

REVIEW ARTICLE

Shared and distinct brain fMRI response during performance of working memory tasks in adult patients with schizophrenia and major depressive disorder

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Abstract

Working memory (WM) impairments are common features of psychiatric disorders. A systematic meta-analysis was performed to determine common and disorder-specific brain fMRI response during performance of WM tasks in patients with SZ and patients with MDD relative to healthy controls (HC). Thirty-four published fMRI studies of WM in patients with SZ and 18 published fMRI studies of WM in patients with MDD, including relevant HC, were included in the meta-analysis. In both SZ and MDD there was common stronger fMRI response in right medial prefrontal cortex (MPFC) and bilateral anterior cingulate cortex (ACC), which are part of the default mode network (DMN). The effects were of greater magnitude in SZ than MDD, especially in prefrontal-temporal-cingulate-striatal-cerebellar regions. In addition, a disorder-specific weaker fMRI response was observed in right middle frontal gyrus (MFG) in MDD, relative to HC. For both SZ and MDD a significant correlation was observed between the severity of clinical symptoms and lateralized fMRI response relative to HC. These findings indicate that there may be common and distinct anomalies in brain function underlying deficits in WM in SZ and MDD, which may serve as a potential functional neuroimaging-based diagnostic biomarker with value in supporting clinical diagnosis, measuring illness severity and assessing the efficacy of treatments for SZ and MDD at the brain level.

KEYWORDS

functional magnetic resonance imaging, major depressive disorder, meta-analysis, schizophrenia, working memory

1 | INTRODUCTION

Based on differing clinical presentations and prognosis, schizophrenia (SZ) and major depressive disorder (MDD) have long been considered two distinct chronic and severely disabling psychiatric disorders (Fischer, 2012; Lundin & Flyckt, 2015; Malhi & Mann, 2018).

However, existing classification criteria (Fischer & Carpenter Jr., 2009) are challenged by results of recent studies which have shown co-aggregation of risk genes (Huang et al., 2010; Lee et al., 2013), shared neurobiological and neuropsychological features (Goodkind et al., 2015), and considerable overlap in clinical presentations (Wei et al., 2017), including affective symptoms such as depression and

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anxiety (Chen et al., 2020a), and impairments in cognitive functioning, particularly working memory (WM) (Hsu et al., 2015; Pu, Noda, Setoyama, & Nakagome, 2018; Wei et al., 2017; Zhu et al., 2019), in SZ and MDD. Accordingly, there is interest to investigate to what extent SZ and MDD share a common pathophysiology and in the present study the question is addressed by performing a meta-analysis of fMRI studies involving WM tasks.

Impairment of WM is common in a range of psychiatric disorders including SZ and MDD and the severity of the deficit depends on diagnosis (Forbes, Carrick, McIntosh, & Lawrie, 2009; Lever, Werkle-Bergner, Brandmaier, Ridderinkhof, & Geurts, 2015; Schwarz, Tost, & Meyer-Lindenberg, 2016; Snyder, 2013; Yamashita et al., 2018), with greater impairments associated with higher values of a factor representing general psychopathology (Caspi et al., 2014). In the case of SZ, there have been consistent reports, including those in reviews, of the existence of WM impairment in patients relative to healthy controls (HC) (Barch & Sheffield, 2014; Kaminski et al., 2020; Kim, Glahn, Nuechterlein, & Cannon, 2004; Mayer, Stablein, Oertel-Knochel, & Fiebach, 2018; Noort et al., 2016; Park & Gooding, 2014; Piskulic, Olver, Norman, & Maruff, 2007; Pu et al., 2019; Schaefer, Giangrande, Weinberger, & Dickinson, 2013; Schlagenhaut et al., 2008; Trapp et al., 2017). On the other hand, in the case of MDD, relative to HC, WM performance has sometimes been reported to be impaired (Chen et al., 2018; Christopher & MacDonald, 2005; Egeland et al., 2003; Liu et al., 2019; Noort et al., 2016; Pu et al., 2011; Pu et al., 2018; Schwert, Stohrer, Aschenbrenner, Weisbrod, & Schröder, 2019) or sometimes not (Channon, Baker, & Robertson, 1993; Murphy et al., 2019; Trapp et al., 2017; Yuksel et al., 2018). Furthermore, WM deficits have been reported to increase over time in SZ (Fu, Czajkowski, & Torgalsboen, 2018; Jimenez-Lopez et al., 2019; Park, Püschel, Sauter, Rentsch, & Hell, 1999; Strugstad, Lau, & Glenne Oie, 2018), but not in MDD (Nuninga et al., 2018; Sankar, Adams, Costafreda, Marangell, & Fu, 2017; Vasavada et al., 2017; Zuidersma, Comijs, Naarding, & Oude Voshaar, 2016). WM is also more impaired in SZ than in MDD (Egeland et al., 2003; Mahmood, Burton, Vella, & Twamley, 2018; Yamashita et al., 2018), and measurement of WM deficit may represent a promising endophenotype for studying the disorders (Glahn et al., 2012). Accordingly, intensive efforts are being made to characterize the neurobiological substrate that underpins impairments in WM performance in SZ and MDD. Many fMRI studies involving performance of WM tasks have been performed in cohorts of patients with SZ and MDD and there is only a partial overlap in the findings pertaining to the two disorders. The findings are summarized below.

One recent meta-analysis of 52 fMRI studies of WM tasks performed by patients with SZ that used an activation likelihood estimation (ALE) approach, found that relative to HC, patients exhibited stronger fMRI response in left anterior cingulate cortex (ACC), supplementary motor area (SMA) and posterior parietal cortex, and weaker fMRI response in bilateral dorso-lateral pre-frontal cortex (DLPFC) and left insula, which are components of the central executive network (CEN) and salience network (SN), together with stronger fMRI response in right ventro-medial prefrontal cortex (VMPFC) and left

posterior cingulate cortex (PCC) which are part of the default mode network (DMN) (Park & Gooding, 2014; Wu & Jiang, 2020). In other studies stronger fMRI response in bilateral pre-frontal cortex (PFC) including medial prefrontal cortex (MPFC), ACC, PCC, superior temporal cortex (STC), middle temporal cortex (MTC) and cuneus, and right occipital cortex and parahippocampus, and weaker fMRI response in bilateral DLPFC, right MPFC, insula, parietal cortex and ventral striatum and left posterior cerebellum, during performance of WM tasks by patients with SZ compared to HC have been reported (Glahn et al., 2005; Meyer-Lindenberg et al., 2001; Van Snellenberg et al., 2016). In several studies, including a meta-analysis (Van Snellenberg, Torres, & Thornton, 2006), a region of interest (ROI) analysis was performed specifically for DLPFC and found stronger fMRI response (Karlsgodt et al., 2009; Manoach et al., 2000; Potkin et al., 2009; Van Snellenberg et al., 2016), weaker fMRI response (Fan et al., 2019; Kaminski et al., 2020; Menon, Anagnoson, Mathalon, Glover, & Pfefferbaum, 2001; Pu et al., 2019) or no significant difference in fMRI response (Van Snellenberg et al., 2006) in patients with SZ compared to HC. Additionally, using independent component analysis (ICA), several fMRI studies of WM tasks have revealed significant alterations of fMRI response in patients with SZ relative to HC, which are either correlated or anti-correlated with WM performance, including stronger fMRI response in bilateral superior frontal gyrus (SFG), PCC, insula, superior temporal gyrus (STG), inferior temporal gyrus, precuneus, parahippocampal gyrus, amygdala, putamen and cerebellum, left DLPFC, cingulate gyrus and inferior parietal lobule (IPL) (Chatterjee et al., 2019; Kim et al., 2009), and weaker fMRI response in bilateral dentate gyrus and cerebellum (Kim et al., 2009). These findings suggest that the aforementioned brain regions may be implicated in the neurobiological mechanisms underlying impairment of WM in SZ (Kim et al., 2009).

A meta-analysis of fMRI studies of WM tasks performed by patients with MDD found that relative to HC, patients exhibited significantly different fMRI response in cortical-limbic circuitry, namely stronger fMRI response in left DLPFC, ventral lateral pre-frontal cortex (VLPFC), precentral gyrus and insula, and right temporal and supramarginal cortex, and weaker fMRI response in right precentral gyrus, insula and precuneus (Wang et al., 2015). Significant alterations of fMRI response in left SFG, angular gyrus, right frontal-parietal regions and thalamus have also been reported in patients with MDD (Yuksel et al., 2018). In addition, weaker fMRI response in bilateral PFC including DLPFC and VLPFC, and STC was consistently reported in two near infra-red spectroscopy (NIRS) studies of patients with MDD (Pu et al., 2011; Schecklmann et al., 2011).

There is considerable heterogeneity among the studies referred to above in terms of sample size, demographic and clinical characteristics of the subjects, psychotropic medication and the image acquisition and analysis protocols used (Fusar-Poli et al., 2007; Jalbrzikowski et al., 2018; Park et al., 2019; Wible et al., 2009), which may account for some of the inconsistent findings reported. Small sample sizes may, in particular, produce false-positive or false-negative results (Button et al., 2013; Oakes, 2017; van Ravenzwaaij & Ioannidis, 2019). To the best of our knowledge, there has been only one

previous meta-analysis of fMRI studies of cognitive control tasks, including WM, performed by patients with a range of psychiatric disorders across Axis I diagnoses, which include SZ and MDD (McTeague et al., 2017). This meta-analysis revealed a trans-diagnostic pattern of significantly different brain fMRI response in patients relative to HC, involving left DLPFC, right VLPFC, ACC, pre-supplementary motor cortex and insula. The present meta-analysis was performed to specifically compare fMRI response due to performance of WM tasks in patients with SZ and MDD, relative to HC. The primary objective of the current study was to determine which response may be shared by patients with SZ and MDD, and the secondary objective was to investigate which anomalies may be specific to either SZ or MDD. In addition, potential confounders (i.e., age, sex-ratio, handedness, and clinical symptoms) that may account for differences in fMRI response between diagnostic groups were investigated.

2 | MATERIALS AND METHODS

2.1 | Literature search

A computer-based literature search was performed using the PubMed (<http://www.pubmed.org>), Embase (<https://www.embase.com>) and Web of Science (<https://apps.webofknowledge.com>) databases to identify fMRI studies in which brain response in patients with SZ and/or MDD during performance of WM tasks was compared to that in HC, and which had been published in the English language in peer-reviewed journals (including articles available online only at the time of the search) prior to August 19, 2020. Only studies of SZ and MDD, located at the extremes of the neurobiological continuum from SZ, schizophreniform, schizoaffective, bipolar disorder to MDD (Benazzi, 2005; Clementz et al., 2016; Pearlson, 2015), were included. In each search engine the following combinations of search terms were used: "schizophrenia OR schizophreni* OR severe mental illness" OR "unipolar depressi* OR depressed OR depress* disorder OR major depression OR major depressive disorder OR MDD" AND "functional Magnetic Resonance Imaging OR functional MRI OR fMRI OR Magnetic Resonance Imaging OR MRI OR neuroimaging OR brain imaging" AND "Working Memory OR WM OR visual span OR spatial span OR digit span OR short-term memory OR STM." Use of these broad search terms minimized the likelihood of missing relevant studies. The retrieved articles, including relevant reviews and meta-analyses, were searched to identify studies that were potentially missed in the computer-based searches. Furthermore, authors of papers were occasionally contacted with a request to clarify details and confirm the appropriateness of certain studies.

2.2 | Data extraction

The meta-analysis was performed according to guidelines proposed by Stroup et al. (2000) for a Meta-analysis Of Observational Studies in Epidemiology (MOOSE). Thus a study was included if (i) precise

diagnosis of SZ or MDD had been made, (ii) fMRI related brain response during performance of WM tasks was compared between patients with SZ, and/or MDD, and HC aged 18 to 65 years, (iii) the study was published in English as an original paper in a peer-reviewed journal, (iv) a whole brain approach was used for analysis and (v) results were reported in standard stereotactic coordinates (i.e., Talairach/Tournoux space or Montreal Neurological Institute [MNI] space). In the case that studies met the inclusion criteria but had overlapping data, only the study with the largest sample size was selected. If results for more than one experiment were reported in a paper, each eligible experiment was included in the meta-analysis as a unique dataset. If a study investigated several sub-group comparisons, then a combined summary result was defined for potential inclusion in the meta-analysis. For studies that used longitudinal treatment designs, only baseline pre-treatment results were included.

A study was excluded if (i) cohorts included individuals with schizoaffective disorder, schizophreniform disorder or bipolar depression, (ii) the diagnosis of SZ or MDD was comorbid with serious medical conditions such as temporal lobe epilepsy or multiple sclerosis, (iii) SZ and MDD had been investigated as a comorbid psychiatric condition, (iv) WM experiments were embedded within affective manipulations (e.g., use of affective stimuli, mood induction and without inclusion of neutral stimuli), in view of the known significant interaction between WM and emotion (Woody et al., 2017), (v) results were reported only after using a small-volume correction or for an ROI or (vi) the data were incomplete (e.g., missing neuroanatomical coordinates) even after the author(s) were contacted via e-mail.

To minimize data extraction errors the search and inclusion of literature was independently conducted by two researchers (XL and BC) according to the AES-SDM method (Radua et al., 2012) and any disagreements were discussed and resolved by consensus.

2.3 | Quality assessment

A quality score was computed for each of the selected studies using a 15 point checklist used in previous meta-analyses (Sanderson, Tatt, & Higgins, 2007; Shepherd, Matheson, Laurens, Carr, & Green, 2012). In particular, the demographic and clinical characteristics, the diagnostic procedures, the selection of participants, WM task design, MRI acquisition parameters, data analysis technique and quality of the reported results were assessed (see Table S1).

2.4 | Voxel-based meta-analysis

Anisotropic Effect-Size Seed-based D Mapping (AES-SDM) software version 5.15 (<http://www.sdmproject.com/>) (Radua, Rubia, et al., 2014) was used to identify those brain regions which showed consistent significant differences in fMRI response between SZ, MDD and HC during performance of WM tasks. The steps of the method can be summarized as follows. Peak coordinates and statistical parametric maps were used to produce whole brain effect size and variance

maps, which are used to perform a random-effect voxel-wise meta-analyses. Importantly, studies with negative findings (i.e., when no significant differences were found between patients with SZ or MDD and HC) can be included with a null effect size (Radua & Mataix-Cols, 2009). AES-SDM also provides the facility for multi-modal analysis to be performed to identify regions where both SZ and MDD groups show common differences in fMRI response relative to HC (Radua, van den Heuvel, Surguladze, & Mataix-Cols, 2010). A filter with Full-Width at Half-Maximum (FWHM) of 20 mm was applied, which is considered to represent a good compromise between high sensitivity for detection of significant effects, and avoidance of false positive results (Radua et al., 2012).

2.4.1 | Main meta-analyses

A brain map of the effect size for each of the studies was recreated from the average of 50 random permutations using peak coordinates and effect sizes (derived, for example, from *t* values) of differences in fMRI response between patients with SZ, or MDD, and HC by means of an anisotropic Gaussian kernel. The threshold was set at $p < .005$ (voxel level), with $z > 1$ (peak height) and a cluster extent ≥ 10 voxels (Radua & Mataix-Cols, 2012).

2.4.2 | Reliability analysis

Jack-knife sensitivity analysis was applied to investigate the effect of an individual study on the estimated pooled effect size by repeating the meta-analysis in successive iterations after discarding each individual study. If a brain region remains significant in more than 80% of the combinations of studies, the finding is considered highly replicable.

2.4.3 | Heterogeneity and publication bias analysis

The statistical heterogeneity of individual clusters was examined using a random effect model with Q/Q_H statistics (χ^2 distribution converted to *z* scores) and tested with a permutation approach ($p < .005$, uncorrected for FDR; peak height $z > 1$; cluster extent = 100 voxels). In addition, publication bias was evaluated by using Egger's test to assess the asymmetry of funnel plots of the data corresponding to each significant cluster in the between-group comparisons (Radua, Grau, et al., 2014).

2.4.4 | Meta-regression analyses

Meta-regression analyses (Radua & Mataix-Cols, 2009) were performed to investigate which confounding variables may contribute to heterogeneity of the findings. In particular, potential effects of age, sex-ratio, age of onset, duration of illness, symptom scores,

medication of subjects and imaging parameters were evaluated by using a linear random-effect model with threshold $p < .0005$. Only brain regions with significant results in the main meta-analysis were considered in the meta-regression analysis.

2.4.5 | Sub-group meta-analyses

To control for heterogeneity between the cohorts in the selected studies, sub-group meta-analyses were performed in which only those studies which recruited patients with stable SZ, or MDD in a current depressive episode, were included and furthermore in which only verbal WM tasks were employed. In this way it was possible to examine potential associations between the brain imaging findings, clinical classification and the integrity of verbal neurocognitive systems in both disorders.

2.4.6 | Conjunction analysis between meta-analysis groups

A conjunction analysis could also be performed using AES-SDM to compare the results obtained between different meta-analytic groups (for example, SZ relative to HC versus MDD relative to HC). In particular, a linear modal tool was employed to perform effect size comparisons between SZ and MDD in respect of the studies included in the main meta-analyses, using a less conservative threshold of $p < .001$ and cluster extent of 100 voxels (Radua et al., 2010). The multi-modal analysis function of AES-SDM also made it possible to identify brain regions where the single main meta-analysis of SZ and MDD groups relative to respective HC showed robust common abnormalities, taking into account the error in the estimation of *p* values within the individual meta-analyses (Radua, Romeo, Mataix-Cols, & Fusar-Poli, 2013; Wise et al., 2016). The statistical significance of each voxel was determined using randomization tests with threshold set to $p < .005$ to avoid false positives (Radua et al., 2013; Wise, Cleare, Herane, Young, & Arnone, 2014).

3 | RESULTS

3.1 | Characteristics of included studies

A total of 52 published papers fulfilled the criteria for inclusion in the meta-analysis (see Figure 1). The WM paradigms used in these papers mainly involved in Back (44 papers), delayed matching to sample (DMTS) (2 papers), and Sternberg Item Recognition (SIR) (2 papers), with four papers using other, less common WM tasks. Demographic and clinical information pertaining to the SZ, MDD and HC cohorts included in the main and sub-group meta-analyses are presented in Table 1. The corresponding quality assessment scores ranged from 8 to 14.5 points (mean 12.3 points), and 10 to 13.5 points (mean 12.4 points), for SZ and MDD studies respectively (see Table S2).

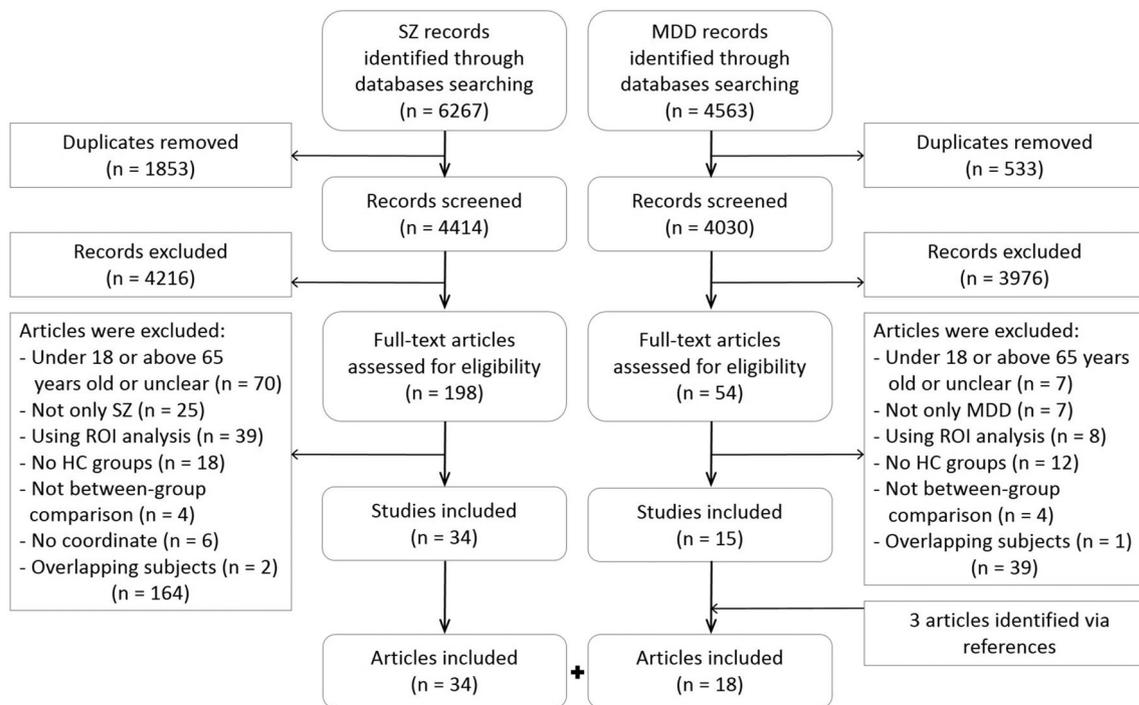


FIGURE 1 Flow chart of literature search

3.1.1 | Schizophrenia

Thirty-four published papers which refer to 38 different fMRI studies of WM in which whole brain response was compared between patients with SZ and HC, and refer to a total of 1,126 patients with SZ and 1,139 HC, were included. The demographic and clinical information for the subjects and details of the WM tasks for the included studies are presented in Table S3. There were no significant differences between SZ and HC groups in respect of age (SZ: 33.35 ± 5.67 years, HC: 32.13 ± 5.34 years, $t = 0.936$, $p = .352$), right handedness (SZ: $732/749 = 97.73\%$, HC: $818/830 = 98.55\%$, $\chi^2 = 0.014$, $p = .914$) or the percentage of the cohorts who were male (SZ: $710/1035 = 68.60\%$, HC: $654/1056 = 61.93\%$, $\chi^2 = 2.156$, $p = .076$).

3.1.2 | Major depressive disorder

Eighteen published papers which refer to 20 different fMRI studies of WM in which whole brain response was compared between patients with MDD and HC, and refer to a total of 426 patients with MDD and 425 HC, were included. The demographic and clinical information for the subjects and details of the WM tasks for the included studies are presented in Table S4. There were no significant differences between MDD and HC groups in respect of age (MDD: 36.05 ± 6.95 years, HC: 34.87 ± 6.76 years, $t = 0.530$, $p = .600$), right handedness (MDD: $325/332 = 97.89\%$, HC: $332/343 = 96.79\%$, $\chi^2 = 0.011$, $p = .956$) or the percentage of the cohorts who were male (MDD: $178/417 = 42.69\%$, HC: $185/416 = 44.47\%$, $\chi^2 = 0.106$, $p = .754$).

3.2 | Differences in fMRI response between patients and HC groups

3.2.1 | SZ patients versus HC

Main analysis

Relative to HC, patients with SZ showed significantly stronger fMRI response in left anterior cingulate gyrus (ACG), including bilateral gyrus rectus, SFG and right ACG, left posterior cingulate gyrus (PCG), including bilateral median cingulate/paracingulate gyri and right PCG, left MTG including left fusiform gyrus, right precentral gyrus including right SMA, right middle temporal gyrus (MTG), including right fusiform gyrus and STG, and right superior occipital gyrus (SOG), together with significantly weaker fMRI response in left MFG including left precentral gyrus, left precuneus, right SMA, including left SFG and SMA, right striatum, including right insula and putamen, right caudate nucleus, and right cerebellar hemispheric lobule including cerebellar vermis (Table 2 and Figure 2a).

Meta-regression analyses

Meta-regression analyses revealed that, relative to HC, SZ patients with more severe psychiatric symptoms as measured by Positive and Negative Syndrome Scale (PANSS) scores showed significantly stronger fMRI response in left PCG (peak MNI = 0, -42, 22, $Z = 1.209$, $p < .001$, 45 voxels, Figure 3a1), and significantly weaker fMRI response in left MFG (peak MNI = -38, 8, 54, $Z = -1.251$, $p < .001$, 39 voxels, Figure 3a2). Differences in mean age, handedness, sex percentage, years of education, age of onset, duration of illness, proportion of subjects taking antipsychotics, dose of chlorpromazine of the SZ

TABLE 1 Demographic and clinical characteristics of studies included in main meta-analyses and subgroup analyses for patients with SZ and MDD

Subjects	General information		Clinical characteristics				Subgroup analyses in different clinical state		Subgroup analyses during n Back tasks		Subgroup analyses during verbal WM					
	N of papers	N of patients	N of papers with good demographical details (%)	N of papers reporting onset age (%)	N of papers reporting illness duration (%)	N of papers reporting illness state (%)	N of papers reporting total symptom severity (%)	N of papers reporting treatment information (%)	N of papers patients (%)	N of papers HC (%)	N of papers patients (%)	N of papers patients (%)	N of papers patients (%)	N of papers patients (%)	N of papers patients (%)	N of papers patients (%)
SZ	34	1,126	29 (85.29)	14 (41.18)	20 (58.82)	12 (35.29)	18 (52.94)	30 (88.24)	12 (35.29)	414	426	28 (82.35)	1,004	1,004	27 (79.41)	972
MDD	18	426	14 (77.78)	4 (22.22)	9 (50.00)	16 (88.89)	14 (77.78)	16 (88.89)	12 (66.67)	199	226	16 (88.89)	392	383	16 (88.89)	386

Abbreviations: HC, healthy controls; MDD, major depressive disorder; N, number; SZ, schizophrenia; WM, working memory.

patients and MRI parameters among the included studies had no significant effect on these findings.

Sub-group meta-analyses

Details of the results of sub-group analyses are presented in Table S5.

3.2.2 | MDD patients versus HC

Main analysis

Relative to HC, patients with MDD showed significantly stronger fMRI response in left median cingulate gyri, including bilateral ACG and right SFG, right STG and fusiform gyrus, together with significantly weaker fMRI response in left middle occipital gyrus (MOG) and right MFG (Table 2 and Figure 2b).

Meta-regression analyses

Meta-regression analyses revealed that relative to HC, MDD patients with increasing severity of depression symptoms as measured by Hamilton Depression Scale (HAMD) scores showed significantly stronger fMRI response in right fusiform gyrus (peak MNI = 32, -38, -18, $Z = 1.738$, $p < .0001$, 552-434 voxels, Figure 3b1), together with significantly weaker fMRI response in right MFG (peak MNI = 30, 44, 28, $Z = -1.785$, $p < .001$, 114 voxels, Figure 3b2). Differences in mean age, handedness, sex percent, years of education, duration of illness, proportion of subjects taking antidepressants and antipsychotics, and MRI parameters among the included studies had no significant effect on these findings. Due to their being less than nine studies in which age of onset was reported in the original publication, the effect of potential differences in this variable could not be investigated.

Sub-group meta-analyses

Details of the results of sub-group analyses are presented in Table S6.

3.3 | Differences in fMRI response between SZ and MDD

Compared to patients with MDD, patients with SZ showed significantly stronger fMRI response in left gyrus rectus, including bilateral ACG, SFG and right gyrus rectus, left PCG including right PCG, right fusiform gyrus, including right STG, MTG, ITG and parahippocampal gyrus, together with significantly weaker fMRI response in left MFG including left precentral gyrus, right striatum, and right cerebellar hemispheric lobule including left cerebellar hemispheric lobule and cerebellar vermic lobule, relative to HC (Table 3 and Figure 2c).

3.4 | Stronger fMRI response shared in SZ and MDD

Conjunction analysis revealed that relative to HC, patients with SZ and patients with MDD showed concordant stronger fMRI response

TABLE 2 Clusters showing differences in fMRI response between patients with SZ or MDD and controls that met the criteria for robustness

Brain regions	Peak MNI coordinates (x, y, z)			SDM-Z value	p value	Voxel size	Cluster breakdown
SZ vs. controls							
<i>SZ > controls</i>							
Left anterior cingulate/paracingulate gyri, BA 10	-4	48	6	2.980	.000000596	3,899	Bilateral anterior cingulate/paracingulate gyri, BA 10 Right anterior cingulate/paracingulate gyri, BA 11/32 Bilateral gyrus rectus, BA 11 Bilateral superior frontal gyrus, medial orbital, BA 10 Bilateral superior frontal gyrus, medial orbital, BA 11
Left posterior cingulate gyrus	0	-42	22	2.202	.000144005	620	Left posterior cingulate gyrus Bilateral median cingulate/paracingulate gyri, BA 23 Bilateral posterior cingulate gyrus, BA 23
Right precentral gyrus, BA 6	20	-26	66	1.829	.001183450	329	Right precentral gyrus, BA 6 Right supplementary motor area, BA 4
Right temporal pole, middle temporal gyrus, BA 36	24	12	-42	1.944	.000643969	259	Right temporal pole, middle temporal gyrus, BA 36 Right fusiform gyrus, BA 36 Right temporal pole, superior temporal gyrus, BA 20; right temporal pole, superior temporal gyrus, BA 38
Left temporal pole, middle temporal gyrus, BA 36	-28	8	-38	1.759	.001667440	105	Left temporal pole, middle temporal gyrus, BA 36 Left fusiform gyrus, BA 36
Right superior occipital gyrus, BA 18	22	-96	18	1.771	.001575708	57	Right superior occipital gyrus, BA 18
<i>SZ < controls</i>							
Right cerebellum, hemispheric lobule VIII	8	-64	-36	-3.218	.000000179	3,382	Cerebellum, vermic lobule VIII Right cerebellum, hemispheric lobule VIII Cerebellum, vermic lobule IX/VII
Right supplementary motor area, BA 8	6	24	50	-2.391	.000029743	880	Bilateral supplementary motor area, BA 8 Left superior frontal gyrus, medial, BA 8
Left middle frontal gyrus, BA 6	-38	8	52	-2.582	.000008583	587	Left middle frontal gyrus, BA 6 Left precentral gyrus, BA 6
Right striatum	26	12	6	-1.782	.000951350	579	Right striatum Right lenticular nucleus, putamen, BA 48 Right insula, BA 47
Right caudate nucleus	12	4	10	-1.781	.000959933	211	Right caudate nucleus
Left precuneus, BA 7	-6	-70	50	-1.828	.000759780	171	Left precuneus, BA 7
MDD vs. controls							
<i>MDD > controls</i>							
Left median cingulate/paracingulate gyri, BA 24	0	-4	36	2.144	.000006497	3,292	Left median cingulate/paracingulate gyri, BA 23/24 Left median cingulate/paracingulate gyri Right superior frontal gyrus, medial, BA 10 Right superior frontal gyrus, medial orbital, BA 10 Bilateral anterior cingulate/paracingulate gyri, BA 10 Right anterior cingulate/paracingulate gyri
Right superior temporal gyrus, BA 48	58	-6	0	1.495	.000971675	437	Right superior temporal gyrus, BA 48
Right fusiform gyrus, BA 37	32	-38	-18	1.253	.003596485	43	Right fusiform gyrus, BA 37

TABLE 2 (Continued)

Brain regions	Peak MNI coordinates (x, y, z)		SDM-Z value	p value	Voxel size	Cluster breakdown	
<i>MDD < controls</i>							
Left middle occipital gyrus, BA 18	-20	-88	4	-1.017	.000139356	774	Left middle occipital gyrus, BA 18
Right middle frontal gyrus, BA 46	24	42	28	-1.253	.000018656	322	Right middle frontal gyrus, BA 46

Abbreviations: BA, Brodmann area; MDD, major depressive disorder; SZ, schizophrenia.

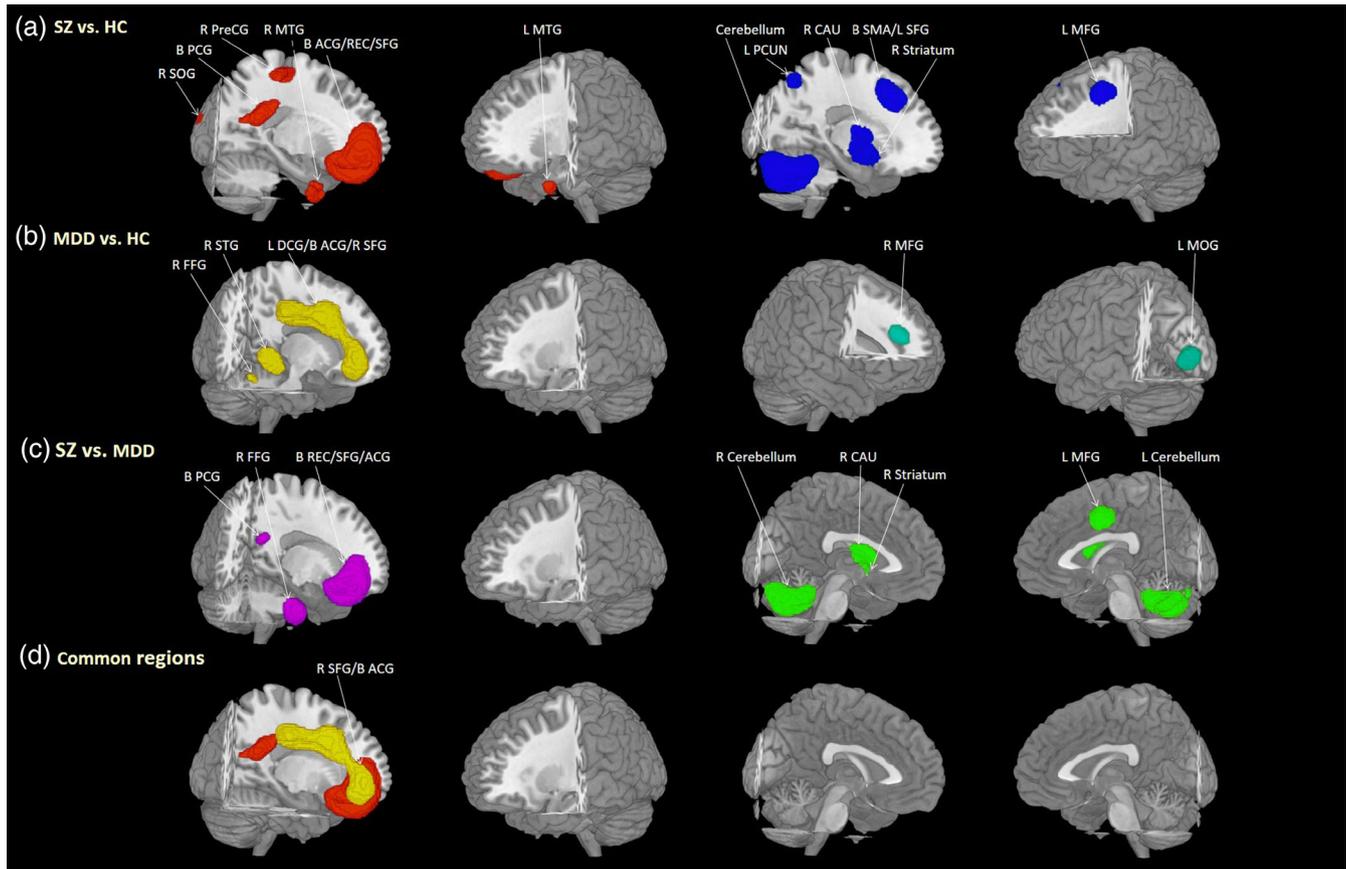


FIGURE 2 (a) Results of meta-analysis of brain fMRI response due to performance of working memory (WM) tasks in patients with schizophrenia (SZ) with red and blue clusters representing significantly stronger response, and significantly weaker response, in patients with SZ relative to healthy controls (HC), respectively. (b) Results of meta-analysis of brain fMRI response due to performance of WM tasks in patients with major depressive disorder (MDD) with yellow and cyan clusters representing significantly stronger response, and significantly weaker response, in patients with MDD relative to HC, respectively. (c) Brain regions showing significant differences in fMRI response due to performance of WM tasks between patients with SZ and patients with MDD. Purple and green clusters represent significantly stronger response, and significantly weaker response in SZ compared to MDD, relative to HC, respectively, with the effects frequently being more substantial in patients with SZ than in patients with MDD. (d) Results of conjunction analysis. Brain regions overlapping in red and yellow (i.e., orange) exhibit similar stronger fMRI response due to performance of WM tasks in SZ and MDD. ACG, anterior cingulate gyrus; CAU, caudate nucleus; DCG, median cingulate gyrus; FFG, fusiform gyrus; L, left; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; PCG, posterior cingulate gyrus; PCUN, precuneus; PreCG, precentral gyrus; R, right; REC, gyrus rectus; SFG, superior frontal gyrus; SMA, supplementary motor area; STG, superior temporal gyrus

during performance of WM tasks in right SFG including bilateral ACG, with the effect being greater in patients with SZ than patients with MDD (Table 3 and Figure 2d). These regions are part of the DMN

(Schilbach et al., 2016), which typically shows task-induced suppression during performance of externally oriented cognitive tasks (Buckner, Andrews-Hanna, & Schacter, 2008; Esposito et al., 2006).

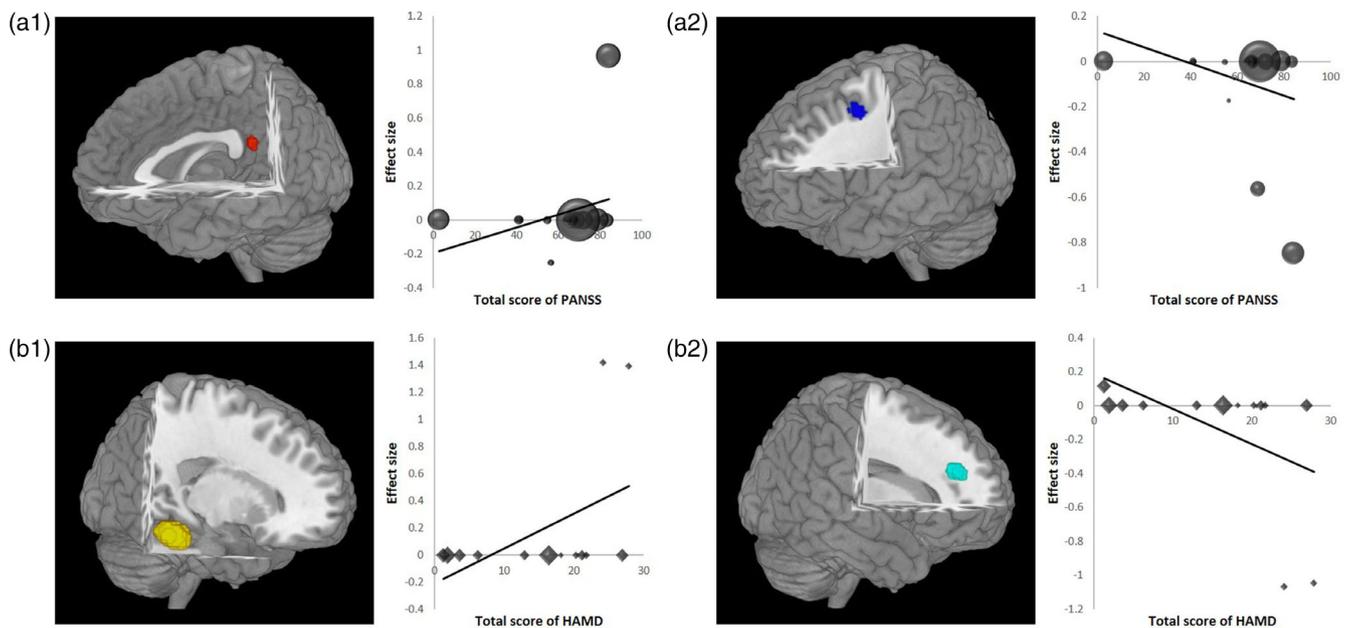


FIGURE 3 (a1-2) Results of meta-regression analysis of the dependence of brain fMRI response on severity of psychotic symptoms in patients with SZ, and (b1-2) results of meta-regression analysis of the dependence of brain fMRI response on severity of depression in patients with MDD

No brain region was identified which showed significantly weaker fMRI response that was common to both SZ and MDD relative to HC.

for all comparisons including SZ versus HC, MDD versus HC, and SZ versus MDD) (see Table S12).

3.5 | Analyses of sensitivity, heterogeneity and publication bias

Whole brain jack-knife sensitivity analysis of the results of the 38 WM studies in patients with SZ included in the main meta-analysis, showed that, relative to HC, significantly stronger fMRI response in bilateral MTG, left ACG and PCG, right precentral gyrus and SOG, and significantly weaker fMRI response in left MFG and precuneus, right caudate and cerebellum were present in all 38 datasets, and significantly weaker fMRI response in right SMA and striatum was present in 37 of the 38 datasets (Table S7). In comparison, whole brain jack-knife sensitivity analysis of the results of the 20 WM studies in patients with MDD included in the main meta-analysis, showed that, relative to HC, significantly stronger fMRI response in left median cingulate/paracingulate gyri was present in all 20 datasets, while significantly stronger fMRI response in right STG and fusiform gyrus, and significantly weaker fMRI response in left MOG and right MFG were present in 18 of the 20 datasets (Table S8).

The heterogeneity analyses revealed that the clusters with significantly stronger or weaker fMRI response in patients with SZ and MDD relative to HC in the main meta-analyses and conjunction analysis showed significant statistical heterogeneity among studies ($p < .005$) (see Tables S9–S11). There was no evidence of publication bias for any of the clusters reported as significant, as indicated by a nonsignificant result for Egger's funnel plot asymmetry test ($p > .05$

4 | DISCUSSION

The present meta-analysis revealed common brain regions exhibiting stronger fMRI response during performance of WM tasks in patients with SZ and MDD relative to HC, including bilateral ACC and right MPFC which are part of the DMN. The magnitude of the effects was significantly greater in patients with SZ than patients with MDD, especially in prefrontal-temporal-cingulate-striatal-cerebellar regions, suggesting a greater neurobiological disruption in SZ than MDD. Disorder-specific weaker fMRI response was observed in right MFG in MDD. These findings provide new evidence of a common neurobiological substrate of SZ and MDD and Disorder-specific substrate of MDD. In addition, the severity of psychotic symptoms in patients with SZ was related to the strength of the fMRI response of MFG and PCG in left hemisphere, and the severity of depressive symptoms in patients with MDD was related to the strength of the fMRI response of MFG and fusiform gyrus in right hemisphere.

4.1 | Common alterations of fMRI response in SZ and MDD

The results of the present meta-analysis are consistent with the suggestion that dysfunction of the DMN is a common feature of the pathophysiology of SZ and MDD (Kim et al., 2009; Li et al., 2013). The brain regions which exhibited stronger fMRI response during

TABLE 3 Clusters showing different and similar alterations in fMRI response in SZ and MDD that met our criteria for robustness

Brain regions	Peak MNI coordinates (x, y, z)			SDM-Z value	p value	Voxel size	Cluster breakdown
SZ vs MDD							
<i>SZ > MDD</i>							
Left gyrus rectus, BA 11	-2	34	-22	3.197	.000002801	2,717	Bilateral gyrus rectus, BA 11 Bilateral superior frontal gyrus, medial orbital, BA 10 Bilateral anterior cingulate/paracingulate gyri, BA 10 Right superior frontal gyrus, medial orbital, BA 11 Bilateral anterior cingulate/paracingulate gyri, BA 32/11 Left superior frontal gyrus, medial, BA 10
Right fusiform gyrus, BA 36	26	10	-44	3.106	.000004947	801	Right fusiform gyrus, BA 36 Right temporal pole, middle temporal gyrus, BA 36/20/38 Right parahippocampal gyrus, BA 36 Right inferior temporal gyrus, BA 20 Right temporal pole, superior temporal gyrus, BA 20
Left posterior cingulate gyrus	0	-48	22	2.440	.000171840	101	Left posterior cingulate gyrus Bilateral posterior cingulate gyrus, BA 26
<i>SZ < MDD</i>							
Right cerebellum, hemispheric lobule VIII	8	-62	-32	-3.508	.000000417	2,289	Right cerebellum, hemispheric lobule VIII left cerebellum, crus I cerebellum, vermic lobule IX bilateral cerebellum, hemispheric lobule VI
Left middle frontal gyrus, BA 6	-38	4	52	-3.597	.000000179	530	Left middle frontal gyrus, BA 6 left precentral gyrus, BA 6
Right caudate nucleus	14	2	12	-2.874	.000013292	302	Right caudate nucleus
Right striatum	22	4	6	-2.041	.000708759	20	Right striatum
Common stronger fMRI response in both SZ and MDD							
Right superior frontal gyrus, medial orbital, BA 10	2	48	-2	2.658	<.0001	953	Right superior frontal gyrus, medial orbital, BA 10 Bilateral anterior cingulate/paracingulate gyri, BA 10

Abbreviations: BA, Brodmann area; MDD, major depressive disorder; SZ, schizophrenia.

performance of WM tasks in patients with SZ and MDD relative to HC, lie predominantly in the DMN, including bilateral ACC and right MPFC, despite some differences in the specific location of stronger fMRI response in MPFC between the two disorders. This observation is consistent with reports of stronger fMRI response of MPFC and ACC in SZ (Chatterjee et al., 2019; Glahn et al., 2005; Kim et al., 2009; Metzak et al., 2012; Van Snellenberg et al., 2016; Whitfield-Gabrieli et al., 2009; Wu & Jiang, 2020) and MDD (Gartner et al., 2018; Murphy et al., 2019; Rodriguez-Cano et al., 2014) relative to HC. In addition, during WM processing stronger fMRI response in multiple sub-networks of the DMN in SZ (Haatveit et al., 2016; Kim et al., 2009) and reduced response suppression of the DMN in MDD (Murphy et al., 2019) relative to HC have been reported. Additional evidence of abnormal resting-state activity of VMPFC in SZ and MDD, comes from an ALE meta-analysis (Kuhn & Gallinat, 2013), and other studies which reported disconnectivity of VMPFC regions of the DMN (Li et al., 2013; Schilbach et al., 2016; Sharma et al., 2017; Yan et al., 2019). Stronger fMRI response and increased connectivity of DMN regions have been reported to be associated with inferior

WM performance in patients with SZ (Van Snellenberg et al., 2016; Whitfield-Gabrieli et al., 2009). MPFC represents the anterior node of the DMN (Schilbach et al., 2016), and suppression of fMRI response in the DMN is considered to be critical for suppressing sources of interference and successful performance of externally-focused tasks by healthy subjects (Anticevic et al., 2012; Buckner et al., 2008; Harrison, Yucel, Pujol, & Pantelis, 2007). The possibility exists that a common neurobiological substrate causes an impaired ability to suppress task-irrelevant information during WM performance in both SZ and MDD, reflected by stronger fMRI response in regions of the DMN (Gartner et al., 2018; Murphy et al., 2019; Van Snellenberg et al., 2016).

There have been many reports that function of large scale brain networks, particularly the so-called triple network comprising DMN, CEN and SN, is disrupted in both SZ and MDD (Brandl et al., 2019; Jiang et al., 2017; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Menon, 2011; Sha et al., 2018; Shao et al., 2018), with high consistency among findings for DMN and SN (Han et al., 2019; Jiang et al., 2017; Menon, 2011; Shao et al., 2018), which may contribute to

shared cognitive and affective impairments in both disorders. For example, it was reported that, relative to HC, there were aberrant intra-network intrinsic resting-state functional connectivity within DMN, CEN and SN in SZ (Manoliu et al., 2013b; Manoliu et al., 2014) and MDD (Liu et al., 2020a; Liu et al., 2020b), and abnormal inter-network intrinsic functional connectivity (iFC) between DMN, CEN and SN in SZ (Bauer et al., 2020; Chen et al., 2016; Jiang et al., 2017; Kang et al., 2018; Kang et al., 2020; Manoliu et al., 2014; Manoliu, Riedl, et al., 2013b) and MDD (Jiang et al., 2017; Manoliu et al., 2013a; Peng et al., 2018; Wang et al., 2020). A dynamical dependence of the connectivity between DMN and CEN on the SN has also been reported to be impaired in SZ and MDD (Dai, Zhou, Xu, & Zuo, 2019; Lefebvre et al., 2016; Manoliu et al., 2014). In addition, load-dependent fMRI response of the task-positive networks (TPN, including the CEN, SN and dorsal attention network) has been reported to be anticorrelated with that in the DMN during performance of WM tasks by patients with SZ spectrum disorders (Haatveit et al., 2016) and MDD (Delaveau et al., 2017), suggesting that a common mechanism may underlie aberrant TPN-DMN interactions in both disorders. Abnormal stronger fMRI response in DMN regions during performance of WM tasks may therefore be interpreted as a failure of task-related suppression of the DMN by the TPN (Zhou et al., 2018), which may lead to less flexible allocation of functional capacity during dynamic transitions between task and rest states (Nygard et al., 2012).

4.2 | Disorder-specific alteration of fMRI response in MDD

In addition to stronger fMRI response in the DMN regions during performance of WM tasks that is common to patients with SZ and patients with MDD, relative to HC, the main and sub-group analyses consistently revealed weaker fMRI response in right MFG only in patients with MDD relative to HC. The weaker fMRI response during performance of a WM task was also reported in PFC including right MFG in patients with MDD relative to HC (Vasic, Walter, Sambataro, & Wolf, 2009). Additional evidence for abnormal functioning of the frontal lobe in MDD comes from two studies using NIRS. In particular, Goethals et al. (2005) reported a reduced perfusion response in right MFG during performance of a range of cognitive tasks including WM, and Zhu et al. (2018) reported weaker fMRI response in PFC during performance of a WM task. Xia et al. (2019) analyzed resting-state fMRI data and reported increased medium-/long-range connectivity in right MFG in patients with MDD relative to HC. Consistent with the above, the finding of the present study suggests that functional abnormalities of right MFG during performance of WM tasks may be a disorder-specific feature of MDD.

4.3 | Greater abnormalities of fMRI response in SZ than MDD

Relative to HC, patients with SZ showed greater abnormalities in fMRI response during performance of WM tasks than patients with MDD,

in prefrontal-temporal-cingulate-striatal-cerebellar regions and fusiform gyrus. Some of these regions are part of the triple network (Dai et al., 2019; Jiang et al., 2017; Wu & Jiang, 2020). Specifically, relative to HC, patients with SZ showed stronger fMRI response in regions of the DMN during performance of WM tasks than patients with MDD, consistent with research of cognitive tasks other than WM (Holmes et al., 2005; Hugdahl et al., 2004). From inter-network connectivity patients with SZ exhibited greater iFC between DMN and CEN (Gong et al., 2017), and less iFC between DMN and SN (Shao et al., 2018) than patients with MDD, which may reflect unbalanced recruitment of the triple network in SZ and MDD. These findings may suggest a greater impairment in SZ than MDD in suppressing task-irrelevant information during performance of WM tasks (Shao et al., 2018).

There were also greater abnormalities in fMRI response during performance of WM tasks in patients with SZ than MDD relative to HC in regions other than the DMN. For example, stronger fMRI response was observed in bilateral SFG, gyrus rectus and PCC, right STG, MTG, ITG, fusiform gyrus and parahippocampal gyrus, together with weaker fMRI response in left MFG, right striatum and bilateral cerebellum. There have been several previous reports of stronger fMRI response in bilateral SFG and PCC, left MTG, precuneus and angle, and right precentral gyrus, and weaker fMRI response in left superior frontal lobe, right SFG, MFG and precentral gyrus, and basal ganglia in patients with SZ than those with MDD during performance of other cognitive tasks (Genzel et al., 2015; Holmes et al., 2005; Hugdahl et al., 2004; Wensing et al., 2017). It was also proposed that patients with SZ tended to over-recruit task-positive regions during low-load operations, perhaps reflecting heightened non-specific vigilance or effort when dealing with cognitive challenges in this disorder (Hahn, Harvey, Gold, Ross, & Stein, 2017). This is consistent with a reported gradient of increasing impairment in neurocognitive function and social outcomes in the order of SZ > bipolar disorder > MDD, which mirrors the clinical severity and outcomes for patients with these disorders (Reichenberg et al., 2009; Velthorst et al., 2017). Taken together, the findings of the present study indicate that patients with SZ show greater alterations of fMRI response for a large number of brain regions, including the DMN, than patients with MDD. This may reflect that patients with SZ face greater challenges in performing WM tasks.

The separate meta-analyses performed for patients with SZ relative to HC and patients with MDD relative to HC are not well matched in terms of the numbers of studies and cohort characteristics, especially clinical variables. In particular, the unbalanced numbers of original papers in the two meta-analyses (34 for SZ versus HC and 18 for MDD versus HC) may affect the accuracy of the findings, especially on account of significant bias arising from the lower number of studies of MDD (Lin, Li, Jing, Ran, & Sun, 2020; Xu et al., 2017). There are also challenges in separating depressive symptoms from psychiatric symptoms and cognitive impairments in patients with SZ (Mintz, Dobson, & Romney, 2003; Pacitti et al., 2019; Sevy, Nathanson, Visweswaraiiah, & Amador, 2004; Xu, Li, Liu, & Zhong, 2018), and especially cognitive impairments from severe depressive symptoms (Chen et al., 2019; Fang, Chen, Wang, Ren, & Zhang, 2019), which may affect performance of WM tasks in fMRI studies. Caution is needed in

applying meta-analytical methods in the presence of between-group heterogeneity, especially in comparing the results of meta-analysis with unbalanced numbers of studies (Seide, Rover, & Friede, 2019).

4.4 | Effects of clinical symptoms on fMRI response

For both SZ and MDD a significant correlation was observed between the severity of clinical symptoms and the strength of fMRI response during performance of WM tasks relative to HC (see Figure 3). In particular, SZ patients with more severe symptoms of psychosis showed weaker fMRI response in left MFG and stronger fMRI response in left PCC relative to HC. This finding is consistent with reports of a negative correlation between positive psychiatric symptoms (i.e., auditory hallucinations and thinking disturbance) and fMRI response in left inferior frontal, superior temporal and inferior parietal regions, and right MFG (Menon et al., 2001; Wible et al., 2009), and between scores on the PANSS general psychopathology and fMRI response in left frontal eye field (Chen et al., 2020b), as well as a positive correlation between negative psychiatric symptoms and fMRI response in right DLPFC (Jalbrzikowski et al., 2018) during performance of WM tasks.

Similarly, relative to HC, MDD patients with more severe symptoms of depression showed weaker fMRI response in right MFG and stronger fMRI response in right fusiform gyrus during performance of WM tasks. Furthermore, there are reports of a negative correlation between severe depressive symptoms and weaker fMRI response of left PFC in unaffected first-degree relatives of probands with MDD (Watters, Carpenter, Harris, Korgaonkar, & Williams, 2019), and a positive correlation between depressive rumination and fMRI response of ACC in MDD (Gartner et al., 2018), during performance of WM tasks. In addition, fMRI response in right DLPFC during a continuous performance WM task significantly predicted post-treatment symptom improvement in MDD (Miller et al., 2015).

4.5 | Limitations

There are several limitations in this meta-analysis that should be acknowledged. First, due to the cross-sectional design of all the studies included in the meta-analysis it is not possible to determine causality. The alterations in brain function during performance of WM tasks in SZ and MDD relative to HC could therefore be either related to the cause (i.e., pathophysiology) or occur as a consequence of the disorders. However, since no effect of illness duration was observed in the meta-regression analyses, the latter would appear to be the less likely interpretation. Second, the comparisons between patients with diagnosis of SZ and MDD and HC were based on spatial effect size maps reported in different published studies and the sample characteristics of the SZ and MDD groups not identical for all relevant clinical variables. For example, there was predicted to be an association between Auditory Verbal Hallucinations (AVHs) and cognitive processes underlying performance of WM tasks in SZ (Gisselgard et al., 2014;

Jenkins, Bodapati, Sharma, & Rosen, 2018). Well-designed prospective studies with matching and controlling clinical variables will allow the potential effects of these variables on functional neuroimaging findings in patients with SZ and MDD to be more accurately compared. Third, there are inherent limitations in interview-based and self-reported scales for measuring clinical symptoms (such as PANSS and HAMD) (Aboraya & Nasrallah, 2016; Bagby, Ryder, Schuller, & Marshall, 2004; Hamera, Schneider, Potocky, & Casebeer, 1996). Objectivity and reliability will be increased in future research by using screening methods based on biomarkers such as heart rate variability (Jung, Jang, & Lee, 2019; Koch, Wilhelm, Salzmann, Rief, & Euteneuer, 2019; Schiweck, Piette, Berckmans, Claes, & Vrieze, 2019), electrodermal activity (Cella et al., 2019; Kim et al., 2018) and electroencephalogram-based measures (Feuerriegel, Churches, Hofmann, & Keage, 2015; Spironelli, Romeo, Maffei, & Angrilli, 2019). Fourth, empirical simulations have suggested that at least 20 studies should be included in a meta-analysis in order to obtain robust results (Eickhoff et al., 2016). The present meta-analysis includes 38 WM studies of patients with SZ and 20 WM studies of patients with MDD and so is consistent with the above guideline although the imbalanced numbers of studies relevant to each disorder could have potentially influenced the findings. Fifth, for the studies included in the meta-analysis patients with SZ often showed poor performance in WM tasks relative to HC while patients with MDD generally showed comparable performance relative to HC, even in high task loads (i.e., 3 Back task). This difference in performance of WM tasks by patients with SZ and MDD can potentially bias the findings. Sixth, for most of the studies included in the meta-analysis the patients with SZ and MDD were being treated with psychotropic medication at the time when fMRI investigations were performed, which could potentially influence the brain fMRI response that were observed (Schlagenhauf et al., 2008). However, consistent with other studies (Kinou et al., 2013; Phillips, Travis, Fagiolini, & Kupfer, 2008), evidence of an effect of the psychotropic medications on brain fMRI response was not revealed by the meta-regression analyses performed in the present study for either patients with SZ or patients with MDD. Finally, the analysis was based on the coordinates of brain fMRI response reported in previously published studies rather than on the direct statistical analysis of acquired images (Salimi-Khorshidi, Smith, Keltner, Wager, & Nichols, 2009).

5 | CONCLUSION

A systematic meta-analysis of data from 52 published papers referring to 58 fMRI studies of WM tasks performed by patients with SZ (38 studies) and MDD (20 studies) revealed stronger fMRI response throughout the DMN in both disorders relative to HC, and the effects were of greater magnitude in SZ than MDD, especially in prefrontal-temporal-cingulate-striatal-cerebellar regions. In addition, a disorder-specific weaker fMRI response was observed in right MFG in patients with MDD relative to HC. In both SZ and MDD the severity of clinical symptoms laterally influenced the brain fMRI response produced by

WM tasks. These findings indicate that there may be common and distinct anomalies in brain function underlying deficits in WM in SZ and MDD, which may serve as a potential functional neuroimaging-based diagnostic biomarker with value in supporting clinical diagnosis, measuring illness severity and assessing the efficacy of treatments for SZ and MDD at the brain level. Longitudinal studies recruiting first-episode drug-naïve patients with SZ and MDD with uniform diagnosis and using MRI techniques such as those employed in the present study will assist in further elucidating the neurobiological mechanisms underlying deficits in the performance of WM tasks in both disorders.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

The study was conceived by Xiuli Wang and Bochao Cheng. Data analysis was performed by Song Wang, Ya Luo, Fangfang Tian, and Suping Yue. Xiuli Wang, Bochao Cheng, and Neil Roberts interpreted the data and together with Song Wang, Ya Luo, Fangfang Tian, and Suping Yue produced a first draft of the manuscript. All authors reviewed and contributed to finalizing the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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