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OPINION REVIEW

False dogmas in mood disorders research: Towards a nomothetic network approach

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Abstract

The current understanding of major depressive disorder (MDD) and bipolar disorder (BD) is plagued by a cacophony of controversies as evidenced by competing schools to understand MDD/BD. The DSM/ICD taxonomies have cemented their status as the gold standard for diagnosing MDD/BD. The aim of this review is to discuss the false dogmas that reign in current MDD/BD research with respect to the new, data-driven, machine learning method to model psychiatric illness, namely nomothetic network psychiatry (NNP). This review discusses many false dogmas including: MDD/BD are mind-brain disorders that are best conceptualized using a bio-psycho-social model or mind-brain interactions; mood disorders due to medical disease are attributable to psychosocial stress or chemical imbalances; DSM/ICD are the gold standards to make the MDD/BD diagnosis; severity of illness should be measured using rating scales; clinical remission should be defined using threshold values on rating scale scores; existing diagnostic BD boundaries are too restrictive; and mood disorder spectra are the rule. In contrast, our NNP models show that MDD/BD are not mind-brain or psycho-social but systemic medical disorders; the DSM/ICD taxonomies are counterproductive; a shared core, namely the reoccurrence of illness (ROI), underpins the intertwined recurrence of depressive and manic episodes and suicidal behaviors; mood disorders should be ROI-defined; ROI mediates the effects of nitro-oxidative stress pathways and early lifetime trauma on the phenome of mood disorders; severity of illness and treatment response should be delineated using the NNP-derived causome, pathway, ROI and integrated phenome scores; and MDD and BD are the same illness.

Key Words: Nomothetic network psychiatry; Depression; Mood disorders; Affective disorders; Inflammation; Oxidative and nitrosative stress; Neuro-immune

Core Tip: We review the merits of machine learning-derived nomothetic network psychiatry (NNP) models of mood disorders. The NNP models of mood disorders show that major depressive disorder/bipolar disorder are not mind-brain or psycho-social but systemic medical disorders. The DSM/ICD taxonomies are counterproductive. A shared core, namely the reoccurrence of illness (ROI), underpins the intertwined recurrence of depressive and manic episodes and suicidal behaviors. Mood disorders should be ROI-defined. ROI mediates the effects of nitro-oxidative stress pathways and early lifetime trauma on the phenome of mood disorders. Severity of illness and treatment response should be delineated using NNP-derived causome, adverse outcome pathways, ROI and phenome scores.

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INTRODUCTION

The current status-quo view is that mood disorders are disorders of the brain associated with chemical imbalances and should be regarded as mental disorders with a multi-factorial etiology. The status-quo is that mood disorders should be diagnosed using DSM criteria[1] or ICD[2] criteria and that different subtypes of mood disorders exist including unipolar [major depressive disorder (MDD)] and bipolar disorder (BD), either manic or a major depressive episode (MDE). It is thought that MDD and BD-type 1 (BP1) are qualitatively distinct categories, although MDD and BD-type 2 (BP2) show quantitative differences. Furthermore, both MDD and BD show many comorbidities with neurological and medical disease and depression due to these conditions may be explained by psychosocial factors including loss of health or independence. Moreover, the status-quo dictates that severity of illness should be measured using the summed score of items of rating scale scores that assess depressive symptoms.

The conceptual MDD/BD frameworks are plagued with a cacophony of controversies, as evidenced by competing and even mutually antagonistic approaches to understanding these disorders including psychoanalysis (depression is a defense against loss and mourning), psychodynamic psychiatry (depression is the consequence of a pathological object relationship between parts of the self), commonsense or folk psychology (depression is a response to a psychological problem), self-system therapy (the primary factor in depression is problematic self-regulation), systemic therapy (systems *e.g.*, the family create depression), biological psychiatry (depression is the consequence of chemical aberrations in the brain, *e.g.*, a deficiency in serotonin), animal experiments (depression is sickness behavior or is the consequence of learned helplessness), the biopsychosocial model (biological as well as psychosocial factors are involved), cognitive-behavioral therapy (depression is the consequence of negative cognitions), cognitive neuropsychiatry (cognitive impairments in memory or attention are involved), the mind-brain dualism (mental and neural processes interact to cause depression), postpsychiatry (community development and engagements with communities are central and boredom and depression are the characteristic moods of our epoch), molecular psychiatry (genes and intracellular networks explain depression) and pan-omics and precision psychiatry (pan-omics data will reveal the true nature of depression phenotypes or transdiagnostic pathway-phenotypes). A latest new development, which indicates that contemporary psychiatry faces a profound crisis, is critical psychiatry with psychiatric survivor networks which question psychiatric practice, treatment, scientific methods, knowledge base, and the decontextualization of experience, and accuse status quo psychiatrists of harmful and unethical principles[3-5].

Another new direction in psychiatry is the research domain criteria (RDoC) developed by the National Institute of Mental Health (NIMH)[6]. Apart from criticizing and further undermining the credibility of the DSM categorizations, RDoC relies on dimensions as critical measures of psychopathology, which arises from aberrations in neural circuits in the brain, and should be examined by a matrix with 8 columns (genes, molecules, cells, circuits physiology, behavior, self-reports and paradigms) and a number of rows including memory, rewards, threat and perception. Nevertheless, there is no evidence base for the RDoC matrix approach which is developed in a top-down manner.

All medical disciplines, except psychiatry, are exclusively based on nomothetic network definitions of disease, as a default mode of clinical and research operations. The term "nomothetic" means the tendency to derive laws from indicator (independent) variables, which explains the variability in phenomena and allows us to generalize the model[7-9]. Nomothetic definitions include a variety of biological signatures which correspond to clinical measures and constitute drug targets for

implementation of treatment. For example, the diagnosis of atherosclerosis, implies that the patient suffers from atherosclerotic plaques caused by a defined process which progressively worsen. In contrast, the diagnosis of MDD and BD according to DSM/ICD criteria are mere de-contextualized narratives devoid of any explanatory mechanisms.

The aim of this paper is to review the many false dogmas which determine current research in mood disorders; and to discuss these flaws with respect to the new, data-driven, machine learning method to model psychiatric illness, namely nomothetic network psychiatry (NNP)[10-13]. In line with a dichotomy[14], it could be considered that there is a co-existing of two major types of scientific psychiatric knowledge. The first is idiographic and is driven by "understanding" of subjective experiences and inter-subjective narratives, and the second is nomothetic and is governed by laws of natural and mathematical sciences representing explanatory models of disease[15,16]. With every respect and awareness of the values represented in subjective narrative and relevant cultural contexts [17], in this review we focus on the many caveats in scientific psychiatry which undermine the nomothetic approach. Moreover, we show that our novel nomothetic models also contain subjective experiences of the patient and that these idiographic experiences increase the richness and complexity of the nomothetic models. Finally, we will introduce a new mathematical index reflecting the reoccurrence of illness (ROI), which is a key factor in our nomothetic models[18,19].

NNP

NNP models

None of the previous psychiatric models tried to reunite the different buildings blocks of an illness into a data-driven model which includes causome and protectome features (or a deduced risk/resilience ratio), adverse-outcome pathways (AOPs), brainome features (the aggregate of aberration in brain regions), cognitome features (the aggregate of cognitive impairments), and ROI, symptomatome (the aggregate of different symptom domains or clinical phenotypes), and phenomenome (the self-description of the self-experience of the illness) features[10-13].

Figure 1 displays a theoretical framework of MDD/BD which is based on current state-of-the-art knowledge and causal reasoning and reunites the different building blocks into a causal model. It should be noted that this framework allows for the entry and analysis of a wide range of data into the model, including genome (genomics) and environmentome (psychosocial aspects, context-centered hermeneutic data), pan-omics data, functional brain imaging including connectome data, neurocognitive test results, descriptive psychopathological assessments including symptoms rated *via* interviews, and idiographic or phenomenological features as assessed with self-rating scales, including health-related quality of life (HR-QoL) data.

This theoretical causal framework can be tested and validated using partial least squares (PLS) pathway analysis[10-13]. Figure 2 shows the outcome of such a PLS model (NNP1) comprising causal links between three risk/resilience ratios, namely early lifetime trauma (ELT) indicators and paraoxonase (PON)1 genotype combined with PON1 enzymatic activity, two AOPs, namely an antioxidant and a neuro-oxidative toxicity indicator, one ROI-index, and the phenome of mood disorders[10]. In NNP1, the severity of ROI is represented as a reflective latent vector extracted from the number of lifetime depressive episodes in MDD, (hypo)manic and depressive episodes in BD and number of lifetime suicidal attempts in either MDD or BD[10]. The phenome of mood disorders is conceptualized as a factor (latent vector) extracted from symptomatome features (severity of depression, anxiety and global clinical impression and current suicidal ideation) and phenomenome features, including self-rated disabilities (scoring three subdomains, namely work/school, social and family) and self-rated HR-QoL (four subdomains, namely physical and psychological health, and social relationships and environment)[10].

Simeonova *et al*[12] constructed another NNP model (NNP2) whereby indicants of increased bacterial translocation [increased immunoglobulin (Ig)A and IgM responses to lipopolysaccharides (LPS) of specific Gram-negative bacteria] were entered as causome factors leading to three AOPs, namely increased autoimmune responses to oxidized low-density lipoprotein, peroxide levels and IgM responses to a multitude of oxidative specific epitopes. These three AOPs and an ROI index significantly predict the phenome which was conceptualized as a factor extracted from the severity of illness score, the presence of mood disorders, MDD and BP1, treatment resistance and melancholia.

Figure 3 shows how PLS analysis was employed to construct and validate novel NNP models. As explained previously, different statistical tests should be used to validate the outer and inner models and the PLS models[11]. Goodness of fit should be checked with standardized root mean square residuals to avoid model misspecifications. The validity reliability of the latent factors should be checked using composite reliability, rho A, or Cronbach's alpha and the average variance extracted. All indicators of the latent vectors should display loadings > 0.5 or by preference > 0.66[10-12] and Confirmatory Tetrad Analysis should be employed to check whether the latent factors are not mis-specified as reflective models. Other tests including blindfolding and PLS predict with 10-fold cross-validation and may be used to assess the predictive value of the model[10-13]. There are different

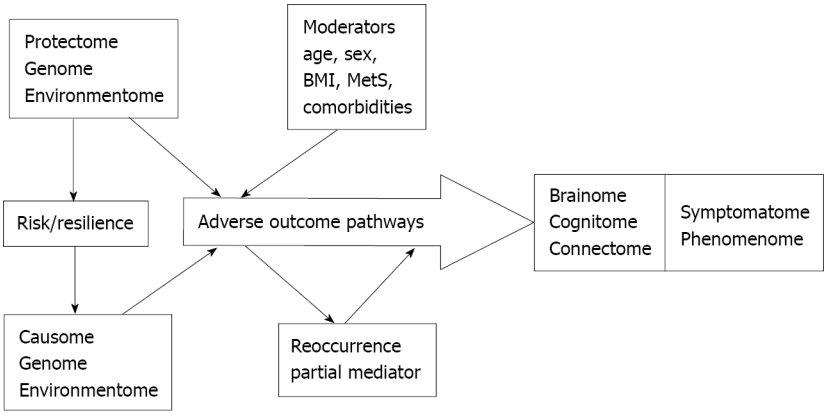

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Figure 1 Theoretical framework of mood disorders. Adapted from Maes *et al*[10]. BMI: Body mass index; Mets: Metabolic syndrome.

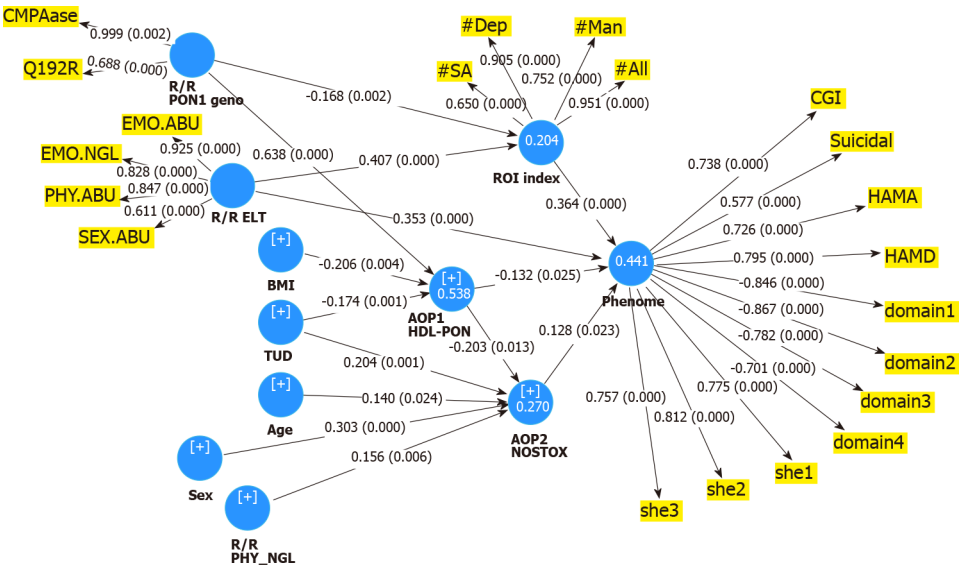

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Figure 2 Results of partial least squares analysis. R/R: Risk/resilience; AOP: Adverse outcome pathways; PON1: Paraoxonase; ELT: Early lifetime trauma; EMO.ABU: Emotional abuse; EMO.NEGLECT: Emotional neglect; PHY.ABU: Physical abuse; PHY.NGL: Physical neglect; SEX.ABU: Sexual abuse; BMI: Body mass index; HDL: High density lipoprotein cholesterol; NOSTOX: Nitro-oxidative stress toxicity; ROI: Reoccurrence of illness; Dep: Depressive; Man: (Hypo)mania; SA: Suicide attempts; CGI: Clinical global impression; HAMD/HAMA: Hamilton Depression and Anxiety Rating Scale; Domains (1-4): Domains of the WHO-Quality of Life questionnaire; She (1-3): Sheehan Disability Scale (domains 1-3).

methods to determine, a priori, the estimated number of cases including methods based on the psychometric properties and the strength of the intercorrelations among the factors and the factor loadings, the number of arrows pointing to a latent factor and its explained variance, and power analysis specific to multiple regression analysis[11]. An advantage is that these methods show that relatively small sample sizes of 70-127 cases may be sufficient to achieve a power of 0.8[11]. Most importantly, complete PLS analysis conducted on bootstrapped samples (*e.g.*, 5.000) allows to compute the path coefficients with *P* values as well as the specific indirect, total indirect and total effects. This method allows to examine multi-step and multiple mediation paths as for example the links from PON1 genotype to ROI to phenome, and PON1 genotype to AOP1 and to AOP2 to phenome.

As such we were able to build reliable and replicable, bottom-up, data-driven nomothetic models of BD/MDD, which comprise key features of mood disorders assembled in a knowledge-based causal framework as indicated in Figures 1 and 2[10-13]. These NNP models integrate phenome with functional and molecular pathways and, therefore, "translate" those pathways into phenome features thereby objectivating the clinical phenome, a method named "reification of the clinical diagnosis"[10-13]. The NNP method also allows to construct pathway-phenotypes (biosignatures), for example, by constructing latent vectors which comprise pathway and phenome features[20] and pathway classes, as described in the next section.

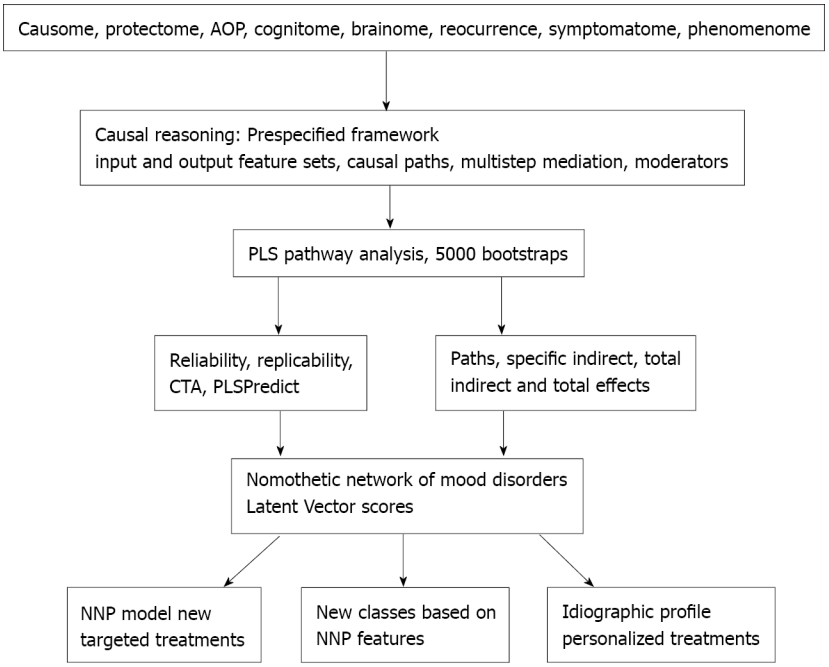

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Figure 3 How to construct nomothetic network psychiatry models and disclose new patient clusters. AOP: Adverse outcome pathways; PLS: Partial least squares; CTA: Confirmatory Tetrad Analysis; NNP: Nomothetic network psychiatry.

Importantly, our NNP models may pass critical rationalism tests as proposed by Popper[21]. First of all, our NNP models can be refuted or corroborated and, thus, are falsifiable. Second, our NNP frameworks are based on state-of-the-art knowledge including on causome, protectome, AOP, and phenome data and, thus, are progressive. Third, new research should elaborate on our NNP models and enrich the indicators or feature sets with pan-omics and brainome data, delete less robust features and therefore, our models are changeable and provisional. Finally, through feature selection (only significant indicators are included in the model) and feature reduction (latent vectors are constructed based on strongly related indicators), our NNP models are parsimonious representations of the building blocks of the illness.

NNP networks reveal drug targets at the model and idiographic level

Once the nomothetic network is constructed, latent variable scores may be calculated which reflect the severity of causome factors, interactions between causome and protectome factors (for example, integrated in a risk/resilience ratio), different AOPs, the ROI-index and the phenome. These latent variable scores, therefore, reflect severity of the different building blocks of the illness. Our NNP models also contain idiographic features as for example self-rated severity of depression and anxiety, and self-rated HR-QoL and disabilities[10]. As a consequence, those latent variable scores not only define the nomothetic network model, but also an idiographic image or feature profile which is unique for every individual.

Consequently, our NNPs disclose new drug targets: (1) At the model level, namely causome factors such as PON1 activity, ELT, bacterial translocation; AOPs, including damage due to oxidative and nitrosative stress (O&NS) and lowered antioxidant defenses, and ROI, which is in part determined by causome features; and (2) In each individual because the idiomatic profile discloses specific aberrations.

New classifications based on NNP features

The NNP factor scores may be employed in consequent unsupervised machine learning techniques including clustering analysis methods to expose novel natural clusters of patients. Previously[10-12], we used K-median, Two-step, K-mean, Ward and Forgy's clustering analysis to discover new categories based on the causome, AOPs, ROI and phenome latent vectors. Cluster analysis conducted on NNP1 models disclosed that 69.5% of mood disorder patients were allocated to a cluster with increased causome factors (interaction PON1 genotypes and PON1 enzymatic activity and ELT), O&NS-associated AOPs and increased ROI and phenome scores. Cluster analysis conducted on the NNP2 model showed that around 70% of the patients were allocated to a cluster with increased bacterial translocation, O&NS-associated AOPs and phenome severity[12]. Consequently, we have proposed to name the clusters with high causome, AOP, and ROI scores "Major DysMood Disorder due to neuro-affective toxicity" and the cluster with normal causome and AOP scores "DysMood Disorder"[10,12].

NNP-associated pathways

Nevertheless, both NNP1 and NNP2 are limited in that they focus on O&NS-related and bacterial-derived features and do not comprise other well-known causome/AOP factors of mood disorders, such as indicants of activated immune-inflammatory pathways[22]. The latter will be addressed in other NNP models as reviewed in false dogmas in mood disorders. Using (un)supervised learning techniques, we repeatedly showed that large subgroups of patients with mood disorders (MDD or MDE) show signs of immune activation including increased expression of T cell activation markers such as CD7+, CD25+ and CD2+, human leukocyte antigen (HLA)DR+ and cell surface antigens such as CD25+ [interleukin (IL)-2 receptor], class II Major Histocompatibility Complex HLA-DR, CD4+CD45RA, CD4+CD45RA+ and surface Ig[23,24]. These findings were further corroborated by data that mood disorders are accompanied by: (1) Increased levels of pro-inflammatory cytokines including IL-2, IL-1β, interferon (IFN)-γ and tumor necrosis factor (TNF)-α; (2) Increased expression of positive acute phase proteins such as haptoglobin and C-reactive protein (CRP); and (3) Lowered levels of negative acute phase proteins including albumin[22,25]. Based on these findings, there is now evidence that MDD/BD are immune-inflammatory and O&NS (IO&NS) disorders[22,25].

Enrichment and annotation analysis using the Gene Ontology knowledgebase pathways (Gene Ontology Resource) indicates that the protein-protein interactions in mood disorders are associated with peripheral IO&NS pathways which are highly significantly associated with a response to a bacterium, a response to LPS, or a cellular response to LPS, indicating that the increased bacterial translocation established in NNP2 is causally associated with IO&NS pathway activation (Maes *et al*, personal data). Moreover, the GO computational model of biological systems (Gene Ontology Resource) also shows that the IO&NS profile established in mood disorders is accompanied by different impairments in neuronal functions including microglial cell activation and neuroinflammation, positive regulation of gliogenesis, modulation of chemical synaptic transmission, synapse assembly, neurogenesis and neuroblast proliferation, axonogenesis, regulation of axon extension, retrograde axonal transport, synaptic pruning and more functional and molecular pathways (Maes *et al*, personal data). As explained previously, the pathway findings in mood disorders may be summarized as indicating increased neurotoxicity and reduced neuroprotection leading to IO&NS-induced neuro-affective toxicity[22,25].

Recently, dysfunctional and degenerative processes were established in the brain of mood disorder patients. For example, altered expressions of connectome circuits in the brain were established including downregulated anterior insula connectivity, and upregulated circuits from middle frontal gyrus and hippocampus to the frontal eye fields, the anterior insula to the amygdala and middle frontal gyrus to the amygdala (Kandilarova *et al*[26], to be submitted). Moreover, using a voxel-based morphometry method using a 3T magnetic resonance imaging (MRI) system, Kandilarova *et al*[26] reported that MDD is characterized by significant reductions in grey matter volume in anterior cingulate cortex and medial frontal and regions on the left side, and inferior frontal gyrus, middle frontal gyrus, medial orbital gyrus and middle temporal gyrus on the right side. Such gray matter degeneration and dysfunctional brain connectome circuits may be predicted by increased neurotoxicity affecting brain functions and neuronal circuits[22,25]. It follows that our NNP1 and NNP2 models should be enriched with connectome (fMRI measurements) and brainome (*e.g.*, MRI measurements) features, yielding causal pathways from peripheral or gene X environmental interactions to peripheral AOPs to central AOPs to connectome and brainome to ROI to phenome. We will now discuss false dogmas in mood disorders research with respect to the new knowledge obtained in our NNP models.

FALSE DOGMAS IN MOOD DISORDERS

False dogma 1: Mood disorders are mind-brain disorders that are best conceptualized using a bio-psycho-social model or mind-brain interactions

MDD/BD is most often conceptualized as a brain - mind illness as it is thought that the brain mediates the mind and that psychosocial factors may alter the brain - mind axis to cause mood disorders[27]. Another predominant view is that MDD/MDE are brain disorders which are caused by a faulty mood regulation as a consequence of interactions between a number of factors including biological features, genetic vulnerability, psychosocial stressors including losses and ELT, temperament and comorbidities [28]. Other theories posit that psychosocial stressors cause changes in chemicals (*e.g.*, serotonin) especially in the brain regions which mediate mood, affection and reward including the thalamus, amygdala and hippocampus[28]. According to Kendler[29], the goal should be to understand how the psychosocial environment interacts with the networks within the mind-brain system that cause psychiatric illnesses. Accordingly, Kendler[29] proposed a philosophical structure for psychiatry with the acceptance of a bidirectional brain to mind and mind to brain causality. Nevertheless, the discussions as exemplified in Kendler[29]'s paper are reductionist. Why would psychosocial stressors be the sole stressors that induce MDD/MDE, while other environmentome variables such as viral and bacterial infections, environmental toxins and dietary factors are not taken into account?

Nevertheless, as described in NNP-associated pathways, we have shown that MDD/BD may have a peripheral origin and as a consequence should be regarded as a systemic disease. There is a growing realization that the AOPs of mood disorders are 'holistic' in nature comprising not only central but also peripheral processes. Thus, NNP2 showed that increased gut permeability and increased peripheral levels of neurotoxic substances (including LPS) are major causome factors in mood disorders which, in turn, may cause activated peripheral IO&NS pathways and neuroinflammation[22,25,30]. Our NNP models showed causal links from strictly peripheral factors (bacterial translocation) or gene X environmental interactions (PON1 gene x ELT) to AOPs (IO&NS pathways) and ROI to phenome. Enrichment and annotation analysis show how these peripheral pathways may cause neuro-affective toxicity which may explain fMRI and 3T MRI findings and the phenome of mood disorders (see NNP-associated pathways). Moreover, it should be added that a larger part of the variance in the severity of the phenome is explained by direct and indirect effects of causome, AOP and ROI features, namely around 57.7% and 44.2% in NNP2 and NNP1, respectively[10,12]. This evidence contrasts the view that mood disorders should be regarded as pure brain disorders or mind-brain disorders and that mind to brain causality and or psychosocial stress to brain dysfunctions are the main drivers of the illness.

False dogma 2: Mood disorders due to brain disease are attributable to psychosocial stress or chemical imbalances

A number on neurological brain disorders are associated with MDD/MDE (symptoms) including Parkinson's and Alzheimer's disease, multiple sclerosis, stroke and Huntington's disease[31]. The widely held belief is that comorbid depression is caused by chemical imbalances in the brain (*e.g.*, dopamine and serotonin), or that it is the result of negative thoughts following a diagnosis, helplessness, severe stress from living with a medical disorder, loss of independence or as a side effect of medication used to treat brain disorders[28]. Nonetheless, comorbid depression may worsen the morbidity and cause increased mortality of some brain disorders and the existence of depression may precede some neurological disorders, such as Alzheimer's and Parkinson's disease, implying that depression is a key component of these conditions[31].

In addition, in these neuro-immune and neurodegenerative brain disorders, depressive symptoms are associated with increased IO&NS pathways. For example, depression due to multiple sclerosis is associated with increased IL-6 and lowered albumin[32]. Depression due to stroke is largely predicted by hypertension and atherosclerosis as indicated by white matter hyperintensities (assessed with T2-weighted and fluid-attenuated inversion recovery MRI) and the volume of the acute stroke lesions (measured with diffusion-weighted MRI)[33]. White matter hyperintensities are a consequence of a chronic mild inflammatory process while the acute stroke lesions are accompanied by peripheral and central IO&NS responses[34-36]. The severity of the disabilities induced by stroke was not associated with the onset of depressive symptoms, indicating that the latter are a consequence of IO&NS pathways associated with the cause of stroke (atherosclerosis) as well as the systemic inflammation and neurodegeneration due to stroke[33]. In schizophrenia, another systemic neuro-immune disease[20], the severity of depression and manic symptoms is significantly associated with IO&NS indicants including increased levels of IL-6, high mobility group box1 and cytokine-induced activation of the tryptophan catabolite pathway[37,38]. In temporal lobe epilepsy (TLE), depression, anxiety and excitation aggregate with the clinical hallmarks of the illness (including seizure frequency, controlled *vs* uncontrolled TLE, presence of post-ictal confusion and aura) and a latent vector extracted from these clinical features is associated with PON-1 genotype-associated reductions in enzyme activity[39,40]. Furthermore, affective symptoms in TLE are strongly associated with protein oxidation and aldehyde formation and lowered-thiol groups indicating that damage to oxidative stress plays a key role in affective symptoms due to TLE[39,40]. In Parkinson's disease, increased CRP, and chemokine (C-C motif) ligand 2 (a pro-inflammatory chemokine) are associated with the severity of depressive symptoms[41].

To sum it up, the current theory that depression in neuroinflammatory and neurodegenerative brain disorders is caused by psychological stress or chemical imbalances in neurotransmission is at best skewed toward reductionism and should be abandoned in favor of the novel findings that (neuro)inflammatory processes are to blame for these disorders' associated mood symptoms.

False dogma 3: Mood disorders due to comorbid systemic illness are attributable to psychosocial stress

According to the ABC of psychiatric medicine, depression caused by medical diseases is explained by a variety of stressors linked to the illness, such as functional losses, the personal meaning ascribed to these stressors and attitudes about the illness itself[42]. Furthermore, personality traits, social support and stage of life, as well as earlier experiences, modify those personal meaning and beliefs[42]. Once sadness, anxiety and somatic distress appear, the risk to develop depressive disorders and persistent subthreshold symptoms is increased and modified by social support, medical complications, genetic loading and coping strategies.

It appears that these authors and the psycho-social school in general take for granted that a load on the mind-brain pathway causes depression, a folk psychology explanation. Folk or commonsense psychology explains the "mental state" of behaviors as the outcome of daily life experiences, as for

example, "depression" is a response to a perception, pain, a belief, *etc*[11]. Based on these folk-like theories, treatment plans are then worked out to treat depression due to medical disease and these comprise advice, education and reassurance, specialized cognitive or dynamic behavioral psychotherapies, interpersonal therapy, problem solving and of course antidepressant treatment[41]. Some of these treatments may even be performed by non-specialists in primary and secondary care, including cognitive therapy to correct distorted thinking, encourage a sense of mastery and promote more accurate coping strategies.

Nevertheless, this psycho-social dogma fails to explain how or why the mind or mental pathways could lead to the behavioral and cognitive changes associated with MDD/MDE. In fact, depression due to a variety of medical illnesses may be attributed to the activated IO&NS pathways which characterize these disorders[31]. Thus, diabetes mellitus type 1 and 2, rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, lupus erythematosus, chronic obstructive pulmonary disease, chronic kidney disease and psoriasis are all IO&NS disorders accompanied by a significantly higher prevalence of mood disorders[31]. The post-partum period, blood dialysis and IFN-α treatment are frequently accompanied by depression and also these conditions are characterized by activated IO&NS pathways [31].

New evidence shows that activated peripheral IO&NS pathways are directly associated with depressive symptoms in medical disorders. For example, depression is strongly comorbid with chronic apical periodontitis (CAP)[43]. Root canal LPS levels are increased in patients with CAP and are significantly associated with clinical depression due to CAP, as well as with severity of depression and HR-QoL[43]. Moreover, MDD due to CAP is characterized by increased indicants of O&NS including increased nitric oxide metabolites, lipid hydroperoxides and advanced oxidation protein products[43].

Moreover, previous NNP research examining depression associated with medical disease demonstrated that depressive and anxious symptoms are part of the same clinical core that encompasses the characteristics of those medical disorders. For example, in atherosclerosis and unstable angina, depression severity is substantially associated with the same core (latent vector), which also includes clinical characteristics such as atherosclerosis, unstable angina, class III/IV unstable angina and enhanced atherogenicity and insulin resistance[43]. The latter features are reflective manifestations of a common core, namely severe heart disease, which, therefore, is the cause of its manifestations. Moreover, a larger part of the variance (66.6%) in this common core was explained by peripheral IO&NS pathways[44].

A recent NNP constructed in children with depression due to transfusion-dependent thalassemia showed that depressive symptoms are strongly associated with indicants of peripheral iron-overload and immune-inflammatory responses caused by thalassemia and the repeated transfusions[45]. Moreover, the constructed NNP model showed that iron-overload indices (increased iron and ferritin) and immune-inflammatory biomarkers (increased IL-1β, TNF-α and IL-10) and key depressive subdomains such as sadness, physio-somatic symptoms (fatigue and pain), social isolation and irritability symptoms and lowered self-esteem belong to the same core. Furthermore, 73.0% of the variance in this common core was explained by number of transfusions and hospital admissions and use of Desferal[45].

We constructed another NNP in depression due to type 2 diabetes mellitus and established that 61.7% of the variance in depressive and anxiety symptoms could be explained by indicants of immune activation and the combined effects of insulin resistance and atherogenicity, which partially mediated the effects of immune activation on depressive symptoms[46]. In patients with depression and anxiety due to established coronavirus disease 2019 infection, we found that 70.0% of the variance in the severity of affective symptoms was explained by the combined effects of lung inflammation (as assessed with lung computed tomography scan) and reduced oxygen saturation and that these effects were partially mediated by IL-6, IL-10, CRP, soluble advanced glycation products and lowered albumin[47]. Overall, the current view that depression caused by medical disorders should be explained by losses or beliefs about the illness is at best reductionist and should be replaced by NNP models indicating that activated IO&NS pathways in medical disease are responsible for comorbid depression.

False dogma 4: DSM/ICD are the gold standards to make the MDD/BD diagnosis

MDD/MDE are commonly defined as a cluster of symptoms which are more severe than sadness and may be discriminated from the latter by the duration of symptoms (more than two weeks according to DSM) and the number of symptoms (more than 5 in DSM). However, the decision whether a patient suffers from MDD/MDE rather that a sadness reaction is made by the clinician (either psychiatrist or general practitioner) who will treat the patient with antidepressants depending on whether MDD is present or not. BD formerly known as manic-depressive psychosis is characterized by recurrent episodes of MDE and mania (BP type 1) or hypomania (BP type 2). ICD classifies "mood disorders" which is further subdivided into MDD and BD, whereas the DSM-5 classifies two separate categories, namely MDD and BD[1,2].

Nevertheless, there are several serious problems with the DSM/ICD case definitions of MDD, MDE and BD, BP1 and BP2. First, the case definitions are often unreliable with an intraclass kappa reliability of 0.28 indicating minimal agreement among psychiatrists[48,49]. Furthermore, the DSM case definitions of affective disorders are unreliable and invalid[49,50]. BD is often over diagnosed with

studies showing that only 42.9% of patients diagnosed with the DSM criteria of BD meet the diagnostic criteria[50]. The misdiagnosis rate is associated with the low demarcation of BD from personality disorders including borderline personality disorder, polysubstance abuse and attention deficit disorder [50]. BD patients are often misclassified as suffering from MDD or other conditions with a rate as high as 60%[51]. Another major problem is that the diagnosis of BD is often underrated when the patient presents with a depressive index episode and an atypical course of manic or hypomanic symptoms[50].

A more fundamental flaw of the DSM/ICD case definitions of mood disorders is their top-down manner of generation[11]. Both taxonomies diagnose mood disorders prior to biomarker and neurocognitive investigation, treating these features as ancillary data that may or may not support the diagnosis [10-13]. Most current biological, neurocognitive and molecular research employs these top-down case definitions as independent variables, while the key features and even causome, protectome and cognitome features are employed as dependent variables in statistical analyses. Nevertheless, causal reasoning indicates that those features should be the explanatory variables, while the diagnosis of mood disorders is a higher-order concept constructed using these features[10-12]. Based on these inadequate model assumptions, researchers then use unreliable diagnostic classes, based on value laden and controversial criteria, as explanatory variables in analysis of variance to analyze biomarker levels, brainome data, and neurocognitive test scores and sometimes even causome/protectome data. As such, current biomarker research continues to employ unreliable diagnostic classes applied in inadequate model assumptions further confounded by the use of inappropriate statistical analysis[10,11]. Overall, no falsification of the dogma-like, top-down DSM/ICD classes or criteria is possible using data from sources other than the DSM/ICD, precluding a deductive approach[11].

False dogma 5: Severity of illness should be measured using rating scales

Another gold-standard dogma is that the severity of mood disorders should be assessed using rating scales such as the Hamilton Depression Rating Scale (HDRS)[52]. Instruments which aim to assess severity of depression encompass a number of observable or self-rated symptoms including loss of interest, sadness, fatigue, concentration problems, insomnia, lowered self-esteem, feelings of worthlessness or suicidal ideation. Because psychiatrists consider such symptoms to be reflective measurements of an underlying phenomenon, they typically add the scores on the separate items and construct an unweighted sum-score, which is thought to reflect severity of illness. However, to compute such sum scores, rating scales should be unidimensional, *i.e.*, all items should load heavily on one primary factor that has additional adequate psychometric properties[53,54]. We discussed before[54] that the indicators of latent vectors should have loadings > 0.5 with Cronbach alpha > 0.7, composite reliability > 0.8, and average explained variance > 0.5 while Confirmatory Tetrad Analysis should show that the model is not mis-specified as a reflective model. Our analyses showed that the HDRS (and other scales as well) do not comply with these criteria and that the total unweighted sum of the items may not be used as a severity index. Fried *et al*[53] reported that the HDRS and other commonly used rating scales of depression do not comply with the unidimensionality criterion. Moreover, these rating scales cannot be used as outcome variables in randomized controlled studies because in order to interpret repeated measurements, rating scales must be unidimensional and show measurement invariance[53].

There are more serious issues with the rating scales currently in use. Numerous items on these rating scales are based on descriptions from folk psychology, such as “I feel down”, “I feel depressed”, “I cry easily”, “I feel sad” and “I feel disappointed”. To obtain meaningful data for psychiatric inventories, folk psychology-like terminology is translated into Likert scale items and useful statistical entities are created after some window dressing[11]. As such, commonsense psychology terms are used as proxies for severe symptoms such as anhedonia and feelings of guilt and incorporated as criteria to make the diagnosis of mood disorders without reference to any independent validator, including causome, AOP or brainome markers.

Of course, psychological concepts such as mood cannot be directly assessed, but the best approach is to assess multiple observable manifestations of the underlying construct, which is the cause of the covariation among its indicators. In fact, our NNP models consist of unidimensional, reliable, validated and replicable latent vectors, including a phenome latent vector[10]. In fact, the severity of illness should not be assessed using one folk-psychology-derived rating scale, but by the causome, AOP, ROI and phenome latent vector scores. The latter should be based on various assessments including interview-based measurements of illness severity and suicidal ideation, and self-rated scores, including HR-QoL and disabilities[10]. We are aware that the final reflective latent vector (based on feature selection and reduction), will almost certainly contain folk psychology-like expressions, but this is less significant in the context of a NNP model, as the clinical phenome latent vector is reified as a concrete construct.

False dogma 6: Clinical remission should be defined using threshold values on rating scale scores

It is common practice to employ rating scale scores to define remission and partial remission. For example, influential psychiatrists, including Eugene Paykel, David Kupfer, Michael Thase and Roger McIntyre developed criteria to delineate remission and partial remission based on a single depression rating scale score, often the HDRS. However, such methods are not accurate. Firstly, as described above, the HDRS cannot be employed as a measure of change during treatment[54]. Secondly, and more importantly, remission, partial remission and relapse should be defined using the modifiable building

blocks of the illness (thus excluding genotypes and the ROI-index), namely causome, AOP, cognitome, brainome and phenome features as computed in our NNPs.

Furthermore, remission of a psychiatric disorder should be delineated using Soft Independent Modelling of Class Analogy (SIMCA) and not by a threshold value applied to an unreliable scale[20]. Thus, a principal component model should be built around the healthy control class using causome, AOP and phenome features (excluding the unmodifiable features) and the apparent remitters should be projected into this SIMCA model and be authenticated as controls (that is, being allocated to the healthy class) or rejected as belonging to the control class[55]. Cases that cannot be authenticated as normal controls are non-remitters and, in the latter, the "relative improvement" should be assessed as an improvement in the modifiable AOPs, brainome, cognitome and phenome latent vector scores.

False dogmas 7: Existing diagnostic boundaries are too restrictive and spectra are the rule

The diagnosis of BD should be inclusive: Another problem is that the diagnosis of BD became more and more inclusive and that the diagnosis of MDD became more restricted[50]. As such, the classical prevalence rate of BD, which is around 0.5% to 1.5%, has increased and may even reach a rate as high as 10%[56]. It is debated whether a lack of well-defined MDD and BD case definitions leads to an overdiagnosis of MDD or BD to the detriment of BD or MDD[50]. The downside of over diagnosing BD is that patients with other conditions will be treated with mood stabilizers some of which have detrimental side effects on HR-QoL[57]. The downside of over diagnosing MDD to the detriment of BD is that those patients will be devoid of more targeted treatments with mood stabilizers. In fact, another pointless debate is that BD is frequently undiagnosed[57] or over diagnosed[59].

An even greater problem is the status of BP2. Some studies suggest that BP2 is a distinct category which should be separated from recurrent MDD and BP1 and this is based on proband studies[60]. Nevertheless, some studies suggest that the reliability coefficient of BP2 is not greater than that of chance, whereas other authors claim that a good interrater reliability may be obtained when BP2 is diagnosed by experienced psychiatrists[60]. Consequently, some authors have relaxed the case definitions of BP2 for example using new hypomania checklists which include subsyndromal hypomania or subthreshold bipolarity, which is considered to belong to the soft BP spectrum[61,62]. Consequently, these authors use this checklist, which shows a sensitivity of 80% to detect true bipolar patients and a specificity of 51% (computed *vs* MDD) to diagnose BD. Consequently, up to 79% of fibromyalgia patients suddenly belong to the bipolar spectrum using a diagnostic algorithm which is grossly inadequate[63].

BD subtypes shape a continuum: Some authors proposed the "bipolar spectrum" concept which considers that bipolarity occurs along a continuum from soft to clear forms of BD, thus contrasting the categorical view of the DSM[64]. As a result, the increased prevalence of BD may be explained by the detection of softer BD phenotypes such as BP-2, BP-3, rapid cyclers and cyclothymia[56]. The BP spectrum may also comprise MDD with hyperthymic traits, depressive mixed states with hypomanic symptoms including sexual arousal, ultrarapid-cycling forms, patients with lifelong temperamental dysregulation, and cyclic irritable-dysphoric, intermittently explosive or impulse-ridden clinical expression[56]. Even the status of agitated depression appears to have remained elusive, with some suggesting that this type of depression is a mixed state or, more accurately, "pseudo-unipolar", and should be renamed "excited mixed depression"[65]. One can only speculate on the number of additional surreal labels that will be coined in the near future.

Mood disorders subtypes are part of a continuum: Another heavily debated issue is whether MDD and BP belong to a continuum (continuous theory) or whether they constitute distinct categories (discontinuous theory)[66,67]. Some authors claim that research consolidated the existence of a broad bipolar spectrum between the extremes of unipolar MDD and psychotic manic-depressive illness[68]. It is thought that the continuity spectrum between MDD and BD is supported by a number of findings including the presence of mixed states (both mania and depressive symptoms co-occur), no real separation between MDD and MDE in BD, and that many MDD patients may shift into BD. On the other hand, some findings would support the discontinuous theory, namely BP occurs more frequently in BP probands' relatives and BD shows an equal sex distribution whereas MDD shows a higher frequency in females; and BP shows a more recurrent course than MDD[66,67]. Nevertheless, some results support the dimensional and categorical approach with the mood disorders extremes (severe MDD and BP1) showing a categorical distinction, and the moderate mood disorders (BP2 and MDD) showing continuous differences[67]. Nevertheless, these studies have no merit because the accurate machine learning tests were not used to examine the continuum *vs* discontinuum theories.

There are different depressive subtypes: Modern psychiatry generally considers that there are different MDD/MDE subtypes including atypical depression, melancholia, recurrent depressive disorder, dysthymia, bipolar depression, double depression, psychotic depression, seasonal affective disorder, depression with postpartum onset, perinatal depression, postpartum depression, prenatal depression, depression with catatonic features, chronic depression, persistent depressive disorder, geriatric depression, premenstrual dysphoric disorder and treatment resistant depression[1,69]. Some of these subtypes came and went including reactive depression, situational depression, vital depression,

endogenous depression, endogenomorph depression, hidden depression, concealed depression, anxious depression and a mixed episode in BDs.

Nevertheless, because the reliability of their parent classes (MDD and MDE) is very low, we may speculate that those different classes have zero reliability. In addition, virtually none of these classes, except melancholia, has been validated using unsupervised and supervised machine learning techniques[70]. Using both supervised (SIMCA) and unsupervised (clustering and factor analysis) methods we were able to show that melancholia is at the same time a continuous and a discrete class [70]. Thus, along the continuum of severity of illness, some symptoms (namely the melancholic symptoms) become more severe and more prevalent and as, a consequence, may shape a distinct symptom profile, *i.e.*, major depression with melancholic features. As such, qualitative distinctions may be the result of quantitative distinctions, implying that all debates over continuum or discontinuum theories are pointless.

There are differences between unipolar MDD *vs* bipolar MDE: Another pointless discussion is whether there are differences between unipolar MDD and bipolar MDE, and whether they are the same or different diseases[71]. As a result, "depression with and without mania might be understood as the same condition", while "BD disorder" could be thought of as mania, with or without depression. Another point of view is that unipolar MDD and BD depression are separate illnesses that can coexist [71]. Biological dysregulation is a risk factor for both MDD and BD, although it appears to be more strongly linked to BD than unipolar MDD, implying that BD is linked to more excessive responses to psychosocial stresses than MDD[71]. From a biological standpoint, the IO&NS pathways in MDD, BP1 and BP2 differ significantly, with those pathways being more expressed in MDD and BP1 than in BP2 and more in MDD than in BP1[72]. In depression, cell-mediated immunity is activated as well, but not in mania or hypomania[73]. All the changes, however, are quantitative rather than qualitative and some studies found immune-inflammatory pathway differences between unipolar and bipolar depression [74], while others found no IO&NS differences between MDE in MDD and BD[75].

It is better to abolish all psychiatric diagnostic systems: Overall, the dimensional approach to the mood disorders spectrum idea, as well as the over diagnosing of BD with more inclusive diagnostic criteria, have blurred the lines between distinct diagnostic categories, lowering the diagnostic reliability of these mood disorders[75]. Given the above it is not surprising that the DSM and ICD taxonomies lack reliability, validity and therefore, are counterproductive for research purposes[6,77-79]. As a result, it is not unexpected that some authors came to the conclusion that all psychiatric diagnostic systems should be abolished[80].

Based on the NNP models we developed in our research, we believe it is best to eliminate all the above-mentioned mood disorders diagnostic classes and labels. To begin with, none of these classes has been designated as a separate category. Second, our NNP models show that none of the major classes MDD, BD, BP1, or BP2 are significant. For example, supervised methods like SIMCA were unable to validate these classes as distinct entities when applied to clinical and biomarker data in our data set (personal data). More importantly, two-step cluster analyses using all features of NNP1 and NNP2 as categorical variables revealed new trans-diagnostic clusters (see new classifications based on NNP features), which are more influential than the classification into MDD, BD, BP1 and BP2[10,12]. These negative findings on the MDD and BD classifications may be explained by the fact that: (1) They are binary concepts (present or not present); (2) They are top-down taxonomies based on unreliable clinical criteria and without external validation; and (3) The latent vector scores of causome, AOP, cognitome, ROI and phenome contain more accurate information on mood disorders than the binary diagnosis into MDD and BD.

Dogma 8: No need to ROI-define mood disorders: The DSM and ICD categorization systems have never placed a high value on course trajectory specifiers. Symptoms, symptom clusters and BD polarity, as well as a few course specifiers like rapid cycling, chronic depression and seasonal patterns, are used to classify DSM/ICD disorders. Interestingly, a recent project proposed to make a clinical course-graphing scale for DSM-5 disorders, namely the Timeline Course Graphing Scale for the DSM-5 Mood Disorders (TCGS)[81]. This new method takes a more systematic approach to graphing the course of mood disorders, allowing researchers to estimate the onset of mood disorders (early *vs* late onset) as well as the severity of the illness (chronicity, subthreshold syndrome, and so on). The TCGS' major goal is to distinguish MDD from the new DSM-5 class Persistent Depression, because it was anticipated that failing to distinguish the two diseases could cause treatment efforts to fail[81]. Another way to prospectively study the alternating symptoms in BD is the NIMH Life Chart Method[82].

Nevertheless, the DSM/ICD categorization systems and the TCGS/NIMH proposals do not take into account the disease's recurrence pattern, severity of recurrence, recurrence of suicidal behaviors, and recurrence-related worsening in cognitive functioning, HR-QoL life, and increased impairments[18]. Previously, some authors proposed staging models which included criteria considering functional and cognitive impairments[83-86]. However, these were theoretical models, whereas the ROI-index produced from the NNP model is calculated using predictive mathematical algorithms and real patient data. Furthermore, earlier theoretical models provided phase-related classifications of unipolar and

Table 1 Characteristics of the three stages of affective disorders[18]

Stages	Phase 1: Early phase	Phase 2: Relapse-regression	Phase 3: Suicidal regression
Early lifetime trauma	-	+	++
Number of depressive episodes	+	++	+++
Number of (hypo)manic episodes	+	++	++
Number of suicidal attempts	+	+	+++
A lifetime history suicidal ideation	+	+	++
Current suicidal ideation	+	+	+++
Lower income	+	++	+++
Disabilities	+	++	++
Reduced health-related quality of life	+	++	++
Reduced cognitive processing speed	+	++	++
Deficits in executive functioning	-	-	+

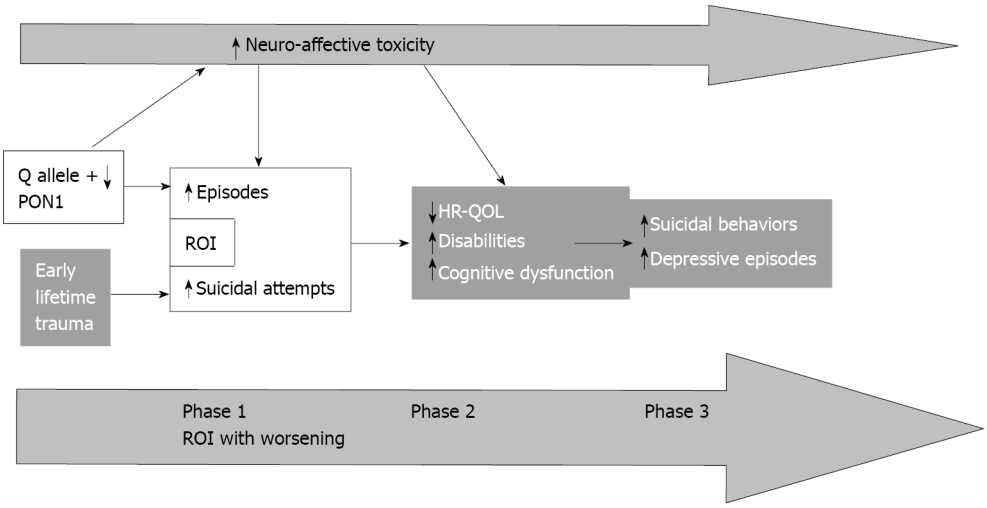

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Figure 4 Causal links from early lifetime trauma and paraoxonase 1 genotype and enzymatic activity to reoccurrence of illness to phenome including health-related quality of life. ROI: Reoccurrence of illness; HR-QOL: Health-related quality of life; PON1: Paraoxonase 1.

bipolar patients, but we computed continuous ROI scores in the combined MDD and BD group and derived externally validated ROI phases by binning the ROI into three ROI groups[18]. This ROI, as discussed in NNP models, includes information on episode and suicide recurrence, as well as the binary classification of BD and MDD/MDE.

The ROI is a crucial component of the NNP models because it predicts the phenome of mood disorders and mediates the effects of the causome (interactions between the PON1 gene and ELT) on the phenome, as detailed in NNP models. Furthermore, ROI was found to be associated with not only the phenome[10], but also the severity of depressive and manic symptoms, current suicidal ideation, and cognitive impairments in semantic memory and executive functions, as well as socioeconomic status, treatment, and biomarkers such as lowered antioxidant defenses, increased nitro-oxidative stressors, insulin resistance, CRP and a variety of other biomarkers[19]. More crucially, the ROI index is influenced by the interactions between ELTs and PON1 enzymatic activity[10].

Most importantly, our ROI latent vector is unidimensional and fits a reflective model with adequate reliability validity and replicability and, therefore, the ROI (*i.e.*, its organic substrate) is the cause of the reoccurrence of depressive episodes in MDD and depressive and manic episodes in BD and suicidal attempts in both MDD/BD as well. By inference, the reoccurrence of these phenomena is determined by a same underlying phenomenon which is partly determined by PON1 genotype and ELT interactions, and IO&NS pathways[10]. The ROI-index is not only strongly associated with PON1 gene x ELT interactions, but also with O&NS pathways indicating lipid and protein oxidation[18]. Moreover, a recent meta-analysis showed that there are strong associations between suicide attempts and ideation

and IO&NS pathways with a high effect size[87]. There is also some evidence that sensitization of IO&NS pathways may underpin this reoccurrence[73].

Through binning, we constructed three patient groups that reflect relevant phases of mood disorders, namely: "(1) An early phase; (2) A relapse-retrogression phase; and (3) A suicidal-retrogression phase" [18]. Table 1 shows that these phases are externally validated by clinical features. Figure 4 shows that the causal links from ELTs and PON1 genotype to ROI to phenome capture the lifetime trajectory of MDD/BD patients from childhood to an increasing number of episodes and suicidal behaviors to the progressive worsening of disease in terms of cognitive deficits, HR-QoL, and disabilities[18].

Such findings indicate that MDD, BD, and recurrent episodes and suicidal attempts share a common substrate and that MDD and BD should be regarded as the same disorder, namely "DysMood disorder" whereby the causome, AOPs, and ROI shape a distinct class namely "Major DysMood Disorder due to neuro-affective toxicity".

CONCLUSION

Psychosocial or mind-brain models have traditionally been used to explain mood disorders, but these models are inadequate because such models are not even falsifiable. The DSM/ICD criteria for mood disorders are narratives that have been stripped of their context and are therefore without any mechanistic explanation. The DSM/ICD classifications of mood disorders are not only unreliable but their dogma-like nature prevents inductive (as top-down) and deductive (as incontrovertible) remodeling of the case-definitions.

We built new bottom-up, data-driven, machine learning NNP models of mood disorders that reify all the components of mood disorders, as is the case in all medical disciplines where diagnosis offers a pathophysiological explanation. Neuro-affective toxicity causes functional and structural impairments in the brain, as shown by these NNP models and enrichment/annotation analysis. In mood disorders, the ROI index plays a critical role in mediating the effects of causome pathways on the phenome. The ROI index is also significantly linked to a progressive worsening of cognitive impairments, phenome severity, disabilities and HR-QoL. As a result, MDD and BD should be treated as if they were one and the same illness.

Our findings show that the causome, AOP and ROI features identified in our NNPs should be new drug targets for treating "Major DysMood Disorder", rather than the binary diagnosis of BD or MDD. The new drug targets include: Reduced PON1 enzyme activity and its consequences, increased Gram-negative bacteria or LPS translocation, increased ELTs and their consequences, lowered levels of antioxidants and elevated reactive oxygen and nitrogen species, lipid peroxidation with higher levels of aldehydes, protein oxidation and formation of oxidative-specific epitopes, nitrosative stress and increased autoimmune responses to oxidative-specific epitopes. As discussed in NNP-associated pathways, these O&NS disorders are strongly linked to activated immune-inflammatory pathways and together they may cause functional and structural changes in the brain indicative of neuro-affective toxicity. It is important to note, as well, that PON1 activity and ELT-associated sensitization of IO&NS pathways are new drug targets, and that targeted treatments may help prevent further episodes and worsening of the disease, including progression into later phases with increased cognitive and functional deterioration, as well as suicide risk.

FOOTNOTES

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OPINION REVIEW

Eco-crisis and mental health of children and young people: Do child mental health professionals have a role?

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Abstract

Child mental health professionals have an extremely important role to play in their distinct roles as clinicians, therapists, researchers, policy makers, advocates, preventative public health professionals and service developers pertaining to eco-crisis in the child and adolescent populations. This article provides examples of how this can be done.

Key Words: Eco-crisis; Children; Mental; Mental health

Core Tip: Child mental health professionals can perform different and effective roles pertaining to eco-crisis and mental health of children and young people. They can be clinicians, researchers, preventative professionals, service builders and policy makers in this regard. I believe this would be a moral obligation and a professional duty to the population that we are privileged to serve.

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INTRODUCTION

International experts widely accept that climate change is under way and it poses a critical threat to the future of mankind. The 2015 Paris Agreement acknowledges that climate change is an urgent and potentially irreversible threat to the planet (Interna-

tional Panel on Climate Change, 2018)[1]. These changes can potentially affect food and water availability, agricultural productivity, natural ecosystems and result in a variety of health disorders (Intergovernmental Panel on Climate Change, 2014)[2].

There are emerging studies that demonstrate the physical health effects of climate change, but research is relatively scarce on the psychological effects. In particular, there is a lacuna in our understanding of psychological effects in children and adolescents who in fact might be disproportionately affected[3]. Climate change could induce or precipitate psychiatric disorders and might worsen existing mental illnesses among children and adolescents experiencing climate anxiety.

Mental health professionals, policy makers and advocates need robust evidence to mitigate the effects of climate anxiety on the short-term and long-term mental health of young people. The role of child mental health professionals as an advocate, researcher, or policy maker is crucial. This review aims to demonstrate the multiple effective roles that they can play in this regard with examples to demonstrate in each of these roles (Figure 1).

AS A CLINICIAN AND A THERAPIST

Empirical evidence demonstrates that both the acute and chronic mental health effects of climate change has risen sharply in the past decade. Several recent studies have explored the mental health effects of climate-related psychological disorders, including depression, anxiety, post-traumatic stress disorder, the exacerbation of psychotic symptoms, suicidal ideation and completed suicides, including in the child and adolescent population[4]. Child mental health clinicians are appropriate professionals for conducting a detailed assessment in addition to developing and implementing appropriate assessment strategies.

In addition to diagnosable mental health disorders, experiences of ecological anxiety (*i.e.* apprehension about anticipated threats to salient ecosystems) and ecological grief (*i.e.* grief in relation to ecological loss) are commonly noted as psychological phenomena (though poorly understood) causing distress in children and adolescents. The grief phenomena associated with loss of the ecosystem is commonly categorised into: grief associated with physical ecological losses, grief associated with the loss of environmental knowledge and grief associated with anticipated future losses[5]. It is to be noted that these phenomena which can be debilitating are not diagnosable as a psychiatric disorder in the current diagnostic & classificatory systems.

Enhanced and detailed clinical assessments are needed for this population. For some people suffering from ecological grief and anxiety, clinical support might be required, particularly if their personal safety or daily functioning are affected. It is important to discern this from reactive emotions which can be unpleasant and at times painful but do not impair daily functioning and rather may assist in making productive and positive changes, including in the implementation of climate change related solutions. Screening for psychiatric comorbidity including mood and anxiety disorders with subsequent management is also crucial for a holistic plan.

Existing individual and group therapy strategies could be adapted and improvised for children and adolescents experiencing co-anxiety. The role of child psychiatrists and psychologists would be crucial in this regard. For example, interpersonal group therapy would be one option to consider[6]. There are some examples of networks that have been created to support climate-related mental wellbeing like the Good Grief Network.

Social prescribing and facilitating social connectedness would be an important part of the management plan. This would help in managing some of these psychological phenomena causing distress but with no diagnosable psychiatric disorder. The benefits would include avoiding over-pathologising and inappropriate management of these issues within a medical model[7]. For example, prescribing spending time in nature, engaging in community-based work for increasing the number of trees in urban spaces, improving the infrastructure for active commuting and reducing air pollution through a shift to clean energy might be beneficial.

Child mental health professionals are well regarded for their systemic approach to managing mental health. In this case, helping the parents/family members acknowledge the challenge, encourage parental insight into children's responses, encouraging empathetic communication with children and adolescents, validating their feelings of fear and disillusionment and mobilising hope through meaningful goal-directed activities would be appropriate measures[7].

AS A RESEARCHER

As mentioned earlier, there is scarce research into the psychological effects of climate change in children and adolescents. The primary focus of the existing studies is assessing participants' knowledge, perceptions and attitudes about climate change. For example, a recent survey-based study of 10000 young people demonstrated significant respondents were worried about climate change (59% very or extremely worried, 84% at least moderately worried)[8]. Existing literature suffers from several method-

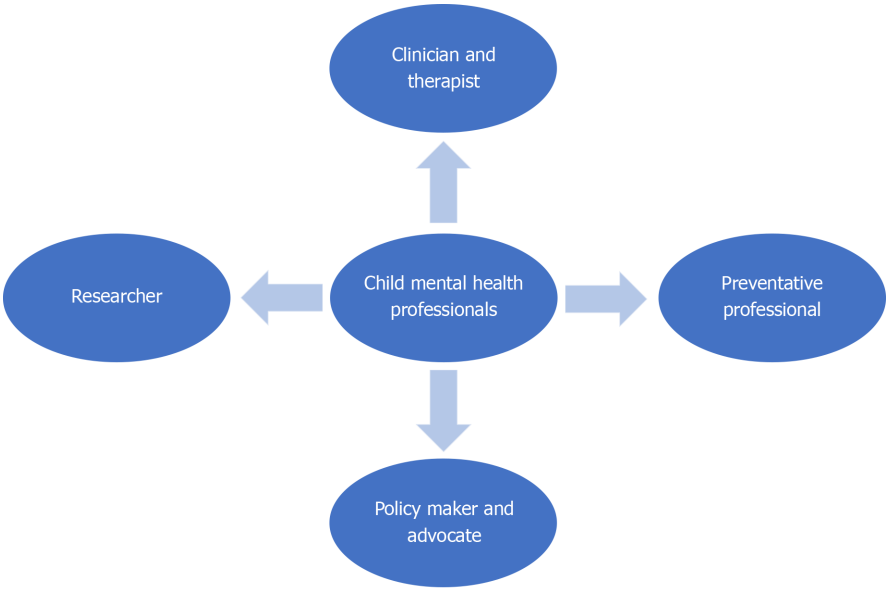

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Figure 1 Roles of child mental health professionals in ecological crisis.

ological challenges that limits the interpretation of study results. This includes the use of self-report instruments exclusively, extrapolating adult surveys to children, limited sample frame (lack of representativeness), use of closed form surveys, common methodological biases, such as social desirability, item ambiguity or demand characteristics that may result in measurement error and not taking developmental perspective (*e.g.*, children *vs* adolescents) into consideration[9].

The need of the hour is to develop psychometric instruments that can accurately screen for and measure the severity of eco-anxiety in children and adolescents. This is important to quantify differences between subjects and across time-points. This is also important for accurately assessing the relationships between climate change distress/anxiety and other known constructs, such as environmental concern and general anxiety. Of course, this is also vital for measuring response to treatment that we provide as child mental health professionals[10]. Prior to developing psychometric instruments, a clear conceptualization of the construct of eco-anxiety is imperative and a consensus needs to be reached on this. This is also important from the perspective of diagnostic and classificatory systems to explore if this could merit a primary psychiatric diagnosis on its own.

In addition to developing valid psychometric instruments, child mental health professionals are well positioned to explore a number of other poorly understood aspects including differences in perception of climate change according to age, differences in perception based on location (*e.g.*, developing *vs* developed countries; rural *vs* urban population; low *vs* higher socio-economic group), prevalence of comorbid psychiatric disorders with eco-anxiety and effectiveness of different therapeutic interventions for the same.

Future high-quality research on this subject should employ a variety of methods both quantitative and qualitative, to elicit a broad understanding of factors in addition to knowledge. Different methodological biases should be carefully considered to devise the study as well as to interpret the study findings. This could be at the individual, collective, and situational levels as all these impact adolescents' climate-related concepts[11]. The use of open-ended questions would be invaluable in exploring the views of this group without limiting their responses. Also, using reverse coding rather than questions with negations would be a useful strategy to circumvent the cognitive limitations particularly in younger children.

AS A PREVENTATIVE PROFESSIONAL (PUBLIC HEALTH)

Research on resilience and positive development identifies the characteristics that will be most valuable for the next generation to adapt successfully to climate change related difficulties. These can be grouped into individual skills and capacities, interpersonal skills and relationships and social/civic engagement [12].

Individual characteristics include emotional self-regulation (*e.g.*, meaning-focused coping strategies), behavioural and attentional self-regulation, empathy and beliefs in social justice, adaptability and creativity. Interpersonal skills include negotiation, conflict-resolution skills and the capacity to work cooperatively. Social and civic engagement includes volunteering and joining community groups, and

engaging in active citizenship (*e.g.*, speaking out on issues of concern, communicating with policy makers)[13]. Models of positive development indicate that these are desirable developmental outcomes.

Child mental health professionals play a valuable role in both researching on as well as implementing these resilience-based preventative public health strategies in both school and other community-based settings. They are obvious stakeholders who should be involved in developing, trialling and implementing the educational/curricular changes in this regard, possibly in conjunction with educational psychologists. Also, developing nature friendly schools projected along with educational professionals is likely to be helpful. Also, this approach is likely to be helpful in developing nature based positive behavioural support strategies for children and adolescents with intellectual disabilities.

AS A POLICY MAKER AND ADVOCATE

Child mental health professionals are extremely well placed to actively advocate for climate change mitigation and adaption. Through their membership in different professional and government committees, they could influence policy making as relevant to children and adolescents. For example, The Royal College of Psychiatry, United Kingdom is a member of the United Kingdom health alliance on climate change bringing together the voices of a multitude of health care professionals to advocate for action on climate change and study its psychological impact. The college also published a position paper on sustainability which highlights the need to develop carbon efficient mental health services as part of sustainable mental health[14].

There are several recently implemented programs at local, national and international levels that support actively engaging children and adolescents in increasing awareness of climate change, promoting renewable energy, developing environmentally sustainable practices and advocating for urgent action on the climate crisis[13]. Child psychiatrists and other child mental health professionals have a lot to contribute to these crucial efforts. They can help in identifying the subset of children and adolescents most likely to benefit from these efforts and help in developing the program and in evaluating its effectiveness.

AS A PROMOTER OF HEALTH EQUITY (PUBLIC HEALTH PERSPECTIVE) AND AS A SERVICE DEVELOPER

Access to mental health care in relation to eco-crisis can be impeded by inadequate mental health-care infrastructure in certain areas, cultural practices and practitioner's familiarity with climate-related anxiety and grief, existing burden on mental health care services and disparities in underlying determinants of health (*e.g.*, socio-economic factors)[14,15]. There is some evidence that those who experience the most acute forms of ecological anxiety are also those with relatively less access to mental health resources[5]. Hence, the role of these professionals is crucial for ensuring fair access for all to the services and building a resilient service in this regard.

Also, looking at a global level, most of the world's children (about 85%) live in low- and middle-income countries, which tend to be in geographic locations more vulnerable to the impacts of climate change. These developing nations also tend to have weaker mental health care infrastructure and fewer support services with which to prepare for and adapt to the impact of climate change[3]. Hence, the role of clinicians serving children and adolescents in the developing world and those working with global agencies [*e.g.*, the World Health Organization (WHO)] are even more crucial for ensuring health equity for children and adolescents globally, pertaining to eco-anxiety. Influencing decision-makers who are crucial for ensuring health equity for children and adolescents globally and pertaining to eco-anxiety is an important role that we could play. This would include local, regional or national leaders; WHO and charitable organizations.

CONCLUSION

As highlighted through numerous examples above, child mental health professionals have an extremely important role to play in their distinct roles as clinicians, therapists, researchers, policy makers, advocates, preventative public health professionals and service developers pertaining to eco-crisis in both the children and adolescent populations. This would be even more important in developing countries where the majority of the children live. These countries typically have weaker pre-existing mental health services which need to be strengthened. I believe this would be a moral obligation and a professional duty to the population we are privileged to serve.

FOOTNOTES

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MINIREVIEWS

Dysregulated cortical synaptic plasticity under methyl-CpG binding protein 2 deficiency and its implication in motor impairments

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Abstract

Caused by the mutation of methyl-CpG binding protein 2 (MeCP2), Rett syndrome leads to a battery of severe neural dysfunctions including the regression of motor coordination and motor learning. Current understanding has revealed the motor cortex as the critical region mediating voluntary movement. In this review article, we will summarize major findings from human patients and animal models regarding the cortical synaptic plasticity under the regulation of MeCP2. We will also discuss how mutation of MeCP2 leads to the disruption of cortical circuitry homeostasis to cause motor deficits. Lastly, potential values of physical exercise and neuromodulation approaches to recover neural plasticity and motor function will be evaluated. All of this evidence may help to accelerate timely diagnosis and effective interventions for Rett syndrome patients.

Key Words: Rett syndrome; Motor function; Motor cortex; Synaptic plasticity; Physical exercise; Methyl-CpG binding protein 2

Core Tip: In this mini-review, Zhang WJ summarized current findings for the synaptic plasticity in the cortex and related motor learning functions under the scenario of Rett syndrome. The discussion of neuropathological mechanisms can help us to better understand the disease progression and more importantly to develop more effective measures to counteract motor deficits.

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INTRODUCTION

Rett syndrome is one neurodevelopmental disorder that is caused by the genetic mutation of methyl-CpG binding protein 2 (MeCP2)[1]. Predominantly found in females with about a 0.01% incidence[2], Rett syndrome has been recognized as one of the major genetic conditions that affects neurodevelopment. As clinical features, about 61% of Rett syndrome patients developed autism spectrum disorder (ASD)-like symptoms[3], making it one major genetic contribution to autistic syndromes. Other behavioral features of Rett syndrome include cognitive and verbal disabilities[4] as well as the retardation of general development[5]. Among various clinical manifestations, deficits of motor function can be found in early stages of disease progression (around 12-18 mo in patients), as displayed by the gradual deterioration of normal motor functions and the occurrence of repetitive movements[6]. As a result, the gradual loss of acquired motor skill has been recognized as one prominent feature of Rett syndrome[7], further highlighting the relationship between motor functions and MeCP2. In this mini-review, we will summarize current major findings regarding motor dysfunctions in Rett syndrome and discuss their correlation with MeCP2-mediated synaptic plasticity of motor circuits, especially those in the motor cortex. In addition, we will also explore the possibility of non-drug intervention strategies including noninvasive neuromodulation and physical exercise in relieving these motor syndromes.

DYSREGULATED CORTICAL SYNAPTIC PLASTICITY IN RETT SYNDROME

Recent studies have demonstrated the pleiotropic functions of MeCP2 in mediating early events of neurodevelopment including neurogenesis, migration and patterning[8-10]. Deficits of neural network formation frequently lead to abnormal functions. In the cortical region, MeCP2 mutation disrupts the normal excitatory-inhibitory (E/I) balance, resulting in altered synaptic computation[4,7,11-13]. In specific studies, MeCP2-null knockout mice presented elevated GABAA and N-methyl-D-aspartic acid (NMDA) receptors in the barrel cortex[13]. However, using MeCP2-mutant mice, both excitatory and inhibitory conductance were reduced *in vivo* while the E/I ratio was increased[11]. In another study using MeCP2-mutant mice, cortical pyramidal neurons (PNs) displayed decreased spontaneous activity probably due to the reduced miniature excitatory postsynaptic currents (mEPSCs) amplitude while the inhibitory input did not change[12]. Those seemingly contradictory results further suggested the complicated mechanism of MeCP2 in mediating cortical network. A possible approach for further investigation can be achieved *via* cell type-specific study of MeCP2 function. For example, parvalbumin (PV)-specific MeCP2 deletion recapitulated reduced cortical excitability by global MeCP2 deletion[11]. Multiple mechanisms including ion permeability, neurotransmitter receptor or synaptic structural proteins can be further interrogated, as MeCP2 works as a transcriptional regulatory factor to potentially affect their gene expression. Since the neural plasticity of the cortical network is closely correlated with motor learning[14,15], the dysregulated function of MeCP2 may confer motor deficits. Further interrogation of MeCP2-dependent synaptic regulation can help to reveal the pathological process of related motor impairments in order to provide diagnostic and treatment targets.

When examining the neural mechanism of Rett syndrome-associated behavioral symptoms, it is suggested that MeCP2 works as one methyl-DNA binding protein[16]. The loss-of-function mutation of MeCP2 in Rett syndrome thus can be generalized as the deprivation of transcription repression, although recent studies are suggesting its multifaceted roles including activation or suppression of specific genes[17]. Across different brain regions, MeCP2 mediates the gene expressional network in a similar pattern[18], suggesting the brain-wide effect. When examining the transcriptional regulatory mechanism, a recent study identified the prominent role of MeCP2 in suppressing the initiation of gene regions with high CG-methylation levels[19]. For those non-CG methylated gene regions, MeCP2 also exerts a suppressor role *via* repressing enhancer activity[20]. In the exploration of MeCP2-targeted molecules, key modulators of neural plasticity have been recovered. For example, MeCP2 affects the transcription of BDNF to affect myelination and remyelination[21]. An early study further showed that MeCP2 associated with the transcriptional activator CREB1 to mediate a wide range of brain genes[17]. Moreover, MeCP2 interacts with a lot of neuronal genes in positive or negative manners. The transcriptional factor forkhead box protein O3 (FOXO3) has been found to be positively regulated by MeCP2 *via* deacetylation[22]. Those effects on transcriptional factors highlight the role of MeCP in the top layer of the gene regulatory network. Besides those transcriptional factors and neurotrophic molecules, MeCP2 also affects the post-translational modification of neuronal genes. For example, the histone modification

has been shown to be mediated by MeCP2 *via* recognizing H3K27me3[23]. Furthermore, the phosphorylation of MeCP2 itself adds further layers onto its regulatory network. The brain-specific phosphorylation of MeCP2 is known to regulate BDNF expression, contributing to neuronal growth and maturation[24]. In a broad sense, activity-dependent MeCP2 phosphorylation affects its interaction with transcriptional repressors[25], providing an epigenetic mechanism. During neurodevelopment, cell cycle-associated MeCP2 phosphorylation modulates adult neurogenesis[26] and nervous system functions[27]. Combining all these results, MeCP2 regulates the expression of neuronal genes *via* different pathways at transcriptional and post-transcriptional levels (Figure 1).

In neural tissues, gene transcription plays a critical role in various forms of synaptic plasticity such as the long-term potentiation (LTP) and long-term depression (LTD)[28]. People are thus beginning to dissect the neuropathological mechanism of Rett syndrome from the synaptic perspective[29]. Current knowledge has observed the disruption of normal synaptic plasticity under MeCP2 loss-of-function mutation across different brain regions including the hippocampus[30], the cerebellum[31], the visual pathway[32] and the amygdala nuclei[33]. As the critical region for high-order cognitive and mental regulation, the cortical region is also affected by MeCP2 mutations. For example, MeCP2 insufficiency in mouse auditory cortex affected the local network and disrupted maternal pup-retrieval behaviors[34]. In mouse primary visual cortex (V1), MeCP2 deficiency remarkably disrupted the early-stage development of neural plasticity during the so-called "critical period"[35,36]. The abnormal synaptic development resulted in the morphological deficits of synapse, including decreased spine density[37], altered spine morphology or dendritic complexity[38], shorter dendritic lengths[39] and alternation of synaptic protein expression in primary motor cortex (M1)[40,41]. Furthermore, the reduced neuronal size can be observed in layer V PNs of M1 in Rett syndrome model mice[42]. These findings provide the first-hand evidence for the disruption of structural and functional plasticity in the cortical region upon MeCP2 deprivation, highlighting the necessity and importance to elaborate the cortical neuropathology of Rett syndrome.

It is important to notice that both cell autonomous and non-autonomous mechanisms reside in MeCP2-mediated cell plasticity. For example, the loss of MeCP2 affects the autocrine brain derived neurotrophic factor (BDNF) signaling in excitatory neurons to affect neural plasticity, as wildtype neurons cannot rescue mutant cells in the area[43]. Such results provide further clues for clinical manifestations as mosaic patterns of mutations frequently occurs in Rett syndrome patients[44]. Although the primary cause of Rett syndrome is believed to be cell autonomous, non-autonomous mechanism has been revealed as the culture medium from MeCP2-mutated astrocytes disrupted dendritic morphology of wildtype hippocampal neurons[45]. Therefore, MeCP2 affects neural function *via* a complex network and further elaborations are required to study the cell-specific effect.

To attribute the factors for disrupted cortical synaptic plasticity under MeCP2 mutation, recent advances are highlighting the role of local inhibitory transmissions. In the mouse auditory cortex, independent lines of evidence are suggesting that the abolishment or insufficiency of MeCP2 suppresses normal activity of PV-interneurons, resulting in failures of maternal caring behaviors[34,46]. In primary somatosensory cortex (S1) and M1, the learning-associated modulation of plasticity of PV-interneurons was impaired in MeCP2 knockout mice as well as under heterogenous mutation of MeCP2[47]. In the barrel region, the loss of MeCP2 also enhanced glutamatergic transmission[13]. Such interruption of normal cortical network homeostasis might be explained by MeCP2 influence on synaptic plasticity during the critical period in early-stage development[36]. Such opinions were further supported by the conditional knockout of MeCP2 in PV-interneurons resulting in the absence of neural plasticity of V1 during the critical time[35]. To figure out the molecular mechanism, current studies are suggesting the role of neurotrophic factors. For example, BDNF was downregulated under MeCP2 deficiency[48]. As an intervention trial, insulin-like growth factor-1 (IGF-1) partially relieved such neurodevelopmental deficits under MeCP2 deficiency[49] and recovered cortical plasticity[50]. An alternative explanation exists in the cortical perineuronal nets (PNNs) whose formation is dependent on MeCP2[51]. Since PNNs are known to mainly surround PV-interneurons[52], the extracellular modulation may provide a model to explain how pan-neuronal mutation of MeCP2 leads to PV-interneuron specific defects.

The converging evidence of deficient GABAergic transmission upon MeCP2 mutation implies the hyper-excitation of the cortical network. In Rett syndrome patients, clinical recording supported such hypothesis by displaying significant increases of the excitation index of M1 in association with reduced short-interval inhibition[53] plus decreased inhibitory motor control[54]. Mouse model studies also suggested aberrantly high cortical excitability upon MeCP2 deficiency[49], probably due to diminished extracellular GABA transporter activity[55] or under-development of dendritic spines[40]. However, other studies supported the enhanced GABA transmission under MeCP2 knockout[13]. In a short summary, both presynaptic function such as GABA transporter and postsynaptic mechanism including spine formation and synaptic transmission are involved in MeCP2-mediated cortical plasticity. To better dissect the molecular pathway, cell-specific genetic manipulation and functional studies can be performed. For example, PV-specific MeCP2 deletion mimics the effect of global gene knockout[11]. In the future, MeCP2 can be studied in other neuronal and glial cell subpopulations in the cortex.

Based on these facts of disrupted cortical E/I balance, the application of neuromodulator drugs or neuromodulation stimulus may provide a promising future for region-specific intervention of motor symptoms under MeCP2 deficiency. In the last part of this article, we will summarize major findings

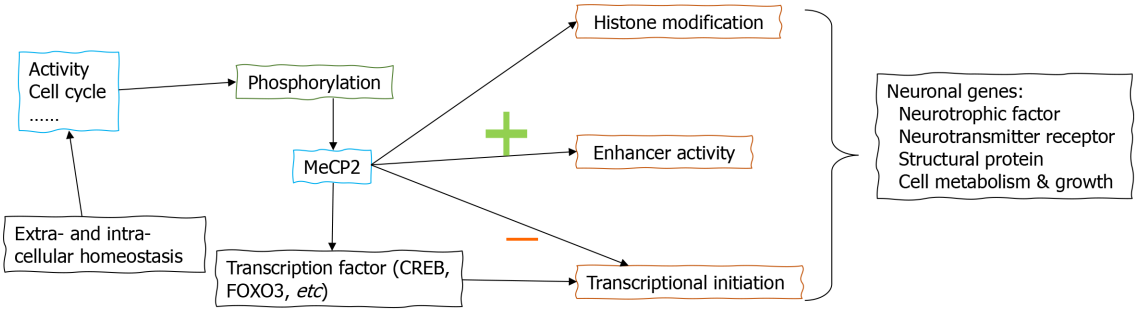

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Figure 1 Graphic illustration for methyl-CpG binding protein 2-mediated pathway of neuronal gene transcription. The activity of methyl-CpG binding protein 2 (MeCP2) is mediated by phosphorylation, which can response to cell cycle or cellular activity. MeCP2 exerts pluripotent functions at genetic and epigenetic layers, including directly or indirectly affecting gene transcription, or modifying chromatin structures. Such modulatory network eventually affects both structure and function of neurons[17-20,23,26].

and prospective regarding the neuromodulation approaches for alleviating motor symptoms of Rett syndrome.

SYNAPTIC DYSFUNCTION IN MOTOR CORTEX IN RETT SYNDROME AND RELATED MOTOR DYSFUNCTIONS

Among the major clinical features of Rett syndrome, motor deficits occur early during the disease development and persist across the whole disease process: The motor delay becomes apparent among 1.5-years-old and 3-years-old, after a seemingly normal early postnatal period[4]. During the adolescent and adulthood period, the progressively declined motor function can be presented as Parkinsonism-like features[56]. Such progression of motor symptoms usually develops into severe ataxia and deprives the patients of the ability to walk or stand during the teenage period[7]. These clinical manifestations can be replicated in mouse models: In MeCP2-null knockout mice, early-onset motor abnormalities were found to induce higher lethal rates[57]. In addition, these model animals presented regression of acquired psychomotor skills under a social interaction scenario[58]. These behavioral deficits clearly suggested the involvement of the motor system in Rett syndrome pathology.

Distinct brain regions and neural ensembles regulate voluntary movement, including the forebrain sensorimotor region, the midbrain nuclei such as the thalamus and basal ganglia, as well as the hindbrain regions plus the cerebellum. The motor cortex is innervated by distinct neuromodulator systems including dopamine, noradrenaline and serotonin. The brain-wide deficiency of MeCP2 thus may affect motor cortical plasticity *via* disruption of subcortical inputs. For example, the ablation of MeCP2 in aminergic neurons produced cell autonomous effects resulting in behavioral abnormalities [59]. The pharmaceutical potentiation of the serotonergic pathway improved cortical microcircuits and recovered motor learning behaviors[60]. Another study further revealed that striatal MeCP2 was critical for maintaining dopaminergic transmission of psychomotor regulation[61]. These findings supported the indispensable role of MeCP2 in the neural network related with cortical activity.

Although the site-specific gene knockout study has suggested the role of MeCP2 in mediating motor behaviors across different neural networks such as the noradrenergic transmission, the motor cortex remains as the prominent brain region in which fine motor control is regulated. Within the motor cortex, both excitatory PNs and GABAergic interneurons form the local network to drive the voluntary movement. PNs were once believed to be the principal projecting neurons in the cortical region and their structural and functional plasticity largely affects motor functions[62,63]. MeCP2 was known to mediate synaptic structures in the motor cortex as it can regulate the dosage of gene expression *via* homeostatic control of DNA methylation. The over-expression of MeCP2, for instance, resulted in altered structural plasticity of cortical dendritic spines[64]. On the other hand, the deficiency of MeCP2 led to remarkably shorter dendrites of PNs in the motor cortex in human patients across different age groups[38]. Similar phenotypes were observed in mouse models, which presented reduced spine density, shorter dendrite lengths[37], irregular spine clustering or shapes[65] and reduced dendritic complexity[39]. Such evidence clearly demonstrates the relationship between MeCP2 and synaptic plasticity and implies the participation of MeCP2-mediated synaptic defects in Rett syndrome.

Besides the excitatory neurons, GABAergic inhibitory neurons in the motor cortex also tightly regulates motor coordination and motor learning functions, as they can provide both inhibitory synaptic inputs and subthreshold oscillation wave onto excitatory neurons. For example, the somatostatin (SST)-interneuron is found to actively participate in the acquisition and retrieval of complex motor skills as suggested by an *in vivo* recording study[66], and our recent work has revealed the abnormally

suppressed activity of those SST-interneurons under a Parkinson's disease (PD) mouse model, leading to pathologically over-excitation of pyramidal cells[67]. Such phenomena revealed cortical dysfunctions due to the loss of normal inhibitory inputs onto the pyramidal projecting neurons, leading to their hyperactivation and related neural symptoms. Besides the local regulation of cortical inhibition, GABAergic neurons received inputs from subcortical nuclei which consisted of multiple monoaminergic systems. For instance, the α2A -adrenoceptor was found to suppress the activity of cortical inhibitory neurons[68]. The dopamine receptor D1 and D2 have been known to affect the density of cortical inhibitory neurons, including PV- and SST-interneurons[69]. In the human motor cortex, serotonin was also reported to enhance GABAergic transmission[70]. No direct study, however, has investigated the modulation of cortical inhibitory neurons by the monoaminergic system under MeCP2 deficiency. Further work thus can be performed to dissect the circuitry pathway of MeCP2 in affecting motor learning functions.

When one broadens their scope of neurological diseases, it is interesting to find that the "cortical disinhibition" model can be found across different neurological disease models such as Alzheimer's disease (AD)[71], amyotrophic lateral sclerosis (ALS)[72] and Huntington's disease (HD)[73]. In a primate model of Rett syndrome, MeCP2 is expressed in both excitatory and inhibitory neurons in cortical regions[74], implying the possible role for mediating glutamatergic and GABAergic transmission. In specific, the conditional knockout of MeCP2 in cortical vasoactive intestinal peptide (VIP)-interneurons resulted in the deficits of social and mental functions[75]. It thus seems that the abovementioned correlation between MeCP2 and motor function may reside in the inhibitory neurons of the motor cortex. In fact, the cellular pathological studies have also attributed motor dysfunction to MeCP2 deficiency in PV-interneurons in the motor cortex as suggested by a conditional gene knockout model[76]. In a similar manner, the deletion of MeCP2 in SST-interneurons resulted in stereotypic and repetitive behaviors, highlighting the distinct functions of interneuron subtypes in fine motor control [76]. On the other hand, PNs may also be affected under MeCP2 deficits which can impair the structural or functional integrity of the excitatory synapse[11,38,42]. For example, MeCP2 deletion in glutamatergic neurons resulted in much more severe symptoms than those from inhibitory neuron-specific deletion[77]. As the restoration of MeCP2 in GABAergic neurons only partially rescued symptoms in null knockout mice[78], the integrity of local E/I homeostasis is of critical importance for relieving cortical neuropathology in Rett syndrome. Combining all data, it is promising that targeting the E/I balance in the motor cortex, especially by potentiating the inhibitory transmission, may aid in retarding or alleviating the motor syndrome in patients.

THE POTENCY OF EXERCISE TRAINING AND NEUROMODULATION IN FUNCTIONAL REHABILITATION

Based on motor deficits and dysregulated neural plasticity of motor circuits upon MeCP2 dysfunction as aforementioned, it is possible that certain neuromodulation approaches targeting circuitry function might help to ameliorate those motor symptoms. As supporting evidence, environmental enrichment helped to relieve the behavioral deficits including motor learning functions in MeCP2 null knockout mice, in addition to the rescue of cortical LTP function[31]. In a clinical trial of Rett syndrome patients under the age of 6 years, the 6-mo environmental enrichment training paradigm improved motor functions[79]. These examples clearly suggested the possibility of environmental intervention in relieving Rett syndrome symptoms.

Physical training, as one widely accepted life-style intervention to facilitate neurogenesis and cognitive functions[80], has been recently demonstrated by our group to improve motor learning abilities *via* stimulating structural and functional plasticity of synapses in mouse motor cortex[81]. Therefore, exercise training may work as one promising approach to relieve motor deficits of Rett syndrome patients. Such a proposal was supported by several clinical reports in which daily activities and rehabilitation helped to maintain motor abilities[82,83] or to prevent functional deterioration[84]. Specifically, a recently published case report found that periodic exercise rehabilitation at 2 years of age helped to maintain normal motor function[82]. Another study recruited 4 girls under the age of 11 years and found that 2-mo treadmill training helped to improve the general body fitness and behavioral scores[84]. Although these preliminary studies only included a small cohort of patients, the potency of physical exercise in early intervention of Rett syndrome-related motor dysfunction can be tested by large-scale clinical trials in the future.

To provide neurobiological evidence for physical exercise, Zoghbi *et al*[85] recently reported the effectiveness of pre-symptomatic training in the mitigation of specific motor impairments using a mouse Rett syndrome model. In particular, exercise training repeatedly activated a specific population of neurons that developed more dendritic arbors and higher excitability to enhance motor function[85]. These data suggested a possibly new intervention strategy by which endurance exercise works to retard the deterioration of motor dysfunctions. When examining the molecular mechanism underlying exercise intervention on Rett syndrome, BDNF upregulation has been reported upon exercise paradigm in both rodent models[86] and human cohorts[87]. At the downstream of BDNF activation, it is worth noting

that physical training boosted the activity of the mechanistic target of rapamycin (mTOR) pathway for improving structural and functional plasticity of dendritic spines in the motor cortex[81]. Since previous knowledge has established the role of mTOR down-regulation upon Mecp2 mutation[88,89] to generate the phenotypes of Rett syndrome[90], it is highly likely that exercise may help to relieve neural dysfunctions *via* moderately stimulating mTOR pathways. As functional evidence, both *in vitro* and *in vivo* data have proved the down-sized neurons across multiple brain regions in mice carrying the A140V mutation of Mecp2, in association with mTOR activity inhibition[88]. On the other hand, human brain samples presented abnormally upregulated mTOR activity under Rett syndrome[91]. Such discrepancy between human patients and animal models may arise from the different mutational sites or distinct disease stages. Nevertheless, the critical role of the mTOR pathway in MeCP2-related dysfunction and the modulatory role of mTOR by exercise training cannot be neglected. This further highlights the promising future of using endurance training for alleviating cellular and behavioral deficits of Rett syndrome.

Currently, few available intervention strategies have been adopted to benefit Rett syndrome patients. Besides the potential usage of exercise training at early stages as aforementioned, non-invasive neuromodulation approaches provide alternative choices for alleviating behavioral deficits. Various methods including electric, magnetic and ultrasound stimulations have been approved as safe means to modulate neural functions, mainly focusing on the cortical region. The application of transcranial magnetic stimulation (TMS) has been accepted to evaluate the excitability and E/I balance of the M1 neural network[53,54], despite relatively small sample sizes. As an alternative neuromodulation approach, transcranial direct current stimulation (tDCS) has recently been tested on Rett syndrome patients. In one study recruiting 31 patients, tDCS effectively improved attention and verbal functions [92]. A second study also reported enhancement of language skills by tDCS[93]. These neuromodulation approaches thus may have potential values in improving neural functions. Due to the early-onset and persistency of motor deficits, the targeted intervention on the motor cortex may be worth further testing by employing large-scale and multi-centered clinical trials. When considering neuromodulation in large cohorts of patients, however, some concerns may arise as it may result in episodes of epilepsy[94], whose susceptibility rises in Rett syndrome patients[95]. These safety issues also remind that environmental intervention such as exercise training might be a more preferrable and safer way in treating Rett syndrome.

CONCLUSION

In summary, MeCP2 mediates the synaptic plasticity and neural circuitry in the motor cortex and its genetic mutation leads to the disruption of neural transmission, thereby causing the dysfunction of fine motor coordination and motor learning abilities in Rett syndrome. Targeting the motor cortex by either physical training or neuromodulation approaches thus have become accessible and promising strategies for alleviating motor symptoms in Rett syndrome and is worth of more investigations from both basic science and the clinical fields.

FOOTNOTES

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MINIREVIEWS

Differences between delusional disorder and schizophrenia: A mini narrative review

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Abstract

Psychotic syndromes are divided into affective and non-affective forms. Even among the non-affective forms, substantial differences exist. The aim of this relatively brief review is to synthesize what is known about the differences between two non-affective psychoses, schizophrenia and delusional disorder (DD), with respect to clinical, epidemiological, sociodemographic, and treatment response characteristics. A PubMed literature search revealed the following: in schizophrenia, hallucinations, negative symptoms and cognitive symptoms are prominent. They are rare in DD. Compared to schizophrenia patients, individuals with DD maintain relatively good function, and their delusions are believable; many are beliefs that are widely held in the general population. Treatments are generally similar in these two forms of psychosis, with the exception that antidepressants are used more frequently in DD and, for acute treatment, effective antipsychotic doses are lower in DD than in schizophrenia. It is with the hope that the contrasts between these two conditions will aid in the provision of safe and effective treatment for both that this review has been conducted.

Key Words: Non-affective psychosis; Delusional disorder; Schizophrenia; Epidemiology; Symptoms; Treatment response

Core Tip: Although patients with delusional disorder and schizophrenia share clinical similarities, epidemiological and treatment outcomes suggest that these two conditions belong to different diagnostic categories. The onset of delusional disorder (DD) occurs at a relatively late age and, in contrast to schizophrenia, everyday functioning is preserved. Treatment is similar, with more frequent use of antidepressants in DD. Effective targeting of symptomatic domains is important in both these forms of psychosis.

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INTRODUCTION

Schizophrenia and delusional disorder (DD) are both non-affective psychoses and symptoms overlap in many ways. Both conditions are characterized by the presence of delusions although, in schizophrenia, hallucinations, cognitive deficits, and features such as thought disorder, apathy, and social isolation are as much in evidence as are delusions. In both disorders, delusions are usually centered around themes of persecution, but grandiosity, morbid jealousy, erotomania, and delusionally interpreted somatic sensations are also very common[1] (Table 1). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), delusions, in whatever psychotic illness they are found, are defined as fixed beliefs that are not easily amenable to correction, despite proof to the contrary.

Although Table 1 represents the current sub-classification of DD, several investigators have attempted to introduce different groupings within this diagnostic category. Wustmann and collaborators[2] classified DD patients into three groups: erotocentric (erotomanic delusions and delusions of jealousy), somatocentric (delusions of health threat and somatic delusions) and securocentric (persecutory, querulous, litigious delusions, and delusions of reference). Some patients present with two or more different types of delusion over time. In the schizophrenia literature, although some contemporary writers still refer to paranoid schizophrenia as a subtype, sub-grouping according to delusional content is largely obsolete.

The aim of this brief narrative review is to search the existing psychiatric literature in order to address the following questions: (1) Do epidemiological data differentiate DD from schizophrenia? (2) Do clinical features or psychiatric comorbidities differ in DD and schizophrenia? And (3) Are there data that show differences between DD and schizophrenia with respect to response to treatment, both pharmacological and psychosocial?

THEORETICAL SPECULATIONS ON THE ORIGIN OF DELUSIONS

How delusions take root and grow in a human mind is a much-debated topic, which, it is agreed, results from the interaction of biological, psychological and environmental factors.

Theorists believe that delusions arise from chance exposure to an event that feels special, out of the ordinary[3]. A preoccupation with "how could this possibly have happened to me?" begins to torment the individual until a 'eureka' moment is reached when everything falls into place[4]. This has been called the "aha" experience[5] when an explanation, sometimes seemingly outlandish, has at last been found.

Despite the fact that the eureka explanation sounds, when shared, implausible to others, it can germinate and plant itself firmly in the mind of a biologically vulnerable individual and become a quasi-permanent, salient feature in that person's life[6]. Family members and friends question the explanation, argue against it, which frequently leads to conflicts that culminate in the social isolation of the deluded person[7]. To account for this process in the context of schizophrenia, most of the literature assumes a genetic predisposition inherent in the deluded person; in DD, on the other hand, because delusions emerge later in life, they are often attributed to acquired brain pathology[7]. In both conditions, biological underpinnings that make the ground fertile to delusions are assumed, but clear evidence of brain structure/function impairment is usually lacking[8].

Psychological origin theories are not excluded[9,10], especially not in DD. Formative traumatic experiences are thought to lead to negative emotions such as shame, guilt, or fear, resulting in a "be on your guard" attitude that transforms ordinary events into threats that grow to become convictions of deliberate persecution[11]. Some have argued that emotionally aroused states facilitate hypervigilance to threat, and that such states of mind lead to both misinterpretations and, especially in schizophrenia, misperceptions[12].

Table 1 Subtypes of delusional disorder in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[1]

Subtypes of delusional content	
Persecutory type	A preoccupation with the belief that one is being persecuted or conspired against
Somatic type	A conviction that one's body is defective or infested or malformed
Jealous type	A conviction that one's lover is unfaithful
Grandiose type	A belief that one is somehow superior to others
Erotomanic type	A false belief that one has aroused the passionate love of someone important
Mixed type	False beliefs that combine the above themes
Unspecified type	A vagueness in the expression of one's beliefs that does not permit sub-classification

It is possible that phenomena such as these arise frequently in many people but are then aborted by feedback from trusted others. Individuals who are socially isolated may not have access to such feedback. It is also possible that, occasionally, delusional explanations for extraordinary events persist because they are reinforced by external affirmation[13].

There is a school of thought that attributes the persistence of a delusion not only to outside reinforcement but also to the susceptible person's habitual form of reasoning, or cognitive biases. Such biases have biological underpinnings but may also represent learned phenomena. One example of a cognitive bias is the tendency to jump too quickly to unwarranted conclusions[14]. As described by Laukkonen *et al*[4], the more that a person comes to faulty conclusions about everyday events, the more 'proofs of concept' are incorporated into an ever-expanding delusional system. It is psychologically easy to attribute mistakes and disappointments to perceived foes and conspirators[15]. Gunn and Bortolotti [16] note that paranoid delusions, by placing blame for missteps on outside persecutors, serve as 'secondary gain,' allaying the guilt and shame of personal failings. In cultural anthropology, an important distinction has been made between guilt cultures, shame cultures, and cultures of fear[17], classified on the basis of traditionally preferred ways by which parents socialize their children. In this context, Matos *et al*[18] speak of shame memories as central to the development of paranoia. Carvalho *et al*[19] emphasize instead the influence of family narratives and childhood memories on the emergence of paranoid ideation. In a much-cited paper, Kirmayer and Ryder[20] conclude that cultural habits are embedded in the brain as neural correlates of emotion[21], and can thus predispose to different forms of mental symptoms in different cultures.

The literature continues to leave the issue of the origin of delusions open. It is possible, however, to arrive at a conclusion that delusional thinking in psychoses that begin at older ages (such as DD) is likely to originate mainly in life experiences whereas delusions that begin in youth (as in schizophrenia) are rooted in neurodevelopment, with most current research centered on aberrations of neurotransmission, especially dopamine transmission[22-24]. A recent positron emission tomography study found dopamine dysregulation in both schizophrenia and DD[25]. This suggests a neurocognitive model for delusion formation that links aberrant salience of a chance stimulus, often threat-related, with mesostriatal dopamine signaling. Secondary cognitive processes are recruited to try to make sense of what is perceived as a highly unusual, highly significant experience. These processes, namely jumping to conclusions, unswerving attachment to one's original conclusions, and inattention to counterarguments, for which dopamine dysregulation may also be responsible, maintain and sustain the delusion [26]. This is a model of delusion formation that also leaves room for a major contributory role for prior experience of trauma and sociocultural input[27].

EPIDEMIOLOGY

The lifetime prevalence of schizophrenia, despite variations in study design, geographic source, and study quality, is estimated at 0.48%-1%[28]. This is in contrast to the lifetime prevalence of DD, rated as 0.2%[1], but reported by some researchers to be a decimal place rarer - 24 to 30 per 100000[29]. Prevalence varies with the characteristics of the study sample and the setting of the investigation[30].

A major difference between schizophrenia and DD is the age of onset, late teens and early adulthood in schizophrenia, middle age and above in DD[30]. Onset age is critical in many ways. For example, the fact that DD first occurs, for the large part, in postmenopausal women may explain why gender differences during the reproductive years are not as marked in this disorder as they are in schizophrenia, where circulating estrogen levels protect the brains of reproductive age women[30,31]. Onset age may also affect the thematic content of delusions. In DD, erotomania, for instance, has been found to be more frequent in women with premenopausal onset while somatic and jealous delusions are more common in women whose onset is postmenopausal[32].

Epidemiological differences between DD and schizophrenia depend to a significant degree on the diagnostic instrument and the diagnostic criteria and the specific syndromes that are included under the two categories. Some syndromes within the schizophrenia spectrum, such as paranoia querulans (incessant legal actions to obtain compensation for perceived wrongs) and paraphrenia (psychotic symptoms first diagnosed in the elderly) have been removed from current classification systems and are now subsumed under either DD or schizophrenia. This is notably the case for paraphrenia, which is now variably categorized as late onset schizophrenia, atypical psychosis, schizoaffective disorder or DD [33]. Shifts such as these in diagnostic labeling contribute to changes in reported prevalence of the two disorders.

With respect to the prevalence of subtypes, most investigations agree that persecutory delusions are the most common in both conditions[34], followed, in DD, by jealous, somatic and erotomanic delusions [32,35].

In contrast to schizophrenia which, in addition to delusions, comes with prominent hallucinations, negative, and cognitive symptoms, DD is usually considered a disorder of delusions only. Phenotypic factorial analyses of DD, however, have identified 4 independent symptom areas: delusions, hallucinations, depression, and irritability[36]. This suggests that DD, as diagnosed today, is symptomatically heterogeneous, with symptoms that overlap to a considerable degree with those of schizophrenia. de Portugal and co-workers[37], who also investigated this question, found 4 symptom categories in DD, paranoid, cognitive, schizoid and affective, which, together, explained 59% of the variance in symptomatology.

In clinical practice, both schizophrenia and DD patients frequently present with psychiatric comorbidities, mainly affective disorders. In DD, depressive disorders have been found in 21%-55.8% of patients[38]. Women may present with more mood symptoms than men, but findings in this area are controversial[2,35]. In schizophrenia, it has been noted that delusional themes can change over time in approximately one-third of cases[39]. In terms of functional ability, patients with DD show a significantly superior global functioning than patients with schizophrenia, suggesting that DD is distinct from schizophrenia, and, on the whole, less severe[40].

CLINICAL APPROACH TO PATIENTS WITH DELUSIONS

The literature strongly suggests that, when beginning treatment with a person who is delusional, whatever the specific diagnosis, the first concern must be safety - safety for the patient, for persons who the patient believes are enemies and for family members and treating personnel who may become incorporated into the patient's delusional system. Suicide is a risk because low self-esteem often lies at the core of delusions. Adding to the concern for safety is the fact that, depending on a jurisdiction's mental health legislation, involuntary treatment can be difficult for the family to arrange, even in situations of imminent danger[41].

Once safety concerns have been allayed, the next challenge is to build a therapeutic alliance by patient and clinician working together toward common goals[42]. Clinical practice suggests that initial goals need not be ambitious but must have patient buy-in. For instance, because delusions take their toll on sleep quality, working together to improve sleep by using sleep hygiene techniques and sedatives is likely to engage initially treatment-resistant patients[43].

Succeeding at something together builds trust and paves the way to information-sharing and, ultimately, to discussion of sensitive topics such as the objective veracity of a delusional belief. But this can wait[44]. Experienced clinicians always acknowledge the subjective veracity of the belief.

When engaging patients who have difficulty with trust, many therapists recommend starting by discussing early childhood because patients are less likely to perceive past issues as threatening compared to the potential threat of the therapist dismissing their accounts of current history[45]. Whereas experience and skill are always clinically useful, there is a consensus that a therapist's genuineness is the most important ingredient in forging a trusting therapeutic bond[46].

Ongoing therapy largely consists of enhancing the patient's self-esteem, bolstering resilience and improving metacognitive skills[47]. Judiciously planting seeds of doubt about the reality of a delusion by exploring alternate explanations is a key metacognitive technique[48]. Cognitive-behavioral techniques have successfully eliminated delusional ruminations, negative beliefs about the self, interpersonal oversensitivity, as well as sleep disturbance, each of which has been shown capable of reinforcing delusions[49].

Techniques recommended for delusional jealousy consist of targeting common tendencies found in such patients, *e.g.*, inferring the emotions and intentions of others, personalizing chance occurrences, overgeneralizing from one or two experiences, and persistently anticipating catastrophe[50]. Other therapeutic targets are hypervigilance, negative self-esteem, and the inclination to mistrust others. Reframing a patient's view of a situation is an important therapeutic technique[51] *e.g.*, "He does go out a lot, but it might be because you give him a hard time at home rather than because he's seeing another woman." Experienced clinicians believe that therapists do well to embrace the role of educator, teaching patients about emotions and the many ways in which strong feelings can drive behavior[52]. Practice

sessions and homework assignments relevant to the expression of emotions are cited as a vital part of cognitive therapy and rehabilitation protocols for all forms of delusions[53].

These recommendations apply to the initial approach to patients with both DD and schizophrenia, but are less effective when the patient's cognition is impaired. Table 2 summarizes the main recommendations for an initial approach to DD.

PHARMACOLOGICAL TREATMENT

Definitions of response to antipsychotic or other pharmacological treatment vary. Response criteria based on reduction in standard rating scale scores, as is done in schizophrenia[54], have been recommended in DD[55] where, thus far, response has been defined on the basis of clinical opinion.

The most recent study in this area was an observational registry- based cohort study in a Swedish population diagnosed with DD[56]. Hospitalization and work disability were found to be less likely occurrences when antipsychotic were prescribed, compared to when they were not. Protection was best conferred by clozapine, olanzapine and all long-acting injectable antipsychotics. When comparisons were made between DD and schizophrenia, a relatively smaller dose of haloperidol (4.7 mg/d) was effective in suppressing delusional symptoms in DD than in schizophrenia (12.7 mg/d)[57]. Treatment was shorter (65 d) in DD compared to 104 d in schizophrenia. At hospital discharge, the global assessment of functioning score was also significantly higher in DD[57]. Although more studies are needed, this suggests that an acute episode of DD may respond to treatment at lower doses and within a shorter time period than an acute episode of schizophrenia. Studies on comparative longer-term response to antipsychotics are, however, lacking.

Factors influencing drug response

Adherence to prescribed drug regimens is generally acknowledged as a critical factor influencing therapeutic response. In turn, adherence is influenced by the patient's gender, age, duration of illness, comorbidities, number of concomitantly prescribed drugs, simplicity of the drug regimen, and quality of the therapeutic relationship[2,58]. Thomas and colleagues[59] have studied these factors as they pertain to schizophrenia, but this has not yet been done in DD.

Specific host genes may enhance or diminish drug response. Morimoto *et al*[57] investigated the relationship between variants of dopamine receptor genes and the tyrosine hydroxylase gene in DD patients, schizophrenia patients, and healthy controls. They found an association between genetic variability in DRD3 and plasma homovannilic acid (pHVA). Specifically, patients with DD homozygous for the DRD3 gene Ser9Ser showed higher pretreatment levels of pHVA than others, an effect especially marked, in this sample, among patients with the persecutory subtype of DD. Aided by structural and functional neuroimaging, work on the genetics of drug response in DD and schizophrenia is underway.

A multicenter positron emission tomography and magnetic resonance spectroscopy study (STRATA) tested whether striatal dopamine synthesis capacity and/or elevated anterior cingulate cortex glutamate levels can differentiate between patients with psychosis who do and do not respond to antipsychotic medications[60]. The findings revealed a potential role of glutamate levels (but not striatal dopamine synthesis) in the prediction of response.

Very few studies have investigated the biological basis of treatment response in DD. In the case of the delusional infestation subtype of DD, one study, however, identified distinct patterns of prefrontal, temporal, parietal, insular, thalamic and striatal dysfunction implicated in response[61].

Therapeutic drug monitoring is currently a promising technique that can evaluate treatment efficacy, correlate adverse events to prescribed doses and assess adherence. While it is often used in the treatment of schizophrenia, it is still rarely done when treating DD patients.

Use of antidepressants

Antidepressants have been used as monotherapy in DD when clinicians believe that the delusion is caused by depression. Paroxetine and clomipramine are examples of antidepressants commonly used [62]. Antidepressants used as an adjunct to antipsychotics is a frequent treatment strategy in both DD and schizophrenia.

NON-PHARMACOLOGICAL TREATMENTS

Cognitive therapy has been shown to be helpful in DD[63], as it is in schizophrenia[64,65]. Patients receiving CBT show a significant reduction in the strength of their delusional conviction, in the intensity of the affect associated with their delusion, and in the frequency of behaviors resulting from their delusion.

Table 3 presents the main pharmacological and psychosocial interventions used in the management of patients with DD and schizophrenia.

Table 2 Initial approach to patients with delusional disorder

Issue	Target	Recommendation
Safety	For patient, imagined persecutor, and personnel	Safety is the first step
Therapeutic alliance	Patient-clinician relationship is crucial (determines adherence to follow-up)	Building trust for working together on common goals
Enhancing self-esteem and improving skills	Supporting self-esteem and modeling cognitive and social skills	Improving metacognitive and social skills
Targeting emotions and behaviors	Helping patients to identify emotions and prevent acting on delusions	Cognitive-behavioral therapies identify stressors and risk behaviors

Table 3 Main interventions for the treatment of delusional disorder and schizophrenia

Interventions	Explanation	Remarks
Antipsychotics[57-60]	Antidopaminergic action of these drugs dominates the literature	Genetic studies are inconclusive about the role of dopamine
Antidepressants[62]	Antidepressants treat comorbid depression	Reversing depression can sometimes eliminate delusions
Cognitive behavioral therapy[63-65]	Addresses cognitive biases and unwanted behavior	Stops adverse behaviors and improves adherence to treatment

RISK OF SUICIDE

Neither suicide antecedents nor suicide rates have, to date, been compared in DD and schizophrenia. Existing studies have established the percentage of suicidal behavior in patients with DD to be between 8% and 21%[66]. In schizophrenia, it hovers around 10%[67]. In both disorders, men are more at risk for completing suicide than women[38]. The somatic subtype and the persecutory subtype of DD are most associated with suicide[30] whereas, in schizophrenia, suicide appears to depend not on delusional theme but on the presence of command hallucinations[68].

DISCUSSION

When we began our review, we wanted to address 3 questions: (1) Do epidemiological data differentiate DD from schizophrenia? (2) Do clinical features or psychiatric comorbidities differ in DD and schizophrenia? And (3) Are there data that show differences between DD and schizophrenia with respect to treatment response to either pharmacological or non-pharmacological treatment?

We found an overlap between the diagnosis of DD and schizophrenia, with boundaries often very blurred. As characterized in DSM-5, the middle age onset of DD distinguishes it from the earlier onset in schizophrenia. The literature gives a prototypical picture of schizophrenia as one of hallucinations, cognitive, and negative symptoms in addition to delusions, with function deteriorating over time. Relatively good function is maintained in DD. While this disorder is also characterized by symptoms other than delusions (mainly affective symptoms), delusions predominate. Treatment response to antipsychotic medication appears to be similar in the two conditions, although DD patients, as a group, are older, and would be expected, as one study has shown, to require comparatively lower doses to achieve symptom reduction. When compared to younger age, older age, however, can limit the benefits of pharmacotherapy because of an increased frequency of potential drug interactions and adverse events. An adequate long term comparison of drug response in the two conditions is lacking. Clinical reports recommend the addition of antidepressants to the medication regimen of patients with DD, but large-scale trials to prove the usefulness of this strategy have not yet been conducted. Specific symptoms, when targeted by cognitive behavioral therapies, respond in both DD and schizophrenia, although efficacy trials in DD are, to date, limited.

The content of delusions seems more understandable in DD than it often is in schizophrenia but the major theme is one of persecution in both conditions. In general, the prevalence rate for delusional disorder is significantly lower than that for schizophrenia.

Importantly, a persecutory delusion is such a firmly held belief that it can often lead to behavior which endangers the believer and the persons implicated in the delusion. Safety is a paramount concern; suicide is an important risk. Evidence for the success of current interventions into prevention of suicide and aggression remains relatively weak.

There are many limitations to this narrative review. There is an extremely large literature on schizophrenia, with well-controlled randomized trials of treatment options. This does not yet exist for delusional disorders. Because of the symptom overlap and the prevalence disparity as well as the age discrepancy, well-defined comparative groups are difficult to recruit. Much of the literature on delusional disorders consists of small case series or reports of individual cases. To accurately answer the questions posed in this review, methodologically well-conducted, multicenter trials are required. The review should nonetheless be helpful for clinicians, especially with respect to initial approaches to patients with delusions, and the cautions about safety.

CONCLUSION

This brief review covers the recent literature on difference between two non-affective psychoses, DD and schizophrenia. The former is much rarer and presents at older ages. More often than schizophrenia, DD is accompanied by depression, which increases the risk for suicide. Acting out against imagined persecutors is a potential danger in both disorders. While delusions are prominent in both schizophrenia and DD, other psychiatric symptoms may also be present and may require targeted treatment. In contrast to schizophrenia, outside the sphere of the delusion, cognitive functions are usually not impaired in DD, so that a therapeutic alliance is possible and is essential for treatment to succeed. Research into the efficacy of specific treatments is, however, sparse in DD.

This review covers what is known and not known about similarities and differences between schizophrenia and DD, with the hope that highlighting contrasts between these two overlapping conditions will ultimately improve the treatment of both. Future research must address the difficult task of designing rigorous clinical trials that compare response to therapeutic interventions for delusions in individuals whose primary diagnoses may vary.

FOOTNOTES

Author contributions: Gonzàlez-Rodriguez A conceived the idea of writing this review, based on our joint clinical experience treating patients with delusional disorder and schizophrenia; both authors contributed equally to decisions about the method and the content; both authors contributed equally to the literature search, and to decisions about what studies to include; both authors shared in the clinical contributions; there were several drafts; Seeman MV perfected the final version.

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Altered thalamic subregion functional networks in patients with treatment-resistant schizophrenia

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Abstract

BACKGROUND

The thalamus plays a key role in filtering information and has extensive interconnectivity with other brain regions. A large body of evidence points to impaired functional connectivity (FC) of the thalamocortical pathway in schizophrenia. However, the functional network of the thalamic subregions has not been investigated in patients with treatment-resistant schizophrenia (TRS).

AIM

To identify the neural mechanisms underlying TRS, we investigated FC of thalamic sub-regions with cortical networks and voxels, and the associations of this FC with clinical symptoms. We hypothesized that the FC of thalamic sub-regions with cortical networks and voxels would differ between TRS patients and HCs.

METHODS

In total, 50 patients with TRS and 61 healthy controls (HCs) matched for age, sex, and education underwent resting-state functional magnetic resonance imaging (rs-fMRI) and clinical evaluation. Based on the rs-fMRI data, we conducted a FC analysis between thalamic subregions and cortical functional networks and voxels, and within thalamic subregions and cortical functional networks, in the patients with TRS. A functional parcellation atlas was used to segment the thalamus into nine subregions. Correlations between altered FC and TRS symptoms were explored.

RESULTS

We found differences in FC within thalamic subregions and cortical functional networks between patients with TRS and HCs. In addition, increased FC was observed between thalamic subregions and the sensorimotor cortex, frontal medial cortex, and lingual gyrus. These abnormalities were associated with the pathophysiology of TRS.

CONCLUSION
Our findings suggest that disrupted FC within thalamic subregions and cortical functional networks, and within the thalamocortical pathway, has potential as a marker for TRS. Our findings also improve our understanding of the relationship between the thalamocortical pathway and TRS symptoms.

Key Words: Treatment-resistant schizophrenia; Thalamus; Rs-fMRI; Functional connectivity; Thalamocortical pathway

Core Tip: The thalamus represents the interface between the sensory and motor systems, and is a major hub for cognitive processes. A large body of evidence has demonstrated involvement of the thalamus in the pathophysiology of schizophrenia. Most previous studies employing resting state functional magnetic resonance imaging used the whole thalamus as a seed region to identify abnormalities in thalamic connectivity. To identify more specific disturbances, we conducted functional connectivity analysis of thalamic subregions with cortical networks and voxels in patients with treatment resistant schizophrenia. Important novel findings regarding the pathophysiology of treatment resistant schizophrenia were obtained.

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INTRODUCTION

The thalamus is an important deep gray matter structure that transmits sensory information from the peripheral sensory nervous system to the cortex, and serves as a major hub for cognitive processes[1]. Given its 'central roles' in perception and cognition, disturbances of which are major symptoms of schizophrenia (SZ), the thalamus has been focused on in brain imaging studies of SZ. Structural magnetic resonance imaging (sMRI) studies revealed thalamic surface deformation in patients with first-episode and chronic SZ, as well as reduced thalamus volume in a cohort of early onset psychosis patients[2-5]. Moreover, resting state functional magnetic resonance imaging (rs-fMRI) studies have consistently revealed decreased thalamic connectivity with the prefrontal cortex (PFC) in SZ, as well as increased connectivity with motor and somatosensory cortical areas[6]. Furthermore, these aberrant connectivities were also observed in clinical high-risk (CHR) individuals, suggesting that thalamic dysconnectivity onsets prior to the disease itself[7,8].

Previous studies treated the thalamus as a homogeneous structure, averaging blood oxygen level-dependent (BOLD) signals across the entire thalamus. However, this approach may fail to capture disturbances in specific networks, so it is necessary to investigate functional connectivity (FC) between sub-regions of the thalamus and cortex to better understand altered neural circuits in SZ. Several atlases segment the thalamus, including histological-[9,10], structural-[11,12] and functional-based atlases[13]. In this study, we used a functional parcellation atlas to identify nine thalamic sub-regions having strong FC with various cortical functional networks[13]. The atlas allows the topological roles of thalamic nuclei in functional brain networks to be elucidated through graph-theoretic network analysis of rs-fMRI data. Few studies have examined altered FC in thalamic sub-regions in SZ. Three studies reported findings similar to those of investigations using average BOLD signals for the thalamus, *i.e.*, weaker PFC-thalamic network connectivity and stronger motor-thalamic and somatosensory-thalamic network connectivity compared to healthy controls (HCs)[14,15,16]. On the other hand, Gong *et al*[17] observed loss of connectivity between several thalamic sub-regions and the sensorimotor system, anterior cingulate cortex, and cerebellum in patients with SZ. To the best of our knowledge, no study has examined the FC of thalamic sub-regions in patients with treatment-resistant schizophrenia (TRS).

We hypothesized that the FC of thalamic sub-regions with cortical networks and voxels would differ between TRS patients and HCs. To identify the neural mechanisms underlying TRS, we investigated FC of thalamic sub-regions with cortical networks and voxels, and the associations of this FC with clinical symptoms.

MATERIALS AND METHODS

Participants

This study included 111 subjects (50 patients with TRS and 61 HCs). SZ was diagnosed based on the DSM-IV[18] criteria by a board-certified psychiatrist and psychiatric residents. The exclusion criteria were as follows: alcohol or substance use disorder; intellectual disability (IQ ≤ 70); current or past neurological disease, serious medical illness, or pregnancy; and claustrophobia. Treatment resistance was defined as follows: failure to respond to at least two different antipsychotic medications administered in adequate doses (equivalent to ≥ 600 mg/day of chlorpromazine [CPZ]) for at least 6 wk; and persistence of clinically relevant positive or negative symptoms (at least one positive or negative symptom and a Positive and Negative Syndrome Scale (PANSS) score of ≥ 4)[19]. The second criterion was not applied to patients on clozapine. The severity of symptoms was evaluated within a week of fMRI using the PANSS[20,21]. HCs were recruited *via* advertisements and interviewed using the Structured Clinical Interview for DSM, Non-Patient Edition (SCID-NP)[22]. A requirement for study inclusion was no previous or current psychiatric disorders, neurological disorders, or significant medical conditions. Controls having a first-degree relative with a psychiatric disorder were also excluded. All participants were aged between 19 and 60 years, and all were confirmed as right-handed by the Edinburgh Handedness Inventory[23]. They all participated voluntarily and provided written informed consent. The study was approved by the Ethics Committee of Jeonbuk National University Hospital (approval number: CUH 2012-08-001).

Image acquisition and preprocessing

The rs-fMRI and sMRI data were obtained at the Jeonbuk National University Hospital using a 3T Verio scanner (Magnetom Verio; Siemens, Erlangen, Germany) with a 12-channel standard quadrature head coil. Three-dimensional T1-weighted images were acquired using a magnetization-prepared rapid gradient echo sequence (repetition time [TR]: 1,900 ms; echo time [TE]: 2.5 ms; flip angle: 9°; field of view [FOV]: 250 mm; image matrix: 256 × 246 mm; voxel size: 1.0 × 1.0 × 1.0 mm^3; 176 slices). A 5-minute resting-state scan consisting of 150 contiguous echo-planar imaging functional images (TR: 2,000 ms; TE: 30 ms; flip angle: 90°; FOV: 220 mm; image matrix: 64 × 64 mm; voxel size: 3.4 × 3.4 × 5.0 mm^3; 26 slices) was also obtained. During resting-state image acquisition, participants were asked to relax with their eyes closed, but not to sleep. MRI data processing was conducted using the Statistical Parametric Mapping software package, version 12 (SPM12; Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (MathWorks, Natick, MA, United States). The first three volumes were discarded to adjust for magnetization equilibrium. Functional images were slice-time corrected, realigned to the first image of each series, and co-registered with each participant's structural image. Then, the co-registered functional data were transformed into standard anatomical space through spatial normalization of each T1 image to the Montreal Neurological Institute (MNI) template. Normalized images were smoothed using an 8 mm full-width at half-maximum isotropic Gaussian kernel. The voxels were resampled (2.0 mm × 2.0 mm × 2.0 mm). Head motion was considered excessive when framewise displacement (FD) was > 0.5 mm. FD values were computed using the CONN toolbox (version 14f; http://www.nitrc.org/projects/conn). Participants for whom more than 10% of the volumes showed excessive head motion were excluded from the analysis[24]. The component correction (CompCor)[25] function of the CONN toolbox was used to increase the accuracy of grey matter (GM) signals by removing physiological noise, such as heart rate and breathing signals, followed by removal of the components of interest from the global, white matter (WM), and cerebrospinal fluid (CSF) signals. The linear trend was then removed and a band-pass filter (0.008 < f < 0.09 Hz) was applied.

Functional connectivity analysis

The functional parcellation atlas[13] was used to segment the thalamus into nine subregions (Supplementary Figure 1). Nine thalamic subregions showing strong FC with nine cortical functional networks were identified, *i.e.,* the default mode (DM), cingulo-opercular occipital (CO), somatomotor (SM), frontal parietal (FP), lateral occipital (LO), medial occipital (MO), medial temporal (MT), temporal, and superior FP networks. The components of each cortical functional network are described in Supplementary Table 1. For each region of interest (ROI) of the thalamus and cortical functional networks, the BOLD signal was averaged to generate the BOLD time series. FC analysis was performed between thalamic ROIs and cortical functional network ROIs, within the nine thalamic and nine cortical functional network ROIs, and between the thalamic ROIs and all cortical voxels (using the CONN toolbox). The patient and HC groups were compared using one-way analysis of variance (ANOVA). We used a voxel-level height threshold of $P < 0.01$ (uncorrected) and a cluster-level extent threshold of $P < 0.05$, corrected for multiple comparisons using the family wise error (FWE). We performed 10,000 permutation tests using the CONN toolbox (www.nitrc.org/projects/conn, RRID:SCR_009550).

Statistical analysis

Demographic and clinical data were compared between the two groups using a two-sample *t*-test or

Chi-square test. For partial correlation analysis, a ROI extraction tool (http://software.incf.org/software/rex)in the CONN toolbox was used to extract Fisher's Z-transformed signal intensity values for brain regions with significant group differences at an uncorrected p-value of < 0.01. Relationships between the extracted Z-scores and PANSS scores were analyzed using age, sex, and FD as covariates. The analyses were performed using SPSS software (ver. 20.0; SPSS Inc., Chicago, IL, United States).

RESULTS

Functional connectivity between and within thalamic subregions and cortical functional networks in TRS

There were no significant differences in age, sex, or education level between the two groups (Table 1). The TRS group showed significantly increased FC between thalamic subregion 2 and the MO network (t = 2.78, P < 0.05) compared to the HC group. The TRS group also exhibited significantly increased FC of the CO network with the MO (t = 3.29, P < 0.05) and superior MT networks, and between the MT network and superior FP network (t = 2.63, P < 0.05) (t = 4.31, P < 0.05) compared to the HC group. On the other hand, the TRS group exhibited decreased FC of thalamic subregion 1 with thalamic subregions 2 and 9 (t = -2.95, P < 0.05) and of thalamic subregion 2 with thalamic subregions 3 and 4 (t = -4.58, P < 0.05), compared to the HC group. Also, in the TRS group, decreased FC of the FP network was observed with the MT (t = -2.69, P < 0.05) and superior FP networks (t = -2.73, P < 0.05), between the DM and CO networks (t = -2.90, P < 0.05), and between the MO and MT networks (t = -2.90, P < 0.05), compared to the HC group (Table 2, Figure 1).

Functional connectivity between thalamic subregions and cortical voxels in TRS

Compared to the HC group, the TRS group exhibited significantly increased FC between thalamic subregion 1 and the left lingual gyrus (t = 5.22, P < 0.05), thalamic subregion 2 and the left precentral gyrus (t = 5.22, P < 0.05), thalamic subregion 3 and the right supplementary motor cortex (t = 5.26, P < 0.05), thalamic subregion 6 and the frontal medial cortex (t = 7.05, P < 0.05), the left postcentral gyrus (t = 5.26, P < 0.05) and right precentral gyrus (t = 4.79, P < 0.05), and thalamic subregion 9 and the left precentral gyrus (t = 5.26, P < 0.05). On the other hand, the TRS group exhibited significantly decreased FC between thalamic subregion 3 and the left intracalcarine cortex (t = -4.18, P < 0.05) compared to the HC group (Table 3, Figure 2).

Correlations between altered ROI-to-ROI functional connectivity and PANSS scores

The Z-values of FP and MT network connectivity were negatively correlated with positive symptoms, negative symptoms, general pathophysiology, and PANSS total scores (r = -0.411, P = 0.005; r = -0.414, P = 0.004; r = -0.427, P = 0.003; and r = -0.472, P = 0.001, respectively) in the TRS group. Also, negative correlations were observed between the Z-value of the DM and MT networks and negative symptoms, general pathophysiology, and the PANSS total score (r = -0.316, P = 0.032; r = -0.322, P = 0.029; and r = -0.298, P = 0.044, respectively) (Table 4, Figure 3).

Correlations between altered seed-to-voxel functional connectivity and PANSS scores

No significant relationship was found between altered FC and PANSS scores at an uncorrected p-value of < 0.01 (Supplementary Table 2). Therefore, the analysis was performed against an uncorrected p-value of < 0.05 (Supplementary Table 3). In the TRS group, the Z-value of thalamic subregion 3 and the right lingual gyrus FC was negatively correlated with positive symptoms, negative symptoms, general pathophysiology, and the PANSS total score (r = -0.342, P = 0.020; r = -0.355, P = 0.015; r = -0.350, P = 0.017; and r = -0.396, P = 0.007, respectively). However, there was a positive correlation between the Z-value of thalamic subregion 2 and the left precentral gyrus and the score for general pathophysiology (r = 0.292, P = 0.049) (Table 5, Figure 4).

DISCUSSION

The thalamus represents the interface between the sensory and motor systems, and is a major hub for cognitive processes. A large body of evidence has demonstrated involvement of the thalamus in the pathophysiology of SZ. Most previous studies employing rs-fMRI used the whole thalamus as a seed region to identify abnormalities in thalamic connectivity. To identify more specific disturbances, we conducted FC analysis of thalamic subregions with cortical networks and voxels in patients with TRS. Important novel findings regarding the pathophysiology of TRS were obtained, and are discussed below.

Table 1 Demographic and clinical characteristics of patients with treatment-resistant schizophrenia and healthy controls

Characteristics	TRS (*n* = 50)	HCs (*n* = 61)	*P* value
Age (yr)	42.64 (9.79)	39.89 (9.52)	0.137
Sex			
Male (%)	32 (64%)	29 (48%)	0.083
Female (%)	18 (36%)	32 (52%)	
Education (years)	13.53 (2.27)	13.33 (1.92)	0.613
Duration of illness (mo)	215.22 (110.09)	-	-
PANSS			
Positive symptoms	15.96 (4.99)	-	-
Negative symptoms	16.00 (7.30)	-	-
General psychopathology	28.40 (7.74)	-	-
Total	60.36 (17.52)	-	-
SOFAS	49.00 (8.81)	-	-
Medication			
Chlorpromazine equivalent (mg/d)	915.33 (411.41)	-	-

Data given as mean (SD). HCs: Healthy controls; PANSS: Positive and Negative Syndrome Scale; SOFAS: Social and Occupational Functioning Assessment Scale; TRS: Treatment Resistant Schizophrenia.

Table 2 Comparison of between- and within-functional connectivity of thalamic subregions and cortical functional networks between patients with treatment-resistant schizophrenia (*n* = 50) and HCs (*n* = 61)

Seed region	*t* value	*P* FWE	*P*-unc	Brain region
TRS > HCs				
Thalamic subregion 2	2.78	< 0.001	0.006	Medial occipital network
Cingulo-opercular network	3.29	0.008	0.001	Medial occipital network
	2.63	0.008	0.010	Superior fronto-parietal network
Medial temporal network	4.31	< 0.001	< 0.001	Superior fronto-parietal network
TRS < HCs				
Thalamic subregion 1	-4.58	< 0.001	< 0.001	Thalamic subregion 2
	-2.95	0.019	0.004	Thalamic subregion 9
Thalamic subregion 2	-3.16	< 0.001	0.002	Thalamic subregion 3
	-3.38	< 0.001	0.001	Thalamic subregion 4
Fronto-parietal network	-2.69	< 0.001	0.008	Medial temporal network
	-2.73	0.008	0.007	Superior fronto-parietal network
Default mode network	-2.90	< 0.001	0.004	Cingulo-opercular network
	-3.37	< 0.001	0.001	Medial occipital network
	-5.40	< 0.001	< 0.001	Medial temporal network

Thresholded at $P < 0.01$, uncorrected; $P < 0.05$, Family Wise Error rate corrected. TRS: Treatment-resistant schizophrenia; HCs: Healthy controls.

The network analysis revealed significant FC only between thalamic subregion 2 and the MO network. By mapping the coordinates of 333 cortical ROIs, identified using the Gordon atlas[26], to the masks of cortical functional networks[13], we were able to identify subcomponents of the MO network, including the superior frontal gyrus, superior parietal gyrus, inferior parietal gyrus, precentral gyrus, postcentral gyrus, supplementary motor area, insula, precuneus, Rolandic operculum, and paracentral

Table 3 Comparison of functional connectivity of thalamic subregions with cortical voxels between patients with treatment-resistant schizophrenia (*n* = 50) and healthy controls (*n* = 61)

Seed Region	MNIcoordinate	Cluster Size	*t* value	*P* FWE	*P*-unc	Name (voxel size - region)
TRS > HCs						
Thalamic subregion 1	-14 -44 -12	612	5.22	0.009	< 0.001	339 - Left lingual gyrus142 - Left cerebellum 4_5
Thalamic subregion 2	-28 -10 66	1309	5.30	< 0.001	< 0.001	604 - Left precentral gyrus483 - Left postcentral gyrus
Thalamic subregion 3	10 6 54	523	5.26	0.003	< 0.001	173 - Right supplementary motor cortex
Thalamic subregion 6	-8 38 -22	1229	7.05	< 0.001	< 0.001	186 - Frontal medial cortex
	-36 -34 62	358	5.26	0.030	< 0.001	342 - Left postcentral gyrus
	26 -28 60	467	4.79	0.006	< 0.001	305 - Right precentral gyrus132 - Right postcentral gyrus
Thalamic subregion 9	-44 -14 42	380	5.26	0.020	< 0.001	281 - Left precentral gyrus
TRS < HCs						
Thalamic subregion 3	6 -90 -2	458	-4.18	0.008	< 0.001	163 - Left intracalcarine cortex

Thresholded at $P < 0.01$, uncorrected; $P < 0.05$, Family Wise Error rate corrected. TRS: Treatment-resistant schizophrenia; HCs: Healthy controls.

Table 4 Correlation between Z score of significantly altered between-and within-connectivity of thalamic subregions and cortical functional networks between groups and Positive and Negative Syndrome Scale[1]

Connectivity	*r* value	*P* value
Positive symptoms		
Thalamic subregion 1 - Thalamic subregion 9	-0.267	0.073
Fronto-parietal network - Medial temporal network	-0.411	0.005
Negative symptoms		
Default mode network - Medial temporal network	-0.316	0.032
Fronto-parietal network - Medial temporal network	-0.414	0.004
General psychopathology		
Default mode network - Medial occipital network	-0.257	0.085
Default mode network - Medial temporal network	-0.322	0.029
Fronto-parietal network - Medial temporal network	-0.427	0.003
Total		
Default mode network - Medial temporal network	-0.298	0.044
Fronto-parietal network - Medial temporal network	-0.472	0.001

[1]Partial correlation analysis with age, sex, and head motion (framewise displacement) as covariates; $P < 0.01$, uncorrected; $P < 0.05$, Family Wise Error rate corrected.

lobule. As the MO network consists of many different regions, it is difficult to determine which of them have the most clinical importance. However, thalamic subregion 2 has a high participation coefficient (PC), indicating that it serves as a connector hub[13]; as such, altered functioning of thalamic subregion 2 may mediate cortical-to-cortical communication in patients with TRS. The other significant FC results were related to connectivity between thalamic subregions and cortical functional networks. Among these, decreased FC between several thalamic subregions in TRS patients was of particular interest, because previous studies mainly focused on the thalamocortical or corticothalamic pathway. In line with our results, Gong *et al* (2019)[17] reported deceased within-thalamic FC in an SZ group compared to controls. Furthermore, a decreased thalamic volume in chronic SZ patients was seen[27,28,29] as well as reduced regional glucose metabolism in the medial dorsal nucleus and posterior thalamus of

Table 5 Correlation between Z score of significantly altered connectivity between thalamic subregions and cortical voxels between groups and Positive and Negative Syndrome Scale[1]

Connectivity	*r* value	*P* value
Positive symptoms		
Thalamic subregion 3 - Right lingual gyrus	-0.342	0.020
Thalamic subregion 2 - Right precentral gyrus	0.270	0.069
Thalamic subregion 7 - Precuneus cortex	-0.285	0.055
Negative symptoms		
Thalamic subregion 3 - Right lingual gyrus	-0.355	0.015
Thalamic subregion 6 - Right precentral gyrus	-0.247	0.098
General psychopathology		
Thalamic subregion 2 - Left precentral gyrus	0.292	0.049
Thalamic subregion 3 - Right lingual gyrus	-0.350	0.017
Thalamic subregion 9 - Left precentral gyrus	0.262	0.079
Total		
Thalamic subregion 3 - Right lingual gyrus	-0.396	0.007

[1]Partial correlation analysis with age, sex, and head motion (framewise displacement) as covariates; $P < 0.05$, uncorrected; $P < 0.05$, Family Wise Error rate corrected.

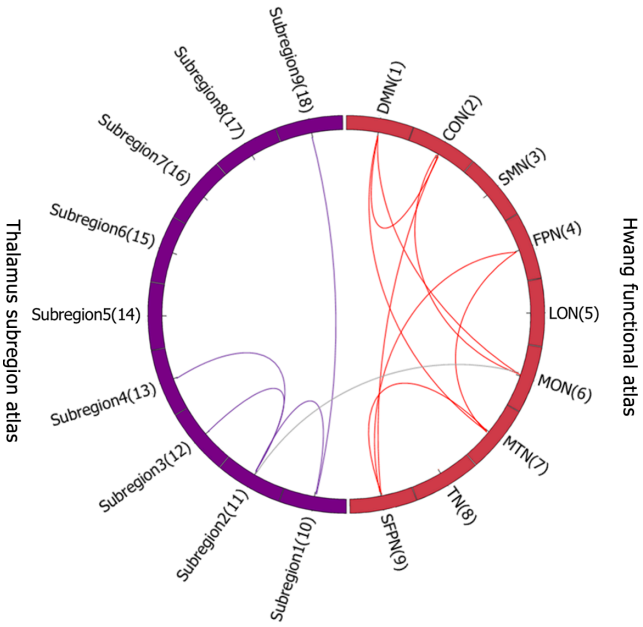

Figure 1 Altered functional connectivity of thalamus subregions and cortical functional networks between treatment resistant schizophrenia and healthy control groups. Between- and within-connectivity were presented in grey color and in each network's color respectively. CON: Cingulo-Opercular Network; DMN: Default Mode Network; FPN: Fronto-Parietal Network; LON: Lateral Occipital Network; MON: Medial Occipital Network; MTN: Medial Temporal Network; SFPN: Superior Fronto-Parietal Network; SMN: Somato-Motor Network; TN: Temporal Network.

antipsychotic-naïve patients with SZ[30]. It may be that reduced intrathalamic connectivity mediates the key role of the thalamus in perception, motor function, and cognitive integration[1], in turn contributing to the development of pathophysiology in TRS. More commonly described abnormalities in TRS include hyperconnectivity and hypoconnectivity between cortical functional networks. In this study, each cortical functional network consisted of many heterogeneous areas, and the results were significant even when using the BOLD time series for large cortical areas. Therefore, these findings may be considered as functional biomarkers for TRS. However, our expectation that the role of the thalamus as a connector hub would be disrupted in TRS was not confirmed.

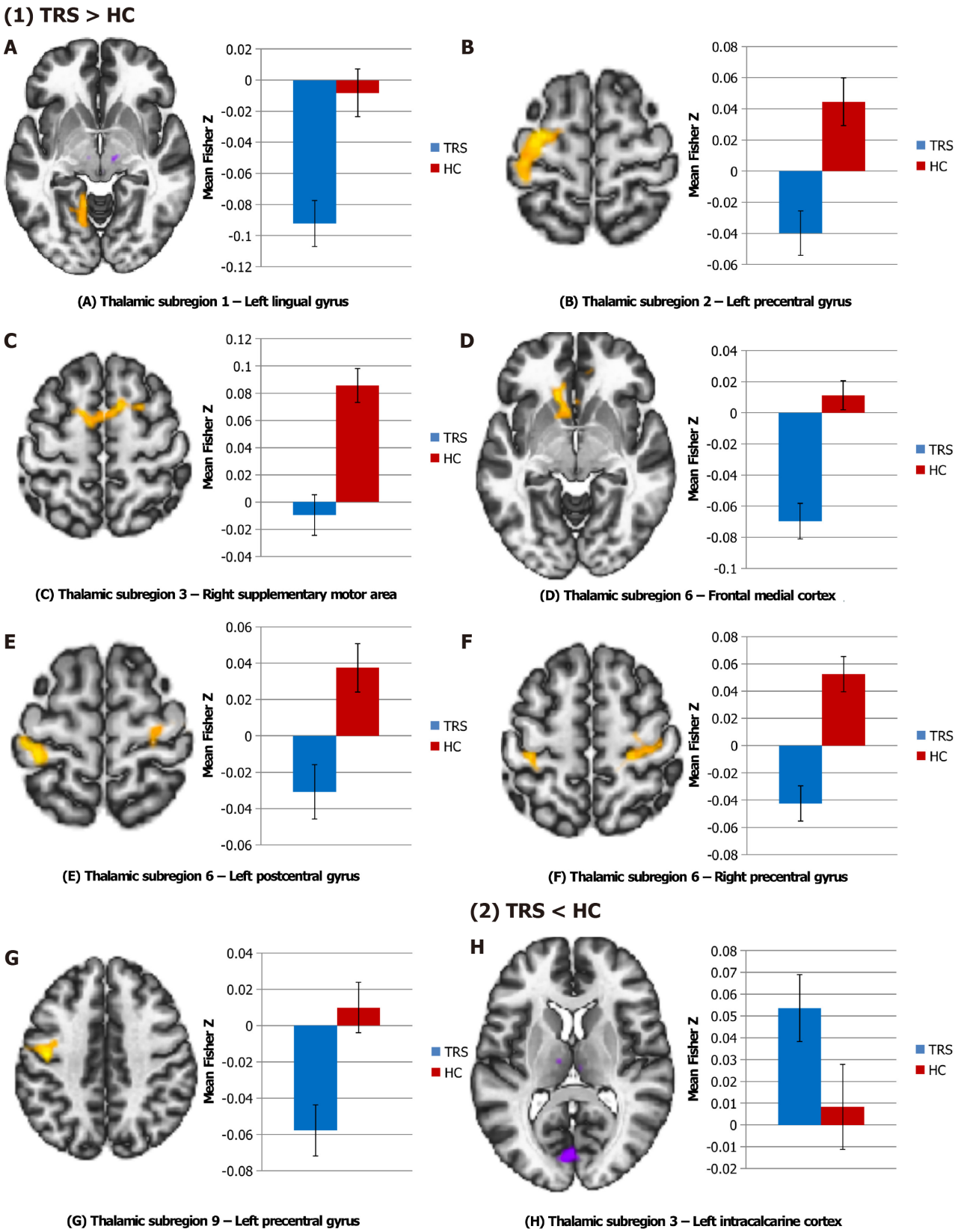

Figure 2 Altered thalamus subregion-based functional connectivity between treatment resistant schizophrenia and healthy control groups. Significant differences were revealed between the (A) Thalamic subregion 1 and Left lingual gyrus; (B) Thalamic subregion 2 and Left precentral gyrus; (C) Thalamic subregion 3 and right supplementary motor area; (D) Thalamic subregion 6 and Frontal medial cortex; (E) Thalamic subregion 6 and Left postcentral gyrus; (F) Thalamic subregion 6 and Right precentral gyrus; (G) Thalamic subregion 9 and Left precentral gyrus; and (H) Thalamic subregion 3 and Left intracalcarine cortex. The functional connectivity Z values of regions showing significant differences are presented in bar graph.

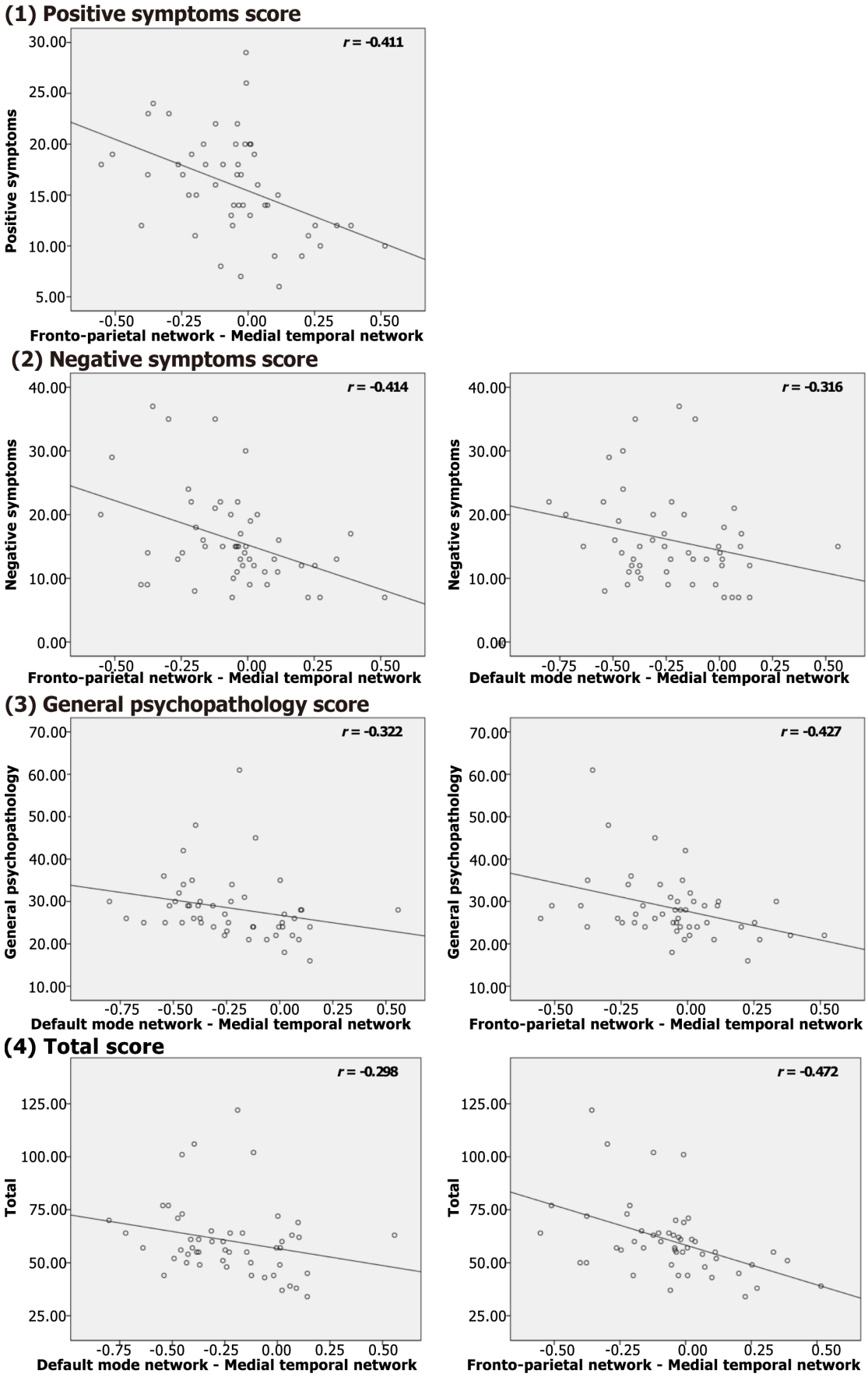

Figure 3 Associations between the significantly altered region of interest to region of interest functional connectivity and Positive and Negative Syndrome Scale scores in the treatment resistant schizophrenia group.

With respect to thalamic connectivity with cortical voxels, we identified significant hyperconnectivity of five thalamic subregions with various cortical regions in patients with TRS compared to HCs. Interestingly, most of these involved increased connectivity to the precentral and postcentral gyri and supplementary motor cortex. Considering the role of these areas in integrating sensorimotor information and coordinating physical movements[31,32], these findings may be relevant to the sensory and motor abnormalities found in TRS, such as hallucinations and neurological soft signs. Many studies have reported increased functional coupling between the thalamus and sensorimotor cortices in SZ[33,34,35,36,37]. However, this is the first study to report hyperconnectivity between thalamic subregions and the sensorimotor cortex in TRS. We also found increased connectivity to the frontal medial cortex and lingual gyrus. This is in contrast to previous research showing a reduction in FC of the thalamus with the prefrontal and cingulate cortices in SZ, based on signals averaged across the entire thalamus [33,34,36,38,39,40,41] as well as separate signals for individual thalamic subregions[15,16,17]. However, the subjects in previous studies were not patients with TRS. The medial PFC has been shown to play a fundamental role in a wide range of social cognitive abilities, such as self-reflection, person perception, and theory of mind/mentalizing[42]. Also, the lingual gyrus has been implicated in visual memory[43] and divergent thinking[44]. Therefore, increased thalamo-frontal or thalamo-lingual connectivity might serve as a marker for TRS. The potential associations of FC with social cognition and divergent thinking warrant further investigation. Finally, decreased connectivity of thalamic subregion 3 with the intracalcarine cortex was observed in our TRS patients. A similar result was reported in chronic SZ[17]. Given that the calcarine cortex is known to be involved in the processing of visual mental imagery[45], an fMRI study using a visual mental imagery task could be useful for exploring the pathophysiological mechanisms of TRS.

With regard to our analyses of altered ROI-to-ROI FCs, FC between the FP and MT networks, and between the DM and MT networks, showed negative relationships with positive symptoms, negative symptoms, general pathophysiology, and PANSS total scores. These findings suggest that altered connectivity between intracortical functional networks is associated with overall pathophysiology rather than specific symptom domains. This is intuitive considering that each cortical functional network consists of many heterogenous cortical regions. Regarding our analyses of cortical voxels, FC between thalamic subregion 3 and the right lingual gyrus showed negative relationships with positive symptoms, negative symptoms, general pathophysiology, and PANSS total scores. Even after considering the role of the lingual gyrus in visual memory and divergent thinking, it is difficult to determine how this altered FC is associated with overall pathophysiology. However, it may be that impairment of thalamic subregion 3, in terms of its role as a connector hub, has significant effects on the integration of cortical information. Finally, the positive association of FC between thalamic subregion 2 and the precentral gyrus with general pathophysiology accords with the findings of prior studies[17,33]. Even though patients with SZ often show abnormal involuntary movements or neurological soft signs related to the function of the precentral gyrus, it is difficult to identify relationships between motor functions and general pathophysiology[46].

CONCLUSION

Several limitations of this study need to be considered. First, although the use of a functional parcellation atlas to segment the thalamus into subregions was a strength of this study, the roles and precise locations of thalamic subregions are still largely unknown, making it difficult to determine which specific regions had the largest effect on the results. Second, we did not recruit all subtypes of TRS patients, as recommended by the Treatment Response and Resistance in Psychosis Working Group[19]. The proportions of positive, negative, and positive and negative subtypes were 22%, 14%, and 32%, respectively. The remaining 32% of patients did not meet the criteria for the positive or negative subtype, because we applied a rating of moderate severity to just one symptom item. This should be addressed in future studies. Third, the TRS patients were all heavily medicated, so it is unclear whether the significant changes in FC reported above were a consequence of the disease process or medication. In this context, it will be important to determine the relative importance of illness duration, the number of psychotic episodes, and medication. Despite these weaknesses, this is the first report on altered FC of the thalamocortical pathway in TRS using thalamic subregions as seeds. In summary, in our TRS patients, we found altered FC between various thalamic subregions, between various cortical functional networks, and between thalamic subregions and various cortical regions. These abnormalities were associated with overall pathophysiology. Collectively, these results suggest that disrupted FC within thalamic and cortical functional networks, and within the thalamocortical pathway, could serve as markers for TRS. This study improves our understanding of the relationships between the thalamocortical pathway and symptoms of TRS.

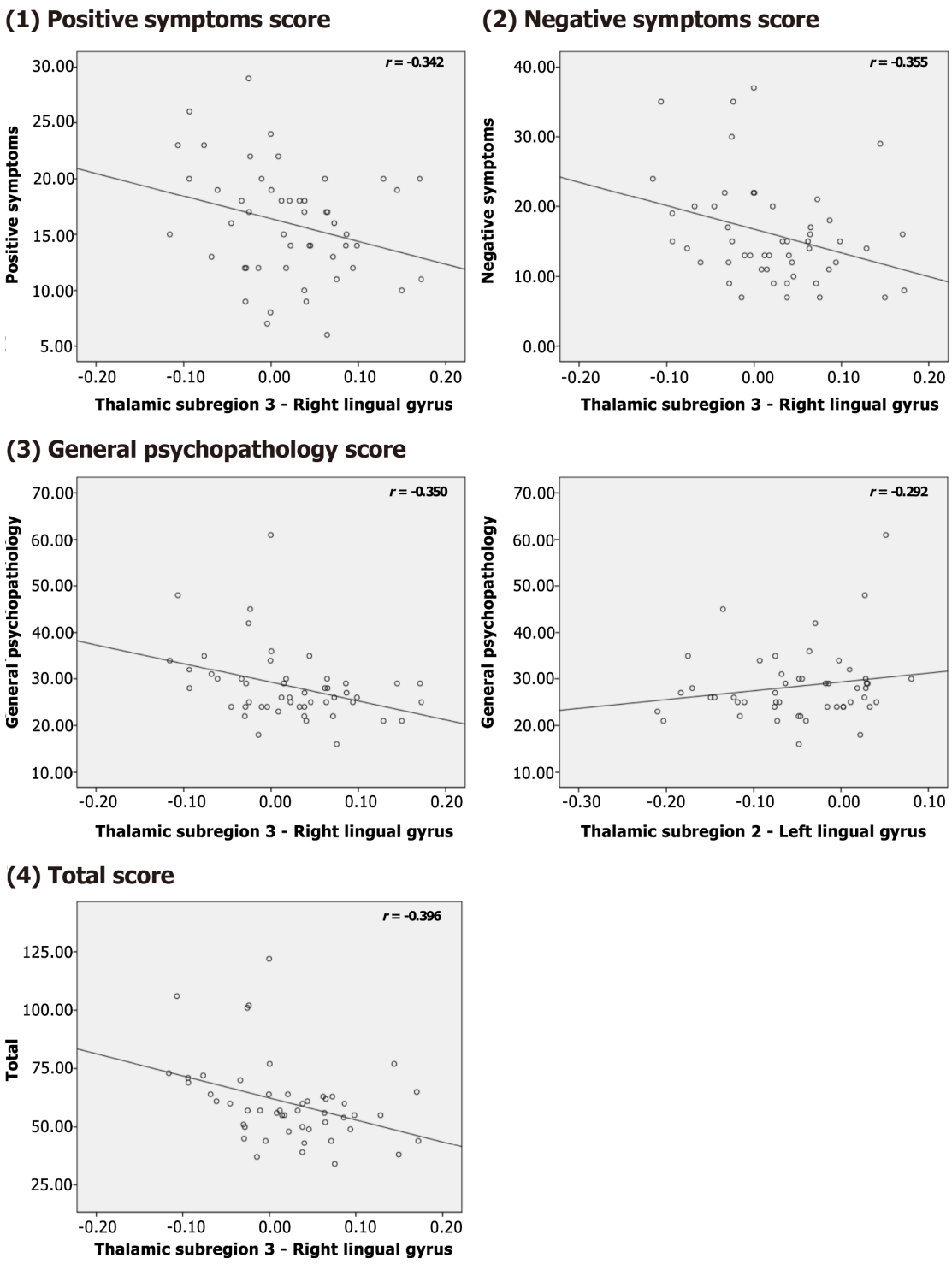

Figure 4 Associations between the significantly altered seed to voxel functional connectivity and Positive and Negative Syndrome Scale scores in the treatment resistant schizophrenia group.

ARTICLE HIGHLIGHTS

Research background

The thalamus is an important deep gray matter structure that transmits sensory information from the peripheral sensory nervous system to the cortex, and serves as a major hub for cognitive processes. Previous studies treated the thalamus as a homogeneous structure, averaging blood oxygen level-dependent signals across the entire thalamus. However, this approach may fail to capture disturbances in specific networks, so it is necessary to investigate functional connectivity (FC) between sub-regions of the thalamus and cortex to better understand altered neural circuits in Schizophrenia (SZ).

Research motivation
To the best of our knowledge, no study has examined the FC of thalamic sub-regions in patients with treatment-resistant schizophrenia (TRS).

Research objectives
To identify the neural mechanisms underlying TRS. We hypothesized that the FC of thalamic sub-regions with cortical networks and voxels would differ between TRS patients and HCs (Healthy Controls).

Research methods
This study included 111 subjects (50 patients with TRS and 61 HCs). The rs-fMRI and sMRI data were obtained at the Jeonbuk National University Hospital using a 3T Verio scanner (Magnetom Verio; Siemens, Erlangen, Germany) with a 12-channel standard quadrature head coil. The functional parcellation atlas was used to segment the thalamus into nine subregions. FC analysis was performed between thalamic ROIs and cortical functional network ROIs, within the nine thalamic and nine cortical functional network ROIs, and between the thalamic ROIs and all cortical voxels. Demographic and clinical data were compared between the two groups using a two-sample *t*-test or Chi-square test. For partial correlation analysis. Relationships between the extracted Z-scores and PANSS scores were analyzed using age, sex, and FD as covariates.

Research results
There were no significant differences in age, sex, or education level between the two groups. We found differences in FC within thalamic subregions and cortical functional networks between patients with TRS and HCs. In addition, increased FC was observed between thalamic subregions and the sensorimotor cortex, frontal medial cortex, and lingual gyrus. These abnormalities were associated with the pathophysiology of TRS.

Research conclusions
The thalamus represents the interface between the sensory and motor systems, and is a major hub for cognitive processes. A large body of evidence has demonstrated the involvement of the thalamus in the pathophysiology of SZ. we found altered FC between various thalamic subregions, between various cortical functional networks, and between thalamic subregions and various cortical regions. These abnormalities were associated with overall pathophysiology. Collectively, these results suggest that disrupted FC within thalamic and cortical functional networks, and within the thalamocortical pathway, could serve as markers for TRS.

Research perspectives
This study improves our understanding of the relationships between the thalamocortical pathway and symptoms of TRS.

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FOOTNOTES
Author contributions: Chung YC conceptualized the study; Tsogt U, Shen J, Kim WS, Odkhuu S, and Chung YC performed the study and acquired data; Kim WS conducted experiment and statistical analysis; Kim WS drafted the manuscript; Tsogt U, Shen J, Kim WS, and Odkhuu critically reviewed the manuscript; Chung YC finalized the manuscript; all authors approved the final manuscript.

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STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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ORIGINAL ARTICLE

Observational Study

Changes in the amplitude of low-frequency fluctuations in specific frequency bands in major depressive disorder after electroconvulsive therapy

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Abstract

BACKGROUND

Major depressive disorder (MDD) tends to have a high incidence and high suicide risk. Electroconvulsive therapy (ECT) is currently a relatively effective treatment for MDD. However, the mechanism of efficacy of ECT is still unclear.

AIM

To investigate the changes in the amplitude of low-frequency fluctuations in specific frequency bands in patients with MDD after ECT.

METHODS

Twenty-two MDD patients and fifteen healthy controls (HCs) were recruited to this study. MDD patients received 8 ECT sessions with bitemporal placement. Resting-state functional magnetic resonance imaging was adopted to examine regional cerebellar blood flow in both the MDD patients and HCs. The MDD patients were scanned twice (before the first ECT session and after the eighth ECT session) to acquire data. Then, the amplitude of low-frequency fluctuations (ALFF) was computed to characterize the intrinsic neural oscillations in different bands (typical frequency, slow-5, and slow-4 bands).

RESULTS

Compared to before ECT (pre-ECT), we found that MDD patients after the eighth ECT (post-ECT) session had a higher ALFF in the typical band in the right middle

frontal gyrus, posterior cingulate, right supramarginal gyrus, left superior frontal gyrus, and left angular gyrus. There was a lower ALFF in the right superior temporal gyrus. Compared to pre-ECT values, the ALFF in the slow-5 band was significantly increased in the right limbic lobe, cerebellum posterior lobe, right middle orbitofrontal gyrus, and frontal lobe in post-ECT patients, whereas the ALFF in the slow-5 band in the left sublobar region, right angular gyrus, and right frontal lobe was lower. In contrast, significantly higher ALFF in the slow-4 band was observed in the frontal lobe, superior frontal gyrus, parietal lobe, right inferior parietal lobule, and left angular gyrus.

CONCLUSION
Our results suggest that the abnormal ALFF in pre- and post-ECT MDD patients may be associated with specific frequency bands.

Key Words: Electroconvulsive therapy; Resting-state functional magnetic resonance imaging; Major depressive disorder; Amplitude of low-frequency fluctuations; Specific frequency bands

Core Tip: In this study, we explored changes in the intrinsic neural activity in major depressive disorder (MDD) patients who underwent electroconvulsive therapy (ECT) procedures by calculating amplitude of low-frequency fluctuations (ALFF) values for different bands. Compared to pre-ECT values, the ALFF in the slow-5 band was significantly increased in the right limbic lobe, cerebellum posterior lobe, right middle orbitofrontal gyrus, and frontal lobe in post-ECT patients, whereas the ALFF in the slow-5 band in the left sublobar region, right angular gyrus, and right frontal lobe was lower. In contrast, significantly higher ALFF in the slow-4 band was observed in the frontal lobe, superior frontal gyrus, parietal lobe, right inferior parietal lobule, and left angular gyrus. Our findings demonstrated that the ALFF alterations in post-ECT patients are dependent on specific frequency bands. These results may help us to understand more fully the potential therapeutic mechanisms of ECT for MDD patients.

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INTRODUCTION

Depression is a common mental illness with a high recurrence rate and risk of suicide. The main clinical manifestations are persistent depression, lack of interest in and pleasure from normal activities, severe grief, and even stupor[1-3]. According to the latest report released by the World Health Organization in 2017[4], approximately 322 million people suffer from depression worldwide. The prevalence rate is 4.4%, and more than 1 million people commit suicide every year due to depression. The lifetime prevalence of major depression is 16.2%. Antidepressants and behavioral therapies are the most commonly used treatments, but as many as one in three patients remain unresponsive to initial treatment[5,6]. With rapid and high response rates, electroconvulsive therapy (ECT) is usually used when other treatments fail. It is particularly important in suicidal, psychotic, or catatonic depression[7]. Although clinical efficacy has suggested that ECT is the most effective treatment for major depressive disorder (MDD), the mechanism of action of ECT is unclear[8], and little is known about the relationship between symptom improvement and the neurobiological effects associated with ECT. Some neurobiological effects are not necessary for therapeutic effects during ECT[9], and the potential adverse reactions require its clinical application to be very cautious and limited.

Antidepressant treatment response studies have reported changes in gray matter volumes and cortical thickness associated with improvement in MDD patients[10-12]. For ECT treatment, some changes have been reported in the structure of the gray matter in MDD patients. Yrondi *et al*[13] reported that gray matter changes occurred after several ECT sessions. Some studies have confirmed that ECT can also induce changes in the hippocampal formation and other brain regions[14-18]. Abbott *et al*[14] found a significant increase in the volume of the right hippocampus. Bouckaert *et al*[15] found that the caudate nucleus increased in volume. ECT also had vital effects on the dentate gyrus[19].

In addition to measuring alterations in brain structure in patients with MDD after ECT treatment, functional magnetic resonance imaging (fMRI) also has been used to detect changes in brain activity. Beall *et al*[20] adopted task fMRI to find that remission after ECT for MDD is connected to decreased activation in emotional regulation but increased resting connectivity. Abbott *et al*[21] used resting-state fMRI to measure the variations in MDD patients after multiple ECT sessions. This research reported that functional connectivity increased in two networks: (1) Posterior default mode (p_DM) and the dorsomedial prefrontal cortex (DMPFC); and (2) The left dorsal lateral prefrontal cortex (l_DLPFC) and p_DM. The fronto-temporal connectivity and the functional connectivity strength of the left angular gyrus in MDD were also found to be responses to ECT[7,22]. Redlich *et al*[9] used fMRI to find an increase in amygdala activity in patients with ECT, whereas activity after ECT was significantly reduced. Sinha *et al*[23] applied graph theory to fMRI data and revealed significant differences in the brain regions of patients with depression before and after ECT. To assess the alterations in depressive patients with ECT, data-driven methods also have been adopted[24,25]. However, there were still no consistent antidepressant responses observed in previous studies[26].

Many studies have revealed different functional activities of the brain since rs-fMRI was adopted by Biswal *et al*[27] to study spontaneous brain activity. To date, most studies have examined spontaneous low-frequency oscillation (LFO) activities at the frequency band of 0.01-0.1 Hz. However, some studies observed that neuronal oscillations are distributed linearly on the natural logarithmic scale and that independent frequency bands are generated by distinct oscillators with specific properties and physiological functions[28-30]. Moreover, neighboring frequency bands within the same neuronal network may compete or interact with each other[31]. The rs-fMRI LFO can be decomposed into the following frequency bands: slow-6 (0-0.01 Hz), slow-5 (0.01-0.027 Hz), slow-4 (0.027-0.073 Hz), slow-3 (0.073-0.198 Hz), and slow-2 (0.198-0.25 Hz). Zuo *et al*[32] found that the low-frequency amplitudes in the slow-5 band are smaller than those in the slow-4 band in the basal ganglia, thalamus, precuneus, and so on. Meanwhile, many studies have presented different measures of the nature of rs-fMRI. Among them, the amplitude of low-frequency fluctuations (ALFF) is a reliable representation of whole-brain rs-fMRI signals[33-35]. ALFF has been widely adopted because it directly correlates with the intensity of spontaneous neural activity in the resting state with regard to energy metabolism[36,37]. Frequency-dependent changes in ALFF have already been used to investigate some brain network mechanisms and disease phenotypes, such as chronic schizophrenia, late-onset depression, chronic tinnitus, and social anxiety disorder[28,30-40]. These studies showed that intrinsic functional activities of brain networks are correlated with different frequency bands.

In the current study, we investigated the alterations of the ALFF at different frequency bands (slow-5 (0.01-0.027 Hz), slow-4 (0.027-0.08 Hz)) in MDD patients before and after ECT. Then, the differences before and after ECT were explored.

MATERIALS AND METHODS

Subjects

Twenty-two inpatients (14 females and 8 males, aged 34.4 ± 10.1, range 21-55 years old) who had been diagnosed with major depression at the Mental Health Center, the First Affiliated Hospital of Chongqing Medical University were recruited. Fifteen gender- and age-matched healthy controls (HCs) (10 females and 5 males, aged 36.1 ± 9.4, range 21-55 years old) were recruited to participate in the investigation. All patients underwent blood tests, electrocardiogram, electroencephalogram, X-ray, and physical examination before ECT[41]. The study was approved by the local ethics committee of Chongqing Medical University accordance with the ethical standards laid down in the Declaration of Helsinki. Each patient gave written informed consent.

The inclusion criteria for the MDD patients included the following: (1) Agreeing to receive ECT; (2) meeting the unipolar major depressive diagnostic criteria according to the Diagnostic Statistical Manual-IV[42] (two trained senior psychiatrists carried out the structured clinical interviews and made the diagnoses); (3) no contraindications to MRI scanning; (4) Hamilton Depression Scale (HAMD)[43] score greater than 21; and (5) age between sixteen and sixty years. The exclusion criteria for the patients were as follows: (1) Severe somatic disease; (2) substance abuse; (3) pregnancy or lactation; (4) depression with other mental illnesses[44]; and (5) exposure to ECT or mood stabilizers in the preceding one month. HCs had no history of their own or family mental illness.

ECT procedures

The Thymatron DGx (Somatics LLC, Lake Bluff, IL, United States) was used to perform the ECT for all 22 MDD patients at the Mental Health Center of the First Affiliated Hospital of Chongqing Medical University. Each patient received eight ECT treatments within three weeks. Specifically, the procedures were administered 3 times per week (Monday, Wednesday, and Friday mornings) for the first two weeks and 2 times per week (Monday and Friday mornings) for the 3rd week. The time and frequency of ECT treatment were the same for all patients. Before ECT, water and food intake were restricted for the patients beginning at midnight. Before receiving the first ECT and after the eighth ECT, all patients were

administered MRI scans, fMRI scans, and HAMD scores. Antidepressants and antipsychotics were not used during the ECT treatment period.

In every ECT process, the patients received anesthesia with sodium thiopental (3.0-5.0 mg/kg) and succinylcholine (0.5-1.0 mg/kg). In this study, the ECT electrodes were placed in the bitemporal position. According to the seizure response and adverse reactions (if any) during ECT, the electrical stimulation intensity was individually accommodated. In the first ECT, the seizure threshold was measured by the minimum electrical dose that elicited a seizure for at least 25 s[45]. Each time the initial dose failed to cause seizures, the output charge of the 5% ECT device was increased, and the patient was re-stimulated after 30 s. The patient underwent up to three electrical stimulations at one ECT. If the seizure threshold measurements failed in the first session, stimulation with 2 times the last dose was performed in the next session. To achieve a therapeutic effect and reduce side effects, the electrical dosage was set at 1.5-2 times the seizure threshold in subsequent ECT treatment sessions according to the extent of seizure. If the clinician determined that the clinical symptoms of depression had not been adequately improved after eight sessions, we continued the ECT course for the patients to up to 12 ECT sessions. For the sake of the comparison, each patient underwent MRI scanning after the eighth ECT treatment.

Mood ratings

Depression symptoms of the patients were measured by the 24-item HAMD Rating Scale on the same day as brain scanning. The psychiatrists performed the clinical assessments of depression for all patients twice. The first time was within 24 h before the 1st ECT treatment (pre-ECT). The second time was within 24 h after the 8th ECT treatment (post-ECT).

Data acquisition

Image data were collected with the MRI scanner system (3.0-T, GE Signa) at the Mental Health Center of Chongqing Medical University. Both the HCs and the MDD patients were instructed to relax, stay awake, keep their eyes closed, and avoid thinking during the scanning process. The resting-state functional images were collected with an echo planar imaging sequence. The image parameters were recorded as follows: repetition time/echo time, 2 s/30 milliseconds; field of view, 240 mm × 240 mm; data matrix, 64 × 64; flip angle, 90°; slices, 30; slice thickness, 5 mm; volumes, 200. The scan lasted 6 min and 50 s per scan.

Functional image data preprocessing

Using the statistical parametric mapping software platform, functional image data preprocessing was carried out by DPABI (Data Processing Assistant for rs-fMRI, http://www.restfmri.net, by YAN Chao-Gan *et al*[46]). The preprocessing procedure on the rs-fMRI data included the following: (1) We abandoned the first 10 volumes because the signals of the participants' adaptation to the scanning environment were unstable. Then, the remaining 190 volumes were retained; (2) Head motion correction was performed. Subjects with a head motion of more than 1.5 mm in any direction of the 3 coordinate axes (x, y, and z) or angular motion of more than 1.5° were excluded from this study; (3) Considering the delay of the acquisition, slice timing was conducted. There were 30 Layers in a scan. The odd-numbered layers started and were followed by the even-numbered layers; (4) Spatial normalization was carried out. The fMRI images were registered to the standard Montreal Neurological Institute space and were resampled to 3 mm × 3 mm; (5) We adopted the Gaussian kernel with full-width at half-maximum of eight mm to fulfill the spatial smoothing; and (6) The linear trend of the functional image data was removed. Finally, the normalized image data were subjected to bandpass filtering with frequency ranges of 0.01-0.08 Hz.

ALFF analyses

A fast Fourier transform can be used to obtain the frequency domain for the time series signal. Moreover, we adopted the average square root of the power spectrum to denote the ALFF value of a given voxel. Then, the intensity of spontaneous LFO can be measured by the ALFF. In the present study, the ALFF was performed by the REST software toolkit (Resting-State fMRI Data Analysis)[47] in two different frequency ranges (slow-5: 0.01-0.027 Hz, slow-4: 0.027-0.073 Hz) separately. The ALFF of the typical band (0.01-0.08 Hz) was also computed for comparative purposes.

Statistical analyses

To explore the changes in ALFF at different frequency bands before and after ECT, the effects of ECT treatment on MDD and frequency alterations were examined by REST[47]. Two-sample two-sided t-tests were adopted to assess the differences between the MDD group and the HC group. We applied paired t-tests to measure the ALFF alterations before and after ECT. The statistical maps were corrected by multiple comparisons with a significance level of $P < 0.05$ (bilateral) using AlphaSim as well as a height threshold of $P < 0.01$ and a minimum cluster size = 85. To find the difference between pre-ECT and post-ECT with the clinical measure, the significant alterations of ALFF values in the regions of interest (ROIs) in the brain were calculated. Moreover, the coordinates (x, y, and z) of the peak density of

Table 1 Demographic data of the major depressive disorder patients and healthy controls

Characteristic	MDDs (*n* = 22)		HCs (*n* = 15)	*P* value
Sex (male/female)	8/14		5/10	
Age (mean ± SD)	34.4 ± 10.1		36.1 ± 9.4	0.495[1]
Education years (mean ± SD)	11.61 ± 3.28		14.93 ± 3.64	0.091[1]
HAMD	Pre-ECT	30.59 ± 4.35	2.18 ± 1.32	< 0.001[2]
	Post-ECT	8.76 ± 5.58		

[1]Mann-whitney *U* nonparametric tests (criteria alpha = 0.05).
[2]Paired *t* tests between pre- and post-electroconvulsive therapy major depressive disorder patients. MDDs: Major depressive disorder patients; HCs: Healthy controls; HAMD: Hamilton Rating Scale for Depressive; ECT: Electroconvulsive therapy.

the ROIs were described in the ALFF map.

RESULTS

Clinical results

In the present study, twenty-two MDD patients (14 women, 8 men, right-handed, 34.4 ± 10.1 years old) were recruited from the Inpatient Department of Psychiatry at the First Affiliated Hospital of Chongqing Medical University. Among them, 21 patients took at least one antidepressant, and the remaining patients were receiving no medication. We adopted the 24-item HAMD to examine all MDD patients. The average score for the patients pre-ECT was 30.59 ± 4.35 (as seen in Table 1).

After 8 ECT sessions, the depression symptoms improved greatly for all patients (t_{21} = 12.61, P < 0.0001; paired t test). According to the clinical results, the HAMD scores of all 22 patients before and after ECT decreased by more than 50%. The HAMD scores of 10 patients were lower than 7. Therefore, they were considered to be remitted.

ALFF results at the typical frequency band

Compared with HCs, pre-ECT MDD patients had significant alterations in ALFF values in some brain regions (as shown in Figure 1). The typical frequency band (0.01-0.08 Hz) is reported as follows. The ALFF values in the brain areas in pre-ECT patients were lower than those in HCs, which included the posterior lobe of the cerebellum, the cerebellar tonsil, inferior semilunar lobule, temporal lobe, inferior temporal gyrus, frontal lobe, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, limbic lobe, parietal lobe, occipital lobe, and inferior parietal lobule.

We used paired *t*-tests to identify differences, which are shown in Figure 2. Moreover, Table 2 shows the group differences in ALFF in the typical frequency band between before ECT and after ECT in patients with MDD. We found that the ALFF of the right middle frontal gyrus, posterior cingulate, right supramarginal gyrus, left superior frontal gyrus, and left angular gyrus increased significantly in MDD patients after ECT. However, that of the right superior temporal gyrus decreased significantly. In our study, Monte Carlo simulations were used to conduct the multiple comparison correction for all the statistical maps with a significance level of P < 0.05. The individual voxel P is lower than 0.05, and the cluster size is larger than 2079 mm^3[48].

Differential ALFF values at the slow-5 frequency band between pre-ECT and post-ECT

The post-ECT MDD patients, relative to the pre-ECT MDD patients, demonstrated significantly higher ALFF in the slow-5 band in the right limbic lobe, bilateral cerebellum posterior lobe, right middle orbitofrontal gyrus, and frontal lobe, whereas they had lower ALFF in the slow-5 band in the left sublobar region, right frontal lobe, and right angular gyrus, as shown in Figure 3 and Table 3.

We measured the ALFF of two frequency bands (slow-4 and slow-5) in the groups after and before ECT. Significant difference maps using paired *t*-tests are shown in Figures 3 and 4.

Differential ALFF values at the slow-4 frequency band between pre-ECT and post-ECT

Compared with the pre-ECT patients, the post-ECT patients showed significantly higher ALFF in the slow-4 band in the frontal lobe, superior frontal gyrus, bilateral parietal lobe, right inferior parietal lobule, and left angular gyrus (as shown in Figure 4 and Table 4).

Table 2 Differences in amplitude of low-frequency fluctuations (0.01-0.08 Hz) between groups before and after electroconvulsive therapy

Brain region	Side	BA	MNI coordinates			Voxels	*t* values
			x	*y*	*z*		
Before ECT < after ECT							
Middle frontal gyrus	R	10, 11	30	54	3	262	3.5547
Posterior cingulate	R and L	29, 30	-3	-45	9	92	4.0993
Supramarginal gyrus	R	7, 39, 40	51	-48	30	187	3.7424
Superior frontal gyrus	L	9, 10	-12	63	24	96	3.4006
Angular gyrus	L	39, 40	-42	-72	42	193	4.0957
Before ECT > after ECT							
Superior temporal gyrus	R	13, 22, 47	54	-3	0	114	-3.1055

MNI: Montreal Neurological Institute; ECT: Electroconvulsive therapy.

Table 3 Brain regions showing significant differences in amplitude of low-frequency fluctuations at slow-5 (0.01-0.027 Hz) between groups before and after electroconvulsive therapy

Brain region	Side	BA	MNI coordinates			Voxels	*t* values
			x	*y*	*z*		
Before ECT < after ECT							
Limbic lobe	R	36	33	-21	-30	105	3.0807
Cerebellum posterior lobe	R and L	18	-12	-82	-27	116	3.4515
Frontal_Mid_Orb_R	R	11	45	48	-15	187	3.7424
Frontal lobe	R	22	48	18	36	147	3.3909
Frontal lobe	R and L	6, 8, 9, 10	-6	48	54	233	4.2748
Before ECT > after ECT							
Sublobar	L	22	-42	3	3	111	-4.015
Angular gyrus	R	13	39	12	-3	124	-3.1741
Frontal lobe	R	24	12	-36	48	228	-3.7067

MNI: Montreal Neurological Institute; ECT: Electroconvulsive therapy.

DISCUSSION

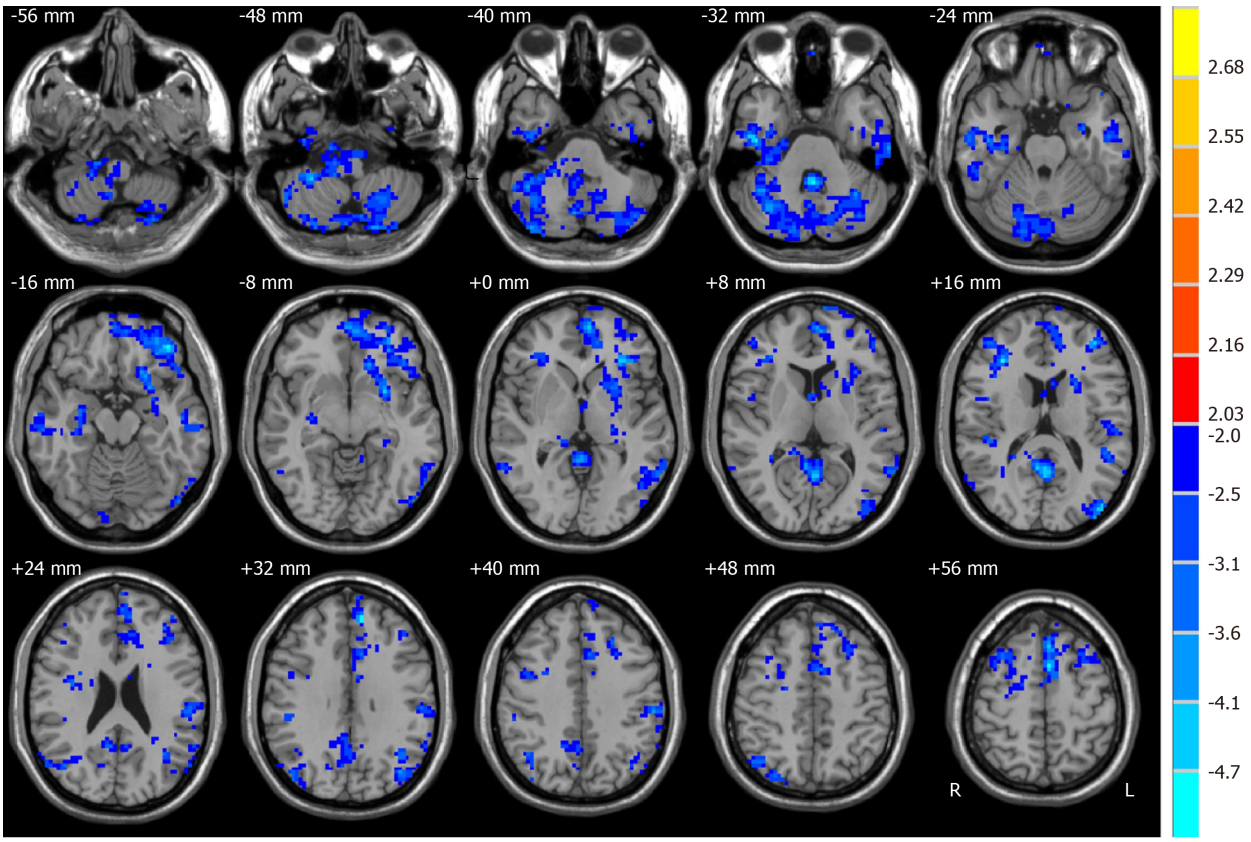
To improve MDD patients' depressive symptoms, several treatments, including ECT and transcranial magnetic stimulation, can be applied[49]. There have also been some studies using resting-state fMRI to assess antidepressant treatment response[49]. Among these methods, ECT is an effective therapy for MDD patients. Abbott *et al*[21] investigated the differences between ECT remitters and nonremitters and suggested that thane increase in functional connectivity between p_DM network areas and the l_DLPFC is a potential biomarker of recovery from depressive disorder patients. Kong *et al*[34] used regional homogeneity and ALFF to measure changes in regional resting state function after ECT in elderly MDD patients. Their results demonstrated that ECT affected regional resting-state brain function in these patients. In this study, we investigated spontaneous neural activity changes in ALFF at different frequency bands (typical frequency, slow-5, and slow-4 bands) in patients with MDD before and after ECT. We found that post-ECT, compared to pre-ECT, patients showed significant alterations in ALFF within the frequency bands in some brain areas. Our findings further showed that the ALFF alterations in post-ECT patients were dependent on specific frequency bands.

Compared with HCs, MDD patients showed significant differences in ALFF with a frequency band of 0.01-0.08 Hz in numerous brain regions[50-53]. The present study also found that pre-ECT patients had lower ALFF values than HCs in widely distributed brain areas, including the cerebellum posterior lobe,

Table 4 Brain regions showing significant differences in amplitude of low-frequency fluctuations at slow-4 (0.027-0.08 Hz) between groups before and after electroconvulsive therapy

Brain region	Side	BA	MNI coordinates			Voxels	*t* values
			x	*y*	*z*		
Before ECT < after ECT							
Frontal lobe, superior frontal gyrus	R and L	9, 10, 11, 47	51	45	-15	243	3.3179
Parietal lobe, inferior parietal lobule	R	39, 40	57	-60	21	131	2.8756
Parietal lobe, angular gyrus	L	39, 40, 19, 7	-45	-63	36	256	4.1322
Parietal lobe	R	7	15	-69	63	129	3.9572

MNI: Montreal Neurological Institute; ECT: Electroconvulsive therapy.

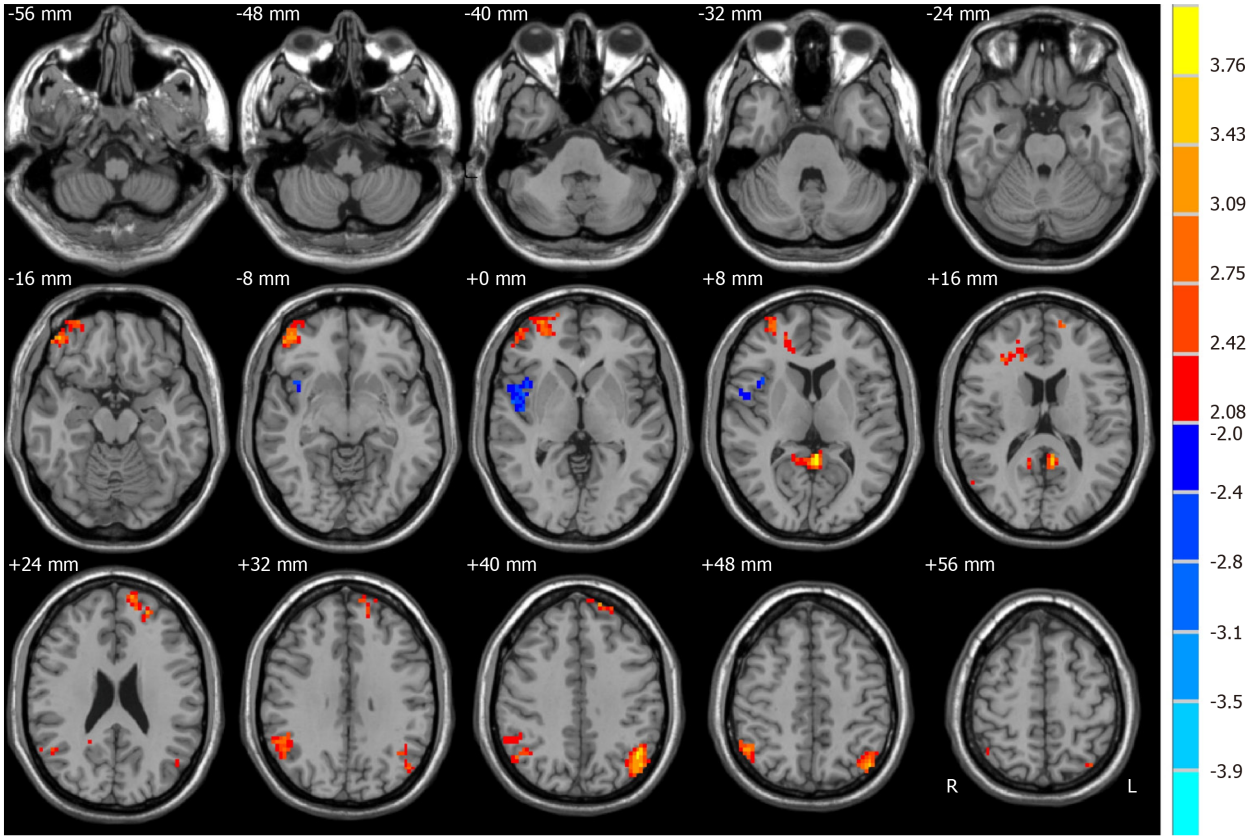


DOI: 10.5498/wjp.v12.i5.708

Figure 1 Brain regions with significant alterations in amplitude of low-frequency fluctuations in the typical band (0.01-0.08 Hz) between healthy controls and pre-electroconvulsive therapy patients. The red region indicates that the amplitude of low-frequency fluctuations in pre-electroconvulsive therapy (ECT) patients was larger than that in healthy controls (HCs). In contrast, the blue region represents HCs that were larger than pre-ECT patients.

cerebellar tonsil, inferior semilunar lobule, temporal lobe, inferior temporal gyrus, frontal lobe, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, limbic lobe, parietal lobe, occipital lobe, and inferior parietal lobule. In the comparison of ALFF in the typical frequency band in MDD patients before and after ECT, we found that the right middle frontal gyrus, posterior cingulate, right supramarginal gyrus, left superior frontal gyrus, and left angular gyrus increased significantly after ECT. However, the right superior temporal gyrus decreased significantly. The results were similar to those of previous studies[34,41].

Baria *et al*[54] found that the lower frequency bands had higher power. Thus, subcortical structures with higher frequency bands usually have less power. In contrast, the brain cortexes, including the prefrontal and parietal cortexes, exhibit higher power[55]. In addition, Zuo *et al*[32] and Han *et al*[56] demonstrated that the regions of the default mode network are more active in the slow-5 band, whereas



DOI: 10.5498/wjp.v12.i5.708

Figure 2 Brain regions with significant alterations in amplitude of low-frequency fluctuations in the typical band (0.01-0.08 Hz) for pre- and post-electroconvulsive therapy. The red region indicates that the amplitude of low-frequency fluctuations (ALFF) in post-electroconvulsive therapy (ECT) patients was larger than that in pre-ECT patients. In contrast, the blue region represents areas for which the ALFF in pre-ECT patients was larger than that in post-ECT patients.

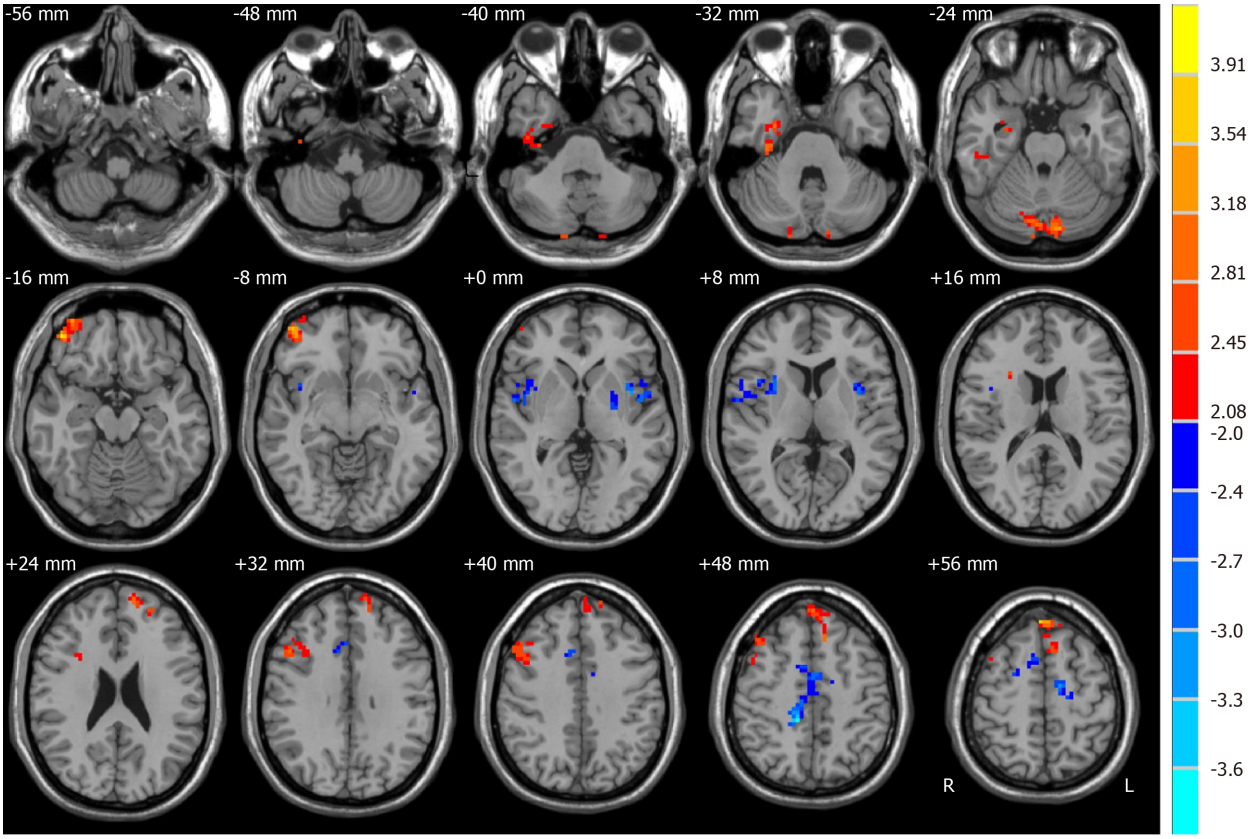
the basal ganglia are dominant in the slow-4 band. In this study, compared to pre-ECT patients, significantly higher ALFF was found in the slow-5 band in post-ECT patients in the right limbic lobe, cerebellum posterior lobe, right middle orbitofrontal gyrus, and frontal lobe. The sublobar region, angular gyrus, and frontal lobe were lower. Significantly higher ALFF in the slow-4 band was also observed in the frontal lobe, superior frontal gyrus, parietal lobe, right inferior parietal lobule, and left angular gyrus.

Many abnormal regions associated with the frontal lobe in MDD have been observed in previous studies[57,58]. Recently, a multisite rs-fMRI study reported MDD patients with hypoactivity in the medial orbitofrontal region[59]. We found a significantly higher ALFF both at the slow-5 band and slow-4 band in the frontal lobe post-ECT. As a result, abnormal activities in these brain areas might be normalized after ECT treatment[60], which might have improved the symptoms of depression. This may be considered evidence of the effectiveness of ECT for MDD.

Alterations of the limbic lobe have important effects in MDD patients[12,61]. For example, the amygdala and hippocampus are usually thought of as potential biomarkers for major depression. Compared to HCs, MDD patients illustrated decreased ALFF values in the limbic regions[50,51]. Jiao *et al*[62] and Liu *et al*[63] also demonstrated that MDD patients had abnormalities in prefrontal-limbic emotional processing. The results of the present study were consistent with these conclusions. Moreover, post-ECT patients, relative to pre-ECT patients, showed increased ALFF in the slow-5 band in the limbic lobe. This feature may also indicate an effective response to ECT treatment.

Recently, more interest has been drawn to the pathophysiology of the cerebellum in MDD[62,64,65]. Previous studies reported decreased ALFF values in the cerebellum in MDD patients[66,67]. Moreover, Zhou *et al*[66] concluded that reduced activity in the cerebellum in MDD might be a biomarker for patients. In the current study, compared with pre-ECT patients, post-ECT patients exhibited a significant increase in ALFF in the slow-5 band in the cerebellum posterior lobe. Thus, the hypothesis of Zhou *et al*[66] was supported by our results.

Post-ECT patients had lower ALFF values than pre-ECT patients for the angular gyrus in the slow-5 band. In contrast, the ALFF value was significantly increased in the slow-4 band. This was an interesting finding in the current study. The angular gyrus might play an important role in many functions, such as memory retrieval, spatial cognition, and semantic processing[68]. Previous studies reported



DOI: 10.5498/wjp.v12.i5.708

Figure 3 Brain regions with significant alterations in amplitude of low-frequency fluctuations at slow-5 (0.01–0.027 Hz) for pre- and post-electroconvulsive therapy. The red region indicates that the amplitude of low-frequency fluctuations in post-electroconvulsive therapy (ECT) patients was larger than that in pre-ECT patients. In contrast, the blue region represents pre-ECT patients that were larger than that in post-ECT patients.

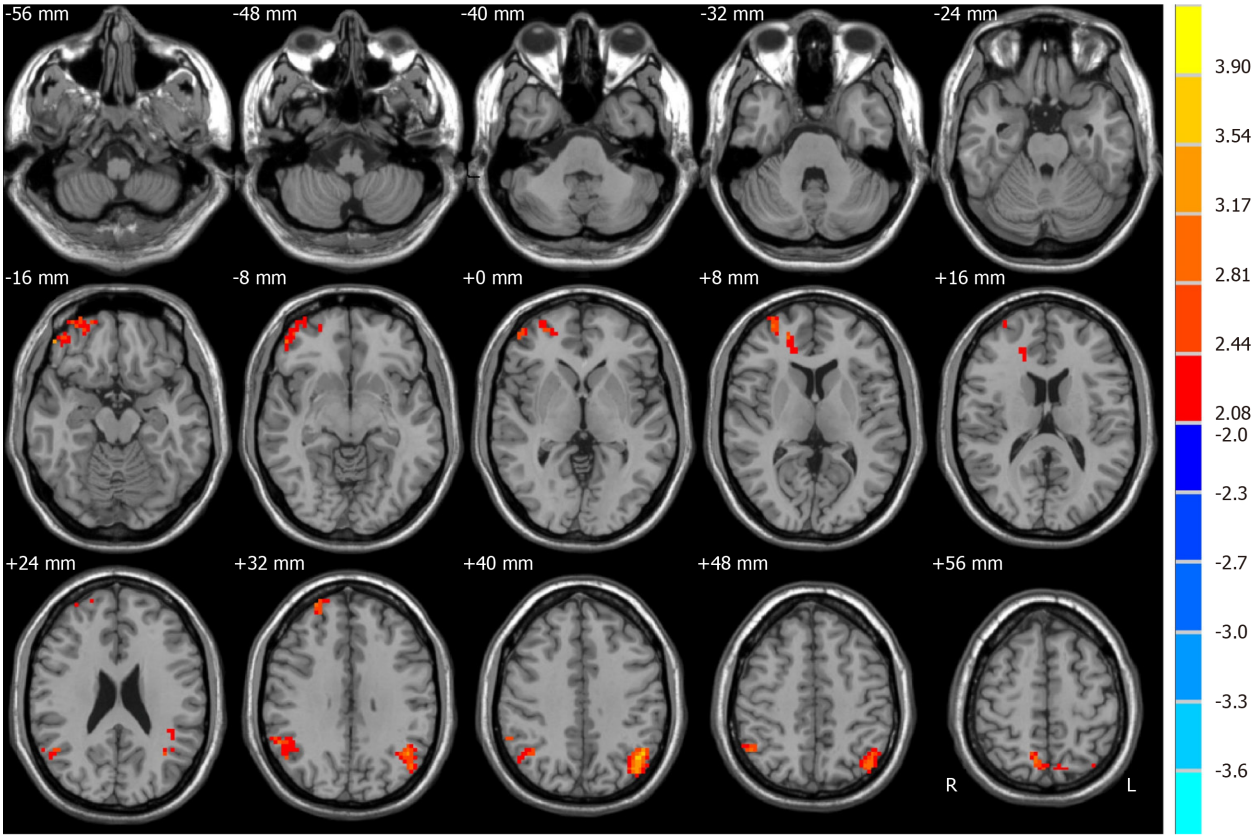
significantly increased spontaneous brain activity in the angular gyrus in MDD patients[69,70]. The alterations of ALFF in the angular gyrus at the slow-5 band in our findings can be viewed as consistent with these studies. Our study also demonstrated that the effectiveness of ECT treatment for MDD may be partly proven by significantly decreased ALFF in the slow-5 band.

Compared with HCs, decreased ALFF was exhibited in the parietal lobe in MDD patients[50,71]. In this study, the results of the comparison between HCs and pre-ECT patients were similar to this point. In addition, we found that ALFF increased significantly in the parietal lobe at the slow-4 band in post-ECT patients compared to pre-ECT patients. However, there was no difference in the slow-5 band.

There are some limitations of our study. First, the MDD patients were scanned only twice (before the first ECT session and after the eighth ECT session). To observe more alterations in spontaneous neural activity, more scans should be carried out during ECT treatment. Second, different MDD patients had divergent responses in speed and effectiveness in the practical clinic. Some unresponsive patients may receive more than eight ECT sessions[16]. For comparison, all patients were scanned after the eighth ECT session in this study. To find a more reliable relationship between ALFF and clinical symptoms, a more detailed longitudinal study should be performed pre- and post-ECT. Finally, the number of MDD patients and control subjects in the present study was relatively small. The multiple comparison tests failed due to the insufficient number of subjects. A larger sample would help us to achieve more robust results.

CONCLUSION

In this study, we explored changes in the intrinsic neural activity in MDD patients who underwent ECT procedures by calculating ALFF values for different bands (typical frequency, slow-5, and slow-4 bands). For post-ECT patients, relative to pre-ECT patients, significantly higher ALFF in the slow-5 band was observed in the right limbic lobe, cerebellum posterior lobe, right middle orbitofrontal gyrus, and frontal lobe. The ALFF of the left sublobar region, right angular gyrus, and right frontal lobe were lower. Significantly higher ALFF in the slow-4 band was also observed in the frontal lobe, superior frontal gyrus, parietal lobe, right inferior parietal lobule, and left angular gyrus. Our findings demonstrated that the ALFF alterations in post-ECT patients are dependent on specific frequency bands.



DOI: 10.5498/wjp.v12.i5.708

Figure 4 Brain regions with significant alterations in amplitude of low-frequency fluctuations at slow-4 (0.027-0.08 Hz) for pre- and post-electroconvulsive therapy. The red region indicates that the amplitude of low-frequency fluctuations in post-electroconvulsive therapy (ECT) patients was larger than that in pre-ECT patients. In contrast, the blue region represents pre-ECT patients that were larger than that in post-ECT patients.

These results may help us to understand more fully the potential therapeutic mechanisms of ECT for MDD patients. In future work, we will recruit more patients and health controls to participate this investigation. More scans will be carried out for participants to obtain more robust results. The changes in cognitive function will also be monitored.

ARTICLE HIGHLIGHTS

Research background

The mechanism of efficacy of electroconvulsive therapy (ECT) for major depressive disorder (MDD) is still unclear. Intrinsic functional activities of brain networks are correlated with different frequency bands.

Research motivation

The amplitude of low-frequency fluctuations (ALFF) at different frequency bands (slow-5 (0.01-0.027 Hz), slow-4 (0.027-0.08 Hz)) in MDD patients may be changed regularly before and after ECT.

Research objectives

To investigate the alterations of the amplitude of low-frequency fluctuations in slow-5 (0.01-0.027 Hz) and slow-4 (0.027-0.08 Hz) in patients with MDD after ECT.

Research methods

Resting-state functional magnetic resonance imaging and the intrinsic neural oscillations in different bands were adopted to analyze the changes in MDD patients before and after ECT.

Research results

Compared to before ECT, we found that MDD patients after ECT had a higher ALFF in the typical band in some regions such as the right middle frontal gyrus and posterior cingulate. Moreover, there were

other changes in slow-5 band and slow-4 band.

Research conclusions

Our findings showed that the ALFF alterations in post-ECT patients were dependent on specific frequency bands.

Research perspectives

These changes may reveal some mechanism of efficacy of electroconvulsive therapy for major depressive disorder.

FOOTNOTES

Author contributions: Li XK conducted the statistical analysis and wrote the manuscript; Qiu HT performed the study design and interpretation of findings; Luo QH recruited the patients, collected the data; Hu J revised the manuscript.

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Institutional review board statement: The study was reviewed and approved by the (the local ethics committee of Chongqing Medical University) Institutional Review Board (Approval No. 2020-97-2).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The authors have no conflict interest.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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Relationship of depression and sleep quality, diseases and general characteristics

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Abstract

BACKGROUND

Depression is the most common type of depressive disorder. The most common sleep disorder associated with depression is insomnia. Insomnia and depression are closely related.

AIM

To investigate the relationship of designed questionnaire items and depression, and analyze the related factors with depression.

METHODS

Questionnaire included Patient Health Questionnaire-9 (PHQ-9) and Pittsburgh sleep quality index (PSQI), 12 kinds of diseases, 8 general characteristics, and 20 insomnia characteristics, totally 56 items were filled out by 411 patients enrolled.

RESULTS

All the 9 items of PHQ-9, 6 components of PSQI (except sleep duration), education, living situation, exercise, years of insomnia, western medicine treatment, Chinese medicine treatment, psychotherapy, kinds of insomnia, treatment expected to treat insomnia, psychological counseling, habit of 1 h before bed, habit of lunch break, diagnosed depression, coronary heart disease, mental illness showed significant difference between without and with depression group. By univariate analysis and multivariate analysis. The odds ratio of education, exercise, kinds of insomnia, habit of 1 h before bed, diagnosed depression, coronary heart disease (P = 0.01) showed significant difference. Their odds ratios were 0.71 (0.55, 0.93), 2.09 (1.32, 3.31), 0.76 (0.63, 0.91), 0.89 (0.81, 0.98), 0.32 (0.17, 0.60), 0.43 (0.23, 0.79).

CONCLUSION
We demonstrated that education, exercise, kinds of insomnia, habit of 1 h before bed, diagnosed depression and coronary heart disease affect the depression.

Key Words: Depression; Patient Health Questionnaire-9; Pittsburgh sleep quality index; Sleep; Insomnia

Core Tip: Depression is the most common type of depressive disorder, manifesting as single or repeated episodes, with a high risk of recurrence. Depression affects the functions of the energy and digestive system and can also lead to varying degrees of sleep difficulties, insomnia, sleep arousal and other sleep disorders. In this study, we aimed to evaluate the related factor with depression, to provide theoretical support for detection and depression therapy.

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INTRODUCTION

Depression is the most common type of depressive disorder, manifesting as single or repeated episodes, with a high risk of recurrence. There can be significant emotional, cognitive, and physical symptoms during episodes, and symptoms can resolve between episodes[1]. The main clinical manifestation is depression, which is not commensurate with the situation. It can range from sullenness to grief and even stupor. Some patients will have obvious anxiety and motor agitation. In severe cases, psychotic symptoms such as hallucinations and delusions may occur. Some patients suffer from self-injury, suicidal behavior, and even death[2]. With the accelerating pace of society, study pressure, work pressure, and life pressure increase, and the incidence of depression shows a significant upward trend. Depression has become the most important cause of the ten causes of disability-adjusted life years in every country in the world. The lifetime prevalence of depression is estimated to be 5% among adults[3, 4]. Depressive disorders have a high prevalence and high disease burden, but the treatment rates are low, with less than 10% of these patients receiving effective treatment in many countries; however, the medical prevention and treatment of depression in China still has a low recognition rate[5]. Hospitals above the prefecture-level city have a recognition rate of less than 20%, and less than 10% of patients receive relevant drug treatment. At the same time, the incidence of depression has begun to show a trend of younger age (college and even primary and secondary school students). The popularization, prevention and treatment of depression need urgent attention[6].

Depression affects the functions of the energy and digestive system and can also lead to varying degrees of sleep difficulties, insomnia, sleep arousal and other sleep disorders. Changes in sleep are one of the diagnostic criteria for depression. The probability of sleep disturbance in patients with depression is as high as 70%, which manifests as insomnia, lethargy, nightmares and disturbance of the sleep-wake cycle[7]. The most common sleep disorder associated with depression is insomnia. Insomnia and depression are closely related and share a bidirectional relationship with each other[8]. Insomnia is a demonstrated and a relative risk factor for depression. Treatment can improve or prevent major depressive episodes. The early identification of insomnia may also improve the outcomes of depression [9]. Insomnia and depression are heterogeneous processes, and the diagnostic components of insomnia and depression are likely to lead to translational progress at their nexus[10,11]. Studies have shown that poor sleep quality can lead to a decline in executive function, making it difficult to avoid negative thoughts, increasing nighttime unpleasantness, and triggering rumination, and repeated negative thoughts lead to increased suicide risk. In addition to insomnia, depressive patients may also experience somnolence during the course of the disease. Approximately 7%-8% of patients with major depressive disorder have somnolence and excessive sleep time, and approximately 25% of patients have both insomnia and somnolence[12]. More severe depression has now been shown to be associated with higher rates of substance use disorder and suicide attempts[13]. In addition, general characteristics, such as marital status and smoking, can affect subjective sleep quality. The relationship between marital status and sleep in women with depression showed that marital status was related to sleep efficiency. Married women had better sleep quality and significantly lower sleep delay than unmarried women. Compared with divorced or widowed patients, married depressed patients had better sleep quality; the stress of marriage breakdown and the loss of a partner had an important impact on sleep, and the

occurrence of an unhappy marriage and depressive symptoms caused changes in physical function, causing alcoholism and lack of sleep[14]. Smokers were reported to have more severe sleep problems than nonsmokers. Nicotine patches led to abnormal sleep, a lack of sleep, shortened sleep latency, and reduced nighttime sleep[15].

In our study, by the questionnaire designed by our team, which included a total of 56 items, we aimed to investigate the relationship between the designed questionnaire items and depression and analyze the factors related to depression.

MATERIALS AND METHODS

Study subjects

With written informed consent, this study was approved by the Fuxing Hospital affiliated with the Capital Medical University Institution Review Board. A total of 424 patients with insomnia in Yuetan Community Health Service Center and its subordinate community health service stations were enrolled as the research subjects in our study. Thirteen patients were excluded because they did not have a qualified questionnaire. Finally, 411 patients were included for further analysis. The inclusion criteria included the following items: (1) Patients who met the diagnostic points of nonorganic insomnia: their main complaints were difficulty falling asleep, difficulty maintaining sleep, or poor sleep quality; this sleep disorder occurred at least three times a week and lasted for one month or more. Focusing on sleep day and night, worrying too much about the consequences of insomnia, and dissatisfaction with sleep quantity and/or quality causes obvious distress or affects social and occupational functions. This criterion was met as long as dissatisfaction with the quantity and/or quality of sleep was the patient's only complaint; (2) Patients who had contacted their family doctor; and (3) Patients aged between 40 and 70 years old. The exclusion criteria included the following items: (1) Patients with insomnia as only one of multiple symptoms of a mental disorder or physical condition were excluded; insomnia was limited to the main mental or physical disorder; and (2) Patients with severe mental disorder were excluded.

The Patient Health Questionnaire-9 (PHQ-9) and the Pittsburgh Sleep Quality Index (PSQI) were included in our questionnaires. In addition, the questionnaires also included 12 kinds of diseases, including diagnosed depression, chronic diseases, high blood pressure, diabetes, coronary heart disease, cerebrovascular disease, enlarged prostate, cancer, mental illness, tuberculosis, chronic hepatitis, and cirrhosis. Eight general characteristics, including sex, age, education level, marital status, living situation, occupational status, income (yuan) per month and exercise, were analyzed. The percentage of sex, education level, marital status, living situation, occupational status, income (yuan) per month and exercise. The 20 insomnia characteristics included the following: years of insomnia; Western medicine treatmen; Chinese medicine treatment; psychotherapy; kind of insomnia; events related to insomnia; treatment expected to treat insomnia; traditional Chinese medicine foot baths; acupressure; psychological counseling; medicated diet; Tai Chi; traditional Chinese medicine; other traditional Chinese medicines; habit of 1 h before bed; habit of drinking tea; habit of drinking coffee; habit of drinking spirits; habit of smoking; and habit of taking a lunch break.

Survey method and quality control

Questionnaires designed by our study team were distributed to respondents by uniformly trained investigators, and the relevant contents of the questionnaires were explained to the respondents face-to-face. Then, the questionnaires were investigated and completed. After taking back the questionnaires, unqualified questionnaires with missing items were eliminated, and valid questionnaires were sorted and numbered. Quality control was carried out at the stages of data collection, data collation and result analysis. The questionnaires were completed by trained investigators instructing the subjects one-on-one. Data were entered and reviewed by trained personnel to ensure the accuracy of data entry.

Depression severity degree assessed by the PHQ-9

The PHQ-9 consists of 9 items as follows: "little interest or pleasure in doing things"; "feeling down, depressed, or hopeless"; "trouble falling or staying asleep, or sleeping too much"; "feeling tired or having little energy"; "poor appetite or overeating"; "feeling bad about yourself or that you are a failure or have let yourself or your family down"; "trouble concentrating on things, such as reading the newspaper or watching television"; "moving or speaking so slowly that other people could have noticed or being so fidgety or restless that you have been moving a lot more than usual"; and "thoughts that you would be better off dead, or thoughts of hurting yourself in some way". This questionnaire was used to evaluate depression and grade the severity of symptoms[16]. Higher PHQ-9 scores are related to decreased functional status and increased symptom-related difficulties. A PHQ-9 score of 0–4 represents no depression. Scores of 5–9 represent mild depression, 10–14 represent moderate depression, and 15–19 represent moderately severe depression. Scores of 20–27 represent severe depression.

Sleep quality assessed by the PSQI

The PSQI was used to assess the sleep quality of the subjects in the last month. It consists of 19 self-assessment items and 5 other assessment items, of which the 19th self-assessment item and the 5 other assessment items are not included in the scoring. Only the remaining 18 self-assessment items are included in the scoring. The 18 items consist of the following 7 components: subjective sleep, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction; each component is scored on a scale of 0 to 3. The cumulative score of each component is the total PSQI score, and the total score ranges from 0 to 21. The higher the score, the worse the sleep quality. It took the subjects 5 to 10 minutes to complete the questionnaire. Scores of 0–5 represent that sleep quality is very good; scores of 6–10 represents that sleep quality is okay; scores of 11–15 represent that sleep quality is average; and scores of 16–21 represent that sleep quality is poor[17].

Statistical analysis

SPSS 22.0 was used for data analysis. Excel and GraphPad Prism were used to draw the figures. Measurement data are expressed as the mean ± SD. Count data are expressed as n (%). The measurement data that conformed to a normal distribution were compared by two independent sample t tests or analysis of variance; the measurement data that did not conform to a normal distribution were compared by the rank sum test. Count data were compared by the χ^2 test. Principal component analysis (PCA) was used to analyze the contributing rate to depression. The correlation between the 9 PHQ-9 items was analyzed by Pearson correlation regression. Univariate and multivariate logistic regression was used to analyze the factors significantly associated with depression. A $P < 0.05$ was considered a statistically significant difference.

RESULTS

Relationship of the PHQ-9 items and depression

According to their PHQ-9 scores, the individuals enrolled in our study were divided into a without depression group (n = 190) and a depression group (n = 221), which included mild (n = 139), moderate (n = 49), moderately severe (n = 22), and severe depression (n = 11). First, the 9 items, including "little interest or pleasure in doing things" (Item 1), "feeling down, depressed, or hopeless" (Item 2), "trouble falling or staying asleep, or sleeping too much" (Item 3), "feeling tired or having little energy" (Item 4), "poor appetite or overeating" (Item 5), "feeling bad about yourself or that you are a failure or have let yourself or your family down" (Item 6), "trouble concentrating on things, such as reading the newspaper or watching television" (Item 7), "moving or speaking so slowly that other people could have noticed, or so fidgety or restless that you have been moving a lot more than usual" (Item 8), and "thoughts that you would be better off dead, or thoughts of hurting yourself in some way" (Item 9), were compared between the without depression group and with depression group. As shown in Figure 1, the 9 items in the without depression group and with depression group were compared, and all 9 items showed significant differences ($P < 0.001$). Then, the 9 items were compared for the mild depression, moderate depression, moderately severe depression, and severe depression groups, as shown in Table 1. All 9 items also showed significant differences ($P < 0.001$). PCA was used to analyze the 9 items contributing to depression. As shown in Figure 2, the contributing rates of Items 1-9 were 36.00%, 15.59%, 9.96%, 9.09%, 7.32%, 6.18%, 5.94%, 5.40% and 4.53%, respectively. This item contributed the most to the depression analysis. In addition, the correlation coefficients of the 9 items were also analyzed. As shown in Figure 3, Item 7 and Item 8 showed the highest positive correlation coefficient, which was 0.585, but Item 7 and Item 3 showed the highest negative correlation coefficient, which was -0.033.

Relationship of the PSQI components and depression

As shown in Table 2, the 7 PSQI components, which were subjective sleep, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction, were compared for the without depression group (n = 190) and the with depression group (n = 221), which included mild (n = 139), moderate (n = 49), moderately severe (n = 22), and severe depression (n = 11). After comparison, subjective sleep ($P < 0.001$), sleep latency ($P < 0.001$), habitual sleep efficiency ($P = 0.001$), sleep disturbances ($P < 0.001$), use of sleep medications ($P = 0.001$), and daytime dysfunction ($P < 0.001$) showed significant differences between the depression groups; however, sleep duration showed no significant difference ($P = 0.054$). As shown in Figure 4, the mean PSQI scores in the without depression group (n = 190), mild depression group (n = 139), moderate depression group (n = 49), moderately severe depression group (n = 22), and severe depression group (n = 11) were 8.58, 10.63, 11.61, 13.41 and 15.00, respectively. With the progression of depression severity, the PSQI score also showed a significant increase ($P < 0.001$). In addition, the degrees of depression for the very good sleep quality (0-5), okay sleep quality (6-10), average sleep quality (11-15), and poor sleep quality (16-21) groups were also analyzed. As shown in Figure 5, for the 0–5 and 6–10 sleep quality groups, the

Table 1 Relationship of Patient Health Questionnaire-9 items and depression

PHQ-9 item	Score	Mild (*n* = 139)		Moderate (*n* = 49)		Moderately severe (*n* = 22)		Severe (*n* = 11)	
		n	Percent	*n*	Percent	*n*	Percent	*n*	Percent
Item 1	0	32	23.02	2	4.08	0	0.00	0	0.00
	1	67	48.20	11	22.45	5	22.73	1	9.09
	2	36	25.90	27	55.10	10	45.45	2	18.18
	3	4	2.88	9	18.37	7	31.82	8	72.73
Item 2	0	62	44.60	8	16.33	1	4.55	0	0.00
	1	62	44.60	14	28.57	4	18.18	0	0.00
	2	15	10.79	24	48.98	14	63.64	3	27.27
	3	0	0.00	3	6.12	3	13.64	8	72.73
Item 3	0	10	7.19	0	0.00	0	0.00	1	9.09
	1	41	29.50	12	24.49	2	9.09	0	0.00
	2	52	37.41	19	38.78	9	40.91	1	9.09
	3	36	25.90	18	36.73	11	50.00	9	81.82
Item 4	0	17	12.23	3	6.12	0	0.00	0	0.00
	1	66	47.48	9	18.37	1	4.55	0	0.00
	2	48	34.53	28	57.14	10	45.45	1	9.09
	3	8	5.76	9	18.37	11	50.00	11	100.00
Item 5	0	69	49.64	10	20.41	3	13.64	0	0.00
	1	49	35.25	20	40.82	5	22.73	3	27.27
	2	19	13.67	17	34.69	7	31.82	1	9.09
	3	2	1.44	2	4.08	7	31.82	7	63.64
Item 6	0	102	73.38	16	32.65	2	9.09	2	18.18
	1	32	23.02	24	48.98	5	22.73	0	0.00
	2	4	2.88	9	18.37	10	45.45	1	9.09
	3	1	0.72	0	0.00	5	22.73	8	72.73
Item 7	0	85	61.15	15	30.61	1	4.55	0	0.00
	1	44	31.65	17	34.69	2	9.09	1	9.09
	2	9	6.47	14	28.57	12	54.55	2	18.18
	3	1	0.72	3	6.12	7	31.82	8	72.73
Item 8	0	105	75.54	17	34.69	6	27.27	0	0.00
	1	28	20.14	25	51.02	5	22.73	0	0.00
	2	5	3.60	6	12.24	9	40.91	3	27.27
	3	1	0.72	1	2.04	2	9.09	8	72.73
Item 9	0	134	96.40	40	81.63	13	59.09	3	27.27
	1	5	3.60	7	14.29	5	22.73	5	45.45
	2	0	0.00	2	4.08	2	9.09	1	9.09
	3	0	0.00	0	0.00	2	9.09	2	18.18

PHQ-9: Patient Health Questionnaire-9.

percentages of the without depression group (*n* = 190), mild depression group (*n* = 139), moderate depression group (*n* = 49), moderately severe depression group (*n* = 22), and severe depression group (*n* = 11) were 16.84%, 8.63%, 0%, 0%, 0% and 58.95%, 40.29%, 38.78%, 13.64%, 0%, respectively. The

Table 2 Relationship of Pittsburgh sleep quality index components and depression

PSQI index	Score	Without (*n* = 190)		With (*n* = 221)		Mild (*n* = 139)		Moderate (*n* = 49)		Moderately severe (*n* = 22)		Severe (*n* = 11)	
		n	Percent	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent
Subjective sleep quality	0	0	0.00	3	1.36	2	1.44	1	2.04	0	0.00	0	0.00
	1	87	45.79	27	12.22	22	15.83	4	8.16	1	4.55	0	0.00
	2	94	49.47	146	66.06	94	67.63	33	67.35	11	50.00	8	72.73
	3	9	4.74	45	20.36	21	15.11	11	22.45	10	45.45	3	27.27
Sleep latency	0	9	4.74	8	3.62	3	2.16	4	8.16	1	4.55	0	0.00
	1	52	27.37	31	14.03	23	16.55	5	10.20	3	13.64	0	0.00
	2	77	40.53	69	31.22	45	32.37	13	26.53	8	36.36	3	27.27
	3	52	27.37	113	51.13	68	48.92	27	55.10	10	45.45	8	72.73
Sleep duration	0	46	24.21	39	17.65	27	19.42	6	12.24	4	18.18	2	18.18
	1	62	32.63	68	30.77	42	30.22	19	38.78	4	18.18	3	27.27
	2	59	31.05	60	27.15	39	28.06	13	26.53	8	36.36	0	0.00
	3	23	12.11	54	24.43	31	22.30	11	22.45	6	27.27	6	54.55
Habitual sleep efficiency	0	64	33.68	48	21.72	34	24.46	10	20.41	3	13.64	1	9.09
	1	44	23.16	42	19.00	27	19.42	10	20.41	4	18.18	1	9.09
	2	41	21.58	48	21.72	28	20.14	12	24.49	4	18.18	4	36.36
	3	41	21.58	83	37.56	50	35.97	17	34.69	11	50.00	5	45.45
Sleep disturbances	0	3	1.58	2	0.90	1	0.72	1	2.04	0	0.00	0	0.00
	1	154	81.05	135	61.09	99	71.22	25	51.02	8	36.36	3	27.27
	2	32	16.84	79	35.75	37	26.62	22	44.90	13	59.09	7	63.64
	3	1	0.53	5	2.26	2	1.44	1	2.04	1	4.55	1	9.09
Use of sleeping medications	0	85	44.74	90	40.72	63	45.32	19	38.78	6	27.27	2	18.18
	1	28	14.74	15	6.79	9	6.47	4	8.16	1	4.55	1	9.09
	2	43	22.63	40	18.10	32	23.02	8	16.33	0	0.00	0	0.00
	3	34	17.89	76	34.39	35	25.18	18	36.73	15	68.18	8	72.73
Daytime dysfunction	0	161	84.74	94	42.53	71	51.08	18	36.73	5	22.73	0	0.00
	1	27	14.21	84	38.01	53	38.13	18	36.73	9	40.91	4	36.36
	2	2	1.05	37	16.74	14	10.07	12	24.49	6	27.27	5	45.45
	3	0	0.00	6	2.71	1	0.72	1	2.04	2	9.09	2	18.18

PSQI: Pittsburgh sleep quality index.

percentage of depression degree de-escalated. In the 11–15 and 16–20 sleep quality groups, the percentages of the without depression group (n = 190), mild depression group (n = 139), moderate depression group (n = 49), moderately severe depression group (n = 22), and severe depression group (n = 11) were 1.58%, 5.04%, 16.33%, 18.18%, 27.27% and 22.63%, 46.04%, 44.90%, 68.18%, 72.73%, respectively. The percentage of depression degree escalated.

Comparison of disease status between the without depression and with depression groups

As shown in Table 3, the disease status of the without depression and with depression groups was analyzed. Twelve kinds of diseases, including diagnosed depression, chronic diseases, high blood pressure, diabetes, coronary heart disease, cerebrovascular disease, enlarged prostate, cancer, mental illness, tuberculosis, chronic hepatitis, and cirrhosis, were compared between the without depression and with depression groups. Diagnosed depression (P < 0.001), coronary heart disease (P = 0.03), and mental illness (P = 0.01) showed significant differences between the two groups. The percentages of

Table 3 Comparison of diseases status between without depression and with depression groups, *n* (%)

Diseases	Status	Without depression	With depression	*P* value
Diagnosed depression	Yes	17 (8.95)	52 (23.53)	< 0.001
	No	173 (91.05)	169 (76.47)	
Chronic diseases	Yes	60 (31.58)	68 (30.77)	0.86
	No	130 (68.42)	153 (69.23)	
High blood pressure	Yes	100 (52.63)	114 (51.58)	0.83
	No	90 (47.37)	107 (48.42)	
Diabetes	Yes	49 (25.79)	58 (26.24)	0.92
	No	141 (74.21)	163 (73.76)	
Coronary heart disease	Yes	21 (11.05)	42 (19)	0.03
	No	169 (88.95)	179 (81)	
Cerebrovascular disease	Yes	14 (7.37)	25 (11.31)	0.17
	No	176 (92.63)	196 (88.69)	
Enlarged prostate	Yes	9 (4.74)	14 (6.33)	0.48
	No	181 (95.26)	207 (93.67)	
Cancer	Yes	6 (3.16)	8 (3.62)	0.80
	No	184 (96.84)	213 (96.38)	
Mental illness	Yes	1 (0.53)	12 (5.43)	0.01
	No	189 (99.47)	209 (94.57)	
Tuberculosis	Yes	0 (0)	1 (0.45)	0.35
	No	190 (100)	220 (99.55)	
Chronic hepatitis	Yes	1 (0.53)	3 (1.36)	0.39
	No	189 (99.47)	218 (98.64)	
Cirrhosis	Yes	3 (1.58)	2 (0.9)	0.53
	No	187 (98.42)	219 (99.1)	

diagnosed depression in the without depression and with depression groups were 8.95% and 23.53%, respectively. The percentages of coronary heart disease and mental illness in the two groups were 11.05% and 19.00%, and 0.53% and 5.43%, respectively. The other 9 kinds of diseases, including chronic diseases, high blood pressure, diabetes, cerebrovascular disease, enlarged prostate, cancer, tuberculosis, chronic hepatitis, and cirrhosis, showed no significant differences ($P > 0.05$).

Comparison of general characteristics between the without depression and with depression groups

Eight general characteristics, including sex, age, education, marital status, living situation, occupational status, income (yuan) per month and exercise, were analyzed. The percentages of sex, education level, marital status, living situation, occupational status, income (yuan) per month and exercise in the without depression and with depression groups were compared by the chi-square test. As shown in Table 4, age was compared by the independent t test. Education level ($P = 0.04$), living situation ($P = 0.002$), and exercise ($P < 0.001$) showed significant differences between the two groups. The other 5 general characteristics showed no significant differences ($P > 0.05$). The most significant general characteristic was exercise; the percentages in the without depression and with depression groups were 78.95% and 62.44%, respectively. The percentages of elementary school education and below, junior high school education, secondary school or high school education, university education and above in the two groups were 1.05%, 13.16%, 38.42%, 47.37% and 1.81%, 23.53%, 29.86%, 44.80%, respectively. The percentages of living alone, living with a husband or wife, living with children, and others in the two groups were 5.79%, 59.47%, 32.11%, and 2.63% and 16.29%, 50.68%, 27.15%, and 5.88%, respectively.

Comparison of insomnia-related characteristics between the without depression and with depression groups

Years of insomnia, Western medicine treatment, Chinese medicine treatment, psychotherapy, kind of

Table 4 Comparison of general characteristics between without depression and with depression groups, *n* (%)

Characteristics	Status	Without depression	With depression	*P* value
Gender	Male	51 (26.84)	55 (24.89)	0.65
	Female	139 (73.16)	166 (75.11)	
Age (yr)		59.36 ± 7.46	59.66 ± 8.36	0.71
Education	Elementary school and below	2 (1.05)	4 (1.81)	0.04
	Junior high school	25 (13.16)	52 (23.53)	
	Secondary school or high school	73 (38.42)	66 (29.86)	
	University and above	90 (47.37)	99 (44.8)	
Marital status	Unmarried	6 (3.16)	10 (4.52)	0.05
	Married	170 (89.47)	178 (80.54)	
	Divorced	5 (2.63)	18 (8.14)	
	Widowed	9 (4.74)	15 (6.79)	
Living situation	Living alone	11 (5.79)	36 (16.29)	0.002
	Live with husband or wife	113 (59.47)	112 (50.68)	
	Live with children	61 (32.11)	60 (27.15)	
	Other	5 (2.63)	13 (5.88)	
Occupational	On-the-job	55 (28.95)	49 (22.17)	0.29
	Retire	130 (68.42)	166 (75.11)	
	Unemployed	5 (2.63)	6 (2.71)	
Income (yuan)	0-2000	4 (2.11)	9 (4.07)	0.09
	2000-4000	53 (27.89)	81 (36.65)	
	4000-6000	71 (37.37)	78 (35.29)	
	≥ 6000	62 (32.63)	53 (23.98)	
Exercise	Yes	150 (78.95)	138 (62.44)	< 0.001
	No	40 (21.05)	83 (37.56)	

insomnia, events related to insomnia, treatment expected to treat insomnia, traditional Chinese medicine foot baths, acupressure, psychological counseling, medicated diet, Tai Chi, traditional Chinese medicine, other traditional Chinese medicines, habit of 1 h before bed, habit of drinking tea, habit of drinking coffee, habit of drinking spirits, habit of smoking, and habit of taking a lunch break were analyzed. As shown in Table 5, among the 20 insomnia-related characteristics, years of insomnia ($P < 0.001$), Western medicine treatment ($P = 0.02$), Chinese medicine treatment ($P < 0.001$), psychotherapy ($P = 0.002$), kind of insomnia ($P < 0.001$), treatment expected to treat insomnia ($P < 0.001$), psychological counseling ($P < 0.001$), habit of 1 h before bed ($P < 0.001$), and habit of taking a lunch break ($P < 0.001$) showed significant differences between the two groups. The other 11 characteristics showed no significant differences ($P > 0.05$). The years of insomnia in the without depression and with depression groups were 5.21 ± 6.06 years and 7.35 ± 7.48 years, respectively.

Logistic analysis of depression and the significant characteristics

After comparing the disease status, general characteristics, and insomnia-related characteristics between the without depression and with depression groups, education level, living situation, exercise, years of insomnia, Western medicine treatment, Chinese medicine treatment, psychotherapy, kind of insomnia, treatment expected to treat insomnia, psychological counseling, habit of 1 h before bed, habit of taking a lunch break, diagnosed depression, coronary heart disease, and mental illness, which showed significant differences between the two groups, were further analyzed by logistic regression. As shown in Table 6, by univariate analysis, the ORs of education level ($P = 0.02$), exercise ($P = 0.02$), kind of insomnia ($P = 0.01$), habit of 1 h before bed ($P = 0.04$), diagnosed depression ($P = 0.03$), and coronary heart disease ($P = 0.02$) showed significant differences. Their odds ratios (ORs) were 0.71 (0.54, 0.94), 1.81 (1.11, 2.95), 0.79 (0.65, 0.95), 0.90 (0.81, 1.00), 0.48 (0.24, 0.94), and 0.46 (0.25, 0.86), respectively. Then, the characteristics that showed significant differences in the univariate analysis were further analyzed

Table 5 Comparison of insomnia related characteristics between without depression and with depression groups, *n* (%)

Indicator	Status	Without depression	With depression	*P* value
Years of insomnia		5.21 ± 6.06	7.35 ± 7.48	< 0.001
Western medicine treatment	Yes	102 (53.68)	143 (64.71)	0.02
	No	88 (46.32)	78 (35.29)	
Chinese medicine treatment	Yes	82 (43.16)	143 (64.71)	< 0.001
	No	108 (56.84)	78 (35.29)	
Psychotherapy	Yes	6 (3.16)	25 (11.31)	0.002
	No	184 (96.84)	196 (88.69)	
Kinds of insomnia	Difficult to fall asleep	89 (46.84)	140 (63.35)	< 0.001
	Difficult to deep sleep	20 (10.53)	16 (7.24)	
	Easy to wake up	53 (27.89)	36 (16.29)	
	Wake up early	28 (14.74)	29 (13.12)	
Events related to insomnia	Work pressure	42 (22.11)	40 (18.1)	0.10
	Family life	58 (30.53)	66 (29.86)	
	Disease related	49 (25.79)	82 (37.1)	
	Sleep environment	37 (19.47)	31 (14.03)	
	Interpersonal communication	4 (2.11)	2 (0.9)	
Treatment expected to treat insomnia	Western medicine	53 (27.89)	36 (16.29)	< 0.001
	Traditional Chinese Medicine	97 (51.05)	133 (60.18)	
	Psychotherapy	14 (7.37)	36 (16.29)	
	Other	26 (13.68)	16 (7.24)	
Traditional Chinese medicine foot bath	Yes	50 (26.32)	49 (22.17)	0.33
	No	140 (73.68)	172 (77.83)	
Acupressure	Yes	51 (26.84)	50 (22.62)	0.32
	No	139 (73.16)	171 (77.38)	
Psychological counseling	Yes	1 (0.53)	19 (8.6)	< 0.001
	No	189 (99.47)	202 (91.4)	
Medicated diet	Yes	16 (8.42)	28 (12.67)	0.17
	No	174 (91.58)	193 (87.33)	
Tai Chi	Yes	11 (5.79)	5 (2.26)	0.07
	No	179 (94.21)	216 (97.74)	
Traditional Chinese medicine	Yes	93 (48.95)	120 (54.3)	0.28
	No	97 (51.05)	101 (45.7)	
Other traditional Chinese medicine	Yes	17 (8.95)	16 (7.24)	0.53
	No	173 (91.05)	205 (92.76)	
Habit of 1 hour before bed	Electronic products	79 (41.58)	125 (56.56)	< 0.001
	Reading news or papers	31 (16.32)	22 (9.95)	
	Chat	7 (3.68)	10 (4.52)	
	Fitness	0 (0)	1 (0.45)	
	None	12 (6.32)	26 (11.76)	
	Watch TV	61 (32.11)	37 (16.74)	
Habit of drinking tea	Yes	57 (30)	81 (36.65)	0.16

	No	133 (70)	140 (63.35)	
Habit of drinking coffee	Yes	38 (20)	35 (15.84)	0.27
	No	152 (80)	186 (84.16)	
Habit of drinking spirits	Yes	3 (1.58)	10 (4.52)	0.09
	No	187 (98.42)	211 (95.48)	
Habit of smoking	Yes	24 (12.63)	19 (8.6)	0.18
	No	166 (87.37)	202 (91.4)	
Habit of lunch break	Yes	52 (27.37)	82 (37.1)	< 0.001
	No	138 (72.63)	139 (62.9)	

Table 6 Logistic analysis of depression and the significant characteristics

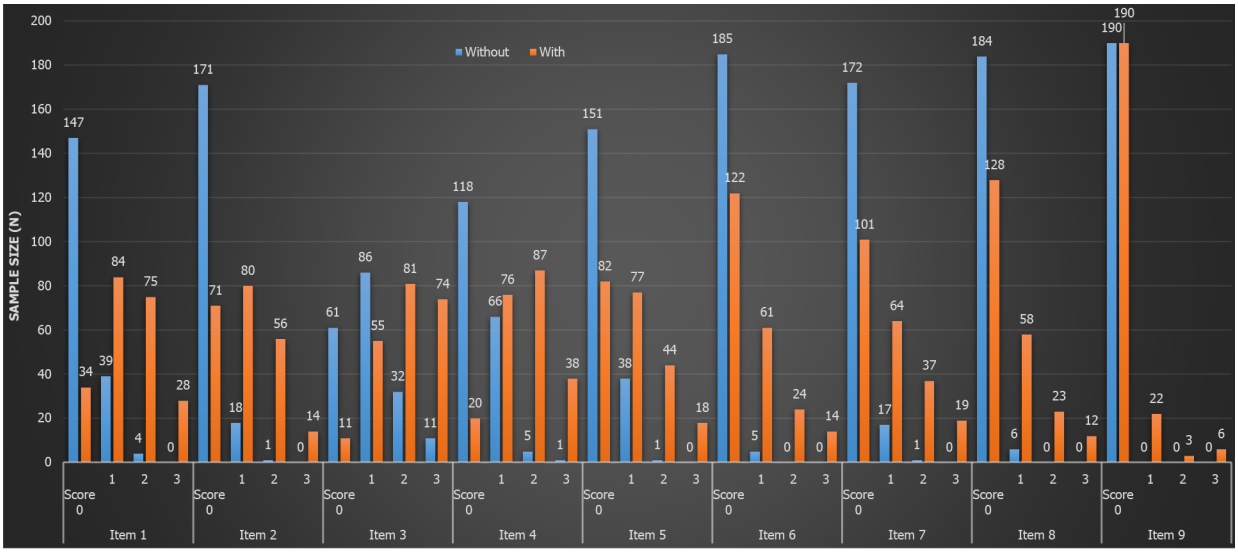
Characteristics	Univariate analysis					Multivariate analysis				
	Wals	*P* value	OR	95% CI of OR		Wals	*P* value	OR	95% CI of OR	
				Lower	Upper				Lower	Upper
Education	5.58	0.02	0.71	0.54	0.94	6.08	0.01	0.71	0.55	0.93
Living situation	0.38	0.54	0.91	0.67	1.23					
Exercise	5.63	0.02	1.81	1.11	2.95	9.89	< 0.001	2.09	1.32	3.31
Years of insomnia	3.40	0.07	1.03	1.00	1.07					
Western medicine treatment	1.05	0.31	0.79	0.50	1.24					
Chinese medicine treatment	0.70	0.40	1.20	0.78	1.82					
Psychotherapy	1.30	0.25	0.53	0.18	1.57					
Kinds of insomnia	5.95	0.01	0.79	0.65	0.95	8.79	< 0.001	0.76	0.63	0.91
Treatment expected to treat insomnia	0.74	0.39	1.12	0.87	1.44					
Psychological counseling	2.96	0.09	0.15	0.02	1.30					
Habit of 1 hour before bed	3.97	0.04	0.90	0.81	1.00	5.48	0.02	0.89	0.81	0.98
Habit of lunch break	0.12	0.73	1.08	0.68	1.71					
Diagnosed depression	4.64	0.03	0.48	0.24	0.94	12.94	< 0.001	0.32	0.17	0.60
Coronary heart disease	5.91	0.02	0.46	0.25	0.86	7.43	0.01	0.43	0.23	0.79
Mental illness	2.87	0.09	0.16	0.02	1.34					

OR: Odds ratio.

by multivariate analysis. The ORs of education level (P = 0.01), exercise (P < 0.001), kind of insomnia (P < 0.001), habit of 1 h before bed (P = 0.02), diagnosed depression (P < 0.001), and coronary heart disease (P = 0.01) were significantly different. Their ORs were 0.71 (0.55, 0.93), 2.09 (1.32, 3.31), 0.76 (0.63, 0.91), 0.89 (0.81, 0.98), 0.32 (0.17, 0.60), and 0.43 (0.23, 0.79), respectively.

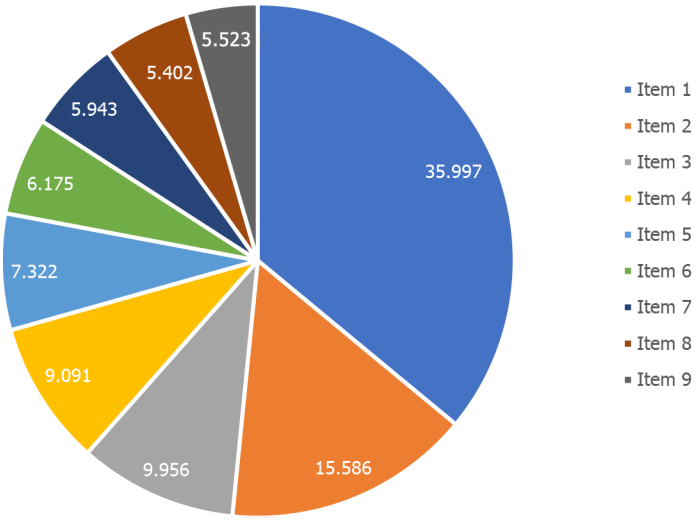
DISCUSSION

Education level was a protective factor against depression and the OR was 0.71 (0.55, 0.93). Studies have found that academic achievement can influence employment, health care, and social communication[18-20]. The relationship between depression and academic achievement has drawn increasing attention. An overall negative association between depression and academic achievement for both sexes was demonstrated. Several studies have examined the associations between depression and academic achievement[21,22]. Our study results were consistent with these studies. People with higher education levels have good learning abilities, receive health-related knowledge, and have stronger abilities to cope with and solve problems, which may have a positive effect on obtaining better sleep quality. Some



DOI: 10.5498/wjp.v12.i5.722

Figure 1 Comparison of the 9 items of Patient Health Questionnaire-9 in the without depression group and with depression group.



DOI: 10.5498/wjp.v12.i5.722

Figure 2 The contributing rate of 9 items of Patient Health Questionnaire-9 to depression (%).

studies have shown that the number of years of education were associated with the recurrence of depression, and the shorter the years of education, the greater the possibility of depression recurrence [23,24]. Considering that years of education indirectly affect the sleep quality of patients through depressive symptoms, the relationship among the three factors needs to be further explored. There are some opposite results between depression and education level. On the one hand, educational attainment protects individuals from depression and improves their symptoms; however, individuals with higher education levels are more likely to suffer severe and recurrent episodes of major depression than individuals with low levels of education[25,26].

In our study, patients who did not exercise had an OR of 2.09 (1.32, 3.31) compared with the patients who did exercise. We demonstrated that exercise was a protective factor against depression. The protective effects of exercise and its mechanism on depression have been demonstrated in many studies [27] and support that physical exercise can reduce depression symptoms in patients[28,29]. In patients with depression (aged 18–60 years) who performed aerobic exercise or stretching exercises, there were significant short-term time effects for improving depression severity[30]. A meta-analysis study including 1452 depression patients found a protective effect on depression, regardless of the mode of exercise[31]. However, there are still some studies that found that there is no protective effect of exercise on treating depression. The provision of advice and encouragement for exercise did not improve the depression therapeutic effect when compared to regular care[32]. In another study, 1-week high cadence cycling did not improve depression symptoms[33]. Recently, exercise was not only used as a single

	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9
Item 1	1.000	0.395	0.138	0.390	0.154	0.227	0.213	0.182	0.142
Item 2	0.395	1.000	0.035	0.319	0.195	0.393	0.401	0.369	0.304
Item 3	0.138	0.035	1.000	0.306	0.011	0.023	-0.033	-0.012	0.014
Item 4	0.390	0.319	0.306	1.000	0.227	0.204	0.229	0.175	0.133
Item 5	0.154	0.195	0.011	0.227	1.000	0.315	0.312	0.307	0.236
Item 6	0.227	0.393	0.023	0.204	0.315	1.000	0.507	0.512	0.443
Item 7	0.213	0.401	-0.033	0.229	0.312	0.507	1.000	0.585	0.400
Item 8	0.182	0.369	-0.012	0.175	0.307	0.512	0.585	1.000	0.381
Item 9	0.142	0.304	0.014	0.133	0.236	0.443	0.400	0.381	1.000

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Figure 3 The correlation coefficient of the 9 items of Patient Health Questionnaire-9.

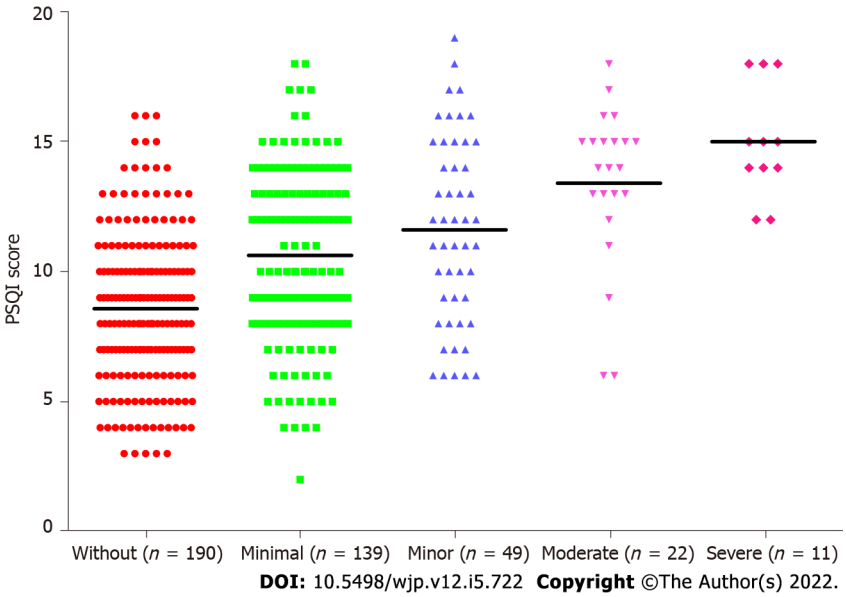

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Figure 4 The mean Pittsburgh sleep quality index score. The mean Pittsburgh sleep quality index score in the without depression group (n = 190), mild (n = 139), moderate (n = 49), moderately severe depression (n = 22), and severe depression (n = 11) was 8.58, 10.63, 11.61, 13.41 and 15.00. PSQI: Pittsburgh sleep quality index.

treatment for depression but also an adjunct intervention therapeutic method for depression[34]. When exercise was used as a single therapy method, depression-related symptoms were significantly decreased after moderate aerobic exercise for 8 wk[35]. In addition, exercise was also recognized as an intervention with significant effects that can be used as an adjuvant therapy for depression[36]. The mechanisms underlying the antidepressant effects of exercise are closely related to psychological and physiological factors. Psychosocial and cognitive factors after exercise may include self-worth, self-esteem, self-efficacy, self-confidence, sleep quality, and life satisfaction[37-39]. Anti-inflammatory and

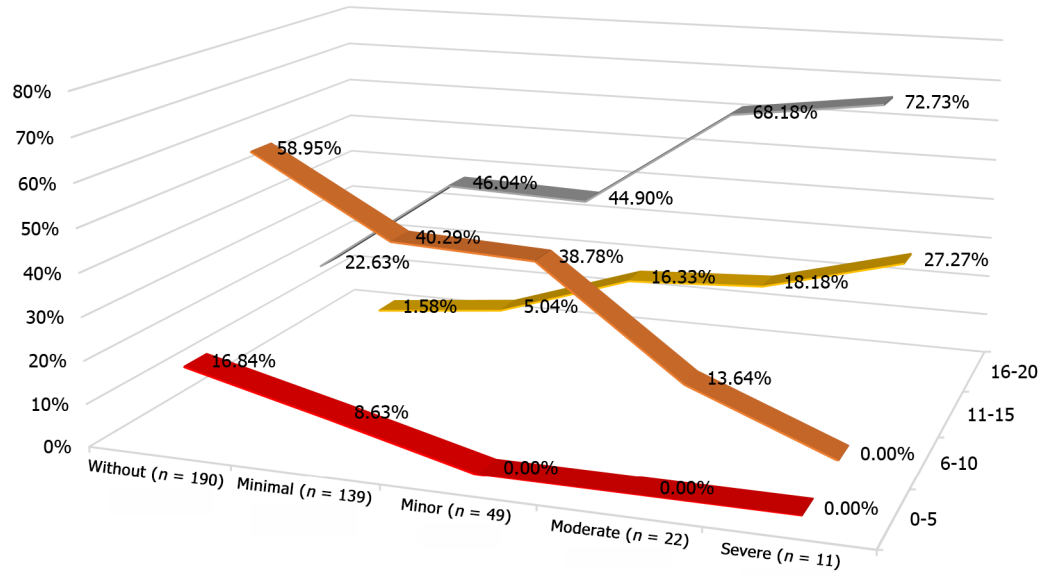

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Figure 5 The percentage of Pittsburgh sleep quality index group. The percentage of Pittsburgh sleep quality index group in without depression group (*n* = 190), mild (*n* = 139), moderate (*n* = 49), moderately severe depression (*n* = 22), and severe depression (*n* = 11).

antioxidant factors (interleukin-18, interleukin-1β, interleukin-6, tumor necrosis factor-α, caspase-1) were also demonstrated to be closely related to depression and anxiety[40-42]. The antidepressant effects of exercise are also related to elevated neurogenesis because of brain-derived neurotrophic factors[43-45].

This study found that the kind of insomnia was related to depression. Patients with major depressive disorder in the community had poor subjective sleep quality, prolonged sleep latency, short sleep duration, low sleep efficiency, sleep disturbances, and impaired daytime functioning[46]. These subjective sleep quality abnormalities were consistent with the objective measurements of sleep[47,48]. Some studies have shown that the polysomnography of patients with major depressive disorder shows that the rapid eye movement latency period is shortened, and the time of the first rapid eye movement period after falling asleep moves forward, which increases the proportion of rapid eye movement sleep and reduces the time of slow wave sleep[49-51]. Possible mechanisms include hyperexcitability of the hypothalamic–pituitary–adrenal axis; a glutamate deficiency, which plays an important role in both depression and sleep regulation; a marked reduction in plasma melatonin levels; alterations in the serotonergic system; and some increases in systemic markers of inflammation. The sleep quality of people with depression disorder in the past is different from that of the normal population[51,52]. The depressive symptoms disappear, but their sleep problems still persist. Some people think that persistent sleep disorder is a manifestation of the residual period of major depressive disorder. Depressive symptoms in patients with previous depressive disorder were not related to current sleep quality, while residence, years of education, work status and mental health were significantly correlated with sleep quality in patients with a previous depressive disorder[53,54]. Depressed patients living in rural areas were twice as likely to have good sleep quality compared with patients with previous depressive disorders living in urban areas. In our study, the absence of coronary heart disease was also demonstrated to be a protective factor against depression. Recently, the relationship between coronary heart disease and depression has received increased attention[55]. Patients with coronary heart disease are more likely to suffer from depression because they often endure unpleasant symptoms without warning and are required to take many medications for their lifestyle[55], leading to negative emotions such as anxiety or depression[56]. Approximately 20%–30% of patients with heart diseases are diagnosed with anxiety or depression. However, the percentage of patients affected with anxiety and depression was reported to be elevated to 15%–43% during the first 12 mo after an acute cardiac event [55]. Compared to depression, self-reported depression is more strongly related to cardiac morbidity and mortality[57].

Although we systematically analyzed the factors related to depression, including a depression evaluation, a sleep quality evaluation, general characteristics, and diagnosed disease status, there are still some limitations in this study. First, the sample size was relatively small. Some group sample sizes may affect the statistical results and lead to bias in the results. Second, although patients with depression in the past and patients who had been recently diagnosed with depression were enrolled in our study, the sample sizes of the two groups were small, and we did not compare their relative factors. Third, different therapeutic methods for depression were not performed. In our future study, we will perform a study that compares the therapeutic effects of different methods for treating depression.

CONCLUSION

In conclusion, we demonstrated that education level, exercise, kind of insomnia, habit of 1 h before bed, diagnosed depression and coronary heart disease were the factors related to depression, which may provide some implications for the clinical practice of depression.

ARTICLE HIGHLIGHTS

Research background

Depression and sleep quality were demonstrated to be affected each other. In addition, the other factor, including diseases, general and insomnia characteristics also affect depression.

Research motivation

The relationship of depression and sleep quality, diseases and general characteristics and depression should be systemically investigated.

Research objectives

In this study, we aimed to investigate the relationship of depression and sleep quality, diseases and general characteristics.

Research methods

Questionnaire included Patient Health Questionnaire-9 (PHQ-9) and Pittsburgh sleep quality index (PSQI), 12 kinds of diseases, 8 general characteristics, and 20 insomnia characteristics, totally 56 items were filled out by 411 patients enrolled.

Research results

All the 9 items of PHQ-9, 6 components of PSQI (except sleep duration), 12 kinds of diseases, 3 general characteristics, and 9 insomnia characteristics showed significant difference between without and with depression group. By univariate analysis and multivariate analysis. The odds ratio of education, exercise, kinds of insomnia, habit of 1 h before bed, diagnosed depression, coronary heart disease showed significant difference.

Research conclusions

Education, exercise, kinds of insomnia, habit of 1 h before bed, diagnosed depression and coronary heart disease are the related factor with depression.

Research perspectives

Larger sample size and long-time span study should be designed and performed in the future study. Different therapeutic methods for depression should also be performed.

FOOTNOTES

Author contributions: Jiang Y and Ding L designed the study; Jiang Y and Jiang T performed the research; Jiang Y, Jiang T and Xu LT analyzed the date; Jiang Y wrote the paper; Ding L revised the manuscript for final submission; Jiang Y and Jiang T contributed equally to this study; Ding L the co-corresponding author; and all authors approved the final version of the article.

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META-ANALYSIS

Mental health impact of the Middle East respiratory syndrome, SARS, and COVID-19: A comparative systematic review and meta-analysis

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Abstract

BACKGROUND

Over the last few decades, 3 pathogenic pandemics have impacted the global

population; severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2. The global disease burden has attributed to millions of deaths and morbidities, with the majority being attributed to SARS-CoV-2. As such, the evaluation of the mental health (MH) impact across healthcare professionals (HCPs), patients and the general public would be an important facet to evaluate to better understand short, medium and long-term exposures.

AIM

To identify and report: (1) MH conditions commonly observed across all 3 pandemics; (2) Impact of MH outcomes across HCPs, patients and the general public associated with all 3 pandemics; and (3) The prevalence of the MH impact and clinical epidemiological significance.

METHODS

A systematic methodology was developed and published on PROSPERO (CRD42021228697). The databases PubMed, EMBASE, ScienceDirect and the Cochrane Central Register of Controlled Trials were used as part of the data extraction process, and publications from January 1, 1990 to August 1, 2021 were searched. MeSH terms and keywords used included *Mood disorders, PTSD, Anxiety, Depression, Psychological stress, Psychosis, Bipolar, Mental Health, Unipolar, Self-harm, BAME, Psychiatry disorders and Psychological distress*. The terms were expanded with a 'snowballing' method. Cox-regression and the Monte-Carlo simulation method was used in addition to I^2 and Egger's tests to determine heterogeneity and publication bias.

RESULTS

In comparison to MERS and SARS-CoV, it is evident SAR-CoV-2 has an ongoing MH impact, with emphasis on depression, anxiety and post-traumatic stress disorder.

CONCLUSION

It was evident MH studies during MERS and SARS-CoV was limited in comparison to SARS-CoV-2, with much emphasis on reporting symptoms of depression, anxiety, stress and sleep disturbances. The lack of comprehensive studies conducted during previous pandemics have introduced limitations to the "know-how" for clinicians and researchers to better support patients and deliver care with limited healthcare resources.

Key Words: COVID-19; Middle East respiratory syndrome; SARS-CoV; SARS-CoV-2; Mental health; Wellbeing; Psychiatry; Healthcare professionals; Patients; Physical health; Public health; Outbreaks and pandemics

Core Tip: Global research into exploring pandemics have been conducted for several decades. However, clinical research associated with mental health (MH) impact of Middle East respiratory syndrome, severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 was limited. This systematic review and meta-analysis is a comparison of the MH impact across, healthcare professionals, patients and the general public using the Monte-Carlo simulation method. Evaluated prevalence of multiple MH variables have been conducted using randomised controlled trials and cross-sectional studies. The study demonstrates the need to conduct comprehensive and longitudinal multi-morbid research to evaluate the true MH impact to aid better future pandemic preparedness. This systematic review and meta-analysis indicate a complex MH impact across all cohorts with the requirement for mechanistic relationships between physical and MH to be explored further.

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INTRODUCTION

Human civilisations have endeavoured various infectious diseases over centuries with multiple causatives, increases in population density, and increases in migration could attribute to increase in risk of emerging infectious diseases leading to global endemics and pandemics. Medicine in the modern era provide solutions to manage and mitigate infectious threats although there are many challenges associated with communicable and non-communicable diseases.

Fast forward to the 21st century, there have been three prominent outbreaks caused by novel coronaviruses[1]. The World Health Organisation (WHO) have classified two of these outbreaks as pandemics. Understanding the coronavirus family to prevent future pandemics would be useful.

The 2003 severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) comprised of the Middle East respiratory syndrome coronavirus (MERS-CoV) which includes a family of enveloped, single-stranded and diverse RNA viruses consisting of four genera: alpha, beta, gamma and delta (*α*-, *β*-, *γ*- and *δ*-*CoV*). Of these, alpha and beta-coronaviruses appear to be more deadly due to its ability to transmit across animals and humans, leading to stronger pathogens. Coronaviruses were first identified in 1965[2]. The SARS-CoV was the first outbreak in 2012. Neither of the outbreaks reached a pandemic status. Genetically similar to SARS-CoV, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), officially declared as a pandemic on March 11, 2020, continues to engulf global populations.

In comparison to the current SARS-CoV-2 pandemic, the SARS-CoV outbreak was effectively managed with aggressive public health measures amongst the countries affected[3]. Although, there are multi-factorial composites to consider to assess physical and mental health impact on the previous and current populations. For example, SARS-CoV reported an incidence and mortality of 8096 and 774 respectively across 29 countries[4].

In contrast, MERS-CoV outbreaks were reported across 27 countries between 2012-2019, mainly within the Middle East, with Saudi Arabia reporting majority of the cases based on WHO data[5]. However, incidence reporting of MERS-CoV over the last 7 years have been sporadic, indicating it is less contagious compared to the current SARS-CoV-2 infection. To date, there have been 2578 reported cases and 888 deaths due to MERS-CoV, with a crude mortality rate of around 34.4%[5]. Management of these infections primarily consist of public health measures to identify and isolate patients and effective infection control measures to reduce transmission rates[6]. Failures in effectively managing these outbreaks have primarily been attributed to the late identification of the disease. Secondary measures include quarantine failures due to non-disclosures by patients and poor communication between officials and the public[7,8].

Most patients with SARS-COV-2 are asymptomatic or develop mild symptoms[9]. However, for a small minority, they are likely to require admission to hospital with severe respiratory compromise which can lead to critical illness with respiratory failure and multiple organ failure[9]. These cases require high-level medical care within an intensive care unit (ICU) setting, including ventilatory support. Dexamethasone and Remdesivir are used alongside supportive measures and have proved effective in reducing mortality and hospital length of stay[10,11]. Interventions such as pruning, which has been recommended in the treatment of severe COVID-19 disease[12], have become common place in ICU settings, but is a labour-intensive procedure, putting further pressure on staff.

The global response to SARS-COV-2

The high degree of viral homology between SARS-COV-2 and previous coronavirus outbreaks directed the initial global response to the coronavirus disease 2019 (COVID-19) pandemic[13]. Given the relatively small population sizes involved in the first two novel coronavirus outbreaks, in addition to the geographical areas affected, the global understanding that shaped our response was probably limited in its scope. We recognise now it is in fact the differences, not the similarities, that have driven the rapid spread of the virus, including more prominent community spread and higher transmissibility of SARS-CoV-2, which includes asymptomatic and mildly symptomatic patients not seen in SARS-CoV [14].

The spread comparison between SARS-CoV, MERS-CoV and SARS-CoV-2

The characteristics of the emerging SARS-CoV-2 appears to be changing with the appearance of new variants, which is different to its predecessors, SARS-CoV and MERS-CoV. At the height of the SARS-CoV era, 140 new infections were reported *per* week, whilst current data suggest SARS-CoV-2 transmits approximately 100000 new infections *per* week during its peak period between February and May 2020 [15,16]. In addition to the common transmission network, viral shedding for SARS-CoV-2 in particular starts prior to symptom onset, which was the opposite with SARS-CoV. Therefore, quarantine measures would have been more effective during SARS-CoV in comparison to SARS-CoV-2.

The mental health impact of SARS-CoV-2

One of the long-term unknowns about the current pandemic is the physical manifestations and its impact on the mental health as well as the well-being of the public, patients and front-line healthcare professionals (HCPs). Experience from the previous novel coronavirus outbreaks suggests that the

psychological impacts will be widespread and long-lasting. Significant psychological symptomatology has been reported in the acute and early recovery phases associated with SARS-CoV[17-22] and MERS-CoV[17,23] in all three groups considered in this review. Importantly, when considering the long-term effects of this pandemic, the impact of the SARS-CoV pandemic was still recorded amongst infected individuals over four years after the reported outbreak, and in some cases with deteriorating symptoms [13].

The morphological and demographic features of the 3 viruses are vital to understand the mental health impact. Physical manifestations drive the mental health impact, often interacting as a planarian.

MATERIALS AND METHODS

A systematic review protocol was designed, internally peer-reviewed and published on PROSPERO (CRD42021228697) with a comprehensive search strategy and data extraction method.

Research question/aims

This study has 3 primary aims of identifying and reporting: (1) Mental health (MH) conditions commonly observed across all 3 pandemics; (2) Impact of MH outcomes across HCPs, patients and the general public associated with all 3 pandemics; and (3) The prevalence of the MH impact and clinical epidemiological significance.

Data searches

Multiple databases of PubMed, EMBASE, ScienceDirect and the Cochrane Central Register of Controlled Trials were used to extract relevant data. MeSH terms and keywords used included *Mood disorders, PTSD, Anxiety, Depression, Psychological stress, Psychosis, Bipolar, Mental Health, Unipolar, Self-harm, BAME* (*Black, Asian and Minority Ethnic*), *Psychiatry disorders* and *Psychological distress*. The terms were expanded with a 'snowball' method that has been demonstrated with a PRISMA diagram. All publications that were peer-reviewed in English were included. The final dataset was reviewed independently before the analysis was conducted.

Data synthesis

The data synthesis is based on the statistical data extracted from the studies included based on the eligibility criteria developed. This includes data associated with the mean ± SD and median along with q_1 (25% quantile) and q_3 (75% quantile). Q1 and q_3 are novel estimation methods used to improve existing meta-analysis as demonstrated by Wan and colleagues[24]. Most of the studies identified reported multiple MH outcomes such as depression, anxiety and psychological distress among people who experienced MERS, SARS-CoV and SARS-CoV-2. For studies that reported the median along with q_1 and q_3, the mean ± SD of the studies were estimated from the median, q_1 and q_3. Therefore, the following equation was used to analyse the data, where the Φ^{-1} represented the inverse of the standard normal distribution, as described below.

Most MERS-CoV studies only reported SD. Some studies included the median only, and these were transformed to q_1 and q_3, where the mean ± SD were estimated using the Monte-Carlo simulation method, with the cut off scores of the MH assessments used within the studies. This data was assumed to be normally distributed. Random effects models were used to conduct the meta-analysis to estimate the pooled prevalence. MH assessments reported within the studies included the Impact of Event Scale-Revised (IES-R), Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire (PHQ-9), Short Form 36 Health Survey (SF-36), General Anxiety Disorder (GAD-7) and State-Trait Anger Expression Inventory (STAXI). For this we assumed normal distribution of the data. A subgroup analysis was conducted to evaluate any identified heterogeneity. Funnel plots and Egger's tests were performed to demonstrate publication bias and a sensitivity analysis. A comparative analysis was conducted using the SAR-CoV and SARS-CoV-2 data published by Chau *et al*[25].

The full data analysis was conducted using the STATA 16.1 software application.

Risk of bias quality assessment

A quality assessment was performed using the Newcastle-Ottawa-Scale (NOS) for studies included systematically (Supplementary Table 1). The NOS is an eight-item scale with three quality parameters: (1) Selection; (2) Comparability; and (3) Outcome. We rated the quality of the studies (good, fair and poor) by allocating each domain with stars in this manner: (1) A Good quality score was awarded 3 or 4 stars in selection, 1 or 2 in comparability, and 2 or 3 stars in outcomes; (2) A Fair quality score was awarded 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes; and (3) A Poor quality score was allocated 0 or 1 star(s) in selection, 0 stars in comparability, and 0 or 1 star(s) in outcomes domain.

RESULTS

The comprehensive multiple database literature search included publications from January 1, 1990 to August 1, 2021. The PRISMA diagram reflects the total yielded studies and systematic inclusions prior to the completion of the meta-analysis as shown in Figure 1.

MERS-CoV

A total of 58 studies were included in the systematic review for MERS as shown in Supplementary Table 2. The search for MERS-CoV yielded 14, 144 of which 152 articles met the inclusion criteria to be reviewed by title and abstract. Eleven duplicates were removed. A further 29 studies were excluded as these were not pertinent to the MERS-CoV demonstrating MH outcomes, and 38 studies were excluded due to the lack of statistical data. Fifteen articles that were not published in English was also excluded. Therefore, the meta-analysis was conducted on 21 studies as demonstrated in Table 1.

SARS-CoV

In relation to the SARS-CoV, the systematic review was conducted on 80 studies, as detailed in Supplementary Table 3, and the meta-analysis included 39 studies, as shown in Table 2.

SARS-CoV-2

A total of 513 studies were included in the systematic review for SARS-CoV-2, as shown in Supplementary Table 4. 287 of these studies are from the meta-analysis conducted by Phiri *et al*[26]. The meta-analysis was conducted on 188 studies, as demonstrated in Supplementary Table 5.

Meta-analysis

Anxiety: Eight studies reported the prevalence of anxiety during the MERS-CoV outbreak. As demonstrated by Figure 2, the pooled prevalence of anxiety was 17.35% with a 95% confidence interval (CI): 8.36-36.02. A heterogeneity of I^2 = 95.62% was identified.

The systematic review indicates 14 studies report the prevalence of anxiety during SARS-CoV, although only 9 report the mean ± SD. Twenty-three studies were included into the meta-analysis. Figure 3 indicates the prevalence of anxiety during SARS-CoV where the pooled prevalence was 25.2%, with a 95%CI of 18.41-34.5. A high heterogeneity of I^2 = 93.47% was identified.

The systematic review identified 175 studies that reported anxiety as an outcome due to SARS-CoV-2 where 40 studies provided mean and SD. By utilizing the Monte-Carlo simulation on the studies that only provide mean and SD, we obtained twenty-five studies that reported the prevalence of anxiety. As for the anxiety resulting from SARS-CoV-2, Figure 4 shows a pooled prevalence of 21.44% with a 95%CI of 18.69-24.61. However, a high heterogeneity of 99.77% was identified.

Based on these results, the prevalence of anxiety during SARS-CoV is more significant in comparison to MERS-CoV and SARS-CoV-2.

Depression

The systematic search for MERS-CoV yielded seven studies reporting depression. The meta-analysis is demonstrated in Figure 5 and shows a pooled prevalence of 33.65%. The 95%CI ranged between 22.02-51.42. A moderate heterogeneity of at I^2 = 69.86% was identified.

Thirty-eight studies reported the prevalence of depression during the SARS-CoV outbreak. Of these, 23 reported prevalence directly and 15 demonstrated the mean score and SD instead. By using the Monte-Carlo simulation method, thirty-eight results were meta-analysed as demonstrated in Figure 6. The pooled prevalence of depression during the pandemic of SARS-CoV was 23.1%, while the 95%CI was between 18.14-29.4. A high heterogeneity was calculated at I^2 = 95.03%.

One hundred and twenty-three studies reported on depression during SARS-CoV-2. Of these, 102 reported the prevalence of depression directly and 21 demonstrated mean and SD values only. Figure 7 indicates the pooled prevalence of depression during SARS-CoV-2 was 27.68%, with a 95%CI ranging from 24.67-31.06. A high heterogeneity of I^2 = 99.71% was identified.

Based on the analysis, MERS-CoV and SARS-CoV-2 appear to report the highest levels of depression based on the pooled prevalence of 27.64% and 33.65% respectively.

Post-traumatic stress disorder

Twenty-seven studies reported post-traumatic stress disorder (PTSD) during the MERS-CoV outbreak. Figure 8 demonstrated a pooled prevalence of 35.97%, with a relatively moderate to high heterogeneity of I^2 = 75.2% and a 95%CI ranging between 29.60-43.72.

Sixty-four of the studies identified had reported on the prevalence of PTSD during SARS-CoV. Of these, 48 studies reported on the prevalence directly, whilst 17 demonstrated the mean score and the corresponding SD. Figure 9 shows the pooled prevalence of PTSD was 18.2% with a CI of 14.94-22.18 and an elevated heterogeneity of I^2 = 91.37%.

Table 1 21 studies that are included in meta-analysis for Middle East respiratory syndrome

Study ID	Ref.	Study type	Sample size	Country	Exposure	Outcome	*P* value	Quality assessment (NOS)
1	Shin *et al*[36]	Quantitative	63	Korea	MERS patients	PTSD, Sleep problem, anxiety, depression, suicidality, phobic anxiety, addiction, aggression	Not specified	7
2	Um *et al*[37]	Quantitative	64	Korea	MERS patients and HCWs	PTSD, depression	Not specified	7
3	Abolfotouh *et al*[38]	Quantitative	1031	Saudi Arabia	HCWs	Level of Concern	Not specified	7
4	Jung *et al*[39]	Quantitative	147	Korea	HCWs	PTSD	Not specified	6
5	Ahn *et al*[40]	Quantitative	63	Korea	MERS Patients	Suicide, fatigue	Not specified	6
6	Lee *et al*[41]	Quantitative	52	Korea	MERS Patients	Depression, PTSD, fatigue	Not specified	6
7	Kim *et al*[42]	Quantitative	112	Korea	HCWs	PTSD, burnout	Not specified	7
8	Oh *et al*[43]	Quantitative	313	Korea	HCWs	Stress	Stress: 0.066	7
9	Seo *et al*[44]	Quantitative	171	Korea	HCWs	Burnout	Not specified	5
10	Son *et al*[45]	Quantitative	280	Korea	HCWs and general public	PTSD	Not specified	6
11	Park *et al*[46]	Quantitative	187	Korea	HCWs	Stress	Not specified	6
12	Jeong *et al*[24]	Qualitative	1692	Korea	MERS patients and general public	Anxiety	Not specified	7
13	Al-Rabiaah *et al*[47]	Quantitative	174	Saudi Arabia	General public	Anxiety	Not specified	7
14	Park *et al*[48]	Quantitative	63	Korea	MERS Patients	PTSD, depression	Not specified	7
15	Cho *et al*[49]	Quantitative	111	Korea	General public	PTSD	PTSD: 0.3	7
16	Kim *et al*[50]	Quantitative	27	Korea	General public	Depression	Not specified	5
17	Lee *et al*[51]	Quantitative	359	Korea	HCWs	PTSD	Not specified	6
18	Kim and Choi[52]	Quantitative	215	Korea	HCWs	Burnout, stress	Not specified	6
19	Bukhari *et al*[53]	Quantitative	386	Saudi Arabia	HCWs	Worry	Not specified	6
20	Mollers *et al*[54]	Quantitative	72	Netherlands	General public	PTSD	Not specified	5
21	Kim and Choi[52]	Quantitative	215	Korea	HCWs	PTSD: 0.017	PTSD: 0.017	6

PTSD: Post-traumatic stress disorder; MERS: Middle East respiratory syndrome; HCW: Healthcare worker.

Nineteen studies reported the prevalence of PTSD during SARS-CoV-2. Figure 10 indicates a pooled prevalence of PTSD of 25.03% with a 95%CI ranging between 18.15-34.51. A high heterogeneity of I^2 = 99.58% was identified.

Based on the findings, PTSD appears to have been reported for SARS-CoV-2, MERS-CoV and SARS-CoV.

A comparative analysis was completed for each MH variable identified and reported, as demonstrated within Tables 3-5.

Table 2 39 studies that are included in meta-analysis for severe acute respiratory syndrome

Study ID	Ref.	Study type	Sample size	Country/region	Exposure	*P* value	Quality assessment (NOS)
1	Kwek *et al*[20]	Cross-sectional	360	Singapore	SARS patients	PTSD: 0.79; Depression: 0.7; Anxiety: 0.51	7
2	Fang *et al*[55]	Cross-sectional	1278	China	SARS patients	Anxiety: 0.291; Depression: 0.705; PTSD: 0.2	8
3	Liang[56]	Prospective cohort	769	China, Taiwan	SARS patients	PTSD: > 0.05; Anxiety: > 0.05	7
4	Dang *et al*[57]	Cross-sectional	549	China	General public	Anxiety: < 0.00001; Depression: 0.000361	7
5	Yip[58]	Prospective cohort	218	China, Hong Kong	SARS patients	Not specified	6
6	Cheng *et al*[59]	Cross-sectional	10	China, Hong Kong	SARS patients	Anxiety: > 0.05; Depression: > 0.05	5
7	Wu *et al*[60]	Cross-sectional	286	China, Hong Kong	SARS patients	PTSD: < 0.001; Depression: < 0.05; Anxiety: < 0.01	6
8	MaK *et al*[61]	Retrospective cohort	126	China, Hong Kong	SARS patients	Not specified	5
9	Lee *et al*[62]	Cross-sectional	10511	China, Hong Kong	Were not HCWs	Not specified	7
10	Hong *et al*[63]	Cross-sectional	1050	China	SARS patients	PTSD: 0.0323	7
11	Wang[64]	Prospective cohort	22	China	SARS patients	Not specified	4
12	Hu *et al*[65]	Cross-sectional	763	China	Attended hospital for other reasons	Not specified	5
13	Chen *et al*[66]	Prospective cohort	325	China, Taiwan	Non-infected HCWs in the largest obligatory SARS hospital, with high SARS contact	Anxiety: 0.55 Depression: 0.93	6
14	Ko *et al*[67]	Cross-sectional	72	China, Taiwan	General public of outbreak area	Depression: 0.02	5
15	Lee *et al*[21]	Cross-sectional	114	China, Hong Kong	General public of outbreak area	Not specified	6
16	Hawryluck *et al*[68]	Cross-sectional	652	Canada, Toronto	General public of outbreak area	Depression: 0.85; PTSD: 0.82	7
17	Liu *et al*[69]	Cross-sectional	96	China, Beijing	Non-infected HCWs of SARS hospital	Depression: < 0.05	7
18	Su *et al*[70]	Prospective cohort	57	China, Taiwan	Non-infected HCWs in SARS outbreak region with high exposure risk *vs* low exposure risk	PTSD: > 0.05; Depression: < 0.05	7
19	Lam *et al*[71]	Retrospective cohort	116	China, Hong Kong	SARS patients	Not specified	6
20	Shi *et al*[72]	Prospective cohort	87	China, Beijing	SARS outbreak region	Not specified	5
21	Huang *et al*[73]	Cross-sectional	4481	China, Beijing	Were not HCWs	Not specified	6
22	Yu *et al*[74]	Prospective cohort	180	China, Hong Kong	General public of outbreak area	Not specified	5
23	Chang and Sivam[75]	Cross-sectional	146	Singapore	General public of outbreak area	Not specified	5
24	Moldofsky and Patcai[76]	Retrospective cohort	107	Canada, Toronto	SARS patients, who were HCWs	Not specified	6
25	Sun *et al*[77]	Prospective cohort	1557	China, Xianxi	SARS patients	PTSD: 0.67	7
26	Lau *et al*[78]	Cross-sectional	333	China, Hong Kong	General public of outbreak area	Not specified	5

27	Reynolds *et al* [79]	Cross-sectional	89	Canada	General public of outbreak area, quarantined; non-infected HCWs in SARS outbreak region, quarantined	Not specified	5
28	Lancee *et al* [80]	Cross-sectional	613	Canada, Toronto	Non-infected HCWs in SARS outbreak region	Not specified	6
29	Lin *et al*[81]	Cross-sectional	6280	China, Taiwan, Taichung	Non-infected HCWs in in region without major SARS outbreak	Not specified	6
30	Gao *et al*[82]	Prospective cohort	127	China, Tianjin	SARS patients	Not specified	5
31	Xu *et al*[83]	Cross-sectional	129	China, Xianxi	Non-infected HCWs in SARS hospital	PTSD: > 0.05	6
32	Wong *et al*[84]	Cross-sectional	0 (?)	China, Hong Kong	Non-infected HCWs from SARS hospitals	Not specified	4
33	Sim *et al*[85]	Cross-sectional	90	Singapore	Non-infected HCWs in SARS outbreak region	Not specified	5
34	Wu *et al*[19]	Cross-sectional	133	China, Beijing	Non-infected HCWs in SARS hospital	Not specified	6
35	Chen *et al*[86]	Cross-sectional	103	China, Taiwan, Kaohsiung	Non-infected HCWs in SARS hospital, with high SARS contact; non-infected HCWs in SARS hospital; with low SARS contact	Not specified	6
36	Tham *et al*[87]	Cross-sectional	90	Singapore	Non-infected HCWs in SARS hospital with extra risk of exposure	Not specified	5
37	Maunder *et al* [88]	Cross-sectional	90	Canada, Toronto	Non-infected HCWs of outbreak area, unspecified (mix of SARS affected and non SARS affected hospitals	PTSD: < 0.01	7
38	Mak *et al*[89]	Retrospective cohort	126	China, Hong Kong	SARS patient	Not specified	6
39	McAlonan *et al*[90]	Cross-sectional	0 (?)	China, Hong Kong	Non-infected HCWs in SARS outbreak region with high exposure risk *vs* low exposure risk	Not specified	3

PTSD: Post-traumatic stress disorder; MERS: Middle East respiratory syndrome; HCW: Healthcare worker; CI: Confidence interval; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

Table 3 Pooled prevalence and confidence interval of anxiety across Middle East respiratory syndrome coronavirus, severe acute respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus-2

Anxiety	Prevalence (%)	95%CI	Heterogeneity I^2 (%)
MERS	17.35	8.36-36.02	95.62
SARS-CoV-2	21.48	18.68-24.71	99.76
SARS-CoV	25.20	18.41-34.5	93.47

CI: Confidence interval; MERS: Middle East respiratory syndrome; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

Table 4 Pooled prevalence and confidence interval of depression across three diseases

Depression	Prevalence (%)	95%CI	Heterogeneity I^2 (%)
MERS	33.65	22.02-51.42	69.86
SARS-CoV-2	27.64	24.59-31.06	99.69
SARS-CoV	23.10	18.14-29.4	95.03

CI: Confidence interval; MERS: Middle East respiratory syndrome; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

Subgroup analysis

Multiple subgroup analyses using age group, cohort and location were conducted as an aim to identify the causation of the heterogeneity reported throughout the meta-analyses.

Age

SARS-CoV-2: The subgroup analysis of age includes 10-19, 20-29, 30-39, 40-49, 50-59, 60-69 (Supplementary Figure 1). In particular, it can be seen from Supplementary Figure 2 that the pooled prevalence for 10–19 year-olds who are likely to have depression due to SARS-CoV-2 is 24.42%. The pooled prevalence for 60–69 years old, on the other hand, was 7.75% with a lower prevalence of depression. Therefore, the details from these analyses demonstrate the statistically reported heterogeneity could be due to the inclusion of multiple age groups.

This is further demonstrated in Supplementary Figure 3, where similar results are indicated for those reporting PTSD among young people, which appears to be higher than the older population (for instance, 32.40% for 20-29 group compared while 5.38% for 50-59 group). However, this is still reflective of a high heterogeneity which could be attributed to the differences in body mass index or race, although, to make a conclusion, further research data is required.

SARS-CoV: The subgroup analysis based on age for the SARS-CoV indicate the prevalence of mental health issues in different age groups during SARS. Supplementary Figure 4 demonstrated that people from 50 to 59 years of age appear to have a higher risk of anxiety (51.62%) in comparison to those between 30-39 (27.4%) as indicated in Supplementary Figure 5. The prevalence of PTSD (Supplementary Figure 6) indicates people within the 30-39 age group report a relatively high risk (32.13%) of PTSD in comparison to those of 60-69 years of age. However, the age group of 60-69 years was based on a single study.

Comparison: Based on the comparison between the 3 meta-analyses, the following results associated with MH outcomes are as indicated within Tables 6-8.

Cohort

SARS-CoV-2: Another facet of the subgroup analysis was based upon the cohorts included within this study, of HCPs, patients and the general public. The MH outcomes are demonstrated in Supplementary Figures 7-9. It is evident that healthcare workers (HCWs) have a higher prevalence of anxiety and depression compared to the general public. The exception to this appears to be the prevalence of PTSD, where the levels appear to be similar for the public and HCWs, at 24.83% and 25.16% respectively.

MERS: Supplementary Figure 10 demonstrates that the general public consists of a smaller pooled prevalence (6.04%) for the MH outcome of anxiety in comparison to patients who contracted MERS-CoV (33.95%), although some of these patients could very well be HCWs themselves. On the contrary, the pooled data for the general public and MERS-CoV survivors indicate a relatively high prevalence of depression (40.7% and 41.69%), while the HCWs appear less likely to have depression (20.52%), as indicated by Supplementary Figure 11. Mild heterogeneity was detected across these 2 groups, with I^2 scores of 41.71%, I^2 = 71.77%. Therefore, statistically, the data and subsequent results appear to be more conclusive and reliable. Supplementary Figure 12 indicated the prevalence of PTSD between HCWs and the general public. PTSD within the general public appears to be relatively low (19.02%) in comparison to depression. Additionally, depression amongst HCWs is more prevalent (49.87%). Moreover, the heterogeneity (I^2 = 0) of this subgroup analysis is negligible, which demonstrates the data are statistically reliable and the conclusions are therefore more conclusive.

SARS-CoV: The subgroup analysis within the SARS-CoV group demonstrated a much higher prevalence of anxiety within HCWs (98.44%) in comparison to the general public (26.19%), as indicated in Supplementary Figure 12. Supplementary Figure 13 indicates that HCWs have a higher prevalence of depression (25.42%) than general public (23.31%) and SARS-CoV patients (21.96%). In contrast, the prevalence of PTSD among HCWs appear to be relatively low (16.97%) in comparison to SARS-CoV patients (19.80%) as well as the general public (18.36%), as indicated in Supplementary Figure 14. However, the heterogeneity score I^2 remains high, thus there may be other potential factors that may affect the statistical findings.

Comparison: Based on the subgroup analysis above, Tables 9-11 showcase the prevalence of different MH outcomes among various cohorts. There are similarities and differences. The prevalence of anxiety within the general public during MERS (6.04%) is the lowest across the three outbreaks, while SARS-CoV demonstrates the largest prevalence of anxiety within general public (26.19%). Meanwhile, HCWs who experienced SARS-CoV were likely to have anxiety (98.44%). The prevalence of anxiety within MERS-CoV patients (33.95%) appear to be the most commonly reported MH outcome. MERS-CoV also demonstrates the highest prevalence of depression within the general public and patients, at 40.70% and 41.69% respectively. Based on the current data on SARS-CoV-2, HCWs are more likely to suffer from depression (37.97%). The highest levels of PTSD were found in HCWs during MERS-CoV and MERS-

Table 5 Pooled prevalence and confidence interval of post-traumatic stress disorder across three diseases

PTSD	Prevalence (%)	95%CI	Heterogeneity I^2 (%)
MERS	35.97	29.6-43.72	75.2
SARS-CoV-2	25.03	18.15-34.51	99.58
SARS-CoV	18.20	14.94-22.18	91.37

PTSD: Post-traumatic stress disorder; CI: Confidence interval; MERS: Middle East respiratory syndrome; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

Table 6 Subgroup analysis on Middle East respiratory syndrome data based on different age groups

Subgroup-age	MERS			
		Prevalence (%)	95%CI	Heterogeneity I^2 (%)
Anxiety	10-19	-	-	-
	20-29	-	-	-
	30-39	-	-	-
	40-49	18.51	8.11-42.23	96.43
	50-59	-	-	-
Depression	20-29	-	-	-
	30-39	-	-	-
	40-49	38.45	25.81-57.26	60.55
	50-59	-	-	-
PTSD	20-29	49.70	38.2-64.67	0
	30-39	19.32	14.82-25.18	0
	40-49	26.69	13.21-53.91	80.63
	50-59	-	-	-
	60-69	17.87	12.4-25.74	0

MERS: Middle East respiratory syndrome; PTSD: Post-traumatic stress disorder; CI: Confidence interval.

CoV patients (49.87% and 37.7%). SARS-CoV-2 appears to demonstrate that PTSD was experienced by 24.83% the general public.

From Supplementary Figures 15-17 we can see that people who experience MERS are more likely to have depression and PTSD than those who experience SARS-CoV-2 and SARS-CoV (the area of the MERS triangles in Supplementary Figures 15 and 17 are larger than the area of the SARS-CoV-2 and SARS-CoV triangles) while people who experience SARS-CoV may have a higher possibility to have anxiety than the other two (the area of the SARS-CoV triangle in Supplementary Figure 16 is larger the area of the MERS and SARS-CoV2 triangles).

Occupation

SARS-CoV-2: Another facet of the subgroup analysis was based upon the occupation of the sample and the reporting of MH outcomes as demonstrated in Supplementary Figures 7-9. It is evident that HCWs have a higher prevalence of anxiety and depression compared to the general public. The exception to this appears to be the prevalence of PTSD, where the levels appear to be similar between the public and HCWs, at 24.83% and 25.16% respectively.

MERS: A subgroup analysis based upon the categories of HCWs, patients and the general public associated with the prevalence of MH outcomes further demonstrates variability. Supplementary Figure 10, for example, demonstrates that the general public is consistent with a smaller pooled prevalence (6.04%) for the MH outcome of anxiety in comparison to patients who contracted MERS-CoV (33.95%), although some of these patients could very well be HCWs themselves. On the contrary, the pooled data for the general public and MERS-CoV survivors indicate a relatively high level of

Table 7 Subgroup analysis on severe acute respiratory syndrome coronavirus-2 data based on different age groups

Subgroup-age	SARS-CoV-2			
		Prevalence (%)	95%CI	Heterogeneity I^2 (%)
Anxiety	10-19	34.40	33.17-35.68	0
	20-29	25.70	19.38-34.08	99.25
	30-39	22.86	17.86-29.26	99.64
	40-49	15.59	9.65-25.17	99.66
	50-59	20.13	10.43-38.84	99.42
	60-69	7.75	0.79-76.29	99.47
Depression	10-19	43.91	42.12-45.77	0
	20-29	31.03	24.04-40.04	99.12
	30-39	30.4	25.15-36.74	99.48
	40-49	20.0	13.26-30.18	99.4
	50-59	19.98	15.84-25.19	92.68
	60-69	4.93	3.45-7.05	90.00
PTSD	20-29	32.40	6.54-160.49	98.29
	30-39	21.96	12.77-37.78	99.33
	40-49	27.72	19.88-38.66	97.59
	50-59	5.38	3.76-7.69	0
	60-69	-	-	-

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; PTSD: Post-traumatic stress disorder; CI: Confidence interval.

Table 8 Subgroup analysis on severe acute respiratory syndrome coronavirus data based on different age groups

Subgroup-age	SARS-CoV			
		Prevalence (%)	95%CI	Heterogeneity I^2 (%)
Anxiety	10-19	-	-	-
	20-29	-	-	-
	30-39	24.60	13.29-45.55	85.81
	40-49	15.63	10.97-22.26	60.57
	50-59	51.62	38.53-69.16	0
Depression	20-29	-	-	-
	30-39	27.47	16.09-46.9	89.58
	40-49	20.30	13.36-30.85	81.57
	50-59	22.49	14.8-34.17	0
	60-69	25.85	17.69-37.75	0
PTSD	20-29	24.43	15.53-38.44	72.18
	30-39	32.13	23.1-44.68	89.33
	40-49	11.68	8.45-16.15	86.20
	50-59	67.80	43.57-100	0
	60-69	7.54	2.64-21.54	53.28

SARS-CoV: Severe acute respiratory syndrome coronavirus; PTSD: Post-traumatic stress disorder; CI: Confidence interval.

Table 9 Subgroup analysis on Middle East respiratory syndrome data based on different type of people

Subgroup-occupation	MERS			
		Prevalence (%)	95%CI	Heterogeneity I^2 (%)
Anxiety	General Public	6.04	2.86-12.79	93.9
	HCW	-	-	-
	Patient	33.95	20.65-55.82	68.57
Depression	General Public	40.70	18.89-87.71	0
	HCW	20.52	11.81-35.67	41.71
	Patient	41.69	23.73-73.22	71.77
PTSD	General Public	19.02	14.01-25.81	0
	HCW	49.87	45.09-55.16	0
	Patient	37.70	27.47-51.74	0

MERS: Middle East respiratory syndrome; HCW: Healthcare worker; PTSD: Post-traumatic stress disorder; CI: Confidence interval.

Table 10 Subgroup analysis on severe acute respiratory syndrome coronavirus-2 data based on different type of people

Subgroup-occupation	SARS-CoV-2			
		Prevalence (%)	95%CI	Heterogeneity I^2 (%)
Anxiety	General Public	21.18	17.88-25.09	99.82
	HCW	22.35	17.42-28.66	99.36
	Patient	-	-	-
Depression	General Public	27.6	23.36-32.24	99.8
	HCW	27.71	23.22-33.08	98.79
	Patient	-	-	-
PTSD	General Public	24.83	14.97-41.18	99.67
	HCW	25.16	16.62-38.08	99.33
	Patient	-	-	-

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; HCW: Healthcare worker; PTSD: Post-traumatic stress disorder; CI: Confidence interval.

prevalence (40.7% and 41.69%) of depression, while the HCWs appear less likely to have depression (20.52%), as indicated by Supplementary Figure 11. Mild heterogeneity was detected across these 2 groups, with I^2 scores of 41.71%, I^2 = 71.77%. Therefore, statistically, the data and subsequent results appear to be more conclusive and reliable. Supplementary Figure 12 indicated the prevalence of PTSD between HCWs and the general public. PTSD within the general public appears to be relatively low (19.02%) in comparison to depression. Additionally, depression is more prevalent in HCWs (49.87%). Moreover, the heterogeneity I^2 = 0 of this subgroup analysis is negligible, which demonstrates the data are statistically reliable and the conclusions are therefore more conclusive.

SARS-CoV: The subgroup analysis within the SARS-CoV group demonstrated a much higher prevalence of anxiety within HCWs (98.44%) in comparison to the general public (26.19%), as indicated in Supplementary Figure 13. Supplementary Figure 14 indicates that HCWs have a higher prevalence of depression (25.42%) than the general public (21.96%) and SARS-CoV patients (23.31%). In contrast, the prevalence of PTSD among HCWs appear to be relatively low (16.97%) in comparison to SARS-CoV patients (19.80%) as well as the general public (18.36%), as indicated in Supplementary Figure 15. However, the heterogeneity score I^2 remains high, thus there may be other potential factors that may affect the statistical findings.

It can be seen from Supplementary Figure 15 that it is less likely for people who experience SARS-CoV to have depression, while people who experience MERS are the most likely to suffer from depression. In particular, the general public and MERS patients have a greater risk of depression than

Table 11 Subgroup analysis on studies under severe acute respiratory syndrome coronavirus data based on different type of people

Subgroup-occupation	SARS-CoV			
		Prevalence (%)	95%CI	Heterogeneity I^2 (%)
Anxiety	General Public	26.19	11.93-57.48	98.22
	HCW	98.44	22.67-427.49	0
	Patient	24.21	17.34-33.79	85.16
Depression	General Public	23.31	14.64-37.11	97.97
	HCW	25.42	13.74-47.03	90.29
	Patient	21.96	16.86-28.6	78.1
PTSD	General Public	18.36	13.59-24.81	81.69
	HCW	16.97	12.28-23.45	91.8
	Patient	19.80	14.28-27.46	90.44

SARS-CoV: Severe acute respiratory syndrome coronavirus; HCW: Healthcare worker; PTSD: Post-traumatic stress disorder; CI: Confidence interval.

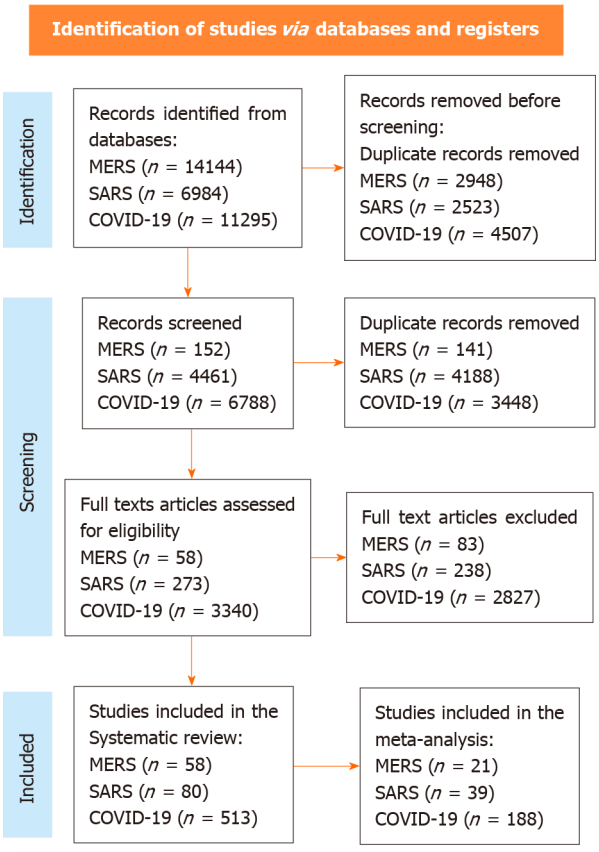

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Figure 1 PRISMA flow diagram. MERS: Middle East respiratory syndrome; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; COVID-19: Coronavirus disease 2019.

those who experience SARS-CoV-2 and SARS-CoV. However, people in the outbreak of SARS-CoV are more likely to have anxiety than people in the outbreak of MERS and SARS-CoV-2 (Supplementary Figure 16). Moreover, it can be noted from Supplementary Figure 16 that HCWs, during the outbreak of SARS-CoV, endured a very high risk of having anxiety. When it comes to PTSD, Supplementary Figure 17 shows that MERS leads to the highest prevalence of PTSD in almost all the mental health diseases across the three pandemics. In particular, HCWs and MERS patients suffer from a serious risk of PSTD after MERS. On the other hand, SARS-CoV seems to lead a relative low risk on the prevalence of PTSD.

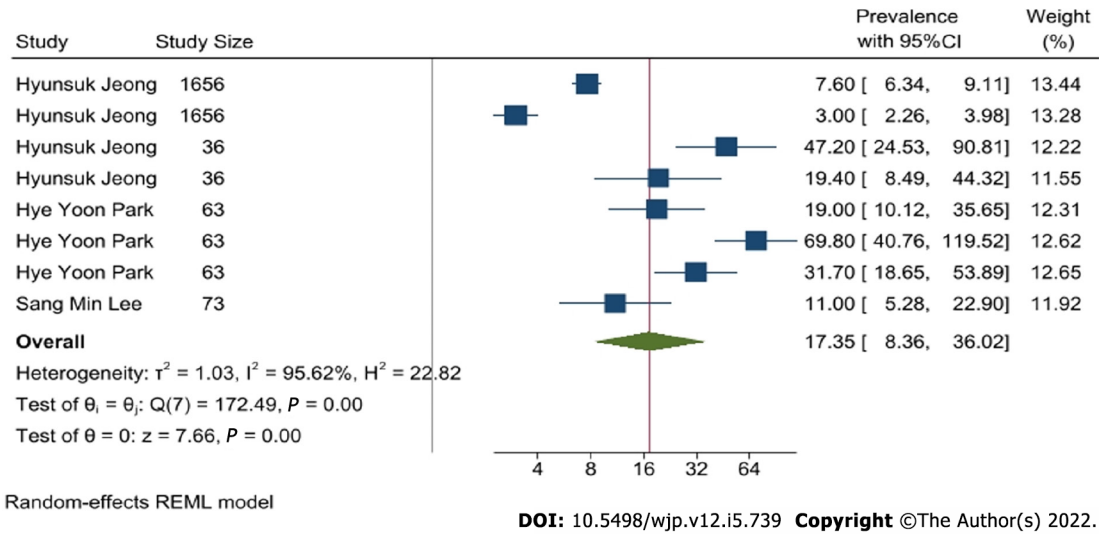

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Figure 2 Forest plot of anxiety caused by Middle East respiratory syndrome.

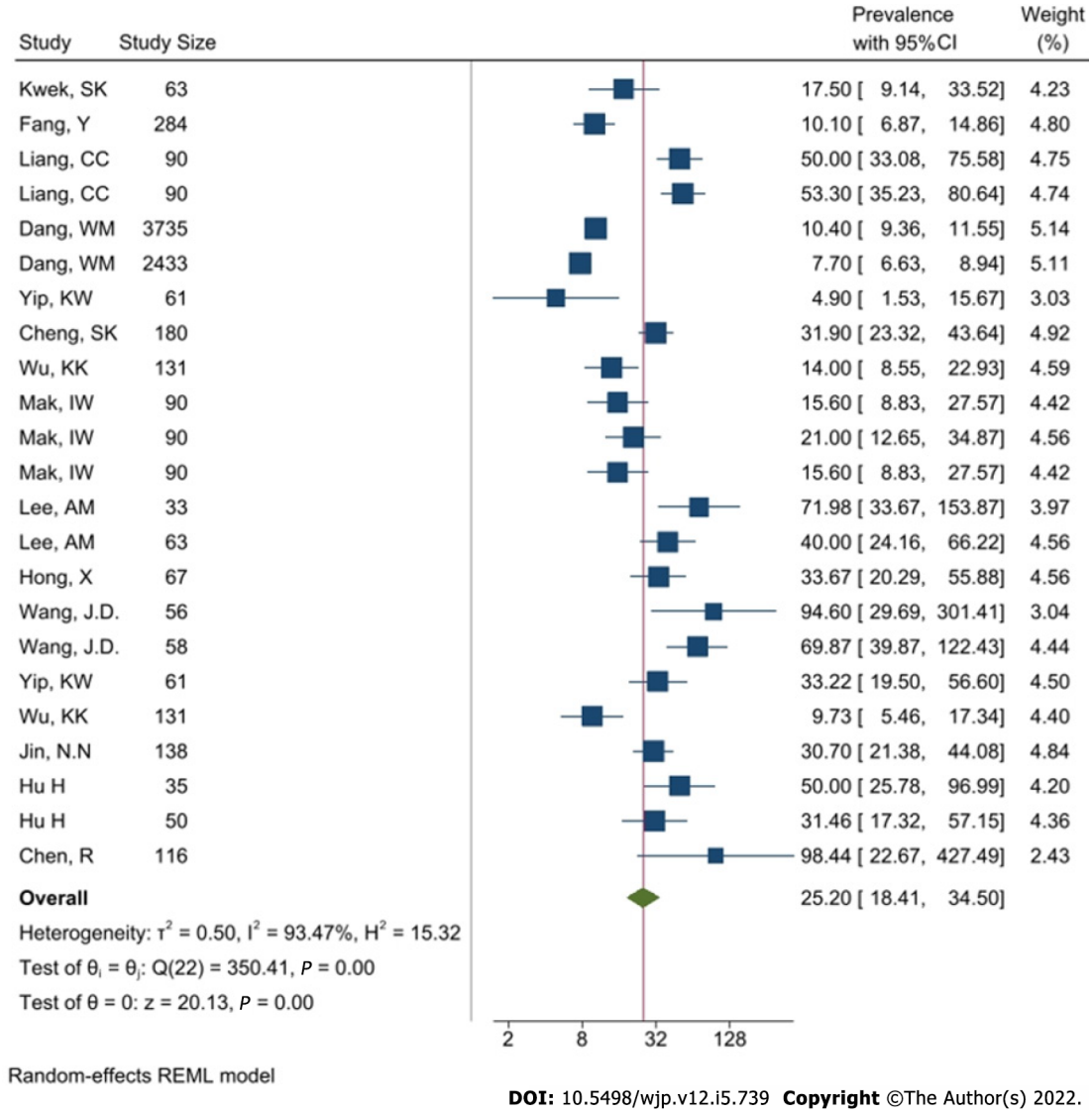

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Figure 3 Forest plot of anxiety that is caused by severe acute respiratory syndrome coronavirus.

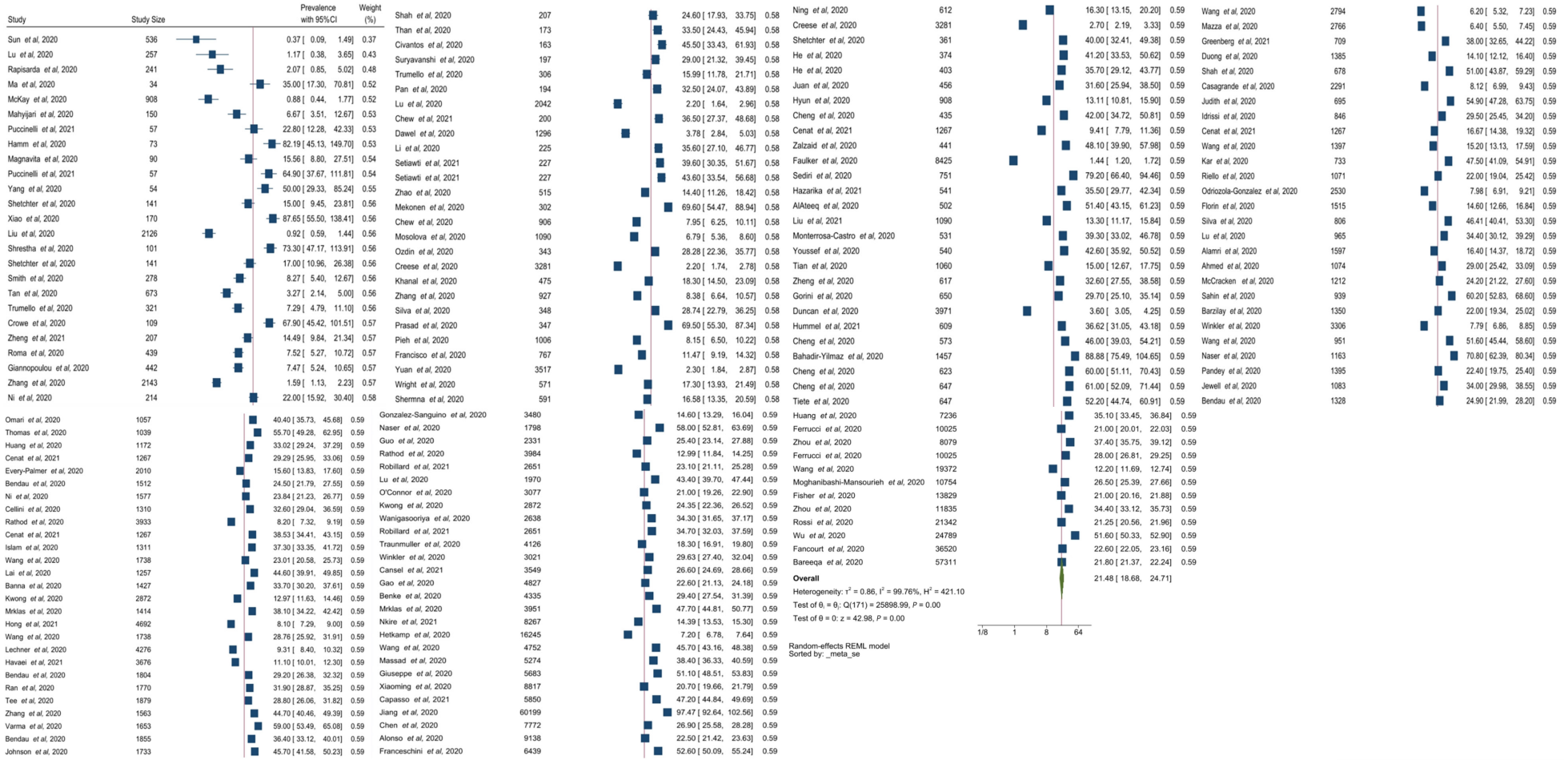

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Figure 4 Forest plot of anxiety caused by severe acute respiratory syndrome coronavirus-2 forest plot.

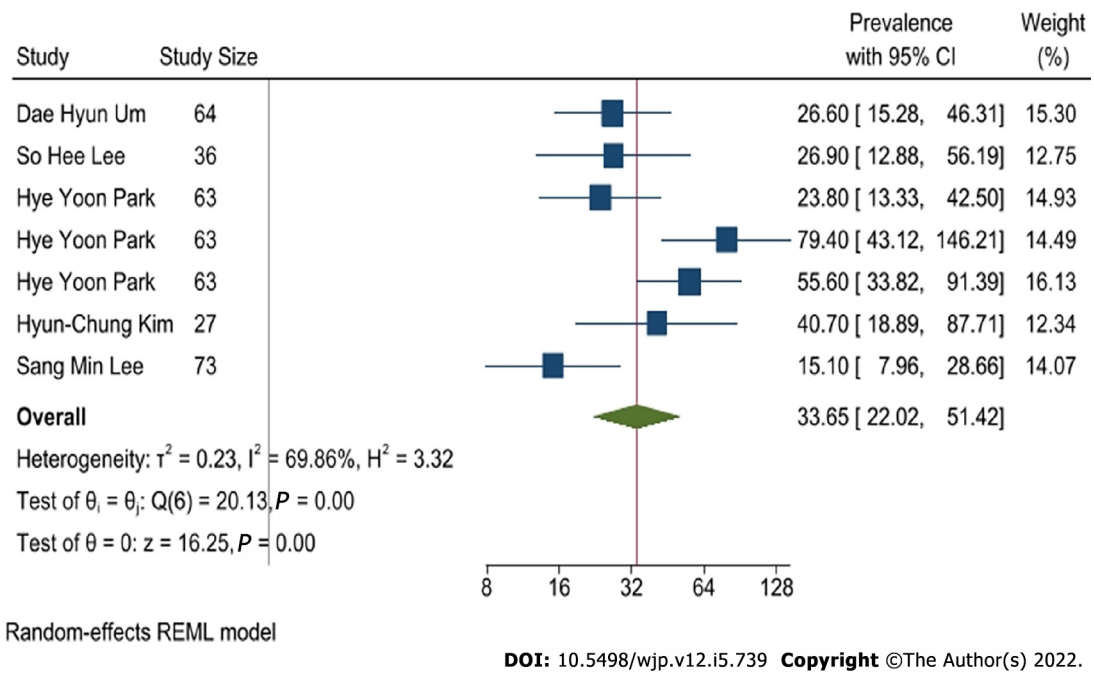
Geographical location

SARS-CoV-2: From Supplementary Figure 18-20, we can see that people in Canada are more likely to have anxiety (80.85%) and PTSD (83.99%) when they experience SARS-CoV-2, and they also showcase a relative high possibility of having depression (57.90%), while people in Palestine suffer from the highest prevalence of depression (88.38%). On the other hand, people in the United Kingdom have the lowest prevalence of depression (1.44%) among all the countries. And people in the United States and Australia have the lowest prevalence of PTSD (5.38%) and anxiety (3.78%) respectively.

Table 12 Sensitivity analysis for anxiety and depression studies under severe acute respiratory syndrome coronavirus-2

	Exposure	Outcome	Prevalence with 95%CI (before)	Prevalence with 95%CI (after)	*P* value
(g)	SARS-CoV-2	Anxiety	21.48 (18.66-24.71)	25.82 (23.98-27.8)	< 0.05
(h)	SARS-CoV-2	Depression	27.64 (24.59-31.06)	29.3 (26.98-31.81)	> 0.05

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; CI: Confidence interval.



DOI: 10.5498/wjp.v12.i5.739

Figure 5 Forest plot of depression caused by Middle East respiratory syndrome.

MERS: A subgroup analysis was not conducted due to the studies taking place in South Korea only.

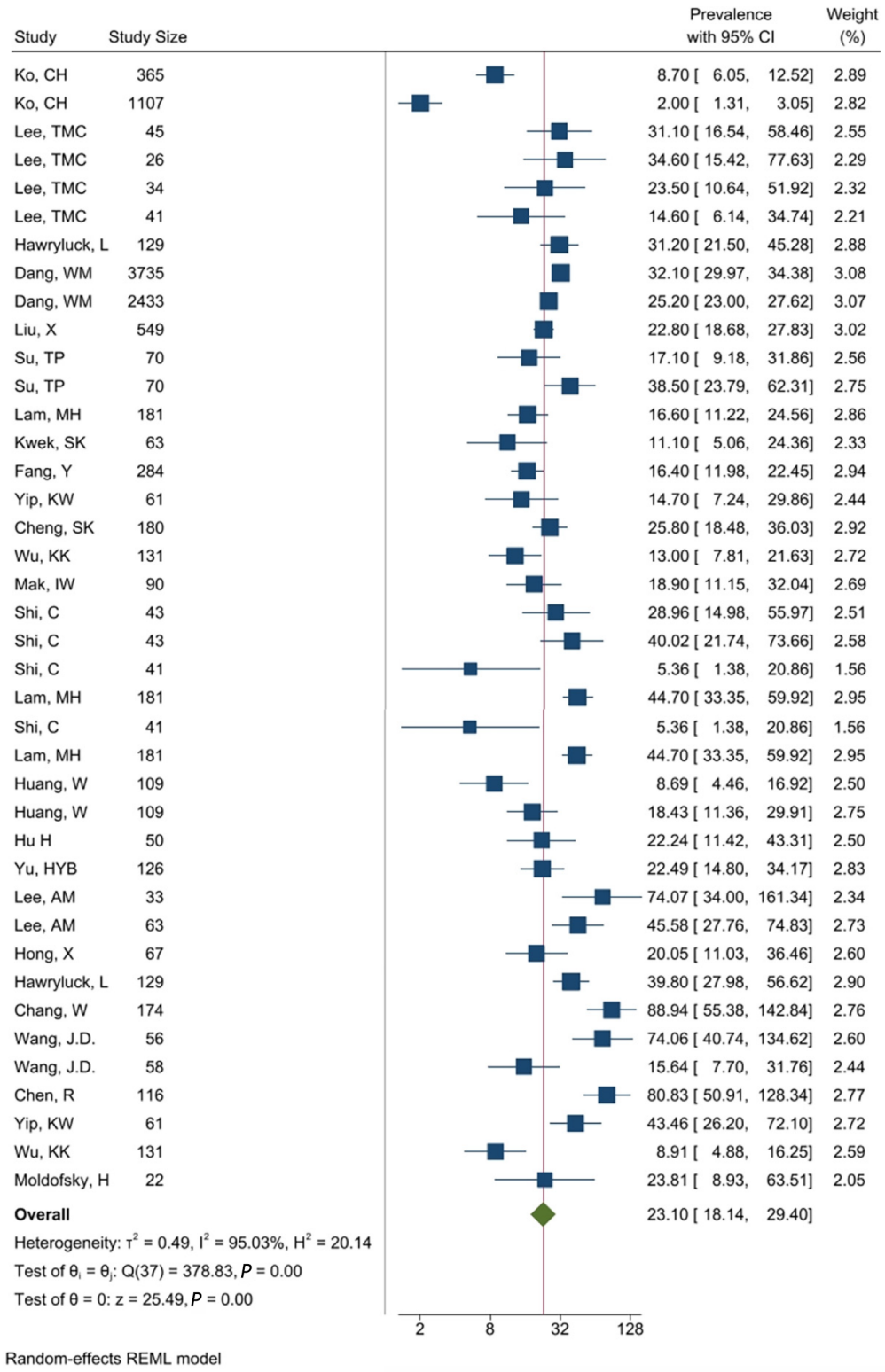
SARS-CoV: Supplementary Figure 21-23 indicate Taipei shows the highest prevalence of depression (38.36%) and anxiety (52.91%) during SARS-CoV. Moreover, people in Kaohsiung/Southern Taiwan also suffer from the highest prevalence of PTSD (45.52%) during SARS-CoV. This indicates that people in the Taiwan area may experience a serious mental health issue due to the outbreak of SARS-CoV. On the other hand, people in Toronto, Singapore and Beijing have the lowest prevalence of PTSD (13.01%), anxiety (17.5%) and depression (21.80%) respectively.

Publication bias and sensitivity analysis

The meta-analyses conducted indicate a high heterogeneity for depression, anxiety and PTSD. This could be due to differences in the reporting criteria and assessment tools used, geographical location and the difference in study designs, which had differing data collection time points. High heterogeneity could cause many studies to fall outside the 95%CI in the conventional funnel plot, which is based on the fixed effects model; therefore, we propose to use the funnel plot based on a random effects model. Both types of funnel plots were compared.

In the fixed effects model, the mean of the underlying model behind each study was fixed; therefore, the measure τ^2 for heterogeneity was 0. Since the random effects model assumes that the mean of each study comes from a normal distribution, the DerSimonian and Laird estimates τ^2 were calculated to show the heterogeneity between studies. The funnel plot based on the random effects model would include most of the studies and, therefore, make it easier to demonstrate publication bias. The pooled prevalence of the three mental health disorders and the 95%CI of the fixed (solid line) and random effects (dotted line) models were both plotted in Supplementary Figure 24 across all 3 pandemics.

When we looked at the funnel plots using the fixed effects model (solid line), most of the studies are located outside of the 95%CI. It is therefore difficult to find the sign of publication bias. They are masked by the widespread studies. By contrast, most of studies are well located within the 95%CI in the funnel plots using the random effects model (dotted line) except sub figs. Supplementary Figure 25A and B. Supplementary Figure 25C and D are typical examples. The large values of τ^2, 1.1110 and 0.4574



DOI: 10.5498/wjp.v12.i5.739

Figure 6 Forest plot of depression that is caused by severe acute respiratory syndrome coronavirus.

confirm the severe heterogeneity, and the random effects model we used addresses this problem well. We can therefore focus on the problem of publication bias.

Based on the 95%CI of the random effects model (dotted line), there is little sign of publication bias in Supplementary Figure 25C-F; the *P* values of Egger's test of 0.082, 0.589, 0.146 and 0.539 echo the findings (Table 7). In Supplementary Figure 25G-I, however, there is a sign of publication bias and the *P* values of the Egger's test are all less than 0.05, confirming the findings (Table 11).

Even if we used the funnel plot based on the random effects model, many studies in Supplementary Figure 25A and B still fall outside the 95%CI, meaning the random effects model cannot address the problem of heterogeneity well. Further investigation is required. The sign of publication

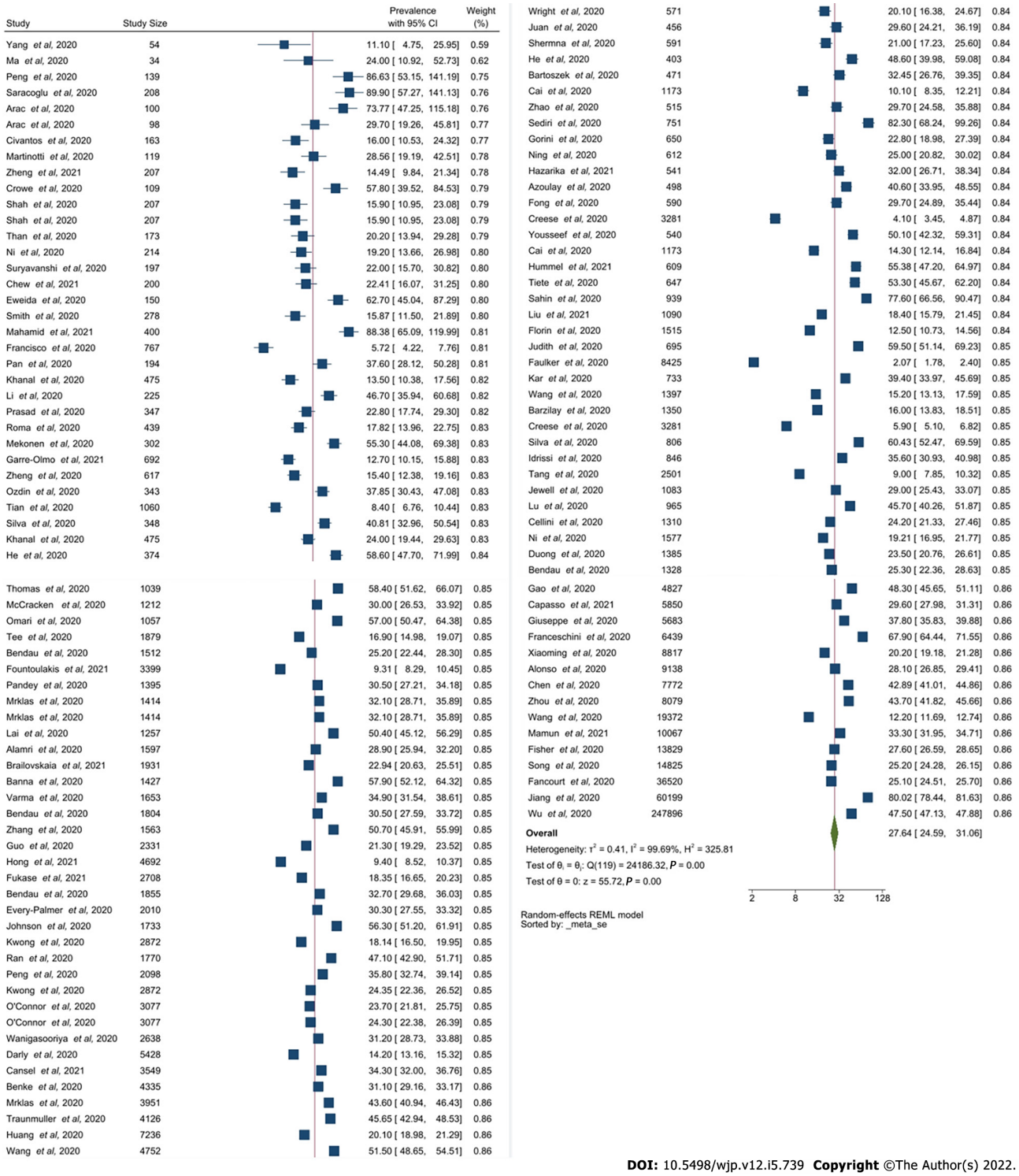


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Figure 7 Forest plot of depression caused by severe acute respiratory syndrome coronavirus-2.

bias is not clear; the *P* values of Egger's test are 0.085 and 0.000 respectively for Supplementary Figure 25A and B.

To reduce the unclear impact of studies that fall outside the 95%CI of random effects model in Supplementary Figure 25A and B, further sensitivity analyses, by removing the studies external to the 95%CI range, was demonstrated in Table 12.

The prevalence of anxiety and depression under SARS-COV-2 (Supplementary Figure 25A and B) are significantly higher after removing the studies external to the 95%CI, with the result changing from 21.44% (18.69-24.61) to 25.54% (23.28-28.02) and 27.68% (24.67-31.06) to 29.7% (27.25-32.39) respectively. It means that factors associated with heterogeneity, say, the design, population and quality of those studies, may have some impact on the conclusion and a further inspection of the study quality and other factors are needed.

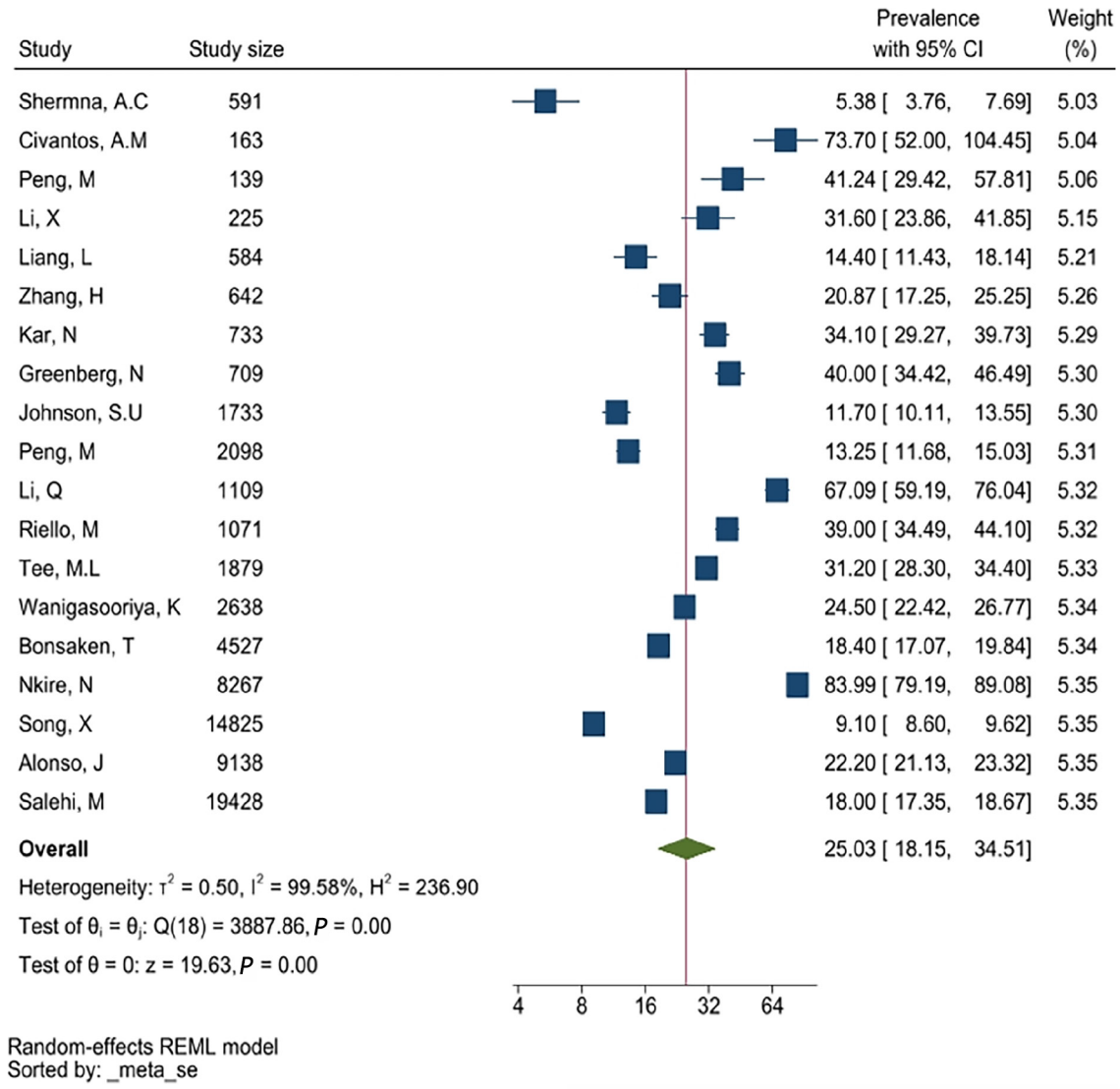

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Figure 8 Forest plot of post-traumatic stress disorder that is caused by Middle East respiratory syndrome.

DISCUSSION

The prevalence of anxiety, depression and PTSD was common across HCWs, patients and the general public. It could be argued HCWs experience psychological burden more profoundly than patients and the general public given that the exposure to negative thoughts would be higher within their work environment. Patients equally could experience a high psychological burden with the exacerbation of their conditions due to a number of factors such as isolation. The general public could equally experience a decline in their mental health due to the lockdown situation in some parts of the world more extensively than others, especially with SARS-CoV-2 as a number of national level lock-downs were imposed in different countries.

The incidence of anxiety across all groups during SARS-CoV-2 (33.16%) was higher in comparison to MERS (17.35%) and SARS-CoV (25.2%). MERS and SARS-CoV-2 demonstrated higher depressive symptoms, at 33.65% and 31.35% respectively, in comparison to SARS-CoV, which reported 23.1%. PTSD was much higher during MERS (35.9%) than SARS-CoV-2 (25.03%) and SARS-CoV (18.2%).

The prevalence of PTSD among HCWs during MERS was 49.87%. The highest prevalence of anxiety for HCWs was during SARS-CoV at 98.44%. Among HCWs, the highest reported prevalence thus far during SARS-CoV-2 appear to be depression and insomnia, at 37.97% and 35.16% respectively. The identified prevalence rates could be influenced directly and indirectly by stigmatisation being an attributor. Stigmatisation within this context could include social processes to discriminate or separate the usual life changes and opportunities. This issue could present a significant barrier in managing access to equitable and quality services. Individual or social construct based beliefs and behaviours could promote social discrimination and moral discredit that may aggravate mental health implications to worsen health outcomes[27]. Interestingly, Dye and colleagues indicated HCWs were unlikely to follow social distancing protocols compared to non-HCWs. This could be associated with bullying as

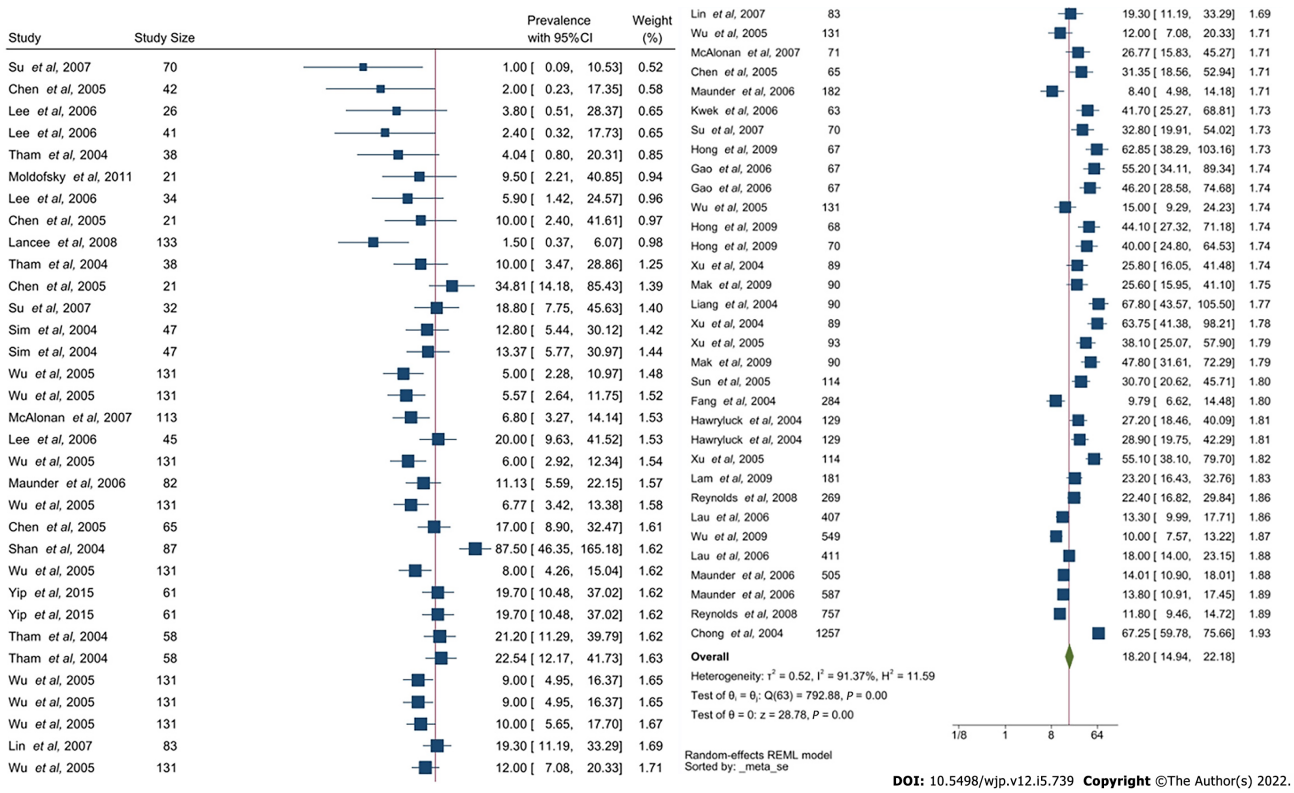

Figure 9 Forest plot of post-traumatic stress disorder that is caused by severe acute respiratory syndrome coronavirus.

demonstrated by Dye *et al*[27] Verbal and physical violence was also associated with bullying or harassment scenarios in comparison to MERS or SARS-CoV. This could be further purported with an influx of patients and workload that exacerbates fatigue and insomnia. This finding is consistent with MERS; therefore, it likely to occur with SARS-CoV-2.

Our results indicated age appear to play a role in mental illness manifestations during SARS-CoV-2, although there was insufficient data during MERS and SARS-CoV to conduct a comparative analysis. The pooled prevalence for ages between 20-29 years appear to demonstrate PTSD at 49.7% during MERS and 32.4% in SARS-CoV-2. Other mental illnesses during SARS-CoV-2 appear to be associated with 10 to 19 years of age with a significant prevalence of anxiety of 35.84% and insomnia (23.3%). In addition, depression was reported at 40.94% within the 30-39 age group.

The indirect influence of SARS-CoV-2 is widespread, especially among young people under 40 years old. For children and teenagers, the social isolation and loneliness of being unable to meet with friends will increase the anxiety. Students worry that the epidemic would limit their future choices and future education, employment and housing. Young workers have a higher rate of unemployment because of their immature skills. During MER-CoV, suicidality was reported at 16.62% with a 95%CI of 10.73-25.75, although the age range associated was non-specific.

Studies relating to SARS-CoV and MERs-COV are limited by several aspects, including the geographical constraints and sample sizes. The majority of studies were published in languages other than English. Psychological symptomatologies associated with depression, anxiety, distress, insomnia and fatigue, as well as comorbidities such as PTSD and neuro-psychiatric syndromes such as psychosis, have been reported in patients and HCWs more during the SARS-CoV-2 pandemic[28,29] which could be due to the scope and scale of the incidence and high transmission rates. The effects of mass lock-downs, economic downturns and mass uncertainty and fear within the general population are harder to characterise and assess, but early evidence suggests that rates of mental health disorders within the population will be higher during and following the pandemic[30,31]. More significant findings of severe psychological disorders including post-traumatic stress disorder and suicidal ideation amongst health care workers have been reported at levels greater than or expected to be seen in military veterans[32] or amongst victims of natural disasters[33]. Within the three groups there is likely to be variations in the levels of mental health disorders based on age, race and socio-economic status due to differences in the risk of mortality[34,35].

Non-specific use of MH interventions to support HCPs during each of the coronavirus disease outbreaks demonstrate the lack of preparedness global healthcare systems appeared to have had. Thereby, the ongoing SARS-CoV-2 will continue to impact their MH and overall well-being due to the lack of protective factors and assessments to identify specific risk factors. The available evidence demonstrates safeguarding measures should be considered by healthcare systems to better strategize

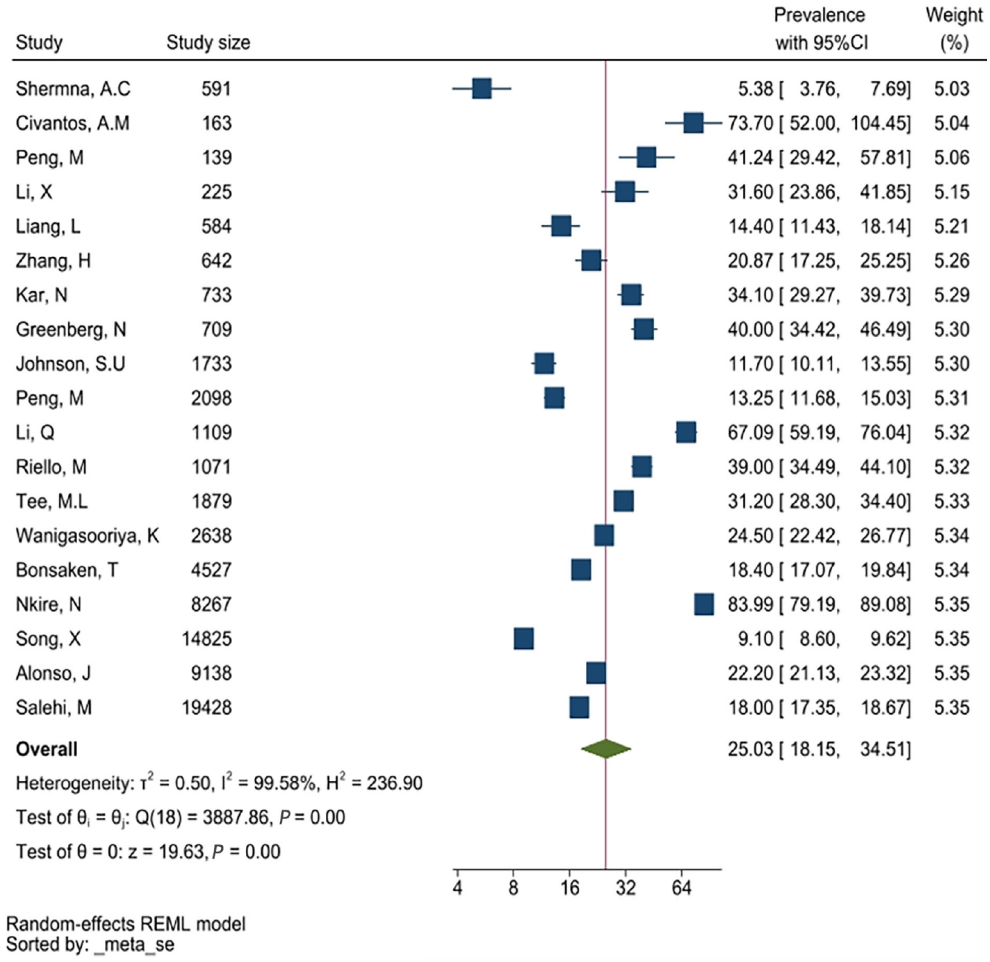

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Figure 10 Forest plot of post-traumatic stress disorder caused by severe acute respiratory syndrome coronavirus-2. CI: Confidence interval.

both collegial support and control steps to support all HCPs.

Limitations

Several factors, including communication and country, as well as regional directives and their differences, were paramount to the inclusion and exclusion of the evidence within this study. All 3 cohorts included within this study reported their mental health impact differently. Multiple mental health assessments were used; thus, cut-off scores were used to better evaluate and inform the statistical analysis conducted. Unified approaches for the assessment of pandemic-specific or related mental health among HCPs, patients and the public should be considered in the future. This is another factor that led to the observations of high variation in outcomes and risks to medium- to long-term mental health impact.

CONCLUSION

As vaccines are rolled out globally, it is hoped that pressures on acute medical services due to the SARS-CoV-2 will slowly improve. The aim of this study is to understand and build on our knowledge of the viruses' impact on mental health, both previously and now, so that we may better manage and prepare to deal with the hidden consequences of this and any future outbreaks. Whilst there are cultural, economic and environmental differences between the countries affected in each pandemic, drawing similarities between the lasting effects on mental health will be important in highlighting where resources and support are needed as we contemplate our recovery–physically, mentally and socially–from this pandemic. The mortality impact of seasonal influenza and a pandemic on the mental health of the general public, patients and HCPs vary.

This study analysed the prevalence of mental health outcomes during the MERS, SARS-CoV and SARS-CoV-2 across multiple cohorts. In terms of mental illness like anxiety, depression and PTSD, the prevalence of depression (33.65% with 95%CI: 22.02-51.42) and PTSD (35.97% with 95%CI: 29.6-43.72) is higher during MERS, while the prevalence of anxiety (33.16% with 95%CI: 25.99-34.5) is higher during

SARS-CoV-2. Patients and HCWs are the first and second most likely groups to suffer from mental health problems. Young people are more likely to be caught up in depressive and anxiety emotions than older people.

Developing evidence-based and cohort-specific MH interventions could be a useful way to optimise MH support. HCPs in particular may benefit from this as it could promote better well-being for staff, increasing the efficiency within the work environment.

ARTICLE HIGHLIGHTS

Research background

The severe acute respiratory syndrome (SARS) virus has been present for centuries in different forms. Whilst civilisation has evolved, so has the virus, including its' ability to transmit. Thus, the comparison of the three most recent severe acute respiratory syndrome coronavirus (SARS-CoV) viruses in terms of the mental health implications infused to patients, healthcare professionals (HCPs) and patients is an important facet both clinically and scientifically. As a result, our study explores an important component that hasn't been addressed from a potential disease sequalae perspective.

Research motivation

Our motivation was to demonstrate the trends associated with the mental health prevalence in terms of specific conditions due to the last three virulent strands of SARS-CoV across patient, HCPs and the general public. The specified cohorts have specific behavioural patterns and differing levels of exposure to the virus, thus the risk of infection varies that influences the mental health impact. This would aid in assessing the true mental health impact that health care systems require to support those needing mental health support. The comparison also allows us to predict the trends in mental health impact due to infectious transmissions which ultimately should be addressed as a public health hazard, globally.

Research objectives

The study has three primary aims of identifying and reporting: (1) Mental health conditions commonly observed across all three pandemics; (2) Impact of mental health outcomes across patients, the general public and HCPs associated with all 3 pandemics; and (3) The prevalence of the mental health impact and clinical epidemiological significance.

Research methods

A systematic methodology was developed and published on PROSPERO (CRD42021228697). The databases PubMed, EMBASE, ScienceDirect and the Cochrane Central Register of Controlled Trials were used as part of the data extraction process, and publications from January 1, 1990 to August 1, 2021 were searched. MeSH terms and keywords used included *Mood disorders, PTSD, Anxiety, Depression, Psychological stress, Psychosis, Bipolar, Mental Health, Unipolar, Self-harm, BAME, Psychiatry disorders and Psychological distress*. The terms were expanded with a 'snowballing' method. Cox-regression and the Monte-Carlo simulation method was used in addition to I^2 and Egger's tests to determine heterogeneity and publication bias.

Research results

The results indicated that there is a mental health impact observed among patients, HCPs and the general public at varying levels. This study analysed the prevalence of some mental health outcomes to the outbreaks of Middle East respiratory syndrome (MERS), SARS-CoV and SARS-CoV-2 and compared the prevalence of the participants and the prevalence of different occupational groups and age groups. In terms of mental illness like anxiety, depression and post-traumatic stress disorder (PTSD), the prevalence of depression [33.65% with 95% confidence interval (CI): 22.02-51.42] and PTSD (35.97% with 95%CI: 29.6-43.72) is higher during MERS, while the prevalence of anxiety (33.16% with 95%CI: 25.99-34.5) is higher during SARS-CoV-2. Patients and healthcare workers are the first and second most likely groups to suffer from mental health problems. Young people are more likely to be caught up in depressive and anxiety emotions than older people.

Research conclusions

Developing evidence-based and cohort-specific mental health (MH) interventions could be a useful way to optimise MH support. HCPs in particular may benefit from this as it could promote better well-being for staff, increasing the efficiency within the work environment. As vaccines are rolled out globally, it is hoped that pressures on acute medical services due to the SARS-CoV-2 will slowly improve. The aim of this study is to understand and build on our knowledge of the viruses' impact on mental health, both previously and now, so that we may better manage and prepare to deal with the hidden consequences of this and any future outbreaks. Whilst there are cultural, economic and environmental differences between the countries affected in each pandemic, drawing similarities between the lasting effects on

mental health will be important in highlighting where resources and support are needed as we contemplate our recovery–physically, mentally and socially–from this pandemic. The mortality impact of seasonal influenza and a pandemic on the mental health of the general public, patients and HCPs vary.

Research perspectives

Studies relating to SARS-CoV and MERS-CoV are limited by several aspects, including the geographical constraints and sample sizes. The majority of studies were published in languages other than English. Psychological symptomatologies associated with depression, anxiety, distress, insomnia and fatigue, as well as comorbidities such as PTSD and neuro-psychiatric syndromes such as psychosis, have been reported in patients and HCWs more during the SARS-CoV-2 pandemic which could be due to the scope and scale of the incidence and high transmission rates. The effects of mass lock-downs, economic downturns and mass uncertainty and fear within the general population are harder to characterise and assess, but early evidence suggests that rates of mental health disorders within the population will be higher during and following the pandemic. We need more comprehensive and longitudinal studies to be conducted to determine the mental health impact in multiple populations globally. This would also aid us to develop better pandemic preparedness frameworks and policies within healthcare systems.

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FOOTNOTES

Author contributions: Delanerolle G and Phiri P developed the systematic review protocol and embedded this within the EPIC project's evidence synthesis phase; Delanerolle G and Goodison W wrote the first draft of the manuscript; The statistical analysis plan was developed by Delanerolle G and was conducted by Shi JQ, Yeng X and Zeng Y; The data was critically appraised by Shetty A, Phiri P, Zeng Y, Yeng X, Shi JQ, Goodison W, Ramakrishnan R, Ranaweera S and Raymont V; The SARS-CoV data was extracted by Chau SWH and his team; The SARS-CoV-2 data was extracted by Phiri P/Delanerolle G and their team; Yeng X and Zeng Y extracted the MERS dataset which was reviewed by Delanerolle G, Phiri P, Shetty S, Shi JQ and Shetty A; Yeng X, Zeng Y and Shi JQ conducted the analysis; Shetty S designed and developed the original illustration; Delanerolle G, Phiri P, Shetty A, Zeng Y, Yeng X, Shetty S, Shi JQ, Goodison W, Ramakrishnan R, Elliot K, Ranaweera S and Raymont V critically appraised and finalised the manuscript; All authors approved the final version of the manuscript.

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LETTER TO THE EDITOR

COVID-19, mental health and Indigenous populations in Brazil: The epidemic beyond the pandemic

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Abstract

The aim of this paper was to report on factors contributing to the deterioration of the mental health of Indigenous populations (IP) in Brazil. Five factors seem to have a direct impact on the mental health of IP in Brazil: (1) The absence of public policies; (2) Intellectual production; (3) Psychiatric medical care for remote areas (*e.g.*, telemedicine) aimed at promoting the mental health of Brazil's IP, which causes a huge gap in the process of assistance and social, psychological, economic and cultural valorization of native peoples; (4) The dissemination of fake news, which exposed, above all, older IP to risk behaviors in the pandemic, such as refusal of vaccination; and (5) The violence carried out on IP lands due to economic interests with mining/agribusiness.

Key Words: Brazil; COVID-19; Indigenous population; Mental health; Public health

Core Tip: In Brazil, the mental health of the Indigenous population (healthy or with psychiatry disorders) suffers from several factors. Over the past 2 years, there has been growing violence against Indigenous people along with a considerable increase of fake news dissemination regarding the coronavirus disease 2019 pandemic currently afflicting them. These two factors, accentuated by the lack of public policies and scarce academic contribution in the area, make the mental health of the Indigenous population in Brazil an important public health problem.

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TO THE EDITOR

With great interest we read the work of Diaz *et al*[1] commenting on how the coronavirus disease 2019 (COVID-19) pandemic affects psychiatric patients disproportionately compared to the general population. Of the highlighted minority groups, the Indigenous population (IP) draws our attention. We would like, therefore, to contribute to the discussion with some factors that in our opinion may further worsen the mental health of these populations in Brazil. A summary of the points we consider important about the topic are presented in Figure 1.

As the authors pointed out, there is a dearth of public policies that address the promotion of mental health in Indigenous patients with psychiatric illnesses (IPPI)[1]. Moreover, in Brazil, this situation is even more precarious. The most recent regulation on the mental health of the IPPI was only released by the Brazilian Ministry of Health in 2007 - the Policy of Comprehensive Mental Health Care for Indigenous Populations ("Política de Atenção Integral à Saúde Mental das Populações Indígenas")[2] (Figure 1). Besides that, academic production is limited. An integrative review carried out on the subject showed that of the 5510 articles found in 20 years of scientific publications, only 14 (0.2%) contemplated the mental health of the IPPI[3]. This factor reinforces their findings: That there is a lack in mental health care for IPPI[1]. However, in Brazil, in addition to the lack of mental health care, there is a gap between academic production and current legislation. At the same time, consecutive antibody seroprevalence surveys against COVID-19 conducted in urban areas in all regions of the Brazil reported a higher prevalence in IP than other ethnicities[4].

In Brazil, the spread of fake news is another important factor causing psychological distress in IPPI according to Figure 1. Studies have already demonstrated that advancement and dissemination of false information incite fear, anger, anguish and worsening of previous depressive and anxiety symptoms and can therefore be considered as an additional epidemic ("Infodemia") within the COVID-19 pandemic[5]. According to non-governmental organizations, which historically have been defending the health of IP, such as Articulação dos Povos Indígenas do Brasil and Conselho Indigenista Missionário, there is increasing fear and worry, especially by older members of IP, due to fake news. In fact, several news articles are aimed at promoting the ineffectiveness of vaccines for COVID-19 or associated nonexistent effects (*e.g.*, "those who took the vaccine would die in a fortnight" or "those who took the vaccine turn into an alligator")[6,7].

Another important factor with a negative impact on the mental health of the IPPI would be the rising rates of violence against IP during the COVID-19 pandemic (Figure 1). According to Conselho Indigenista Missionário, the cases of "invasions, illegal exploitation of resources and damage to property" in indigenous lands rose from 109 in 2018 to 256 in 2019. Occurrences of this type affected 151 indigenous lands and 143 peoples in twenty-three Brazilian states. There were also 35 cases of territorial conflicts, 33 cases of death threats, 34 cases of other types of threats, 13 cases of personal injury and 31 cases of deaths due to lack of assistance in the last year[7]. The continuous rise observed between 2018 and 2019 has possibly worsened during the pandemic.

Thus, the absence of telemedicine/internet services, prejudice and religious barriers are important factors that worsen the IPPI's mental health (Figure 1). In Brazil, in addition to these factors, the lack of knowledge of the epidemiological situation of mental illnesses in this population, the violence and the Infodemia are factors that increase psychological distress and make it difficult to draft and carry out public policies.

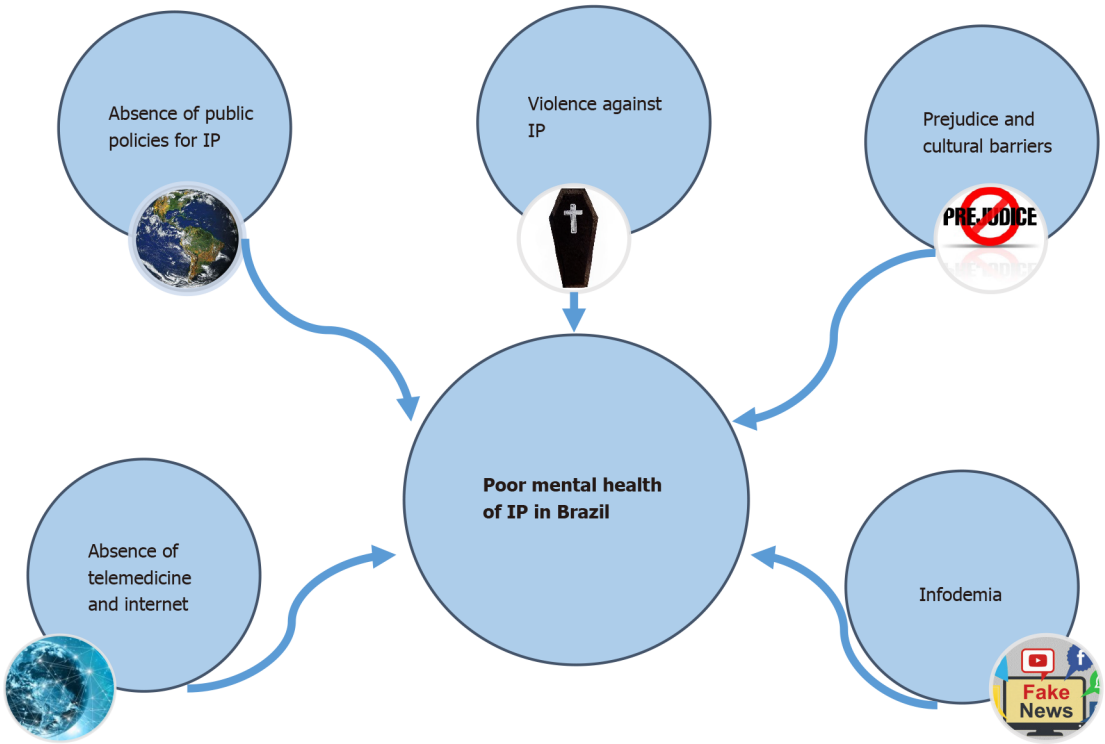

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Figure 1 Factors that contribute to the worsening mental health of Indigenous peoples. IP: Indigenous people.

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FOOTNOTES

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LETTER TO THE EDITOR

Biological mechanisms and possible primary prevention of depression

Chih-Yun Kuo, Ivo Stachiv

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Abstract

Individuals with unipolar depressive disorder (UDD) are having an increased risk of death and development of dementia in later life. It is widely expected that in a near future UDD would be the leading cause of death; therefore, a primary inexpensive prevention of UDD will be of a great importance to the society. Several studies provide evidences supporting the positive effect of Mediterranean diet on a reduced risk for development of depression.

Key Words: Unipolar depressive disorder; Mediterranean diet; Depression; Primary prevention; Dementia

Core Tip: Dietary interventions, especially Mediterranean diet, may help to reduce the risk for development of depression. It is the high levels of various antioxidant compounds, adequate B-group vitamin and folate content which make the Mediterranean diet a possible candidate for an inexpensive primary intervention of depression. However, the long-term clinical trials on the large cohorts are still necessary to understand the relationship between dietary pattern and development of depression or dementia.

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TO THE EDITOR

Unipolar depressive disorder (UDD) is characterized by an increased mortality in the general population. The healthy diet, especially Mediterranean diet, has been found being associated with the one`s health status including mental health. Unfortunately, up to date the exact relationship between the healthy diet and the risk for development of depression, biomarkers and overall improvements in the one`s quality of life is still not fully understood. With this in mind we read the narrative review by Pano *et al*[1] with a considerable interest. In their study, they have summarized the available evidences on the biological mechanisms of UDD and cardiometabolic diseases as well as the primary preventive strategies for depression such as dietary interventions. They have suggested that Mediterranean diet interventions could potentially be considered as an inexpensive strategy enabling to notably reduce the risk for depression, that is, Mediterranean diet can be viewed as the protective factor against depression. In addition, authors have also pointed out main advantages of this healthy diet (*i.e.*, Mediterranean diet) such as the high levels of various antioxidant compounds, adequate B-group vitamin and folate content.

We commend the authors for this important research and agree with their opinion and conclusions. Note that their data which are in a good agreement with other recently reported studies on association between dietary patterns and depression[2-4] or even dietary pattern and dementia in later life[5], are of great importance to public health. These recent studies provide evidences suggesting that oxidative stress, gut microbiota, the hypothalamic-pituitary-adrenal dysregulation and mitochondrial dysfunction are the possible driving mechanisms of depression. Despite the mechanisms associating the dietary interventions with depression are still not fully explained, there is a consensus among researchers that healthy diet, that is, particularly Mediterranean diet, can notably reduce the incidence of depression. In addition, Mediterranean diet has also been shown affecting depression *via* other chronical comorbid diseases such as diabetes mellitus or cardiovascular diseases. Pano *et al*[1] have also proposed that the systematic long-term clinical trials would be necessary to support the protective effect of dietary interventions. We foresee that these studies should also account for behavioral, biological and other factors such as sex and culture differences. Hence, the effect of other healthy diet and individual factors would be required to develop novel treatment strategies and clinical practice guidelines.

To conclude, we once again commend the authors on this interesting work and highly welcome their findings on this important topic. We emphasize here that research associating healthy lifestyle and depression should be of emergent importance, and a larger sample size and well-designed clinical trials are needed in the future studies.

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