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# Working memory deficit in schizophrenia: a systematic review and meta-analysis of fMRI studies examining frontal and parietal brain activity

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## Abstract

***Introduction:*** *The role of functional magnetic resonance imaging (fMRI) findings in investigation of working memory (WM) deficit in schizophrenia patients is still debatable. The aim of the study was to investigate the role of fMRI findings of the frontal and parietal brain activity in investigation of WM deficit in schizophrenia patients.*

***Material and methods:*** *We used Medline, Embase, and the Cochrane Database to conduct a comprehensive search up to January 2023. Functional MRI findings of schizophrenia patients were compared with healthy patients in comparative studies for assessing their WM capacity in terms of dorsolateral prefrontal cortex and parietal region activation. The Cochrane Risk of Bias Assessment Tool was used to evaluate the research quality.*

***Results:*** *Ten trials and 676 schizophrenia patients were included in our analysis. For the comparative assessment of primary outcome – alteration in dorsolateral prefrontal cortex and parietal region activity in schizophrenic patients versus healthy controls – we found the pooled odds ratio (OR) of 1.58 [95% CI: 1.09-2.29], $I^2$ = 61% and p = 0.01 and risk ratio (RR) was 1.27 [95% CI: 1.06-1.53], $I^2$ = 55% and p = 0.01. The AUC value of 0.944 indicates a favourable overall diagnostic performance of fMRI for the diagnosis of schizophrenia.*

***Conclusions:*** *fMRI findings showing abnormalities in the parietal and frontal regions can be used to study schizophrenia patients' WM deficits.*

***Key words:*** *fMRI, meta-analysis, schizophrenia, working memory deficit, altered parietal activation.*

## Introduction

People with schizophrenia frequently demonstrate significant difficulties with such complex activities as executive functioning, linguistic learning and memory, and attention, in addition to having poorer working memory (WM) skills [7]. Consequently, it has been suggested that a deficiency in WM could potentially explain a significant portion of the cognitive dysfunction observed in the disease. Research using functional magnetic resonance imaging (fMRI) has provided evidence of deficits in WM and cognitive control among individuals diagnosed with schizophrenia. In schizophrenia, hippocampal impairment frequently co-occurred with impairments in prefrontal function, indicating a disruption in frontotemporal connectivity [43]. Deficits in WM have been related to lower functional results in people with schizophrenia, motivating decades of research into the underlying neurobiological causes [14,24]. The influence of dopamine and norepinephrine on the

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glutamatergic and GABAergic networks that are crucial for WM representations is necessary for achieving effective performance in WM tasks. These tasks rely on the activity of dopamine in the dorsolateral prefrontal cortex (DLPFC) [3,19]. The DLPFC of individuals diagnosed with schizophrenia exhibits apparent disturbances in WM representations [2]. However, the specific nature of this disruption remains unclear due to the presence of various abnormalities in dopaminergic functioning associated with schizophrenia, as well as the growing body of evidence indicating disruptions in glutamate and GABA neurotransmission [30,34].

Functional magnetic resonance imaging is a neuroimaging technique utilized to identify alterations in blood oxygenation and blood flow velocity as a result of neural activity. These data can subsequently be employed to ascertain the region of the brain that exhibits the highest level of activity and oxygen consumption. Functional MRI is a commonly employed noninvasive method for assessing the functionality of the DLPFC during the execution of WM tasks. Previous studies utilizing fMRI have observed decreased activity in the DLPFC among individuals performing WM tasks. This finding aligns with the notion of compromised dopamine function in the DLPFC, as dopamine has been shown to play a crucial role in WM performance in non-human primates [10,18,27]. Nevertheless, a number of studies have encountered challenges in reproducing these findings and have ascertained that the DLPFC exhibited heightened activity in individuals with the condition [4,5,28].

The objective of this review and meta-analysis was to examine the activation patterns of the dorsolateral prefrontal cortex and the parietal region in individuals with schizophrenia and healthy individuals during the performance of WM tasks. This investigation aimed to shed light on the WM impairment observed in individuals with schizophrenia, as it is primarily associated with alterations in the prefrontal and parietal cortices.

## Material and methods

### Search strategy

This study utilized a systematic search strategy to retrieve articles published in the English language from January 2000 to January 2023. The search was conducted in three databases: Medline, Embase, and the Cochrane database. The search criteria included the following terms: (I) "functional magnetic resonance imaging" or "fMRI"; (II) "schizophrenia"; (III) "working memory deficit" or "WM"; (IV) "alteration in parietal activation"; (V) "alteration in frontal activation"; and (VI) "abnormal cortex activity". The utilization of the Boolean operator "AND" was employed in the search strategy to merge the Medical Subject Headings (MeSH) with the text keywords. Two researchers (XD and HF) conducted an independent search and reviewed the bibliographies in order to identify papers that may be relevant to the study.

### Eligibility criteria

The two researchers, XD and HF, assessed the titles and abstracts of the obtained publications using the inclusion criteria outlined below. The criteria for selecting studies in this review were as follows: (i) the studies had to be published in the English language; (ii) the studies had to involve comparative analyses between individuals diagnosed with schizophrenia and healthy controls; (iii) the studies had to incorporate fMRI investigations specifically targeting the parietal cortex; (iv) the studies had to incorporate fMRI investigations specifically targeting the frontal cortex; and (v) the studies had to examine the impact of abnormal activation in the prefrontal and parietal regions on WM capacity. The study excluded articles that failed to report the main outcomes or that presented all outcomes solely as the median and interquartile range.

### Data extraction and outcome measures

The present meta-analysis encompasses a total of ten comparative studies [6,12,21-23,31,37,39-41] and adheres to the methodological guidelines outlined in the latest edition of the Cochrane Handbook for Systematic Reviews of Intervention [32]. The researchers employed a pre-designed data collection form to extract information from the primary research. The data extraction process was carried out independently by two investigators, XD and HF. The primary measure of interest was the change in activation patterns in the frontal and parietal regions during low-level tasks in individuals diagnosed with schizophrenia compared to a group of individuals without any psychiatric disorders.

### Assessment of risk of bias

The evaluation of the included studies' quality was performed utilizing the "risk of bias" table in Review Manager (REVMAN) software, version 5.3, developed by The Nordic Cochrane Center in Copenhagen, Denmark [26]. This table presents a comprehensive catalogue of various sources of bias, including random sequence creation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, inadequate outcome data, selective reporting, and other factors. By utilizing the provided table, we successfully allocated a rating of "low", "high", or "uncer-

tain" to each parameter during our evaluation of the research's quality. The investigation was conducted by two investigators, namely JX and JW, who worked independently of each other.

### Statistical analysis

The analysis for this study utilized the Review Manager (REVMAN) software, specifically version 5.3, developed by The Nordic Cochrane Center in Copenhagen, Denmark. The study computed relative risks (RRs) and odds ratios (ORs) along with their corresponding 95% confidence intervals (CIs) for both dichotomous and continuous outcome data. Both the chi-squared ($\chi^2$) and *I*-squared ($I^2$) statistics were utilized to assess the heterogeneity of the study. The thresholds for low, middle, and high heterogeneity were defined as the $I^2$ values of 25%, 50%, and 75%, respectively. Heterogeneity was considered to be significant when the *p*-value was less than 0.1 [17]. Due to the significant variability observed among the papers included in the study, the random effects model was predominantly employed for all analyses. A funnel plot was employed to assess the presence of publication bias. A significance level of $p < 0.05$ was considered to indicate statistical significance. The receiver operating characteristic (ROC) curve is a statistical tool that is utilized to evaluate the comprehensive diagnostic efficacy of fMRI and to make comparisons between fMRI studies conducted on individuals with schizophrenia and those conducted on healthy individuals, with the objective of discerning the existence or non-existence of a particular medical condition [9].

## Results

### Study characteristics and extraction

The PRISMA chart for study selection is depicted in Figure 1. A comprehensive examination of various online sources yielded a grand total of 785 studies. After removing duplicate entries, a comprehensive analysis was conducted on the abstracts and titles of 212 studies. A total of 36 studies met the criteria for full-text review. Ten publications were included in this meta-analysis based on the PICOS criteria [20] as presented in Table I.

Table II presents the primary attributes of the trials encompassing WM impairments in individuals diagnosed with schizophrenia. All of the ten studies included in the analysis reported the primary outcome, which was the comparison of fMRI findings related to changes in frontal and parietal activation during WM tasks between individuals with schizophrenia and healthy controls.

### Evaluation of risk of bias and publication bias

Out of the ten studies that were included, seven demonstrated a low risk of bias, whereas two exhibited

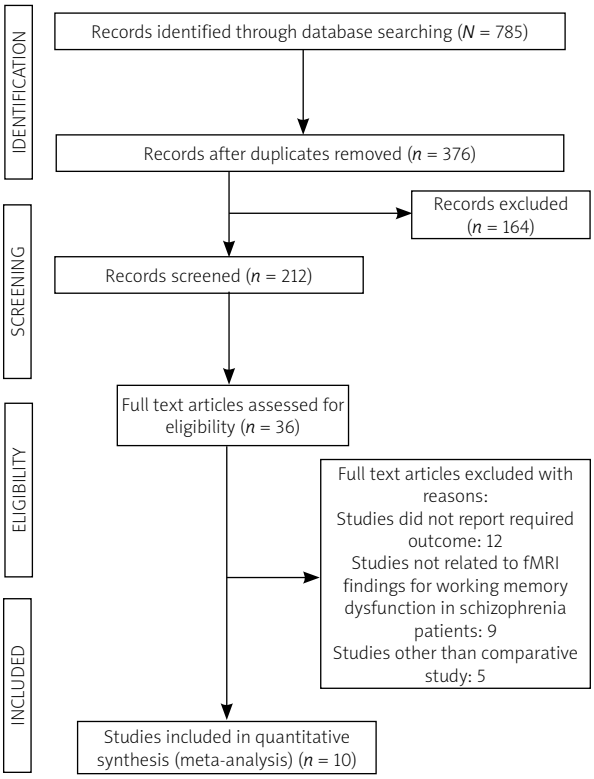


**Fig. 1.** Study flow diagram as per PRISMA guidelines.

**Table I.** PICOS search

| PICOS | |
|---|---|
| P (Patient, problem, population) | Schizophrenia patients |
| I (Intervention) | Role of fMRI for investigation of working memory deficit in schizophrenia patients |
| C (Comparison, control or comparator) | Comparison of schizophrenia patients with healthy controls for alteration in frontal and parietal activation during working memory tasks |
| O (Outcome [s]) | Schizophrenic patients have aberrant alteration in the frontal and parietal activation and have working memory deficits |
| S (study type) | Comparative studies |

**Table II.** Brief summary of included studies

| Study ID and year | Publication journal | Type of study | Parameter studied | Technique used | Sample size | Schizophrenia patients | Healthy controls | Primary outcome | Conclusion |
|---|---|---|---|---|---|---|---|---|---|
| Barch *et al.* 2007 [5] | The American Journal of Psychiatry | Comparative study | Activity in the regions of prefrontal and parietal cortices activation during WM task | fMRI | 177 | 57 | 120 | Alteration in frontal and parietal activation during WM tasks | Bilateral deficits in dorsal frontal and parietal activation were recorded during both verbal and nonverbal working memory tasks in schizophrenia patients |
| Bleich-Cohen *et al.* 2014 [6] | European Psychiatry | Comparative study | Activation of right dorsolateral prefrontal cortex (DLPFC) and the right caudate nucleus during WM task | fMRI | 53 | 33 | 20 | Alteration in frontal and parietal activation during WM tasks | Schizophrenia patients showed a reduction in activation in the right dorsolateral prefrontal cortex and right caudate region along with decreased functional connectivity |
| Eryilmaz *et al.* 2016 [12] | Neuropsycho-pharmacology | Comparative study | Dorsolateral prefrontal cortex activation, resting-state connectivity within the frontoparietal control network and WM circuitry | fMRI | 80 | 40 | 40 | Alteration in frontal and parietal activation during WM tasks | Schizophrenia patients showed abnormal connectivity among regions such as ventromedial prefrontal cortex, lateral orbitofrontal cortex, and parahippocampal gyrus during both rest and task and altered thalamic connectivity |
| Jansma *et al.* 2004 [22] | Schizophrenia research | Comparative study | Activation of the dorsolateral prefrontal cortex (DLPFC) during WM task | fMRI | 20 | 10 | 10 | Alteration in frontal and parietal activation during WM tasks | Increasingly poor performance in schizophrenic patients, increased activity in DLPFC, inferior parietal cortex bilaterally and in anterior cingulate, with increasing load |
| Jiang *et al.* 2015 [23] | PLoS One | Comparative study | Response in the right dorsolateral prefrontal cortex and bilateral ventrolateral prefrontal cortex during WM task | fMRI | 80 | 40 | 40 | Alteration in frontal and parietal activation during WM tasks | Schizophrenia patients showed an exaggerated response in the right dorsolateral prefrontal cortex (Brodmann area) and bilateral ventrolateral prefrontal cortex, and reduced activation in bilateral dorsolateral prefrontal cortex |

**Table II.** Cont.

| Study ID and year | Publication journal | Type of study | Parameter studied | Technique used | Sample size | Schizophrenia patients | Healthy controls | Primary outcome | Conclusion |
|---|---|---|---|---|---|---|---|---|---|
| Raalten *et al.* 2008 [40] | Schizophrenia research | Comparative study | Activation in regions of left dorsolateral prefrontal cortex (LPFC), anterior cingulate cortex, left superior parietal cortex, right superior parietal cortex and visual cortex during WM task | fMRI | 36 | 18 | 18 | Alteration in frontal and parietal activation during WM tasks | Reduced activation was recorded in regions of left dorsolateral prefrontal cortex, anterior cingulate cortex, left superior parietal cortex, right superior parietal cortex and visual cortex in schizophrenia patients |
| Sapara *et al.* 2014 [31] | Schizophrenia research | Comparative study | Activation in inferior-superior frontal gyrus and cerebellum during WM task | fMRI | 60 | 40 | 20 | Alteration in frontal and parietal activation during WM tasks | Schizophrenic patients had reduced activity most consistently in the precuneus and bilateral cerebellum during WM tasks |
| Snellen-berg *et al.* 2016 [41] | Biological Psychiatry | Comparative study | Activation in left dorsolateral prefrontal cortex and behavioural deficits in WM capacity | fMRI | 96 | 51 | 45 | Alteration in frontal and parietal activation during WM tasks | Schizophrenic patients showed suppression of medial prefrontal cortex activity during WM tasks |
| Tan *et al.* 2005 [37] | The American Journal of Psychiatry | Comparative study | Bilateral dorsolateral prefrontal cortex activation and ventrolateral prefrontal cortex activation during WM task | fMRI | 22 | 11 | 11 | Alteration in frontal and parietal activation during WM tasks | Schizophrenic patients showed less bilateral dorsolateral prefrontal cortex activation and greater ventrolateral prefrontal cortex activation |
| Thomas *et al.* 2022 [39] | Journal of the International Neuropsycho-logical Society | Comparative study | Activity of posterior dorsolateral prefrontal and parietal association cortices during WM task | fMRI | 52 | 27 | 25 | Alteration in frontal and parietal activation during WM tasks | Schizophrenic patients showed aberrant activity within the anterior dorsolateral prefrontal cortex and parietal association cortices during WM task |

*fMRI: functional magnetic resonance imaging, WM: working memory, DLPFC: dorsolateral prefrontal cortex*

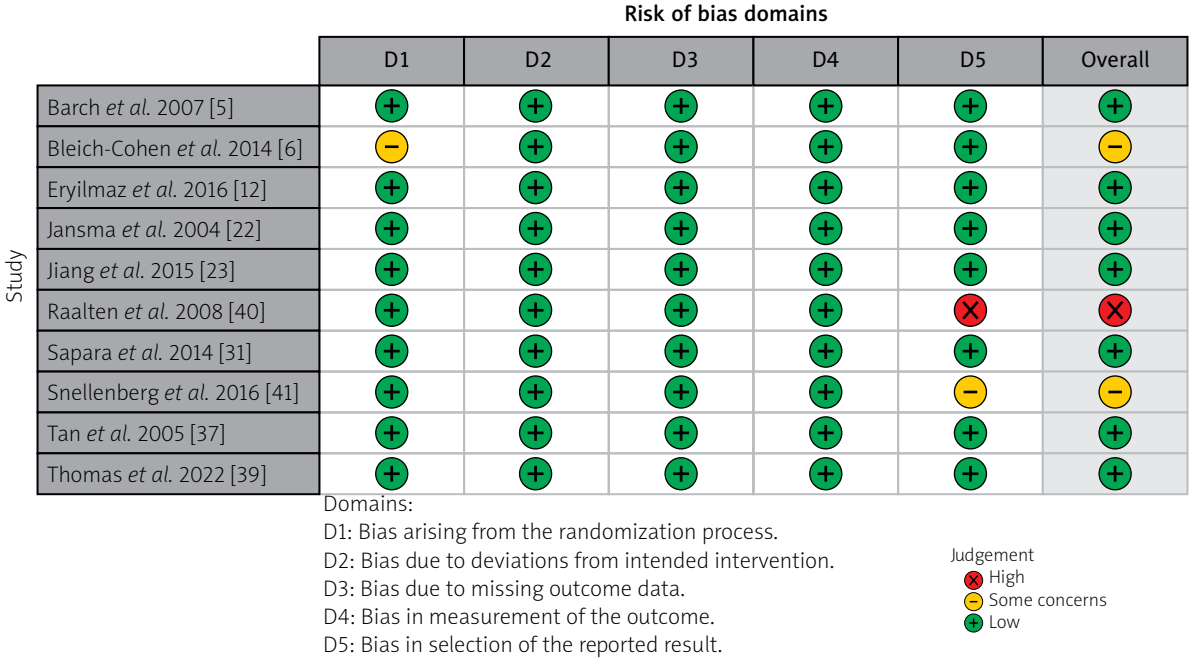


**Fig. 2.** Risk of bias summary.

a significant risk of bias stemming from issues related to the randomization process and the selection of reported results. A single study was found to possess a high risk of bias in the selection of reported results, as indicated by the risk of bias summary (Fig. 2) and risk of bias graph (Fig. 3). The funnel plot depicted in Figure 4 exhibits a low probability of publication bias, as indicated by a significant *p*-value of 0.4039 obtained from Begg's test [38].

## Statistical analysis of primary outcome

### Odds ratio of all the studies included in the analysis

All ten trials, comprising a cumulative total of 676 participants, yielded data regarding fMRI observations pertaining to changes in frontal and parietal activation during WM tasks in individuals diagnosed with schizophrenia compared to those without the condition. Figure 5 illustrates the comparative evaluation between individuals diagnosed with schizophrenia and those who are considered healthy controls. The pooled OR was calculated to be 1.58, with 95% CI ranging from 1.09 to 2.29. The $I^2$ value, which measures heterogeneity, was found to be 61%. Additionally, the *p*-value associated with this analysis was determined to be 0.01.

### Risk ratio of all included studies

Figure 6 shows the comparative assessment of alteration in frontal and parietal activation during WM tasks in schizophrenic patients vs. healthy controls.

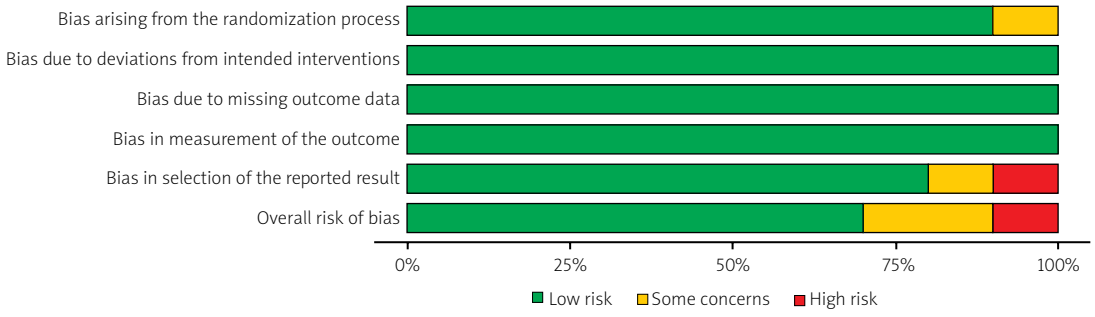


**Fig. 3.** Risk of bias graph.

The pooled RR was 1.27 with the 95% CI of 1.06-1.53, $I^2$ value of 55% and $p$ equal to 0.01.

### Outcomes of ROC analysis

Figure 7 depicts a ROC curve. This curve serves as a means to assess the overall diagnostic efficacy of fMRI in diagnosing schizophrenia. The evaluation is based on the observed disparities in the activation of the parietal and frontal cortex during WM tasks, comparing individuals with schizophrenia to a control group of healthy individuals. The ROC curve illustrates the relationship between two parameters, namely the true positive rate (also known as sensitivity) and the false positive rate (specifically, 1-specificity), across all possible categorization thresholds. The graph represents the relationship between two variables: the sensitivity, also known as the true positive rate, and the specificity, which is the complement of the false positive rate. The area under the curve (AUC) was calculated to be 0.944, with a 95% CI ranging from 0.85 to 1.00. A higher AUC indicates that fMRI exhibits a notable capability in effectively differentiating between positive and negative cases.

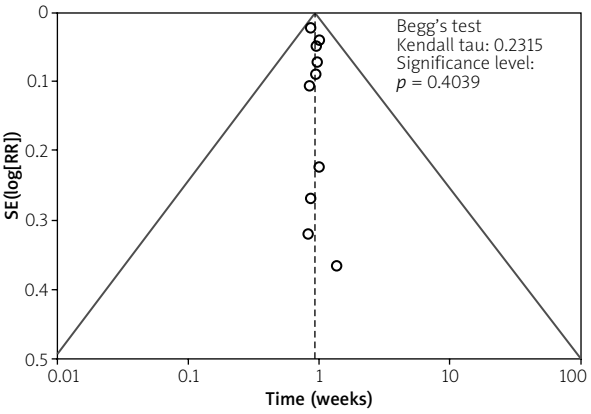


**Fig. 4.** Funnel plot for publication bias.

## Discussion

Schizophrenia is a serious mental condition that can manifest itself in a number of ways, including hallucinations and delusions. When a person has schizophrenia, their brain undergoes a variety of chemical changes, which can lead to structural and functional abnormalities in the brain. The patient's cognitive, emo-

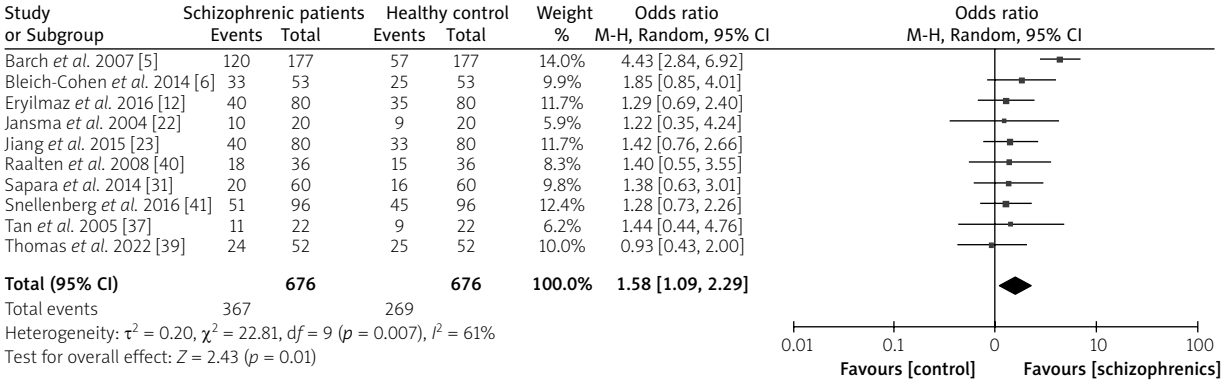


**Fig. 5.** Forest plot odds ratio schizophrenia patients vs. healthy controls.

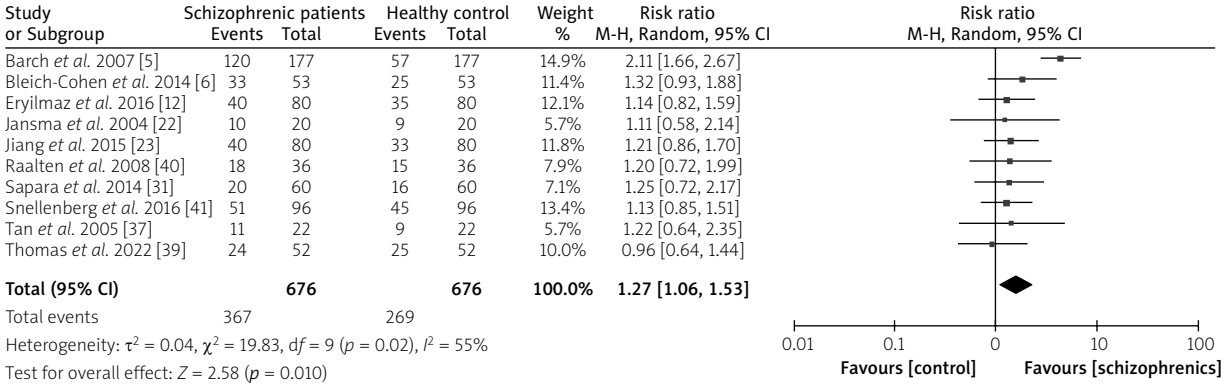


**Fig. 6.** Forest plot risk ratio schizophrenia patients vs. healthy controls.

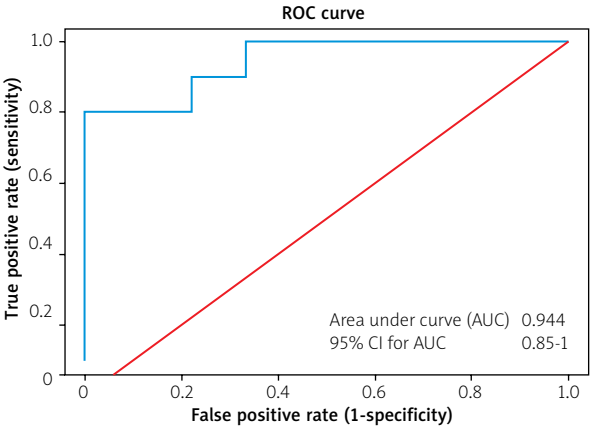


**Fig. 7.** Receiver operating characteristic (ROC) curve.

tional, and behavioural capacities are all negatively impacted as a result of these alterations [44]. In addition, people who have schizophrenia frequently show signs of having a problem with their WM, which can have a negative effect on a person's attention as well as their behavioural features [44]. A person's WM is a form of short-term memory that assists in the processing of language, as well as decision making and logical thinking. WM is responsible for recognizing items that are relevant to immediate consciousness, and it serves to maintain information while selectively processing that information [10].

The utilization of fMRI has contributed to the identification and management of neurological and psychiatric disorders, as well as the advancement of our understanding of the brain. This is due to the inclusion of three-dimensional images of various regions within the brain volume over a period of time in fMRI data [15]. The utilization of the blood oxygenation level-dependent (BOLD) technique has been commonly utilized in fMRI studies. This method relies on the magnetic susceptibility of deoxyhaemoglobin. When a specific region of the brain is activated by a cognitive task, it necessitates a greater supply of oxygenated blood, leading to an overall increase in signal intensity [11].

Based on the extant literature pertaining to fMRI findings in individuals with schizophrenia, it has been observed that there are alterations in the structure and functioning of various crucial brain systems, including the prefrontal and medial temporal lobe regions. These regions are primarily associated with WM and declarative memory, respectively [33]. Individuals diagnosed with schizophrenia exhibit impairments in several tasks that rely on prefrontal cortical functions. These deficits encompass attention, cognitive inhibition, cognitive flexibility, delayed response, and N-back tasks that involve WM. These impairments can be attributed to the progression of grey matter abnormalities, which initially manifest in the parietal and occipital lobes and subsequently extend to the frontal regions [13].

This study focuses on the examination of alterations in parietal and frontal brain activation in individuals diagnosed with schizophrenia, in comparison to a control group of healthy individuals. Our analysis involves the utilization of 10 selected comparative studies, encompassing a total of 676 schizophrenia patients. The objective is to investigate the impact of these observed changes on the WM performance of individuals with schizophrenia. In these investigations, the acquisition, processing, and first-level modelling of fMRI data involved the initial acquisition of pictures using multiple scanners. The acquired images were then subjected to processing steps, including accurate slice-timing, motion alignment, normalization based on a standard template, and finally, smoothing [8,29,35,36]. A comparative analysis was conducted on the fMRI scan findings obtained from individuals diagnosed with schizophrenia and a control group of healthy individuals. The primary finding remained consistent across multiple studies, indicating that individuals diagnosed with schizophrenia exhibited impairments in WM, as evidenced by their diminished WM capacity in comparison to individuals without the disorder. This discrepancy can be attributed to reduced activation levels within the dorsolateral prefrontal cortex during tasks involving WM.

In their study, Barch *et al.* [5] discovered bilateral abnormalities in the activation of the dorsal frontal and parietal regions during verbal and nonverbal WM tasks among individuals diagnosed with schizophrenia. These findings provide empirical support for the notion that individuals with schizophrenia exhibit deficits in WM. In a study conducted by Bleich-Cohen *et al.* [6], it was observed that individuals diagnosed with schizophrenia exhibit diminished activity in the right DLPFC and right caudate, in comparison to a control group of healthy individuals. Additionally, the schizophrenia patients also demonstrated impairments in WM. In their study, Eryilmaz *et al.* [12] reported a decrease in resting-state connectivity within the frontoparietal control network (FPCN) and observed impaired functioning of the WM circuitry in individuals diagnosed with schizophrenia. In a study conducted by Jansma *et al.* [22], it was observed that individuals with schizophrenia exhibited reduced activation in the right DLPFC and right caudate, along with decreased functional connectivity (FC), when compared to a group of healthy individuals serving as controls. According to Jiang *et al.* [23], individuals diagnosed with schizophrenia exhibit impairments in WM, which can be detected in patients and are linked to reduced activation in the bilateral dorsolateral pre-

frontal cortex as measured by fMRI. According to van Raalten *et al*. [40], individuals with schizophrenia exhibit impaired WM function, which is characterized by suboptimal utilization of WM resources and reduced capacity.

Sapara *et al*. [31] found a correlation between WM capacity in specific subgroups of individuals with schizophrenia and the neuronal activity observed in the frontal cortex and cerebellum. The authors further suggested that deviations from normal neuronal functioning in these brain regions lead to impairments in WM performance. In a study conducted by Slifstein *et al*. [34], individuals diagnosed with schizophrenia exhibited reduced suppression of the medial prefrontal cortex (mPFC) during tasks involving WM. This diminished suppression was found to be associated with a decrease in WM capacity. The study conducted by Tan *et al*. [37] revealed that individuals diagnosed with schizophrenia exhibit impaired WM, a critical cognitive function. This impairment was characterized by reduced activation in the bilateral dorsolateral prefrontal cortex, as compared to a control group of healthy individuals. The study conducted by Thomas *et al*. [39] demonstrated a correlation between schizophrenia and impaired WM, which can be attributed to atypical functioning of the posterior dorsolateral prefrontal and parietal cortices.

The odds ratio of 1.58 (95% CI: 1.09-2.20) was calculated based on a meta-analysis of the included studies, which focused on changes in activity within the dorsolateral prefrontal and parietal cortical areas as the primary outcome. Individuals diagnosed with schizophrenia have a higher propensity, in comparison to individuals without the disorder, to demonstrate atypical functioning of the dorsolateral prefrontal cortex when engaging in tasks that require WM. This association holds true when the odds ratio exceeds a value of 1 [1]. In a similar vein, the risk ratio of 1.27 (with a 95% CI of 1.06-1.53) suggests a substantial likelihood of reduced activation in the posterior dorsolateral prefrontal and parietal cortices among patients, along with impaired WM capacity [42]. All of the obtained results exhibit statistical significance at a significance level of $p < 0.05$. The fMRI diagnostic performance for schizophrenia can be determined by analysing the variations in parietal and frontal brain activation during WM tasks.

In this context, a larger AUC value of 0.944 suggests a superior overall diagnostic capability of fMRI for schizophrenia diagnosis. AUC values approaching 1 indicate that the fMRI research is capable of accurately distinguishing between all positive and negative class points [25]. The results of our study align with the findings of Lee *et al*. [25] and Gold *et al*. [16]; in both cases, the authors reached the same conclusion that individuals with schizophrenia exhibit diminished activation in the posterior dorsolateral prefrontal and parietal cortex regions. The researchers also discovered that individuals diagnosed with schizophrenia exhibit deficiencies in both basic memory capacity and a significant portion of the overall cognitive impairment. Consequently, they demonstrated impairments in WM.

## Study limitations

The present study is subject to numerous limitations. It is probable that a limited study effect was present, given that a significant proportion of the studies included in the analysis had relatively small sample sizes. Furthermore, it should be noted that the analysis conducted in this study adhered to the necessary scientific standards. However, it is important to acknowledge the limitations of the results drawn, as the available pool of comparative studies was limited to only 10. Additionally, it is worth mentioning that these studies exhibited varying degrees of heterogeneity, ranging from moderate to high. In conclusion, it would be advantageous to have the capability to examine diverse study-specific attributes that could potentially be associated with the variability observed in reported effects within this particular meta-analysis framework. The presence of contradicting conclusions has led to the current state of affairs. Confounding features encompass several factors that can potentially distort the results of a study. These factors may include discrepancies in the size of the sample, variations in the methods employed for data collecting and analysis, as well as specific clinical or demographic variables that are unique to the issue under investigation. It may be inferred that all of the parameters described above could potentially influence the magnitude of impact and topographical consequences on the brain under consideration.

## Conclusions

In conclusion, the findings derived from this meta-analysis of fMRI investigations indicate that individuals diagnosed with schizophrenia exhibit reduced levels of activation in the dorsolateral prefrontal cortex and parietal region when engaged in the execution of WM tasks, in comparison to individuals without any psychiatric disorders. Therefore, the investigation of decreased functional output of the entire WM system and WM loss in patients with schizophrenia can be conducted by examining the aberrant modifications observed in the parietal and frontal brain regions, as evidenced by fMRI findings.

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## Disclosure

The authors report no conflict of interest.

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