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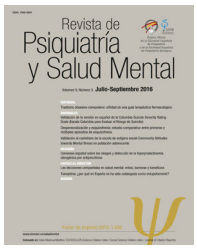

REVIEW ARTICLE

Precuneus and insular hypoactivation during cognitive processing in first-episode psychosis: Systematic review and meta-analysis of fMRI studies

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KEYWORDS
First-episode psychosis;
Cognitive tasks;

Abstract
Introduction: The neural correlates of the cognitive dysfunction in first-episode psychosis (FEP) are still unclear. The present review and meta-analysis provide an update of the location of the abnormalities in the fMRI-measured brain response to cognitive processes in individuals with FEP.

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Frontal lobe;
Insula;
Functional MRI

Methods: Systematic review and voxel-based meta-analysis of cross-sectional fMRI studies comparing neural responses to cognitive tasks between individuals with FEP and healthy controls (HC) according to PRISMA guidelines.
Results: Twenty-six studies were included, comprising 598 individuals with FEP and 567 HC. Individual studies reported statistically significant hypoactivation in the dorsolateral prefrontal cortex (6 studies), frontal lobe (8 studies), cingulate (6 studies) and insula (5 studies). The meta-analysis showed statistically significant hypoactivation in the left anterior insula, precuneus and bilateral striatum.
Conclusions: While the studies tend to highlight frontal hypoactivation during cognitive tasks in FEP, our meta-analytic results show that the left precuneus and insula primarily display aberrant activation in FEP that may be associated with salience attribution to external stimuli and related to deficits in perception and regulation.

PALABRAS CLAVE
Primer episodio psicótico;
Tareas cognitivas;
Lóbulo frontal;
Ínsula;
Resonancia magnética funcional

Hipoactivación precúnea e insular durante el procesamiento cognitivo en el primer episodio psicótico: revisión sistemática y metaanálisis de estudios de fMRI

Resumen
Introducción: Los correlatos neurales de la disfunción cognitiva en el primer episodio psicótico (PEP) aún no están claros. Esta revisión y este metaanálisis proporcionan una actualización de la localización de las anormalidades en la respuesta cerebral medida por fMRI a los procesos cognitivos en individuos con PEP.
Métodos: Revisión sistemática y metaanálisis basado en vóxeles de estudios cros-seccionales de fMRI que comparen respuestas neuronales a tareas cognitivas entre individuos con PEP y controles sanos de acuerdo con las guías PRISMA.
Resultados: Se incluyeron 26 estudios, que comprendían 598 individuos con PEP y 567 controles sanos. Los estudios individuales reportaban hipoactivación estadísticamente significativa en la corteza prefrontal dorsolateral (6 estudios), el lóbulo frontal (8 estudios), el cíngulo (6 estudios) y la ínsula (5 estudios). El metaanálisis mostró hipoactivación estadísticamente significativa en la ínsula anterior izquierda, el precúneo y el cuerpo estriado bilateral.
Conclusiones: Si bien los estudios tienden a resaltar la hipoactivación frontal durante las tareas cognitivas en PEP, nuestros resultados metaanalíticos muestran que el precúneo izquierdo y la ínsula presentan principalmente una activación aberrante en PEP que puede estar asociada con la atribución de saliencia a estímulos externos y relacionada con déficits en la percepción y la regulación.

Introduction

First-episode psychosis (FEP) is characterized by the first period experiencing suprathreshold psychotic symptoms in an individual's life. Psychotic disorders are associated with impairment in many areas of life and the risk of all-cause mortality associated with these disorders is more than twice that of the general population.[1] Therefore, understanding the mechanisms involved throughout the course of the illness is crucial.[2] The clinical symptoms of psychosis have been described and conceptualized as positive and negative. Positive symptoms include hallucinations, delusions, and disorganized thinking, while negative symptoms include affective flattening, apathy, anhedonia and cognitive impairment.[3] In addition, recent studies in FEP show that functional deficits of the right middle frontal gyrus (Broadman area, BA, 9) during attentional and memory performance may be central in the pathophysiology of psychosis.[4] However, these results must be cautiously interpreted given the complexity and heterogeneity of existing studies.[5,6] That said, sufficient evidence exists to support improving and developing tools for early intervention in FEP to reduce dysfunction and enhance the quality of life of patients.[7]

One instrument used in biomarker research for FEP is functional magnetic resonance imaging (fMRI). Unfortunately, no fMRI technique has proven to be sufficiently specific or sensitive for clinical diagnosis. Furthermore, results from different studies do not appear to be consistent, likely due to heterogeneity of samples, cognitive tasks, neuroimaging methodologies, and statistical analyses. A single fMRI study may provide insights about the abnormalities observed using a specific task in patients with specific characteristics, and thus results may change from one study to another. Therefore, meta-analyses may be useful because they focus on the commonalities (across patients, across tasks, etc.) and discard the specificities.

Multivariate patterns of functional dysconnectivity across FEP, as suggested by Fusar-Poli et al.[8], and a recent systematic review of functional brain changes in task-based and resting state fMRI suggest impairment of the fronto-temporal pathways are the core issue in FEP.[9] These findings align with the classical hypothesis of fronto-temporal dysfunction in chronic patients with schizophrenia.[10]

Nevertheless, many questions remain regarding the patterns of activation according to the cognitive task fMRI studies in FEP. Thus, the primary question compares the main areas of dysfunction in FEP vs HC. We hypothesized that FEP patients show reduced functional activity in frontal and temporal lobes, across cognitive tasks, compared with HC.

We conducted a systematic review and a meta-analysis using anisotropic effect-size seed-based mapping[11] to investigate the patterns of activation according to the cognitive tasks used during fMRI acquisition in FEP patients versus HC with a specific focus on the relevance of methodology, the different cognitive tasks used during scans and the mode of presentation. This review intends to show different methodological biases and activation results to explore their relationships and contribute to the methodological optimization of cognitive fMRI task studies. In addition, we expect to identify and compare cerebral activation correlates of FEP patients and HC during cognitive task performance to clarify the areas most associated with differences in brain activation.

Methods

Search strategy and study selection

The systematic review was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations,[12] and the meta-analysis according to the best practice recommendations by Müller et al.[13] We searched PubMed and the Web of Science databases to identify functional neuroimaging studies (Fig. 1 for an outline of this process). We used the following key terms: ''(fMRI AND (First episode psychosis))''. The automatic searches were accompanied by manually reviewing the references of the eligible articles after the final selection. We identified 704 articles that were published between January 2000 and July 2017.

Inclusion criteria were: (a) studies comparing the blood oxygenation level-dependent (BOLD) response to a cognitive task such as attention, perception, memory, or cognitive control between individuals with a first-episode sample, defined as individuals who had been diagnosed with a psychotic disorder for the first time in their lives; (b) the diagnosis (schizophrenia, schizophreniform disorder, bipolar disorder, schizoaffective disorder, brief psychotic episode, and psychosis not otherwise specified) must be verified by structured clinical interviews; and (c) the BOLD response must be measured using task-based fMRI. Exclusion criteria were: (a) studies using resting state and structural MRI modalities; (b) studies using non-cognitive tasks; (c) reviews and meta-analyses; and (d) studies that included participants with >1 acute psychotic episode. Finally, specific exclusion criteria for the meta-analysis were (a) region of interest and small volume correction results; (b) studies using partial coverage of the gray matter; and (c) studies that do not report the required data (coordinates and *t*-values of the peaks of abnormal brain response).

Twenty-six studies met the inclusion criteria for the systematic review, 16 of which also met the criteria to be included in the voxel-based meta-analysis (Fig. 1).

Data extraction

Two researchers (PSM and GGM) independently read the full text of each potentially eligible article, and disagreements regarding eligibility criteria were resolved by consensus. The selection of these studies was performed hierarchically.[12] A primary screening was performed based on title, a second screening on abstract, and a third screening on a full text review. When data were either unpublished or incomplete, the corresponding author was invited to send additional information.

Relevant data of selected articles were extracted in a predefined structured table (Table 1). The following variables were included in the review: author and year of publication; sample size (FEP patients and HC); sex and mean age of participants; medication, duration of untreated illness, stimulus modality; cognitive task paradigm and summary of brain activation. Moreover, we included an additional table listing the location and activation of brain areas according to the experimental cognitive task applied in the studies. For the meta-analysis, we also extracted the peak coordinates and *t*-values of the findings.

Meta-analysis

The quantitative approach was carried out meta-analyzing 16 studies with SDM software version 5 using anisotropic effect-size seed-based mapping (AES-SDM, https://www.sdmproject.com/).[14] Studies included in the meta-analysis are marked with an asterisk (*) in Table 1.

First, AES-SDM used the coordinates (converted to MNI space) and *t*-values of the peaks of maximum statistical significance reported in the studies to generate a three-dimensional image of the effect-size of the differences in activation between patients and HC, separately for each study. Specifically, AES-SDM assigned each voxel an effect size that depended on the spatial covariance with the close peaks, of which the effect size was known. Second, a three-dimensional image of the variance of the effect size was generated – again, separately for each study. This step is straightforward because the variance of a given effect size depends only on the effect size and the samples sizes. Third, a standard random-effects meta-analysis was fitted separately for each voxel. Finally, a permutation test for spatial convergence was conducted to detect those regions that showed larger effect sizes between groups compared with most regions.[15]

We also conducted several complementary analyses. First, for each of the identified clusters in the results, we created the funnel plot of the effect size of the peak with regards to its standard error for visual detection of potential publication bias. Additionally, we quantitatively assessed the potential publication bias with the Egger test, and the heterogeneity with the I^2 statistic. Additional sensitivity analyses were performed using a jackknife leave-one-out

Table 1 fMRI studies comparing individuals with a first episode psychosis (FEP) and healthy controls included in the systematic review.

First author and year	Patients information	Healthy controls	Scales	Medication	DUI	Field strength of scanners	Space coordinates	Software for analysis of fMRI	Stimulus modality	Cognitive task paradigm	Summary of brain activation
Braus et al., 2000*	*N* = 12 Age: 25 Men: 50% Diagnosis: FES	*N* = 12 Age: 28 Men: 50% Diagnosis: NA	BPRS	Antipsychotic-Naive	34 months	1.5 T	Talairach	SPM99	Visual	Sequential finger opposition	Reduce in motor cortical dysfunction
Braus et al., 2002*	*N* = 12 Age: 25 Men: 50% Diagnosis: FES	*N* = 11 Age: 29 Men: 55% Diagnosis: NA	BPRS	Antipsychotic-Naive	Not specified	1.5 T	Talairach	SPM99	Auditory and visual	Information processing	Reduce thalamus, LSTG, and parietal lobe
Boksman et al., 2005*	*N* = 10 Age: 22 Men: 90% Diagnosis: FES	*N* = 10 Age: 23 Men: 90% Diagnosis: NA	SANS SANP	Antipsychotic-Naive	17 months	4.0 T	Talairach	SPM99	Visual	Word fluency	Reduce DLPFC, STG. Increase LFL, anterior cingulate, thalamus, insula, IFL, IOG and FG
Tan et al., 2005*	*N* = 11 Age: 25 Men: 45% Diagnosis: FES	*N* = 11 Age: 26 Men: 45% Diagnosis: NA	PANSS GAF	2.3 mg/day: risperidone (*n* = 6) 11 mg/day: olanzapine (*n* = 5)	2 months	3.0 T	Talairach	Brainvoyager	Visual and verbal	Working memory	Reduce bilateral DLPFC. Increase VLPFC
Schneider et al., 2007*	*N* = 48 Age: 31 Men: 54% Diagnosis: FES (42 paranoid, 2 disorganized, 3 undifferentiated, 1 schizophreniform disorder)	*N* = 57 Age: 30 Men: 59% Diagnosis: NA	PANSS GAF HAMD	Medication was double blind and presently unknown (risperidone vs. haloperidol)	Not specified	1.5 T	MNI	SPM2	Visual	Working memory (N-back)	Reduce STG, thalamus, and hippocampus Increase VLPFC
Bleich-Cohen et al., 2007	*N* = 12 Age: 30 Men: 50% Diagnosis: FES	*N* = 17 Age: 31 Men: % Diagnosis: NA	PANSS	3.2 mg/day: risperidone (*n* = 9) 700 mg/day quetiapine (*n* = 1) 16 mg/day perphenazine (*n* = 1), 2 mg/day haloperidol (*n* = 1)	Not specified	1.5 T	Talairach	Brainvoyager	Auditory	Word Fluency	Reduce LIFG and Wernicke area. Increase RSTS

Table 1 (*Continued*)

First author and year	Patients information	Healthy controls	Scales	Medication	DUI	Field strength of scanners	Space coordinates	Software for analysis of fMRI	Stimulus modality	Cognitive task paradigm	Summary of brain activation
Achim et al., 2007*	*N* = 26 Age: 22 Men: 69% Diagnosis: FES (15 schizophrenia, 4 schizoaffective disorder, 7 psychosis not otherwise specified	*N* = 20 Age: 23 Men: 55% Diagnosis: NA	SAPS SAPN HAMD	2.11 mg/day risperidone (*n* = 11), 10.5 mg/day olanzapine (*n* = 5), 325 mg/day quetiapine (*n* = 2), 300 mg/day clozapine (*n* = 1), 1.5 mg/day haloperidol (*n* = 1), Mixed (*n* = 2) Antipsychotic-Naïve (*n* = 4)	18 months	1.5 T	Talairach	SPM2	Visual and verbal	Encoding strategies; subsequent memory effect; semantic relatedness	Reduce bilateral MTG.
Fusar-Poli et al., 2007	*N* = 10 Age: 25 Men: 100% Diagnosis: FES	NONE	PANSS NART	1.7 mg/day risperidone 63.75 mg/day quetiapine	Not specified	1.5 T	Talairach	SCM	Visual	Word Fluency	Reduce DLPFC, cingulate, thalamus and FPC. Increase VLPFC
Benetti et al., 2009	*N* = 10 Age: 25 Men: 70% Diagnosis: FES	*N* = 14 Age: 26 Men: 64% Diagnosis: NA	PANSS NART	Antipsychotic-Naïve (*n* = 3) 121 mg/day chlorpromazine equivalents (*n* = 7)	Not specified	1.5 T	MNI	SPM5	Visual	Encoding strategies; maintenance; recognition	Increase in encoding SPG, SMG. In maintenance bilateral anterior insula, right anterior cingulate. In recognition Bilateral (IFG and STG), insula and MTG
Crossley et al., 2009*	*N* = 10 Age: No specified Men: No specified Diagnosis: FES	*N* = 13 Age: No specified Men: No specified Diagnosis: NA	None	Antipsychotic-Naïve (*n* = 3) 1.7 mg/day risperidone 63.75 mg/day quetiapine	12 months	1.5 T	MNI	SPM5	Visual	Working memory	Increase in STL and MFG
Woodward et al., 2009*	*N* = 15 Age: 22 Men: 80% Diagnosis: FES	*N* = 32 Age: 22 Men: 71% Diagnosis: NA	PANSS GAF	Antipsychotic-Naïve	5 months	1.5 T	Talairach	SPMs	Visual	Choice reaction time	Increase SMA and MFG

Table 1 (*Continued*)

First author and year	Patients information	Healthy controls	Scales	Medication	DUI	Field strength of scanners	Space coordinates	Software for analysis of fMRI	Stimulus modality	Cognitive task paradigm	Summary of brain activation
Lencer et al., 2011*	*N* = 40 Age: 23 Men: 70% Diagnosis: FES (21 schizophrenia, 2 schizoaffective disorder, 1 schizophreniform disorder, 13 bipolar I disorder)	*N* = 20 Age: 24 Men: 50% Diagnosis: NA	PANSS WASI	2.5 mg/day risperidone (*n* = 35), 20 mg/day olanzapine (*n* = 1), 15 mg/day aripiprazole (*n* = 1)	Not specified	3.0 T	Talairach	AFNI	Visual	Motion processing	Reduce intraparietal sulcus, DLPFC. Increase Dorsomedial thalamus and insula.
Purdon et al., 2011	*N* = 17 Age: 21 Men: 76% Diagnosis: FES	*N* = 17 Age: 22 Men: 76% Diagnosis: NA	PANSS GAF	Antipsychotic-Naïve	4 Months	1.5 T	Talairach	MPRAGE	Visual	Serial reaction time	Reduce Bilateral MFG Striatum-thalamus-cortical circuits. Increase Left STG
Guerrero-Pedraza et al., 2012	*N* = 30 Age: 26 Men: 70% Diagnosis: FES (7 schizophrenia, 9 schizophreniform disorder, 1 delusional disorder, 3 brief psychosis, 10 unspecified psychosis)	*N* = 28 Age: 27 Men: 71% Diagnosis: NA	PANSS TAP	299 mg/day chlorpromazine equivalents	18 months	1.5 T	MNI	FSL	Visual	Working memory (N-back)	Reduce MFC, thalamus and cingulate. Increase DLPFC, VLPFC, insula.
Smieskova et al., 2012	*N* = 21 Age: 28 Men: 76% Diagnosis: FES	*N* = 20 Age: 26 Men: 50% Diagnosis: NA	BPRS SANS SANP GAF BSIP	Antipsychotic-naïve (*n* = 7), Antipsychotic free (*n* = 6), Quetiapine (*n* = 5), Paliperidone (*n* = 2) Olanzapine (*n* = 1)	Not specified	3.0 T	MNI	SPM8	Visual	Working memory (N-back)	Reduce Precuneus, SFG, MFG, IFG, insula
Yoon et al., 2012	*N* = 51 Age: 20 Men: 76% Diagnosis: FES	*N* = 51 Age: 20 Men: 51% Diagnosis: NA	GAF SANS SAPS BPRS	Antipsychotic-naïve (*n* = 19) Antipsychotic treatment not specified (*n* = 32)	12 months	1.5 T	MNI	SPM5	Visual	Attentional processing (AX continuous Performance)	Reduce DLPFC
Kambeitz-Ilankovic et al., 2013*	*N* = 20 Age: 25 Men: 70% Diagnosis: FES	*N* = 20 Age: 26 Men: 70% Diagnosis: NA	PANSS PSYRATS	252 mg/day Chlorpromazine equivalents	18 months	3.0 T	Talairach	SPM8	Visual	Attentional processing	Reduce MTG, insula and precuneus

Table 1 (*Continued*)

First author and year	Patients information	Healthy controls	Scales	Medication	DUI	Field strength of scanners	Space coordinates	Software for analysis of fMRI	Stimulus modality	Cognitive task paradigm	Summary of brain activation
Lesh et al., 2013	*N* = 43 Age: 28 Men: 79% Diagnosis: FES (41 schizophrenia, 1 schizoaffective, 1 schizophreniform)	*N* = 54 Age: Men: 64% Diagnosis: NA	SANS SAPS BPRS	Antipsychotic-naïve (*n* = 15), Atypical antipsychotic (*n* = 27), Typical and Atypical antipsychotic (*n* = 1)	12 months	1.5 T	MNI	SPM8	Visual	Attentional processing (AX continuous Performance)	Reduce DLPFC and parietal
Schmidt et al., 2013*	*N* = 21 Age: 28 Men: 76% Diagnosis: FES	*N* = 20 Age: 26 Men: 50% Diagnosis: NA	BPRS GAF BSIP	Antipsychotic-naïve (*n* = 7), Antipsychotic free (*n* = 6), Quetiapine (*n* = 5) Paliperidone (*n* = 2), Olanzapine (n = 1)	Not specified	3.0 T	Talairach	SPM	Visual	Working memory	Reduce MFG and superior parietal lobe
Benetti et al., 2015	*N* = 46 Age: 25 Men: 59% Diagnosis: FES	*N* = 22 Age: 24 Men: 50% Diagnosis: NA	PANSS PSYRATS	197 mg/day Chlorpromazine equivalents	Not specified	3.0 T	MNI	SPM8	Auditory	Word fluency	Reduce LIFG and left MTG. Increase MTG and VLPFC
Bendfeld et al., 2015	*N* = 19 Age: 28 Men: 76% Diagnosis: FES	*N* = 19 Age: 26 Men: 50% Diagnosis: NA	BPRS SANS SANP GAF BSIP	Antipsychotic free (*n* = 9), Antipsychotic naïve (*n* = 4), Antipsychotic medicated without specified either mg/day or type of antipsychotic (*n* = 6)	Not specified	3.0 T	MNI	SPM8	Visual	Working memory and verbal fluency	Reduce Parietal lobe and precuneus. Increase Cingulate and Frontal lobe
Buchy et al., 2015	*N* = 25 Age: 24 Men: 80% Diagnosis: FES	*N* = 24 Age: 25 Men: 79% Diagnosis: NA	SANS SAPS	Antipsychotic medicated without specified either mg/day or type of antipsychotic (*n* = 17)	16 months	3.0 T	MNI	SPM8	Visual	Memory processing	Increase VLPFC

Table 1 (*Continued*)

First author and year	Patients information	Healthy controls	Scales	Medication	DUI	Field strength of scanners	Space coordinates	Software for analysis of fMRI	Stimulus modality	Cognitive task paradigm	Summary of brain activation
Hawco et al., 2015*	*N* = 26 Age: 24 Men: 85% Diagnosis: FES	*N* = 24 Age: 25 Men: 79% Diagnosis: NA	SANS SAPS HAMD	Antipsychotic free (*n* = 26)	16 months	3.0 T	MNI	SPM8	Visual	Memory processing	Reduce: frontal lobe, parietal lobe. Increase Cingulate, FG and DLPFC
Keedy et al., 2015*	*N* = 21 Age: 24 Men: 76% Diagnosis: FES	*N* = 21 Age: 24 Men: 47% Diagnosis: NA	PANSS HAMD	Antipsychotic naïve (*n* = 14)	1 month	3.0 T	Talairach	AFNI	Visual	Attentional processing	Reduce SFG, insula, SMG, cingulate and bilateral, ILC
Raij et al., 2015*	*N* = 20 Age: 27 Men: 60% Diagnosis: FES (6 schizophrenia, 2 schizophreniform disorder, 2 psychotic disorder not otherwise specified)	*N* = 20 Age: 29 Men: 60% Diagnosis: NA	BPRS	462 mg/day Chlorpromazine equivalents.	Not specified	3.0 T	MNI	SPM8	Visual	Attentional processing	Reduce Putamen, cingulate and insula.
Schmidt et al., 2016*	*N* = 29 Age: 24 Men: 65% Diagnosis: FES	*N* = 19 Age: 26 Men: 52% Diagnosis: NA	BPRS SANS SANP GAF	Antipsychotic medicated without specified mg/day.	Not specified	3.0 T	MNI	SPM8	Visual	Reward task.	Reduce Insula and cingulate cortex

FEP: First-Episode Psychosis; FES: First Episode Schizophrenia; NA: Not Applicable; BSIP: Basel Screening Instrument for Psychosis; PSYRATS: Psychotic Symptoms Rating Scale; SPM: Statistical Parametric Mapping; AFNI: Analysis of Functional NeuroImages; MPRAGE: Magnetization-Prepared Rapid Gradient-Echo; PANSS: Positive and Negative Scale Syndrome; SANS: Scale of the Assessments of Negative Syndrome; SAPS: Scale for the Assessment of Positive Syndrome; TAP: Word Accentuation test; DUI: Duration of Untreated Illness; GAF: Global Functional Scale; BPRS: Brief Psychiatry Rating Scale; NART: National Adult Reading Test; HAM-D: Hamilton Rating Scale for Depression; AG: Angular Gyrus; CPT: Continuous Performance Test; DLPFC: Dorsolateral Prefrontal Cortex; FG: Fusiform Gyrus; FPC: Frontal Posterior Cingulate; HPC: Hippocampus; IFG: Inferior Frontal Gyrus; IFL: Inferior frontal lobe; ILC: Inferior Lingual Cortex; IOG: Inferior Occipital Gyrus; LFL: Left Frontal Lobe; LG: Lingual Gyrus; LIFG: Left Inferior Frontal Gyrus; LSTG: Left Superior Temporal Gyrus; LTG: Left temporal Gyrus; MFG: Middle Frontal Gyrus; MOFG: Medial Orbitofrontal gyrus; MNI: Montreal Neurological Institute space coordinates; MTG: Middle Temporal Gyrus; RSTS: Right Superior Temporal Sulcus; SFG: Superior Frontal Gyrus; SMA: Supplementary Motor Area; SMG: Supramarginal gyrus; SPG: Superior Parietal Gyrus; STG: Superior Temporal Gyrus; STL: Superior Temporal Lobe; VLPFC: Ventrolateral Prefrontal Cortex; VS: Ventral Striatal; WASI: Wechsler Abbreviated Scale of Intelligence.

* Studies included in the meta-analysis.

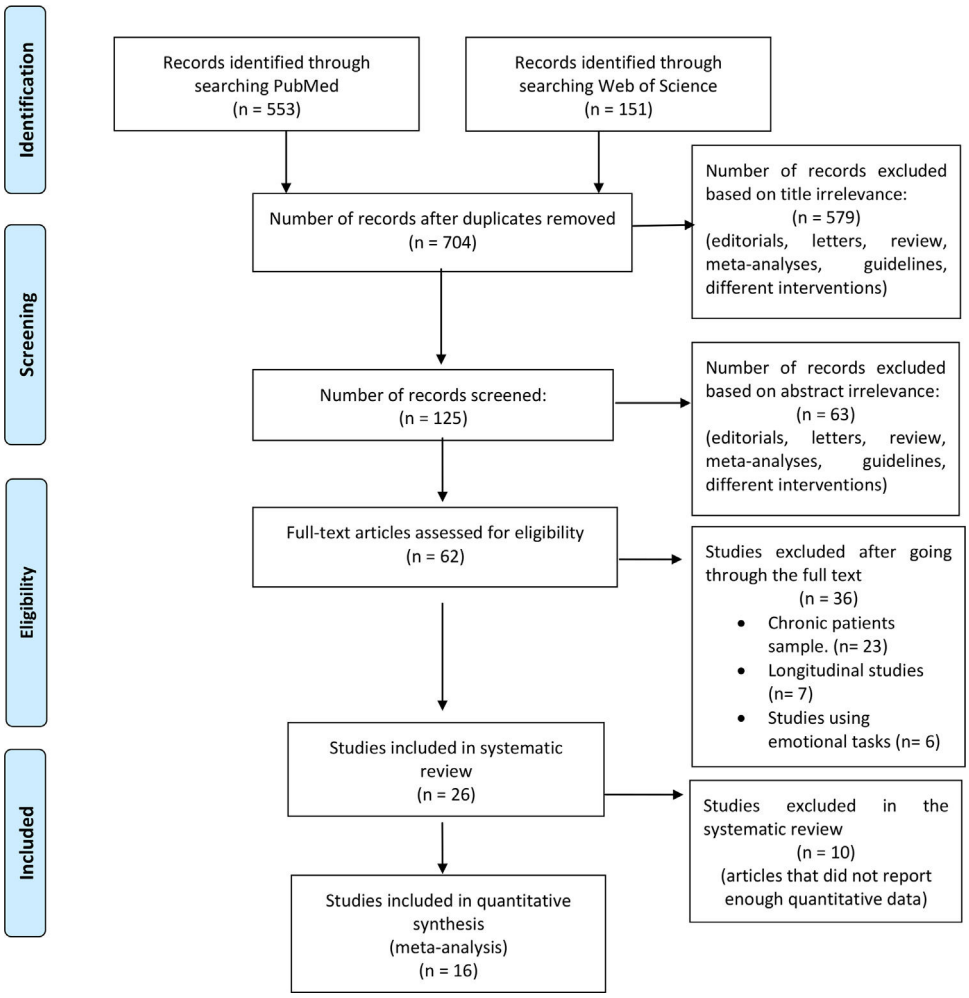

Figure 1 PRISMA flow diagram of study inclusion.

procedure, which consisted of sequentially removing each study individually and repeating the analysis as many times as studies we had include in the main analysis (i.e., 16 sub-analyses, each including 15 studies). If a region were detected abnormal in all 16 iterations, we concluded that we would have detected this region in the meta-analysis even if any of the studies had not been published. We used a composite threshold for statistical significance (uncorrected voxel $P < 0.005$, peak SDM-Z value >1, plus cluster extent >100 voxels), which is more conservative than the recommended threshold for ES-SDM.[11]

Results

A total of 704 records were identified through database searching, with 26 studies meeting eligibility criteria. The pooled sample size in the FEP group was $n = 598$, the mean age was 24 years old (range 20–31), 30% of subjects were women and 80% were receiving antipsychotic medication. The HC group had a sample size of $n = 567$ and a mean age of 25 years old (range 20–34 years old), and 46% of the subjects were women. FEP and HC groups were already age- and sex-matched in all eligible studies.

Characteristics from included studies

The included studies demonstrated reduced activation of the temporal lobe, parietal lobe, frontal lobe and limbic areas.[16–21] Conversely, five studies reported increased activation in the ventro-lateral prefrontal cortex.[22–24] Furthermore, nine studies showed reduced and increased activation in different brain regions, including the frontal and prefrontal cortex, insula, temporal lobe, occipital lobe and thalamus.[22,25–29]

The most significant finding in the systematic review of cognitive task fMRI and brain activation was found in the prefronto-temporal pathways (Table 2).[16,23,30–33] Interestingly, activity appears to be decreased in the left inferior frontal gyrus,[26,34,35] orbital frontal gyrus,[21,27] superior parietal lobe[35,36] and thalamus[17,20,23,30] in FEP patients compared with HC.

However, numerous studies reported an increased task-related BOLD activity in the insula[29,31] and inferior frontal gyrus[31,37] of FEP patients compared with HC.

An Ontario group[25] showed that antipsychotic-naïve first-episode patients exhibited relatively lower activation in the prefrontal and anterior cingulate during a word fluency task. Further, Bleich-Cohen et al.[26] reported reduced activation in

Table 2 Brain activation abnormalities in individuals with First Episode Psychosis (systematic review).

First author and year	Cognitive task paradigm	Stimulus modality	FL		DLPFC		VLPFC		TL		PL		Cingulate		Insula		Putamen		Thalamus	
			Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side
Braus et al. *2000*	Repetitive sequential finger	Visual	-	-	-	-	-	-	-	-	▲	R	-	-	-	-	-	-	-	-
Braus et al. *2002*	Information processing	Auditory visual	-	-	-	-	-	-	▼	L	▼	L	-	-	-	-	-	-	▼	R
Boksman et al. *2005*	Word fluency	Visual	●	L	▼	L	-	-	▼	L	-	-	●	A	●	R	-	-	●	R
Tan et al. *2005*	Working memory	Visual and verbal	-	-	▼	L	●	L	-	-	-	-	●	B,A	-	-	-	-	-	-
Schneider et al. *2007*	Working memory N-back	Visual	-	-	-	-	●	B	▼	R	-	-	-	-	-	-	-	-	▼	R
Bleich-Cohen et al. *2007*	Word fluency	Auditory verbal	▼	L	-	-	-	-	▼	L	●	R	-	-	-	-	-	-	-	-
Achim et al. *2007*	Encoding strategies subsequent memory effect; semantic relatedness	Visual verbal	-	-	-	-	-	-	▼	R,M	-	-	-	-	-	-	-	-	-	-
Fusar-Poli et al. *2007*	Word fluency	Visual	-	-	▼	L	●	L	-	-	-	-	▼	L,A	-	-	-	-	▼	L
Benetti et al. *2009*	Encoding strategies; maintenance; recognition	Visual	●	L,I	-	-	-	-	▼	B	-	-	●	R	●	R,A	-	-	-	-
Crossley et al. *2009*	Working memory	Visual	●	L,M	-	-	-	-	●	L,S	-	-	-	-	-	-	-	-	-	-
Woodward et al. *2009*	Choice reaction time	Visual	●	R,B	-	-	-	-	-	-	●	R	-	-	-	-	-	-	-	-
Lencer et al. *2011*	Visual motion processing	Visual	-	-	▼	R	-	-	-	-	-	-	▼	L	▼	B	-	-	▼	R
Purdon et al. *2011*	Serial reaction time	Visual	▼	L	-	-	-	-	●	L	-	-	●	R,A	-	-	-	-	-	-

Table 2 (*Continued*)

First author and year	Cognitive task paradigm	Stimulus modality	FL		DLPFC		VLPFC		TL		PL		Cingulate		Insula		Putamen		Thalamus	
			Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side
Guerrero-Pedraza et al. *2012*	Working memory N-back	Visual	▼	I,M	●	R	●	R	-	-	-	-	▼	P	●	B,A	-	-	▼	L
Smieskova et al. *2012*	Working memory N-back	Visual	▼	B,S,M	-	-	-	-	-	-	▼	B	-	-	▼	L	-	-	-	-
Yoon et al. *2012*	Attentional processing (AX continuous Performance)	Visual	-	-	▼	L	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kambeitz-Ilankovic et al. *2013*	Attentional processing	Visual	-	-	-	-	-	-	▼	R	▼	R	-	-	▼	L	-	-	-	-
Lesh et al. *2013*	Attentional processing (AX continuous Performance)	Visual	-	-	▼	B	-	-	-	-	▼	R	-	-	-	-	-	-	-	-
Schmidt et al. *2013*	Working memory	Visual	▼	R	-	-	-	-	-	-	▼	R	-	-	-	-	-	-	-	-
Benetti et al. *2015*	Word task	Auditory	▼	L		-	●	B,I	▼	L	-	-	-	-	-	-	-	-	-	-
Bendfeld et al. *2015*	Working memory and verbal fluency	Visual	●	R,M	-	-	-	-	-	-	▼	L,I,S	●	R	-	-	-	-	-	-
Buchy et al. *2015*	Memory	Visual	-	-	-	-	▲	B	-	-	-	-	-	-	-	-	-	-	-	-
Hawco et al. *2015*	Memory	Visual	▼	L,I	●	R,M	-	-	-	-	▼	B,S	▲	-	▲	L,A	-	-	-	-
Keedy et al. *2015*	Attentional processing	Visual	▼	B,S	-	-	-	-	▼	B,S	-	-	▼	L,P	▼	B	-		-	-
Raij et al. *2015*	Attentional processing	Visual	-	-	-	-	-	-	-	-	-	-	▼	L,A	▼	B	▼	L	-	-
Schmidt et al. *2016*	Reward task	Visual	-	-	-	-	-	-	-	-	-	-	▼	R,A	▼	R	-	-	-	-

A: Anterior; B: Bilateral; DLPFC: Dorsolateral prefrontal cortex; FL: Frontal lobe; I: Inferior; L: Left side; M: Medial; P: Posterior; PL: Parietal lobe; R: Right side; S: Superior; TL: Temporal lobe; VLPFC: Ventrolateral prefrontal cortex; ● : significant differences ($P < 0.05$) in increased activation; ▼ : significant differences ($P < 0.05$) in reduced activation; ▲ : non-significant difference; Hyphen (-): indeterminate data. Note. (1) The data were collected based on the accuracy rate reported in the included studies.

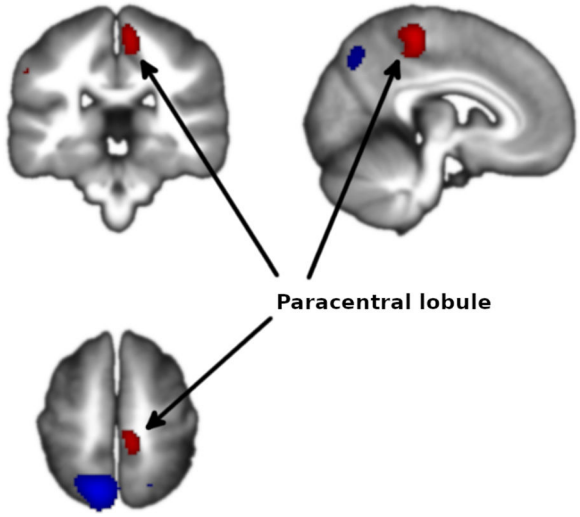

Figure 2 Increased activation in the paracentral lobule.

the left inferior frontal gyrus and increased activity in the right superior temporal sulcus in FEP patients compared with HC during an auditory language task.

Achim et al.[18] examined encoding strategies and detected reduced activation in the bilateral medial temporal lobes in FEP patients relative to HC. Yoon et al.[38] reported decreased activation in the dorsolateral prefrontal cortex (DLPFC), suggesting that neurophysiological markers of illness may not be less evident in FEP patients versus patients with a more established psychotic illness. In addition, Lesh et al.[39] determined that FEP patients exhibited reduced activity in the DLPFC and inferior parietal cortex, which was not seen in HC. In contrast, in a study of patients after treatment, Keedy et al.[28] reported a marked increase in activity in the DLPFC in FEP, similar to that shown in HC. Another study reported that putamen signaling was lower in the FEP group, and the degree of this alteration was positively correlated with delusion scores and negatively correlated with the antipsychotic equivalent dose,[40] which was in accordance with the dysfunction of striate-cortical connectivity.[32]

Meta-analysis of functional response to cognitive processing in FEP

Four clusters with >100 voxels were identified. Patients with FEP showed statistically significant increased activation in paracentral lobule (MNI 8,−30,58 with $Z = 1.75$ and $P = 2 \times 10^{-4}$) and statistically significant decreased activation in precuneus (BA7, MNI −12,−64,58 with $Z = 3.351$ and $P = 3 \times 10^{-7}$) extending to bilateral superior parietal gyrus, left insula (mostly BA47, MNI −34,18,−12 with $Z = 2.62$ and $P = 3.7 \times 10^{-5}$) extending to left striatum, and right striatum (BA48, MNI 26,4,−4 with $Z = 1.965$ and $P = 1.4 \times 10^{-3}$) (Figs. 2 and 3 and Table 3).

The analysis revealed no heterogeneity ($I^2 = 0\%$ in all clusters). In the jackknife analysis, the paracentral lobule and the left insula clusters were present in all sub-analyses except for the sub-analysis excluding Schneider et al.,[23] showing that the significance of these results hinges on the inclusion of this study in the meta-analysis. The right striatum cluster was not present in the sub-analyses excluding Schneider et al.[23] or Keedy et al.,[28] indicating that the significance of these results depends on the inclusion of both studies in the meta-analysis. The left precuneus cluster was present in all the jackknife sub-analysis, indicating that this result is not dependent on the inclusion on any single study in the meta-analysis.

No publication biases could be identified from the Egger tests or the funnel plots (eFigures 1–4). For the activation at the paracentral lobule, the Egger test was statistically significant ($P = 9 \times 10^{-3}$) and the funnel plot showed a slight asymmetry. Larger studies were associated with larger effects, which is the opposite pattern expected in the existence of publication bias. Similarly, for the right striatum deactivation, the Egger test was statistically significant ($P = 0.016$) but the funnel plot showed again asymmetry in the direction opposite to that expected of publication bias.

Discussion

To the best of our knowledge, this report is the largest review and meta-analysis of studies comparing brain activity between FEP patients and HC.

The primary findings of the systematic review are that there are differences in activation in several brain regions during cognitive tasks between FEP and HC, including in DLPFC, frontal lobe, thalamus, cingulate cortex, precuneus and insula. This is consistent with the classical model of fronto-temporal abnormality being a key issue in schizophrenia.[3,41,42] This finding is also commensurate with previous meta-analytic findings on altered frontal activation in chronic patients[43] and with a recent study comparing fMRI of FEP patients with chronic patients.[44]

However, our voxel-based meta-analysis reveals that the frontal lobe might not be the most extensively altered region when comparing FEP patients with HC. Our results showed significant differences in only two brain areas with decreased functional activity in the left insula (BA47) and left precuneus (BA7). These differences in the results between individual studies and the meta-analysis highlight the important effect of methodological differences between studies; as more studies were included, more brain areas appeared to be significantly different between groups. The number of studies included in the systematic review ($N = 26$) is larger than in the meta-analysis ($N = 16$). This assumes that the meta-analysis, as a set of quantitative procedures, generates conclusions that are more accurate, reliable, and more rigorous than those generated from any single study or in a non-quantitative review.[45]

The present meta-analyses of all 16 studies indicated that the left precuneus, part of the parietal lobe, is the most clearly implicated area.

Functional experiments have shown the precuneus to be part of the default mode network (DMN).[46] The precuneus is an association area with wide-spread extra parietal connections, and there is evidence that the fronto-parietal control network is disrupted in psychosis.[47] The precuneus has been recently shown to alter the DMN in FEP[48] and also in FEP during auditory verbal hallucinations.[49] This alteration in DMN intrinsic activity is associated with poor cognitive function.[50] In addition, decreased functional con-

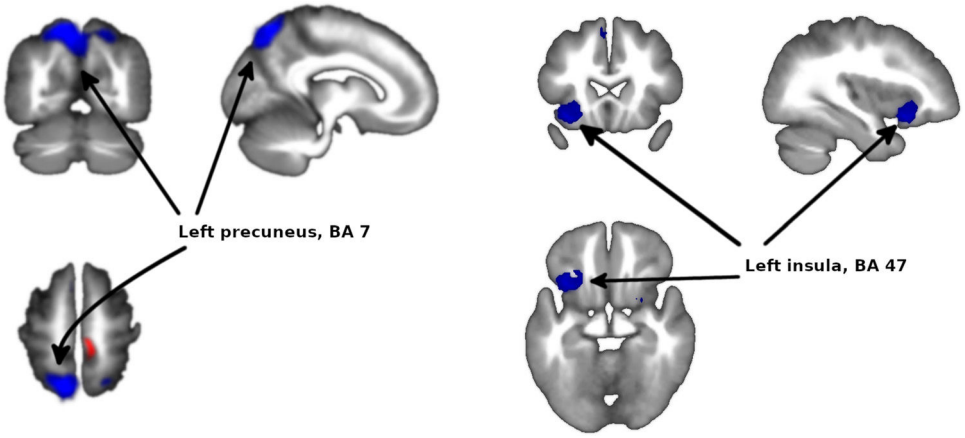

Figure 3 Decreased activation in precuneus and insula.

Table 3 Brain activation abnormalities in individuals with First Episode Psychosis (meta-analysis).

Peak MNI coordinate	Peak SDM-Z	Peak *P*	Voxels	Description
8,−30,58	1.753	0.0002	202	Paracentral lobule
−12,−64,58	−3.351	0.0000003	2052	Left precuneus, BA 7
−34,18,−12	−2.620	0.00004	492	Left insula, BA 47
26,4,−4	−1.965	0.001	136	Right striatum

Threshold for statistical significance (uncorrected voxel $P < 0.005$, peak SDM-Z value > 1, plus cluster extent > 100 voxels).

nectivity between the hippocampus and precuneus has been demonstrated in unmedicated patients.[51] This structure plays an important role in memory retrieval and self-related visuospatial imagery,[46] both of which have been shown to be altered in psychosis.

The other main area implicated in the meta-analysis is the left insula, which is a brain area with broad influences on numerous parts of the cortex and limbic system, primarily the amygdala. The insula incorporates external sensory input with the limbic system.[52] Many deficits reported in psychosis include insula functions, which may be associated with altered processing of emotions, visual and auditory perceptions and representations of the self.[53] In addition, most studies have reported reduced functional activity of the insula in FEP patients relative to HC.[28,54,55] We must note that insula hypoactivation lost statistical significance when we excluded the study by Schneider et al.,[23] though this may well be an problem of statistical power given that this study had the largest sample size ($n = 105$) in the meta-analysis.

In contrast, several studies reported increased activation in the insula during different cognitive tasks[25,29,31,56] and with auditory verbal hallucinations.[49] Although there is no clear explanation for these inconsistencies, we can speculate different reasons for either the increased or decreased activation in the insula. First, the results may depend on the clinical state of the patients at the time of the fMRI, such as their cognitive state, positive symptoms, and the duration of the illness. Many studies have used structural MRI to explore the longitudinal course of FEP finding progressive cortical changes after the onset of a FEP, most notably in anterior cingulate cortex and insula.[57,58]

There are few longitudinal studies of FEP using fMRI. In a systematic review of this issue,[59] we showed that most studies reported a hypoactivation in the limbic system, hippocampus and striatum at baseline. At follow-up, almost all studies reported normalization of activation in these regions. Still, fMRI is not currently used in clinical practice as a predictor of treatment response. The primary explanation for this gap is the heterogeneity in the methodology, particularly in the use of different tasks and fMRI acquisition procedures.

The meta-analysis also showed hypoactivation in the striatum, although this result should be taken with more caution given that it failed to reach statistical significance in two subgroup analyses of the jackknife procedure. Once was when excluding the study by Schneider et al.,[23] though as we noted earlier this may well be related to statistical power as this was the largest study in the meta-analysis. The other sub-analysis involved the exclusion of Keedy et al.,[28] a smaller study with no apparent particularities other than a short duration of untreated illness (Table 1). We speculate that its relevance in the jackknife analysis is mostly due to chance.

Role of methodological differences in the comparability of results across studies

Both MR equipment hardware (magnet's strength, manufacturer, antenna, etc.)[60,61] and software (acquisition sequence, processing and analysis pipeline, etc.)[62–67] have impact in final results published. Unfortunately, the full list of parameters, thresholds, and critical values are not usually included in the methods section of published papers; thus, many of these parameters cannot be clearly considered and analyzed separately. This contributes a confounding effect when considering findings from FEP fMRI studies.

It must be noted that this review has some limitations. First, the meta-analysis was limited to studies with *t* values of activation peaks to provide the quantitative data. Second, we cannot reject the possibility that the medication effects may be confounded by factors such as the length and severity of psychosis, socioeconomic status, or neurocognitive variables. Third, another potential limitation is that many studies chose to include patients only when they were considered stable enough to undergo the imaging procedure and comply with the task requirements, and thus there may be a gap between the onset of the episode and the scan. Unfortunately, few studies reported these data accurately, which prevented a covariate analysis. Similarly, only some studies reported the actual medication doses, thus a meta-regression with chlorpromazine equivalents was not possible. Finally, the review and meta-analyses were limited to studies using cognitive tasks. Results may be different in studies using other tasks[68,69]. However, the study has several strengths. First, to our knowledge, this is the first meta-analytic study presenting comprehensive evidence to suggest that the frontal lobe might not be the most extensive altered region related to the pathophysiology of the illness at an early stage of psychosis. Second, the strict selection criteria for the meta-analysis resulted in very low heterogeneity. This study improves our understanding of the neurobiology of comparing the response to cognitive tasks in FEP and HC and provides a foundation that will hopefully lead to greater precision and tailoring of the treatment offered to patients.

Conclusions

Our meta-analytic results show that the left precuneus and insula primarily display aberrant activation in FEP that may be associated with salience attribution to external stimuli and related to the deficits in perception and regulation. Further studies with identical technical procedures in larger samples are warranted to obtain clear conclusions regarding differences in task-related brain activation in FEP patients and HC.

Authors' contributions

Pau Soldevila-Matias: Conceptualization, Methodology, Investigation, Formal analysis, Writing – Original draft preparation, Visualization. *Anton Albajes-Eizagirre*: Conceptualization, Methodology, Formal analysis, Data curation, Writing – Original draft preparation. *Joaquim Radua*: Formal analysis, Data curation, Writing – Reviewing and Editing, Supervision. *Gracián García-Martí*: Writing – Original draft preparation. *José M. Rubio*: Supervision. *Diana Tordesillas-Gutierrez*: Writing – Original draft preparation. *Inmaculada Fuentes-Dura*: Writing – Original draft preparation. *Aleix Solanes*: Writing – Review and Editing. *Lydia Fortea*: Writing – Review and Editing. *Dominic Oliver*: Writing – Review and Editing. *Julio Sanjuán*: Conceptualization, Writing – Reviewing and Editing, Supervision.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rpsm.2020.08.001

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