Psychoradiology, 2024, **4**, kkae022

DOI: 10.1093/psyrad/kkae022
Advance access publication date: 4 November 2024
Review

Common and divergent neuroimaging features in major depression, posttraumatic stress disorder, and their comorbidity

Jing Jiang [1,2], Stefania Ferraro [3,4], Youjin Zhao[2], Baolin Wu[2], Jinping Lin[2], Taolin Chen [2], Jin Gao[1,*] and Lei Li [2,*]

[1]Department of Radiology, The Affiliated Hospital of Southwest Jiao Tong University, The Third People's Hospital of Chengdu, Chengdu, Sichuan 610036 , China
[2]Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, Chengdu, Sichuan 610041, China
[3]Department of Neuroradiology, Fondazione IRCCS Istituto Neurologico 'Carlo Besta', Via Celoria 11, Milan, 20133, Italy
[4]Clinical Hospital of the Chengdu Brain Science Institute, School of Life Science and Technology, MOE Key Laboratory for Neuroinformation, University of Electronic Science and Technology of China, Chengdu, Sichuan 610054, China
*Correspondence: Lei Li, leili_huaxi@foxmail.com; Jin Gao, jingao_syy126@126.com

Abstract

Posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) are common stress-related psychiatric disorders. Genetic and neurobiology research has supported the viewpoint that PTSD and MDD may possess common and disorder-specific underlying mechanisms. In this systematic review, we summarize evidence for the similarities and differences in brain functional and structural features of MDD, PTSD, and their comorbidity, as well as the effects of extensively used therapies in patients with comorbid PTSD and MDD (PTSD + MDD). These functional magnetic resonance imaging (MRI) studies highlight the (i) shared hypoactivation in the prefrontal cortex during cognitive and emotional processing in MDD and PTSD; (ii) higher activation in fear processing regions including amygdala, hippocampus, and insula in PTSD compared to MDD; and (iii) distinct functional deficits in brain regions involved in fear and reward processing in patients with PTSD + MDD relative to those with PTSD alone. These structural MRI studies suggested that PTSD and MDD share features of reduced volume in focal frontal areas. The treatment effects in patients with PTSD + MDD may correlate with the normalization trend of structural alterations. Neuroimaging predictors of repetitive transcranial magnetic stimulation response in patients with PTSD + MDD may differ from the mono-diagnostic groups. In summary, neuroimaging studies to date have provided limited information about the shared and disorder-specific features in MDD and PTSD. Further research is essential to pave the way for developing improved diagnostic markers and eventually targeted treatment approaches for the shared and distinct brain alterations presented in patients with MDD and PTSD.

Keywords: posttraumatic stress disorder; major depressive disorder; comorbidity; transdiagnostic; disorder-specific

Introduction

Posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) are common stress-related psychiatric disorders associated with significant psychosocial and neurocognitive dysfunction (Godard *et al.*, 2012; Thomas *et al.*, 2010). Further, comorbid MDD is common in patients with PTSD, with approximately half of people with PTSD being diagnosed with comorbid MDD (Flory and Yehuda, 2015; Rytwinski *et al.*, 2013). Prolonged trauma seems to be a major risk factor for comorbid PTSD and MDD (PTSD + MDD) (Kostaras *et al.*, 2017). One explanation for the high comorbidity rate is that it may reflect overlapping symptoms of the two disorders, such as sleep disturbance, anhedonia, and concentration impairments (Flory and Yehuda, 2015). An alternative view is that the co-occurrence of PTSD and MDD possibly represents a subtype of PTSD (Flory and Yehuda, 2015). Individuals with PTSD + MDD tend to have more severe clinical symptoms and neurocognitive impairments (e.g. verbal memory and attention deficits), greater risk for suicidal behavior than individuals with PTSD or MDD alone (Dold *et al.*, 2017; Nijdam *et al.*, 2013; O'Donnell *et al.*, 2004), and diminished overall treatment efficacy and increasing chronicity (Kaplan and Klinetob, 2000; Pukay-Martin *et al.*, 2012). Recently, a meta-analysis of randomized controlled trials proved that the co-occurrence of depression may act as a risk factor for attenuated response in PTSD psychotherapies (Kline *et al.*, 2021). Together, these issues call for intensive research on the overlaps and differences in the neural mechanisms in MDD and PTSD.

A series of studies of various research areas have been conducted to deepen our understanding of the underlying mechanisms of MDD and PTSD, mainly involving genetic and epigenetic factors, gene–environment interactions, neurotransmitter systems, and neuroendocrine function. Genetic and epigenetic research has supported the viewpoint that PTSD and MDD may possess common and disorder-specific gene expression patterns, mainly associated with neuroendocrine and neurotransmitter systems. Specifically, previous genetics studies revealed that PTSD and MDD had consistent and opposing directionality of molecular findings in epigenetic processes and genes expression of glucocorticoid receptor and FK506 binding protein 51 (FKBP5) (Yehuda *et al.*, 2015; Zannas and Binder, 2014). A recent cross-trait meta-analysis identified 29 genomic loci shared in PTSD and MDD, and held the view that MDD is influenced by a broader

Received: 13 April 2024; **Revised:** 20 October 2024; **Accepted:** 31 October 2024

spectrum of causal gene variants than PTSD (Zhang *et al.*, 2022). Moreover, one post mortem study performing RNA sequencing in the prefrontal cortex (PFC) and amygdala regions revealed that overlapping gene expression patterns were associated with decreased immune signaling and neuroinflammation in MDD and PTSD, and a limited number of PTSD-specific differentially expressed genes were associated with subpopulations of GABAergic inhibitory neurons (Jaffe *et al.*, 2022). A positron emission tomography study reported lower monoamine oxidase-B levels in corticolimbic brain areas in PTSD with comorbid MDD compared with PTSD alone (Gill *et al.*, 2022). In the aspect of gene-environment interaction, the most extensive analyses have focused on FKBP5 and have elucidated that interaction between FKBP5 genotype and childhood trauma is associated with increased risk for stress-related disorders including PTSD and MDD (Smoller, 2016). In terms of neuroendocrine function and neurotransmitter systems, common and distinct changes have been reported in MDD and PTSD. Concretely, the abnormal functioning of the hypothalamic–pituitary–adrenal axis has been supposed to play a key role in the development of PTSD and MDD (Dunlop and Wong, 2019; Pariante and Miller, 2001). Both MDD and PTSD were associated with alterations in dopaminergic (Ney *et al.*, 2021; Shen *et al.*, 2012) and serotonergic transmission (Dell'Osso *et al.*, 2016; Southwick *et al.*, 1999). Collectively, these genetic and neurobiology studies have contributed to setting a stronger foundation for research on the shared and distinct neuroimaging markers of MDD and PTSD.

The mono-diagnostic and transdiagnostic neuroimaging studies have enabled qualitative and quantitative comparisons of MDD and PTSD, respectively. To date, numerous mono-diagnostic neuroimaging studies using magnetic resonance imaging (MRI) have identified functional and structural abnormalities in MDD and PTSD. Functional MRI (fMRI) studies have demonstrated alterations in core functional networks including the default mode network (DMN), executive control network (ECN), and salience network (SN) in both disorders (Albert *et al.*, 2019; Bao *et al.*, 2021). Similar effects of behavioral treatments on normalizing neural functional alterations have been reported (Shou *et al.*, 2017; Yang *et al.*, 2018a, 2018b). Common neural correlates in structural MRI have also been frequently found in the two disorders, including reduced gray matter volume in the insular and anterior cingulate cortices (ACC) (Bora *et al.*, 2012; Bromis *et al.*, 2018; O'Doherty *et al.*, 2015). In summary, these mono-diagnostic neuroimaging studies provided indirect evidence for similar functional and structural abnormalities in MDD and PTSD. In the past two decades, a limited number of case-control transdiagnostic neuroimaging studies have focused on direct comparisons of MDD and PTSD, aiming to identify common and divergent underlying neural signatures. In particular, increasing attention has been paid to individuals with PTSD + MDD. Some studies examined the effects of MDD comorbidity on brain activity and structure in the context of PTSD (Kemp *et al.*, 2007; Lanius *et al.*, 2007; van Rooij *et al.*, 2015). Advances in estimating the relevance/interaction effect between MDD and PTSD are now available. We therefore performed a systematic review to provide a more comprehensive knowledge of extant studies probing the similarities and differences in the underlying neural pathophysiology of MDD and PTSD in adult population, displaying the existing research gaps and making corresponding suggestions for future research. Of note, the summative conclusions may provide potential targets for neuroregulatory intervention in MDD and PTSD, especially comorbid MDD and PTSD.

Methods

The present review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. We searched PubMed using the following key words: 'MDD' OR 'major depressive disorder' OR 'depression'; 'PTSD' OR 'posttraumatic stress disorder' OR 'post-traumatic stress disorder'; and 'functional MRI' OR 'task-based' OR 'fMRI' OR 'resting-state' OR 'functional connectivity' OR 'diffusion' OR 'DTI' OR 'GMV' OR 'grey matter' OR 'gray matter' OR 'VBM' OR 'voxel-based morphometry' OR 'surface-based morphometry' OR 'cortical thickness'. The reference lists of the articles included in related review and meta-analyses were also checked for relevant studies. We screened 735 studies published before 30 August 2024, and included original neuroimaging studies that: (i) directly compared patients with PTSD and those with MDD; (ii) compared individuals with PTSD + MDD to those with PTSD alone or MDD alone; (iii) explored the effects of treatments on ameliorating depression and PTSD symptoms in patients with PTSD + MDD; and (iv) found potential neuroimaging features for classification of MDD and PTSD (MDD alone vs PTSD alone, MDD alone vs PTSD + MDD, or PTSD + MDD vs PTSD alone). Studies in children, adolescents or geriatrics were not included in the present review. We excluded studies that did not examine the neuroimaging features using MRI. We also excluded case reports and review articles, unless they included a meta-analysis. To provide supplementary information, we gave an overview of these meta-analyses providing a quantitative analysis of neuroimaging findings between PTSD and MDD.

We extracted authors, year of publication, sample categories and size, neuroimaging methods, and key findings. Each enrolled cross-sectional study was assessed for quality by two independent reviewers (L.L. and J.J.) using a 12-point checklist adapted from previous meta-analytic studies (Brambilla *et al.*, 2003; Shepherd *et al.*, 2012). This checklist was modified to reflect critical variables essential in assessing the quality of included original studies. Each item was scored 1, 0.5, or 0 if the criteria were fully, partially or not met, respectively (summarized in Table S1). Additionally, we recorded the therapy, symptom relief, neuroimaging predictors, and treatment-related findings for studies in patients with PTSD + MDD.

Results

The literature search using PubMed yielded 735 results. We screened the titles and abstracts of these 735 records. Two original studies were not included as they enrolled patients with MDD or PTSD who experience own-thought auditory verbal hallucinations (Zhuo *et al.*, 2020a, 2020b). It left 28 relevant studies for review (see Fig. 1). Among them, 17 original studies focused on the disease-related neural traits, including eight papers using resting-state fMRI (Averill *et al.*, 2024; Gong *et al.*, 2017, 2019a; Kennis *et al.*, 2013; Koopowitz *et al.*, 2023; Yuan *et al.*, 2019; Zhu *et al.*, 2017; Zilcha-Mano *et al.*, 2020), six studies using task-based fMRI (Bryant *et al.*, 2021; Keller *et al.*, 2022; Kemp *et al.*, 2007; Lanius *et al.*, 2007; van Rooij *et al.*, 2015; Whalley *et al.*, 2009), and three structural MRI studies (Dai *et al.*, 2020; Gong *et al.*, 2019b; Kroes *et al.*, 2011) (summarized in Table 1). The quality scores ranged from 10.5 to 11.5 (mean score 11.1) shown in Table S2, demonstrating that most included original studies were of relatively high quality. Five original studies explored the potential neural mechanisms and/or predictors of response to treatments in PTSD + MDD

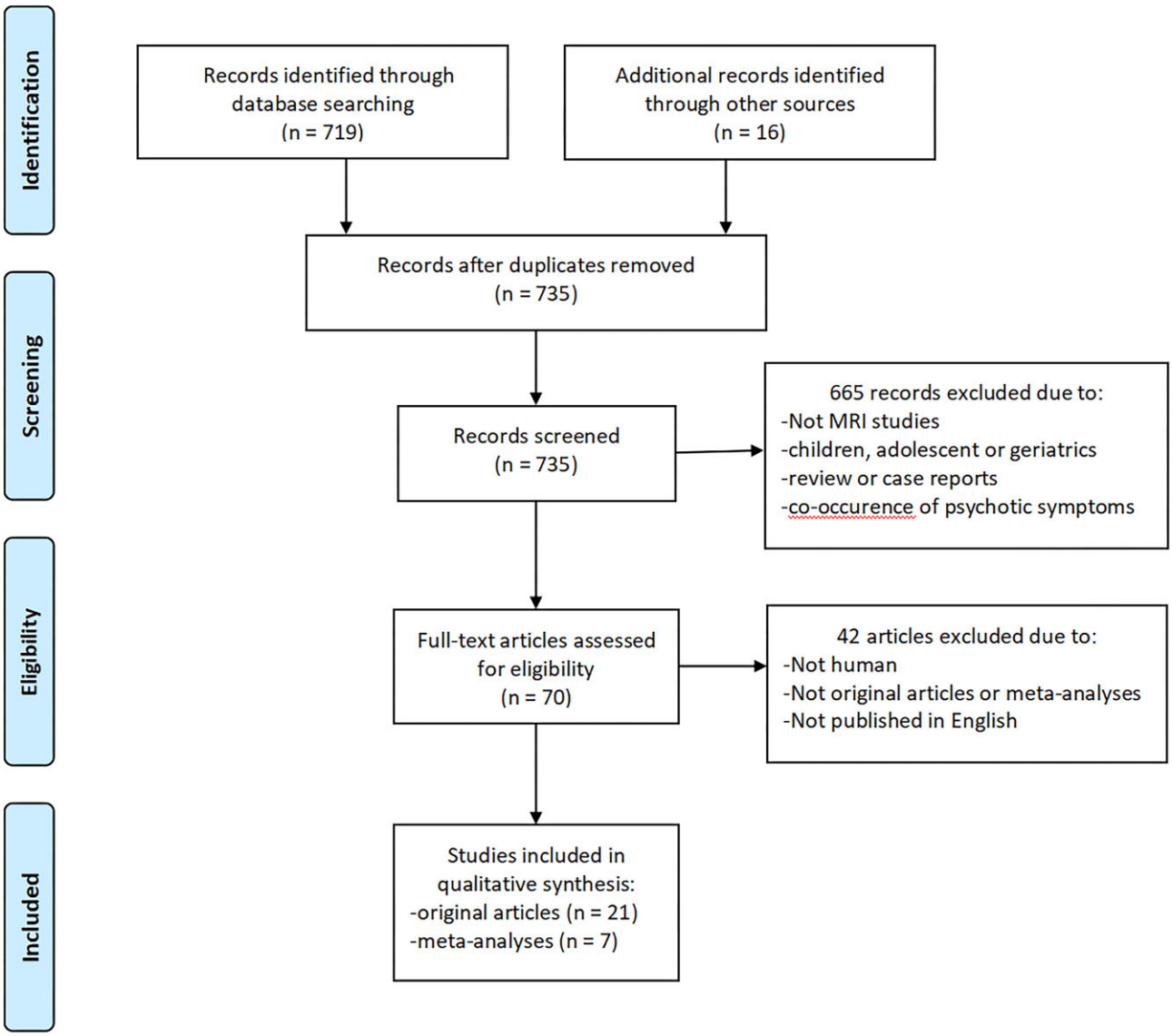

Figure 1: Flow chart showing the selection of studies.

populations (Barredo *et al.*, 2021; Dai *et al.*, 2020; Henigsberg *et al.*, 2011; Philip *et al.*, 2018; Yang *et al.*, 2018b) (summarized in Table 2). A total of seven meta-analyses have reported the shared and/or distinct neuroimaging findings between MDD and PTSD (Bromis *et al.*, 2018; Janiri *et al.*, 2020; Jenkins *et al.*, 2016; McTeague *et al.*, 2017; Schulze *et al.*, 2019; Serra-Blasco *et al.*, 2021; Wang *et al.*, 2024) (summarized in Table 3). A graphical representation of the key brain regions with similar or distinct neuroimaging features among MDD alone, PTSD alone, and PTSD + MDD cohorts is shown in Fig. 2.

Functional MRI in PTSD and MDD

Comparisons between PTSD and MDD

We identified three task-based fMRI studies directly comparing the MDD and PTSD groups (Bryant *et al.*, 2021; Keller *et al.*, 2022; Whalley *et al.*, 2009). The region of interest (ROI) fMRI study by Bryant *et al.* reported that patients with PTSD demonstrated significantly greater activation than MDD in multiple regions involved in amygdala and striatal-subcortical pathways during an emotion processing task (Bryant *et al.*, 2021). Common effects across MDD and PTSD groups relative to controls were not explored in that study. Furthermore, Whalley *et al.* demonstrated greater activation during the memory retrieval process in patients with PTSD compared to depressed group in multiple brain regions including amygdala, hippocampus, and insula, while areas of shared alteration relative to healthy controls (HC) were not reported (Whalley *et al.*, 2009). In addition, Keller *et al.* reported less focal neural activation in the right dorsomedial PFC and inferior frontal gyrus during cognitive reappraisal in both MDD and PTSD relative to HC, as well as MDD-specific reduced activation in the left middle temporal cortex and supplementary motor cortex (Keller *et al.*, 2022). Notably, Keller *et al.* found clinical group differences in multiple regions involving DMN, SN, ECN, and auditory network using the seed-to-voxel and voxel-to-voxel functional connectivity (FC) analyses during cognitive reappraisal process, emphasizing the PTSD-specific features of overactive and hyperconnected SN (Keller *et al.*, 2022). Despite involving various trauma events, these studies showed that MDD and PTSD had shared hypoactivation in the PFC, a region critical for threat detection and evaluation, and inhibitory control of emotion and memory expres-

Table 1: Findings of neuroimaging studies enrolling PTSD, MDD, and/or PTSD + MDD patients.

Study	Patients: Diagnosis, participants, *n* (females, *n*), age, years	HC: participants, *n* (females, *n*), age, years	Analysis methods	Neuroimaging findings: Comparisons (PTSD vs MDD; PTSD + MDD vs HC; PTSD + MDD vs MDD/PTSD; HC vs MDD/PTSD) and potential mechanisms (MDD or PTSD symptoms related)
Resting-state fMRI				
Averill *et al.* (2024)	PTSD/PTSD + MDD, 27 (0), 37.41; MDD, 22 (0), 33.87	–	longitudinal alterations of FC following a mild experimental stressor (DMN)	PTSD-specific alterations: a stress-induced significant reduction in DMN strength; MDD-specific alterations: a stress-induced significant increase in DMN strength; main effect of group: significant reduction in DMN strength in the PTSD group compared to the MDD group
Gong *et al.* (2019a)	PTSD, 50 (34), 43.10; MDD, 50 (34), 38.89	122 (64), 29.61	effective connectivity (between the MDN and the cortex)	HC vs MDD and HC vs PTSD: transdiagnostic feature: left MDN displayed significant effective connectivity increases with five regions including the right postcentral gyrus, left SMG, right putamen, right SMG/angular gyrus and right medial SFG; the right MDN displayed significant effective connectivity increases with five regions including the bilateral SMG, right postcentral gyrus, right medial SFG and left MCC
Gong *et al.* (2017)	PTSD, 50 (34), 43.10; MDD, 50 (34), 38.89	122 (64), 29.61	FC analysis (DMN, CEN, SN)	HC vs MDD and HC vs PTSD: transdiagnostic feature: both MDD and PTSD groups reductions in intranetwork connectivity of the DMN; PTSD vs MDD: no significant difference in internetwork connectivity among the HC, PTSD, and MDD groups
Kennis *et al.* (2013)	PTSD + MDD, 27 (0), 37.41; PTSD, 22 (0), 33.87	–	FC analysis (ROI: sgACC and insula)	sgACC as seed: PTSD ± MDD ≤ PTSD, bilateral thalamus; PTSD ± MDD ≥ PTSD, perigenual ACC; bilateral insula as seeds: PTSD ± MDD ≤ PTSD, left HIP. PTSD ± MDD group: CAPS cluster B scores correlated negatively with connectivity of the sgACC with the perigenual ACC; PTSD group: CAPS cluster C scores correlated negatively with connectivity of the sgACC with the left thalamus
Koopowitz *et al.* (2023)	PTSD, 22 (22), 31.1; MDD, 18 (18), 28.2; PTSD + MDD, 17 (17), 30.4	28 (28), 26.1	FC analysis (within and between SN, DAN, frontoparietal network, and DMN	Within DMN: PTSD ± MDD ≤ HC, ACC-left precuneus, precuneus-left hippocampal gyrus; PTSD ± MDD ≤ PTSD, ACC-left precuneus; MDD ≥ HC, ACC-left hippocampal gyrus, right angular gyrus-left hippocampal gyrus, right angular gyrus-right hippocampal gyrus, left precuneus-left hippocampal gyrus, right PCG-right hippocampal gyrus, right PCG-right precuneus; PTSD ≥ HC, ACC-left hippocampal gyrus; PTSD ≤ MDD, left precuneus-right precuneus Within right frontoparietal network: PTSD ± MDD ≥ MDD, right dorsolateral PFC-right IPL, right IPL-right MTG, right IPL-left IPL, right IPL-left, right cingulate gyrus, right MTG- left IPL, left IPL-left, right cingulate gyrus; PTSD ± MDD ≥ PTSD, right dorsolateral PFC-right IPL; PTSD ± MDD ≥ HC, right dorsolateral PFC-right middle frontal, right MTG-left IPL; MDD ≤ HC and PTSD ≤ HC, right IPL-left IPL Within left frontoparietal network: MDD ≤ HC, left middle frontal gyrus-left MTG, left middle frontal gyrus-left precuneus, left middle frontal gyrus-right IPL, left IFG-right IPL; MDD ≤ PTSD ± MDD, left middle frontal gyrus-left MTG, left middle frontal gyrus-right IPL, left IFG-left precuneus; MDD ≤ PTSD, left middle frontal gyrus-left MTG, left middle frontal gyrus-left precuneus, left IFG-left precuneus, left IFG-right IPL; PTSD ≤ HC, left middle frontal gyrus-right IPL Between-network connectivity: no significant group effect
Yuan *et al.* (2019)	PTSD + MDD, 18 (17), 45.3; PTSD, 28 (17), 45.8	50 (32) (TEHC), 45.0	whole brain FC analysis (seeds: BLA, CMA)	TEHC < PTSD (uncorrected): BLA-left ACC/SMA connectivity and BLA-right putamen/pallidum connectivity; PTSD + MDD < PTSD: right BLA connectivity with left ACC/SMA and bilateral putamen/pallidum; PTSD + MDD > PTSD: CMA connectivity with left ACC/SMA; TEHC vs PTSD + MDD: no significant difference; PTSD + MDD group: negative relationship between BLA-right putamen/pallidum connectivity and depression severity; PTSD alone group: no significant correlations between the FC values and depression severity; both patient groups: no correlation with FC values for PTSD symptom

Table 1: Continued

Study	Patients: Diagnosis, participants, *n* (females, *n*), age, years	HC: participants, *n* (females, *n*), age, years	Analysis methods	Neuroimaging findings: Comparisons (PTSD vs MDD; PTSD + MDD vs HC; PTSD + MDD vs MDD/PTSD; HC vs MDD/PTSD) and potential mechanisms (MDD or PTSD symptoms related)
Zhu *et al.* (2017)	PTSD + MDD, 21 (14), 36.1; PTSD, 27 (15), 36.0	34 (23) (TEHC), 35.1	between-ROI FC analysis (ROI: BLA, CMA, NAcc, orbitofrontal cortex, thalamus, HIP, and sgACC)	TEHC vs PTSD: no significant difference; PTSD ± MDD ≤ PTSD: NAcc-thalamus, NAcc-HIP, BLA-orbitalfrontal cortex pathways; PTSD ± MDD ≤ TEHC: NAcc-thalamus, NAcc-HIP and BLA-orbitalfrontal cortex pathways; in all PTSD patients: AMYG pathway connectivity (BLA-orbitalfrontal cortex, CMA-thalamus) negatively correlated with PTSD symptom severity; MDD symptoms were negatively associated with the BLA-orbitalfrontal cortex and NAcc-thalamus pathways
Zilcha-Mano *et al.* (2020)	PTSD + MDD, 52 (23), 43.9; PTSD, 51 (22), 40.6	76 (40) (TEHC), 40.8	between-ROI FC analysis; machine learning: linear kernel support vector machine model; group analyses of the most discriminative features	PTSD + MDD < PTSD: within connectivity in the BGN, and connectivity in BGN-other networks, SN–DMN, DAN–ECN, and SMN–other networks; PTSD + MDD > PTSD: within connectivity in the ECN, SN, and DAN; no significant correlation between depressive/PTSD symptoms and biomarkers identified from PTSD + MDD and PTSD alone classification
Task-related fMRI				
Bryant *et al.* (2021)	PTSD, 45 (24), 40.4; MDD, 26 (21), 31.5	25 (14) (TEHC), 45.1	fMRI during an emotion processing task; hypothesized ROI (brain activation); whole-brain voxel-wise analysis	subliminal processing of sad faces: (Sad vs Neutral, ROI): PTSD ≥ MDD, the left AMYG, caudate, putamen, right caudate and left pallidum; (Happy vs Neutral, ROI): no group differences; whole-brain voxel-wise analysis: no group differences
Kemp *et al.* (2007)	PTSD + MDD, 8 (5), 40.25; PTSD, 8 (NA), 35.38	32 (20), 35.94	fMRI during fear processing; hypothesized ROI (brain activation)	PTSD alone ≥ HC: right AMYG; PTSD ± MDD ≤ PTSD alone: medial PFC and AMYG; PTSD ± MDD ≤ HC: left AMYG
Keller *et al.* (2022)	PTSD, 20(10), 43.4; MDD, 35 (17), 37.3	34 (17), 39.4	fMRI during cognitive reappraisal; whole-brain fMRI analysis (brain activation), hypothesized ROI (brain activation), task-related FC	whole-brain fMRI analysis (reappraise > view): MDD ≤ HC, right triangular and opercular parts of the IFG, and right precentral gyrus; PTSD vs HC: no significant differences; MDD vs PTSD: no significant differences; negative correlations between clinical severity of anxiety or depression and activation of the right IFG during cognitive reappraisal hypothesized ROI (reappraise > view): HC ≥ MDD, left MTG, dorsomedial PFC, supplementary motor cortex as well as right dorsomedial PFC and IFG; HC ≥ PTSD, right dorsomedial PFC and IFG; MDD vs PTSD: no significant differences FC (seed-to-voxel, right IFG as seed; reappraise > view): PTSD ≥ HC, left frontal orbital cortex, temporal pole, IFG, frontal operculum, and insula; HC ≥ MDD, none of the voxels survived correction; PTSD ≥ MDD, precuneus, anterior and PCG, bilateral paracingulate gyrus, bilateral SFG, left frontal orbital cortex, left temporal pole FC (voxel-to-voxel): PTSD ≥ HC, precuneus, PCG, bilateral lingual gyrus, bilateral intracalcarine cortex, bilateral cuneal cortex, right supracalcarine cortex and bilateral OC; MDD ≥ HC, precentral gyrus: PTSD ≥ MDD, right lateral OC, right angular gyrus, right MTG, right SMG, and right STG
Lanius *et al.* (2007)	PTSD + MDD, 15 (11), 34.6; PTSD, 11 (7), 35.6	16 (13) (TEHC), 33.8	fMRI during trauma script-driven imagery procedure; fMRI random effects analysis (brain activation)	TEHC ≥ PTSD: bilateral dorsal ACC; right ventrolateral PFC; PTSD ≥ PTSD ± MDD: left insula; PTSD ± MDD ≥ PTSD: bilateral dorsal ACC; bilateral PCG; TEHC ≥ PTSD ± MDD: left thalamus; bilateral ventral ACC; bilateral ventromedial prefrontal cortices; right middle frontal gyrus; PTSD ± MDD ≥ TEHC: right dorsal ACC; bilateral PCG

Table 1: Continued

Study	Patients: Diagnosis, participants, *n* (females, *n*), age, years	HC: participants, *n* (females, *n*), age, years	Analysis methods	Neuroimaging findings: Comparisons (PTSD vs MDD; PTSD + MDD vs HC; PTSD + MDD vs MDD/PTSD; HC vs MDD/PTSD) and potential mechanisms (MDD or PTSD symptoms related)
van Rooij *et al.* (2015)	PTSD + MDD, 16 (0), NA, PTSD, 13 (0), NA	28 (0) (TEHC), 36.84; 25 (0) (HC), 35.38	fMRI during trauma-unrelated emotional processing; hypothesized ROI (brain activation)	PTSD ± MDD ≤ PTSD: sgACC response to neutral, negative and positive pictures; no significant correlation within the whole PTSD group was observed between PTSD severity and sgACC activity
Whalley *et al.* (2009)	PTSD, 16 (10), 36.8; MDD, 16 (12), 33.6	16 (10) (TEHC), 32.5	fMRI during an episodic memory retrieval task; fMRI random effects analysis (brain activation)	old > new contrast: PTSD ≥ TEHC, left dorsal AMYG and right middle OC; PTSD ≤ TEHC, right lateral PFC: PTSD ≥ MDD, left dorsal AMYG and right middle OC; PTSD ≤ MDD, right PFC emotional > neutral hit contrast: PTSD ≥ TEHC, left putamen and HIP, right precuneus, MCC and OC; PTSD ≥ MDD, left putamen and HIP, right precuneus, MCC and OC negative > neutral hit contrast: PTSD ≥ TEHC, left SFG and right precuneus; PTSD ≤ TEHC, left STG; PTSD ≥ MDD, left SFG and right precuneus; PTSD ≤ MDD, left STG positive > neutral hit contrast: PTSD ≥ TEHC, bilateral precentral gyrus, insula, right MTG, right MCC, right OC and right cerebellum; PTSD ≥ MDD, bilateral precentral gyrus, insula, right MTG, right MCC, right OC and right cerebellum
structural MRI (T1WI)				
Dai *et al.* (2020)	PTSD + MDD, 10 (5), 33.50; MDD, 11 (7), 37.82	29 (15), 32.90	tensor-based morphometry (brain volume)	PTSD ± MDD ≤ HC: right opercular IFG; MDD ≤ HC: right opercular IFG and left orbital IFG; PTSD ± MDD vs MDD: no significant difference. MDD participants: significant correlation between opercular IFG volume and depressive severity
Gong *et al.* (2019b)	PTSD, 91 (62), 42.73; MDD, 92 (49), 34.96	201 (123), 29.61	VBM (brain volume)	HC vs MDD and HC vs PTSD: transdiagnostic feature: higher gray matter volume in bilateral putamen
Kroes *et al.* (2011)	PTSD, 24 (15), 35.9; MDD, 29 (21), 33.4	29 (16) (TEHC), 32.45	VBM (brain volume)	PTSD vs MDD: no significant difference; combined clinical groups ≤ TEHC: MCC, medial PFC extending from the medial SFG at the precentral gyrus to the orbitofrontal cortex and ACC; right dorsolateral PFC spanning the middle frontal gyrus and SFG; PTSD group: negative relationship between brain volume in the right SFG, fusiform gyrus, lingual gyrus and left cuneus with depression severity; MDD group: positive relationship between brain volume in the bilateral cuneus and precuneus, and left fusiform gyrus

Abbreviations: AMYG, amygdala; CAPS, Clinician Administered PTSD scale; CEN, central executive network; F, female; FC, functional connectivity; HIP, hippocampus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MCC, midcingulate cortex; MDN, medio-dorsal thalamic nucleus; MTG, middle temporal gyrus; NR, not reported; OC, occipital cortex; PCG, posterior cingulate gyrus; SFG, superior frontal gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; SMN, sensorimotor network; STG, superior temporal gyrus; TEHC, trauma-exposed; T1WI, T1 weighted imaging.

Table 2: Neuroimaging studies of treatment effects on the brain in PTSD + MDD patients.

Study	Patients, *n* (females, *n*), age, years	HC, *n* (females, *n*), age, years	Analysis methods	Therapy	Symptom relief	Neuroimaging findings
						Predictors (improved depressive symptoms and PTSD symptoms); Potential mechanisms (MDD/PTSD related)
Barredo *et al.* (2019)	PTSD + MDD, 21 (10), 52.0	–	Diffusion-weighted MRI; probabilistic tractography (frontal WM pathways: the forceps minor, ATR, cingulum, and uncinate fasciculi)	TMS with targeted region in left DLPFC	9 participantss met threshold response criterion for both PTSD and MDD	Predictors for improved depressive symptoms: FA in bilateral ATR was marginally associated with left amygdala-to-left MPFC FC (uncorrected; right ATR (P); left ATR (N)); bilateral ATR FA accounted for significant variance in right amygdala-left MPFC FC predictor (uncorrected; right ATR (P); left ATR (N)); significant relationship between RD and right amygdala-left MPFC functional predictors (right ATR (N), corrected; left ATR (P), uncorrected) Predictors for improved PTSD symptoms: FA in bilateral ATR accounted for significant variance in left amygdala-to-left MPFC FC predictors (right ATR survived Bonferroni correction; right ATR (P); left ATR (N)); significant relationship between FA in bilateral ATR and right amygdala-to-left MPFC FC predictors (corrected; right ATR (P); left ATR (N)); significant effect of RD in ATR on right amygdala-to-left MPFC FC (uncorrected); FA in the forceps minor and bilateral ATR accounted for significant variance in right sgACC-left lateral PFC functional predictor (left right ATR and forceps minor (N), uncorrected; left ATR (P), corrected)
Dai *et al.* (2020)	PTSD + MDD, 10 (5), 33.5	29 (15), 32.90	T1 weighted imaging; tensor-based morphometry (brain volume)	ketamine	both depressive and PTSD symptoms were significantly improved	Potential Mechanisms, pre- vs posttreatment: no significant volume change; the volume of right opercular IFG showed a minor increase after treatment; pretreatment ≤ HC: right opercular IFG; posttreatment vs HC: no group differences in the volume of right opercular IFG; the correlations between local volume changes and depressive/PTSD symptoms were not assessed
Henigsberg et al. (2011)	PTSD + MDD, 11 (NA), NA	–	proton magnetic resonance spectroscopy (DLPFC)	selective serotonin reuptake inhibitors	early response to antidepressant treatment within 3–6 weeks	Potential Mechanisms: significant increase in choline to creatine ratio from the first to the second spectroscopic scan during the antidepressant treatment
Yang *et al.* (2018b)	PTSD, 15 (15) (5 with comorbid MDD), 32.9; MDD, 16 (14), 34.6	19 (15), 33.4	fMRI during emotional conflict task; whole-brain analysis (brain activation)	12 weeks of either CBT for MDD or CPT for PTSD	depressive symptoms were significantly improved in both patient groups	Potential Mechanisms: increased activation of the left DLPFC was negatively correlated with depressive symptoms across all participants, and this brain-symptom association did not differ between MDD patients and those with PTSD

Table 2: Continued

Study	Patients, *n* (females, *n*), age, years	HC, *n* (females, *n*), age, years	Analysis methods	Therapy	Symptom relief	Neuroimaging findings Predictors (improved depressive symptoms and PTSD symptoms); Potential mechanisms (MDD/PTSD related)
Philip *et al.* (2018)	PTSD + MDD, 25(12), 51.8	–	resting-state fMRI; ROI-basic FC (sgACC, DLPFC, HIP, and BLA), data-driven MVPA	TMS with targeted region in left DLPFC	12 and 11 participantss met threshold response criterion for PTSD and MDD, respectively	Predictors for improved depressive symptoms: (pre-treatment) left BLA seed: increased FC with bilateral MPFC; right BLA seed: increased FC with frontopolar cortex; MVPA-derived clusters: right IPL, right dorsal ACC, left INS, and right superior temporal gyrus Predictors for improved PTSD symptoms: (pre-treatment) right sgACC seed: more negative FC with midline precuneus/PCC; more negative FC with left visual regions and medial/superior bilateral frontal regions of the DMN and SN; greater positive FC between sgACC and left IFG; left BLA seed: Increased FC with left MPFC; right BLA seed: increased FC with left VMPFC and frontopolar cortex; MVPA-derived clusters: right IPL, right amygdala, left parahippocampal gyrus, right DLPFC, and bilateral VMPFC Potential Mechanisms (MDD related): (post- vs pretreatment) sgACC seed: decreased FC of sgACC with midline precuneus/PCC, midline dorsal ACC and bilateral somatosensory/motor regions; anterior HIP seed: FC between the anterior HIP and multiple SN regions (right INS, left IPL), and left putamen; MVPA-derived clusters: right INS, midline dorsal ACC, left ACC, right caudate, bilateral motor cortex, and right fusiform gyrus Potential Mechanisms (PTSD related): (post- vs pretreatment) sgACC seed: decreases in FC between right sgACC and left precuneus/PCC, dorsal ACC, left DLPFC, bilateral INS, and visual regions; anterior HIP seed: decreases in anterior hippocampal FC with midline dorsal ACC, right INS, and left putamen; MVPA-derived clusters: bilateral motor cortex, left HIP, left VMPFC, left medial frontal gyrus, left dorsal ACC, right caudate, left putamen, left fusiform and right amygdala

Abbreviations: CBT, cognitive behavioral therapy; CPT, cognitive processing therapy; DLPFC, dorsolateral PFC; F, female; FC, functional connectivity; HIP, hippocampus; IFG, inferior frontal gyrus; INS, insula; IPL, inferior parietal lobule; MPFC, medial PFC; MVPA, multivoxel pattern activation; N, negative; NA, not available; P, positive; RD, radial diffusivity; VMPFC, ventromedial PFC; WM, white matter.

Table 3: Shared and/or distinct neuroimaging findings between MDD and PTSD cohorts revealed by these meta-analyses.

Study	Imaging methods	Number of studies			Meta-analysis tools	Main findings of MDD and PTSD
		MDD	PTSD	others		
Task-related fMRI						
McTeague *et al.*, 2017	whole brain, activation (cognitive control)	24	6	schizophrenia, 135; obsessive compulsive disorder, 25, etc.	ALE	Transdiagnostic abnormalities: abnormal activation in the left PFC, as well as anterior insula, right ventrolateral PFC, right intraparietal sulcus, and midcingulate/pre-supplementary motor area
Schulze *et al.*, 2019	whole brain, activation (affective processing)	32	14	borderline personality disorder, 24	SDM v5.141	Diagnosis-specific meta-analyses: MDD ≥ HC, the right posterior insula, right rolandic operculum, right postcentral gyrus, right inferior occipital gyrus, bilateral median cingulate/paracingulate gyri, left caudate nucleus, right anterior cingulate/paracingulate gyri, and a cluster comprising the thalamus; MDD ≤ HC, the right amygdala, right inferior temporal gyrus, left superior parietal gyrus, left precentral gyrus, right middle frontal gyrus, left insula, and left IFG, triangular. PTSD ≥ HC, the orbital and triangular parts of left IFG, bilateral striatum (encompassing parts of the right amygdala), and left MTG; PTSD ≤ HC, bilateral postcentral gyrus, right superior temporal gyrus, and right insula (voxel-level uncorrected $P < 0.005$, cluster-level threshold of $k \geq 20$ voxels) Comparison of MDD and PTSD: PTSD ≥ MDD, the left IFG (including ventrolateral PFC), bilateral amygdala and hippocampus, bilateral striatum, left MTG, left dorsolateral SFG and the right middle frontal gyrus. MDD ≥ PTSD: no suprathreshold clusters Transdiagnostic abnormalities: hyper-activation of the right median cingulate gyrus as well as hypo-activations of the right middle frontal gyrus and the right middle occipital gyrus
Janiri *et al.*, 2020	whole brain, activation	83	35	bipolar disorder, 66; anxiety disorders, 42	ALE	Pooled analysis: transdiagnostic hypoactivation were identified centered in the right inferior PFC/insula, inferior parietal lobule, and putamen Diagnosis-specific meta-analyses: did not identify any additional disorder-specific clusters of hypo- or hyperactivation in diagnosis-specific meta-analyses of MDD and PTSD
Wang *et al.*, 2024	whole brain, activation	125	35	–	SDM	Transdiagnostic abnormalities: increased neural activation in the bilateral inferior frontal gyrus Comparison of MDD and PTSD: PTSD ≥ MDD, the right insula, left supplementary motor area extending to median cingulate gyrus and SFG, and left fusiform gyrus; PTSD ≤ MDD: the right posterior cingulate gyrus, right MTG, right paracentral lobule, and right inferior parietal gyrus
Structural MRI (gray matter)						
Bromis *et al.*, 2018	ROI, volume	NR	66	–	Hedges' *g* (Cohen effect size with small-sample correction)	Meta-analysis in PTSD: PTSD ≤ HC, brain volume, intracranial volume, and volumes of the insula (left, right, and total), SFG, left MTG, inferior temporal gyrus, anterior cingulate (left and total), rostral ACC, lateral orbitofrontal cortex, and total amygdala Comparison of MDD and PTSD: PTSD ≤ MDD, total brain volume; PTSD ≥ MDD, the thalamus volume Transdiagnostic abnormalities: smaller hippocampal volume compared with HC

Table 3: Continued

Study	Imaging methods	Number of studies			Meta-analysis tools	Main findings of MDD and PTSD
		MDD	PTSD	others		
Serra-Blasco *et al.*, 2021	whole brain, VBM	45	12	anxiety disorders, 20	SDM v.6.21	Diagnosis-specific meta-analyses: MDD ≤ HC, the bilateral cerebellum and left IFG ($P < 0.05$, TFCE corrected), as well as the right IFG including bilateral insula, left SFG including anterior cingulate subregions and right ventromedial PFC, bilateral hippocampi and left rolandic operculum including right posterior cingulum ($P < 0.01$, uncorrected). MDD ≥ HC, no regional GMV increases. PTSD ≤ HC, the left lingual gyrus extending to fusiform gyrus and the bilateral SFG ($P < 0.05$, TFCE corrected), as well as the left postcentral gyrus, right fusiform gyrus, left calcarine fissure, left parahippocampal. and left middle cingulate cortex ($P < 0.01$, uncorrected); PTSD ≥ HC, no regional GMV increases Comparison of MDD and PTSD: no significant differences at any explored threshold Transdiagnostic abnormalities: no significant results ($P < 0.05$, TFCE corrected); reduced GMV in the left middle cingulate cortex ($P < 0.01$, uncorrected)
Structural MRI (white matter)						
Jenkins *et al.*, 2016	whole brain, FA	12	4	bipolar disorder, 10; social anxiety disorder, 3; obsessive-compulsive disorder, 8	SDM v.4.31	Pooled analysis: transdiagnostic reduced FA were identified in several clusters, including the left forceps minor of the corpus callosum/ATR/inferior fronto-occipital fasciculus/uncinate fasciculus, left SLF, left cerebellum, left superior corona radiata/corticospinal tract, and right SLF Disorder-specific meta-analyses: MDD ≤ HC, left ATR, bilateral SLF, right cerebellum, and left inferior fronto-occipital fasciculus/uncinate fasciculus; PTSD ≤ HC, left uncinate fasciculus, left SLF, left cingulum, and right inferior longitudinal fasciculus These regions of reduced FA in PTSD did not overlap with those of other disorders

Abbreviations: ALE, activation likelihood estimation; CT, cortical thickness; ES, effect size; GMV, gray matter volume; IFG, inferior frontal gyrus; MTG, middle temporal gyrus; NR, not reported; SDM, seed-based d mapping; SFG, superior frontal gyrus; SLF, superior longitudinal fasciculus; TFCE, threshold-free cluster enhancement.

sion, while higher activation in SN and fear processing regions including amygdala, hippocampus, and insula was mainly observed in PTSD relative to MDD group during cognitive and emotional processing (Fig. 2). One relevant study found that left dorsolateral PFC activation during a cognitive control task was negatively correlated with depression severity across MDD and PTSD (Yang *et al.*, 2018b), suggesting the common neural alteration possibly associated with the overlapping depressive symptoms.

These meta-analyses based on task-related fMRI studies have provided additional information to support the viewpoint that MDD and PTSD may have transdiagnostic and disorder-specific features in brain function during the execution of tasks, mainly involving the SN and fear processing regions (Janiri *et al.*, 2020; McTeague *et al.*, 2017; Schulze *et al.*, 2019; Wang *et al.*, 2024). Aiming to investigate transdiagnostic and disorder-specific neural abnormalities during the processing of negative affective stimuli, Schulze *et al.* conducted comparative meta-analyses in task-related fMRI studies in borderline personality disorder, MDD, and PTSD (Schulze *et al.*, 2019). Results for individual disorders demonstrated decreased activation in the right amygdala in MDD contrasting with enhanced activation in PTSD compared with HC. Directly compared to MDD, individuals with PTSD showed enhanced activation in the left inferior and superior frontal gyri, right middle frontal gyrus, and bilateral amygdala and hippocampus. Conjunction analysis identifying the transdiagnostic neural activation illustrated a hyperactivation of the right median cingulate gyrus as well as hypoactivation of the right middle frontal gyrus and middle occipital gyrus. Another meta-analysis of task-related fMRI studies by Janiri *et al.* identified transdiagnostic clusters of hypoactivation in regions primarily involved in inhibitory control and salience processing (i.e. inferior PFC/insula, inferior parietal lobule, and putamen) across psychiatry disorders including MDD and PTSD (Janiri *et al.*, 2020). Moreover, a transdiagnostic neuroimaging meta-analysis by McTeague *et al.* investigated the neural circuitry disruptions underlying cognitive control processing across psychiatric disorders including MDD and PTSD (McTeague *et al.*, 2017). This study revealed abnormal activation in multiple regions, such as the PFC, anterior insula, and so on. Recently, the meta-analysis by Wang *et al.* also supported the viewpoint that PTSD and MDD share similar neural activation in the PFC (Wang *et al.*, 2024).

In addition, we identified four resting-state fMRI studies that compared MDD and PTSD directly (Averill *et al.*, 2024; Gong *et al.*, 2017, 2019a; Koopowitz *et al.*, 2023). Among them, the two studies by Gong *et al.* enrolled patients with PTSD who had experienced the same trauma event of 2008 Sichuan earthquake (Gong *et al.*, 2017, 2019a). Focusing on networks of interest (i.e. DMN, ECN, and SN), Gong *et al.* revealed transdiagnostic reductions in intra-network connectivity of the DMN and no significant difference in inter-network connectivity among HC, PTSD, and MDD groups (Gong *et al.*, 2017). Another study by Gong *et al.* applied psychophysiological interaction analysis to measure the resting-state effective connectivity between the medio-dorsal thalamic nucleus and rest of the cortex (Gong *et al.*, 2019a). In this study, Gong *et al.* identified transdiagnostic features of stronger effective connectivity between the medio-dorsal thalamic nucleus and neocortex (several prefrontal and parietal regions bilaterally such as postcentral gyrus, supramarginal gyrus, and medial superior frontal gurus) in medication-naïve MDD and PTSD cohorts relative to the HC. Koopowitz *et al.* recently recruited mothers at the 18-month postpartum time point and divided them into four groups: PTSD, MDD, PTSD + MDD, and controls (Koopowitz *et al.*, 2023). FC within and between higher order cognitive control networks, including the SN, dorsal attention network (DAN), frontoparietal network, and DMN were compared across the four groups. Koopowitz *et al.* found that PTSD with comorbid MDD showed greater intrinsic FC within the right frontoparietal network, relative to the controls and the monodiagnostic groups. Compared to PTSD group and controls, MDD group showed greater FC within the DMN, and weaker FC within the left frontoparietal network. No group differences in inter-network connectivity were observed in this study. Recently, Averill *et al.* compared the longitudinal alterations of DMN strength following a mild experimental stressor in MDD and PTSD (Averill *et al.*, 2024). This study revealed a stress-induced reduction in DMN strength in PTSD group while increased DMN strength in MDD group. Notably, the researchers also demonstrated a significant main effect of group, showing significantly reduced DMN strength in the PTSD group relative to MDD group. Overall, these fMRI studies support the viewpoint that DMN dysfunctions, especially a functional impairment of the PFC, are implicated in the pathophysiology of MDD and PTSD. A fuller presentation of findings of these original fMRI studies is shown in Table 1.

Comparisons between PTSD + MDD and PTSD alone

Patients diagnosed with PTSD might have either subthreshold depression or meet criteria for MDD. Individuals with PTSD + MDD often exhibit greater functional and occupational impairments and poorer treatment response than participants with PTSD alone (Kessler *et al.*, 2005), raising interest in underlying neurobiological differences and similarities between patients with PTSD alone and those with PTSD + MDD. In the present review, we identified three task-related neuroimaging studies examined the effects of MDD comorbidity on neural activity in the context of PTSD (Kemp *et al.*, 2007; Lanius *et al.*, 2007; van Rooij *et al.*, 2015). During a trauma script-driven imagery procedure, Lanius *et al.* found that both PTSD + MDD and PTSD alone groups revealed decreased brain activation in the ACC and right ventrolateral PFC relative to traumatized controls, whereas the PTSD + MDD group had lower insula activation, less reduction in ACC and higher posterior cingulate cortex (PCC) activation versus patients with PTSD alone (Lanius *et al.*, 2007). Another fMRI study reported that decreased subgenual ACC (sgACC) activation was related to the MDD status within the PTSD group during trauma-unrelated emotional processing (van Rooij *et al.*, 2015). The opposite findings in the ACC of the two studies (Lanius *et al.*, 2007; van Rooij *et al.*, 2015) possibly relate to the various trauma type (veteran experience vs motor vehicle accident) and imagery procedure stimuli (trauma-driven vs trauma-unrelated), but this needs further examination. Some fear-related regions such as amygdala and PFC in PTSD are more likely to be activated by negative stimuli than they are in PTSD + MDD. Supporting this view, Kemp *et al.* found lower activity in the amygdala and medial PFC in response to fear stimuli in patients with PTSD + MDD compared to patients with PTSD alone (Kemp *et al.*, 2007). Of special interest, the PTSD alone group in this study showed increased activation in the right amygdala while the PTSD + MDD group showed decreased activation in the left amygdala relative to the HC. As the most common fMRI finding in individuals with PTSD, amygdala hyperactivity has been thought to facilitate associative fear learning and result in stronger fear associations (Harnett *et al.*, 2020). The findings of Kemp *et al.* hinted the effects of comorbid depression on amygdala activation in the context of PTSD.

Several resting-state fMRI studies investigating whether PTSD + MDD comorbidity holds an underlying neural basis

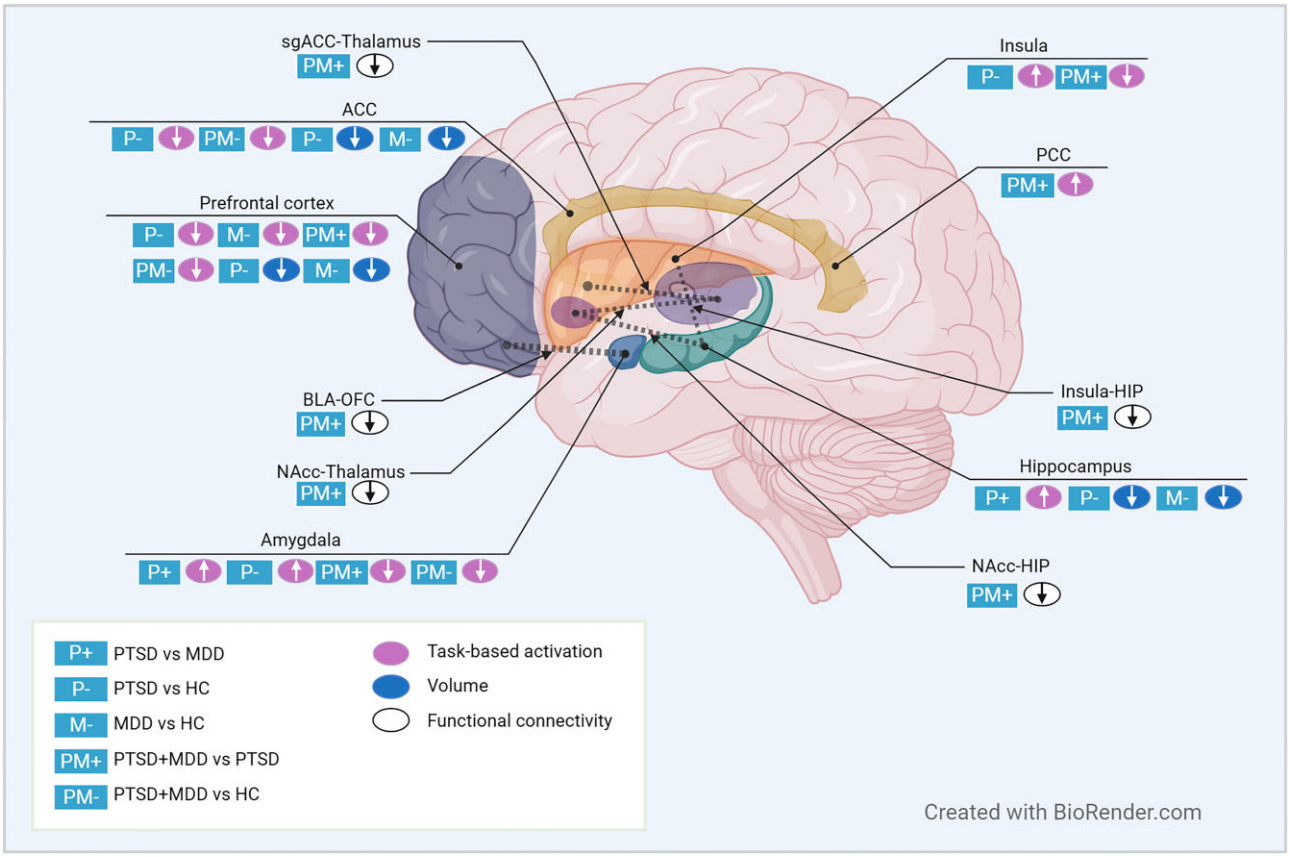

Figure 2: Key brain regions that showed similar or distinct neuroimaging features among MDD alone, PTSD alone, and PTSD + MDD cohorts. Abbreviations: HIP, hippocampus; OFC, orbitofrontal cortex.

different from PTSD alone have focused on regions related to fear and reward processing, such as ACC, insula, amygdala, and nucleus accumbens (NAcc) (Fig. 2). The study by Kennis *et al* . used the sgACC and insula as seeds to investigate whether or not comorbid MDD contributes to the FC alterations in veterans with PTSD (Kennis *et al*., 2013). Kennis *et al*. found that FC of the sgACC with the thalamus and perigenual parts of the ACC can distinguish PTSD + MDD from PTSD alone, suggesting that these features may serve as a neurobiological marker for comorbid depression in PTSD population (Kennis *et al*., 2013). Besides, Kennis *et al*. also reported that reduced FC of insula-hippocampus in PTSD + MDD relative to PTSD alone might be due to medication effects, raising an issue that needs more attention in future research. The amygdala, another core region in the fear circuit, has been suggested to be involved in the pathophysiology of both PTSD and MDD. Recent studies have identified the specialized roles of basolateral (BLA) and centromedial amygdala (CMA) during fear conditioning (Ciocchi *et al*., 2010; Mahan and Ressler, 2012). Considering the dissociable functions of the BLA and CMA, Zhu *et al*. conducted the first study investigating amygdala FC at the subregional level between PTSD alone and PTSD + MDD with seeds of BLA, CMA, and NAcc (Zhu *et al*., 2017). They found that PTSD + MDD group exhibited weaker FC of BLA-orbitofrontal cortex, Nacc-thalamus, and NAcc-hippocampus relative to either PTSD alone or trauma-exposed HC, whereas there was no significant difference between PTSD alone and trauma-exposed HC, suggesting that deficits in NAcc and amygdala pathways involved in fear and reward processing are prominently and selectively altered in PTSD + MDD. The findings of Zhu *et al*. are consistent with evidence that individuals with PTSD + MDD have more severe illness and need more robust intervention.

To eliminate the potential influences of predefined ROI, various trauma types and medication treatment, Yuan *et al*. performed a whole-brain group analysis to comprehensively explore the functional networks involving the subregional amygdala in drug-naïve individuals with PTSD + MDD and PTSD alone exposed to the same massive earthquake (Yuan *et al*., 2019). Yuan *et al*. found that weaker BLA-right putamen/pallidum connectivity in PTSD + MDD was related to comorbid depression severity, as opposed to greater PTSD symptom severity in PTSD + MDD. In addition, PTSD + MDD group also showed weaker FC between right BLA with left ACC/supplementary motor area and left putamen/pallidum, as well as greater CMA connectivity with left ACC/supplementary motor area. These findings suggest that specific FC dysfunctions may distinguish PTSD + MDD from PTSD alone at the whole-brain level. In line with this view, Zilcha-Mano *et al*. further demonstrated the clinical utility of within- and between-networks connectivity features in differentiating individuals with PTSD alone from those with PTSD + MDD by means of a support vector machine model with accuracy achieving 76.7% (Zilcha-Mano *et al*., 2020). The most discriminative features included within-network FC in the basal ganglia network (BGN), DAN, and SN. Group analysis of these FC biomarkers demonstrated higher within-network connectivity in the BGN but lower within-network connectivity in the ECN, SN, and DAN in PTSD alone, versus PTSD + MDD. Overall, these studies propose proof for the effects of comorbid MDD on the brain in PTSD populations, suggesting the potential application of neuroimaging markers in differential diagnosis of PTSD.

Structural MRI in PTSD and MDD

Although past mono-diagnostic neuroimaging studies demonstrated that PTSD and MDD may share similar abnormalities in neuroanatomical substrates, few studies have contrasted the neuroanatomical alterations in MDD with those in PTSD. In the present review, we identified two studies using voxel-based morphometry (VBM) (Gong *et al.*, 2019b; Kroes *et al.*, 2011), and one study using tensor-based morphological method (Dai *et al.*, 2020). Various trauma types, analysis methods and sample types of these structural MRI studies make it impossible to make any summative conclusions. Specifically, Kroes *et al.* used VBM analysis to identify associated volumetric changes of PTSD and MDD, versus trauma-exposed HC. The research group found similar volume reductions predominantly in prefrontal areas (i.e. middle cingulate gyrus, medial PFC, ACC, orbitofrontal cortex, and dorsolateral PFC) but no significant difference between PTSD and MDD (Kroes *et al.*, 2011). Considering the similar levels of depression severity in the PTSD and MDD groups, Kroes *et al.* suggested that existing findings of gray matter reductions in prefrontal areas may not be specific to PTSD but rather related to features shared with other conditions, such as depression. In another VBM study, Gong *et al.* identified a transdiagnostic marker of increased putamen volume in four psychiatric groups (i.e. PTSD, MDD, obsessive-compulsive disorder, and psychosis) relative to HC by diagnosis-specific comparisons (e.g. PTSD vs HC, and MDD vs HC) (Gong *et al.*, 2019b). It is worth noting that the comorbid disorders of these participants were not recorded, and the research group did not conduct a direct comparison between MDD and PTSD in this study. Using tensor-based morphological analysis, Dai *et al.* investigated the regional volume differences for 29 HC participants and 21 patients with MDD, including 10 participants with comorbid PTSD (Dai *et al.*, 2020). They found that both MDD alone and PTSD + MDD groups showed smaller volume in right opercular inferior frontal gyrus relative to HC, only the MDD alone group showed smaller volume in left orbital inferior frontal gyrus compared to HC, and no significant difference was found between the MDD alone and PTSD + MDD groups (Table 1). The reliability and reproducibility of the findings need to be further verified in view of the small sample size. To provide more information, we also paid attention to relevant studies aiming to identify specific depression-related neuroanatomical abnormalities in the context of PTSD. Using FreeSurfer to analyze the volume of hippocampal subfields, Averill *et al.* provided the first evidence relating both PTSD and depression symptoms to structural alteration in the hippocampus-amygdala transition area, one region highly connected to prefrontal-amygdala circuitry, while dentate gyrus abnormalities were associated with depression severity but not PTSD symptoms (Averill *et al.*, 2017).

Several meta-analyses of structural MRI studies have been conducted recently to provide additional information. Bromis *et al.* conducted a statistical comparison of the ROI meta-analysis of PTSD with a previous meta-analysis of MDD (Bromis *et al.*, 2018). Both PTSD and MDD showed reduced hippocampal volume compared to HC, with no difference between the patient groups in this region. Compared to patients with PTSD and HC, patients with MDD had significantly reduced thalamus volume. Patients with PTSD had reduced total brain volume, relative to MDD and HC. Serra-Blasco *et al.* recently analyzed common and specific gray matter volume characteristics by conducting a meta-analysis of VBM studies of MDD, anxiety disorders, and PTSD with samples with no or minimal percentages of comorbidities (Serra-Blasco *et al.*, 2021). The pairwise comparison results (MDD vs PTSD) showed no significant difference for MDD and PTSD, whereas the conjunction analysis did show that the two disorders shared gray matter reduction in the left middle cingulate cortex when applying a more liberal threshold ($P < 0.01$, uncorrected). From a connectomic perspective, the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA)–Psychiatric Genomics Consortium used cortical thickness to construct structural covariance networks, and then calculated the cortical thickness-based centrality, a measure that characterizes the number of connections of a region. The researchers found that participants with PTSD + MDD showed higher centrality in the medial PFC and lower centrality in right visual cortex compared to PTSD alone (Rakesh *et al.*, 2023). Synthesizing the findings of these original studies and meta-analyses, we concluded that structural abnormalities in the PFC would be the most reliable findings across MDD and PTSD.

To identify transdiagnostic white matter alterations, Jenkins *et al.* conducted transdiagnostic meta-analysis and disorder-specific meta-analyses of fractional anisotropy (FA) studies across five emotional disorders including MDD and PTSD (Jenkins *et al.*, 2016). The transdiagnostic meta-analysis revealed commonalities in reduced FA in emotional disorders compared to HC in multiple white matter tracts, including the left anterior thalamic radiation (ATR), bilateral superior longitudinal fasciculi, and so on. The disorder-specific meta-analyses showed that the two largest peaks of reduced FA in MDD contrasts were in the left ATR and superior longitudinal fasciculus. Reduced FA in the left uncinate fasciculus and superior longitudinal fasciculus was identified in the PTSD contrasts, however, the two regions were inferior to those identified in MDD. To sum up, the PTSD group was the most distinct, with no clusters of reduced FA overlapping with any other emotional disorders. Yielding the largest studies, the ENIGMA Consortium examined the overlap in white matter deficit patterns across disorders (Kochunov *et al.*, 2022). The researchers adopted diffusion tensor imaging analytic workflow based on tract-based spatial statistics to extract 24 regional tractwise FA values for the entire white matter skeleton. They demonstrated that white matter deficits of PTSD showed only weak parallels with those seen in MDD. The two meta-analyses of FA studies support the anatomical specificity of white matter deficits in MDD and PTSD (Jenkins *et al.*, 2016; Kochunov *et al.*, 2022). Although these gray and white matter structural findings derived from secondary analyses of these original studies need further verification, they raise awareness of the potential importance of further studying the common and unique neuroanatomical alterations associated with MDD and PTSD.

Potential neural mechanisms and predictors of response to treatments in PTSD + MDD populations

To date, a series of reviews have summarized the clinical application of these therapeutic methods in treating MDD and PTSD mainly including antidepressants (e.g. selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, and ketamine), repetitive transcranial magnetic stimulation (TMS), and psychological intervention (e.g. acceptance and commitment therapy, cognitive therapy, and cognitive behavioral therapy) (Akhtar and Pilkhwal Sah, 2021; Cui *et al.*, 2024; Hidalgo and Davidson, 2000; Hung *et al.*, 2011; Jeffreys *et al.*, 2012). Given that individuals with PTSD + MDD tend to have more severe clinical symptoms and greater risk for suicidal behavior compared to patients with PTSD alone or MDD alone, we therefore

specifically focused on these studies exploring the underlying neural mechanisms of therapeutic effects that may correlate with the overlapped and/or disorder-specific neuroimaging features in PTSD + MDD populations. So far, a limited number of MRI studies have purely investigated the potential neural mechanisms of therapeutic response in PTSD + MDD populations, mainly involving selective serotonin reuptake inhibitors, ketamine, and repetitive TMS.

Antidepressant medication

There is increasing evidence to support the use of antidepressants, particularly the selective serotonin reuptake inhibitors, as first-line therapy in MDD and PTSD (Akhtar and Pilkhwal Sah, 2021; Cui *et al.*, 2024; Hidalgo and Davidson, 2000). Enrolling patients with PTSD + MDD, Henigsberg *et al.* measured changes of neuronal marker *N*-acetyl-aspartate, choline (CHO), and creatine using proton magnetic resonance spectroscopy in responders to antidepressant treatment with selective serotonin reuptake inhibitors (Henigsberg *et al.*, 2011). They found significant increase in choline/creatine ratio following the antidepressant treatment, suggesting increased turnover of cell membranes as a mechanism of the antidepressant drug therapy. Of note, research into pharmacotherapy for PTSD + MDD indicated that higher doses of antidepressant drugs may be needed than for patients with PTSD alone (Chiba *et al.*, 2016). Available first-line antidepressant medications require several weeks to produce a full therapeutic response, and many patients fail to achieve remission. Thus, regarding individuals with PTSD + MDD, most attention has been focused on the antidepressant ketamine, an *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist that can rapidly (within 1 day) produce an antidepressant response and treat suicidality (Feder *et al.*, 2014; Kritzer *et al.*, 2022; Zarate *et al.*, 2006).

Neuronal atrophy and glutamatergic signaling dysfunction catalyzed by stress have been implicated in cognitive deficits associated with PTSD and depression (Millan *et al.*, 2012; Musazzi *et al.*, 2013; Popoli *et al.*, 2011). Ketamine has shown potential as a novel glutamate-targeting antidepressant for patients who do not respond to treatment with first-line antidepressants with MDD and PTSD (Derakhshanian *et al.*, 2021; Kritzer *et al.*, 2022). It rapidly increases serotonergic neurotransmission and restores effective PFC synaptic connections (Holmes *et al.*, 2022; Li *et al.*, 2010). Evidence suggests that repeated ketamine infusions are efficacious in rapidly ameliorating both PTSD and MDD symptoms (Albott *et al.*, 2018; Artin *et al.*, 2022) and contribute to improvement of working memory in individuals with PTSD + MDD (Albott *et al.*, 2022). Dai *et al.* reported significant improvement of both depression and PTSD symptoms in PTSD + MDD participants after a single infusion of ketamine administration (Dai *et al.*, 2020). Artin *et al.* found distinct effects of ketamine on depression and PTSD symptoms (Artin *et al.*, 2022), suggesting potentially different modes of action on corresponding underlying mechanisms. Recently, Johnston *et al.* provided an overview of ketamine use in psychiatric disorders and related comorbidities, and came to a conclusion that ketamine can effectively target multiple symptom domains, such as depression, anhedonia, and suicidal ideation (Johnston *et al.*, 2024).

However, few studies have explored the effects of ketamine infusions on brain structure and function in patients with PTSD + MDD to date. Dai *et al.* found a minor increase of the volume in the right opercular inferior frontal gyrus after a single ketamine infusion in patients with PTSD + MDD relative to baseline, suggesting that acute ketamine administration normalize structural alterations associated with depression but not PTSD symptoms (Dai *et al.*, 2020). For functional alterations in PTSD + MDD, Albott *et al.* have recently proposed a research plan to verify the hypothesis that ketamine infusions could improve PTSD and MDD clinical symptoms by reversal of FC alterations (Albott *et al.*, 2021). The researcher suggested that the completion of this study will strongly support the concept of a biologically based model of PTSD + MDD in the future. Overall, the effects of ketamine treatment on brain in patients with PTSD + MDD require more investigation. Additionally, predictive neuroimaging biomarkers for ketamine treatment in PTSD + MDD have not yet been systematically assessed.

Repetitive TMS treatment

As a type of noninvasive neurostimulation in clinical medicine, TMS has shown its ability to treat MDD and promise in several other conditions including PTSD (Huntley *et al.*, 2023). Recent evidence suggests that TMS can be an effective treatment for patients with PTSD + MDD (Philip *et al.*, 2022, 2016; Wilkes *et al.*, 2020). Dorsolateral PFC, a core region of the central executive network responsible for top-down regulation of other networks such as DMN and SN, is the most common region targeted by TMS in psychiatric studies (Barredo *et al.*, 2019). Studies in patients with MDD have demonstrated that TMS to the dorsolateral PFC could induce physiologic changes distal to the stimulation site, particularly in sgACC. Increased sgACC blood flow and higher sgACC metabolic activity at baseline predicted subsequent response to TMS, and posttreatment changes in blood flow and metabolism in the sgACC were associated with improved depression symptoms (Baeken *et al.*, 2015; Kito *et al.*, 2011, 2012). Philip *et al.* conducted the first study evaluating TMS-associated changes in FC in patients with PTSD + MDD, and underscored the involvement of sgACC, DMN, and SN in potential mechanisms of TMS response (Philip *et al.*, 2018). In this study, Philip *et al.* found that both depressive and PTSD symptom improvements were associated with reduced sgACC-to-DMN connectivity and hippocampus-to-SN connectivity after TMS treatment in patients with PTSD + MDD. This study also indicated that different potential mechanisms correlated to MDD and PTSD symptom amelioration after TMS, including reduced connectivity between sgACC and visual regions related to PTSD symptom improvement and reduced connectivity between sgACC and somatosensory/motor regions related to depression amelioration (summarized in Table 2).

Regarding neuroimaging predictors of TMS response, Philip *et al.* found that reduced sgACC-to-DMN connectivity and increased amygdala-to-PFC connectivity predicted TMS response in patients with PTSD + MDD (Philip *et al.*, 2018), while in patients with MDD alone, Liston *et al.* found that hyperconnectivity between sgACC and DMN predicted subsequent response to TMS (Liston *et al.*, 2014). Effects of different stimulation protocols (varied frequencies and intensities) and MRI data processing pipelines in the two studies need to be considered in comparing their findings, but differences are suggested. It raises issues about verification and comparison of neuroimaging predictors of TMS response in MDD alone, PTSD alone, and their comorbidity. Philip and colleagues further constrained tract-based probabilistic tractography via pre-TMS diffusion-weighted imaging data from patients with PTSD + MDD, and the weighted pathway averages of white matter integrity metrics were then extracted from four frontal white matter pathways: the forceps minor, ATR, cingulum, and uncinate fasciculi (Barredo *et al.*, 2019). Then Philip *et al.* used backward stepwise regressions to evaluate whether the metrics in these fronto-limbic pathways (i.e. explanatory

variables) accounted for significant variance in functional predictors of TMS outcome (i.e. dependent variables) revealed by their former study (Philip *et al.*, 2018). They demonstrated that pretreatment FA in the left ATR was negatively associated with amygdala-to-PFC functional predictors for PTSD and depressive symptom improvements after TMS treatment, while FA in the right ATR was positively associated with these predictors (Barredo *et al.*, 2019). These findings provide information about the underlying structural elements of functional predictors of treatment response to TMS. The reproducibility and reliability of these finding should be further verified. More efforts need be made to explore the neural mechanisms in relation to TMS action and biomarkers predicting and tracking response in PTSD + MDD populations, as well as corresponding similarities and differences among MDD alone, PTSD alone, and PTSD + MDD cohorts.

Other related studies and corresponding suggestions for future research

As an effective late-line treatment for refractory MDD, electroconvulsive therapy has been found associated with significant reductions of both PTSD and MDD symptoms in comorbid PTSD + MDD (Ahmadi *et al.*, 2016; Callens and Sienaert, 2024), which may be predicted by response to dexamethasone suppression test (Ahmadi *et al.*, 2018; Watts and Groft, 2010). However, the related underlying neural mechanisms have been rarely investigated. Similarly, external stimulation of the trigeminal nerve as an emerging adjunct to pharmacotherapy showed the efficacy for individuals with PTSD + MDD (Cook *et al.*, 2016) with the neural mechanism poorly understood. The clinical implications and efficacy of cognitive–behavioral treatment program for individuals with PTSD + MDD have been examined (Nixon and Nearmy, 2011). Of note, a unified study examining brain activity induced by an emotional conflict task has reported that MDD and PTSD had similarly increased activation of cognitive control regions, implicating improved cognitive control activation as a transdiagnostic mechanism for the cognitive–behavioral treatment response (Yang *et al.*, 2018b). The meta-analysis by Marwood *et al.* demonstrate that there are consistent activation decreases in ACC, inferior frontal gyrus and insula after psychological therapy across multiple disorders including MDD and PTSD (Marwood *et al.*, 2018). The reproducibility and reliability of these findings need to be further verified.

Specialized search strategies would be beneficial to a better understanding of the underlying transdiagnostic mechanisms for MDD and PTSD. A review by Moustafa *et al.* recommend a symptom-based approach investigating neural substrates associated with different clusters of symptoms (Moustafa *et al.*, 2016), rather than the comparison of disorders. Using this approach, Satterthwaite *et al.* identified foci of resting-state functional dysconnectivity associated with depression severity in the bilateral amygdala across MDD and PTSD (Satterthwaite *et al.*, 2016). Follow-up seed analyses revealed that depression severity in the pooled sample was associated with amygdalo-frontal hypo-connectivity in a network involving regions of bilateral dorsolateral PFC, ACC, and anterior insula. Future research adopting the symptom-based approach may help understand commonalities between MDD and PTSD considering their overlapping symptoms. The identification of neural substrates related to key clinical features in MDD and PTSD may help to tailor individualized programs to treat emotion and cognitive deficits. Furthermore, Seitz *et al.* recently investigated transdiagnostic dysfunction of DMN and some other key regions (e.g. ventral striatum and amygdala) with childhood maltreatment as the predictor in a transdiagnostic adult sample including patients with MDD, PTSD, and somatic symptom disorder (Seitz *et al.*, 2024, 2023; Valencia *et al.*, 2024). These studies showed us novel research approaches based on the shared risk factors.

From connectome perspectives, Suo *et al.* systematically reviewed neuroimaging studies using graph theoretical approaches for six major psychiatric disorders including MDD and PTSD (Suo *et al.*, 2018). Summaries of altered small-world properties showed no consistent alterations in MDD and PTSD, making cross-disease comparisons impossible. From the perspectives of segregation and integration, Suo *et al.* classified altered small-world properties into four patterns: namely, regularization, randomization, stronger small-worldization, and weaker small-worldization. Benefitting from these conceptualized patterns, future studies in MDD and PTSD may provide novel insights into the transdiagnostic and disorder-specific pathophysiological mechanisms underlying MDD and PTSD from a connectomic perspective.

Early diagnosis and treatment of comorbidity would contribute to more rapid symptom reduction and any chronic illness progression. In the future machine learning may be beneficial to provide objective categorical diagnoses of MDD alone, PTSD alone, and PTSD + MDD, and to develop comprehensive models that can effectively predict an individual's risk for comorbidity as well as the treatment response. The predictive models may need to combine the underlying biological mechanisms of MDD and PTSD from dimensions of psychopathology including genetics, behavior, and neuropathology that may extend across diagnostic categories. It may help to identify change patterns involving interactions among genetics, environment exposure, and neuroimaging as predisposing factors for developing comorbidities. In addition, the effects of progressive depression in patients with PTSD remain unclear. Further longitudinal studies are crucial to illuminate possibly different neuroimaging presentations at different stages of the illness course, and to provide a better understanding of the interacting effect of PTSD and depression in patients with comorbidity.

Conclusions

Relevant neuroimaging studies to date have provided important information about the shared and disorder-specific neural features in MDD and PTSD, whereas it is difficult to obtain some reliable models from these findings considering their various analysis methods and different sample types. We just made some conceptual summaries at this stage. Direct comparisons in task-related brain functional activation in MDD and PTSD groups showed shared hypoactivation in the PFC, but higher activation in SN and fear processing regions in PTSD alone relative to MDD alone and comorbid PTSD + MDD groups during cognitive and emotional processes. Comparisons between PTSD + MDD and PTSD alone suggest that deficits in brain regions involved in fear and reward processing might be markers for distinguishing PTSD with and without MDD. Furthermore, both patients with PTSD and those with MDD displayed volume reductions in frontal areas including dorsolateral PFC and ACC. With respect to the treatments of ketamine and TMS in patients with PTSD + MDD, the underlying neural mechanisms associated with symptom improvements as well as predictive biomarkers for treatment effects need further investigation. Future research on the common and disease-specific features of MDD and PTSD may benefit from the novel approaches based on the symptom clusters and shared risk factors. Machine learning models combining genetics, behav-

iors, and neuropathology will be beneficial to predicting an individual's risk for PTSD + MDD comorbidity as well as treatment response.

Supplementary data

Supplementary data is available at *Psychoradiology Journal* online.

Author contributions

Jing Jiang (Data curation, Formal analysis, Investigation, Visualization, Writing – original draft), Stefania Ferraro (Visualization, Writing – original draft, Writing - review & editing), Youjin Zhao (Formal analysis, Funding acquisition, Writing – original draft), Baolin Wu (Data curation, Formal analysis, Visualization), Jinping Lin (Data curation, Formal analysis), Taolin Chen (Funding acquisition, Visualization, Writing – review & editing), Jin Gao (Conceptualization, Supervision, Writing – review & editing), and Lei Li (Conceptualization, Funding acquisition, Validation, Writing – original draft, Writing – review & editing)

Conflict of interests

None declared.

Acknowledgments

The authors thank all authors of the included studies, and especially thank Dr. John A Sweeney for his kind help and suggestions during the preparation of this paper. This study was supported by the National Natural Science Foundation of China (Grant Nos. 82302159 and 82001795), Post-Doctor Research Project of West China Hospital of Sichuan University (2021HXBH025), and Sichuan Province Science and Technology Program (2022YFS0069, 2021YFS0242, and 2023YFS0076).

References

Ahmadi N, Moss L, Hauser P, *et al.* (2018) Clinical outcome of maintenance electroconvulsive therapy in comorbid posttraumatic stress disorder and major depressive disorder. *J Psychiatr Res* **105**:132–6.

Ahmadi N, Moss L, Simon E, *et al.* (2016) Efficacy and long-term clinical outcome of comorbid posttraumatic stress disorder and major depressive disorder after electroconvulsive therapy. *Depress Anxiety* **33**:640–7.

Akhtar A, Pilkhwal Sah S. (2021) Advances in the pharmacotherapeutic management of post-traumatic stress disorder. *Expert Opin Pharmacother* **22**:1919–30.

Albert KM, Potter GG, Boyd BD, *et al.* (2019) Brain network functional connectivity and cognitive performance in major depressive disorder. *J Psychiatr Res* **110**:51–6.

Albott CS, Lee S, Cullen KR, *et al.* (2021) Characterization of comorbid posttraumatic stress disorder and major depressive disorder using ketamine as an experimental medicine probe. *J Psychiatr Brain Sci* **6**:e210012.

Albott CS, Lim KO, Erbes C, *et al.* (2022) Neurocognitive effects of repeated ketamine infusions in comorbid posttraumatic stress disorder and major depressive disorder. *J Affect Disord* **308**: 289–97.

Albott CS, Lim KO, Forbes MK, *et al.* (2018) Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression. *J Clin Psychiatry* **79**:17m11634.

Artin H, Bentley S, Mehaffey E, *et al.* (2022) Effects of intranasal (S)-ketamine on veterans with co-morbid treatment-resistant depression and PTSD: a retrospective case series. *EClinMed* **48**:101439.

Averill CL, Averill LA, Akiki TJ, *et al.* (2024) Findings of PTSD-specific deficits in default mode network strength following a mild experimental stressor. *NPP—Digit Psychiatry Neurosci* **2**:9.

Averill CL, Satodiya RM, Scott JC, *et al.* (2017) Posttraumatic stress disorder and depression symptom severities are differentially associated with hippocampal subfield volume loss in combat veterans. *Chronic Stress* **1**:2470547017744538.

Baeken C, Marinazzo D, Everaert H, *et al.* (2015) The impact of accelerated HF-rTMS on the subgenual anterior cingulate cortex in refractory unipolar major depression: insights from 18FDG PET brain imaging. *Brain Stim* **8**:808–15.

Bao W, Gao Y, Cao L, *et al.* (2021) Alterations in large-scale functional networks in adult posttraumatic stress disorder: a systematic review and meta-analysis of resting-state functional connectivity studies. *Neurosci Biobehav Rev* **131**:1027–36.

Barredo J, Bellone JA, Edwards M, *et al.* (2019) White matter integrity and functional predictors of response to repetitive transcranial magnetic stimulation for posttraumatic stress disorder and major depression. *Depress Anxiety* **36**:1047–57.

Barredo J, Berlow Y, Swearingen HR, *et al.* (2021) Multimodal elements of suicidality reduction after transcranial magnetic stimulation. *Neuromodulation* **24**:930–7.

Bora E, Fornito A, Pantelis C, *et al.* (2012) Gray matter abnormalities in major depressive disorder: a meta-analysis of voxel based morphometry studies. *J Affect Disord* **138**:9–18.

Brambilla P (2003) Brain anatomy and development in autism: review of structural MRI studies. *Brain Res Bull* **61**:557–69.

Bromis K, Calem M, Reinders AATS, *et al.* (2018) Meta-analysis of 89 structural MRI studies in posttraumatic stress disorder and comparison with major depressive disorder. *Am J Psychiatry* **175**:989–98.

Bryant RA, Andrew E, Korgaonkar MS. (2021) Distinct neural mechanisms of emotional processing in prolonged grief disorder. *Psychol Med* **51**:587–95.

Callens L, Sienaert P (2024) The role of electroconvulsive therapy in posttraumatic stress disorder: a systematic review. *J Ect*

Chiba H, Oe M, Uchimura N (2016) Patients with posttraumatic stress disorder with comorbid major depressive disorder require a higher dose of psychotropic drugs. *Kurume Med J* **62**:23–8.

Ciocchi S, Herry C, Grenier F, *et al.* (2010) Encoding of conditioned fear in central amygdala inhibitory circuits. *Nature* **468**:277–82.

Cook IA, Abrams M, Leuchter AF (2016) Trigeminal nerve stimulation for comorbid posttraumatic stress disorder and major depressive disorder. *Neuromodulation* **19**:299–305.

Cui L, Li S, Wang S, *et al.* (2024) Major depressive disorder: hypothesis, mechanism, prevention and treatment. *Sig Transduct Target Ther* **9**:30.

Dai D, Lacadie CM, Holmes SE, *et al.* (2020) Ketamine normalizes the structural alterations of inferior frontal gyrus in depression. *Chronic Stress* **4**:2470547020980681.

Dell'osso L, Carmassi C, Mucci F, *et al.* (2016) Depression, serotonin and tryptophan. *CPD* **22**:949–54.

Derakhshanian S, Zhou M, Rath A, *et al.* (2021) Role of ketamine in the treatment of psychiatric disorders. *Health Psychol Res* **9**:25091.

Dold M, Bartova L, Kautzky A, *et al.* (2017) The impact of comorbid post-traumatic stress disorder in patients with major depressive disorder on clinical features, pharmacological treatment strate-

gies, and treatment outcomes—results from a cross-sectional European multicenter study. *Eur Neuropsychopharmacol* **27**:625–32.
Dunlop BW, Wong A (2019) The hypothalamic-pituitary-adrenal axis in PTSD: pathophysiology and treatment interventions. *Prog Neuropsychopharmacol Biol Psychiatry* **89**:361–79.
Feder A, Parides MK, Murrough JW, *et al.* (2014) Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry* **71**:681–8.
Flory JD, Yehuda R (2015) Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. *Dialog Clin Neurosc* **17**: 141–50.
Gill T, Watling SE, Richardson JD, *et al.* (2022) Imaging of astrocytes in posttraumatic stress disorder: a PET study with the monoamine oxidase B radioligand [(11)C]SL25.1188. *Eur Neuropsychopharmacol* **54**:54–61.
Godard J, Baruch P, Grondin S, *et al.* (2012) Psychosocial and neurocognitive functioning in unipolar and bipolar depression: a 12-month prospective study. *Psychiatry Res* **196**:145–53.
Gong Q, Hu X, Pettersson-Yeo W, *et al.* (2017) Network-level dysconnectivity in drug-naïve first-episode psychosis: dissociating transdiagnostic and diagnosis-specific alterations. *Neuropsychopharmacol* **42**:933–40.
Gong Q, Puthusseryppady V, Dai J, *et al.* (2019a) Dysconnectivity of the medio-dorsal thalamic nucleus in drug-naïve first episode schizophrenia: diagnosis-specific or trans-diagnostic effect? *Transl Psychiatry* **9**:9.
Gong Q, Scarpazza C, Dai J, *et al.* (2019b) A transdiagnostic neuroanatomical signature of psychiatric illness. *Neuropsychopharmacol.* **44**:869–75.
Harnett NG, Goodman AM, Knight DC (2020) PTSD-related neuroimaging abnormalities in brain function, structure, and biochemistry. *Exp Neurol* **330**:113331.
Henigsberg N, Bajs M, Hrabac P, *et al.* (2011) Changes in brain metabolites measured with magnetic resonance spectroscopy in antidepressant responders with comorbid major depression and posttraumatic stress disorder. *Coll Antropol* **35**:145–8.
Hidalgo RB, Davidson JR (2000) Selective serotonin reuptake inhibitors in post-traumatic stress disorder. *J Psychopharmacol* **14**:70–6.
Holmes SE, Finnema SJ, Naganawa M, *et al.* (2022) Imaging the effect of ketamine on synaptic density (SV2A) in the living brain. *Mol Psychiatry* **27**:2273–81.
Hung C-I, Wang S-J, Liu C-Y, *et al.* (2011) Comorbidities and factors related to discontinuation of pharmacotherapy among outpatients with major depressive disorder. *Compr Psychiatry* **52**:370–7.
Huntley JH, Rezvani Habibabadi R, Vaishnavi S, *et al.* (2023) Transcranial magnetic stimulation and its imaging features in patients with depression, post-traumatic stress disorder, and traumatic brain injury. *Acad Radiol* **30**:103–12.
Jaffe AE, Tao R, Page SC, *et al.* (2022) Decoding shared versus divergent transcriptomic signatures across cortico-amygdala circuitry in PTSD and depressive disorders. *Am J Psychiatry* **179**:673–686.
Janiri D, Moser DA, Doucet GE, *et al.* (2020) Shared neural phenotypes for mood and anxiety disorders: a meta-analysis of 226 task-related functional imaging studies. *JAMA Psychiatry* **77**:172–9.
Jeffreys M, Capehart B, Friedman MJ (2012) Pharmacotherapy for posttraumatic stress disorder: review with clinical applications. *JRRD* **49**:703–15.
Jenkins LM, Barba A, Campbell M, *et al.* (2016) Shared white matter alterations across emotional disorders: a voxel-based meta-analysis of fractional anisotropy. *NeuroImage Clin* **12**:1022–34.
Johnston JN, Kadriu B, Kraus C, *et al.* (2024) Ketamine in neuropsychiatric disorders: an update. *Neuropsychopharmacol* **49**:23–40.
Kaplan MJ, Klinetob NA (2000) Childhood emotional trauma and chronic posttraumatic stress disorder in adult outpatients with treatment-resistant depression. *J Nerv Ment Dis* **188**: 596–601.
Keller M, Mendoza-Quiñones R, Cabrera Muñoz A, *et al.* (2022) Transdiagnostic alterations in neural emotion regulation circuits—neural substrates of cognitive reappraisal in patients with depression and post-traumatic stress disorder. *BMC Psychiatry* **22**:173.
Kemp AH, Felmingham K, Das P, *et al.* (2007) Influence of comorbid depression on fear in posttraumatic stress disorder: an fMRI study. *Psychiatry Res Neuroimag* **155**:265–9.
Kennis M, Rademaker AR, Van Rooij SJH, *et al.* (2013) Altered functional connectivity in posttraumatic stress disorder with versus without comorbid major depressive disorder: a resting state fMRI study. *F1000Res* **2**:289.
Kessler RC, Chiu WT, Demler O, *et al.* (2005) Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* **62**:617–27.
Kito S, Hasegawa T, Koga Y (2011) Neuroanatomical correlates of therapeutic efficacy of low-frequency right prefrontal transcranial magnetic stimulation in treatment-resistant depression. *Psychiatry Clin Neurosci* **65**:175–82.
Kito S, Hasegawa T, Koga Y (2012) Cerebral blood flow in the ventromedial prefrontal cortex correlates with treatment response to low-frequency right prefrontal repetitive transcranial magnetic stimulation in the treatment of depression. *Psychiatry Clin Neurosci* **66**:138–45.
Kline AC, Cooper AA, Rytwinski NK, *et al.* (2021) The effect of concurrent depression on PTSD outcomes in trauma-focused psychotherapy: a meta-analysis of randomized controlled trials. *Behavior Therapy* **52**:250–66.
Kochunov P, Hong LE, Dennis EL, *et al.* (2022) ENIGMA-DTI: translating reproducible white matter deficits into personalized vulnerability metrics in cross-diagnostic psychiatric research. *Hum Brain Mapp* **43**:194–206.
Koopowitz S-M, Zar HJ, Stein DJ, *et al.* (2023) PTSD and comorbid MDD is associated with activation of the right frontoparietal network. *Psychiatry Res Neuroimaging* **331**:111630.
Kostaras P, Bergiannaki J-D, Psarros C, *et al.* (2017) Posttraumatic stress disorder in outpatients with depression: still a missed diagnosis. *J Trauma Dissociation* **18**:233–47.
Kritzer MD, Mischel NA, Young JR, *et al.* (2022) Ketamine for treatment of mood disorders and suicidality: a narrative review of recent progress. *Ann Clin Psychiatry* **34**:33–43.
Kroes MCW, Rugg MD, Whalley MG, *et al.* (2011) Structural brain abnormalities common to posttraumatic stress disorder and depression. *J Psychiatry Neurosci* **36**:256–65.
Lanius RA, Frewen PA, Girotti M, *et al.* (2007) Neural correlates of trauma script-imagery in posttraumatic stress disorder with and without comorbid major depression: a functional MRI investigation. *Psychiatry Res Neuroimag* **155**:45–56.
Li N, Lee B, Liu R-J, *et al.* (2010) mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* **329**:959–64.
Liston C, Chen AC, Zebley BD, *et al.* (2014) Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biol Psychiatry* **76**:517–26.
Mahan AL, Ressler KJ (2012) Fear conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder. *Trends Neurosci* **35**:24–35.

Marwood L, Wise T, Perkins AM, *et al.* (2018) Meta-analyses of the neural mechanisms and predictors of response to psychotherapy in depression and anxiety. *Neurosci Biobehav Rev* **95**:61–72.

Mcteague LM, Huemer J, Carreon DM, *et al.* (2017) Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. *Am J Psychiatry* **174**:676–85.

Millan MJ, Agid Y, Brüne M, *et al.* (2012) Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov* **11**:141–68.

Moustafa AA, Phillips J, Kéri S, *et al.* (2016) On the complexity of brain disorders: a symptom-based approach. *Front Comput Neurosci* **10**:16.

Musazzi L, Treccani G, Mallei A, *et al.* (2013) The action of antidepressants on the glutamate system: regulation of glutamate release and glutamate receptors. *Biol Psychiatry* **73**:1180–8.

Ney LJ, Akhurst J, Bruno R, *et al.* (2021) Dopamine, endocannabinoids and their interaction in fear extinction and negative affect in PTSD. *Prog Neuropsychopharmacol Biol Psychiatry* **105**:110118.

Nijdam MJ, Gersons BP, Olff M (2013) The role of major depression in neurocognitive functioning in patients with posttraumatic stress disorder. *Eur J Psychotraumatology* **2**:4.

Nixon RD, Nearmy DM (2011) Treatment of comorbid posttraumatic stress disorder and major depressive disorder: a pilot study. *J Trauma Stress* **24**:451–5.

O'doherty DCM, Chitty KM, Saddiqui S, *et al.* (2015) A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. *Psychiatry Res Neuroimag* **232**:1–33.

O'donnell ML, Creamer M, Pattison P (2004) Posttraumatic stress disorder and depression following trauma: understanding comorbidity. *Am J Psychiatry* **161**:1390–6.

Pariante CM, Miller AH (2001) Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biol Psychiatry* **49**:391–404.

Philip NS, Barredo J, Van 'T Wout-Frank M, *et al.* (2018) Network mechanisms of clinical response to transcranial magnetic stimulation in posttraumatic stress disorder and major depressive disorder. *Biol Psychiatry* **83**:263–72.

Philip NS, Doherty RA, Faucher C, *et al.* (2022) Transcranial magnetic stimulation for posttraumatic stress disorder and major depression: comparing commonly used clinical protocols. *J Trauma Stress* **35**:101–8.

Philip NS, Ridout SJ, Albright SE, *et al.* (2016) 5-Hz transcranial magnetic stimulation for comorbid posttraumatic stress disorder and major depression. *J Trauma Stress* **29**:93–6.

Popoli M, Yan Z, Mcewen BS, *et al.* (2011) The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. *Nat Rev Neurosci* **13**:22–37.

Pukay-Martin ND, Pontoski KE, Maxwell MA, *et al.* (2012) The influence of depressive symptoms on suicidal ideation among U.S. Vietnam-era and Afghanistan/Iraq-era veterans with posttraumatic stress disorder. *J Trauma Stress* **25**:578–82.

Rakesh G, Logue MW, Clarke-Rubright E, *et al.* (2023) Network centrality and modularity of structural covariance networks in posttraumatic stress disorder: a multisite ENIGMA-PGC Study. *Brain Connectivity* **13**:211–25.

Rytwinski NK, Scur MD, Feeny NC, *et al.* (2013) The co-occurrence of major depressive disorder among individuals with posttraumatic stress disorder: a meta-analysis. *J Trauma Stress* **26**:299–309.

Satterthwaite TD, Cook PA, Bruce SE, *et al.* (2016) Dimensional depression severity in women with major depression and post-traumatic stress disorder correlates with fronto-amygdalar hypoconnectivty. *Mol Psychiatry* **21**:894–902.

Schulze L, Schulze A, Renneberg B, *et al.* (2019) Neural correlates of affective disturbances: a comparative meta-analysis of negative affect processing in borderline personality disorder, major depressive disorder, and posttraumatic stress disorder. *Biol Psychiatry Cogn Neurosci Neuroimag* **4**:220–32.

Seitz KI, Sicorello M, Schmitz M, *et al.* (2024) Childhood maltreatment and amygdala response to interpersonal threat in a transdiagnostic adult sample: the role of trait dissociation. *Biol Psychiatry Cogn Neurosci Neuroimag* **9**:626–34.

Seitz KI, Ueltzhöffer K, Rademacher L, *et al.* (2023) Your smile won't affect me: association between childhood maternal antipathy and adult neural reward function in a transdiagnostic sample. *Transl Psychiatry* **13**:70.

Serra-Blasco M, Radua J, Soriano-Mas C, *et al.* (2021) Structural brain correlates in major depression, anxiety disorders and posttraumatic stress disorder: a voxel-based morphometry meta-analysis. *Neurosci Biobehav Rev* **129**:269–81.

Shen LH, Liao MH, Tseng YC (2012) Recent advances in imaging of dopaminergic neurons for evaluation of neuropsychiatric disorders. *J Biomed Biotechnol* **2012**:1.

Shepherd AM, Matheson SL, Laurens KR, *et al.* (2012) Systematic meta-analysis of insula volume in schizophrenia. *Biol Psychiatry* **72**:775–84.

Shou H, Yang Z, Satterthwaite TD, *et al.* (2017) Cognitive behavioral therapy increases amygdala connectivity with the cognitive control network in both MDD and PTSD. *NeuroImage Clin* **14**:464–70.

Smoller JW (2016) The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. *Neuropsychopharmacol* **41**:297–319.

Southwick SM, Paige S, Morgan CA 3rd, *et al.* (1999) Neurotransmitter alterations in PTSD: catecholamines and serotonin. *Semin Clin Neuropsychiatry* **4**:242–8.

Suo X, Lei D, Li L, *et al.* (2018) Psychoradiological patterns of small-world properties and a systematic review of connectome studies of patients with 6 major psychiatric disorders. *J Psychiatry Neurosci* **43**:416.

Thomas JL, Wilk JE, Riviere LA, *et al.* (2010) Prevalence of mental health problems and functional impairment among active component and National Guard soldiers 3 and 12 months following combat in Iraq. *Arch Gen Psychiatry* **67**:614–23.

Valencia N, Seeger FR, Seitz KI, *et al.* (2024) Childhood maltreatment and transdiagnostic connectivity of the default-mode network: the importance of duration of exposure. *J Psychiatr Res* **177**:239–48.

Van Rooij SJH, Rademaker AR, Kennis M, *et al.* (2015) Neural correlates of trauma-unrelated emotional processing in war veterans with PTSD. *Psychol Med* **45**:575–87.

Wang Z, He D, Yang L, *et al.* (2024) Similarities and differences between post-traumatic stress disorder and major depressive disorder: evidence from task-evoked functional magnetic resonance imaging meta-analysis. *J Affect Disord* **361**:712–9.

Watts BV, Groft A (2010) Retrospective evaluation of the dexamethasone suppression test as a predictor of response to electroconvulsive therapy in patients with comorbid major depressive disorder and posttraumatic stress disorder. *J Ect* **26**:213–7.

Whalley MG, Rugg MD, Smith APR, *et al.* (2009) Incidental retrieval of emotional contexts in post-traumatic stress disorder and depression: an fMRI study. *Brain Cogn* **69**:98–107.

Wilkes S, Ona C, Yang M, *et al.* (2020) Impacts of rTMS on refractory depression and comorbid PTSD symptoms at a military treatment facility. *Mil Med* **185**:e1420–7.

Yang Z, Gu S, Honnorat N, *et al.* (2018a) Network changes associated with transdiagnostic depressive symptom improvement follow-

ing cognitive behavioral therapy in MDD and PTSD. *Mol Psychiatry* **23**:2314–23.

Yang Z, Oathes DJ, Linn KA, *et al.* (2018b) Cognitive behavioral therapy is associated with enhanced cognitive control network activity in major depression and posttraumatic stress disorder. *Biol Psychiatry Cogn Neurosci Neuroimag* **3**:311–9.

Yehuda R, Flory JD, Bierer LM, *et al.* (2015) Lower methylation of glucocorticoid receptor gene promoter 1F in peripheral blood of veterans with posttraumatic stress disorder. *Biol Psychiatry* **77**: 356–64.

Yuan M, Pantazatos SP, Zhu H, *et al.* (2019) Altered amygdala subregion-related circuits in treatment-naïve post-traumatic stress disorder comorbid with major depressive disorder. *Eur Neuropsychopharmacol* **29**:1092–101.

Zannas AS, Binder EB (2014) Gene-environment interactions at the FKBP5 locus: sensitive periods, mechanisms and pleiotropism. *Genes Brain Behav* **13**:25–37.

Zarate CA, Singh JB, Carlson PJ, *et al.* (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* **63**:856–64.

Zhang F, Rao S, Cao H, *et al.* (2022) Genetic evidence suggests posttraumatic stress disorder as a subtype of major depressive disorder. *J Clin Invest* **132**:e145942.

Zhu X, Helpman L, Papini S, *et al.* (2017) Altered resting state functional connectivity of fear and reward circuitry in comorbid PTSD and major depression. *Depress Anxiety* **34**: 641–50.

Zhuo C, Lin X, Wang C, *et al.* (2020a) Unified and disease specific alterations to brain structure in patients across six categories of mental disorders who experience own-thought auditory verbal hallucinations: a pilot study. *Brain Res Bull* **160**: 33–9.

Zhuo C, Wang C, Song X, *et al.* (2020b) A unified model of shared brain structural alterations in patients with different mental disorders who experience own-thought auditory verbal hallucinations-a pilot study. *Brain Behav* **10**:e01614.

Zilcha-Mano S, Zhu X, Suarez-Jimenez B, *et al.* (2020) Diagnostic and predictive neuroimaging biomarkers for posttraumatic stress disorder. *Biol Psychiatry Cogn Neurosci Neuroimag* **5**: 688–96.

Received: 13 April 2024; **Revised:** 20 October 2024; **Accepted:** 31 October 2024