bech-Rafaelsen Mania Scale; C: Control; CMNF: Crisis management with naturalistic follow-up; DAS: Disability assessment scale; DASS-21: Depression, Anxiety, Stress Scale; FES: Family Environment Scale (Cohesion, Expressiveness e Conflict)-Relationship subscales; FFT: Program of pharmacotherapy and family-focused

psychoeducational treatment; GAF: Global Assessment of Functioning; GHQ12: General Health Questionnaire 12; GCPBD: Guide for Caregivers of People with Bipolar Disorder; HAM–D: Hamilton Rating Scale for Depression–17-item; IEQ: Involvement evaluation questionnaire; IFT: Individual family therapy; IPP: Inventory of psychosocial problems; IPSQ: Interactional Problem Solving Questionnaire; KBDS: Knowledge of Bipolar Disorder Scale; KPI: Interactional coding system-assessed verbal and nonverbal communication behaviors of patients and their family; MFGP: Multifamily Group Psychoeducation; N: Total number l; ND: Not described; P: Psychoeducation; PFI: Psychoeducational family intervention; SADS-C: Schedule for Affective Disorders and Schizophrenia-Change Version; SCL-90: Symptom Checklist; SFGP: Solution Focused Group Psychotherapy; GT: Group therapy; WHOQOL Brief: World Health Organization Quality of Life, Brief version; WI: Without intervention; WL: Waiting list; YMRS: Young Mania Rating Scale.

to the perception of professional support received and help in times of emergency[51].

Two studies compared multifamily group psychoeducation, individual family therapy (IFT), and solution focused group psychotherapy (SFGP)[52,54]. There were no differences between these strategies regarding reduction in frequency of mood episodes[53,56], quality of life[52], or changes in functional status[53,54]. One study found that parents submitted to IFT reduced the incidence of hospital admissions[54].

The Guide for Caregivers of People with BD[50] was not associated with changes in relatives' symptoms of anxiety, depression or mania; stress discharge; knowledge of the disease; or changes in the caregiver burden[50].

DISCUSSION

Psychoeducation applied to BD patients and their relatives is associated with a reduction in the frequency of new mood episodes and a reduction in the number of hospital admissions and LOS. Psychoeducational interventions applied to patients contribute to improvement in pharmacological treatment adherence. Psychoeducation does not seem to influence the severity of depressive or manic symptoms or functionality. PMBD was associated with a higher adherence to pharmacological treatment and a higher quality of life in one study[23]. Psychoeducation strategies applied to relatives had no effect on adherence to pharmacological treatment.

Psychoeducational strategies in patients with BD are associated with a lower frequency of mood swings. These results are in line with a previous meta-analysis that evaluated 650 patients; 45% did not present a new mood episode compared to 30% of controls[54]. A possible explanation for this association is that the occurrence of subsyndromal symptoms is one of the main risk factors for new episodes[57,58]. Psychoeducational strategies in patients promote increased understanding about their own disease[59], improve the abilities of recognizing mood subsyndromal symptoms, enable early interventions, and might contribute to refraining new mood episodes[60]. Psychoeducational strategies also provide information about healthier lifestyles, sleep routines, exercise and stress management tips. All these steps are important to the maintenance of the euthymic state in BD[59].

Psychoeducation interventions were effective in reducing the frequency of hospitalizations and LOS and enhanced adherence to pharmacological treatment. Knowledge regarding their own illness might enrich comprehension of the importance of medication use and its effects on mood[61]. Moreover, a higher adherence to treatment is associated with monotherapy and reduced drug side effects[4,62]. Psychoeducational approaches to family members had no influence on treatment adherence.

When applied to patients and family members, psychoeducational approaches did not have an effect on mood severity symptoms, functionality or the quality of life of BD patients. Mood changes might lead to social, interpersonal and occupational impairments and contribute negatively to quality of life[63,64]. Depressive episodes are the most common and the most persistent affective states in BD and are the main cause of functional disability[4]. Residual and persistent depressive symptoms, cognitive decline, sleep deprivation, past history of psychotic symptoms[65,66], current presence of psychiatric comorbidities, use of psychoactive substances[65-68], long course of the disease, number of mood episodes[69-71], and hospitalizations[72] are associated with a reduction in functionality[73].

Family member psychoeducation is related to a lower frequency of mood swings and to a reduction in LOS. As family members acquire knowledge of the disease, they become more able to help patients identify early mood changes, apply assertive strategies to deal with daily situations and crisis management[48,74]. Through the provision of care, acceptance of the disease and dialogue, family members present themselves to the patient as a source of aid and support for decisions about their treatment[75-77].

In regard to the limitations of the present study, we might consider meta-analysis to be unable to be performed, owing to the methodological differences between heterogeneous studies (sample size, duration of follow-up, main results, type of comparison group), the population characteristics (severity, comorbidity, clinical status of patients in recruiting phase) and the intervention itself (target population, format, content, duration). All of these factors hamper the generalization of the results. In addition, the findings of the present study reveal that the characteristics of the sampling must be carefully considered. Patients with severe chronic disease may have poorer treatment responses. Future research to clarify the effectiveness of psychoeducation and to identify the determinants of response to treatment might be required for this population.

CONCLUSION

The data from this systematic review show the positive effects of the psychoeducational intervention on both patients and family members. Despite the lack of effectiveness in some parameters, psychoeducation has been associated with other treatments as an additional intervention. It is recommended that additional studies should approach strategies that aim to maximize the benefits of those therapies, adding interventions focused on family and interpersonal relationships.

ARTICLE HIGHLIGHTS

Research background

The bipolar disorder (BD) treatment is challenging, and there is some evidence that non-pharmacological interventions promote effects in the treatment of acute mood episodes and maintenance treatment. Psychoeducation is an intervention strategy based on providing patients and/or relatives with information about the disorder to enhance their understanding and enable early identification of warning signs and mood changes, improving treatment adherence, and have showed some results in order to help the BD treatments.

Research motivation

Even using adequate drug strategies, BD is characterized by high rates of occurrence of mood episodes, number of hospital admissions, and a progressive impairment. We aimed to summarize the best evidence of psychoeducation in the treatment of BD, considering patients and their family members.

Research objectives

This systematic review aims to investigate the role of psychoeducation in BD in patients and in their family members.

Research methods

A systematic search of original studies on psychoeducation with patients with Bipolar Affective Disorder and their families was carried out using Medline, Scopus and Lilacs databases. A data extraction table was created based on the Cochrane model and the methodological quality of the studies was assessed according to the criteria of the Newcastle-Ottawa scale.

Research results

Psychoeducation applied to BD patients and their relatives is associated with a reduction in the frequency of new mood episodes and a reduction in the number of hospital admissions and length of stay. Psychoeducational interventions applied to patients contribute to improvement in pharmacological treatment adherence, although the same effect it is not observed when applied to relatives. Psychoeducation does not seem to influence the severity of depressive or manic symptoms or functionality.

Research conclusions

Psychoeducation as an adjunct strategy to pharmacotherapy has been shown to be effective in the treatment of Bipolar Affective Disorder.

Research perspectives

To systematize the effectiveness of psychoeducation intervention on BD patients and family members.

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