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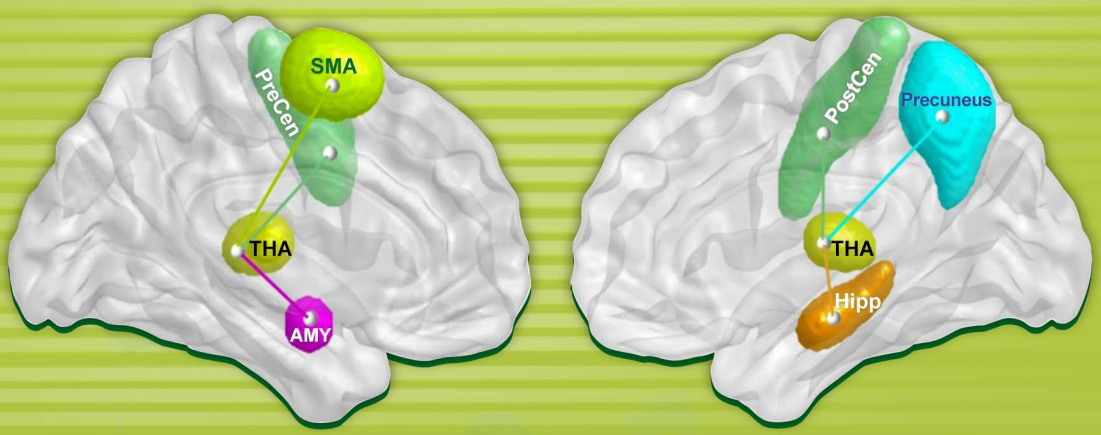

Fibers showed decreased fractional anisotropy value in patients with functional constipation relative to healthy controls

Magnetic resonance imaging and functional constipation

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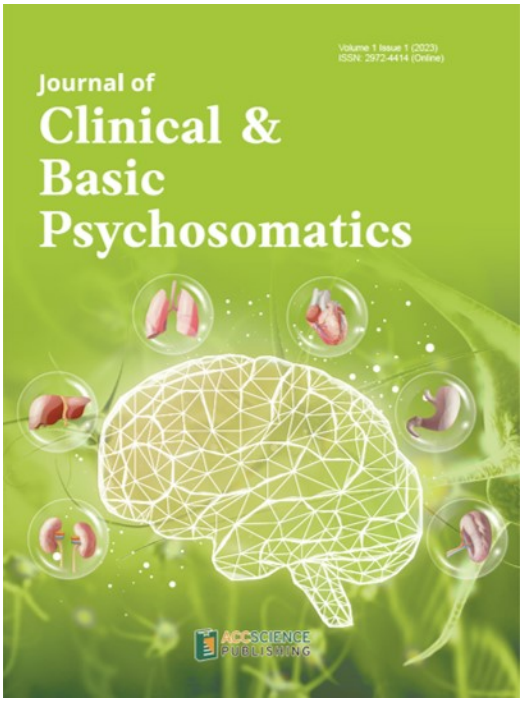

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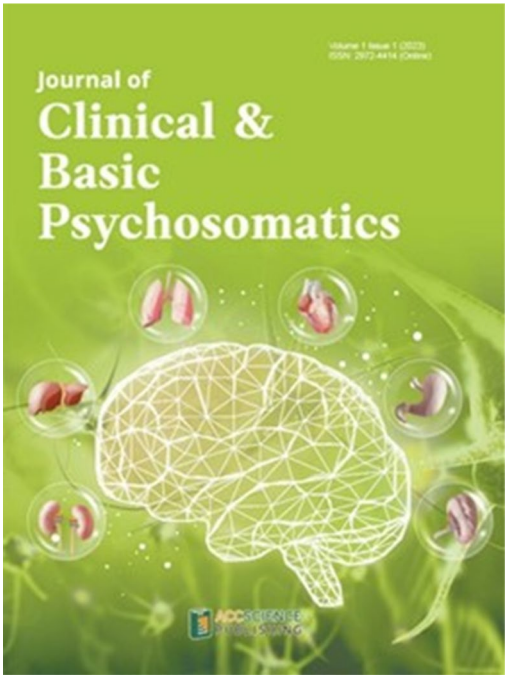

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Journal of Clinical and Basic Psychosomatics

EDITORIAL

Journal of Clinical and Basic Psychosomatics in 2023: A growing and active academic platform

Wenhao Jiang†, and Yonggui Yuan††*

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In early 2023, we launched the *Journal of Clinical and Basic Psychosomatics* (*JCBP*)[1] with significant support from our colleagues in psychosomatic medicine. The journal has successfully published two issues, featuring a total of 16 articles, comprising eight original research articles, three reviews, two brief reports, one case report, one letter, and one editorial. The collaborative efforts of over 300 authors and the contributions of 100 reviewers have played crucial roles in the success of the journal. In addition, the publishing house has dedicated great effort to promotion. The network metrics indicate rapid growth, with over 10,000 views achieved. This has facilitated the dissemination of cutting-edge findings and critical knowledge in the field of psychosomatic research throughout the scientific community.

The journal benefits from a diverse and highly professional editorial board comprising 66 members. Importantly, our senior and honorary editors have sparked the passion and initiated research in psychosomatic medicine and related societies[2,3]. We are pleased that the journal serves as a platform where people can share, discuss, and publish their sparkles. It aligns with our original idea – it should be more than a journal; it should be a home for people focusing on the body–mind interaction but lacking appropriate attention and publication chances.

In the coming new year, the journal will continue to strengthen connections within the psychosomatic medicine community, making it a robust yet active academic publishing platform. First, we expect an expansion of the editorial board and review experts, with a focus on providing opportunities for qualified early career researchers to contribute as special youth editors. Second, we will organize an annual meeting, offering additional avenues for academic dissemination and social opportunities in addition to regular editorial board communications. This initiative is expected to serve as a valuable supplement to regional psychosomatic societies. Third, workshops focusing on psychosomatic research will be organized and open to different disciplines in the medical and psychological fields. Finally, special issues, including "Psychodermatology Today" and "Advanced in Psychotherapy and Clinical Psychology," have been scheduled. Cover papers will be selected from distinguished submissions to ensure their influence is well recognized.

The *JCBP* achieved numerous milestones in the past year and will continue to encourage integrative psychosomatic research. We would like to extend our gratitude to the entire community, especially our editorial board, review experts, authors, and readers. Your passion for psychosomatic medicine and unwavering support is essential for our baby steps and future development.

†Associate Editor of *Journal of Clinical and Basic Psychosomatics*
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The authors have no conflicts of interest to declare.

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Journal of Clinical and Basic Psychosomatics

REVIEW ARTICLE

Magnetic resonance imaging and functional constipation

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Abstract

With the rapid development of society, the incidence of functional constipation (FC) is steadily increasing annually. As it poses an elevated risk for various physical and neuropsychiatric illnesses, the occurrence and development mechanisms of FC have garnered escalating attention from researchers. Accumulating evidence from studies using magnetic resonance imaging (MRI) suggests that FC is associated with alternations in brain function and structure, particularly within brain regions and networks involved in emotion regulation, motor control, somatic sensation, and self-reference. Specifically, significant differences in baseline brain activity and functional connectivity integrity exist between patients with FC and healthy controls. Patients with FC exhibit abnormal cortical morphometry, a lower gray/white matter volume, and impaired white matter integrity. These changes correlate with somatic symptoms, such as the difficulty level of defecation and the sensation of incomplete evacuation. Differences between patients with anxiety/depressive disorders (FCAD) and those without such disorders (FCNAD) underscore the pivotal role of psychiatric factors in FC development. In addition, studies have verified that female patients experience decreased emotional regulation, contributing to a higher prevalence of FC and more severe constipation symptoms than their male counterparts. This paper provides a comprehensive literature review, drawing upon existing MRI studies to explore the various brain abnormalities evident in patients with FC. Through the analysis of these studies, our aim is to shed light on the underlying neural mechanisms and offer valuable insights into the development of novel and effective treatments for FC.

Keywords: Magnetic resonance imaging; Functional constipation; Neural mechanisms; Psychiatric factors; Brain function and structure

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1. Introduction

With the rapid development of society, substantial changes in people's dietary structures and living habits have occurred. Coupled with the escalating pressures across various

facets of life, these shifts have led to corresponding adjustments in nutrient intake and digestion, contributing to a heightened incidence of functional gastrointestinal disorder (FGID). Among the prevalent FGIDs, functional constipation (FC) exhibits an annual increase[1,2]. FC is defined as constipation lacking an organic etiology and is diagnosed based on the Rome criteria. This condition is characterized by reduced stool frequency, the presence of hard and/or large stools, painful defecation, the sensation of incomplete evacuation, and often accompanied by abdominal distension and pain[3,4]. Global surveys utilizing the Rome IV criteria indicate a 10.1% incidence of FC, with a higher prevalence among female patients than males (2.1:1)[5]. Additionally, studies have indicated that patients experiencing long-term FC are prone to anxiety and depressive symptoms. The incidence of FC is higher in patients with mental disorder than healthy control (HC)[6]. Patients with FC frequently expressed challenges in finding relief from persistent constipation symptoms[7]. The repercussions of FC extend beyond individual experiences, placing a substantial burden on both families and society.

The bidirectional brain-gut interaction plays a crucial role in gastrointestinal function and health. The brain exerts influence on the gastrointestinal tract by sending commands that impact motility, secretion, and sensation. Simultaneously, the gastrointestinal tract communicates with the brain, conveying information about its status and function[8]. This interaction involves various pathways, including neural connections, neurotransmitters, hormones, the immune system, and the gut microbiota. The gut microbiota not only directly interacts with the gastrointestinal tract but also communicates with the immune system and the nervous system through various signaling systems. Its homeostasis is the premise for the normal functioning of the brain-gut axis[9,10]. Studies have confirmed the sensitivity of the gut microbiota to mood and environmental stimuli (stress). Changes in its metabolite levels have been related to neurological diseases such as anorexia nervosa, long-term anxiety, and depression[11]. Disordered brain-gut interactions are believed to be the underlying cause of symptom generation in several FGIDs. Previous studies have confirmed that abnormalities in autonomic nervous system regulation and the immune system contribute to irritable bowel syndrome (IBS), a prevalent FGID[12]. Additionally, patients with FGIDs exhibit disordered gut microbiota composition and function[13]. These findings unveil the close association of FGIDs with psychological factors. Nevertheless, the direct impact of FGIDs and psychological factors on brain functions and structures remains unclear.

Therefore, brain imaging is gaining traction as a method for exploring brain abnormalities in patients with FGID[14]. A growing body of research has employed magnetic resonance imaging (MRI), a non-destructive, non-invasive, high spatial resolution imaging technique, to characterize both functional and structural changes in the brain[15]. One widely studied mode, functional MRI (fMRI), is employed to deduce local neuronal activity by measuring changes in blood-oxygen-level dependent (BOLD) signals resulting from alterations in the paramagnetic properties of hemoglobin[16,17]. Analysis of the BOLD signal through fMRI provides valuable insights into the function of different brain regions and their involvement in various cognitive processes. Resting-state fMRI (RS-fMRI) is employed to evaluate baseline brain activity levels and intrinsic functional connectivity[18,19]. Structural MRI (sMRI) is utilized to gather data about gray-matter (GMV) and white-matter volumes (WMV)[20], as well as cortical morphometry[21]. Diffusion tensor imaging (DTI) provides information about the microstructure and connectivity of white matter (WM) by measuring the directional characteristics of water molecule diffusion within tissues[22]. A plethora of neuroimaging studies have been conducted in patients with IBS[23]. These studies have successfully pinpointed dysfunctions within brain regions responsible for regulating both somatic and visceral pain[18,24]. Additionally, sMRI studies in patients with FGID have shown changes in cortical morphometry[25]. The existing literature has systematically reviewed the mechanisms of brain-gut interactions and abnormal internal brain activity in patients with IBS[26]. However, as a typical FGID, a systematic review discussing the pathological mechanism of FC in terms of abnormal brain activity has not yet been published.

In this review, we synthesized findings from MRI-based studies that delve into the brain anomalies observed in patients with FC, along with its underlying pathological mechanisms. All subjects in these studies met the diagnostic criteria for Rome Ⅳ pairs of FC and excluded patients with psychiatric disorders or those who may have taken medications affecting the central nervous system. Studies focusing on psychological factors utilized anxiety/depressive status rating (self-rating anxiety scale, Zung's self-rating depression scale [SDS], state anxiety inventory, and Trait Anxiety Inventory [TAI]) to accurately identify FC subtypes as patients with anxiety/depressive disorders (FCAD) and those without anxiety/depressive disorders (FCNAD). We commenced by examining the effects of FC on both brain functional and structural abnormalities. Pertaining to brain dysfunction, we explored alterations in regional activity and the integrity of functional connections. Concerning brain structure, our focus was on alterations in cortical morphology, as well as GMV/WMV changes. We

further discussed WM integrity and structural connectivity assessed with DTI. In addition, we illustrated the association between abnormalities in the brain and constipation symptoms. The overall framework of MRI research related to FC is presented in Figure 1, and the main results are exhibited in Table 1. Parts of the results are more intuitively presented in the form of magnetic resonance images in Figures 2 and 3. This review aims to reveal the underlying neural mechanisms of FC and provide valuable insights into the development of novel and effective treatments.

2. Functional MRI studies of FC

RS-fMRI can be used to assess the activity of specific brain regions and resting-state functional connectivity between different brain regions and networks. This technique quantifies brain aging pathological states and has been widely utilized to assess the vascular, metabolic, and cognitive effects associated with FC[27], shedding light on the corresponding dysfunction.

2.1. Abnormal regional brain activity

The amplitude of low-frequency fluctuation (ALFF) serves as a metric for gauging the spontaneous fluctuation of BOLD signals, providing an indicator of brain activity levels. Comparative analyses between patients with FC and HC have revealed significant increases in ALFF within regions associated with the emotional arousal network, such as the anterior insula (aINS), hippocampus (HIPP), dorsal anterior cingulate cortex (dACC), and orbital frontal cortex (OFC)[28]. Conversely, decreased ALFF was observed in the precentral gyrus (PreCen), supplementary motor area (SMA), pregenual anterior cingulate cortex, dorsolateral medial prefrontal cortex (DMPFC), and precuneus (PCUN)[28,29]. These findings suggest abnormal emotional modulation in response to painful visceral stimuli and altered somatic sensory processing during defecation in patients with FC. Furthermore, a negative correlation emerged between ALFF in the SMA and aINS with the difficulty level of defecation. Additionally, ALFF in the OFC exhibited a positive correlation with the sensation of incomplete evacuation, indicating a close relationship between dissatisfaction with defecation and changes in brain activity, thereby exacerbating constipation symptoms[27]. Epidemiological studies, considering a male-to-female patient ratio of 2.1:1, have examined the impact of gender. Studies have shown that female patients with FC (FC_F) exhibited lower ALFF than male patients with FC (FC_M) in the PreCen, thalamus (THA), insula (INS), OFC, ventromedial prefrontal cortex (VMPFC), and SMA[30,31]. Sex-related differences in brain activity revealed that FC_F displays more abnormality in

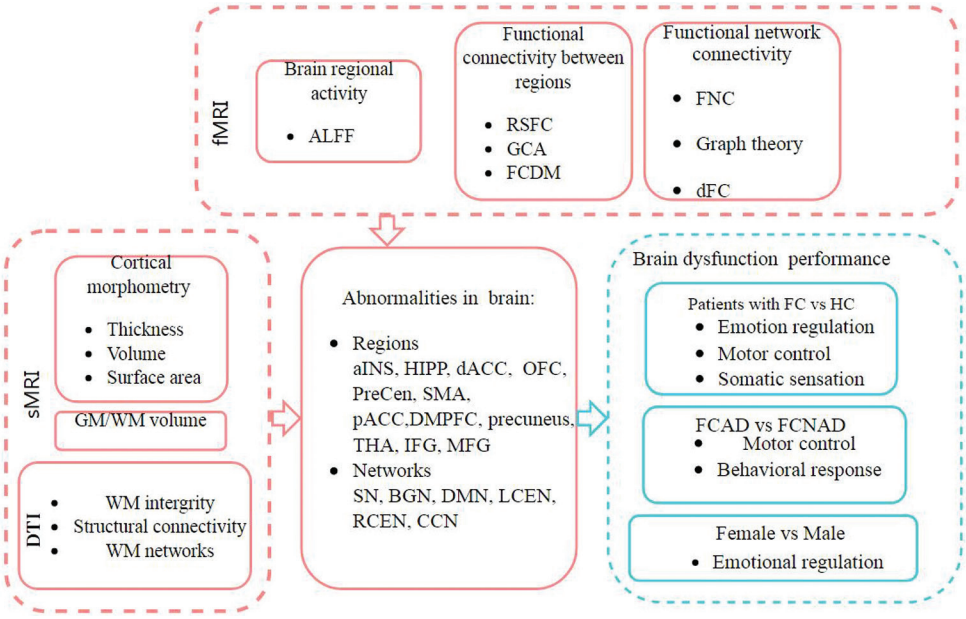

Figure 1. The framework of magnetic resonance imaging studies related to functional constipation.
Abbreviations: aINS: Anterior insula; ALFF: Amplitude of low-frequency fluctuation; BGN: Basal ganglia network; CCN: Cognitive control network; dACC: Dorsal anterior cingulate cortex; dFC: Dynamic functional connectivity; DMN: Default mode network; DMPFC: Dorsolateral medial prefrontal cortex; DTI: Diffusion tensor imaging; FC: Functional constipation; FCAD: Patients with anxiety/depressive disorders; FCDM: Functional connectivity density mapping; FCNAD: Patients without anxiety/depressive disorders; FNC: Functional network connectivity; GCA: Granger causality analysis; GM: Gray matter; HC: Healthy control; HIPP: Hippocampus; IFG: Inferior frontal gyrus; LCEN: Left control executive network; MFG: Middle frontal gyrus; OFC: Orbital frontal cortex; PreCen: Precentral gyrus; RCEN: Right control executive network; RSFC: Resting-state functional connectivity; SMA: Supplementary motor area; sMRI: Structural magnetic resonance imaging; SN: Salience network; THA: Thalamus; WM: White matter.

Table 1. Studies related to brain abnormality in patients with functional constipation based on magnetic resonance imaging

Study	Case number (FC/HC)	Duration of constipation of patients (mean±SE)	Main results found in patients with FC
Zhu *et al.*[28]	14/26	11.1±2.2 (years)	Baseline brain activities increased in the aINS, HIPP, dACC, and OFC and decreased in the PreCen and SMA. Stronger effective connectivity from OFC to aINS, HIPP, and dACC; from dACC to aINS and HIPP. Weaker connectivity from PreCen to aINS, HIPP, dACC and OFC; from SMA to aINS, HIPP, dACC and PreCen; from OFC to SMA
Li *et al.*[29]	37/28 (FCAD/FCNAD)	8.8±1.1/9.4±1.5 (years)	Baseline brain activities decreased in the OFC and THA; RSFC strength increased in OFC-HIPP of FCAD patients compared to FCNAD
Jin *et al.*[30]	34/12 (FC_F/FC_M)	10.3±1.4/9.4±2.1 (years)	Baseline brain activities decreased in PreCen, THA, INS, and OFC; RSFC strength decreased in the INS-OFC of FC_F compared to FC-M
Zhang *et al.*[34]	39/36 (FC_F/HC_F)	None	FC_F had stronger FNC in the SN-BGN and DMN-LCEN and weaker FNC in the SN-RCEN than female HC
Zhang *et al.*[43]	20/20	7.3±3.7 (months)	Decreased interactive connectivity between RSNs, primarily including the connections to the visual perception network
Liu *et al.*[45]	42/41	None	Normalized clustering coefficient and small-worldness were lower; changes in nodal degree/efficiency were mainly observed in the THA-cortical network; decreased inter-module connectivity between the BGN and limbic networks
Yu *et al.*[47]	28/29	12.282±8.81 (years)	Nodal degree increased in the SMN and decreased in the DMN; nodal efficiency increased in the SMN and DMN
Yin *et al.*[52]	83/80	60.08±31.14 (months)	Occurrence rate reduced and mean dwell time decreased in the state characterized by complex and tight connectivity between the DMN and the cognitive control network; anterior insula-cortical coupling patterns were aberrant in this state
Hu *et al.*[57]	29/29	10.6±1.5 (years)	Cortical thickness was reduced in the left MFG, DMPFC and VMPFC, right dACC, left OFC, PCC/PCUN, MTG, and SMA; cortical volume was reduced in the MTG, PreCen and PCUN/cuneus, along with cortical surface area reduced in the PreCen
Jia *et al.*[62]	48/52	None	GMV reduced in the right MFG, left INS, and ACC; FA of the right MFG-ACC, left INS-left MFG, and right INS-right MFG decreased
Cai *et al.*[63]	30/30	None	GMV was reduced in the right OFC, left PreCen, and THA
Hu *et al.*[65]	26/31	6.33±1.09 (years)	FA decreased, and MD/RD increased in the specific regions in the corpus callosum and corona radiate
Zhang *et al.*[70]	31/29	None	FA decreased in the fibers connecting the THA with AMY, HIPP, PostCen, SMA, PCUN, and PreCen; MD and RD increased in the THA-AMY, THA-HIPP, and RD increased in the THA-SMA
Peihong *et al.*[73]	70/45	61.04±29.44 (months)	Nodal characteristics increased in the SFG, MFG, and ACG and paracingulate and decreased in the left caudate and left THA

Abbreviations: aINS: Anterior insula; BGN: Basal ganglia network; dACC: Dorsal anterior cingulate cortex; DMN: Default mode network; FA: Fractional anisotropy; FNC: Functional network connectivity; GMV: Gray matter volume; HIPP: Hippocampus; LCEN: Left control executive network; MD: Mean diffusivity; MFG: Middle frontal gyrus; MTG: Middle temporal gyrus; OFC: Orbital frontal cortex; PCUN: Precuneus; PreCen: Precentral gyrus; RCEN: Right control executive network; RD: Radial diffusivity; RSFC: Resting-state functional connectivity; RSNs: Resting-state networks; SFG: Superior frontal gyrus; SMA: Supplementary motor area; SMN: Sensorimotor network; SN: Salience network; SOG: Superior occipital gyrus; THA: Thalamus.

emotional regulation, suggesting that negative emotions induced by constipation symptoms cannot be effectively modulated, thereby aggravating the condition[30]. Equally important is the distinction between FCAD and FCNAD. Studies indicate that FCAD has higher ALFF in the OFC, PreCen, and SMA and lower ALFF in the anterior cingulate cortex (ACC), HIPP, INS, and hypothalamus (Hy), indicating that FCAD manifests more severe symptoms of abnormal motor control and behavioral response than FCNAD[29,32].

2.2. Abnormal resting-state functional connectivity between brain regions

Grounded in the concept that brain regions with similar functional activity tend to exhibit synchronized

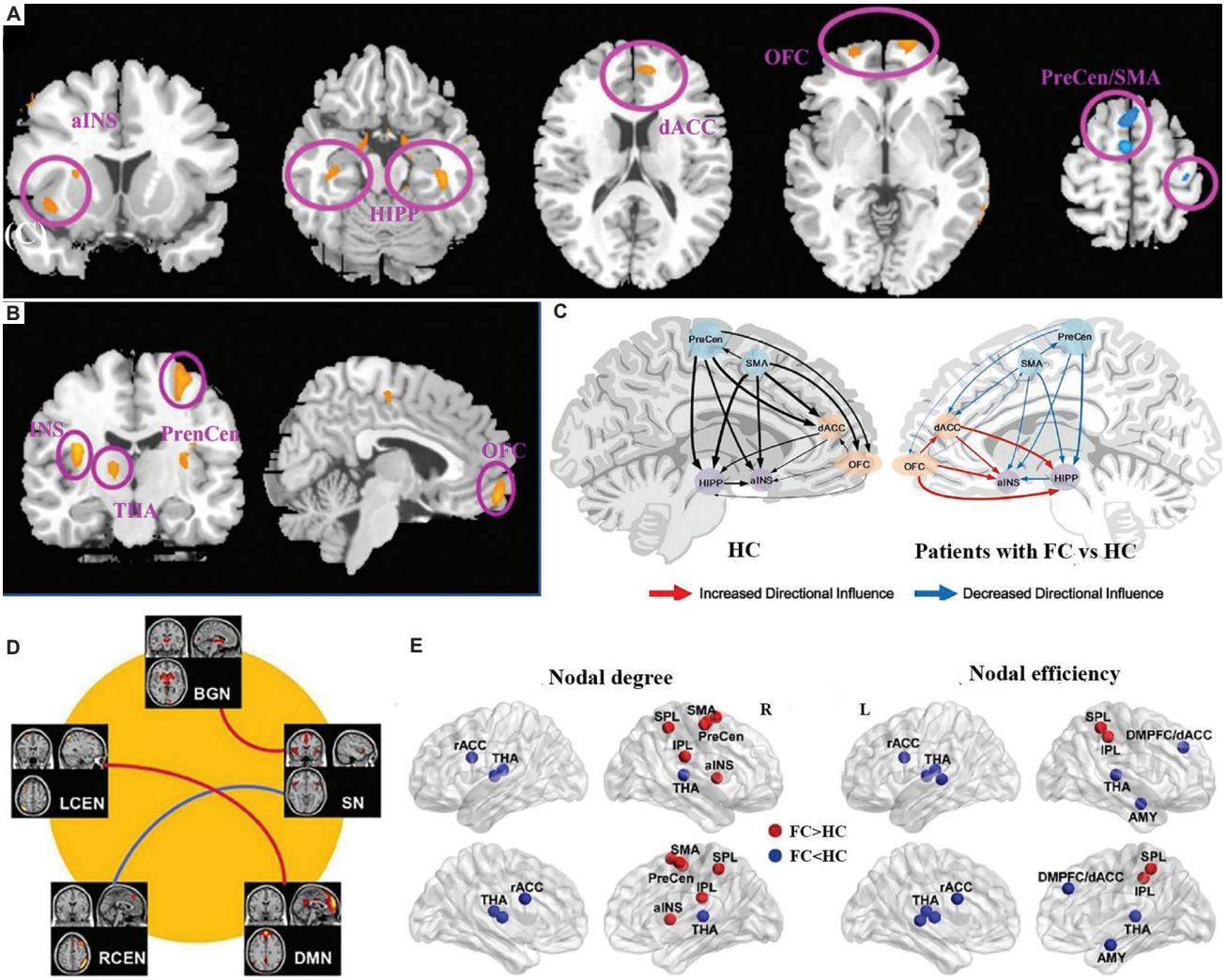

Figure 2. Results of fMRI studies. (A) Brain regions represented altered ALFF in patients with FC compared to HC[28]. (B) Brain regions showed changes in ALFF in FC_M relative to FC_F[30]. (C) Alterations in causal influence between brain regions in patients with FC compared to HC[28]. (D) Changes in functional network connectivity in patients with FC compared to HC. The red line shows significant connectivity where patients with FC have a higher correlation than HC, while the blue line shows connectivity where HC has a higher correlation than FC[34]. (E) Brain regions showed abnormal nodal degree and nodal efficiency in functional brain networks in FC compared to HC[34]. The abbreviations of the 90 brain regions are given in the Appendix. Abbreviations: fMRI: Functional magnetic resonance imaging; ALFF: Amplitude of low-frequency fluctuation; FC: Functional constipation; HC: Healthy controls.

fluctuations in their BOLD signal, resting-state functional connectivity (RSFC) examines the temporal correlation (i.e., functional connectivity) of spontaneous brain activity in different regions during resting-state[33].

RSFC analyses revealed that patients with FC exhibited heightened RSFC in the connections of PreCen-THA, inferior frontal gyrus (IFG)-DMPFC, and IFG-PCUN[29,34]. Conversely, weaker RSFC was observed in the connection of PCUN-THA compared to HC[29]. The THA, which receives information from the basal ganglia (BG) and projects to the PreCen, responsible for motor control[35], and the IFG, implicated in inhibition and attentional control[36], together with the DMPFC, associated with attention regulation and conflict regulation, and the PCUN, pivotal in the default mode network (DMN) responsible for self-reference and self-state assessment[37], demonstrated abnormal RSFC, indicating dysfunctions in motor control, emotional regulation, and constipation status. Significant differences in RSFC were also evident between FCAD and FCNAD. FCAD exhibited stronger RSFC than FCNAD and HC in connection with OFC-HIPP, positively correlated with SDS rating[29]. The HIPP, acting as the attention monitor for perceptual data constituting working memory[38], and

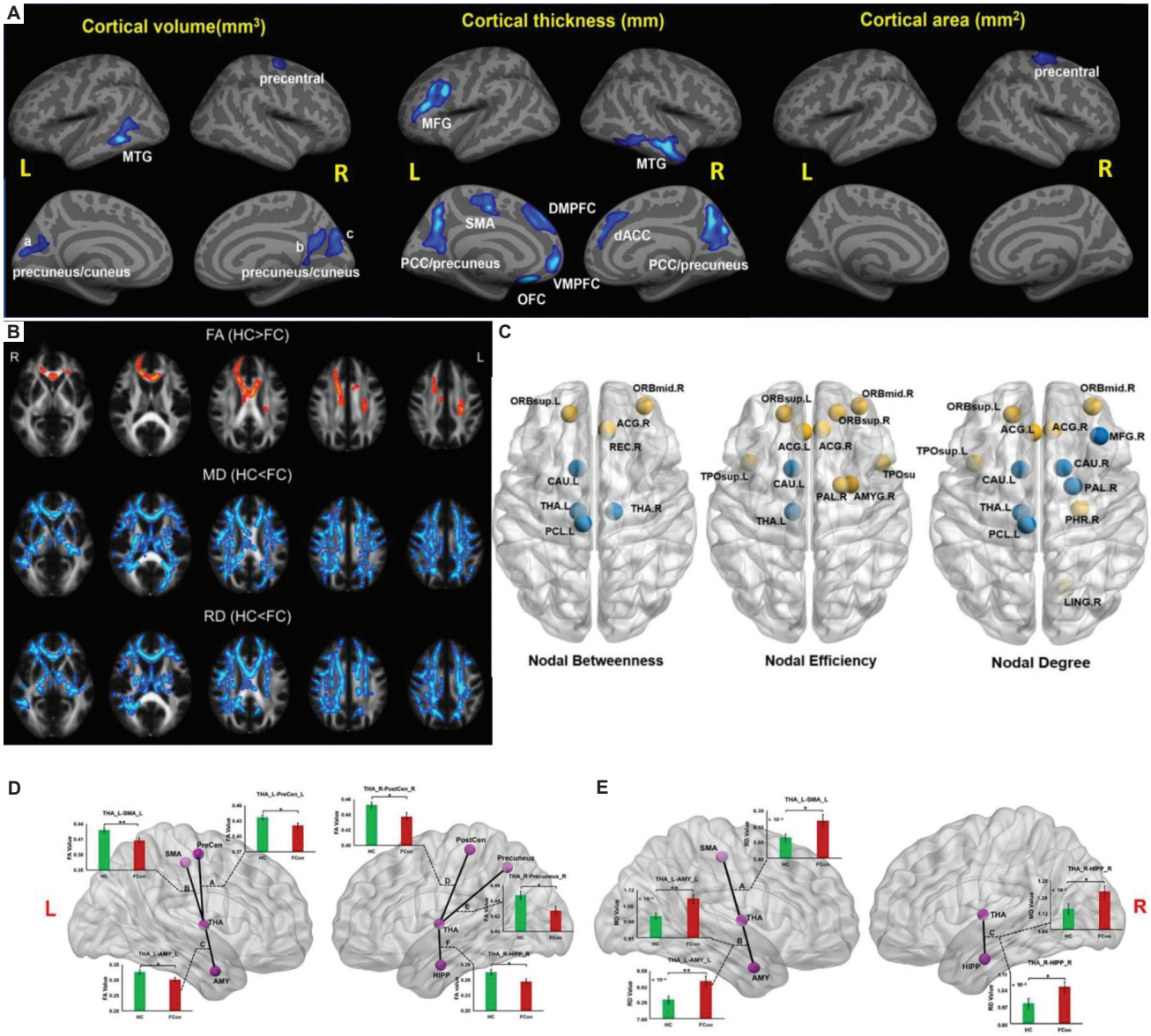

Figure 3. Results of sMRI studies. (A) Brain regions represented altered morphometry in FC patients compared to HC[59]. (B) TBSS analysis showed significantly decreased FA (first row, red-yellow), increased MD (second row, blue-light blue), and increased RD (third row, blue-light blue) in multiple brain regions in patients with FC compared to HC[65]. (C) Regions showed significant differences in nodal degree and efficiency. The blue nodes represent the value of FC < HC and the yellow nodes represent the value of FC > HC[73]. (D) Fibers showed decreased FA values in FC patients relative to HC[70]. (E) Fibers showed increased RD and MD in FC patients compared to HC[70]. The abbreviations of the 90 brain regions are given in the Appendix.
Abbreviations: fMRI: Functional magnetic resonance imaging; TBSS: Tract-based spatial statistics; FD: Fractional anisotropy, MD: Mean diffusivity, RD: Radial diffusivity, FC: Functional constipation; HC: Healthy controls.

the OFC, involved in sensory integration and decision-making[39], indicated abnormal emotional processing, shedding light on why the majority of patients with FC present with depressive-associated symptoms. Additionally, a study reported that FC_F had higher RSFC of PreCen/PostCen (postcentral gyrus)-INS than FC_M, a correlation that was positively associated with abdominal pain. FC_F also exhibited lower RSFC of INS-lateral OFC, a finding that was negatively associated with anxiety[30]. The posterior insula (pINS), responsible for receiving somatic and visceral information and transmitting it to the aINS, which integrates it with emotional information[40], suggested significant gender differences in perceiving visceral stimuli and regulating emotions.

To gain a deeper understanding of the directional causal relationships between different brain regions,

reflecting as effective connectivity, Granger causality analysis (GCA) has been conducted in past studies. The results demonstrated that, in comparison to HC, patients with FC exhibited heightened effective connectivity originating from OFC to aINS, HIPP, and dACC, as well as from dACC to aINS and HIPP. On the contrary, weaker effective connectivity was observed from PreCen to aINS, HIPP, dACC, and OFC; from SMA to aINS, HIPP, dACC, and PreCen; and from OFC to SMA[27,31]. The enhanced effective connectivities may induce abnormal visceral responses and sensory integration, while the weakened effective connectivities indicate a decline in motor control and a reduced readiness for the defecation response. In addition, a study reveals that, when compared to FCNAD, FCAD exhibits stronger effective connectivity from SMA, PreCen, and HIPP to ACC, OFC, as well as from PreCen, HIPP, and INS to SMA, from HIPP to PreCen, and from ACC and PreCen to Hy. Conversely, FCAD shows weaker effective connectivity from INS to ACC, PreCen, HIPP, and Hy and from OFC, SMA, HIPP, and INS to Hy[31]. The heightened effective connectivities between brain regions responsible for emotional arousal and somatosensory sensation explain why FCAD presents with more psychiatric disorders, including anxiety and depression, along with abnormalities in motor control and behavioral response. With regard to the impact of gender, the study reveals that FC_F have stronger effective connectivity from INS, THA, and SMA to amygdala (AMY) and HIPP, and weaker effective connectivity from VMPFC to INS and HIPP compared to FC_M[31], suggesting that FC_F are likely to exhibit abnormal cross-talk between regions involved with interoception and emotional processing.

As a voxel-wise data-driven technique, functional connectivity density (FCD) mapping surpasses the constraints of seed-based approaches that identify hubs in the human brain[41]. Studies have demonstrated decreased local FCD in the left IFG, bilateral middle frontal gyrus (MFG), ACC, and right PreCen in patients with FC[34]. Furthermore, FC_F exhibited significantly higher local FCD values than FC_M in the left THA and left HIPP. Additionally, local FCD values in the PreCen/PostCen were negatively associated with the State-TAI (STAI), and local FCD value in the MFG was negatively associated with SDS[34]. These results reflect abnormal visceral sensation and emotional processing functions, which are consistent with RSFC and GCA results, proving evidence that FC_F are more susceptible to emotional stress.

2.3. Abnormal functional network connectivity (FNC)

The brain, being one of the most complex systems, relies on the integrated functioning of neural networks[42].

Measurement of functional connectivity within and between resting-state networks (RSNs) plays a crucial role in revealing the organizational structure of the brain. This method reflects the communication and collaboration among different brain regions, thereby identifying distinct functional systems[43]. Studies have demonstrated that, when compared with HC, patients with FC exhibited stronger FNC between RSNs. Specifically, there is increased FNC in network connections of the salience network (SN)-basal ganglia network (BGN) and DMN-left control executive network (LCEN). Conversely, there is a significant reduction in FNC in network connections of the SN-right control executive network (RCEN)[34,43]. Within the BGN-SN connection, functional connectivity showed stronger functional connectivity in left caudate (CAU)-left INS, right THA-left INS, right CAU-left INS, and left THA-ACC. Within the SN-RCEN connection, functional connectivity exhibits weaker functional connectivity in left INS-right dorsolateral prefrontal cortex (DLPFC) and right INS-right DLPFC. Within the DMN-LCEN connection, functional connectivity displays stronger functional connectivity in VMPFC-left angular gyrus (ANG), PCUN-left ANG, and VMPFC-left DLPFC[34]. Additionally, the FNC of SN-DMN, SN-LCEN, and SN-RCEN in FC_F is significantly lower than that in FC_M. These results reflect abnormal self-referential and emotional processing in patients with FC[34]. Gender differences in FNC related to visceral perception and emotion regulation further confirm that FC_F is more susceptible to psychiatric factors such as anxiety and depression.

In conjunction with graph theory, RS-fMRI can be employed to investigate the abnormal topological organization of intrinsic brain functional networks in patients with FC[44]. Studies have revealed a decrease in local information transmission within the functional network[45], with changes in nodal degree/efficiency mainly observed in the THA-cortical network[45]. Significant differences were identified between FCAD and FCNAD[46,47]. Specifically, compared with HC, studies examining global topological properties have demonstrated that patients with FC exhibit a decrease in the normalized clustering coefficient and small-worldness[45,46,48]. Studies examining regional topological properties have reported that patients with FC exhibited a decreased nodal degree/efficiency in the THA and rostral ACC (rACC). Additionally, decreased nodal efficiency was found in DMPFC/dACC and AMY while exhibiting an increased nodal degree/efficiency in the inferior and superior parietal lobules. Moreover, an increased nodal degree was found in aINS, SMA, and PreCen[45,48]. Furthermore, in comparison to FCNAD, patients with FCAD displayed an increased nodal degree in the PreCen[46]. Modular topological studies have revealed

that patients with FC exhibited decreased inter-module connectivity between the BGN and limbic networks[45]. They also showed an increased nodal degree in the right PostCen and PreCen within the sensorimotor network (SMN), decreased nodal degree in the left PCUN within DMN, and increased nodal efficiency in the right PostCen, PreCen, middle INS, and left superior temporal gyrus (STG) within SMN, as well as the right ventral lateral prefrontal cortex within DMN[47]. In conclusion, patients with FC showed abnormal node degree/efficiency in regions and intra-module connections involved in somatic and sensory processing, emotional processing, and motor control, reflecting an abnormal reaction to visceral discomfort and the adjustment of emotional consciousness.

In fact, during resting-state scanning, subjects also experience uncontrolled fluctuations in neural activity[49]. The connectivity patterns of brain networks differ across different temporal scales[50]. Dynamic functional connectivity (dFC), based on sliding-window analysis, quantifies the temporal variations of RSFC and significantly enhances our understanding of the functional dynamics of the brain[51]. The dFC analyses revealed that, compared with HC, patients with FC demonstrated a reduced occurrence rate and decreased mean dwell time in a state characterized by complex and tight connectivity between the DMN and the cognitive control network (CCN)[52]. Both CCN and DMN play crucial roles in coordinating information in the human body, particularly endogenous information[53]. The absence of this state suggests that patients with FC may have impaired internal task processing. Further investigations have revealed significant differences in dynamic functional coupling patterns between patients with FC and HC, particularly in connections related to the aINS. Specifically, patients with FC showed stronger RSFC between aINS and regions such as ACC, posterior cingulate cortex (PCC)/medial OFC, right angular gyrus, and cerebellum crus II, and weaker RSFC between aINS and THA, superior frontal gyrus (SFG), lingual gyrus, and superior occipital gyrus (SOG) than HC[52]. These changes in functional coupling patterns could imply that patients with FC might have a diminished perception and responsiveness to gut stimuli[54,55].

These neuroimaging studies have consistently demonstrated that FC was primarily linked to functional abnormalities in brain regions and networks involved in emotion regulation, motor control, and somatic sensation.

3. Structural MRI studies of FC

Previous studies have indicated that brain functional abnormalities may be linked to structural changes[56]. Furthermore, morphometric changes could potentially be linked to changes in WM microstructure[57]. The intricate influence of underlying structural connections on functional networks has also been demonstrated[58]. Surface-based and voxel-based morphological analyses were performed to assess cortical thickness, volume, and surface, as well as GMV and WMV of brain regions. DTI coupled with probabilistic tractography was conducted to detect WM microstructure and assess structural connectivity.

3.1. Changes in morphometry of brain regions

Surface-based and voxel-based morphology analyses, utilizing conventional structural MRI techniques, suggest that FC exhibits alterations in the morphometry of brain regions involved in emotional regulation, somatic-sensory and motor control, and self-referential processing.

Studies investigating cortical morphology indicate that patients with FC exhibit reduced cortical thickness in the left MFG, DMPFC, VMPFC, right dACC, left OFC, PCC/PCUN, middle temporal gyrus (MTG), and SMA. Additionally, reduced cortical volume is observed in the MTG, PreCen, and PCUN/cuneus[59,60]. The decreased cortical thickness and volume may be linked with the impaired functions of cognitive control, executive functions, emotional processing, and self-reflection. Additionally, reduced cortical surface was found in the PreCen, which might be associated with dysfunctions of motor control[59,60]. Gray matter is formed by brain neuronal cells, enveloped in a myelin sheath, which forms WM[61]. Voxel-based morphology studies indicate that patients with FC display reduced GMV in the right MFG, left INS, ACC, right OFC, left PreCen, and THA[62,63]. FC_F demonstrated higher GMV than FC_M in regions implicated in homeostatic afferents (e.g., left INS and bilateral THA), emotional arousal (e.g., right AMY, right HIPP, and right OFC), and sensorimotor cortex (e.g., right PreCen, bilateral PostCen, and bilateral supramarginal gyrus [SMG]), along with higher WMV in the bilateral HIPP, right SMG, and left PostCen[62]. All these regions play an important role in emotion and autonomic regulation, pain perception, and cognitive processing. Changes in structure reflect abnormalities in these corresponding functions in patients with FC.

3.2. Alterations in white matter microstructure

In DTI analysis, the metrics considered include fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). A high FA value indicates well-organized and coherent bundles of WM fibers. An increased MD value indicates greater water diffusion, potentially indicative of tissue damage. AD measures water diffusion along the principal orientation of WM fibers,

while RD reflects diffusion in directions orthogonal to the principal orientation. These metrics offer valuable insights into specific aspects of WM microstructure[64]. Previous studies have demonstrated altered metrics in patients with FC compared with HC, particularly in regions associated with sensory and motor functions. Notably, a decrease in FA was observed in the corpus callosum (CC), corona radiata (CR), and right cingulate gyrus (CG). Both MD and RD increased in the CC, CR, and widespread fiber tracts connecting with the cerebral cortex. In addition, in the left CG, RD was higher[65]. In the investigation of variations in WM microstructure based on gender, results showed that, compared with FC_M, FC_F also exhibited decreased FA alongside increased RD in the CC, CR, and CG[66]. The CC is responsible for the communication of perception, volitional information, and cognitive learning[67]. The compromised integrity of the WM fiber bundle of the CC can impact the regulation and processing of visceral sensory information. The WM fiber of the CG belongs to the emotional arousal network, which regulates the emotional fluctuations caused by visceral sensation[68]. The CR is responsible for information transmission, connecting the brainstem to the frontal cortex, somatosensory, and motor cortices, participating in the regulation of somatosensory/motor control[69]. These aforementioned alterations in WM microstructure signify compromised communication responsible for sensory and motor functions and abnormal functional integration. Results also provide a deeper understanding of the decreased emotional regulation in FC_F from the perspective of WM microstructure changes, contributing to the higher prevalence of constipation symptoms in women compared to men.

3.3. Alterations in structural connectivity between brain regions

Both functional and structural abnormalities in the THA have been identified in patients with FC[32,43,63]. A study specifically selected THA as a seed region for probabilistic tractography, revealing decreased FA in the left THA-SMA, left THA-PreCen, left THA-AMY, right THA-PostCen, right THA-PCUN, and right THA-HIPP compared to HC. Moreover, increased MD and RD were observed in the left THA-AMY and right THA-HIPP tracts, along with higher RD in the left THA-SMA tract in patients with FC[70]. The FA of left THA-HIPP and right THA-PostCen was negatively associated with the sensation of incomplete evacuation, while FA of left THA-PreCen was negatively associated with the difficulty of defecation[70]. THA serves as a critical link connecting the medial prefrontal cortex (mPFC) and HIPP, playing a significant role in emotional processing[71]. The observed abnormal structural connectivity reflects the dysfunction of THA in integrating and transmitting sensory information within the cerebral cortex and processing intestinal sensory information in patients with FC. In addition, when selecting regions with abnormal GMV such as INS, ACC, and MFG as seed regions, a study found significantly lower FA in the right MFG-ACC, left INS-left MFG, and right INS-right MFG tracts in patients with FC compared to HC[66]. This finding suggests that the dysfunction of emotion regulation and visceral sensation in patients with FC is not only associated with structural abnormalities in these brain regions but also with abnormal structural connections among them.

3.4. Alterations in white matter networks

WM networks serve as the foundational structure for central information transfer across various brain regions[71,72]. Utilizing the graph theory method, the examination of WM network characteristics in patients with FC revealed noteworthy changes. The nodal level analysis demonstrated increased nodal betweenness, efficiency, and degree in specific regions such as the SFG, MFG, and anterior cingulate gyrus (ACG). Additionally, nodal efficiency increased in the right AMY, the right lenticular nucleus in the pallidum (PAL_R), and STG, while nodal degree increased in the parahippocampal gyrus, lingual gyrus, PAL_R, and STG. On the other hand, decreases were observed in nodal betweenness, efficiency, and degree in the left paracentral lobule, left CAU, and left THA. Furthermore, nodal betweenness decreased in the right gyrus rectus, and nodal degree decreased in the right MFG and right CAU[73]. The topological characteristics of WM networks mirror the brain's capacity for information processing[74]. Close collaboration between the ACG and frontal lobe regions in a wide range of functions, such as emotions, attention, decision-making, executive functions, and social cognition, contributes to the intricate cognition and behavior in humans[75]. These alterations induce the disruption in normal visceral modulation and sensory transduction processes in patients with FC. The decreased nodal characteristics in CAU and THA indicate disrupted or reduced interregional communication in visceral sensory processing[76]. Furthermore, nodal betweenness in the THA was negatively associated with the duration of symptoms in patients with FC[73]. These results suggest that a longer disease duration may be linked to more significant structural alternations, and these structural alternations in WM networks may contribute to observed brain functional changes in patients with FC[77]. Overall, these findings provide valuable insights into the alterations in WM network properties in patients with FC, highlighting specific brain regions implicated in the processing of visceral sensation and their potential contributions to the pathophysiology of FC.

4. Conclusion

Neuroimaging studies have unveiled functional and structural abnormalities in brain regions and networks responsible for regulating emotions, motor control, and somatic sensation in patients with FC. These changes demonstrate correlations with somatic symptoms, psychiatric factors, and gender effects. The attributes of WM microstructure and networks reflect the brain's ability for information dissemination and functional integration, offering further insights into the abnormal physiological and psychological behaviors observed in patients with FC. The interplay between alterations in structure and function, along with the presence of anxiety and depression, underscores the important role of psychiatric factors in the onset and progression of FC. Furthermore, gender-related differences in brain regions mainly involved in emotional processing and visceral perception contribute to the heightened susceptibility of female patients to the negative effects of mental factors and constipation symptoms.

This comprehensive review reveals that FC is associated with dysfunction and structural abnormalities, providing imaging evidence and a theoretical basis for exploring the pathological mechanism underlying FC. It also facilitates an examination of the influence of psychiatric and gender factors on the condition, steering the direction of effective treatment and preventive strategies.

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Conflict of interest

The authors declare that they have no competing interest.

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Appendix

Regions	Abbreviation
Precentral gyrus	PreCG.L
Precentral gyrus	PreCG.R
Superior frontal gyrus, dorsolateral	SFGdor.L
Superior frontal gyrus, dorsolateral	SFGdor.R
Superior frontal gyrus, orbital part	ORBsup.L
Superior frontal gyrus, orbital part	ORBsup.R
Middle frontal gyrus	MFG.L
Middle frontal gyrus	MFG.R
Middle frontal gyrus, orbital part	ORBmid.L
Middle frontal gyrus, orbital part	ORBmid.R
Inferior frontal gyrus, opercular part	IFGoperc.L
Inferior frontal gyrus, opercular part	IFGoperc.R
Inferior frontal gyrus, triangular part	IFGtriang.L
Inferior frontal gyrus, triangular part	IFGtriang.R
Inferior frontal gyrus, orbital part	ORBinf.L
Inferior frontal gyrus, orbital part	ORBinf.R
Rolandic operculum	ROL.L
Rolandic operculum	ROL.R
Supplementary motor area	SMA.L
Supplementary motor area	SMA.R
Olfactory cortex	OLF.L
Olfactory cortex	OLF.R
Superior frontal gyrus, medial	SFGmed.L
Superior frontal gyrus, medial	SFGmed.R
Superior frontal gyrus, medial orbital	ORBsupmed.L
Superior frontal gyrus, medial orbital	ORBsupmed.R
Gyrus rectus	REC.L
Gyrus rectus	REC.R
Insula	INS.L
Insula	INS.R
Anterior cingulate and paracingulate gyri	ACG.L
Anterior cingulate and paracingulate gyri	ACG.R
Median cingulate and paracingulate gyri	DCG.L
Median cingulate and paracingulate gyri	DCG.R
Posterior cingulate gyrus	PCG.L
Posterior cingulate gyrus	PCG.R
Hippocampus	HIP.L
Hippocampus	HIP.R
Parahippocampal gyrus	PHG.L
Parahippocampal gyrus	PHG.R
Amygdala	AMYG.L

Regions	Abbreviation
Amygdala	AMYG.R
Calcarine fissure and surrounding cortex	CAL.L
Calcarine fissure and surrounding cortex	CAL.R
Cuneus	CUN.L
Cuneus	CUN.R
Lingual gyrus	LING.L
Lingual gyrus	LING.R
Superior occipital gyrus	SOG.L
Superior occipital gyrus	SOG.R
Middle occipital gyrus	MOG.L
Middle occipital gyrus	MOG.R
Inferior occipital gyrus	IOG.L
Inferior occipital gyrus	IOG.R
Fusiform gyrus	FFG.L
Fusiform gyrus	FFG.R
Postcentral gyrus	PoCG.L
Postcentral gyrus	PoCG.R
Superior parietal gyrus	SPG.L
Superior parietal gyrus	SPG.R
Inferior parietal, but supramarginal and angular gyril	IPL.L
Inferior parietal, but supramarginal and angular gyril	IPL.R
Supramarginal gyrus	SMG.L
Supramarginal gyrus	SMG.R
Angular gyrus	ANG.L
Angular gyrus	ANG.R
Precuneus	PCUN.L
Precuneus	PCUN.R
Paracentral lobule	PCL.L
Paracentral lobule	PCL.R
Caudate nucleus	CAU.L
Caudate nucleus	CAU.R
Lenticular nucleus, putamen	PUT.L
Lenticular nucleus, putamen	PUT.R
Lenticular nucleus, pallidum	PAL.L
Lenticular nucleus, pallidum	PAL.R
Thalamus	THA.L
Thalamus	THA.R
Heschl gyrus	HES.L
Heschl gyrus	HES.R
Superior temporal gyrus	STG.L
Superior temporal gyrus	STG.R

Regions	Abbreviation
Temporal pole: superior temporal gyrus	TPOsup.L
Temporal pole: superior temporal gyrus	TPOsup.R
Middle temporal gyrus	MTG.L
Middle temporal gyrus	MTG.R
Temporal pole: Middle temporal gyrus	TPOmid.L
Temporal pole: Middle temporal gyrus	TPOmid.R
Inferior temporal gyrus	ITG.L
Inferior temporal gyrus	ITG.R

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REVIEW ARTICLE

The endocannabinoid system: A new frontier in addressing psychosomatic challenges

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Abstract

Psychosomatic disorders (PSD), alternatively referred to as psychophysiologic disorders, are characterized by hypothalamic-pituitary-adrenal (HPA) axis activation, posing a substantial challenge in clinical practice. These disorders constitute a collection of intricate medical conditions marked by the considerable impact of psychological and emotional factors on the onset, intensification, or persistence of physical symptoms. The endocannabinoid system, a complex regulatory network consisting of endocannabinoids, cannabinoid receptors, and associated enzymes, emerges as a key player in modulating the body's stress response, emotional regulation, and immune function. This review delves into the bidirectional relationship between the endocannabinoid system and the HPA axis, elucidating the impact of endocannabinoid system modulation on stress responsiveness, immune modulation, and the intricate interplay between emotional well-being and physical symptoms. Through the synthesis of current scientific knowledge, this review aims to provide a comprehensive understanding of the role of the endocannabinoid system in PSD, offering insights that may pave the way for novel therapeutic approaches.

Keywords: Endocannabinoids; Hypothalamic-pituitary-adrenal axis; Immune system; Psychosomatic medicine; Psychophysiologic disorders

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1. Introduction

The intricate interplay between the mind and body has long captivated the realms of medical inquiry, giving rise to the enigmatic domain of psychosomatic disorders (PSDs). Also referred to as psychophysiologic or somatoform disorders, PSD constitutes a heterogeneous group of medical conditions wherein psychological and emotional factors wield a profound influence over the initiation, exacerbation, or perpetuation of physical symptoms[1,2].

At the core of PSD lies the convergence of emotional and psychological well-being with physiological states, resulting in a tapestry of symptoms that span pain, gastrointestinal distress, neurological manifestations, and an array of somatic complaints. The challenge in comprehending these disorders stems from their inherent complexity, a complexity that defies conventional diagnostic paradigms. In the conventional model, diseases are deciphered through the lens of objective signs and subjective symptoms. However, PSD

disrupts this paradigm, plunging clinicians into the depths of diagnostic ambiguity[3-8].

Historically, PSD carried the weight of societal misunderstanding and stigma. These conditions were once relegated to a distinct category where stress and psychological distress were erroneously perceived as the primary causative agents. Individuals grappling with PSD found themselves unfairly labeled as attention-seekers or hypochondriacs. The manifestation of psychosomatization, characterized (defined) by multiple, recurrent, and often-changing physical symptoms persisting for at least 2 years before seeking medical attention, perpetuated these misconceptions[9-11].

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, has since ushered in a paradigm shift, consolidating various presentations of PSD under the umbrella of somatic symptom disorder. This inclusive classification encompasses somatization disorder, hypochondriasis, pain disorder, and undifferentiated somatoform disorder, reflecting a more nuanced and comprehensive understanding[12].

Contemporary perspectives have ushered in a new era of enlightenment, expanding our comprehension of the intricate mechanisms underpinning psychosomatic phenomena. It is now acknowledged that stress, depression, and a dearth of social support, in tandem with biological factors, play pivotal roles in both the etiology and outcome of diseases associated with PSD. Stressors, irrespective of their nature – whether physical, psychological, or emotional – set in motion a complex cascade of physiological responses, orchestrating the body's preparation for an adaptive reaction[3].

The narrative unfolds beyond the confines of traditional categorizations, inviting a holistic exploration of the factors at play in the genesis and progression of PSD. As we navigate through this scientific review, we will delve into the diverse manifestations of PSD, each a unique thread in the complex tapestry of PSD. From the neurological intricacies to the visceral manifestations, we aim to demystify the enigma surrounding these conditions, providing a comprehensive understanding accessible to readers across diverse disciplines.

The significance of unraveling the complexities of PSD extends beyond the realms of academic curiosity. It permeates the clinical landscape, where misdiagnoses and inadequate treatment plans pose formidable challenges. As we articulate the intricacies of PSD, our aim is not only to broaden theoretical frameworks but to enhance the efficacy of clinical practice. By fostering a deeper comprehension of the intricate dance between the mind and body in PSD, we aspire to pave the way for more targeted and effective interventions.

In the pages that follow, we will traverse the historical nuances that have shaped our perception of PSD, dissect the contemporary insights that have transformed our understanding, and underscore the imperative of a multidisciplinary approach in deciphering and managing these conditions. Embarking on this journey, we invite readers from diverse backgrounds to join us in unraveling the mysteries of PSD, where the convergence of psychology and physiology paints a canvas of unparalleled complexity and intrigue.

2. Neurobiological mechanisms of PSD

2.1. The hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis, serving as the central coordinator of neuroendocrine responses to stress, assumes paramount significance in individuals afflicted with PSD[13-19]. The HPA axis, comprised the hypothalamus, pituitary gland (hypophysis), and adrenal glands, is a vital neuroendocrine system tasked with responding to stressors and maintaining homeostasis. Dysregulation of this axis can have far-reaching effects on diverse physiological and psychological processes, influencing the presentation of psychosomatic symptoms[13,19].

On encountering a stressor, whether it is of a physical, psychological, or emotional nature, a complex cascade of physiological events is initiated. The hypothalamus, acting as the HPA axis's "control center," releases corticotropin-releasing hormone (CRH)[20-25]. This hormone, in turn, stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH), which serves as a signal for the adrenal glands to produce and release glucocorticoids, notably cortisol (Figure 1A)[20,25].

This process initiates with the release of norepinephrine (NE) and acetylcholine (Ach), which act on receptors on the surface of neurons of the paraventricular nucleus (PVN) of the hypothalamus. This initiation triggers a cascade of intracellular signaling events, including the activation of adenylate cyclase and subsequent elevation of cyclic adenosine monophosphate (cAMP) levels. Elevated cAMP activates protein kinase A (PKA), leading to the phosphorylation of transcription factors such as cAMP response element-binding protein (CREB). Phosphorylated CREB then binds to cAMP response elements in the promoter region of the CRH gene, thereby instigating the transcription and synthesis of CRH. Once synthesized, CRH is transported to the median eminence of the hypothalamus, where it is released into the hypophyseal portal system, ultimately reaching the anterior pituitary

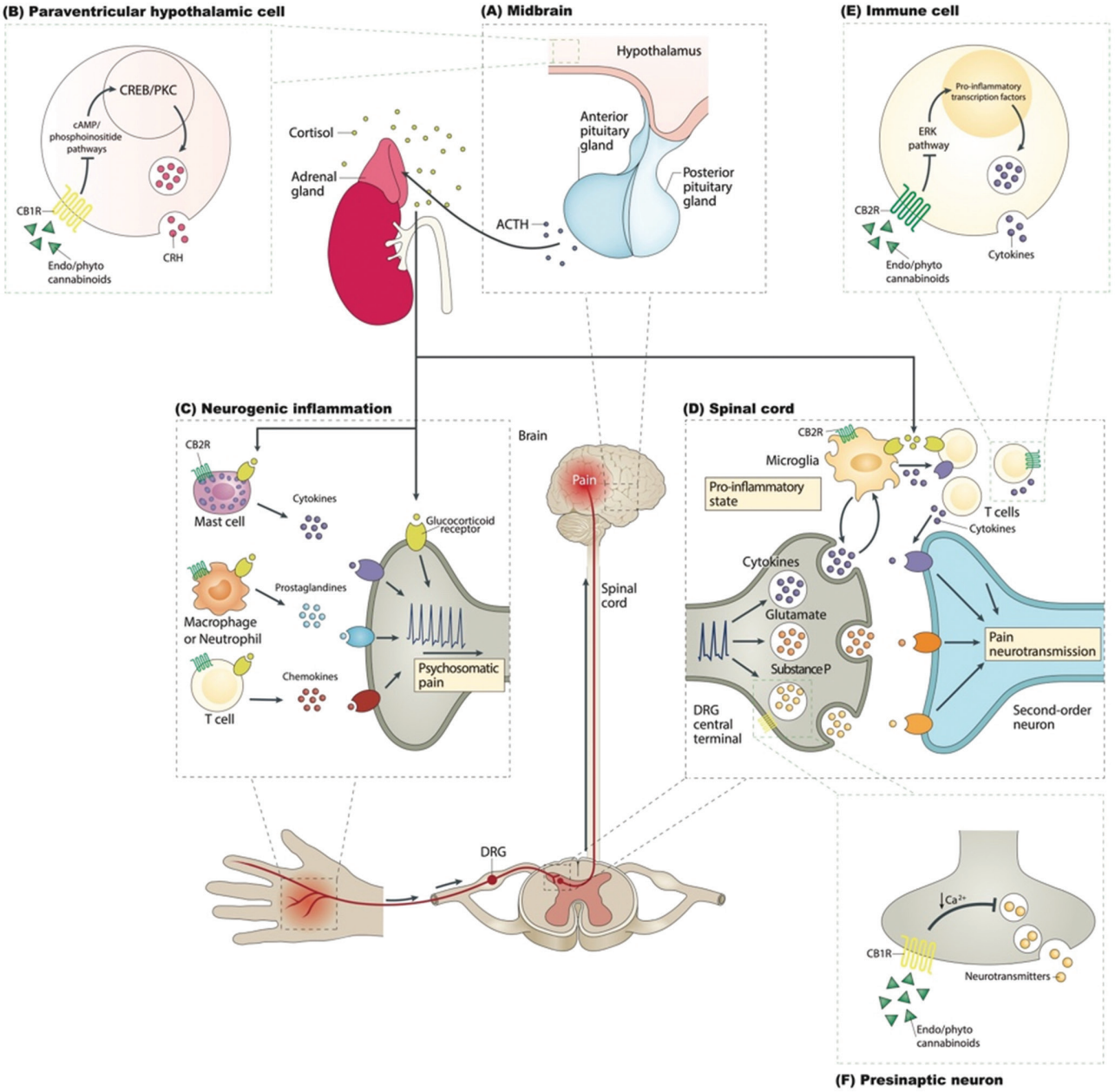

Figure 1. Mechanisms of stress response in psychosomatic disorders. This schematic representation illustrates the intricate molecular processes involved in the stress response within the neuroendocrine axis. (A) Released ACTH travels through the bloodstream to the adrenal cortex. ACTH stimulates the synthesis and release of cortisol. (B) Stressors activate neurons in the hypothalamus, leading to the release of CRH. CRH binds to its receptor on corticotropes in the anterior pituitary. (C) Cortisol binds to GRs on immune cells, modulating gene expression and suppressing the release of proinflammatory cytokines. Simultaneously, cortisol activates GRs on sensory neurons, influencing neuronal signaling. (D) This activation leads to the release of neurotransmitters and neuropeptides, aggravating neurogenic inflammation. The released neuropeptides, such as substance P, contribute to increased vascular permeability and immune cell recruitment, exacerbating the inflammatory response. (E) CB2R activation induces an anti-inflammatory phenotype in immune cells by inhibiting the ERK pathway. (F) Activation of presynaptic CB1Rs attenuates Ca^{2+} influx into the presynaptic terminal, blocking vesicle fusion and thus decreasing transmitter release. Figure 1 is modified from Baral *et al.*[161]

Abbreviations: ACTH: Adrenocorticotropic hormone; cAMP: cyclic adenosine monophosphate; CB1R: Cannabinoid type 1 receptor; CB2R: Cannabinoid type 2 receptor; CREB: cAMP response element-binding protein; CRH: Corticotropin-releasing hormone; DRG: Dorsal root ganglion; ERK: Extracellular signal-regulated kinase; GRs: Glucocorticoid receptors; PKC: Protein kinase C.

gland. The binding of CRH to its receptor on corticotropes activates intracellular signaling pathways, involving the activation of adenylate cyclase and leading to an increase in intracellular cAMP levels. Elevated cAMP, in turn,

activates PKA, which phosphorylates various proteins, including transcription factors like CREB. Phosphorylated CREB then binds to cAMP response elements in the promoter region of the proopiomelanocortin (POMC) gene, initiating transcription (Figure 1B).

POMC is the precursor molecule for ACTH[26-30]. The synthesized POMC undergoes post-translational processing, giving rise to the biologically active form, ACTH. Subsequently, ACTH is released into the bloodstream and travels to the adrenal cortex, where it stimulates the synthesis and secretion of cortisol. The binding of ACTH to its receptors on the cell membrane elicits both the cAMP pathway and the phosphoinositide pathway. In the cAMP pathway, ACTH activates adenylate cyclase, leading to the conversion of ATP to cAMP. Elevated cAMP levels activate PKA, which phosphorylates the transcription factor CREB. Activated CREB translocates to the nucleus, where it binds to the cAMP response element (CRE) in the promoter region of genes crucial for cortisol synthesis, such as those encoding steroidogenic enzymes. Simultaneously, the phosphoinositide pathway involves ACTH-induced activation of phospholipase C (PLC), leading to the production of inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 induces the release of calcium ions, elevating intracellular calcium levels. Along with DAG, this activates protein kinase C (PKC), which modulates the activity of proteins involved in cortisol synthesis. These converging pathways collectively stimulate the transcription and synthesis of cortisol, ensuring a regulated response to stress and maintaining basal cortisol levels. The intricate feedback loop, wherein cortisol inhibits the release of ACTH and CRH, further fine-tunes the system to maintain hormonal balance. Dysregulation of these signaling pathways can contribute to disorders characterized by abnormal cortisol levels, thereby impacting the body's adaptive response to stressors[26,30].

Cortisol, a biologically active hormone, plays a crucial role in aiding the body in adapting to stress[31-34]. Alterations in cortisol levels, driven by activity in the HPA axis, can result in enduring detrimental changes within the limbic system. Research has demonstrated a correlation between elevated cortisol levels and past stress and depression. Notably, approximately 50% of newly diagnosed depression patients exhibit excessive cortisol secretion. As stress persists, cortisol concentrations remain elevated until the stressor is removed[32-34].

The HPA axis, central to this regulatory process, is intrinsically interconnected with the brain and neurotransmitter systems. Cortisol, as the primary glucocorticoid released in response to HPA axis activation, exerts a profound influence on the equilibrium of neurotransmitters, with a particular impact on dopamine and serotonin, which are pivotal for mood regulation. Dysregulation of the HPA axis, therefore, has the capability to contribute to mood disturbances, including anxiety and depression, both of which are common facets of PSD[34-36].

The dopaminergic system, another crucial player, exerts a profound impact on the pathogenesis of numerous psychophysiological conditions. Distributed throughout the central nervous system, dopamine operates within various neuronal pathways, predominantly in the mesolimbic and mesocortical subsystems. The mesolimbic pathway is instrumental in processing and amplifying activating stimuli, thereby motivating behavioral responses and stimulating goal-directed actions. Its inhibition can lead to emotional indifference and a lack of initiative. This system is highly sensitive to stress, with its functioning influenced by factors such as the controllability of the situation, the organism's genetic background, and its life cycle. In contrast, the mesocortical pathway plays a critical role in cognitive functions such as evaluating and planning behavioral responses. Stress can exert differential effects on the functioning of dopamine in the mesocortical system, contingent on various factors. Simultaneously, the mesocortical pathway is instrumental in higher cognitive functions, including the assessment and planning of behavioral responses. Stress can exert diverse effects on dopamine functioning in the mesocortical system, dependent on various factors such as the controllability of the situation, genetic predisposition, and the individual's life stage. Alterations within this system have been linked to cognitive deficits and impaired problem-solving abilities, contributing to emotional disturbances associated with PSD[37-40].

Serotonin, another key neurotransmitter, is integral to the development of psychophysiological stress. Recognized for its role in mood regulation, serotonin extends its influence to the HPA axis, a central component of the body's stress response system. Within the hypothalamus, serotonin binds to receptors, notably 5-HT1A and 5-HT2 receptors, thereby modulating the release of CRH. This interaction acts as a regulatory mechanism, inhibiting the release of CRH and subsequently influencing the initiation of the HPA axis response to stress [41]. Progressing to the pituitary gland, serotonin maintains its regulatory role by affecting serotonin receptors, thereby contributing to the modulation of ACTH release. ACTH, in turn, stimulates the adrenal glands to release cortisol, a pivotal stress hormone. The intricate interplay between serotonin and the HPA axis is crucial for fine-tuning the stress response, with dysregulation potentially contributing to conditions such as depression, anxiety, and other stress-related disorders.

Individual differences and genetic factors further add complexity to this relationship, influencing the variability in stress responses among individuals. In essence, serotonin's involvement in the HPA axis underscores its broader significance in maintaining both emotional well-being and the physiological response to stress. Negative emotional states and stress are implicated in the disruption of serotonergic function[42,43].

2.2. Immune dysregulation

The immune system, tasked with safeguarding the organism against pathogens and preserving tissue homeostasis, undergoes profound modulation by the HPA axis. The multifaceted role of cortisol in orchestrating the stress response encompasses its potent anti-inflammatory capacity, a mechanism designed to curb immune reactions, and forestall excessive inflammation[44-46].

While adaptive in the short term, persistent activation of the HPA axis, a characteristic feature of individuals grappling with PSD, yields deleterious consequences. Cortisol, a glucocorticoid steroid hormone, diffuses through the cell membrane and binds to cytoplasmic glucocorticoid receptors (GRs). On binding, these receptors undergo conformational changes, allowing them to translocate into the cell nucleus, where they function as transcription factors. Within the nucleus, activated GRs modulate gene expression by binding to glucocorticoid response elements (GREs) in the promoters of target genes. This transcriptional regulation influences the synthesis of various anti-inflammatory proteins, such as lipocortin-1 and IκB, and inhibits the expression of proinflammatory cytokines such as interleukin-1 alpha (IL-1α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). In addition, cortisol-activated GRs interfere with the activation of transcription factors like nuclear factor-kappa B (NF-κB), crucial for the initiation of inflammatory responses. Consequently, cortisol exerts an immunosuppressive effect, dampening immune cell activation, and the release of inflammatory mediators. While this anti-inflammatory action is essential for resolving acute inflammation and maintaining immune homeostasis, chronic or excessive cortisol exposure may lead to immunosuppression, contributing to increased susceptibility to infections, and alterations in immune function observed in conditions associated with dysregulated cortisol levels, including stress-related disorders and psychosomatic manifestations. This sustained activation induces immune dysregulation marked by compromised immune cell functionality and heightened vulnerability to inflammatory processes. Such immune dysregulation plays a pivotal role in both the genesis and exacerbation of physical symptoms within the realm of PSD, intensifying sensations of pain, fatigue, and other somatic manifestations[47-50].

The persistent activation of the HPA axis, a hallmark feature of PSD, carries profound repercussions for immune dynamics, resulting in a state of immunosuppression. This prolonged activity disrupts immune cell function, rendering them less effective while concurrently elevating susceptibility to inflammatory events. This immune dysregulation is posited as a driving force behind the emergence and aggravation of physical symptoms within the PSD spectrum[51,53].

During stress, the sympathetic nervous system activates, releasing neurotransmitters and neuropeptides that exert influence over blood flow, immune function, and the integrity of the skin barrier. The ensuing neurogenic inflammation, an intricate interplay between the nervous system and the skin, alters cutaneous physiology, giving rise to manifestations such as redness, itching, and the formation of rashes. Psychological stressors modulate this interaction, disrupting the normal functioning of skin cells and immune responses. Therefore, leads to vulnerability to skin rashes over individuals grappling with PSD[53-55].

2.3. Alterations of cardiovascular and gastrointestinal systems

Elevated cortisol levels, stemming from HPA axis dysregulation in individuals with PSD, have significant implications for the cardiovascular system, dysregulating blood pressure and heart rate, and contributing to symptoms such as palpitations and chest pain[56-61].

The activation of cortisol receptors, specifically mineralocorticoid receptors (MRs) and GRs, plays a pivotal role in mediating the molecular responses associated with elevated cortisol levels. These responses result from HPA axis dysregulation in individuals with PSD, leading to cardiovascular manifestations. Cortisol's binding to MR predominantly influences vascular smooth muscle cells, promoting sodium retention and potassium excretion. This leads to vasoconstriction, contributing to increased systemic vascular resistance and elevated blood pressure, hallmark features in PSD. Simultaneously, cortisol's interaction with GR in cardiac muscle cells enhances myocardial contractility, augmenting the force of cardiac contractions. This effect contributes to palpitations and altered cardiac function observed in individuals with PSD[62-64].

Moreover, GR activation modulates the autonomic nervous system, impacting the balance between sympathetic and parasympathetic activity. Increased sympathetic activity, a consequence of GR activation, further intensifies the cardiovascular response, resulting

in a heightened heart rate. The intricate interplay between molecular involving MR and GR activation, influencing vascular and cardiac tissues, respectively, provides a mechanistic understanding of how dysregulated cortisol levels contribute to the cardiovascular manifestations that are characteristic of PSD[65-67].

Moreover, cortisol's influence on the autonomic nervous system also affects heart rate and cardiac output, causing individuals with PSD to experience palpitations and a racing heart, which can be both alarming and distressing. This heightened sympathetic nervous system activity, characterized by increased heart rate, is further intensified by stress and emotional distress[68].

On the other hand, cortisol also significantly impacts the gastrointestinal system. The gastrointestinal tract hosts an abundance of GRs, and their activation by cortisol modulates neuronal signaling within the gut. This modulation, in turn, influences visceral sensitivity and has the potential to amplify the perception of pain. On activation by cortisol, GR can exert regulatory control over the expression of genes associated with the production and release of neurotransmitters involved in pain perception, such as substance P and serotonin. Consequently, changes in the levels of these neurotransmitters can impact neuronal signaling and sensitivity in the gastrointestinal tract. In addition, alterations in gene expression driven by GR activation may lead to neuronal sensitization, a phenomenon wherein gut neurons become more responsive to stimuli. This heightened sensitivity can intensify the perception of pain signals, thereby contributing to increased visceral sensitivity (Figure 1C)[69].

In addition, GR activation modulates the expression of genes associated with the production of inflammatory mediators. For example, GR activation leads to the inhibition of proinflammatory genes by preventing the binding of other transcription factors, such as NF-κB, a key regulator of inflammatory gene expression, to their respective promoter regions. Simultaneously, GR activation promotes the transcription of anti-inflammatory genes, such as glucocorticoid-induced leucine zipper (GILZ) and annexin-1. These genes play pivotal roles in the resolution of inflammation. Chronic inflammation within the gut may further sensitize neurons and contribute to heightened pain perception[69,72].

Moreover, the activation of GRs exerts regulatory effects on intestinal motility. Cortisol's interaction with these receptors has the potential to influence the smooth muscle activity of the intestines, consequently impacting the pace of contractions. This modulation of intestinal motility may manifest in symptoms such as diarrhea, which is commonly reported in individuals experiencing elevated cortisol levels due to chronic stress. The intricate relationship between cortisol, GRs, and gut function extends beyond motility regulation and can contribute to alterations in the composition of the gut microbiota. This, in turn, may give rise to increased gas production and abdominal distension, both contributing factors to the sensation of bloating[73,74].

Furthermore, the activation of GRs within the gastrointestinal tract is intricately linked to the gut-brain axis. Dysregulated cortisol levels disrupt the communication between the gut and the central nervous system. This disruption has the potential to amplify the perception of visceral pain, intensifying the patient's discomfort and complicating their clinical presentation within the context of PSD[72,75-79].

2.4. Altered sensitivity to pain and discomfort

Cortisol significantly influences pain perception and sensitivity, contributing to the complex symptomatology of PSD. The modulation of pain perception by cortisol is mediated through its interaction with both central and peripheral corticosteroid receptors[80].

The impact of cortisol on pain perception involves its action on nociceptors, specialized sensory receptors responsible for detecting painful stimuli (Figure 1C). This interaction may result in enhanced pain transmission or the amplification of pain signals. Notably, in individuals with PSD, this heightened sensitivity to pain and discomfort is a characteristic feature[81].

The intricate molecular mechanism through which cortisol influences pain perception, particularly by acting on nociceptors – specialized sensory receptors responsible for detecting painful stimuli – involves a cascade of events at the cellular and molecular levels. On binding to GRs on the membrane of nociceptor cells, cortisol initiates a series of intracellular processes. The activated GRs translocate into the nucleus, where they function as transcription factors, modulating the expression of genes crucial for nociceptor function and pain perception. This regulatory process includes the regulation of ion channels pivotal for nociceptor excitability, such as voltage-gated sodium channels, essential for action potential generation and propagation. In addition, cortisol, through GR activation, can influence the expression of genes related to neurotransmitter release from nociceptor terminals. This modulation encompasses the regulation of neuropeptides, such as substance P, and neurotransmitters, such as glutamate and gamma-aminobutyric acid (GABA), all of which play pivotal roles in nociceptive signaling (Figure 1D). Furthermore, cortisol's impact extends to the modulation of inflammatory mediators, including

cytokines and prostaglandins, by influencing the expression of genes involved in the inflammatory response. This intricate network of transcriptional regulation and neurotransmitter modulation collectively contributes to the overall sensitivity of nociceptors to painful stimuli. Moreover, cortisol may participate in the endogenous pain modulation system by influencing the expression of genes related to endorphins and enkephalins, which are natural pain-relieving substances. This complex interplay highlights the multifaceted role of cortisol in shaping nociceptor function and the intricate molecular processes that contribute to the perception and modulation of pain in response to various stimuli[81-85].

This complex interplay additionally contributes to the amplification of visceral pain perception, thereby intensifying the patient's discomfort and introducing another layer of complexity to the symptomatology of PSD[86].

2.5. Disturbances in sleep patterns

The intricate functioning of the HPA axis holds significant ramifications for the regulation of the human body's circadian rhythm, rendering it an influential factor in sleep patterns. Dysregulation of HPA axis activity can give rise to a cascade of sleep disturbances, encompassing insomnia, sleep fragmentation, and modifications in sleep architecture. These perturbations in sleep are frequently observed in individuals grappling with PSD, thereby further exacerbating their overall symptomatology[87].

The dysregulated activity of the HPA axis serves as a harbinger of sleep disturbances through a sequence of intricate molecular mechanisms. As a central player in orchestrating the body's stress response, the HPA axis possesses the capacity to disrupt the finely tuned equilibrium of the circadian rhythm and influence various elements that impact the sleep-wake cycle[87,88].

Ordinarily, cortisol adheres to a diurnal pattern, with its levels peaking in the morning and tapering off as night descends. Dysregulated HPA axis activity, however, can precipitate a disruption in this rhythm, giving rise to untimely surges in cortisol levels, notably during the evening and nighttime hours[88].

These erratic cortisol levels can precipitate a deleterious impact on the GABAergic system, a pivotal inhibitory neural network. A diminution in GABAergic inhibition can translate into heightened neural excitability, rendering the initiation and sustenance of sleep a herculean task[89].

Moreover, the HPA axis engages in a complex interplay with genes associated with the circadian clock, such as PER1 and PER2. Dysregulated cortisol release can disturb the conventional expression of these genes, culminating in imbalances within the body's intrinsic chronometer and disrupting the precise timing of sleep-wake cycles. This discordance can further compromise the pineal gland's proficiency in generating melatonin, the hormone paramount for regulating the sleep process. Normally, melatonin experiences a surge in production during the evening hours, signaling to the body that it is time to embrace slumber. Dysregulated cortisol levels, however, can interrupt this harmonious process, making the onset of sleep more elusive[90-94].

The repercussions of dysregulated cortisol are not confined to the realm of hormonal fluctuations but extend to the autonomic nervous system as well. Increased sympathetic nervous system activity, a hallmark of the body's fight-or-flight response, perpetuates a state of heightened alertness and readiness to grapple with stressors. This state of hyperarousal can render relaxation and the initiation of sleep a challenging endeavor[88].

In addition, the hippocampus, a cerebral region intricately involved in memory and stress regulation, is densely populated with GRs. Altered cortisol function can lead to a detriment in hippocampal performance, thus adversely affecting sleep quality and the consolidation of memories. Furthermore, it paves the way for the upsurge of proinflammatory cytokines, which are notorious for disrupting sleep patterns and fomenting the scourge of insomnia[88-96].

3. Endocannabinoid system

The endocannabinoid system (ECS) constitutes a multifaceted signaling network that pervades the human body, originally unearthed through research into the pharmacological effects of compounds derived from the cannabis plant. Over time, it has evolved into an indispensable regulatory system crucial for maintaining equilibrium across a myriad of physiological and psychological domains[97,100].

The ECS encompasses a constellation of components, including endogenous cannabinoids (endocannabinoids), cannabinoid receptors labeled as cannabinoid type 1 receptors (CB1Rs) and cannabinoid type 2 receptors (CB2Rs), and a suite of enzymes entrusted with the synthesis and degradation of endocannabinoids. Within all the endocannabinoids, Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are of primary interest. Unlike conventional neurotransmitters, endocannabinoids are not stockpiled within synaptic vesicles but are rather synthesized by neurons as the need arises, making use of the lipid constituents of cell membranes[101].

These endocannabinoids serve as retrograde messengers, transmitting signals from postsynaptic neurons back to presynaptic terminals, effectively curbing the release of neurotransmitters. This feedback mechanism plays a crucial role in the regulation of synaptic functions, synaptic plasticity, and an array of behavioral aspects, including learning, memory, reward, addiction, pain perception, and anxiety[101].

Endogenous cannabinoids engage with and activate cannabinoid receptors, primarily CB1Rs and CB2Rs, which are distributed widely throughout the body. These receptors belong to the family of G protein-coupled receptors (GPCRs), characterized by their seven transmembrane domains and comprising extracellular aminoterminal and intracellular carbonyl terminal segments. On binding to a ligand, these activated cannabinoid receptors interface with specific G proteins within the cell. CB1Rs, in particular, initiate the activation of Gαi/o proteins, while CB2Rs may additionally interact with Gαs proteins, initiating a chain of events that trigger the disintegration of G proteins into their subunits, thereby influencing intracellular signaling pathways[102-106]. CB1Rs are abundantly found within the brain, predominantly on neurons within the central nervous system (CNS). They are particularly prominent in brain regions associated with motor coordination, cognitive functions such as decision-making, learning, memory, and the intricacies of human emotions. Furthermore, CB1Rs are also found, although in more modest densities, in certain organs and peripheral tissues, including endocrine glands, salivary glands, leukocytes, the spleen, the heart, and components of the reproductive, urinary, and gastrointestinal systems[107]. In contrast, CB2Rs primarily reside in immune cells and tissues, with a limited presence in the pancreas. Recent research has even identified the presence of CB2Rs within the CNS, specifically on glial and microglial cells, though in diminished quantities[106].

The ECS emerges as an indispensable player in a spectrum of physiological processes, spanning the modulation of pain, the regulation of immune function, the control of inflammation, the management of appetite, the maintenance of metabolic homeostasis, the orchestration of neuronal plasticity, and the handling of stress responses. It operates as a sentinel of homeostasis, diligently guarding the body's equilibrium. The ECS contributes to the perception of pain, immunomodulation, and the regulation of appetite and energy balance. Furthermore, it plays a pivotal role in memory, the processes of learning, neuroprotection, and the regulation of emotions. Dysregulation of the ECS has been implicated in a multitude of health conditions, encompassing chronic pain, inflammatory disorders, neurodegenerative diseases, metabolic disorders, mood disorders, and addiction[108,109].

3.1. Endocannabinoid system and the regulation of stress

The ECS asserts its influence over the HPA axis through the activation of cannabinoid receptors, particularly CB1Rs. The HPA axis's core responsibility is to coordinate the body's response to stress, mainly by regulating the release of cortisol and other stress hormones. On activation, CB1Rs can modulate the HPA axis's stress response, thereby contributing to a mitigation of the release of cortisol and other stress-related mediators[110-114].

Endocannabinoids, such as AEA and 2-AG, are synthesized and released in response to stress. These compounds can bind to CB1Rs in various brain regions, including the hypothalamus, the central regulator of HPA axis activity. The activation of these receptors leads to a reduction in the release of CRH and ACTH, ultimately restraining the release of cortisol (Figure 1B)[115-117].

Preclinical research involving animal models has demonstrated that the activation of CB1Rs can ameliorate the physiological and behavioral effects of stress. These effects encompass a reduction in the secretion of stress hormones, a blunting of the stress-induced activation of the HPA axis, and mitigation of anxiety-like behaviors[118,119].

Human studies have provided valuable insights into the therapeutic potential of ECS modulation in conditions linked to stress. Several trials have explored the use of cannabinoids, such as cannabidiol (CBD), in alleviating symptoms of anxiety and post-traumatic stress disorder (PTSD). These studies indicate that cannabinoids may help regulate the HPA axis's response to stress and ameliorate the psychological symptoms associated with stress-related disorders[120].

Chronic stress can induce the dysregulation of the ECS, setting the stage for a vicious cycle of heightened stress response and emotional turmoil. Restoring equilibrium within the ECS through modulation may offer a promising approach to mitigating the deleterious effects of chronic stress[121].

PSDs, characterized by the intricate interplay between psychological distress and somatic symptoms, frequently involve an amplified stress response and emotional turbulence. The capacity of ECS modulation to attenuate the HPA axis's stress response and alleviate anxiety and mood-related symptoms holds particular relevance in the management of PSD. By tempering the physiological and psychological aspects of chronic stress, ECS modulation may contribute to the amelioration of psychosomatic

symptoms, a development of paramount therapeutic import. This development holds particular promise in addressing the multifaceted nature of PSD, where the interplay between emotional well-being and physical symptoms is a defining feature[122].

In PSD, dysregulation of the ECS may contribute to heightened stress levels. Conversely, modulating the ECS through various means, such as lifestyle changes, pharmacological interventions, or even cannabinoids from external sources like cannabis, may offer therapeutic potential in managing stress-related symptoms associated with PSD. However, it is essential to note that the effects can vary among individuals, and more research is needed to fully understand the complex interplay between ECS and stress in the context of PSD.

3.2. Modulation of immune function and inflammation

The ECS intricately governs the regulation of immune function, placing a pronounced emphasis on CB2Rs, which are abundant in immune cells. These receptors are predominantly expressed in cells of the immune system and play a pivotal role in modulating the body's immune responses. The interplay between the ECS and immune function is of great scientific intrigue due to its potential implications for comprehending and addressing conditions characterized by immune dysregulation, including PSD[123].

CB2Rs are prevalent in various immune cells, including leukocytes, monocytes, macrophages, B-cells, T-cells, and natural killer cells (Figure 1C and D). Their presence in these cells underscores the significance of CB2Rs in governing immune responses. While CB2Rs are most widespread in immune cells, they are also found in tissues associated with the immune system, such as the spleen and tonsils. Furthermore, they are expressed in bone marrow, a hub of immune cell production[123-125].

Activation of CB2Rs in immune cells induces anti-inflammatory effects. Stimulation of CB2Rs inhibits the production of proinflammatory cytokines and chemokines, which are molecules responsible for initiating and amplifying inflammatory responses (Figure 1E). The ECS plays a pivotal role in maintaining immune homeostasis, ensuring that the immune system responds appropriately to threats while averting excessive or chronic inflammation. This immunomodulatory function aids in sustaining a balanced and regulated immune response[126,127].

Immune dysregulation is a prevalent feature of PSD, with symptoms often linked to chronic inflammation and imbalances in the immune system. Chronic stress, a recurrent element in PSD, can induce chronic low-level inflammation. Dysregulation of the ECS can further exacerbate this inflammatory response. In PSD, symptoms such as fatigue, pain, and gastrointestinal distress can be attributed to immune dysregulation and inflammation. Modulating the ECS to govern immune function may help mitigate these symptoms[128,129].

Scientific research is diligently exploring the therapeutic potential of ECS modulation, particularly the use of cannabinoids, in the management of conditions associated with immune dysregulation and chronic inflammation. These studies strive to provide scientific insights into the role of the ECS in alleviating immune-related psychosomatic symptoms[130].

The ECS's interaction with immune function, particularly through CB2Rs in immune cells, carries significant implications for understanding and addressing immune dysregulation linked to psychosomatic symptoms. This is achieved by inhibiting the extracellular signal-regulated kinase (ERK) pathway through mitogen-activated protein kinase-phosphatase (MKP) induction (Figure 1E). The ECS's capacity to govern immune responses and inflammation at the molecular level opens potential avenues for therapeutic interventions in these intricate conditions, with ongoing scientific research contributing to our understanding of this intricate relationship[131].

Despite significant progress in understanding the interaction between the ECS and immune function or inflammation, several critical gaps persist in the current research landscape. The specific mechanisms underlying how cannabinoids, both endogenous and exogenous, influence immune responses remain incompletely elucidated, necessitating further exploration. Cell-specific effects of cannabinoids on different immune cell types, including T-cells, B-cells, and macrophages, need to be thoroughly investigated to provide a nuanced understanding of their impact. Limited clinical evidence exists regarding the efficacy and safety of cannabinoids in treating inflammatory and immune-related disorders, emphasizing the need for robust clinical trials. Establishing dose-response relationships, understanding long-term effects and safety profiles, and exploring interactions with the gut microbiome are essential for translating preclinical findings into effective therapeutic strategies. In addition, addressing the variability in individual responses to cannabinoids based on genetic, environmental, and lifestyle factors is crucial for developing personalized approaches to cannabinoid-based therapies. Closing these gaps in knowledge will contribute to harnessing the therapeutic potential of the ECS in modulating immune function and inflammation for various health conditions[131-140].

3.3. Mood regulation

CB1Rs, which are abundant in the CNS, can exert anxiolytic effects by modulating GABA and glutamate neurotransmission. When activated, CB1Rs intricately modulate the release of these neurotransmitters, thereby contributing to the intricate regulation of anxiety-related processes (Figure 1F). CB1Rs are particularly densely expressed on GABAergic neurons in key brain regions such as the amygdala, hippocampus, and prefrontal cortex, all implicated in anxiety regulation. Activation of CB1Rs inhibits the release of GABA, the primary inhibitory neurotransmitter, leading to a reduction in inhibitory input onto postsynaptic neurons and, consequently, a decrease in neuronal excitability. This disinhibition is a key mechanism through which CB1R activation contributes to anxiolysis. Furthermore, CB1Rs influence the release of glutamate, the primary excitatory neurotransmitter. In regions such as the amygdala and hippocampus, CB1R activation inhibits glutamate release, dampening excitatory signaling, and decreasing overall excitatory neurotransmission. These effects are particularly relevant in neural circuits associated with anxiety and emotional processing. In essence, the anxiolytic effects of CB1R modulation involve a delicate balancing act between inhibitory and excitatory signaling within crucial brain regions implicated in anxiety regulation, contributing to the overall regulation of anxiety-related behaviors[141-146].

Human studies have investigated the utilization of cannabinoids, particularly CBD, in the management of symptoms associated with anxiety disorders. These studies provide scientific insights into the potential of ECS modulation to alleviate anxiety.

Dysregulation of the ECS has been implicated in mood disorders, including depression. ECS modulation may influence the brain's reward and pleasure pathways, subsequently impacting depressive symptoms. Human research has explored the role of ECS modulation in managing depression. Evidence suggests that cannabinoids can influence depressive symptoms, potentially through their effects on the ECS[145].

PSD often entail emotional disturbances, such as anxiety and depression, that intricately interact with physical symptoms. The ECS's ability to modulate mood and reduce psychological symptoms holds relevance for the management of these conditions. ECS modulation may help alleviate the psychological symptoms associated with PSD, enhancing overall well-being and quality of life[147,148]. This modulation contributes to anxiolysis, balancing inhibitory and excitatory signaling in key brain regions associated with anxiety and emotional processing. Ultimately, the therapeutic potential of ECS modulation offers a holistic approach to addressing both emotional and physical aspects of PSD, aiming to enhance overall well-being and improve the quality of life for individuals experiencing these complex conditions.

3.4. Pain perception and sensitivity

Pain is a recurring component of PSD, where emotional distress and physical symptoms intertwine. Endocannabinoids, such as AEA and 2-AG, play a pivotal role in modulating the perception of pain. These compounds can influence various points along the pain pathway, spanning the peripheral nervous system, the spinal cord, and the brain[149].

Nociceptors, specialized sensory neurons attuned to noxious stimuli, represent prime targets of ECS components, such as endocannabinoids and CB1Rs. These elements have the capacity to influence nociceptor sensitization and attenuate the signaling of pain. CB1Rs, widely distributed in both the central and peripheral nervous systems, can inhibit the transmission of pain signals, consequently modulating pain perception[150,151].

Inflammatory pain, which often involves nociceptor sensitization, can be alleviated through ECS modulation, thereby mitigating inflammatory pain. Endocannabinoids act as retrograde messengers, shaping the release of neurotransmitters and culminating in the inhibition of pain signals, contributing to pain modulation. In the brain, particularly within regions implicated in pain processing, CB1Rs play a significant role in pain modulation. ECS activation in these areas can reshape pain perception and emotional reactions to pain[152,153].

ECS modulation holds promise in mitigating pain-related symptoms in PSD, addressing the intricate interplay between emotional distress and physical complaints. The scientific evidence presented here underscores the potential of ECS modulation in managing PSD, particularly in addressing pain-related symptoms and enhancing the overall well-being of affected individuals[154-159].

4. Discussion

The modulation of the ECS emerges as a promising therapeutic approach for PSD, characterized by the intricate interplay between emotional distress and physical symptoms. The ECS, a complex regulatory network, plays a pivotal role in mood regulation, stress perception, pain modulation, and immune function. The potential of ECS modulation to ameliorate both psychological and somatic symptoms in PSD has garnered attention. However, to realize the therapeutic benefits and translate this approach into clinical practice, comprehensive research and a

nuanced understanding of the complexities involved are crucial.

The ECS, consisting of endocannabinoids, cannabinoid receptors (CB1Rs and CB2Rs), and associated enzymes, serves as a homeostatic regulator influencing various physiological processes. Evidence suggests that ECS modulation holds promise in alleviating symptoms of PSD. Nevertheless, achieving a comprehensive understanding and successful clinical translation necessitates addressing key challenges and conducting extensive research.

The potential therapeutic effects of ECS modulation in PSD are multifaceted. ECS plays a crucial role in mood regulation, and its modulation has shown promise in alleviating symptoms of anxiety and depression associated with PSD. In addition, ECS influences pain perception, and studies indicate its potential to modulate somatic symptoms. The immunomodulatory effects of ECS also open avenues for addressing the complex interplay between emotional distress and immune function in PSD.

For a robust understanding and successful application of ECS modulation in PSD, future research should prioritize longitudinal studies and well-designed clinical trials. Investigating the safety, efficacy, optimal dosing, and potential side effects of cannabinoid-based therapies is paramount. Individualized treatment approaches, incorporating genetic factors, biomarkers, and psychosocial variables, can enhance outcomes by accounting for the heterogeneity of PSD.

The ultimate goal is to establish evidence-based, personalized interventions for PSD through a nuanced understanding of ECS modulation. The approach includes identifying biomarkers predicting treatment response, exploring neurobiological mechanisms, and considering potential synergies with other therapeutic modalities.

Despite the potential benefits, challenges abound. The safety of cannabinoid-based therapies, particularly in the long term, is a primary concern. Potential side effects such as cognitive impairment, dependence, and psychomotor disturbances must be carefully examined. Determining appropriate dosages poses a challenge due to individual variations and ethical considerations surrounding vulnerable populations demand thorough exploration.

Advancing knowledge requires exploring dose-response relationships, utilizing advanced neuroimaging techniques, and investigating the potential differential effects of various cannabinoids. Ethical considerations should guide research, and legal frameworks must align with responsible and equitable access to cannabinoid-based therapies.

The field of ECS modulation in PSD is at a critical juncture, demanding a comprehensive, multidisciplinary approach. While the potential benefits are substantial, the complexities involved necessitate thorough investigation and responsible implementation. This line of research is paramount in addressing the unmet needs of individuals with PSD. By deciphering the intricacies of ECS modulation, clinicians can move toward personalized, evidence-based interventions that enhance the quality of life for those grappling with the challenges of PSD.

The limits of ECS modulation, including potential adverse psychological reactions and dependency issues, must be acknowledged. Yet, its merits lie in offering a holistic approach to address both psychological and somatic aspects of PSD. Successful translation into clinical practice hinges on rigorous research, ethical considerations, and a nuanced understanding of both the therapeutic potential and limitations of ECS modulation in the context of PSD[160].

5. Conclusion

While the current body of research on ECS modulation for PSD is promising, it remains in its infancy, necessitating robust clinical trials for a comprehensive understanding of safety and efficacy. The potential benefits of ECS modulation in alleviating both psychological and somatic symptoms offer a beacon of hope; yet, caution must be exercised regarding the potential limitations and dangers associated with cannabinoid administration in this vulnerable population. These potential limitations and dangers underscore the imperative for careful consideration, rigorous research, and well-designed clinical trials. Monitoring patients closely and establishing individualized treatment plans that account for the intricate nature of PSD and the diverse responses to cannabinoid interventions is paramount. The theoretical implications of this research lie in unraveling the complex interplay between the endocannabinoid system and psychosomatic symptoms, providing insights into potential avenues for targeted interventions. Methodologically, refining biomarkers, understanding neurobiological mechanisms, and exploring synergies with existing therapeutic modalities are critical for advancing the field. Future research directions should focus on longitudinal studies, comparative effectiveness research, and exploring the nuanced effects of different cannabinoids. This line of inquiry not only holds theoretical significance but also has the translational potential to reshape clinical practice, offering tailored and evidence-based interventions for individuals navigating the challenges of PSD.

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ACCSCIENCE PUBLISHING

Journal of Clinical and Basic Psychosomatics

ORIGINAL RESEARCH ARTICLE

Correlations between depressive disorder, obstructive sleep apnea, and hypothalamic inflammation

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Abstract

Obesity is a significant public health concern in China, with a 2.5-fold increase in prevalence over the past 30 years. This increase corresponds to a rise in the prevalence of obstructive sleep apnea (OSA). This study aims to investigate the associations of OSA with depressive disorders and hypothalamic inflammation in obese young men. Between January 2020 and December 2021, 62 obese male patients were selected and divided into two groups: a depressive disorder group (18 cases) and a non-depressive disorder group (44 cases) according to the diagnostic criteria of the DSM-5 combined with depressive disorder. All patients were monitored using a portable sleep monitor. Hypothalamic inflammation was evaluated using quantitative magnetic resonance imaging (MRI) by calculating the signal intensity (SI) ratio of the T2-weighted phase of the hypothalamus/amygdala (H/A). Differences were observed in the respiratory event index (REI), lowest oxygen saturation, and oxygen desaturation index ($P < 0.05$). In the depressive disorder group, the left H/A was significantly higher than in the non-depressive disorder group ($P = 0.002$), whereas the right H/A did not differ significantly between the two groups ($P > 0.05$). Furthermore, the left H/A exhibited correlations with REI and body mass index (BMI) ($P < 0.05$), while no correlation was found between the right H/A and AHI ($P > 0.05$). In conclusion, our findings suggest that the left hypothalamic inflammation is positively correlated with the severity of OSA, implying that left hypothalamic inflammation may represent a potential mechanism underlying OSA in obese young patients with depressive disorders.

Keywords: Obesity; Hypothalamus inflammation; Depressive disorders; Obstructive sleep apnea

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1. Introduction

Obesity is a major public health concern in China. The latest statistics (2015–2019) show that more than half of adult Chinese residents are obese or overweight[1]. Over the past 30 years, the prevalence of obesity in China has increased 2.5 times. This increase corresponds to a rise in the prevalence of obstructive sleep apnea (OSA)[2]. Among the group aged 30 – 69 years, the prevalence of OSA in China exceeds 240 million[3]. Overweight, especially obesity, is the most significant risk factor for OSA. A 10% of increase in body weight is associated with a 30% of increase in the apnea-hypopnea index (AHI)[4]. From a clinical perspective, obesity is strongly associated with the incidence and severity of OSA[5]. Bariatric surgery alleviates OSA severity, confirming a causal link between the two[6]. Conversely, OSA has many obesity-promoting effects, such as a reduction in physical activity, energy metabolism, and motivation. Moreover, there is a bidirectional association between obesity and OSA[7]. On the one hand, insomnia can affect energy intake and expenditure. On the other hand, obesity is a well-known risk factor for OSA.

OSA and depression share similar clinical features, such as poor concentration and fatigue[8]. Obesity exacerbates the impact of OSA on depressive disorders, serving as a mediator for the symptom association between OSA and depressive disorders[9]. The prevalence of depressive disorders is high among obese young adults[10]. However, there is limited research on the clinical characteristics of OSA in obese young patients with depressive disorders[11]. Animal studies have demonstrated that insomnia and inflammation contribute to increased severity of depressive disorders, which is consistent with clinical observations[12]. In addition, inflammatory mechanisms play an important role in both OSA and depressive disorders[13]. Specifically, the left hypothalamic inflammation is significantly associated with the severity of depressive disorders in obese young patients[10]. The relationships between hypothalamic inflammation and OSA are unclear in this population.

It is well-known that the incidence of OSA in women before menopause is significantly lower than that in men[14]. This difference is associated with lower levels of inflammation in premenopausal women[15]. However, the incidence of OSA in postmenopausal women is similar to that in men[16]. Age did not affect the level of inflammation in male OSA patients. In addition, the levels of inflammatory markers are higher in men with significant daytime sleepiness than in women[17]. In this study, we exclusively focused on young, obese male patients.

The primary aim of this study is to explore the correlation between depressive disorders and OSA in young, obese male patients and investigate the associations between hypothalamic inflammation and OSA severity.

2. Materials and methods

2.1. Participant recruitment procedures

The participants in this study comprised 62 obese male patients who underwent elective bariatric surgery at the Department of Gastrointestinal Surgery, Changzhou Second People's Hospital, affiliated with Nanjing Medical University, between January 2020 and December 2021.

The inclusion criteria were as follows: (i) male individuals aged ≥18 and ≤45 years; (ii) body mass index (BMI) ≥28 kg/m^2; (iii) completion of at least four years of schooling; and (iv) no history of serious neurological diseases.

The exclusion criteria were as follows: (i) patients with excessive obesity preventing completion of cranial MRI; (ii) unclear cranial MRI images or severe artifacts; (iii) severe vision or hearing impairment; (iv) absence of a signed informed consent form; and (v) no history of antidepressant therapy.

The diagnostic criteria for DSM-5 depressive disorder were determined by a psychiatrist[18]. Based on the diagnosis, patients were divided into two groups: A depressive disorder group (n = 18) and a non-depressive disorder group (n = 44).

The diagnostic criteria were jointly determined by a neurologist and a psychiatrist. A deputy chief physician in the imaging department was responsible for reviewing the films and excluding unqualified cases.

2.2. Clinical characteristics

Data on participant demographics, including age, education, height, and weight, were collected the day before surgery. BMI was calculated for each participant by dividing their weight (in kilograms) by the square of the height (in meters). Biochemical indicators, such as blood glucose, blood lipids, and renal function, were determined using the ADVIA XPT system. All subjects fasted for a minimum of 8 h before the collection of blood samples.

2.3. Sleep monitoring

Before going to sleep, all patients wore a portable monitor (Alice NightOne, Philips, Netherlands). The analysis was conducted by healthcare professionals using Sleepware G3 software. The monitoring included the assessment of nasal airflow (via airflow sensing), respiratory movement (with one guide), and fingertip oxygen saturation[19].

2.4. Image processing and analysis

Scanning was performed using a GE Discovery MR750W 3.0T magnetic resonance imager at the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou. The scanning parameters and methods employed in this study have been described in our previous studies[10]. The ITK-SNAP software (developed by the University of Pennsylvania) was utilized for image preprocessing, which included the following steps: (i) conversion of imaging data format to DCM; (ii) importing data in the ITK-SNAP software; (iii) parameter adjustment; (iv) selection of regions of interest ROIs located between the posterior mammillary body and the anterior optic chiasm[20-23], with an area of 10 mm^2; (v) identification of bilateral amygdala[20-23]; (vi) deriving the average value of gray intensity; and (vii) calculating the hypothalamus-to-amygdala (H/A) ratio.

Neurologists independently analyzed imaging data from all obese patients, calculating the H/A ratio based on the average gray intensity value[10].

2.5. Statistical analyses

Data analysis was conducted using SPSS 22.0 statistical software. Descriptive statistics were used to express the data as mean ± standard deviation ($\bar{x} \pm s$). The normality of data distribution was assessed using the Shapiro–Wilk test. For data with normal distribution, the *t*-test was applied. Data with a non-normal distribution were expressed using the median and analyzed using the rank-sum test. Correlation analysis of non-bivariate normal distribution data was performed using Pearson's correlation analysis.

3. Results

3.1. Demographic and clinical characteristics of participants

A total of 62 obese patients were enrolled in this study, comprising 18 individuals with depression and 44 without depression. There were no significant differences in age, educational level, fasting blood glucose, glycosylated hemoglobin, low-density lipoprotein, high-density lipoprotein, total cholesterol, uric acid, creatinine, or urea nitrogen between the two groups ($p > 0.05$). However, a significant difference in triglyceride levels was observed between the non-depressive disorder group and the depressive disorder group ($p < 0.05$; Table 1).

3.2. Sleep monitoring

The monitoring data in Sleepware G3 are interpreted in accordance with the 2017 rules of the American Academy of Sleep Medicine. During this process, technicians review and interpret the raw data. Respiratory events were defined as sleep apnea, including apnea and hypopnea events, as well as instances where the heat-sensitive airflow sensor signals were lost. The respiratory event index (REI) can be calculated by dividing the number of apneas

Table 1. Comparison of demographic and clinical characteristics of patients between the depressive disorder group and the non-depressive disorder group

Variable	Non-depression disorder group (*N*=44)	Depressive disorder group (*N*=18)	T or F	*p*
Age ($\bar{x}\pm s$)	28.86±6.71	28.28±5.35	0.33	0.119
Education (n [%])			1.15	0.287
Primary school and below	10 (22.73%)	2 (11.11%)		
Secondary school	5 (11.36%)	2 (11.11%)		
Undergraduate and above	29 (65.91%)	14 (77.78%)		
BMI (kg/m^2, $\bar{x}\pm s$)	41.02±6.23	40.28±7.01	0.41	0.635
FBG (mmol/L, M [P25, P75])	5.51 (4.96, 5.87)	6.98 (4.75, 10.44)	1.06	0.307
HbA1c (%, M [P25, P75])	5.65 (5.40, 6.20)	6.80 (5.55, 8.95)	3.24	0.077
LDL-C (mmol/L, $\bar{x}\pm s$)	2.92±0.87	3.14±0.85	0.87	0.673
HDL-C (mmol/L, $\bar{x}\pm s$)	1.04±0.24	0.95±0.17	1.44	0.491
TG (mmol/L, M [P25, P75])	1.74 (1.35, 2.38)	2.41 (1.97, 3.46)	4.79	0.032
TC (mmol/L, M [P25, P75])	4.59 (4.10, 5.19)	4.90 (4.40, 5.61)	2.83	0.098
UA (mmol/L, $\bar{x}\pm s$)	435.36±121.56	428.22±88.68	0.23	0.074
Scr (mmol/L, M [P25, P75])	72.50 (63.75,79.50)	66.00 (55.43,76.50)	0.87	0.355
BUN (mmol/L, M [P25, P75])	4.15 (3.48, 5.05)	4.05 (3.60, 5.00)	0.06	0.802

Legends: M [P25, P75]: Median and interquartile range; $\bar{x}\pm s$: Mean±standard deviation.
Abbreviations: BMI: Body mass index; BUN: Blood urea nitrogen; FBG: Fasting blood glucose; HbA1C: Hemoglobin A1C; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglyceride; UA: Uric acid; Scr: Serum creatinine.

and hypopneas recorded by the total monitoring time. Notably, when comparing obese young male patients with and without depressive disorder, statistically significant differences were observed in several key parameters, including REI (apnea-hypopnea index [AHI]), lowest oxygen saturation, maximum duration of sleep apnea, and oxygen desaturation index (ODI) ($p < 0.05$). Conversely, other parameters such as time in bed, maximum duration of sleep apnea, actual sleep time, maximum duration of hypoventilation, and ODI did not exhibit statistically significant differences between the two groups ($p > 0.05$) (Table 2).

3.3. Correlation of depressive disorder on bilateral hypothalamic inflammation

In obese young male patients, the ratio of the left H/A signal intensity (SI) within the depressive disorder group was observed to be significantly higher than within the non-depressive disorder group ($p = 0.002$). However, no significant difference was identified in the right H/A signal ratio between the two groups ($p > 0.05$) (Figure 1).

3.4. Correlation between hypothalamus/amygdala (H/A) SI ratio and BMI, REI, ODI, and lowest oxygen saturation

Changes in SI within brain tissue can be observed on T2-weighted images, and subtle changes can be quantitatively assessed using techniques[24] such as astrocyte or microglial accumulation. The H/A SI ratio serves as an alternative marker for the study of hypothalamic inflammation[21]. Notably, there was no observed correlation between the right H/A SI ratio and BMI, as well as the lowest oxygen saturation ($p > 0.05$; Figures 2 and 3). However, a significant correlation was identified between the right H/A SI ratio and REI and ODI ($p < 0.05$; Figures 4 and 5). Similarly, the left H/A SI ratio displayed correlations with REI, BMI, and ODI ($p < 0.05$; Figures 6-8). Conversely, no correlation was found between the left H/A SI ratio and the lowest oxygen saturation ($p > 0.05$; Figure 9).

4. Discussion

This study has identified the association between depressive disorders, values of REI and ODI, and H/A ratio in young obese male patients. Furthermore, there is a positive correlation observed between an increase in the left H/A SI ratio and both REI and BMI.

The previous studies have indicated that[25] obese patients are at a heightened risk of experiencing sleep disorders, particularly insomnia and OSA. One of the studies has demonstrated that in the absence of emotional

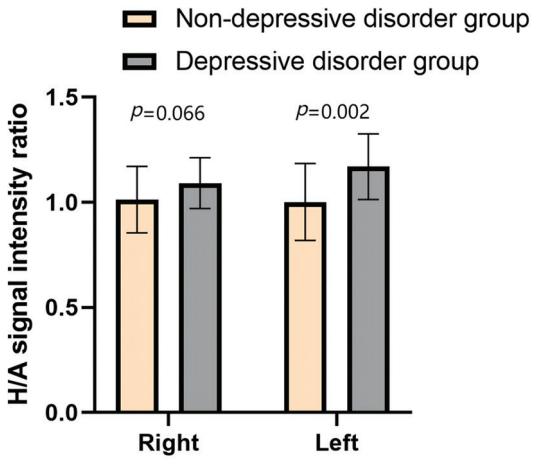

Figure 1. Comparison of bilateral hypothalamic inflammation between non-depressive disorder group and depressive disorder group. The means of the non-depressive disorder group are 1.013 ± 0.158 (right) and 1.001 ± 0.183 (left), while the means of the depressive disorder group are 1.091 ± 0.121 (right) and 1.169 ± 0.156 (left).

Table 2. Comparison of sleep monitoring results between depressive disorder group and non-depressive disorder group

Variable	Non-depressive disorder group (*N*=44)	Depressive disorder group (*N*=18)	T or F	*p*
Time in bed (min, $\bar{x}$±s)	447.34±135.18	463.84±117.32	0.48	0.494
Actual sleep time (min, M [P25, P75])	422.0 (341.0, 473.0)	370.5 (307.9, 512.9)	0.08	0.776
AHI M (P25, P75)	25.80 (14.08, 50.50)	51.20 (26.98, 68.55)	4.32	0.042
Lowest oxygen saturation (M [P25, P75])	82.50 (70.50, 88.00)	69.00 (59.25, 78.75)	11.07	0.001
Maximum duration of sleep apnea (seconds, M [P25, P75])	42.00 (25.75, 59.00)	64.00 (50.38, 72.00)	4.76	0.033
Maximum duration of hypoventilation (seconds, M [P25, P75])	86.00 (35.25, 94.50)	83.00 (59.13, 95.25)	2.04	0.159
ODI (M [P25, P75])	22.05 (12.73, 43.10)	48.55 (22.70, 60.73)	6.09	0.016
Oxygen loss quantity (%, M [P25, P75])	3.10 (1.00, 20.50)	24.60 (6.40, 41.00)	3.86	0.054

Legends: M [P25, P75]: Median and interquartile range; $\bar{x}$±s: Mean±standard deviation.
Abbreviations: AHI: Apnea-hypopnea index; ODI: Oxygen desaturation index.

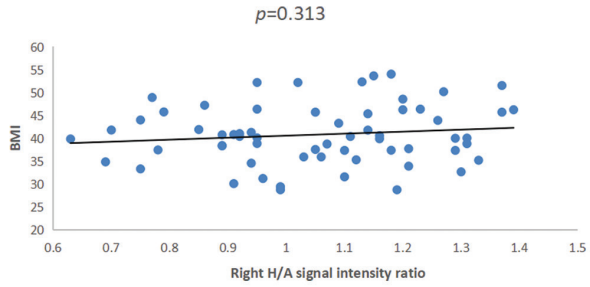

Figure 2. Correlation between the right hypothalamus/amygdala signal intensity ratio and body mass index.

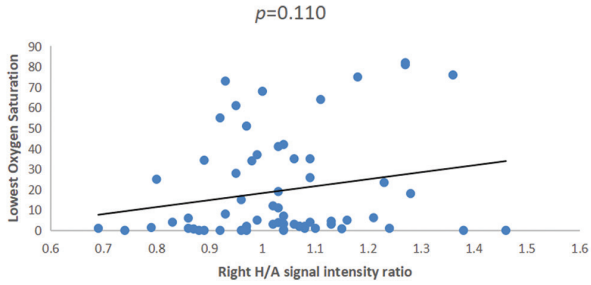

Figure 3. Correlation between the right hypothalamus/amygdala signal intensity ratio and the lowest oxygen saturation.

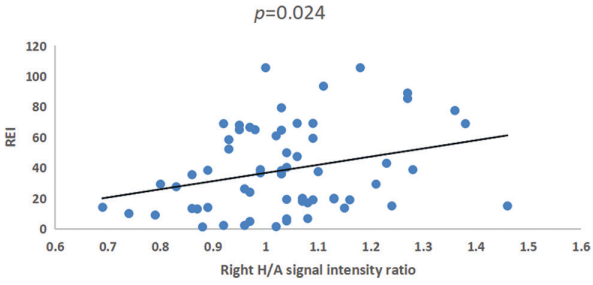

Figure 4. Correlation between the right hypothalamus/amygdala signal intensity ratio and respiratory event index.

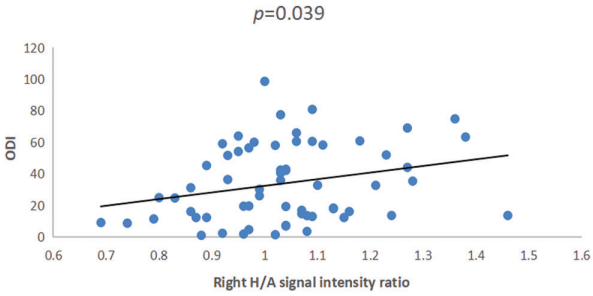

Figure 5. Correlation between the right hypothalamus/amygdala signal intensity ratio and oxygen desaturation index.

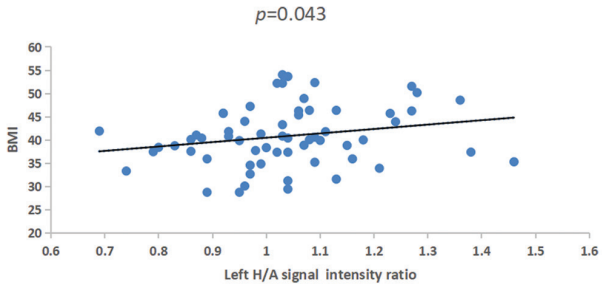

Figure 6. Correlation between the left hypothalamus/amygdala signal intensity ratio and body mass index.

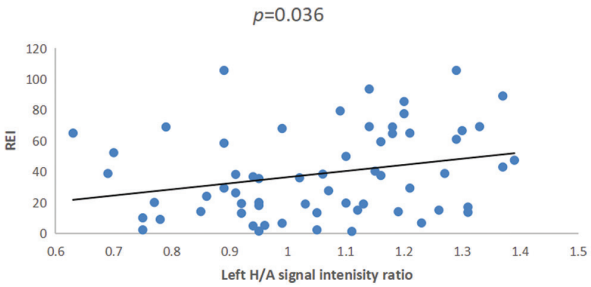

Figure 7. Correlation between the left hypothalamus/amygdala signal intensity ratio and respiratory event index.

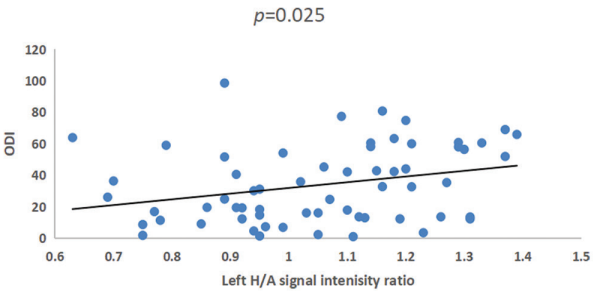

Figure 8. Correlation between the left hypothalamus/amygdala signal intensity ratio and oxygen desaturation index.

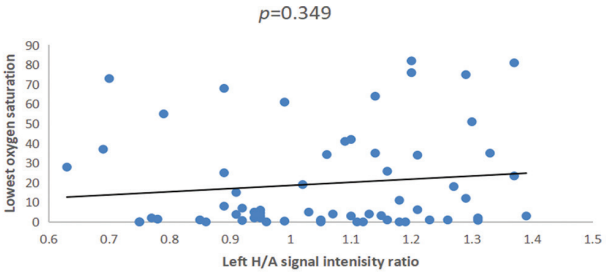

Figure 9. Correlation between the left hypothalamus/amygdala signal intensity ratio and the lowest oxygen saturation.

stress, obese patients and individuals with normal weight exhibit similar sleep durations. This observation suggests that emotional stress plays a pivotal role in influencing sleep disturbances in obese patients[26]. According to a

previous report[27], the prevalence of OSA in patients with depressive disorder surpasses that in patients with bipolar disorder or schizophrenia. In addition, it is worth noting that the BMI serves as a predictor for OSA.

Depression is among the most prevalent mood disorders in obese patients. In this study, middle-aged and young obese male patients with depressive disorders exhibited a significant increase in REI and a lesser decrease in the lowest oxygen saturation. Among the 110 psychiatric patients we examined, 72.48% had an AHI of ≥15, and 84.4% had an AHI of ≥5 sleep events per hour, as recorded by polysomnography (PSG)[28]. The diagnostic criteria for OSA primarily relied on the number of respiratory events recorded on PSG, which included obstructive apnea, mixed apnea, hypopnea, and effort-related arousal. It is worth noting that depressive disorders are associated with an increased incidence of AHI and reduced blood oxygen saturation. These effects may be related to share underlying factors, including dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, insulin resistance, and immune inflammation activation. In addition, depressive disorders exacerbate the use of oxygen therapy in obese middle-aged men. The ODI is closely related to the AHI. A higher ODI corresponds to a higher AHI, indicating a more severe condition. Notably, depressive disorders exacerbate the severity of OSA. In addition, the use of sedative and hypnotic drugs is more prevalent in obese men with depressive disorders. However, it is essential to recognize that these drugs have the potential to reduce respiratory muscle tone[29], which, in turn, leads to an increase in apnea and hypopnea events, thereby exacerbating the hypoxia associated with OSA. Therefore, the use of benzodiazepines and opioids should be closely controlled and monitored in obese patients with OSA[30].

OSA and depressive disorders are two of the most prevalent comorbidities in obese patients, sharing similar clinical manifestations, such as daytime sleepiness, inattention, irritability, and withdrawal from social activities[31]. Despite these shared symptoms, the relationship between these two disorders remains unclear. Patients with OSA frequently exhibit depressive symptoms or disorders[32], with up to 30% of OSA patients experiencing comorbid depressive disorders[33]. This association may be a direct result of sleep disturbances or a secondary consequence influenced by the social implications of the disorder[34]. One study reported that 39% of 51 patients with depression met the diagnostic criteria for OSA[35], with AHI and blood oxygen saturation serving as diagnostic criteria for OSA. It is important to note that a depressed mood can elevate AHI, but this does not necessarily imply a causal relationship. In a longitudinal study, no significant differences were found in the prevalence of depressive disorders between patients with mild OSA and those without[36]. However, it is worth mentioning that treatment with continuous positive airway pressure can improve not only the AHI in OSA patients but also alleviate depressive symptoms[37]. The intricate relationship between OSA and depression in obese patients remains a topic that warrants further investigation[7].

OSA and obesity stand out as two of the most prevalent public health problems. One important avenue of research lies in the exploration of hypothalamic inflammation, which is an important area for investigation[38]. Hypothalamic inflammation pertains to the involvement of hypothalamic neurons or non-neuronal cells in the activation of pro-inflammatory signals[39]. An animal study has demonstrated a link between a high-fat diet and increased hypothalamic inflammation[40]. Such a diet can directly trigger hypothalamic inflammation, while chronic peripheral inflammation is known to instigate metabolic abnormalities[41]. Hypothalamic inflammation, in turn, can disrupt energy balance, enhance insulin and leptin resistance, and promote the accumulation of fat in adjacent tissues, resulting in the development of obesity[42]. The correlation between BMI and hypothalamic inflammation has been affirmed in clinical trials that employ quantitative imaging techniques to investigate hypothalamic inflammation[21]. The correlation between BMI and left hypothalamic inflammation was notably pronounced[22], aligning with our experimental findings and previous studies[10,43]. The previous studies have also identified a left-right asymmetry in hypothalamic function. The hypothalamus demonstrates asymmetrical regulation of the HPA axis, circadian rhythm, reproductive system, immune system, thyroid function, and satiety status, all of which have implications for emotional regulation. At present, while there are no reports on hypothalamic inflammation in patients with OSA[38], acute sleep deprivation of any cause has been associated with increased production of two pro-inflammatory factors, IL-6 and tumor necrosis factor (TNF)[44]. Individuals with OSA frequently experience periodic hypoxia due to impaired breathing, causing spontaneous arousals and promoting inflammation. An analysis of obese patients with and without OSA revealed abnormalities in cortisol release and HPA axis function in obese patients with OSA, suggesting that OSA can lead to abnormal hypothalamic function[45]. In this study, a positive correlation was established between the left H/A ratio and the OSA index. This indicates the presence of hypothalamic inflammation in obese patients with OSA and its positive correlation with OSA severity. These findings underscore the association of

hypothalamic inflammation with BMI and AHI. The left hypothalamic inflammation may represent a potential mechanism underlying the comorbidity of obesity and OSA. Anti-inflammatory therapy emerges as a potential therapeutic approach for weight management and the mitigation of OSA-hypopnea.

This study presents a few limitations. PSG is regarded as the gold standard for diagnosing OSA. It can be coupled with electroencephalography to accurately determine actual sleep time and sleep cycles. In our research, a portable sleep apnea monitor was used, and while the three parameters we assessed demonstrated good consistency with PSG in diagnosing moderate-to-severe OSA[46,47], the use of PSG remains the most precise diagnostic tool. In addition, obese male patients were less likely to opt for bariatric surgery compared to obese female patients. Although we collected data spanning 2 years, the sample size remained relatively small. Further expansion of the sample size is essential to attain more accurate results.

5. Conclusion

In summary, depressive disorders are associated with the severity of OSA and left hypothalamic inflammation in obese young men. Notably, left hypothalamic inflammation exhibits a positive correlation with the severity of OSA, which suggests that left hypothalamic inflammation may be the underlying mechanism of OSA in obese young patients with depressive disorders.

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Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interests in the subject matter or materials discussed in this manuscript.

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Writing – original draft: All authors
Writing – review and editing: All authors

Ethics approval and consent to participate

All procedures involving human participants performed in this study were in accordance with the ethical standards of the Institutional Ethics Committees of the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University (2020KY204-01) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2100052438). Informed consent was obtained from all study participants.

Consent for publication

Informed consent was obtained from all study subjects.

Availability of data

The datasets generated during the present study are available from the corresponding author on reasonable request.

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ORIGINAL RESEARCH ARTICLE

Exploring the sociocultural perception of post-traumatic stress disorder in Ghana

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Abstract

Post-traumatic stress disorder (PTSD) is one of the significant public mental health concerns globally. While Western medical and psychological models dominate in the etiological explanations and treatments of this disorder, alternative interpretations and treatments stemming from health belief model are available in specific cultural contexts such as Ghana. In this exploratory research, a total of 28 participants including 20 PTSD survivors from Accra and Pantang Psychiatric Hospitals and eight culturally informed individuals from Ashaiman, Nima, and Afienya were enrolled for interviews and focus group discussions. The purposive and snowball sampling methods were used. The results showed that participants generally perceived the cause and symptoms of PTSD as spiritual, and most of them had sought herbal and spiritual relief if afflicted with PTSD symptoms. In summary, cultural factors should be considered in the therapeutic management of PTSD by integrating traditional approaches with Western medical and psychological approaches.

Keywords: Sociocultural; Ghana; Western-based medicine; Health belief model; Herbospiritual beliefs; Post-traumatic stress disorder

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1. Introduction

Post-traumatic stress disorder (PTSD) is a serious mental health condition that contributes 4% of the world's global burden of disease[1]. PTSD is likely to develop in individuals having been exposed to traumatic events, such as violence, loss, threats of death, rape, abduction, physical and sexual abuse, accidents, and natural disasters[2,3]. Based on the fifth edition of Diagnostic and Statistical Manual (DSM-5), the symptoms of PTSD include disturbing thoughts, feelings, dreams related to traumatic events, mental or physical distress to trauma-related cues, attempts to avoid trauma-related cues, alterations in the way a person thinks and feels, and an increase in the fight-or-flight response[4]. When these symptoms persist for more than a month in an individual after the traumatic event, he or she may be diagnosed with PTSD, which affects the quality of life[4].

The prevalence of traumatic events varies from region to region, reflecting the differences in cultural, political, and historical factors[5]. Although the prevalence of traumatic events in low- and middle-income countries remains unknown, it is recognized that factors such as poverty, armed or political conflict, resource deficits, and shortage of

trained health-care professionals could contribute to higher rates of PTSD compared to developed countries[6-8]. Given this situation, cultural contexts are commonly adopted in the etiological interpretations of mental illnesses, which also influence the subsequent treatment. However, Western medical models have established a dominant role in the etiological interpretations and treatments of mental illnesses, sometimes overshadowing other perspectives within the mental health-care system of these countries[9]. This is typified by the phenomenon that most mental illnesses including PTSD are formally diagnosed and treated by Western-trained experts in Africa, particularly Ghana, and the diagnosed patients are pharmacotherapy and psychotherapy. Meanwhile, the health belief model suggests that people's beliefs and perceptions about health and illness determine their health-seeking behaviors[10]. According to this model, people's core beliefs often develop from their culture, traditions, and socialization, which may influence their interpretations of illness and inform their health-seeking behaviors. While the Western approach to treating mental illness is effective, the culturally derived perceptions and modalities of treatment must not be neglected in treatment planning.

A Ghanaian study has found that herbospiritual beliefs and interpretations have a strong influence on how the local population respond to health issues, including mental health problems[11]. It is such beliefs that have led to the thriving of herbal medicine practice in Ghana as well as the continuous growth of spiritual healers and soothsayers on the Ghanaian health scene[12,13]. Despite the increasing media reports and research on the negative outcomes for patients over the years, these practices still continue to grow[13]. In this regard, more efforts should be invested to investigate the perceived cause and symptoms of PTSD, generate empirical evidence regarding how belief systems shape PTSD interpretations and responses within the Ghanaian context, and devise effective interventions.

2. Materials and methods

2.1. Study design

The interpretivist paradigm is the philosophy that undergirded this study. The qualitative research approach and exploratory design were adopted to deepen our understanding of PTSD symptoms and response methods from the participants' perspectives[14].

2.2. Study area

This study was conducted in the Greater Accra region of Ghana. Specifically, the study participants were recruited from Accra and Pantang Psychiatric Hospitals as well as Nima, Ashaiman, and Afienya communities.

2.3. Study population

In this study, we investigated two groups of individuals. The first group consists of individuals who have been clinically diagnosed with PTSD by a professional psychiatrist using the DSM-5 criteria and who were receiving treatments (medication and psychotherapy sessions as well as traditional means) at the Accra and Pantang Psychiatric Hospitals. The other group consists of culturally informed individuals in Ashaiman, Nima, and Afienya.

2.4. Inclusion and exclusion criteria

The study included individuals diagnosed with PTSD who have been receiving Western treatment for 3 months and more. This was to ensure that the participants, who had been treated or was still under treatment, would not fall prey to secondary traumatic distress during the interview. On the other hand, a culturally informed individual was an individual aged 18 years and above who lived in either one of the Ashaiman, Nima, and Afienya communities for a decade or more.

2.5. Sampling procedure

The ideal sample size for a qualitative study ranges from 5 to 25, taking into consideration data saturation (a methodological principle where based on the data collected, further data collection is not necessary)[15]. In this study, 20 individuals diagnosed with PTSD and who have been receiving treatment from the Accra and Pantang Psychiatric Hospitals and eight culturally informed individuals were recruited in this study.

2.6. Data collection procedure

Data were collected from respondents within a period of 6 weeks. With the help of the hospital staff, individuals who met the criteria for PTSD group were interviewed using a semi-structured interview guide. The culturally informed individuals were identified with the help of community gate keepers and using vignettes. Focus group discussions were conducted to interview the recruited subjects. The discussions were held for two groups, each consisting of four people. Responses were recorded for transcription using an audio recorder.

2.7. Data collection instrument

A semi-structured interview guide developed by the researchers was used to probe participants' experiences with PTSD to understand the participants' precise symptoms, their subjective interpretations of the events, and their preferred treatments. The questions in the interview guide are given in the following:

(i) What was your exact traumatic experience?
(ii) What are the unusual behaviors you experienced after the incident?

(iii) How did you overcome the symptoms after your experience?
(iv) Were there any specific cultural practices and traditional belief systems that you adopted to help you overcome your unusual experience following the incident?

Furthermore, a vignette that depicts a traumatic event which occurred in Ghana on March 7, 2021, was used to trigger discussions in the focus groups. In that event, several young children drowned at the beach in the Ghanaian town of Apam. The vignette outlined a scenario of a woman who lost her only teenage son during that incident. The woman experienced symptoms such as anxiety, flashbacks, recurrent stressful dreams, and distressing thought patterns. Participants were asked to interpret their understanding of the event and specifically suggest culturally inclined treatments that could help in eliminating the symptoms. The questions that followed the guide to enhance the group discussions are as follow:

(i). From your cultural worldview, what caused the drowning incident?
(ii). Where are the woman's symptoms coming from?
(iii). Considering your cultural practices, what should the woman do to reduce or completely deal with the unusual behaviors?

2.8. Data analysis

Thematic network analysis, which is a six-step process, was utilized in this study for data analysis[16]. After familiarizing with the data collected, we generated the initial codes (evil spirits, imam bible, *Momordica charantia*). Using these codes, the subsequent themes were generated. They were reviewed and a report containing thematic maps was generated. In developing the initial codes, sections that were related to the objectives of the study were identified. To enhance the credibility of the study, the researchers used independent coders throughout the coding stage. The researchers and independent coders continually peer checked to refine the codes before developing themes by merging the codes. During this process, codes developed from the interviews and focus group discussions were compared to identify commonalities and distinctive features to find cluster of themes.

Trustworthiness of the data was ensured through data triangulation using the interviews and focus group discussions. In several instances where a few participants provided information in the Akan language, the interviews were transcribed and translated by the researchers who are also the native speakers of Akan before coding began.

3. Results

3.1. Sociodemographic characteristics of participants

All 28 participants were Ghanaians ages 20 – 74 years. Table 1 depicts the sociodemographic characteristics of participants. All 20 individuals with PTSD were arranged to participate in the interviews while the eight culturally informed individuals were recruited to participate in the focus group discussions.

Among those diagnosed with PTSD, there were three university graduates, five undergraduate students, six senior high school students, and six who had informal education (and worked as shop attendants and petty traders). The university graduates' ages ranged between 34 and 42 years old. Three of the university undergraduate students were 20 years old and the other two were 23 years old. The senior high school students were between 21 and 48 years old and the ages of the individuals who had informal education ranged between 37 and 62 years old. Fifteen participants considered themselves Christians, while two and three participants associated more with Islam and traditional religion, respectively. There were 13 women and seven men in the PTSD group.

A second group of eight culturally informed participants were recruited to participate in focus group discussions for the study. It consists of four males and four females. Three of these participants were university graduates and the other five had informal education. These participants aged between 28 and 74. Four participants were Christians, two were Muslims, and the remaining two were more inclined to the traditional religion. The graduate participants in this group worked as teachers in reputable institutions in

Table 1. Sociodemographic characteristics of participants

Sociodemographic characteristic	Interview (n=20)	Focus group discussion (n=8)
Age range	20 – 74 years	28 – 74 years
Education Level	3 university graduates 5 undergraduates 6 high school graduates 6 informal education students	3 university graduates 5 informal education students
Occupation	University students High school graduates Shop attendants Petty traders	3 teachers 5 traders
Religious affiliation	15 Christians 2 Muslims 3 traditionalists	4 Christians 2 Muslims 2 traditionalists
Gender	13 females 7 males	4 females 4 males

Ghana, whereas the remaining participants were traders in their localities. All eight participants selected for this study demonstrated high knowledge of normed practices within their cultural contexts and responded to questions from a cultural viewpoint. Two of these participants were gatekeepers of two of the local communities from where they were recruited, and they assisted with participant selection within their communities.

The results of the study provide insight into the sociocultural perceptions of and responses to PTSD that were shared by the participants during the interviews and focus group discussions. Participants for the interviews had experienced events such as the death of a loved one, maiming from vehicular accidents and terminal illness. Participants seemed to believe in herbal and spiritual approaches in treating the symptoms of PTSD even though they were also seeing psychiatrists and psychologists in the hospitals from where they were recruited.

Themes generated from the interview data centered on (i) spiritual interpretations of the traumatic event, (ii) spiritual interpretations of symptoms of PTSD, (iii) spiritual responses to symptoms of PTSD, and (iv) herbal responses to symptoms of PTSD.

3.2. Spiritual interpretations of the traumatic event

The subthemes generated for spiritual interpretations were evil spirits and curses. Almost all participants seemed to believe that evil spirits were behind the traumatic event. Participants explained that these spirits have powers superseding the understanding and control of humans and manipulate human destiny. One participant revealed that "*My car accident for example is clearly caused by evil spirits because the other driver and I could see each other from the long distance… Evil spirits exist and you know they have powers stronger than humans'. When they set out to cause you harm, who can we blame this on?*"

Another respondent said, "*My wife's death is the work of the evil spirit. We have these spirits around us and they are so strong that they can cause danger to anyone. How can someone who just had her meal together with family in the evening and had a nice chat before going to bed be pronounced dead on arrival after a rapid admission to the hospital because of cough and headache?*"

In addition, participants mentioned curses as another cause of traumatic events. Some participants believed that when people are involved in a misunderstanding, one person could invoke curses by pleading with deities (gods of the sea or land) to inflict pain and trauma on the other person. An account provided by a participant was "*You see, our tongue is powerful and when you curse someone, it will happen if the person doesn't do anything about it. For my case, my husband was owing the person and because they had argument about the differences, the person got angry and said "asaase yaa" [, a curse originating in] his hometown [to] deal with my husband. My husband didn't take any action and here we are with his demise.*"

3.3. Spiritual interpretations of symptoms of PTSD

As part of the interpretations, all 20 participants believed that their symptoms had spiritual connotations. One participant said, "*Evils can cause some of these problems. The evil spirit can still haunt you in your sleep and still make you fear [for driving] car again, you think it is a joke? These evil spirits exist oo……. My fear for sitting in a car again was too much and also seeing accidents in my dreams makes me unable to sleep well.*"

One participant said, "*I knew my wife's illness is all spiritual. As long as the events were caused by spirits, they don't leave you until you get help to uproot the spirits totally… I am sad I did not go for help early to cure my wife so it makes me sad and I have sleepless nights and bad dreams as if some people are chasing [after] me.*"

3.4. Spiritual responses to symptoms of PTSD

Prayers and rituals were found as subthemes for responses to symptoms. Praying to a higher deity (God or Allah) was identified as a response to symptoms of PTSD. Ritual performance by traditional healers was also a response given by two participants. Participants' narratives suggested that symptoms with spiritual underpinnings could be battled through communication with supernatural forces, thus alleviating symptoms associated with PTSD. These beliefs were present in the narratives provided by three participants:

> "*… I prayed [several times] in my room and sometimes went to church to tell God about what I was going through and this helped me to sleep well and also have better dreams.*"
>
> "*My fear for sitting in a car again was too much and also seeing accidents in my dream was horrible so I was in the mosque almost every day to pray to Allah. In fact, praying is something I do every day and especially when I have problems so this is how I was able to gather the courage to sit in vehicles again.*"
>
> "*After the death of my daughter, I was informed that the spirit of the sea was at work so I had to visit a traditional healer to pour libation to pacify the god of the sea and ask our ancestors to protect my family from untimely death.*"

3.5. Herbal responses to symptoms of PTSD

The use of herbs was also a common response among all 20 interview participants. Particularly, the use of the plant

M. charantia was essential to healing among the participants from the southern part of Ghana (*i.e.*, Akan, Ga, and Ewe). Participants referred the plant to as "Nyannya," "Nyanyra," and "Kakla" in their local languages. The plant is also known with a local name "Morri" – which is literally translated as "grass" or "herbs" – among the Muslims for treating the symptoms of PTSD. All participants expressed that these plants are associated with spirits; therefore, it is vital to resort to using these herbs in the treatment since their symptoms have spiritual connotations.

One participant indicated that "*I knew those bad dreams and fear were all spiritual so I consulted a healer who performed some rituals for me [at] night and also asked me to put the "Nyanyra" in [bath] water and [take] bath at night.*"

Participant 4 also responded that "*Mostly when the event is traumatic, you are given a leaf called 'Morri' which you will drink and put some in your water to bath. When you do that, it drives all the evil spirits away. All I did was to go to the traditional healer [who] did certain rituals and also gave me the "morri." I could sleep and do my usual job after using the herbs.*"

Table 2 depicts the summarized main findings of this study.

4. Discussion

The study reveals the influential role of spiritual and herbal constructs in shaping cultural interpretations of trauma and preferred PTSD treatment in Ghana. The present study explored the perceived causes, symptoms, and preferred responses to PTSD among individuals in the Ghanaian cultural context. The findings highlight the sociocultural interpretations of traumatic events and responses to PTSD, focusing on the influence of spiritual and herbal factors.

The study revealed that participants attributed traumatic events to spiritual causes, specifically evil spirits and curses. This finding aligns with the previous studies in Ghana indicating the huge implication of treating supernatural forces as the cause of mental illnesses, including PTSD[12,17]. These studies found that Ghanaians are typically people who attribute mental illness to lesser spirits that are evil. Furthermore, participants emphasized that these spiritual forces possess powers beyond human control, which shaped their interpretation of traumatic events and their consequences[18]. Our study showed that interpersonal conflicts, such as those instigated by enemies or rivals, can create opportunities for curses to manifest, potentially leading to mental illness. These further exemplified how interpersonal conflicts contribute to traumatic experiences.

Table 2. Summary of main findings

Theme	Subthemes
Spiritual interpretations of the traumatic event	Evil spirits Curses
Spiritual interpretations of the symptoms of PTSD	Evil spirits
Spiritual responses to symptoms of PTSD	Prayers Rituals
Herbal responses to symptoms to PTSD	*M. charantia* and other herbs

Abbreviations: PTSD: Post-traumatic stress disorder; *M. charantia: Momordica charantia*

Furthermore, regarding the PTSD symptoms, all participants perceived symptoms as manifestations of evil spirit affliction. This reflects the tendencies in Ghanaian culture to view mental distress through a spiritual lens[12,17], highlighting the traditional perception of mental illness. Several studies have established an important framework under which the symptoms such as anxiety, flashbacks, and distressing thoughts are attributed to the influence of evil spirits. Given the significant influence of cultural aspect in the treatment of mental illnesses, incorporating approaches tailored to patients' spiritual beliefs as part of the therapeutic management of PTSD symptoms should be taken into consideration, given the cultural context of Ghana.

The preferred responses to PTSD symptoms are spiritual and herbal approaches. According to participants, praying to a higher deity, such as God and Allah, was a means of seeking relief. Furthermore, traditional healers were also sought for performing rituals and obtaining specific herbs. The herbs were specifically picked by the traditional healers who were perceived to have spiritual connections with the plants and could, therefore, determine which plant was useful to drive evil spirits away. The herbal responses were culturally grounded, with the plant *M. charantia* playing a significant role in healing. *M. charantia* has been proven to be effective in treating depression[19]. The involvement of traditional healers in prescribing herbs demonstrates that participants strongly believe that the herbs picked by herbalist are strong enough to heal them, further accentuating the significance of cultural practices and the integration of spiritual and medicinal elements in addressing PTSD symptoms[20].

These findings emphasize the significance of culturally informed approaches to treating mental illnesses in Ghana. At present, Western medical models dominate the etiological explanations and treatment approaches for PTSD worldwide[11]. However, this study revealed that such approaches may not fully resonate with the cultural beliefs and individual interpretations in Ghana. Consequently, neglecting culturally informed perceptions and treatment options may lead to a disconnect between health-care providers and the local population, potentially hindering

effective interventions. In other words, it is advisable to advocate the health belief model.

To promote effective interventions and to better address the needs of individuals with PTSD in Ghana, it is crucial to infuse cultural sensitivity into mental health practices. Mental health professionals working in this context should consider the spiritual and herbal dimensions of healing and explore ways to integrate these approaches with evidence-based treatments. Collaborating with traditional healers and incorporating traditional practices can help bridge the gap between Western medical models and local cultural beliefs.

Several limitations of this study should be acknowledged. The sample size was relatively small, and the findings may not be generalizable to the entire Ghanaian population. In addition, the study focused on one specific region of Ghana, limiting the understanding of regional variations in beliefs and responses to PTSD. Future research should aim for larger and more diverse samples to gain a comprehensive understanding of cultural perspectives on PTSD across different regions and populations in Ghana.

5. Conclusion

This study highlights the crucial significance of considering cultural factors when addressing PTSD in the Ghanaian context. We found that spiritual causes are commonly blamed for traumatic experiences, and individuals often interpret PTSD symptoms through a spiritual lens. Our findings also revealed that spiritual and herbal approaches are the preferred responses to PTSD, emphasizing the importance of integrating cultural beliefs into mental health practices.

Overall, this study underscores the need for culturally sensitive interventions in the management of PTSD. The interventions can be tailored by incorporating cultural perspectives into mental health practices to meet the specific needs of the Ghanaian population, with the aim of improving patient outcomes and enhancing overall well-being. Central to the idea of recognizing and respecting the spiritual and cultural beliefs of individuals in the provision of comprehensive care and support, there is a need for advocating the integration of culturally sensitive practices that are practiced across the world, not only in Ghana but also in other indigenous and aboriginal areas, into mental illness treatments.

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Conflict of interest

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Author contributions

Conceptualization: Sandra Thompson-Assan
Investigation: Sandra Thompson-Assan
Methodology: Sandra Thompson-Assan
Formal analysis: Sandra Thompson-Assan
Writing – original draft: Sandra Thompson-Assan
Writing – review & editing: Derrick Kakraba Kaitoo, Gloria Ayebea Aguadze

Ethics approval and consent to participate

Ethical clearance form was submitted to the Research Ethics Committee (Human) (RECH) at Nelson Mandela University. Ethical approval (H18-HEA-PSY-011) was obtained before the commencement of the data collection. Both written and verbal permission was obtained from each of the subjects before participation in the study.

Consent for publication

Both written and verbal permission was obtained from each of the subjects to publish their data, and effort has been made by the authors to conceal any identifying information of the participants that appear in the paper.

Availability of data

The audio recorded, or transcribed data collected can be obtained from the corresponding author following formal request.

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ORIGINAL RESEARCH ARTICLE

Evolving or unchanged? Investigating perceptual profiles over time in psychosis and comparing with healthy controls

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Abstract

There is a growing body of evidence indicating altered perceptual profiles in psychosis, which can be assessed by evaluating exteroceptive (e.g., auditory and visual) and interoceptive (e.g., heartbeat and breathing) sensory processing through self-administered questionnaires. However, the unexplored question remains whether perceptual alterations depend on the phase of illness. In this observational, STROBE-compliant study, we adopted the Multidimensional Assessment of Interoceptive Awareness (MAIA; eight domains), Adult/Adolescent Sensory Profile (AASP; four domains), and Positive and Negative Symptoms Scale (PANSS) to measure interoception, exteroception, and symptom severity, respectively. Our primary aim was to compare MAIA, AASP, and PANSS differences in patients with psychosis (PSY patients) between post-acute (PSY-T1) and remission phases (PSY-T2). Student's *t*-tests or Wilcoxon paired-sample tests were used based on the variable distribution. MAIA/AASP data were also collected from healthy controls (HCs). As a secondary aim, we examined MAIA/AASP differences between PSY-T1/T2 and HC using MANOVA and Mann–Whitney tests. Bonferroni–Holm correction was implemented. Data were collected from 23 PSY patients (55% females; mean age: 38.35 ± 12.46 years) and 210 HC (46% females; mean age: 39.81 ± 13.78 years). No differences were found between PSY-T1 and PSY-T2 (Bonferroni–Holm $P > 0.05$) for MAIA/AASP scores, while PANSS total and positive scores were higher in PSY-T1 compared to PSY-T2, with Bonferroni–Holm *p*-values of 0.032 and 0.045, respectively. Although MAIA/AASP domains (noticing/body listening and low registration) were increased in PSY-T1 compared to HC, no differences were observed between PSY-T2 and HC. The heterogeneous results in the literature regarding perceptual profiles should be contextualized by considering that fluctuations in patients with psychosis can become significant when compared to the general population.

Keywords: Sensory processing; Psychosis; Schizophrenia; Sensory profile

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1. Introduction

Perception serves as the backdrop of every experience we have of the world[1]. Each second, we integrate a multitude of sensory stimuli originating from both our internal body and the external environment, translating them into conscious perceptions. These processes are fundamental for generating a stable sense of self, an inherent feeling of unity that allows us to perceive ourselves as unique individuals distinct from the surrounding world[2]. In essence, through the cohesive integration of diverse stimuli, we establish clear boundaries between our self and non-self. This awareness allows us to recognize ourselves as something different from the objects we perceive. In this context, it becomes impossible to disentangle the concept of self and perception, as these two psychological constructs are deeply intertwined.

Understanding the relationship between perception and the self becomes even more complex when considering mental disorders, specifically psychosis. On the one hand, phenomenological psychopathology has pointed out that schizophrenia and psychotic disorders, in general, are characterized by an impaired sense of the basic self, which mediates the pre-reflective experience of reality[3]. On the other hand, perceptual abnormalities, such as hallucinations, are among the core symptoms of the psychosis spectrum[4,5]. However, the pathways through which alterations in perception and self are intertwined in the pathogenesis of psychotic symptoms remain largely unknown[6,7]. In light of the growing interest in this field, preliminary evidence from behavioral tasks suggests that individuals with psychosis exhibit impaired sensory profiles compared to the general population[8,9]. In psychosis, sensory channels undergo dissociation, eroding the connections between the internal and external worlds, thus giving rise to incoherent and paradoxical multisensory experiences[10]. This state is termed "perceptual incoherence," and certain authors propose that, to mitigate or resolve it, the brain might produce incongruent mental contents or altered sensory experiences (i.e., delusions and hallucinations)[11]. These observations are in line with the phenomenological description of *Wahnstimmung* experiences, which are characterized by the overlapping of perceptual stimuli felt as significant. However, if everything is significant, then nothing is significant, ending up in the loss of significance of the world and the delusional restructuring of experiences[12,13]. In line with these theories, it has been postulated that auditory hallucinations result from distorted sensory perceptions[14]. Other authors identified the heightened or disorganized perception of stimuli as the process responsible for attentive dysregulations in noisy environments and filtering deficits of the less relevant stimuli[15]. In summary, an increasing amount of evidence suggests that individuals with psychosis exhibit perceptual and self-disturbances compared to the general population. The intensity of these alterations varies inversely with treatment responsiveness and directly with symptom severity[16]. This insight has potentially relevant clinical implications, as perceptual alterations could provide a starting point for a deeper understanding of psychotic-like experiences and even become a future therapeutic target.

Perceptual disorders can also be identified during high-risk states preceding the first psychotic episode[17]. Therefore, it is crucial to ascertain whether perceptual alterations remain consistent over time or are linked to the phase of illness. This understanding is pivotal not only for validating the theoretical underpinnings of perceptual and self-related disturbances in psychosis but also from a clinical standpoint. In fact, understanding specific perceptual dysfunctions and their dynamics could help develop specific markers and allow the early identification of vulnerability traits. Nevertheless, the literature on this topic is very limited to date. This limitation is also due to the lack of specific means of investigation that has garnered consensus within the scientific community and been validated in clinical practice. Perceptual profiles are often evaluated with self-administered questionnaires that find extensive use in the general population[18,19]. More specifically, the Multidimensional Assessment of Interoceptive Awareness (MAIA)[20] is among the most utilized self-questionnaires for assessing the perception of internal bodily states (i.e., interoception). Conversely, the Adolescent/Adult Sensory Profile (AASP)[8] is a validated approach for evaluating external sensory processing (i.e., exteroception). Although these questionnaires are not typically integrated into routine clinical evaluations conducted in psychiatric settings, they could prove highly valuable for psychiatric patients, offering a meaningful marker of their subjective experiences[21].

Building upon the abovementioned premises, our study aimed to use MAIA and AASP to measure perceptual profiles in a group of 23 patients with psychosis (PSY patients) in the post-acute and remission phases of illness (PSY-T1 and PSY-T2, respectively). Due to the high stability of perceptual profile scores in the general population[18,22,23], we hypothesized that perceptual profiles would be more related to a vulnerability trait rather than linked to the active phase of illness. To enhance the reliability of our findings, we also compared patients' perceptual profiles in the two different phases of illness to those of 210 healthy

controls (HCs). We expected to observe stable differences (or similarities) in perceptual profiles when comparing PSY-T1 with HC and, likewise, when comparing PSY-T2 with HC.

2. Methods

2.1. Study design

We performed a monocentric observational longitudinal study that adhered to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines[24]. In compliance with the Declaration of Helsinki, our research received approval from the local ethical committee of the IRCCS Policlinico San Matteo (Pavia, Italy) under protocol number 20210003663. Each participant was informed of the study's purposes and provided written informed consent in accordance with their legal civilian capabilities.

2.2. Participants

We recruited 23 PSY patients who were admitted to the Acute Psychiatric Inpatient Unit of ASST Pavia at IRCCS Policlinico San Matteo in Pavia, Italy, between May 1st, 2021 and May 1st, 2022. The sampling procedure used was convenience based; the study was proposed to all the patients hospitalized during the indicated period who met the inclusion and exclusion criteria. Those who agreed to participate were enrolled in the study. Inclusion criteria encompassed age between 18 and 65, a DSM-5 diagnosis of psychotic disorder (including schizophrenia, other psychotic disorders, psychosis due to substance use, and psychosis not otherwise specified), or unipolar/bipolar mood disorder with psychotic symptoms, fluency in Italian, and the ability to sign a written informed consent. Exclusion criteria included comorbid neurological disorders that may be the primary cause of psychotic symptoms, intellectual disability, and any permanent condition potentially impairing sensory processing (i.e., blindness, deafness, major motor concerns, dysgeusia, and anosmia). Evaluations were carried out by trained medical doctors, and all diagnoses were confirmed by two psychiatrists according to DSM-5 criteria. We also collected data from 210 HC selected from the general population. Inclusion criteria for HC were age between 18 and 65, fluency in Italian, and the ability to sign a written informed consent. Exclusion criteria encompassed being diagnosed with a psychiatric disorder and/or intellectual disability, use of psychoactive substances within 1 month before test submission, and any permanent condition potentially impairing sensory processing (i.e., blindness, deafness, major motor concerns, dysgeusia, and anosmia). Furthermore, patients subject to a legal guardianship measure were preventively excluded from the study.

2.3. Study protocol

For PSY patients, the first evaluation was conducted within 48 h of admission to the Acute Psychiatric Inpatient Unit (T0, acute phase), during which the Positive and Negative Syndrome Scale (PANSS)[25] was administered and scored by a trained medical doctor. Perceptual profiles (MAIA and AASP) were not collected at this time point due to the potentially excessive distress their administration could have caused to participants. The second evaluation (T1, post-acute phase) took place at discharge. Patients were re-evaluated using PANSS, and the MAIA and AASP questionnaires were administered[20] to assess interoceptive and exteroceptive profiles, respectively. Demographic variables, including age, gender, DSM-5 diagnosis, illness duration, mean antipsychotic dosage (olanzapine equivalents)[26], mean antidepressant dose (fluoxetine equivalents)[27], and mean benzodiazepine dose (diazepam equivalents)[28], were collected at this time point. The final assessment (T2) was performed 6 – 12 weeks after discharge and involved the same tests administered at T1. The timing of assessment at T2 varied, as participants needed to be free from active symptoms that would require hospitalization. In the present study, remission was defined not solely as the absence of symptom s but rather as the absence of an acute psychotic phase. HCs were administered only the AASP and MAIA questionnaires at a single time point.

2.4. Measurements of outcomes

The MAIA is an instrument designed to evaluate subjective sensitivity toward inner body sensations. It consists of 32 items scored according to the frequency of each behavior, with "0" indicating "never" and "5" indicating "always." These items are grouped into eight subscales: "Noticing," "Not distracting," "Not worrying," "Attention regulation," "Emotional awareness," "Self-regulation," "Body listening," and "Trusting." In addition to its application in psychosis[29,30], the MAIA questionnaire has been used in various psychiatric conditions, such as autism, eating disorders, depression, and other disorders involving interoception, such as chronic pain syndrome, fibromyalgia, and low back pain[20,22,31-36].

The AASP is an evaluation scale designed to measure individual responses to sensory experiences encountered in everyday life. Participants were asked to indicate the frequency with which they adopt specific behaviors, ranging from rarely (5% or less of the time) to very frequently (95% or more of the time). The AASP scale consists of 60 items subdivided into four major categories that evaluate specific responses to sensory stimuli. The "Sensory sensitivity" and "Low regulation" subscales evaluate the passive sensory

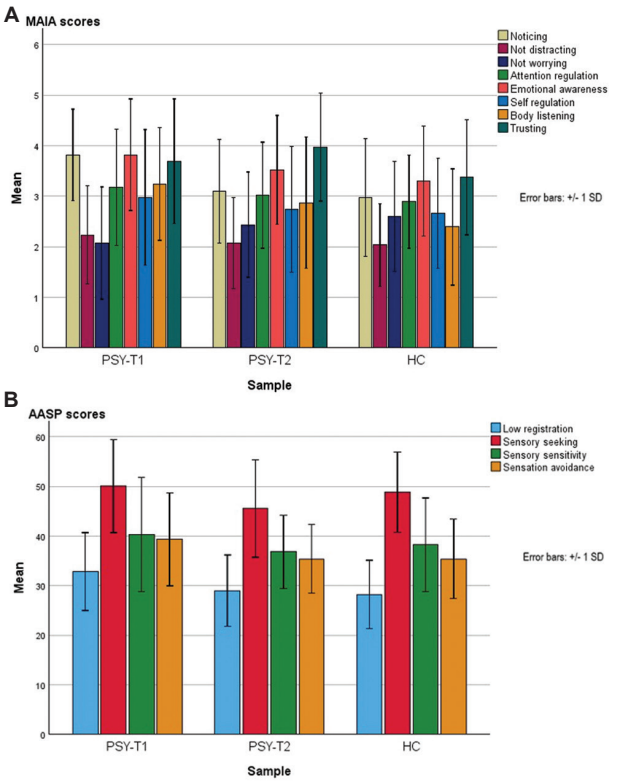

Figure 1. Barplots displaying differences between patients with psychosis in the post-acute phase (PSY-T1), remission phase (PSY-T2), and healthy controls (HC). (A) Differences in interoception (MAIA scores). (B) Differences in exteroception (AASP scores). Error bars: ±1 SD.
Abbreviations: AASP: Adult/Adolescent sensory profile; MAIA: Multidimensional Assessment of interoceptive awareness; SD: Standard deviation.

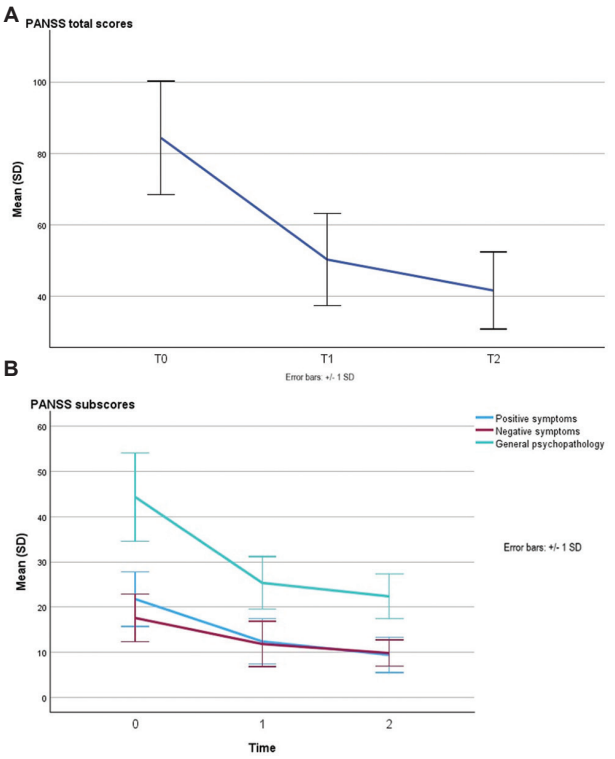

Figure 2. Graphs depicting PANSS scores at T0, T1, and T2 time points that correspond to acute, post-acute, and remission phases, respectively. (A) PANSS total score. (B) PANSS subscores. Error bars = ±1 SD.
Abbreviations: PANSS: Positive and Negative Symptoms Scale; SD: Standard deviation.

response to stimuli. Higher scores in "Sensory sensitivity" suggest hypersensitivity and a more intense reactivity to stimuli, while "Low regulation" scores are proportional to reduced detection or response to less noticeable stimuli. Conversely, "Sensation avoidance" and "Sensory seeking" subscales examine the active behavior adopted by the participant toward sensory experiences.

The PANSS is a 30-item semi-structured interview administered by the clinician to quantify symptom severity in patients affected by schizophrenia and other psychotic disorders. Clinicians assign a score from 1 to 7 for each item ("1" being "absent," "2" for "minimal," "3" for "mild," "4" for "moderate," "5" for "moderate-severe," "6" for "severe," and "7" for "extreme"). These items are generally grouped into three subscales. The "Positive symptoms" subscale reflects an excess or distortion of typical psychological processes. Examples include hallucinations, delusions, disorganized thinking, and odd behavior. The "Negative symptoms" subscale evaluates symptoms associated with a reduction or loss of normal functioning, including blunted affect, reduced emotional expression, social withdrawal, lack of motivation, and poor speech. The "General psychopathology" subscale assesses non-psychotic symptoms, including anxiety, depression, and cognitive impairment.

2.5. Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 28.0). As a first step, descriptive analyses were performed for all participants, which encompassed 23 PSY patients and 210 HC matched for age and gender.

Regarding the primary outcome, comparisons were made for MAIA, AASP, and PANSS subscales between patients at T1 and T2 to evaluate changes in interoceptive, exteroceptive, and symptomatic dimensions associated with the clinical phases of psychosis. Specifically, T1 represented the post-acute phase, and T2 represented the remission phase. As the normal distribution of the sample was not confirmed for PANSS and certain MAIA subscores ("Attention regulation" and "Noticing"), the Wilcoxon signed-rank test for paired samples was used to compare

these items at T1 and T2[37]. Differences between the two time points in the remaining MAIA and AASP domains were compared using a paired Student's *t*-test[38].

As a secondary outcome, we compared MAIA and AASP scores between PSY patients and HC at PSY-T1 and PSY-T2 to examine the consistency of group differences across both time points. MANOVA was used to compare the two groups[39]. Significantly different comparisons from MANOVA were further analyzed using the Mann–Whitney non-parametric test[40] due to violated normality assumptions in the HC group.

For completeness, results were reported at both the uncorrected $P \leq 0.05$ level and the multiple comparisons adjusted threshold of Bonferroni–Holm $P \leq 0.05$[41].

3. Results

The demographic characteristics of the study groups are shown in Table 1. Concerning within-group comparisons in the PSY patient group, none of the MAIA or AASP scores at T2 showed statistically significant differences from T1 (all uncorrected $P > 0.05$) (Table 2). Conversely, the PANSS total score ($P = 0.002$, Bonferroni–Holm $P = 0.032$) and "Positive symptoms" subscores ($P = 0.003$, Bonferroni–Holm $P = 0.045$) were reduced at T2 compared to T1 (Figure 1). "Negative symptoms" and "General psychopathology" subscores also exhibited trends of improvement ("Negative symptoms": $P = 0.037$, Bonferroni–Holm $P > 0.05$; "General psychopathology": $P = 0.009$, Bonferroni–Holm $P > 0.05$), suggesting greater variations in clinical symptoms compared to perceptual profiles.

Concerning the secondary analysis, i.e., comparisons between the PSY patient and HC groups (Figure 2), the MANOVA demonstrated statistically significant differences at T1 but not at T2 (Table 3). Based on the MANOVA analysis, Mann–Whitney U-tests were performed to compare PSY-T1 and HC (Table 4). Regarding MAIA subscores, "Body listening" ($p < 0.001$, Bonferroni–Holm $P = 0.011$) and "Noticing" ($P < 0.001$, Bonferroni–Holm $P = 0.012$) were increased in PSY-T1 compared to HC. "Emotional awareness" ($P = 0.017$, Bonferroni–Holm $P > 0.05$; PSY-T1 > HC) and "Not worrying" ($P = 0.019$, Bonferroni–Holm $P > 0.05$; HC > PSY-T1) also exhibited trends that did not survive the correction for multiple comparisons. Regarding AASP scores, increased "Low regulation" scores in PSY-T1 compared to HC exhibited borderline significance after correction for multiple comparisons ($P = 0.005$, Bonferroni–Holm $P = 0.050$).

4. Discussion

This study is the first to assess the stability of self-measured interoceptive and exteroceptive indexes in psychosis at different time points. Our results demonstrate that perceptual profiles in participants with psychosis are more stable over time compared to symptom severity from the post-acute to the remission phase. However, while perceptual profiles were stable when considered within the patient group, this stability was less evident in the comparison with the HC group.

Considering that psychosis is characterized by acute, intermittent phases, the fluctuations in perceptual indexes displayed by patients suggest the presence of two major components. The first one is a trait perceptual feature that persists through time. All the perceptual scores that did not show differences either at T1 or T2 followed this

Table 1. Demographic characteristics of patients with psychosis in this study

Demographic characteristics	PSY patients (N=23)		HC (N=210)
	PSY-T1	PSY-T2	
Age (mean [SD], years)	38.35 (12.46)		39.81 (13.78)
Female (*n* [%])	13 (55.5)		100 (46.70)
Diagnosis (*n* [%])			
Non-affective psychosis (*n* [%])	9 (39.2)		/
Affective psychosis (*n* [%])	11 (47.8)		/
Substance-induced psychosis (*n* [%])	3 (13.0)		/
Duration of illness (mean [SD], days)	1648.87 (2525.16)		/
Antipsychotic dosage (olanzapine equivalents) (mean [SD], mg/day)	20.38 (6.58)		/
Antidepressant dosage (fluoxetine equivalents) (mean [SD], mg/day)	2.51 (6.64)		/
Benzodiazepine dosage (diazepam equivalents) (mean [SD], mg/day)	5.05 (6.12)		/
PANSS total at T0 (acute phase) (mean [SD])	83.73 (15.73)		/

Abbreviations: HC: Health controls; PANSS: Positive and Negative Symptoms Scale; PSY patients: Patients with psychosis; PSY-T1: Scores of patients with psychosis during post-acute phase; PSY-T2: Scores of patients with psychosis during remission phase; SD: Standard deviation.

Table 2. Pairwise comparisons of MAIA, AASP, and PANSS scores among patients with psychosis during the post-acute phase (PSY-T1), the remission phase (PSY-T2), and healthy controls (HC)

Variable	PSY-T1 (mean±SD)	PSY-T2 (mean±SD)	Paired *t*-test (t)	Wilcoxon test (W)	*P*-value	Bonferroni–Holm *P*-value
MAIA						
Noticing	3.82±0.91	3.10±1.02		2.995	0.014*	0.167
Not distracting	2.23±0.97	2.07±0.90	0.641		0.528	1.105
Not worrying	2.07±1.11	2.43±1.04	−1.417		0.171	1.071
Attention regulation	3.17±1.15	3.02±1.05		0.766	0.444	1.105
Emotional awareness	3.82±1.10	3.52±1.07	1.182		0.250	1.105
Self-regulation	2.98±1.34	2.74±1.24	1.158		0.259	1.105
Body listening	3.24±1.11	2.87±1.30	1.260		0.221	1.105
Trusting	3.70±1.23	3.97±1.07		-1.336	0.181	1.105
AASP						
Low regulation	32.83±7.84	28.96±7.20	2.469		0.022*	0.264
Sensory seeking	50.04±9.35	45.57±9.86	2.359		0.028*	0.308
Sensory sensitivity	40.30±11.48	36.83±7.37	1.882		0.073	0.639
Sensation avoidance	39.35±9.36	35.39±6.94	1.898		0.071	0.639
PANSS						
Total	50.32±12.61	41.59±10.54		3.043	0.002*	0.032*
Positive symptoms	12.64±4.99	9.41±3.89		2.988	0.003*	0.045*
Negative symptoms	12.05±5.03	9.82±2.92		1.972	0.049*	0.490
General psychopathology	25.64±5.78	22.36±4.98		2.792	0.005*	0.070

Note: *$P \leq 0.05$.
Abbreviations: AASP: Adult/Adolescent Sensory Profile; MAIA: Multidimensional Assessment of Interoceptive Awareness; PANSS: Positive and Negative Symptoms Scale; SD: standard deviation.

Table 3. MANOVA testing potential differences in MAIA and AASP scores between healthy controls (HC) and patients with psychosis at the post-acute (PSY-T1) and remission (PSY-T2) phases

MANOVA groups	Pillai's trace value	*F*	*P*
PSY-T1 versus HC	0.140	3.031	<0.001
PSY-T2 versus HC	0.81	1.642	0.081

Note: *$P \leq 0.05$.

pattern. The second one is a state perceptual feature that may be more related to active phases of the psychotic disorder. In fact, while "Noticing," "Body-listening," and "Low regulation" were higher in PSY patients compared to HC during the post-acute phase, these values returned to normal levels during the remission phase.

4.1. Interoception and psychosis

Within the context of MAIA (Figure 1), higher scores in the general population should align with increased interoceptive sensibility. While this holds true for HC, no studies are available for psychosis, and mixed trends have been observed for patients with schizophrenia. Considering the existing literature, only two studies have investigated MAIA differences between patients diagnosed with schizophrenia and HC. Torregrossa *et al.*[30] identified increased "Not distracting" but reduced "Attention regulation," "Not worrying," and "Trusting" scores in patients with schizophrenia compared to healthy individuals. No difference in "Body listening," "Emotional awareness," "Noticing," and "Self-regulation" scores was found. Conversely, Koreki *et al.* reported higher scores of "Noticing" and lower scores of "Not distracting" in patients compared to HC[29].

Considering this scarce and contrasting evidence, the comparison of our findings with existing ones becomes complex. It is important to specify that the "Noticing" domain refers to the general "*awareness of uncomfortable, comfortable, and neutral body sensations*." "Noticing" implies being aware that these sensations exist but does not imply a deliberate effort to pay close attention to them[20]. This heightened, passive sensibility could be seen as a maladaptive defense by which patients tend to rely on their internal thoughts and perceptions more than on the external reality[42]. Similar to Koreki *et al.*, we also

Table 4. *Post hoc* pairwise comparisons between HC and PSY-T1 performed after the significant MANOVA results for these two groups

Variable	PSY-T1 (mean±SD)	HC (mean±SD)	Mann–Whitney U	*P*-value	Bonferroni–Holm *P*-value
AASP					
Low regulation	32.83±7.84	28.22±6.90	3343.0	0.005*	0.05*
Sensory seeking	50.04±9.35	48.87±8.06	2643.5	0.559	1.152
Sensation seeking	40.30±11.48	38.26±11.48	2703.0	0.438	1.152
Sensation avoidance	39.35±9.36	35.37±8.02	3021.5	0.073	0.511
MAIA					
Noticing	3.82±0.91	2.97±1.17	3499.5	<0.001*	0.012*
Not distracting	2.23±0.97	2.04±0.81	2731.0	0.384	1.152
Not worrying	2.07±1.11	2.60±1.09	1730.5	0.019*	0.153
Attention regulation	3.17±1.15	2.89±0.92	2973.0	0.101	0.606
Emotional awareness	3.82±1.10	3.29±1.08	3208.0	0.017*	0.153
Self-regulation	2.98±1.34	2.66±1.09	2878.0	0.181	0.8
Body listening	3.24±1.11	2.39±1.15	3499.0	<0.001*	0.011*
Trusting	3.70±1.23	3.37±1.14	2897.5	0.160	0.8

Note: *$P \leq 0.05$.

Abbreviations: AASP: Adult/Adolescent Sensory Profile; HC: Health controls; MAIA: Multidimensional Assessment of Interoceptive Awareness; PSY-T1: Scores of patients with psychosis during post-acute phase; PSY-T2: Scores of patients with psychosis during remission phase; SD: Standard deviation.

found higher "Noticing" scores in PSY patients compared to HC but only during the post-acute phase. Thus, the inconsistent findings regarding heightened sensitivity to internal stimuli shown by patients might be attributed to the state feature of the perceptual profile. A similar pattern was observed for MAIA "Body listening" scores. The "Body listening" domain refers to the ability to actively pay attention to internal signals and sensations, such as heart rate, breathing, and muscle tension. It involves a deeper level of engagement with these sensations, where individuals actively tune in and listen to internal bodily sensations[20]. By integrating these considerations, we can conclude that awareness toward internal states is altered in both its passive and active components during the post-acute phase of psychosis, where symptoms are more pronounced.

4.2. Integrating interoception, exteroception, and psychosis

Contrary to our expectations, differences between PSY patients and HC in the "Low registration" domain were evident during the post-acute phase but not during remission. "Low regulation" refers to the tendency to overlook external sensory stimuli[8], a phenomenon well-documented in psychosis[21]. In this context, we observed that this reduced awareness or responsiveness to the external environment contrasts with the heightened interoceptive sensibility measured using the "Noticing" and "Body listening" scores. This imbalance indicates that individuals experiencing post-acute psychosis exhibit an intensified focus on internal cues at the expense of processing external sensory inputs. A consequence of this shift in attention is the disruption of the multisensory levels where perceptual cues are typically integrated[43]. The link between attributing an excessive valence to internal stimuli compared to external ones and psychotic symptoms holds an intuitive aspect. Hallucinations and delusions frequently stem from the ascription of aberrant salience to internal mental processes, overpowering the ostensibly "objective" external reality[44,45].

4.3. Beyond the present: perceptual disorders and self-continuity

In PSY patients, perceptual components that are more subject to change ("Noticing," Body listening," and " Low regulation") increase during the post-acute phase and tend to align with the values observed in the HC group during the remission phase. Interestingly, no interceptive/exteroceptive score shows differences in the opposite direction, that is, differences between PSY patients and HC during the remission phase but not during the post-acute phase. These initial results indicate that both interoceptive and exteroceptive scores tend to normalize during the remission phase. This phenomenon can be understood by considering that the impact of perceptual signals on the self is not only strong but also dynamic[46,47].

The metastable integration of various sensory modalities over time indeed contributes to the essential stability required for generating our implicit sense of self-continuity[48]. This stability is grasped through the absence of significant changes in perceptual indexes between PSY-T1 and PSY-T2. Although sensory indexes in psychosis displayed greater stability than symptoms, it was lower than those observed in the general population and other pervasive conditions, including autism[49]. Conversely, phasic, unpredictable changes in sensory or multisensory pathways may provide inconsistent references to higher-order mental processes, contributing to the generation of psychotic symptoms. Self-assessed interoceptive/exteroceptive scores may thus evaluate a transient state of disrupted perceptual processing rather than a trait of vulnerability to psychosis. A better understanding of the interplay between exteroception, interoception, and psychosis could help unravel the etiopathological mechanisms underlying perceptual alterations in this condition. On the one hand, the perceptual dimension could differentiate clinical subtypes of psychosis. On the other hand, the temporal fluctuations of perceptual scores suggest their potential use in measuring treatment outcomes or, more interestingly, in identifying treatments that are potentially specific for this dimension.

4.4. Limitations

Our study has some limitations to acknowledge. First of all, the limited sample size of the PSY patients allows us to elaborate only on preliminary, although novel, considerations. Furthermore, the HC group has a larger sample size compared to PSY patients, partially explaining why the PSY-T1/PSY-T2 differences are not statistically significant, although they exhibit a similar absolute magnitude to the PSY-T1/HC differences. As an additional limitation, the self-administered questionnaires explore the behavioral aspects of perceptual profiles. The administration of these questionnaires becomes notably challenging during the acute psychotic phase when hallucinations and delusions reach maximum severity, and more pronounced perceptual alterations may be observed. The administration of self-questionnaires to psychotic participants deserves particular attention. Although it is impossible to explore the individual perceptive experience through objective tests, the psychopathological conditions of the participants can obviously affect their ability to respond to the self-administered questionnaires. This may be the case with MAIA scores in our sample, where higher values are considered a positive index in the general population but were even more increased in PSY patients compared to HC. These differences may be due to a reduced insight in patients, as proposed by Koreki *et al.*[29]

These limitations, along with the promising findings observed in the present work, underscore the need for future longitudinal studies with larger samples. In addition, the incorporation of objective measures to complement the existing questionnaires for sensory processing is warranted.

5. Conclusion

The majority of perceptual indexes were stable in patients with psychosis, comparable to the scores observed in controls. In contrast, indexes assessing passive/active sensory attention revealed increased sensibility toward interoceptive stimuli and reduced sensibility toward exteroceptive stimuli in patients during the post-acute phase. The outcomes of this study represent an initial step toward clinically evaluating the dynamic interplay among interoception, exteroception, and psychotic disorders. The heterogeneous results from the literature regarding perceptual profiles should be contextualized by considering that fluctuations in PSY patients can be significant when compared to the general population.

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Conflict of interest

The authors declare no conflict of interest.

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Ethics approval and consent to participate

The research was approved by the local ethical committee of the IRCCS Policlinico San Matteo Pavia, Italy (Approval no: 20210003663). All participants have signed the informed consent form.

Consent for publication

All participants have signed the informed consent form.

Availability of data

Data used in this work are available from the corresponding author upon reasonable request.

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CASE REPORT

Abnormal elevation of serum amylase in a patient with acute depression in a state of sub-stupor: A case report

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Abstract

Serum amylase predominantly comprises pancreatic and salivary amylases and its elevation is commonly associated with pancreatitis and other physical diseases. This case report presents a 63-year-old male with first-episode depression who exhibited abnormally elevated serum amylase. Shortly after admission, the patient entered a sub-stupor state. The patient developed symptoms such as high fever and excessive sweating on the second night. In addition, myocardial damage was observed. The serum amylase was found to be elevated in the morning on the 3rd day. Following symptomatic and supportive treatments, the patient's serum amylase level gradually dropped to drop to normal over approximately 2 weeks. On careful analysis of the patient's medical condition, we suspect the increased serum amylase level may be linked to his psychiatric symptoms. Based on this case, we speculate that besides physical illness, the stupor symptoms observed in patients with depression may also lead to elevated serum amylase. Therefore, clinicians must prioritize addressing psychiatric symptoms when encountering such situations.

Keywords: Serum amylase; Depression; Psychiatric symptoms; Sub-stupor state; Physical illness; Case report

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1. Introduction

Serum amylase could be classified into two main types in almost equal proportions: pancreatic-type, primarily secreted by the pancreas, and salivary-type, which is the predominant fraction in normal serum and is derived from salivary gland tissue and other organs[1,2]. Clinically, elevated serum amylase level is commonly associated with various abnormal medical conditions, including pancreatitis, pneumonia, shock, and post-cardiac surgery[1,3]. In addition, cases of abnormally elevated serum amylase have been observed in the psychiatric department. For instance, mirtazapine causes acute pancreatitis and subsequent elevation of amylase level[4]. Moreover, patients taking lithium may also experience elevated serum amylase with an unknown mechanism[5]. Studies suggest that even in the absence of pancreatic injury, abnormal elevation of serum amylase should be carefully monitored due to the increased risk of death[6].

In this case, we report an unexplained, abnormal increase in serum amylase in a critically ill patient without the above-mentioned related factors.

2. Case presentation

The patient was a 63-year-old male with no history of mental illness and was admitted to the hospital due to experiencing gradual low mood and pessimism for the past 6 months. Six months ago, the patient began to exhibit symptoms of low mood, thought inhibition, and insomnia. Two months later, he developed suicidal thoughts, decreased interest, reduced speech, fatigue, and feelings of being monitored. Over time, the patient's symptoms worsened, and he began experiencing soliloquize, hallucinations, feelings of insecurity, and one episode of subliminal stupor at home. Four months later, the patient started taking sertraline (increased to 200 mg/morning) and olanzapine (increased to 5 mg/night) until his hospitalization. On admission to the hospital, the patient presented with a week-long history of cough and yellow sputum and had self-administered cefprozil 0.25 mg twice a day for 3 days.

On the day of admission, the patient underwent blood routine and biochemical examinations (Table 1). The ECG examination showed a heart rate of 74 bpm with a sinus rhythm. There was counterclockwise rotation, Embryonic R wave, abnormal Q wave (in leads V_4–V_6), intraventricular block, and a possibility of old side wall heart infarction. In addition, the chest CT revealed inflammation in the right middle lobe. Initially, the patient was conscious and able to walk into the ward independently. However, shortly after interacting with the doctors and nurses, he became nervous and passive and started exhibiting mutism while tightly closing his eyes. Eventually, he developed a state of sub-stupor (Table 2 for the medications administered to the patient after admission).

On the 2nd day, the patient developed hyperthermia with a rectal temperature of 40°C, accompanied by excessive sweating and tremor, at night. The heart rate was 160 beats/min, the blood pressure was 160/90 mmHg, and the blood oxygen saturation was 90%. Consequently, the doctor decided to stop all medications that night and provide supportive treatment. A series of blood tests were conducted (Table 1). The electrocardiogram revealed the following results: (i) Sinus rhythm, (ii) non-specific intraventricular conduction delay, (iii) electrical right axis deviation, and (iv) abnormal Q waves in leads V_4–V_6, indicating myocardial injury. After an emergency consultation with the cardiology department, no specific treatment for myocardial injury was recommended. However, it was advised to perform a dynamic review of myocardial enzymes.

In the morning on the 3rd day, the patient's temperature dropped (axillary temperature 37.6–37.8°C), and the ECG showed the following results: (i) Sinus rhythm, (ii) QTc prolongation (485), and (iii) intraventricular conduction block. The chest CT showed no inflammation. Following the cardiologist's recommendation, we conducted reviews of the patient's myocardial function at 06:00, 09:40, and 14:40. At 09:40, we also performed a comprehensive biochemical examination to understand the patient's electrolyte level. Unexpectedly, we discovered that the serum amylase was as high as 884 U/L (reference range 0–100 U/L), but the CT scan of the entire abdomen that afternoon reported no obvious abnormalities in the pancreas.

From admission until noon on the 3rd day, the patient remained in a state of sub-stupor, with clear consciousness but tension, passivity, closed eyes, and mutism. However, when the patient's daughter visited at noon on the 3rd day, his symptoms underwent a dramatic change, and his nervousness was relieved. With the support of his family, he was able to communicate with the doctor and denied experiencing any physical discomforts, including chest pain and abdominal pain, since the fever. The patient's symptoms, signs, and examination did not support a diagnosis of acute pancreatitis. On the 5th day, the patient began to consume small amounts of food and walked in the ward with the assistance of his wife. After taking venlafaxine on the 6th day, the patient's depressive symptoms gradually improved, and various blood biochemical indicators showed gradual recovery. Troponin I was normal on the 8th day and serum amylase level was normal on the 16th day.

3. Discussion

The patient's serum amylase was abnormally elevated, but there were no signs of pancreatitis or any relevant imaging findings. The previous studies have suggested that elevated serum amylase in the absence of pancreatic damage indicates a high risk of death in patients[6]. In addition, this patient went through a dangerous stage with unstable vital signs and myocardial damage. Consequently, we were keen to investigate the cause of the elevated serum amylase level. There can be several reasons for such an increase. After reviewing previous studies and reconsidering the patient's case, we initially explored the possible causes of the elevated amylase level, including pneumonia, cardiac conditions, and medication usage[3].

The patient had suffered from coughing with sputum for a week before admission. On the day of admission, a CT showed pneumonia, but on the 3rd day of admission (the day when elevated serum amylase was found), the CT scan did not report pneumonia. Considering the time

Table 1. Laboratory results at admission and during follow-up

Biochemical indicators	Normal range	Day 1	Day 2	Day 3			Day 4	Day 5	Day 6	Day 8	Day 16	Day 23
				06:00	09:40	14:40						
Complete blood count												
White blood cells	4–10×10^9/L	9.99	14.96	16.18	-	-	10.88	8.68	8.82	9.1	10.11	7.35
Percentage of neutrophils	50–65%	75.2	76.4	79.9	-	-	84.1	80.9	81.8	68.8	66	61.2
Coagulation												
D dimer	0–243 ng/mL	-	778	-	-	-	-	-	-	-	-	-
Antithrombin III	83–128%	-	149	-	-	-	-	-	-	-	-	-
Fibrin degradation product	0–5 ug/mL	-	6.5	-	-	-	-	-	-	-	-	-
Myocardial function												
Creatine kinase-MB	0–3.7 ng/mL	-	22.1	63.1	73.3	60.2	2.01	17.4	-	5.6	-	-
Myoglobin	0–73 ng/mL	-	>1000	>1000	>1000	>1000	517.44	491.37	-	117.37	-	-
Troponin I	0–0.06 ng/mL	-	0.15	1.02	0.69	0.63	0.18	0.1	-	0.03	-	-
Brain natriuretic peptide	0–100 pg/mL	-	64	73	120	-	-	-	-	-	-	-
Liver function												
Alanine aminotransferase	5–40 U/L	50	54	-	60	-	70	73	75	50	31	21
Aspartate aminotransferase	5–40 U/L	50	68	-	120	-	179	161	117	58	21	21
Blood culture												
Left	Negative	-	Normal	-	-	-	-	-	-	-	-	-
Right	Negative	-	Normal	-	-	-	-	-	-	-	-	-
Other tests												
C-reactive protein	<5 mg/L	Normal	Normal	-	-	-	47.12	33.27	12.33	-	-	-
High-sensitivity C-reactive protein	<0.5 mg/L	Normal	Normal	-	-	-	>5	>5	>5	-	-	-
Lactate dehydrogenase	110–240 U/L	-	-	-	458	-	-	-	-	341	234	164
Creatine kinase	25–200 U/L	-	-	-	3614	-	-	-	-	524	60	-
Serum amylase	0–100 U/L	-	-	-	884	666	283	235	317	152	73	-
Serum calcium	2.15–2.57 mmol/L	2.55	2.61	-	-	-	2.29	2.3	2.27	-	-	-
Procalcitonin	<0.5 ng/mL	-	Normal	-	-	-	-	-	-	-	-	-

frame, the 3rd day may be a critical time point. It is possible that the serum amylase had already increased before then, but it gradually decreased after the resolution of pneumonia on the 3rd day. There has been a reported case of elevated serum amylase in association with pneumonia, identified as benign pancreatic hyperenzymemia or Gullo's syndrome, where the serum amylase remained high even in the following year[7]. Some scholars have suggested that the increase in serum amylase is observed only when there are lung infections and respiratory failure simultaneously[8]. However, in the present case, the patient did not meet the criteria of having conditions concurrently, making it unlikely that pneumonia caused the increase in amylase level.

Another possibility is that myocardial infarction affects the blood supply of the pancreas, resulting in impaired function and increased serum amylase level. Previous cases have reported that cardiac arrest or hemorrhagic shock can cause pancreatitis and elevated serum amylase level[6,9]. However, in this patient, the heart function was not impaired, and CT did not reveal abnormalities in the pancreas. As a result, myocardial injury cannot provide a satisfactory explanation for the elevated serum amylase level.

The patient, in this case, had been on multiple medications before admission (Table 2). Regarding medication, the instruction manual for cefprozil did not mention an association with pancreatitis or amylase elevation, and no relevant information was found when searching for the terms "cefprozil amylase" on online resources. Ambroxol has a similar profile to cefprozil in this regard. On the other hand, ceftazidime has been

Table 2. Medication for 2 days after admission

Medications	Day 1	Day 2		
	Evening	Morning	Noon	Evening
Cefprozil (g)	0.25	-	-	-
Ceftazidime (g)	-	2	-	-
Ambroxol (mg)	30	30	30	-
Paroxetine (mg)	-	10	-	-
Olanzapine (mg)	2.5	-	-	-
Lorazepam (mg)	0.5	-	0.5	-
Silybin meglumine tablets (mg)	200	200	200	-
Zopiclone (mg)	3.75	-	-	-
Compound paracetamol tablet (paracetamol 500 mg and caffeine 65 mg)/1 tablet	-	-	-	1 tablet

reported to have pancreas-protective properties and can reduce amylase level[10]. In this case, the patient had only taken a small amount of paroxetine. In addition, an animal experiment even showed that paroxetine can lower serum amylase level[11]. Therefore, it is highly unlikely that paroxetine contributed to the increase in amylase level in this patient. Among all the medications, the most likely candidate to cause the elevation of serum amylase is olanzapine. The previous studies and reports have indicated that a rare adverse reaction of olanzapine is acute pancreatitis, which typically occurs approximately 12 weeks after administration. CT scans have revealed acute edematous pancreatitis, acute hemorrhagic pancreatitis, and acute necrotizing pancreatitis in patients receiving olanzapine[12]. Therefore, the influence of olanzapine cannot be completely ruled out in the present case. This case report aims to explore additional possibilities and provide clinicians with further considerations and insights.

For this case, determining the exact cause of the increased serum amylase level is challenging, and it cannot be solely attributed to olanzapine. Several other possibilities exist, such as psychiatric symptoms contributing to the elevation in serum amylase level. Prior reports have associated elevated serum amylase with psychiatric symptoms. First, depression patients have inherently higher salivary amylase level compared to healthy individuals[13,14], suggesting that the baseline serum amylase level in a depressed patient might be higher. Second, the patient's nervousness and sub-stupor state after admission might further increase salivary amylase level, as salivary amylase is a marker of sympathetic nerve activity[15] and tends to rise significantly under psychological pressure[16]. Cases of schizophrenia in catatonic stupor have demonstrated significantly increased salivary amylase level[17], similar to the patient's condition in this case. After admission to the hospital, the patient remained in a state of sub-stupor and tension until the 3rd day, when the elevation of amylase was detected. Even on the 5th day, despite being able to walk in the ward with the support of family, the patient displayed extreme tension and resistance when visiting the doctor's office, accompanied by muscle stiffness that causes slipping off the chair. Therefore, it is plausible that the patient's salivary amylase was at a high level during that time, potentially resulting in elevated serum amylase level[18]. It has been proposed that salivary-type amylase is the predominant fraction of serum amylase and is derived from salivary gland tissue and other organs[2].

4. Conclusion

In summary, the patient's high tension and sub-stupor state due to depression may contribute to the secretion of salivary amylase in the serum, leading to elevated serum amylase level.

While elevated serum amylase is commonly associated with pancreatitis and other serious physical diseases, it is essential to consider psychiatric factors as well. In this case, we observed a potential link between the patient's psychiatric symptoms and the elevation of serum amylase. Serum amylase could serve as an important blood biochemical marker indicative of the severity of depression. Based on this case, we speculate that in addition to physical illness, the stupor symptoms experienced by patients with depression may also lead to elevated serum amylase level. Therefore, when encountering such situations clinically, it is crucial for clinicians to prioritize addressing psychological symptoms.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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Ethics approval and consent to participate

Verbal consent was obtained from the patient. This study was approved by the Research Ethics Review Board (Approval ID: 2015-KY022) of the Affiliated Brain Hospital of Nanjing Medical University.

Consent for publication

Verbal consent was obtained from the patient for publishing his data in this paper.

Availability of data

The data used in this work are presented in the text and original data can be obtained from corresponding author following formal request.

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ACCSCIENCE PUBLISHING

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CASE REPORT

Effective prediction of somatic symptom disorder–B criteria in China: A case report

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Abstract

According to the diagnostic criteria for somatic symptom disorder (SSD) outlined in the Diagnostic and Statistical Manual of Mental Disorders-5th (DSM-5), there is a necessity for a rapid, simple, and effective diagnostic tool in the outpatient setting to predict the SSD–B criteria. This study aims to evaluate the screening diagnostic value of combining the duration of concern about physical discomfort per day with the Whiteley Index-8 (WI-8) scale. In a previous multicenter cross-sectional study, patients were recruited from outpatient clinics in general hospitals (n = 699). In this comparative study, we recruited an additional 100 patients from a psychosomatic outpatient unit. Receiver operating curve (ROC) analysis was applied to obtain the optimal cutoff value for the time spent worrying about physical discomfort per day and the WI-8 scale. The analysis of both datasets reveals significant differences in the amount of time spent on symptoms per day between the groups. In the previous multicenter study, patients in the high-score group expressed more concern about physical discomfort than those in the low-score group (4.5 ± 4.8 h/day [h/d] vs. 0.9 ± 1.9 h/d; t = 13.943; P < 0.01). In the current comparative study (n = 100), the high-score group spent 5.3 ± 4.2 h/d worrying about physical symptoms, while the low-score group spent 2.3 ± 3.7 h/d. ROC curve analysis indicated that the cutoff value for time in the previous multicenter study was 1.25 h (area under the ROC curve [AUC] = 0.839), and the WI-8 scale score was 19 (AUC = 0.907). Combining the two

increased the AUC–0.921 ($P < 0.001$). The cutoff value for time in the comparative study was 1.9 h (AUC = 0.801), and the WI-8 scale score was 11 (AUC = 0.925). Combining the two increased the AUC to 0.935 ($P < 0.001$). The combination of time and the WI-8 scale offers a simple, cost-effective, rapid, and direct method for clinical doctors to screen for somatic symptom disorders–B criteria.

Keywords: Somatic symptom disorder; Psychological criteria; Symptom-related behavior; Reference score; Somatic Symptom Disorder–B Criteria Scale; Receiver operating curve

1. Introduction

Many primary care patients complain of physical symptoms not caused by any conventionally defined diseases. While most symptoms are mild and self-limiting, some can be severely disabling and often associated with illness anxiety[1,2]. These patients sought prolonged medical attention from different hospitals and departments in an attempt to elucidate the cause of the physical symptoms. These somatic symptoms are frequently referred to as medically unexplained or functional, causing confusion among patients. Various medical specialties have introduced their own diagnoses for this cohort, such as fibromyalgia in rheumatology, chronic fatigue syndrome in neurology, and irritable bowel syndrome in gastroenterology. There have been evolutions in the diagnostic nomenclature for classifying psychiatric disorders, including terms such as "somatization," "medically unexplained symptoms," and "somatoform disorders," aiding in the differentiation between mental disorders and psychosomatic diseases. In 2013, a newly defined disorder known as somatic symptom disorders (SSD) was gazetted in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), separating it from the conventional diagnostic definition for somatic symptoms and related disorders. A major departure from the past lies in the emphasis on the importance of "positive" psychological criteria (SSD–B criteria), indicating that patients exhibit excessive thoughts, feelings, and behaviors that are symptom related[3]. In March 2022, the revised version of DSM-5 (DSM-5-TR), released by the American Psychiatric Association, retained the original diagnostic criteria. Notably, organic somatic diseases are no longer used as an exclusionary diagnosis. The current diagnostic criteria incorporate the role of psychological factors in disease development of the disease and exclude the previous psychosomatic dualism disease attribution model[4].

Multiple studies have substantiated that SSD patients exhibit suboptimal medical-seeking behavior and heightened health anxiety in response to health-related symptoms, resulting in a decline in their overall quality of life[1,2,5]. Many of these patients engage in excessive self-monitoring as a coping mechanism, undertaking behaviors such as regular skin inspections, frequent blood pressure and pulse measurements, and extensive online research on medical diseases and treatments. The persistence of distressing physical symptoms often prompts SSD patients to seek care across different hospitals. In contrast to psychiatric and other mental health settings, individuals with SSD are more commonly encountered in primary health care and other medical settings, including dermatology, emergency departments, pediatrics, otolaryngology, and similar fields. Some studies propose that this prevalence may be linked to a lack of SSD diagnosis by non-psychologists or a lack of patients' understanding of the condition[6-9]. From the perspective of etiology, the pathogenesis of SSD remains unclear; however, multiple studies underscore the significance of psychosocial factors in shaping the distinctive clinical manifestations observed in SSD patients. These factors include negative childhood traumatic experiences, cultural influences, adverse personality foundations, and life stress events[10-12]. These psychological factors may drive SSD patients to avoid confronting their inner emotions, manifesting these emotional concerns through physical symptoms. Moreover, these somatic symptoms are associated with heightened health-related anxiety and catastrophic thinking within this population[13].

While some evidence suggests that positive psychological characteristics can serve as key criteria for predicting disease progression and improving diagnostic accuracy when physical complaints are classified as mental disorders[14-19], there remains controversy regarding the assessment of SSD–B criteria due to the absence of a specific threshold for quantifying somatic symptoms associated with excessive thoughts, feelings, or behaviors[20,21]. The SSD–B Criteria Scale (SSD-12), developed to measure B-criteria, not only offers clarity but also enables a rapid assessment of patients' psychological burden and behavior related to symptoms[22,23]. The SSD-12 demonstrates high internal consistency and favorable item characteristics. In addition, research indicates that the total score of SSD-12 is significantly higher in patients with chronic diseases (such as hypertension and diabetes) compared to those without

self-reported chronic diseases[23], indicating the SSD-12's ability to differentiate between patient groups. However, even though the total score of the scale can reflect patients' psychological burden related to symptoms, assessing the disproportion of symptoms is challenging for patients and clinical doctors, especially when SSD coexists with known physical disease diagnoses. The daily time spent worrying about physical discomfort, as a subjective experience and feeling for patients, emerges as an important variable in the SSD–B criteria. A cross-sectional survey in Germany revealed a significant difference in the amount of time spent worrying about physical symptoms between the SSD and non-SSD groups on a daily basis[24]. It is plausible that time can serve as a quick and preliminary assessment of the extent to which patients excessively concern themselves with their symptoms. Our previous research on the latest version of the Whiteley Index-8 (WI-8) has demonstrated its excellent ability to distinguish between patients with and without health anxiety (area under the receiver operating curve [ROC] [AUC = 0.822])[25]. Moreover, a robust correlation between WI-8 and SSD-12 in the outpatient population of general hospitals in China suggests that health anxiety is an important feature of SSD[26]. Thus, we posit that the combination of time and WI-8 for screening SSD–B criteria enhances the reliability and validity of health concerns related to physical symptoms and subjective feelings of "excessive."

While a measurement standard for the SSD–B criteria currently exists, its applicability to non-psychiatric experts remains uncertain[22]. Consequently, we aimed to evaluate the screening diagnostic value of combining the time spent worrying about physical discomfort per day with the WI-8 scale. This approach is intended to furnish physicians with a rapid and simple tool for screening purposes.

2. Methods

2.1. Participants

All patients were sourced from the Departments of Biomedicine (Department of Cardiology, Departments of Neurology, and Department of Gastroenterology), Traditional Chinese Medicine (TCM), and Psychosomatic Medicine – fields frequently visited by SSD patients seeking medical attention. Data were collected from patients across two distinct time frames: (i) the earlier period corresponds to the previous multicenter cross-sectional study conducted from May 2016 to January 2018, which involved nine tertiary general hospital outpatient units situated in different regions of China (Beijing, Shanghai, Chengdu, Wuhan, and Jincheng) and (ii) the latter period corresponds to the data collection from the Psychosomatic Outpatient Unit at Shanghai Tongji Hospital, conducted between February 2023 and August 2023 for validation purposes. Results from two studies were meticulously compared and analyzed.

Inclusion criteria encompassed individuals who were (i) over 18 years old; (ii) capable of reading and writing; (iii) able to cooperate in completing surveys; and (iv) suffering from physical symptoms and seeking medical attention. Exclusion criteria were applied to those with (i) major psychosis; (ii) strong suicidal tendencies; (iii) communication difficulties or language barriers; (iv) severe liver and kidney damage, or other systemic diseases; (v) cognitive impairment, organic brain disorders, or dementia; and (vi) a history of long-term use of psychoactive substances or drug abuse.

The earlier multicenter study was approved by the Ethics Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences (ethical batch number: S-K276). The comparative study involving human participants was reviewed and approved by the Ethics Committee of Tongji Hospital affiliated with Tongji University (protocol number: SBKT-2023-122). Before the survey, all researchers received training from experienced psychiatrist deputy directors or higher. All participants were requested to sign an informed consent document after understanding the aims of the study. Patients were explicitly informed that participation is voluntary and that there are no disadvantages associated with their decision to participate or not. Following separate screening, 699 participants were included in the previous multicenter study, and 100 participants were included in this comparative study, excluding those who did not meet the inclusion criteria and lacked necessary data.

2.2. Study tools

This study was a multicenter cross-sectional investigation that collected basic patient data and clinical information through the administration of questionnaires. The time required for participants to complete the questionnaires was approximately 20 min.

2.2.1. General situation-related questionnaires

Self-report questionnaires were utilized to collect demographic data and assess the time individuals spent on physical discomfort per day. One specific query inquired, "How many hours per day are you concerned with your physical complaints?" The exact self-report questionnaires/tools employed in this study include:

(i) Patient Health Questionnaire-15 (PHQ-15): A self-report questionnaire assessing the severity of physical

symptoms, the PHQ-15 has been translated into various languages, such as Korean and Spanish[27-29], and is widely used in medical institutions and scientific research[30]. Comprising 15 common physical symptoms, it quantifies the number and severity of physical symptoms experienced by patients over the past 4 weeks. The scoring method is as follows: "0" = No trouble, "1" = Slight trouble, "2" = Many troubles. A total score of less than 4 points is considered mild, 5 – 9 points are categorized as mild, 10 – 14 points as moderate, and 15 – 30 points as severe. The Chinese version utilized in this study has demonstrated good reliability and validity[23].

(ii) SSD–B Criteria Scale (SSD-12): This self-report scale is designed to assess cognition, feelings, and behavior toward symptoms. Consisting of 12 items, each scored on a scale of 0 – 4 points, the total score ranges from 0 – 48 points. Psychometric evaluation using a cutoff value of 16 points or more indicates good reliability and validity, justifying referral to a psychiatric department for further diagnosis (Cronbach $\alpha = 0.95$)[22]. Aligned with DSM-5 for evaluating SSD diagnostic criteria B, the scale comprehensively covers dimensions of cognition, emotion, and behavior. It is suitable for assessing psychological symptom load, enabling rapid screening for SSD, and facilitating the monitoring of treatment effectiveness. Simultaneously, its applicability extends to primary health-care institutions[31].

For the present study, patients were grouped based on the validated SSD-12 score as follows: the high-score group (SSD-12 ≥ 16, $n = 322$) and the low-score group (SSD-12 < 16, $n = 477$), with a sensitivity of 0.76 and a specificity of 0.80.

2.2.2. Health anxiety-related questionnaires

The health anxiety-related questionnaire employed in this study is WI-8. It comprises 8 items, each scored on a 1 – 5 point scale. A total score exceeding 19 points indicates the presence of health anxiety[25]. WI-8 is particularly suitable for evaluating anxiety, disease perception, and attention to physical symptoms or health.

2.2.3. Statistical analyses

The statistical analysis was conducted using SPSS 24.0 software. Specifically, *t*-tests were used for comparing measurement data, and Chi-square tests were used for comparing categorical data. Pearson correlation analysis and multiple linear regression were used to analyze the correlation factors affecting the psychological characteristics assessed by SSD-12. The significance level for all analyses was set at $\alpha = 0.05$. In addition, ROC analysis was applied to determine the optimal cutoff value for the time spent worrying about physical discomfort per day and the WI-8 scale.

3. Results

3.1. General demography data

In the previous multicenter study, a total of 699 patients were enrolled, comprising 429 (61.4%) females and 270 (38.6%) males, with an average age of 42.9 ± 14.2 years. Among them, 427 (61.1%) belonged to the low-score group, while 272 (38.9%) were in the high-score group. Notably, the low-score group exhibited a higher proportion of married individuals compared to the high-score group. No statistically significant differences were observed in other social demographic factors between the two groups (Table 1).

In the comparative study, a total of 100 patients were included, consisting of 63 females and 37 males, with an average of 45.36 ± 14.6 years. This cohort was evenly distributed, with 50 cases each in the low- and high-score groups. Notably, there were no statistically significant differences in demographic information observed between the two groups (Table 2).

3.2. Characteristics of physiology and psychopathology

In the previous multicenter study, patients exhibited average scale scores of 10, 14, and 17 on PHQ-15, SSD-12, and WI-8, respectively. The high-score group consistently scored higher on all three scales, and the observed differences between the two groups were statistically significant ($P < 0.01$) (Table 3). Similarly, in the comparative study, patients had average scale scores of 11, 12, and 17 on PHQ-15, SSD-12,

Table 1. Comparison of general demographic factors in the previous multicenter study

Variables	High-score group (n=272)	Low-score group (n=427)	χ^2 or t	P
Age ($\bar{x}$±s years; range 18–99)	42.73 (14.28)	43.76 (14.24)	−1.910	0.057
Sex (n [%] female)	169 (62.1)	260 (60.9)	0.108	0.654
Marital status (n [%] married individuals)	181 (66.5)	327 (76.6)	15.018	0.007
Having an insurance plan (n [%])	227 (83.5)	375 (87.8)	2.032	0.165
Race (n [%] Han ethnicity)	254 (93.4)	396 (92.7)	0.105	0.764
Residence (n [%] residing in the city)	219 (80.5)	356 (83.4)	0.749	0.415

Notes: High-score group: SSD-12≥16; Low-score group: SSD-12<16.

and WI-8, respectively, and these differences were also statistically significant ($P < 0.01$) (Table 4).

3.3. Time spent on somatic symptoms

To explore the predictive potential of patients' duration spent worrying about physical symptoms regarding the SSD–B criteria, we incorporated the question, "How many hours do you spend worrying or paying attention to physical symptoms every day?".

Table 2. Comparison of general demographic factors in the comparative study

Variables	High-score group (*n*=50)	Low-score group (*n*=50)	χ^2 or *t*	*P*
Age (x̄±s years; range 18–99)	44.7 (14.85)	46.02 (14.38)	−0.452	0.653
Sex (n [%] female)	32 (62.1)	31 (60.9)	0.043	1.000
Marital status (n [%] married)	40 (80.0)	42 (84.0)	0.271	0.795
Having an insurance plan (n [%])	37 (74.0)	42 (84.0)	1.507	0.326
Race (n [%] Han ethnicity)	-	-	-	-
Residence (n [%] residing in the city)	43 (86.0)	47 (94.0)	1.778	0.318

Notes: High-score group: SSD-12≥16; Low-score group: SSD-12<16; "-" represents no relevant data.

Table 3. Comparison of psychological and physiological scale scores in the previous multicenter study

Variables	High-score group (*n*=272)	Low-score group (*n*=427)	χ^2 or *t*	*P*
PHQ-15	12.4±5.5	7.4±4.4	13.491	<0.01
SSD-12	27.2±8.0	5.6±4.8	44.853	<0.01
WI-8	25.5±7.6	13.6±4.8	25.496	<0.01

Notes: High-score group: SSD-12≥16: Low-score group: SSD-12<16; PHQ-15: Patient Health Questionnaire-15; SSD-12: Somatic Symptom Disorder–B Criteria Scale; WI-8: Whiteley Index-8; all the scores are expressed in x̄±s.

Table 4. Comparison of psychological and physiological scale scores in the comparative study

Variables	High-score group (*n*=50)	Low-score group (*n*=50)	χ^2 or *t*	*P*
PHQ-15	14.3±6.3	8.2±4.5	5.618	<0.01
SSD-12	27.7±8.9	7.6±4.7	14.067	<0.01
WI-8	17.6±6.6	6.4±4.5	9.892	<0.01

Notes: High-score group: SSD-12≥16; Low-score group: SSD-12<16; PHQ-15: Patient Health Questionnaire-15; SSD-12: Somatic Symptom Disorder–B Criteria Scale; WI-8: Whiteley Index-8; all the scores are expressed in x̄±s.

The results from the previous multicenter study revealed that patients in the high-score group spent 4.5±4.8 h per day (h/day) on their symptoms, significantly surpassing the 0.9 ± 1.9 h/day observed in the low-score group ($P < 0.01$) (Table 5). Similarly, in the comparative study, patients in the high-score group spent 5.3±4.2 h/day on their symptoms, significantly exceeding the 2.3±3.7 h/day recorded for the low-score group ($p<0.01$) (Table 5).

3.4. Correlation and regression

In the previous multicenter study, the Pearson correlation analysis revealed strong positive correlations between symptom-related cognitive behavior and health-related anxiety ($r = 0.823$, $P < 0.01$), as well as the duration of worrying about physical discomfort per day ($r = 0.570$, $P < 0.01$). Conversely, a weak positive correlation was observed with the number and severity of physical symptoms ($r = 0.541$, $P < 0.01$) (Table 6). Moreover, employing the total score of SSD-12 as the dependent variable, the correlation analysis incorporated statistically significant general demographic data and scale scores as independent variables in a multiple regression equation. The results demonstrated that the number and severity of somatic symptoms, time spent worrying about physical discomfort per day, and health-related anxiety significantly

Table 5. Comparison of time spent on somatic symptoms

Study	High-score group (N=272, *n*=50)	Low-score group (N=427, *n*=50)	χ^2 or *t*	*P*
Previous (time [h/d])	4.5±4.8	0.9±1.9	13.943	<0.01
Comparative (time [h/d])	5.3±4.2	2.3±3.7	3.777	<0.01

Notes: High-score group: SSD-12≥16; Low-score group: SSD-12<16; h/d: hours per day; N: Number of patients in the previous multicenter study; n: Number of patients in the current comparative study.

Table 6. Correlation analysis between SSD–B criteria and other factors in the previous multicenter study

Variables	SSD-12	PHQ-15	WI-8	Time (h/d)
SSD-12	1	0.519	0.823	0.570
PHQ-15	-	1	0.552	0.246
WI-8	-	-	1	0.518
Time (h/d)	-	-	-	1

Notes: Somatic Symptom Disorder–B Criteria Scale (SSD-12) is used to quantify symptom-related psychological behaviors; Patient Health Questionnaire-15 (PHQ-15) is used to quantify the number of physical symptoms and the degree of distress; Whiteley Index-8 (WI-8) is used to quantify disease beliefs and health-related concerns; Time refers to the amount of time patient spent on physical symptoms per day (h/d: hours per day); "-" represents no relevant data.

impacted symptom-related cognitive behavior, collectively explaining 71% of the variation in symptom-related cognitive behavior (Table 7).

In the comparative study, the Pearson correlation analysis demonstrated a strong positive correlation between symptom-related cognitive behavior and health-related anxiety ($r = 0.797$, $P < 0.01$). However, weak positive correlations were observed with the duration of worrying about physical discomfort per day ($r = 0.427$, $P < 0.01$) and the number and severity of physical symptoms ($r = 0.466$, $P < 0.01$) (Table 8). Furthermore, using the total score of SSD-12 as the dependent variable, the correlation analysis identified that only the time spent worrying about physical discomfort per day and health-related anxiety significantly impacted symptom-related cognitive behavior. These factors collectively accounted for 66% of the variation in symptom related-cognitive behavior (Table 9).

3.5. Receiver operating characteristic

A ROC analysis was employed to examine the predictive ability of time spent on symptoms and the WI-8 scale in determining SSD-12. The results from the previous multicenter study indicated that when WI-8 was used in the predictive diagnosis of SSD-12, the AUC was 0.907 ($P < 0.001$). The cutoff value for WI-8 was 18.5, with sensitivity and specificity values of 80.8% and 85.4%, respectively. In the case of utilizing time for the predictive diagnosis of SSD-12, the highest diagnostic accuracy for SSD–B criteria was achieved with a cutoff value of 1.25 h or higher, yielding an AUC of 0.839 ($P < 0.001$), and sensitivity and specificity values were 68.3% and 84.5%, respectively. Upon combining WI-8 with time in the predictive diagnosis of SSD-12, a binary logistic regression analysis was performed, resulting in the linear model as follows:

$$\text{Logit(P)} = -5.740 + 0.215 \times \text{Time} + 0.262 \times \text{WI-8} \quad \text{(I)}$$

This combined approach improved the AUC to 0.921 ($P < 0.001$), with sensitivity and specificity values of 88.6% and 80.7%, respectively (Table 10 and Figure 1).

In the comparative study, the utilization of WI-8 in the predictive diagnosis of SSD-12 resulted in an AUC of 0.925 ($P < 0.001$), with a WI-8 cutoff value of 10.5. The corresponding sensitivity and specificity were 90% and 84%, respectively. When time was used in the predictive diagnosis of SSD-12, the highest diagnostic accuracy for SSD–B criteria was achieved with a cutoff value of 1.9 h or higher, yielding an AUC of 0.801 ($P < 0.001$) and sensitivity

Table 7. Multiple linear regression analysis of the influencing factors of SSD–B criteria in the previous multicenter study

Variables	SE	Standardized β	t	P
PHQ-15	0.056	0.103	4.200	<0.01
WI-8	0.041	0.660	23.765	<0.01
Time (h/d)	0.077	0.203	8.463	<0.01

Notes: SE: Standard error; Patient Health Questionnaire-15 (PHQ-15) is used to quantify the number of physical symptoms and the degree of distress; Whiteley Index-8 (WI-8) is used to quantify disease beliefs and health-related concerns; Time refers to the amount of time patient spent on physical symptoms per day (h/d: hours per day).

Table 8. Correlation analysis between SSD–B criteria and other factors in the comparative study

Variables	SSD-12	PHQ-15	WI-8	Time (h/d)
SSD-12	1	0.466	0.797	0.427
PHQ-15	-	1	0.567	0.253
WI-8	-	-	1	0.321
Time (h/d)	-	-	-	1

Notes: Somatic Symptom Disorder–B Criteria Scale (SSD-12) is used to quantify symptom-related psychological behaviors; Patient Health Questionnaire-15 (PHQ-15) is used to quantify the number of physical symptoms and the degree of distress; Whiteley Index-8 (WI-8) is used to quantify disease beliefs and health-related concerns; Time refers to the amount of time patient spent on physical symptoms per day (h/d: hours per day); "-" represents no relevant data.

Table 9. Multiple linear regression analysis of the influencing factors of SSD–B criteria in the comparative study

Variables	SE	Standardized β	t	P
WI-8	0.096	0.736	11.912	<0.01
Time (h/d)	0.180	0.191	3.092	<0.01

Notes: SE: standard error; Whiteley Index-8 (WI-8) is used to quantify disease beliefs and health-related concerns; Time refers to the amount of time patient spent on physical symptoms per day (h/d: hours per day).

Table 10. Predicting SSD-12 using Time, WI-8, and WI-8 and Time in the previous multicenter study

Items	WI-8	Time	WI-8 and Time
ROC (AUC)	0.907	0.839	0.921
Cutoff value	18.5	1.25	0.284
Youden index	0.662	0.528	0.693
Sensitivity	0.808	0.683	0.886
Specificity	0.854	0.845	0.807
95% confidence interval	0.885 – 0.929	0.809 – 0.869	0.901 – 0.940
P-value	<0.001	<0.001	<0.001

Notes: WI-8 and Time: −5.740+0.215×Time+0.262×WI-8; Whiteley Index-8 (WI-8) is used to quantify disease beliefs and health-related concerns; Time refers to the amount of time patient spent on physical symptoms per day; AUC: Area under the ROC curve; ROC: Receiver operating curve.

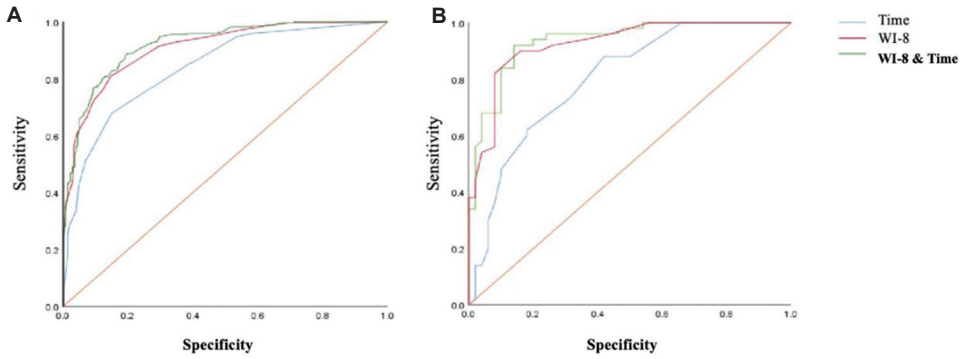

Figure 1. Receiver operating curve of the ability is to predict somatic symptom disorders (SSD)-12 based on the time spent on symptoms and the WI-8 scale. (A) Receiver operating cure of time and WI-8 in predicting SSD-12 in the previous multicenter study. (B) Receiver operating cure of time and WI-8 in predicting SSD-12 in the comparative study.

and specificity values of 80% and 58%, respectively. Upon combining WI-8 d with time in the predictive diagnosis of SSD-12, a binary logistic regression analysis was performed, yielding the linear model as follows:

$$\text{Logit}(P) = -4.705+0.128\times\text{Time}+0.375\times\text{WI-8} \quad \text{(II)}$$

This combined approach improved the AUC to 0.935 ($P < 0.001$), with sensitivity and specificity values of 92% and 86%, respectively (Table 11 and Figure 1).

3.6. Reliability

Internal consistency was assessed using Cronbach's alpha for the total scale score. In the previous multicenter study, Cronbach's alpha for the SSD-12 was 0.953, and it decreased to 0.949 after the removal of the 12th item. For both PHQ-15 and WI-8, the values were 0.808 and 0.937, respectively, indicating acceptable reliability. In the comparative study, Cronbach's alpha for the SSD-12 was 0.947, and it decreased to 0.943 after the removal of the 12th item. For the PHQ-15 and WI-8, the values were 0.822 and 0.916, respectively, indicating acceptable reliability.

4. Discussion

This study conducted two rounds of information collection and investigation among outpatient patients with physical complaints in nine tertiary comprehensive hospitals in China. The aim was to explore the predictive value of the time spent focusing on physical symptoms and the WI-8 scale for screening SSD, as measured by the SSD-12. For analysis, we categorized our participants into low- and high-score SSD groups and compared the statistical differences between them. The results of the previous multicenter study revealed that patients in the high-score group (n =272) spent 4.5 h/day on physical symptoms, while those in the low-score group only spent 0.9 h/day. This finding aligns with a representative national general population survey

Table 11. Prediction of SSD-12 with time, WI-8, and WI-8 and time in the comparative study

Items	WI-8	Time	WI-8 and Time
ROC (AUC)	0.925	0.801	0.935
Cutoff value	10.5	1.9	0.429
Youden index	0.74	0.46	0.78
Sensitivity	0.9	0.88	0.92
Specificity	0.84	0.58	0.86
95% confidence interval	0.875–0.976	0.715–0.887	0.888–0.981
P-value	<0.001	<0.001	<0.001

Notes: WI-8 and Time: −4.705+0.128×Time+0.375×WI-8; Whiteley Index-8 (WI-8) is used to quantify disease beliefs and health-related concerns; Time refers to the amount of time patient spent on physical symptoms per day; AUC: Area under the ROC curve; ROC: Receiver operating curve.

in Germany (n = 2,395), which measured the time spent by SSD patients worrying about physical symptoms (SSD group = 4 h, non-SSD group = 0.5 h)[24]. It is noteworthy that the German study used a combination of scales for diagnosing SSD, dividing participants into SSD and non-SSD groups[32]. In our comparative study, the high-score group (n = 50) spent 5.3 h/day on physical symptoms, while patients in the low-score group only spent 2.3 h/day. The longer duration of both groups compared to the previous multicenter study may be related to the fact that the patients were from a post-pandemic psychosomatic department, and the sample size was smaller than that of the previous multicenter study. However, findings from both domestic and international research consistently demonstrate significant differences in time between the two groups, indicating that SSD patients or patients with high psychological scores (SSD-12 scores) do spend more time worrying and paying attention to physical symptoms every day.

The physical component of SSD can escalate the severity and complexity of depression and anxiety disorders, resulting in heightened psychological distress and functional impairment[14,33]. A comparative study on health anxiety between SSD and illness anxiety disorder (IAD) revealed that individuals with SSD experience more pronounced functional impairment are more prone to panic and generalized anxiety disorder, and seek medical consultation more frequently than IAD patients. In other words, SSD is associated with heightened health anxiety due to disease[14,34]. In our studies, the results have indicated that WI-8 is an effective predictor of symptom-related cognitive behavior. In the previous multicenter study, WI-8 (r = 0.823, P < 0.01), time spent worrying about physical symptoms (r = 0.570, P < 0.01), and PHQ-15 (r = 0.519, P < 0.01) were all significant predictors in a multiple regression analysis. The findings indicate that anxiety related to one's health, the duration of attention to symptoms, and the number and severity of physical symptoms all exert a decisive impact on SSD–B criteria. However, in the comparative study, PHQ-15 was not included in the equation. This omission may be related to the fact that patients with severe physical symptoms tend to prefer non-psychiatric clinics.

In addition, to further predict the diagnosis of SSD–B criteria using the WI-8 scale and time spent worrying about physical symptoms, we separately calculated their ROC curves. Both of our studies indicated a higher AUC and a greater predictive accuracy for the WI-8 scale compared to time alone. In the previous multicenter study, when the WI-8 scale and time were combined for predictive diagnosis, the prediction accuracy reached its peak (AUC =0.921), with an improved sensitivity of 88.6%. This enhancement facilitates more effective screening of SSD–B criteria. As demonstrated in our earlier research[25], the WI-8 has a determined cutoff value of 19, and the current study established a time cutoff value of 1.25 h (sensitivity: 68.3%, specificity: 84.5%). Combining these two measures can be utilized for screening of SSD–B criteria. Our comparative study closely aligns with the results of previous multicenter studies, highlighting the stability of time and the WI-8 as joint predictors. This research holds favorable representativeness and generalization in the three aspects: (i) it provides valuable insights into predicting and understanding SSD criteria, specifically focusing on the Chinese context; (ii) by addressing the unique cultural and societal aspects relevant to China, this research adds significant depth to the understanding of SSD and paves the way for targeted interventions and support for individuals experiencing somatic symptoms in this region; (iii) it offers a promising avenue for improving diagnostic accuracy and ultimately enhancing the overall management of SSD.

However, the research is subject to limitations inherent in cross-sectional studies with large sample sizes. One notable limitation is the absence of SCID-5-RV gold standard diagnostic interviews with patients to confirm SSD diagnosis. In addition, the selection of departments where SSD patients visit more frequently may introduce biases in the results, potentially leading to an offset in the findings. The current study mainly focused on exploring the use of time spent worrying about physical discomfort and the WI-8 scale as standards for measuring SSD psychological behavior. Consequently, no further analysis was conducted on anxiety and depression. The specificity of the joint predictive diagnosis results from the ROC analysis did not exhibit improvement. This finding suggests that outpatient patients can undergo more effective screening for SSD, reducing the likelihood of overlooking suspicious cases. However, caution should be exercised regarding the potential situation of "over-diagnosis." In future research endeavors, researchers are encouraged to employ the gold standard for diagnosis and broaden the scope of targeted departments. This approach aims to attain a more accurate and comprehensive understanding of temporal quantification values or other meaningful indicators that can effectively screen SSD–B criteria.

5. Conclusion

This study presents a simple, cost-effective, rapid, and direct method for clinical doctors to assess the SSD–B criteria, which can be easily used even by non-psychiatric specialists. The combination of WI-8 and time spent worrying about physical symptoms demonstrates noteworthy screening and predictive diagnostic values for SSD-12. In clinical consultations, if patients report spending more than 1.25 h/day attending to their physical symptoms or if their WI-8 scale score equals or exceeds 19, and they have experienced at least one somatic symptom persistently for more than 6 months, suspicions of SSD should be raised, warranting further evaluations.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

The previous multicenter study involving human participants was reviewed and approved by the ethics committees of Peking Union Medical College Hospital (PUMCH) and the University Medical Centre, Freiburg, Germany (Protocol Number: S-K276). The comparative study involving human participants was reviewed and approved by the Ethics Committee of Tongji Hospital affiliated with Tongji University (protocol number: SBKT-2023-122). The patients/participants provided their written informed consent to participate in this study.

Consent for publication

Written consent has been obtained from human subjects, and permission has been obtained for each subject to publish their data.

Availability of data

Data used in this work is available from the corresponding author upon reasonable request.

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ACCSCIENCE PUBLISHING

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BRIEF REPORT

Psychological high-risk factors for acne: A prospective and cohort study

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Abstract

The present study explored the role of psychological factors and sleep quality in acne. Participants were recruited to assess the occurrence of acne monthly, and depression, anxiety, and sleep status were evaluated using the patient health questionnaire-9, self-rating anxiety scale, and the pittsburgh sleep quality index. Generalized estimating equations compared the effects of different factors on the occurrence of acne. Depression and moderate sleep quality were significantly related to acne ($P < 0.05$). Meanwhile, depression and sleep quality (moderate and poor) were significantly associated with inflammatory acne ($P < 0.05$). In conclusion, depression and sleep problems may be involved in the pathogenesis of acne, especially inflammatory acne. We recommend paying more attention to depression and sleep quality in patients to prevent acne.

Keywords: Acne; Depression; Anxiety; Sleep quality

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1. Introduction

Acne is a common chronic inflammatory disease involving the sebaceous glands, with a prevalence of up to 73.5% in adolescents[1]. Due to its specific impact on appearance, acne can cause many negative experiences in the daily life. The typical lesions of acne include pimples, papules, pustules, nodules, and cysts, of which the appearance of papules, pustules, nodules, and cysts is closely related to the local inflammatory response, and psychological factors can promote inflammatory skin disease[2-5]. Studies have also shown that acne patients have poorer mental health than those without acne[6] and are more likely to experience social anxiety and depression[7]. However, no studies provide substantial evidence as to whether there is a causal relationship between emotional status and acne occurrence. This study aimed to investigate the effect of emotional state and sleep quality on the occurrence of acne and to provide ideas for acne prevention and treatment.

2. Materials and methods

2.1. Participants

A total of 169 participants aged 18 – 35 years were recruited through online social software, URL: www.wjx.cn. All participants signed statements of informed consent

before the study, and the questionnaire was completed once a month for 1 year. Those with confirmed mental illness or impaired consciousness were excluded from the study. All participants were informed that the data collected were used for scientific research and that all data were treated anonymously.

2.2. Method

The general profile (gender, age, occupation, and education level) of the participants was recorded. Patient Health Questionnaire-9 (PHQ-9), self-rating anxiety scale (SAS), the pittsburgh sleep quality index (PSQI), and acne condition questionnaires were sent out regularly every month, and the participants completed the assessment independently.

Informed consent was obtained and participants were trained to accurately distinguish between acne types (pimples, papules, pustules, nodules, and cysts). We define that if a new papule, pustules, nodules, or cysts occurs, it is considered inflammatory acne. The appropriate data were collected monthly for follow-up analysis.

PHQ-9 is a 9-item self-rating scale with four options of 1, 2, 3, and 4 scores. The sum is calculated as the depression score, with 0 – 4 being no depression, 5 – 9 being mild depression, 10 – 14 being moderate depression, 15 – 19 being moderate-severe depression, and 20 or more being severe depression.

In SAS, four options are 1, 2, 3, and 4, where 5, 9, 13, 17, and 19 are the reverse options. The sum is calculated and multiplied by 1.25 to obtain the anxiety score. A score <50 is no anxiety, 50 – 60 is mild anxiety, 60 – 70 is moderate anxiety, and 70 or more is severe anxiety.

PSQI contains seven items, each with a value range of 0 – 3. A score of 0 – 5 is good sleep quality, 6 – 10 is moderate sleep quality, and 11 or more is poor sleep quality.

2.3. Statistical analysis

All analyses were performed using SPSS 26.0 (Version 26, IBM Corp., Armonk, NY). The demographic data were analyzed descriptively. Continuous variables were expressed as mean±standard deviation and examined using a *t*-test. Categorical variables were expressed as numbers and proportions and examined by the Chi-square or Fisher's exact test. The relationship among anxiety, depression, sleep, and acne was examined using generalized estimating equations (GEE). The significance level was set at 0.05.

3. Results

From July 2020 to June 2021, 178 participants were recruited and assessed monthly. At the end of the study, 9 (5.05%) were lost, and the study was finally completed with 169 participants; 1605 valid questionnaires were returned. Among them, 50 (29.59%) were male, and 119 (70.41%) were female; all of them aged 21.37 ± 1.93 years. There were 135 (79.88%) students. Twenty-six participants (15.38%) were engaged in general indoor occupations, while 8 (4.73%) were involved in other occupations. Regarding the educational background of the participants, 21 (12.43%) participants did not possess an undergraduate degree, while 137 (81.07%) participants held undergraduate degrees, and 11 (6.51%) had obtained master's degrees and higher. The general information is summarized in Table 1.

The majority of participants had no or mild anxiety, depression, and sleep quality, and the distribution of the number of people with depressed mood, anxiety, and sleep quality is shown in Figures 1-3.

In evaluating the relationship between anxiety, depression, sleep quality, and the occurrence of acne, the self-assessment results of the participants were utilized. Depression, anxiety, and sleep were considered the independent variables, while the presence of acne in the participants was treated as the dependent variable. These variables were included in the GEE model, with a binary logistic model selected. Depression and moderate sleep quality were found to be significantly correlated with the presence of acne ($P < 0.05$). Meanwhile, depression and moderate and poor sleep quality were found to be statistically associated with the presence of inflammatory acne ($P < 0.05$). However, no statistically significant relationship was found with anxiety. Detailed GEE results are shown in Tables 2 and 3.

Table 1. General information of participants

Characteristics	Total (*n*=169) (%)
Gender	
Male	50 (29.59)
Female	119 (70.41)
Age	
19 – 23	146 (86.39)
24 – 28	23 (13.61)
Occupations	
Students	135 (79.88)
General indoor occupations	26 (15.38)
Other occupations	8 (4.73)
Education level	
No undergraduate degrees	21 (12.42)
Undergraduate degrees	137 (81.07)
Master's degrees and above	11 (6.51)

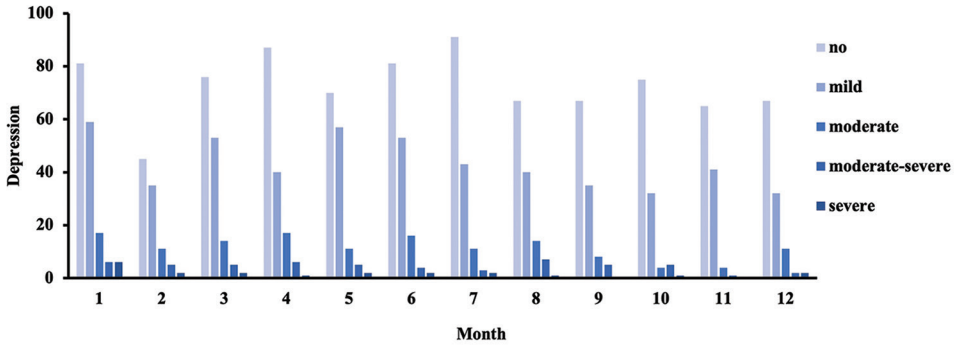

Figure 1. Distribution of the number of people with depression.

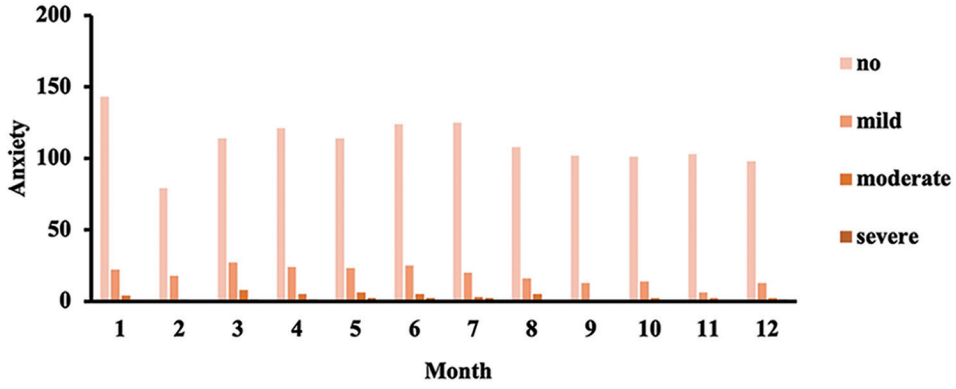

Figure 2. Distribution of the number of people with anxiety.

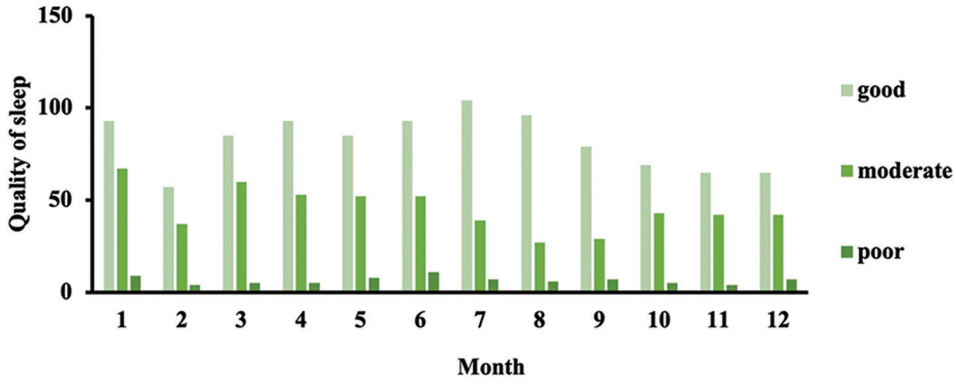

Figure 3. Distribution of the number of people with sleep quality.

4. Discussion

We found that acne is more likely present in individuals experiencing depression and reduced sleep quality. Depression has been reported in 5.6 – 8.8% of patients with acne vulgaris[8], which is 2 – 3 times higher than that of the general population[9]. Garg *et al.* studied the relationship between psychological stress and epidermal permeability barrier function in 27 students without skin disease and measured their permeability barrier function in high versus low psychological stress states. They found that barrier function decreased during high-pressure periods and recovered during low-pressure periods, suggesting that stress-induced epidermal dysfunction is a predisposing factor for inflammatory skin diseases[10]. Moreover, stress has been found to decrease skin permeability while increasing sebaceous hyperplasia[11]. Duchaine *et al.* evaluated the relationship between exposure to psychosocial stressors at work and the inflammatory

Table 2. Relationship between mood and sleep quality and the occurrence of acne

Variables	B	96% CI	*P*-value
Depression			
No depression	Reference		
Have depression	0.483	0.288 – 0.678	0.000
Anxiety			
No anxiety	Reference		
Have anxiety	−0.132	−0.439 – 0.176	0.401
Sleep quality			
Good	Reference		
Moderate	0.333	0.118 – 0.548	0.002
Poor	0.468	−0.022 – 0.958	0.061

Abbreviation: CI: Confidence interval.

Table 3. Relationship between mood and sleep quality and the occurrence of inflammatory acne

Variables	B	96% CI	*P*-value
Depression			
No depression	Ref		
Have depression	0.404	0.178 – 0.629	0.000
Anxiety			
No anxiety	Ref		
Have anxiety	−0.243	−0.558 – 0.071	0.129
Sleep quality			
Good	Ref		
Moderate	0.320	0.106 – 0.535	0.003
Poor	0.643	0.051 – 1.235	0.033

Abbreviation: CI: Confidence interval.

indicators CRP and interleukin-6 (IL-6). They found that inflammatory indicators were higher in people with high job stress and low social support (high psychosocial stress) at work, suggesting that lower psychological levels promote inflammation and greater susceptibility to acne[12]. These findings align with our research, indicating a significant association between depression and the occurrence of acne.

Our findings align with previous literature, supporting a link between psychology and skin diseases, particularly acne. Arck *et al.* found that ingesting a lactobacillus strain in mice inhibited stress-induced neurogenic skin inflammation, supporting the role of the brain-gut-skin axis and significant psychological influence[13]. Wang *et al.* introduced psychological intervention for papulopustular rosacea. After 8 weeks of treatment, both groups showed significantly reduced erythema, papulopustular, and pruritus symptom scores. The intervention group showed a greater improvement in symptoms than the controls, demonstrating that combined psychological intervention can enhance the treatment effectiveness in papulopustular rosacea[14].

According to studies, depressed individuals with poor sleep quality have high levels of substance P[4-5]. Substance P promotes the expression of pro-inflammatory cytokines such as IL-1, IL-6, tumor necrosis factor α, and interferon-γ by monocytes, keratinocytes, and mast cells and enhances IL-8 production by neutrophils and skin vascular endothelial cells. These processes influence and regulate immune and inflammatory responses in the skin, leading to follicular sebaceous gland hyperkeratosis in the funnel ducts and the formation of acne[2-3]. At the same time, studies have demonstrated that acne patients have a higher plasma level of levels of substance P compared to individuals without acne. Substance P can stimulate the hypothalamic-pituitary-adrenal system, promoting adrenocortical hormone secretion. This, in turn, reduces the patient's stimulation threshold for stress, resulting in changes in endocrine hormones and neurotransmitters in the body. Ultimately, these factors affect mental health and contribute to forming a vicious circle[15,16].

In our study, we did not find a significant relationship between anxiety and the occurrence of acne. This lack of association may be attributed to the fact that our participant sample consisted of students. In the future research, we plan to expand the sample size to further investigate and explore the relationship between anxiety and the occurrence of acne.

5. Conclusion

Our study indicates that within the same individual, the presence of acne is more likely when their psychological well-being is low (e.g., with depression and decreased sleep quality). Furthermore, the occurrence rate increases as the decline in psychological well-being worsens. The decrease in psychological well-being can lead to changes in neurotransmitters and endocrine hormones that promote inflammation and exacerbate acne. In turn, acne can diminish the patient's psychological well-being, resulting in a vicious cycle. Therefore, in clinical practice, it is crucial to pay attention to the psychological aspects of acne patients, particularly depression and sleep quality. Prompt intervention is necessary to prevent entering a vicious cycle.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Yidan Zhang, Yi Wang, Haiping Zhang
Formal analysis: Yi Wang
Investigation: Yidan Zhang, Yi Wang, He Zeng, Yi Zhang, Nan Wu
Methodology: Yidan Zhang
Writing – original draft: Yidan Zhang, Yi Wang, He Zeng, Yi Zhang, Nan Wu
Writing – review and editing: Haiping Zhang

Ethics approval and consent to participate

This is an observational study and the investigators do not assign any interventions to the participants. All participants signed statements of informed consent before the study and all data were treated anonymously.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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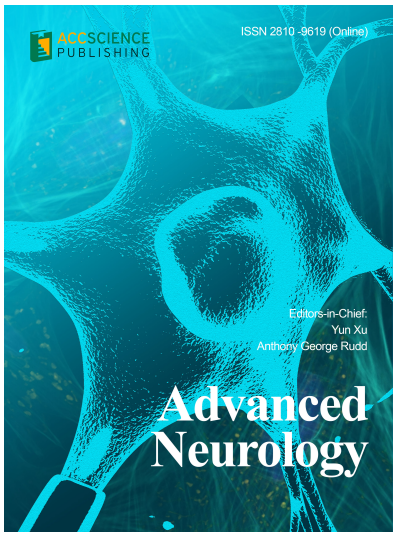

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