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UNIVERSITÀ DI ROMA

Functional neural correlates of first-episode psychoses during sensory, cognitive, language, and emotional processing

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Coordinatore Prof. Alfredo Berardelli

Candidato
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Abstract

Background: Several studies reported neural functional alterations in patients with schizophrenia-spectrum first-episode psychosis (FEP) during performance of tasks that involve sensory, attentional-memory, language, and emotional (SAMLE) processing.

Aim: To compare meta-analytically FEP and healthy control (CTR) samples regarding the circuitries engaged in responding to a set of SAMLE tasks and identifying commonalities and differences in task-related brain activations.

Method: We performed an activation likelihood estimation (ALE) meta-analysis using a database built on 26 fMRI studies, conducted on 516 FEP patients and 546 CTRs during SAMLE task performance.

Results: Within-Group analyses showed that the CTR group has significant SAMLE task-related cortical activations in the context of a bilateral fronto-parietal network; FEP patients showed task-related activations of a bilateral parietal-precentral network. Between-Groups analyses showed hyperactivation of the right inferior parietal lobule, left middle frontal gyrus, and right temporal cortex in CTRs, and hyperactivation of the right cingulate gyrus in FEP. Segregated analyses of tasks showed that brain activations to attentional and memory-related tasks mainly occurred in prefrontal areas in CTRs, and in bilateral parietal areas in FEP; emotional task-related activations concerned the bilateral dorsolateral prefrontal cortex (DLPFC), right parietal cortex, left cingulate cortex and right amygdala in CTRs, whereas in FEP the activation concerned the right fusiform gyrus; we found significant left-sided language task-related activations only in the CTR group, centred on the insula, DLPFC, and temporal cortex.

Conclusions: The major finding of this study is the evidence of a functional deficit of the left DLPFC in FEP during the SAMLE task performance. A prominent role in the neuropathophysiology of FEP appears also to be played by the right dorsal anterior cingulate, bilateral parietal, and right temporal cortices. This study also underlined that FEP patients activate different circuits than CTRs in response to attentional- and memory-tasks (predominant activation of bilateral parietal areas), emotional (predominant activation of the right fusiform gyrus), and language (lack of activation of left-sided cortical areas) tasks.

Correlati neurofunzionali degli esordi psicotici durante l'elaborazione sensoriale, cognitiva, linguistica ed emotiva

Riassunto

Background. Numerosi studi hanno evidenziato che i pazienti affetti da esordi sindromici dello spettro schizofrenico presentano alterazioni neurofunzionali durante l'esecuzione di compiti che coinvolgono le funzioni sensoriali, cognitive, linguistiche ed emotive.

Obiettivo. Paragonare pazienti con esordio psicotico a individui sani al fine di studiare il network neurale coinvolto nelle risposte a compiti sensoriali, cognitive, linguistiche ed emotive, identificando le similarità e le differenze nelle attivazioni cerebrali correlate all'esecuzione degli stessi compiti.

Metodo. Abbiamo eseguito una meta-analisi ALE utilizzando il database costruito su ventisei studi di risonanza magnetica funzionale condotti su 516 pazienti con esordio e 546 soggetti sani durante l'esecuzione di *task* sensoriali, cognitivi, linguistici ed emotivi.

Risultati. Le analisi *within-group* hanno dimostrato che i controlli sani manifestavano in risposta a tutti i *task* attivazioni significative in un circuito bilaterale fronto-parietale, mentre i pazienti in un circuito bilaterale parietale-precentrale. Le analisi *between-groups* hanno evidenziato iperattivazioni del lobulo parietale inferiore di destra, del giro medio frontale sinistro e della corteccia temporale destra nei sani e del cingolo di destra nei pazienti. L'analisi condotta separatamente per gruppi di compiti ha evidenziato che la performance di *task* attentivo-mnestici si correlava ad attivazione di aree prefrontali nei sani e parietali bilaterali negli esordi; l'esecuzione di *task* emotivi si correlava ad attivazione della corteccia dorsolaterale prefrontale (DLPFC) bilaterale, della corteccia parietale destra, del cingolo di sinistra e dell'amigdala di destra nei sani e del giro fusiforme di destra nei pazienti; solo i sani hanno evidenziato attivazioni in aree corticali di sinistra incentrate sull'insula, la DLPFC e la corteccia temporale in correlazione a compiti linguistici.

Conclusioni. Il risultato principale di questa meta-analisi è l'evidenza di deficit funzionale della DLPFC di sinistra in pazienti con esordio psicotico durante l'esecuzione di *task* sensoriali, cognitivi, linguistici ed emotivi. Il giro del cingolo di destra, le cortecce parietali e la temporale di destra hanno anch'esse un ruolo importante nella neurofisiopatologia degli esordi. Questo studio ha anche evidenziato che i pazienti attivano circuiti cerebrali diversi rispetto ai sani in risposta a compiti attentivo-mnestici (attivazione predominante in aree parietali bilaterali), emotivi (attivazione predominante nel giro fusiforme destro) e linguistici (mancata attivazione di aree corticali di sinistra).

Functional neural correlates of first-episode psychoses during sensory, cognitive, language, and emotional processing

INTRODUCTION

Background. The majority of studies focused on patients with a first-episode psychosis (FEP) used this term as a pseudonym for schizophrenia onset. Diagnosis is sometimes extended to schizophrenia spectrum psychoses so as to include schizophreniform and schizoaffective disorders. The whole schizophrenia spectrum psychoses annual incidence has been estimated of around 10.8/100,000 aged >15, this being higher in males (15.3) than in females (6.0) (Baldwin et al., 2005).

FEP is characterised by several brain function disturbances, from the most basic to the highest-order, including dysfunctions in sensory (Morenz et al., 2015; Sun et al., 2013), cognitive (Aas et al., 2014), language (Roche et al., 2016), and emotional processing (Bediou et al., 2007).

Cognitive impairment is a major feature of FEP, and correlated with reduced fractional anisotropy, a measure reflecting white matter fibre density and myelination (Kuswanto et al., 2012), changes in the N-methyl-D-aspartate (NMDA)/glutamate receptor system (Anticevic et al., 2012; Kahn & Sommer, 2015; Schwartz et al., 2012), and decreased levels of gamma-amino-butyric acid (GABA) in both FEP and schizophrenia (Kahn & Sommer, 2015; Rowland et al., 2013; Goto et al., 2009; Yoon et al., 2010). During brain development, NMDA receptors play a crucial role in brain maturation through their effects on synaptic plasticity, which forms the basis of adequate higher cognitive function development, like learning and memory (Wang et al., 2013). Decreased NMDA receptor activation leads to increased striatal dopamine release, which in turn has been related to the induction of psychotic symptoms (Adell et al., 2012).

Voxel-based morphometry (VBM) studies have provided valuable data on the nature and distribution of grey and white matter abnormalities in schizophrenia relative to the whole brain. Most VBM studies have focused on chronic patients, but there is accumulating evidence of first-episode schizophrenia and other high-risk groups, such as first-degree relatives. The most consistent reduction in chronic patients lies in the superior temporal cortex, whereas in first-episode/high-risk individuals, it is found in frontal brain regions (Williams, 2008). Structural brain alterations may be particularly prominent, already at illness onset, in those individuals more likely to have poorer outcomes (i.e., higher number of hospital admissions, poorer symptom remission, lower level of functioning, and reduced response to the first antipsychotic drug treatment) (Dazzan, 2014).

Several studies reported neural functional alterations in FEP patients during executive tasks that correlate with attentional functioning (Keedy et al., 2009; 2015; Niendam et al., 2014; Lesh et al., 2013), working memory (Tan et al., 2005; Akim et al., 2007), facial expression appraisal (Reske et al., 2007; 2009; Anilkumar et al., 2008), verbal fluency (Boksman et al., 2005; Schaufelberger et al., 2005), emotional processing (Catalucci et al., 2011; Modinos et al., 2015; Reske et al., 2007; 2009), and sensory processing (Keedy et al., 2015; Ji et al., 2013).

In brief, a better knowledge of structural and functional brain changes in FEP during sensory, cognitive, language and emotional functioning can have a positive impact for improved diagnosis, prognosis, and optimised and personalised treatments.

Aim. Meta-analyses of neuroimaging studies are useful in shedding light onto the neurobiological underpinnings of psychiatric disorders because they single-out consistent data in a field where results are sometimes contradictory. Recently, the activation likelihood estimation (ALE) method has become the standard for neuroimaging meta-analyses. ALE

meta-analyses have been used to investigate emotional processing in depression (Delaveau et al. 2011; Diener et al. 2012) and schizophrenia (H. Li et al. 2010), as well as in assessing neural abnormalities in schizophrenia (Di et al. 2009; Yao et al. 2013) depression (Liao et al. 2013), and obsessive-compulsive disorder (Del Casale et al., 2015).

The ALE meta-analytic tool models 3-dimensional coordinates (from reported activations in a standard space) as the centre of a 3-dimensional Gaussian distribution. This obviates the need for raw data and thus increases the potential set of studies subject to meta-analysis and whole-brain analyses corrected for multiple comparisons (Laird et al. 2005). ALE has been implemented to address a variety of research questions in both healthy people and clinical samples (Fox et al. 2005).

We used the ALE method to assess neural dysfunction in FEP patients by including studies reporting whole brain fMRI data during performance of a variety of sensory, attentional-memory, language, and emotional (SAMLE) tasks and comparing FEP patients with healthy controls (CTRs). Our aim was to compare FEP and CTR samples regarding the circuitries engaged in responding to the tasks and identifying commonalities and differences in brain activations related to a set of SAMLE tasks.

METHODS

Study selection. A PubMed literature search was performed to identify peer-reviewed studies that investigated sensory, cognitive, language, and emotional functions in patients with FEP and CTRs using functional magnetic resonance imaging (fMRI). A step-wise procedure was used to identify relevant experimental articles focusing on fMRI in FEP patients.

First, studies were selected through a standard search in PubMed (http://www.pubmed.gov). On October 4, 2015 the search "(first episode psychosis [title/abstract] OR first episode

schizophr* [title/abstract] OR drug naive schizophr* [title/abstract] OR drug naive psychosis [title/abstract]) AND fMRI [title/abstract]" produced 64 papers.

Second, additional studies were collected by reviewing the reference list of relevant papers in the first step or through the "related article" function of the PubMed database and the reference lists of reviews. This step allowed another 27 items to be added.

We included studies using tasks associated with SAMLE tasks in patients with FEP. These included task correlated with working memory, attentional and sensory-motor functions, encoding strategies, subsequent memory effect, verbal fluency, speech trial, semantic relatedness, verb generation and passive music listening, auditory stimulation, reaction time, sensory gating-out, prosaccades and predictive saccades, face encoding and recognition, facial emotion expression discrimination, emotional salience, hedonic appraisal, and motivational salience processing.

We excluded papers that did not use fMRI, did not report coordinates in either Montreal Neurological Institute (MNI) (Collins et al. 1998) or Talairach (Talairach and Tournoux 1998) space, and did not involve SAMLE tasks. Studies that did not report whole-brain data, exclusively focusing on functional connectivity, resting-state, region-of-interest (ROI) method, structural neuroimaging, or brain-genetic correlations were excluded. We also excluded studies with mixed populations of patients with both schizophrenia-spectrum and bipolar or depressive psychotic first episodes, since this meta-analysis was focused only on schizophrenia-spectrum disorders.

We excluded 22 studies for lack of relevance, and other 43 studies because on the bases of our inclusion and exclusion criteria: 16 were functional neuroimaging studies did not reporting whole-brain data; 8 did not fit our inclusion criteria; 7 adopted a region-of-interest based methods; 4 did not report stereotactic coordinates; 3 used amplitude of low frequency

fluctuations method; 2 were pharmacological MRI studies; 2 were focused on brain-genetic correlation; 1 was a resting-state study.

We resumed our search strategy in Figure 1.

Finally, on the basis of these criteria, we included twenty-six fMRI studies published prior to November 2015 (Table 2) (Akim et al., 2007; Anilkumar et al., 2008; Bleich-Cohen et al., 2009; Boksman et al., 2005; Catalucci et al., 2011; Chan et al., 2015; Fassbender et al, 2014; Guerrero-Pedraza et al., 2012; Ji et al., 2013; Jones et al., 2004; Kambeitz-Ilankovic et al., 2013; Keedy et al., 2009; Keedy et al., 2015; Lesh et al., 2013; Modinos et al., 2015; Nejad et al., 2011; Niendam et al., 2014; Reske et al., 2007; Reske et al., 2009; Schaufelberger et al., 2005; Schneider et al., 2007; Smieskova et al., 2012; Smieskova et al., 2015; Tan et al., 2005; Woodward et al., 2009; Yoon et al., 2008).

Study design is illustrated in Table 1, including clinical characteristics of samples, i.e., sex ratio, illness duration, and medication status.

We summarised the set of SAMLE tasks and the within-group activations and between-group differences considered in our meta-analysis into four groups, i.e., activations in CTRs, activations in FEP, increases in CTRs relative to FEP patients, and increases in FEP patients relative to CTRs (Table 2).

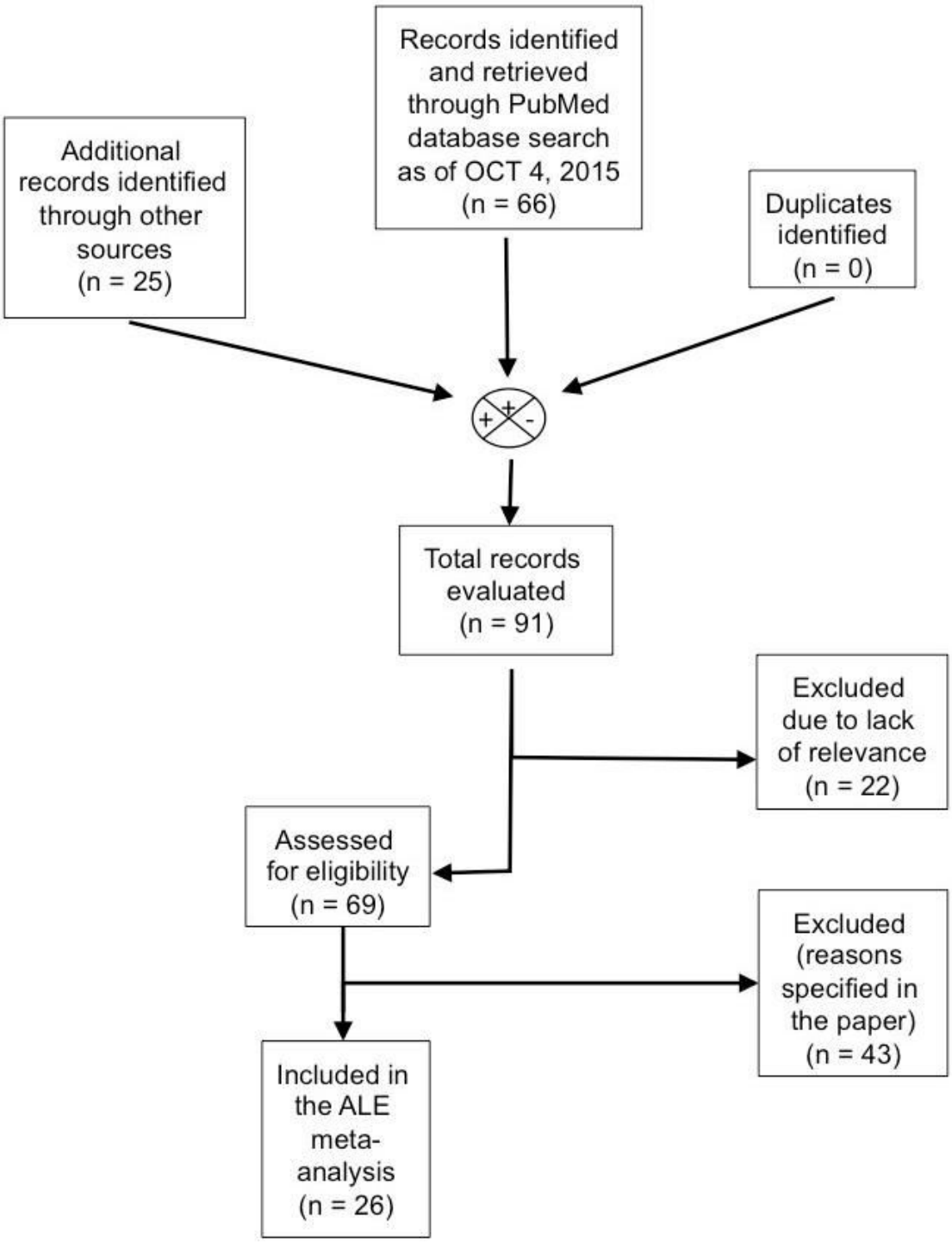

Figure 1. Search strategy

Table 1. Sample characteristics of the included studies

Study	FEP Sample	Men	Women	Mean age, y	SD	Handedness (L)	Illness Duration, weeks	Medicated patients	Healthy controls	Men	Women	Mean Age, y	SD
Akim et al., 2007	26	8	18	22,6	3,4	25 (1)	57,7	22	20	11	9	23,6	3,3
Anilkumar et al., 2008	13	7	6	26,08	9,47	N/A	8	0	13	7	6	28,23	9,75
Bleich-Cohen et al., 2009	12	6	6	26	N/A	12 (0)	N/A	12	12	10	7	age range 22-46	N/A
Boksman et al., 2005	10	9	1	23	4	8 (2)	68	0	10	9	1	22	5
Catalucci et al., 2011	12	7	5	26,93	8,7	12 (0)	12	0	12	7	5	27,92	8,9
Chan et al., 2015	13	5	8	20,08	3,38	13 (0)	80,16	13	14	8	6	21,71	3,81
Fassbender et al, 2014	25	18	7	19,9	3,8	25 (0)	30	16	26	10	16	19,3	3,6
Guerrero-Pedraza et al., 2012	30	21	9	25,93	5,82	30 (0)	< 72	27	28	20	8	27,43	7,01
Ji et al., 2013	15	9	6	26,27	7,24	15 (0)	28,4	0	15	8	7	24,73	5,34
Jones et al., 2004	7	6	1	28,4	11,9	7 (0)	> 24	0	8	6	2	27,2	3,7
Kambeitz-Ilankovic et al., 2013	20	14	6	25,8	6,3	20 (0)	> 4 < 72	17	20	14	6	26,2	6,1
Keedy et al., 2009	9	6	3	22,2	3,5	N/A	> 5	8	9	6	3	22,8	3,5
Keedy et al., 2015	21	16	5	23,9	7,9	N/A	> 1 < 6	7	21	10	12	24,7	4,6
Lesh et al., 2013	43	34	9	N/A	N/A	43 (0)	< 48	28	54	N/A	N/A	N/A	N/A
Modinos et al., 2015	18	13	5	27,9	5	N/A	N/A	10	22	10	12	23,8	4,6
Nejad et al., 2011	23	18	5	26.18	5.02	22 (1)	N/A	0	35	24	11	26.84	8.82
Niendam et al., 2014	35	26	9	18,27	2,63	N/A	< 48	24	35	19	16	17,55	3,16
Reske et al., 2007	10	6	4	37,4	6,06	10 (0)	> 24	10	10	6	4	35,3	8,71
Reske et al., 2009	18	10	8	31,94	6,41	18 (0)	< 8	18	18	10	8	31,94	6,41
Schaufelberger et al., 2005	7	3	4	30	± 9,5	N/A	20	3	9	3	6	31	± 9,3
Schneider et al., 2007	48	26	22	31	9,9	48 (0)	96	48	57	31	26	30,9	8,3
Smieskova et al., 2012	21	16	5	28,57	7,2	19 (2)	139	8	20	10	10	26,5	4
Smieskova et al., 2015	29	19	10	25,89	6,61	25 (4)	31,04	17	19	10	9	26,42	4,1
Tan et al., 2005	11	5	6	25	5,5	11 (0)	23,6	11	11	5	6	25,9	6,4
Woodward et al., 2009	15	12	3	22,5	3,3	15 (0)	19,2	0	18	9	9	22,5	3,3
Yoon et al., 2008	25	17	8	19,6	3,8	24 (1)	< 48	16	24	13	11	21,6	4,24

(L), left-handed, N/A, not available; SD, standard deviation; y, years.

Table 2. Design characteristics of the ALE-meta-analysis included studies

Study	Task	Coordinates	Contrasts			
			Within-group CTR	*Within-group FEP*	*CTR > FEP*	*FEP > CTR*
Akim et al., 2007	Semantic relatedness	TAL	N/A	N/A	Arbitrary vs Related Pairs	N/A
	Encoding strategy		N/A	N/A	Associative vs Item-Oriented	N/A
	Subsequent memory effect		N/A	N/A	N/A	Subsequent Memory Effect
Anilkumar et al., 2008	Face encoding and recognition	MNI	Face encoding and recognition	Face encoding and recognition	N/A	N/A
Bleich-Cohen et al., 2009	Verb generation and passive music listening	TAL	Language > Music Music > Language	Language > Music Music > Language	N/A	N/A
Boksman et al., 2005	Word fluency	MNI	Fixed effects activation-baseline	Fixed effects activation-baseline	Fixed effects activation-baseline	N/A
Catalucci et al., 2011	Hedonic appraisal	TAL	N/A	N/A	Disgust vs scrambled	N/A
Chan et al., 2015	Fist–Edge–Palm task	MNI	PT- and PS-rest; All-rest; All-PT	PT- and PS-rest; All-rest; All-PT	PT-rest; All-rest	N/A
Fassbender et al, 2014	Reaction time	TAL	Long vs short reaction time	Long vs. short reaction time	Long vs short Reaction Time	N/A
Guerrero-Pedraza et al., 2012	N-Back	MNI	N/A	N/A	N/A	2-back vs baseline
Ji et al., 2013	Sensory gating-out	MNI	N/A	N/A	Repeated clicks vs single click	N/A
Jones et al., 2004	Verbal fluency	TAL	N/A	N/A	Verbal fluency	N/A
	Auditory stimulation		N/A	N/A	Auditory stimulation	N/A
Kambeitz-Ilankovic et al., 2013	Speech trial	TAL	N/A	N/A	Speech trial	N/A
Keedy et al., 2009	Behavioural (attentional, sensory-motor)	TAL	N/A	N/A	Visually guided saccade	Visually guided saccade
Keedy et al., 2015	Prosaccades and predictive saccade	TAL	N/A	N/A	Prosaccades, predictive saccades	N/A
Lesh et al., 2013	Colour word Stroop	MNI	Stroop I vs C	Stroop I vs C	N/A	N/A
	AX Continuous Performance		AX-CPT B vs A	N/A	AX-CPT B vs A	N/A
	AX-CPT vs Stroop		N/A	N/A	AX-CPT B–A vs Stroop I–C	N/A
Modinos et al., 2015	Emotional salience	MNI	Emotional vs Neutral Pictures	Emotional vs Neutral Pictures	Emotional vs neutral pictures	Neutral pictures vs fixation
Nejad et al., 2011	N-Back	MNI	N/A	N/A	N/A	N-back
Niendam et al., 2014	AX Continuous Performance	MNI	Cue B vs Cue A	N/A	Cue B vs Cue A	N/A
Reske et al., 2007	Facial expressions exposure	MNI	N/A	N/A	Sadness, happiness exposure	Sadness, happiness exposure
Reske et al., 2009	Facial expressions exposure	MNI	Emotion-related activations	Emotion-related activations	Emotion-related effect of group	Emotion-related effect of group
Schaufelberger et al., 2005	Phonological verbal fluency	TAL	N/A	N/A	Verbal fluency	Verbal fluency
Schneider et al., 2007	N-Back	MNI	N/A	N/A	0-back vs baseline 2-back vs 0-back	0-back vs baseline 2-back vs 0-back
Smieskova et al., 2012	N-Back	MNI	N/A	N/A	N-back	N/A
Smieskova et al., 2015	Motivational salience processing	MNI	N/A	N/A	Adaptive reward	N/A
Tan et al., 2005	Verbal working memory	TAL	N/A	N/A	Task-related activations	Task-related activations
Woodward et al., 2009	Choice reaction time	TAL	N/A	N/A	N/A	Choice reaction time
Yoon et al., 2008	AX Continuous Performance	MNI	Continuous Performance	Continuous Performance	Continuous Performance	N/A

CTR, healthy controls; FEP, patients with First-Episode-Psychosis; MNI, Montreal Neurological Institute space coordinates; TAL, Talairach space coordinates.

Activation likelihood estimation.

Foci in Talairach space were converted to MNI space with the converting tool included in GingerALE 2.3.5 (http://www.brainmap.org/ale), and all coordinates reported in this study are in the MNI space. Meta-analyses were based on the ALE method, using the revised ALE algorithm with an uncorrected p value set to 0.0001 in GingerALE 2.3.5 (Eichoff et al., 2009; Turkeltaub et al. 2012). We also performed segregated meta-analyses of within-group data for the three main available dominions, including attention and memory, language, and emotion with an uncorrected *p* value set at 0.0001.

All within- and between-group meta-analyses cluster volumes were set to a minimum of 20 mm^3.

We also repeated the above meta-analyses using the optimal thresholding algorithms Family-wise error (FWE), which simulate random data sets using the same characteristics of our data set. The FWE method tracks the distribution of maximal ALE scores from each permutation. The FWE corrected threshold is set to the ALE value that no more than a specified fraction of the distribution exceeds that value. Since FWE thresholds are more conservative we set a value of $P = 0.05$.

The obtained ALE result images were visualised using the software Mango (rii.uthscsa.edu/mango) and overlaid onto an anatomical template (http://www.brainmap.org/ale/colin_tlrc_1x1x1.nii.gz). GingerALE also allowed for statistical comparisons between the ALE maps of two distinct sets of foci.

Thus, subtraction and conjunction analyses were carried-out to reveal statistically significant differences as well as similarities between two data sets (i.e., studies conducted on patients and healthy volunteers). These contrast analyses were conducted on within-group data (CTR vs. FEP) using the rather conservative uncorrected *p* value fixed to 0.01 and minimum cluster volume set to 20 mm^3, with 10,000 *p* permutations.

RESULTS

Global analysis of all studies.

Twenty-six studies conducted on 516 FEP patients (337 men, 179 women, weighted mean age: 25.49 years) and 546 CTR subjects (276 men, 216 women, 54 with gender unspecified, weighted mean age: 25.79 years) were included in the meta-analysis.

In the FEP group, 198 patients (38.2%) were drug-free, 315 (61.8%) on medication at the time of the study, 221 with atypical antipsychotics, 23 typical antipsychotics or neuroleptics, 22 were taking other drug classes, 13 an unspecified pharmacological treatment; 24 patients reported substance use, past or current.

The meta-analyses included 58 total experiments (531 foci). Eleven experiments (143 foci) examined within-group task-related activations in CTRs, and nine (95 foci) referred to within group task-related activations in FEP; 25 experiments (206 foci) referred to between-group greater activations in CTRs than FEP patients, and 13 (87 foci) to greater activations in FEP patients than CTRs.

We summarised all significant activations obtained with our global ALE meta-analyses in Table 3, and results of segregated task analyses of within-group data in Table 4.

Within-Group analyses. These analyses showed that CTR group has significant task-related cortical activations in the bilateral middle frontal gyri (Brodmann Area [BA] 9), left inferior frontal gyrus (BA 9), right medial frontal gyrus (BA 6), right precuneus (BA 19), left superior parietal lobule (BA 7), and left postcentral gyrus (BA 3) (Figure 2).

FWE algorithm confirmed left BA 9 task-related activation in healthy subjects (Figure 3).

FEP patients showed task-related activations of bilateral superior parietal lobule (BAs 7), bilateral precentral gyrus (left BA 6 and right BA 9), and left postcentral gyrus (BA 3) (Figure 4).

Table 3. Brain Regions Exhibiting Significant Activity across the Full Set of SAMLE Tasks

CTR within-group [Uncorrected *p*=0.0001]

Cluster #	Volume (mm^3)	*Extrema* Value	x	y	z	Label
1	704	0.02446528	-46	32	24	Left Cerebrum. Frontal Lobe. Middle Frontal Gyrus. Grey Matter. Brodmann area 9
2	416	0.017860577	-44	6	30	Left Cerebrum. Frontal Lobe. Inferior Frontal Gyrus. Grey Matter. Brodmann area 9
3	184	0.016029269	-36	-28	58	Left Cerebrum. Parietal Lobe. Postcentral Gyrus. Grey Matter. Brodmann area 3
4	112	0.014865194	4	22	46	Right Cerebrum. Frontal Lobe. Medial Frontal Gyrus. Grey Matter. Brodmann area 6
5	96	0.0142256385	38	-62	46	Right Cerebrum. Parietal Lobe. Precuneus. Grey Matter. Brodmann area 19
6	72	0.013943182	46	16	30	Right Cerebrum. Frontal Lobe. Middle Frontal Gyrus. Grey Matter. Brodmann area 9
7	40	0.013606819	52	12	34	Right Cerebrum. Frontal Lobe. Middle Frontal Gyrus. Grey Matter. Brodmann area 9
8	32	0.0134004485	-30	-60	52	Left Cerebrum. Parietal Lobe. Superior Parietal Lobule. Grey Matter. Brodmann area 7

CTR within-group [FWE *p*=0.05]

1	208	0.02446528	-46	32	24	Left Cerebrum. Frontal Lobe. Middle Frontal Gyrus. Grey Matter. Brodmann area 9

FEP Patients within-group [Uncorrected *p*=0.0001]

Cluster #	Volume (mm^3)	*Extrema* Value	x	y	z	Label
1	240	0.0151422415	32	-60	54	Right Cerebrum. Parietal Lobe. Superior Parietal Lobule. Grey Matter. Brodmann area 7
2	216	0.0142109	-48	4	36	Left Cerebrum. Frontal Lobe. Precentral Gyrus. Grey Matter. Brodmann area 6
3	192	0.01431007	-28	-58	50	Left Cerebrum. Parietal Lobe. Superior Parietal Lobule. Grey Matter. Brodmann area 7
4	80	0.011660013	-36	-26	50	Left Cerebrum. Parietal Lobe. Postcentral Gyrus. Grey Matter. Brodmann area 3
5	24	0.011089671	42	12	36	Right Cerebrum. Frontal Lobe. Precentral Gyrus. Grey Matter. Brodmann area 9

Within-group contrast analyses [Uncorrected *p*=0.01]

CTR+FEP conjunction analysis

Cluster #	Volume (mm^3)	*Extrema* Value	x	y	z	Label
1	24	0.012413918	-46	4	34	Left Cerebrum. Frontal Lobe. Precentral Gyrus. Grey Matter. Brodmann area 6

CTR-FEP; FEP-CTR subtraction analysis

No significant differences

Greater Activity in CTR than FEP (between-group) [Uncorrected *p*=0.0001]

Cluster #	Volume (mm^3)	*Extrema* Value	x	y	z	Label
1	168	0.021676324	52	-46	48	Right Cerebrum. Parietal Lobe. Inferior Parietal Lobule. Grey Matter. Brodmann area 40
2	144	0.018996013	-44	16	38	Left Cerebrum. Frontal Lobe. Middle Frontal Gyrus. Grey Matter. Brodmann area 9
3	56	0.017126873	52	-38	8	Right Cerebrum. Temporal Lobe. Superior Temporal Gyrus. Grey Matter. Brodmann area 41
4	32	0.015816087	42	-18	-28	Right Cerebrum. Temporal Lobe. Sub-Gyral. Grey Matter. Brodmann area 20

Greater Activity in FEP than CTR (between-group) [Uncorrected *p*=0.0001]

Cluster #	Volume (mm^3)	*Extrema* Value	x	y	z	Label
1	160	0.017010868	6	22	40	Right Cerebrum. Limbic Lobe. Cingulate Gyrus. Grey Matter. Brodmann area 32

Table 4. Brain Regions Exhibiting Significant Activity – Segregated-Tasks Analyses of Within-Group Data

Attention and memory task-related activations in CTR

Cluster #	Volume (mm^3)	*Extrema* Value	x	y	z	Label
1	464	0.020677298	-48	34	24	Left Cerebrum. Frontal Lobe. Middle Frontal Gyrus. Grey Matter. Brodmann area 9
2	312	0.016029269	-36	-28	58	Left Cerebrum. Parietal Lobe. Postcentral Gyrus. Grey Matter. Brodmann area 3
3	144	0.013345087	46	16	30	Right Cerebrum. Frontal Lobe. Middle Frontal Gyrus. Grey Matter. Brodmann area 9
4	120	0.013558151	-44	4	30	Left Cerebrum. Frontal Lobe. Precentral Gyrus. Grey Matter. Brodmann area 6
5	64	0.012610502	2	24	46	Left Cerebrum. Frontal Lobe. Medial Frontal Gyrus. Grey Matter. Brodmann area 6
6	48	0.014240192	48	38	28	Right Cerebrum. Frontal Lobe. Middle Frontal Gyrus. Grey Matter. Brodmann area 9
7	24	0.011355925	-44	-52	42	Left Cerebrum. Parietal Lobe. Inferior Parietal Lobule. Grey Matter. Brodmann area 40

Attention and memory task-related activations in FEP

Cluster #	Volume (mm^3)	*Extrema* Value	x	y	z	Label
1	352	0.014310069	-28	-58	50	Left Cerebrum. Parietal Lobe. Superior Parietal Lobule. Grey Matter. Brodmann area 7
2	304	0.0151422415	32	-60	54	Right Cerebrum. Parietal Lobe. Superior Parietal Lobule. Grey Matter. Brodmann area 7
3	184	0.011660013	-36	-26	50	Left Cerebrum. Parietal Lobe. Postcentral Gyrus. Grey Matter. Brodmann area 3
4	80	0.011089671	42	12	36	Right Cerebrum. Frontal Lobe. Precentral Gyrus. Grey Matter. Brodmann area 9
5	24	0.010385888	-48	4	36	Left Cerebrum. Frontal Lobe. Precentral Gyrus. Grey Matter. Brodmann area 6

Emotional task-related activations in CTR

Cluster #	Volume (mm^3)	*Extrema* Value	x	y	z	Label
1	256	0.013301039	40	-62	46	Right Cerebrum. Parietal Lobe. Inferior Parietal Lobule. Grey Matter. Brodmann area 39
2	216	0.011904738	-32	32	32	Left Cerebrum. Frontal Lobe. Middle Frontal Gyrus. Grey Matter. Brodmann area 9
3	184	0.012098305	0	-40	38	Left Cerebrum. Limbic Lobe. Cingulate Gyrus. Grey Matter. Brodmann area 31
4	160	0.0115732625	24	-10	-14	Right Cerebrum. Sub-lobar. *. Grey Matter. Amygdala
5	112	0.010645024	-52	16	40	Left Cerebrum. Frontal Lobe. Middle Frontal Gyrus. Grey Matter. Brodmann area 8

Emotional task-related activations in FEP

Cluster #	Volume (mm^3)	*Extrema* Value	x	y	z	Label
1	144	0.009915951	48	-52	-16	Right Cerebrum. Temporal Lobe. Fusiform Gyrus. Grey Matter. Brodmann area 37

Language task-related activations in CTR

Cluster #	Volume (mm^3)	*Extrema* Value	x	y	z	Label
1	232	0.010400293	-34	22	0	Left Cerebrum. Sub-lobar. Insula. Grey Matter. Brodmann area 13
2	104	0.008546603	-42	30	26	Left Cerebrum. Frontal Lobe. Middle Frontal Gyrus. Grey Matter. Brodmann area 9
3	24	0.007908451	-48	16	-2	Left Cerebrum. Sub-lobar. Insula. Grey Matter. Brodmann area 13
4	24	0.0077672396	-54	-46	12	Left Cerebrum. Temporal Lobe. Middle Temporal Gyrus. Grey Matter. Brodmann area 21

Language task-related activations in FEP

No significant activations

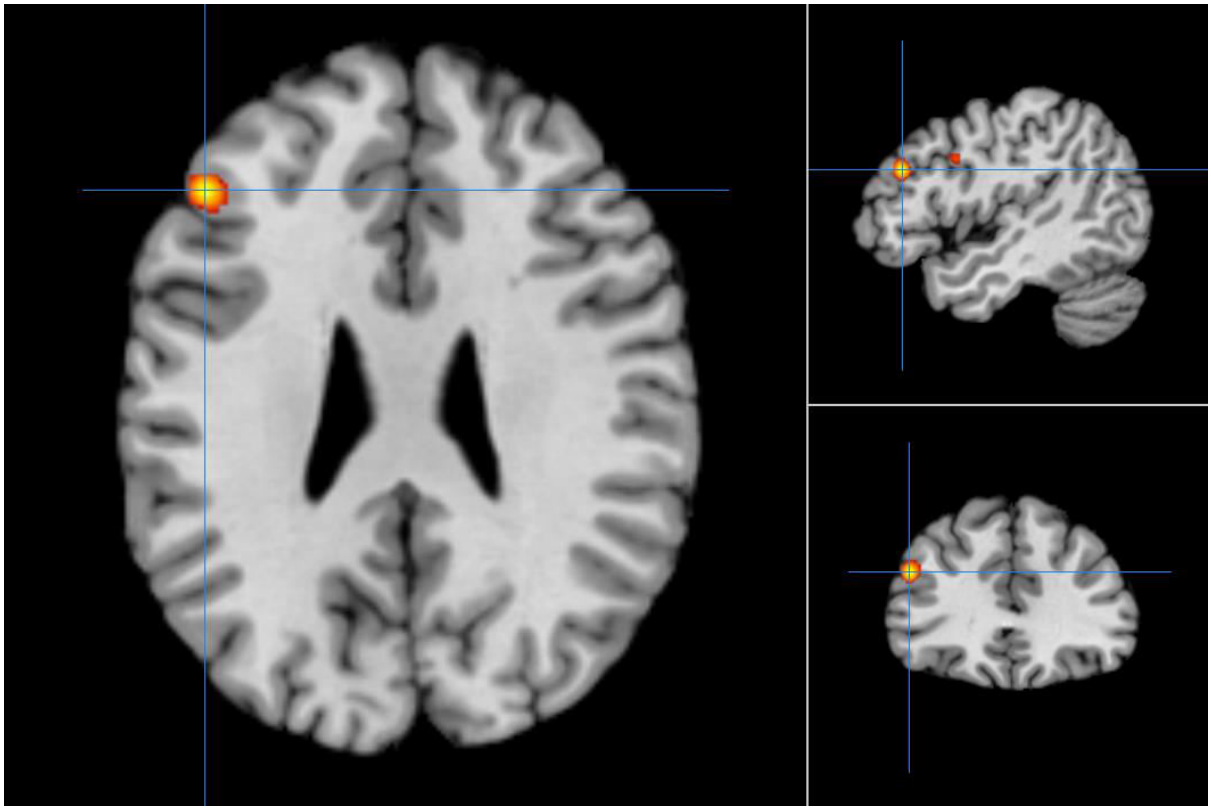

Figure 2a. Left Middle Frontal Gyrus (Brodmann area 9) task-related activation in CTR

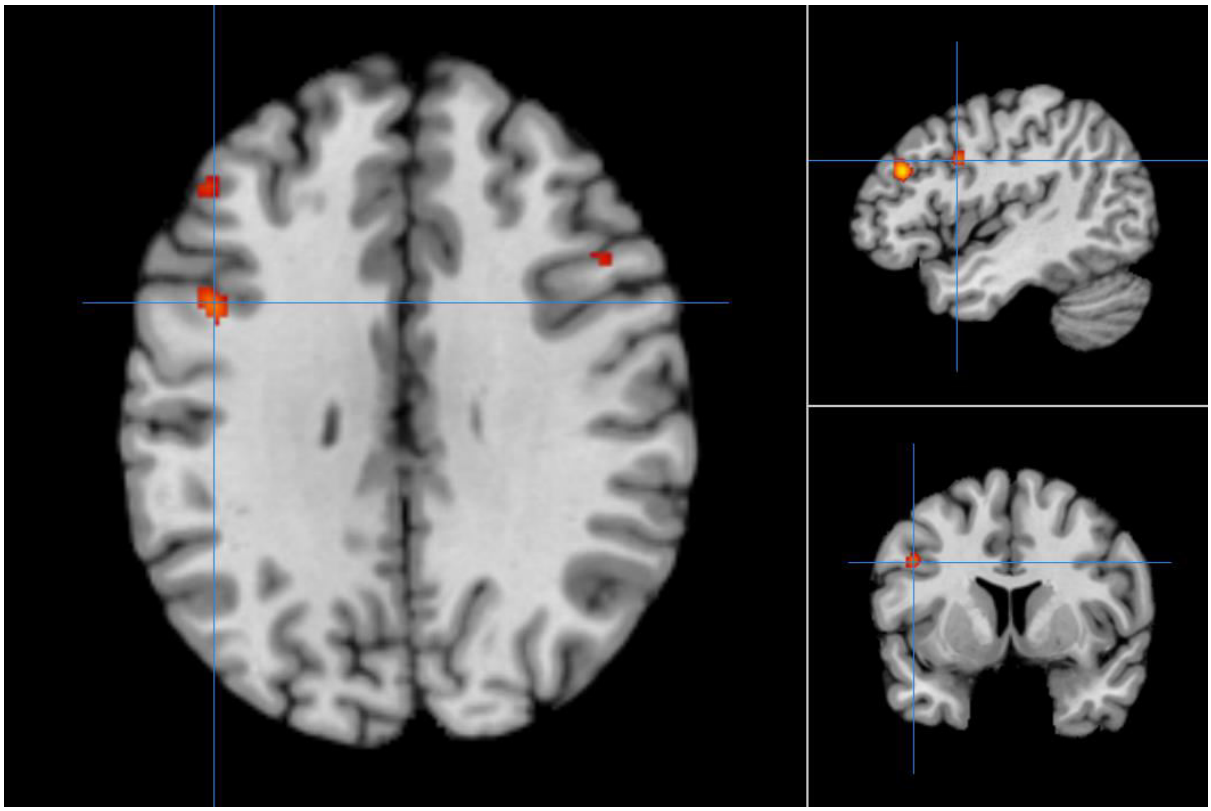

Figure 2b. Left Inferior Frontal Gyrus (Brodmann area 9) task-related activation in CTR

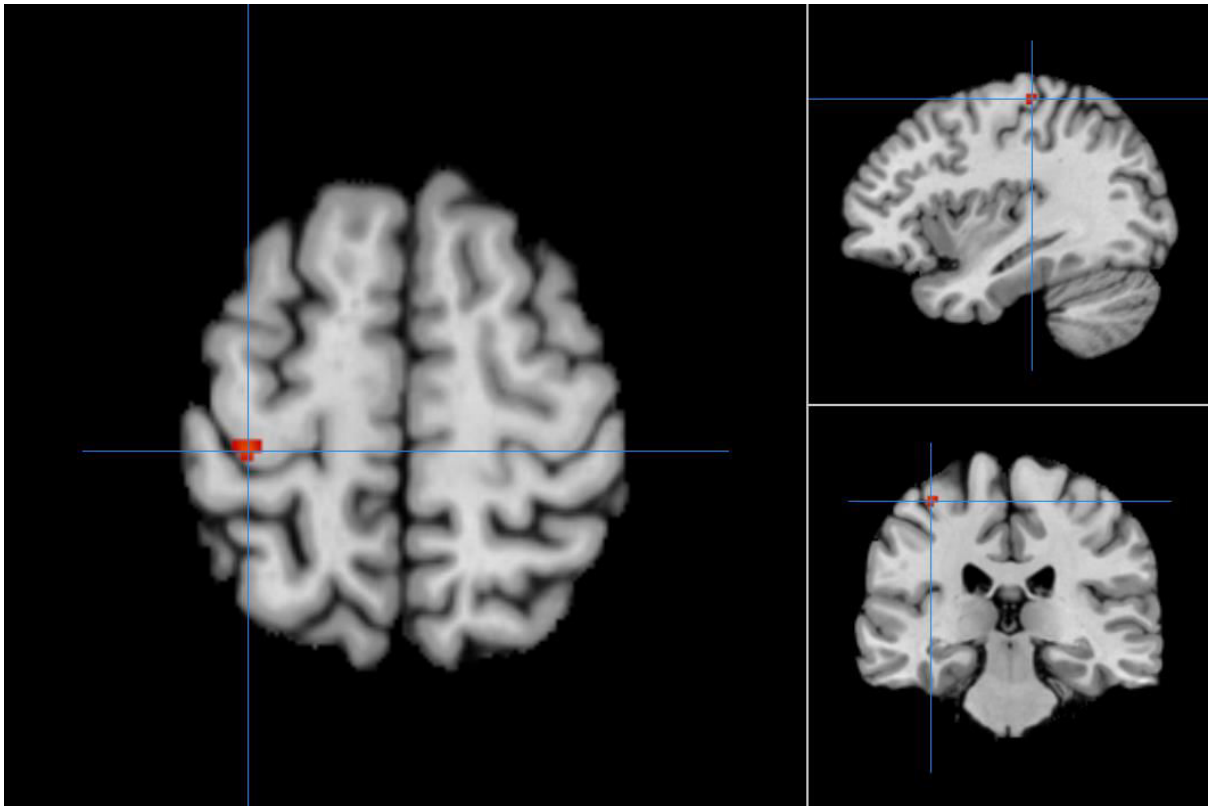

Figure 2c. Left Postcentral Gyrus (Brodmann area 3) task-related activation in CTR

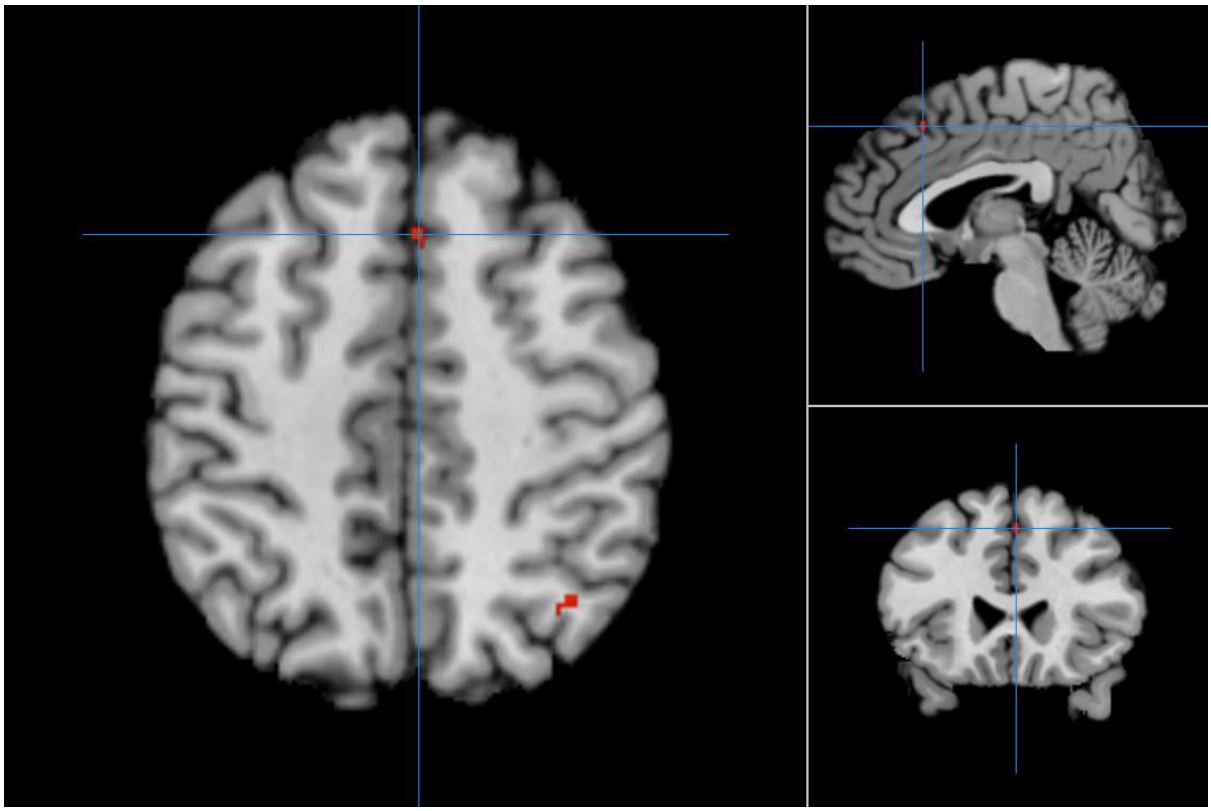

Figure 2d. Right Medial Frontal Gyrus (Brodmann area 6) task-related activation in CTR

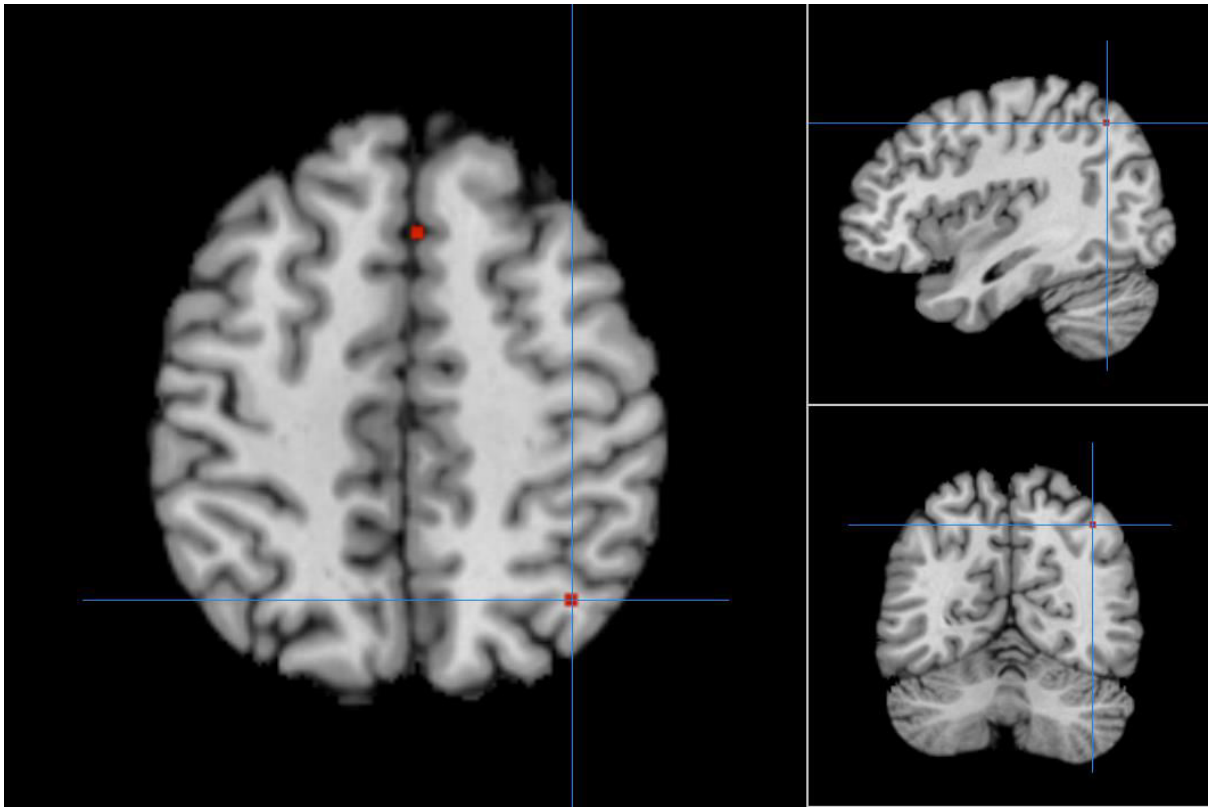

Figure 2e. Right Precuneus (Brodmann area 19) task-related activation in CTR

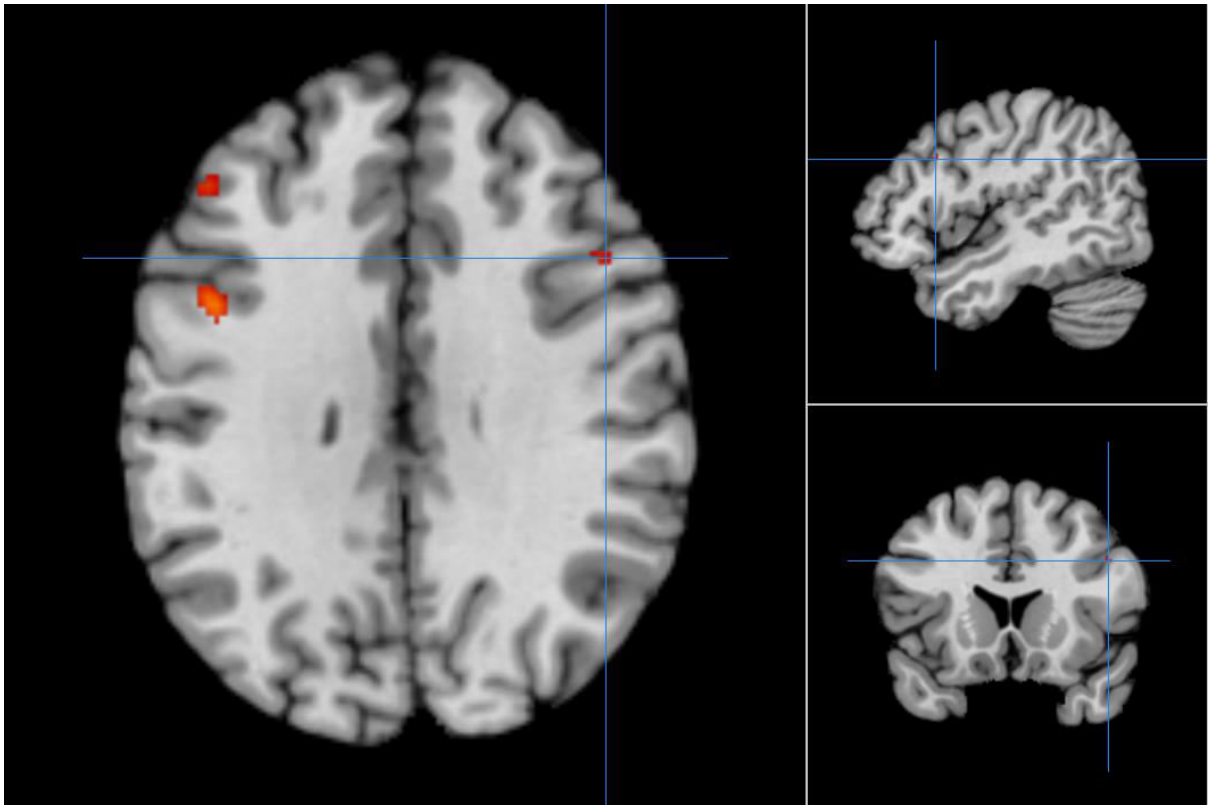

Figure 2f. Right Middle Frontal Gyrus (Brodmann area 9) task-related activation in CTR

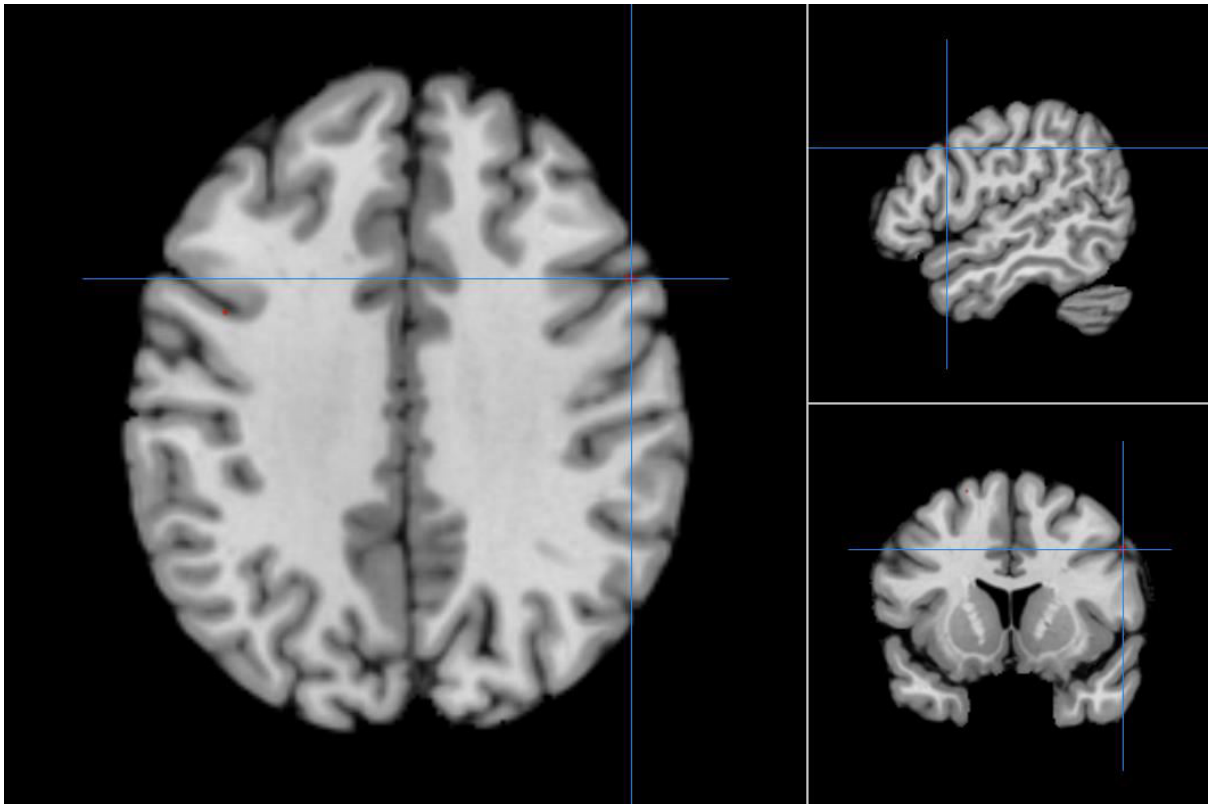

Figure 2g. Right Middle Frontal Gyrus (Brodmann area 9) task-related activation in CTR

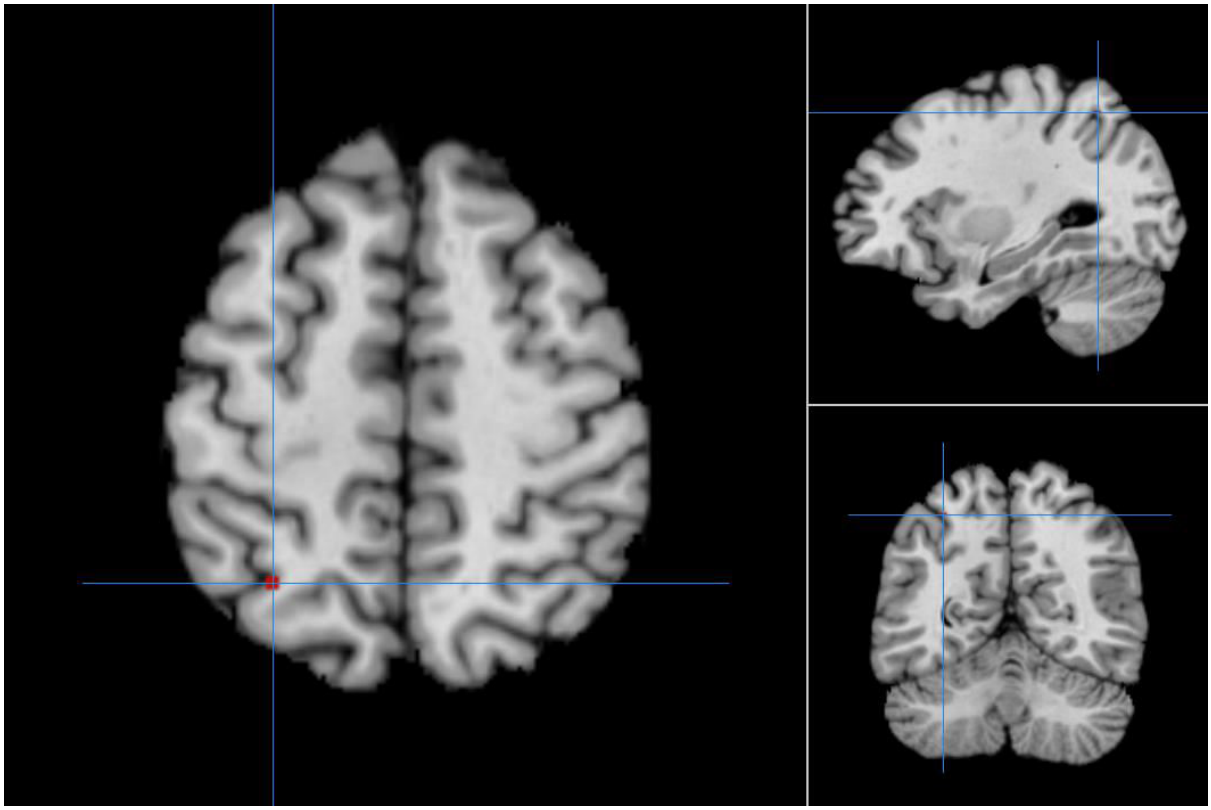

Figure 2h. Left Superior Parietal Lobule (Brodmann area 7) task-related activation in CTR

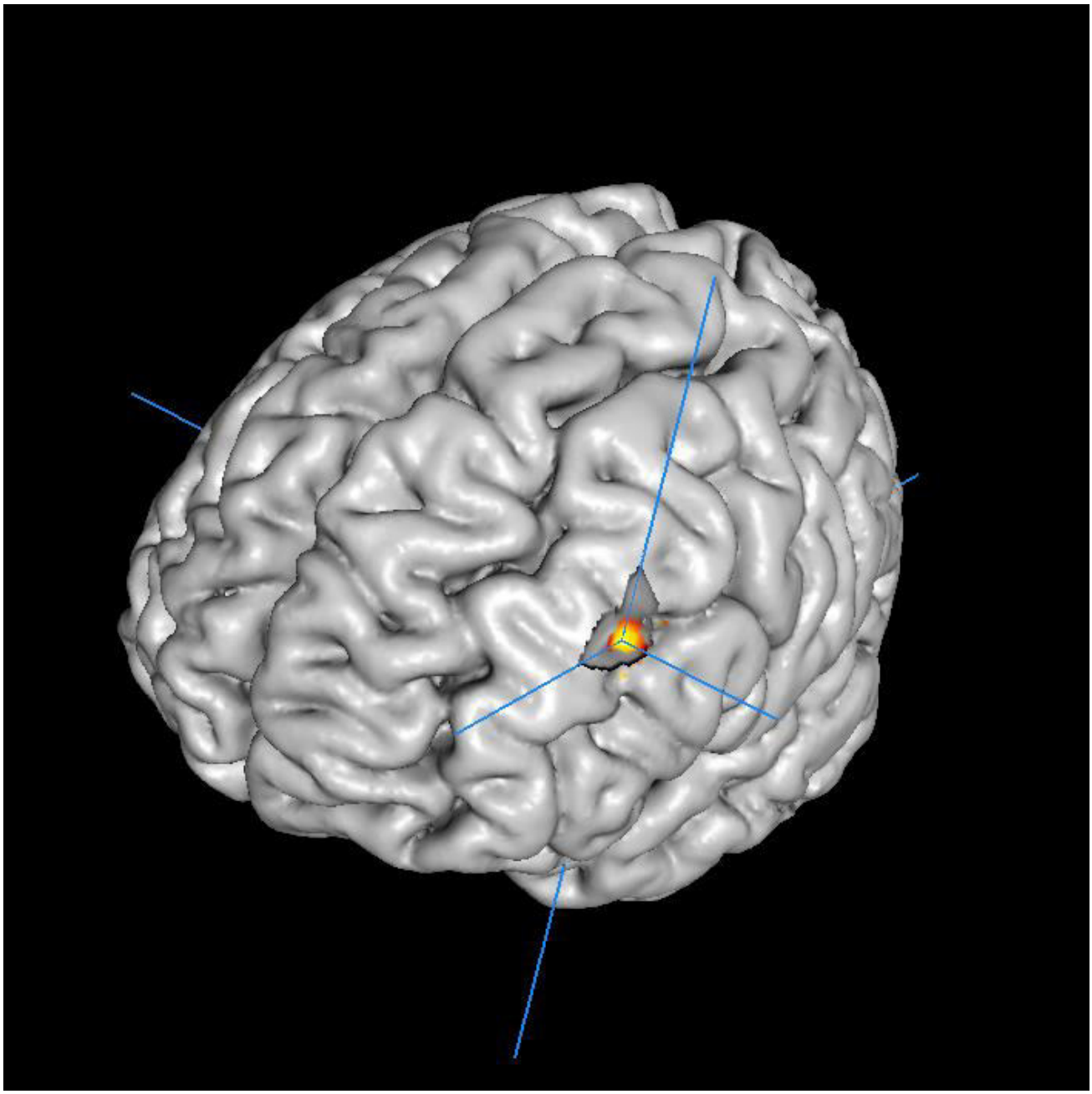

Figure 3. Left Middle Frontal Gyrus (Brodmann area 9) task-related activation in CTR (FWE p=0.05). Surface image.

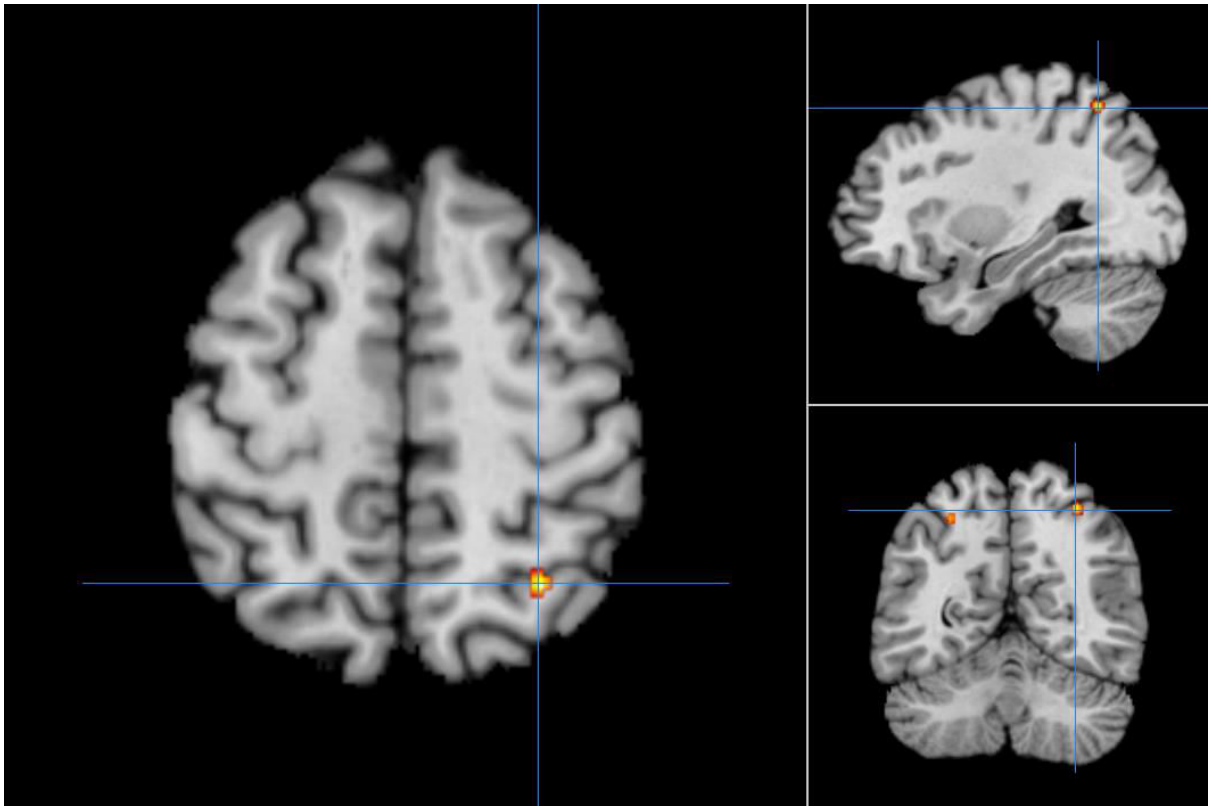

Figure 4a. Right Superior Parietal Lobule (Brodmann area 7) task-related activation in FEP

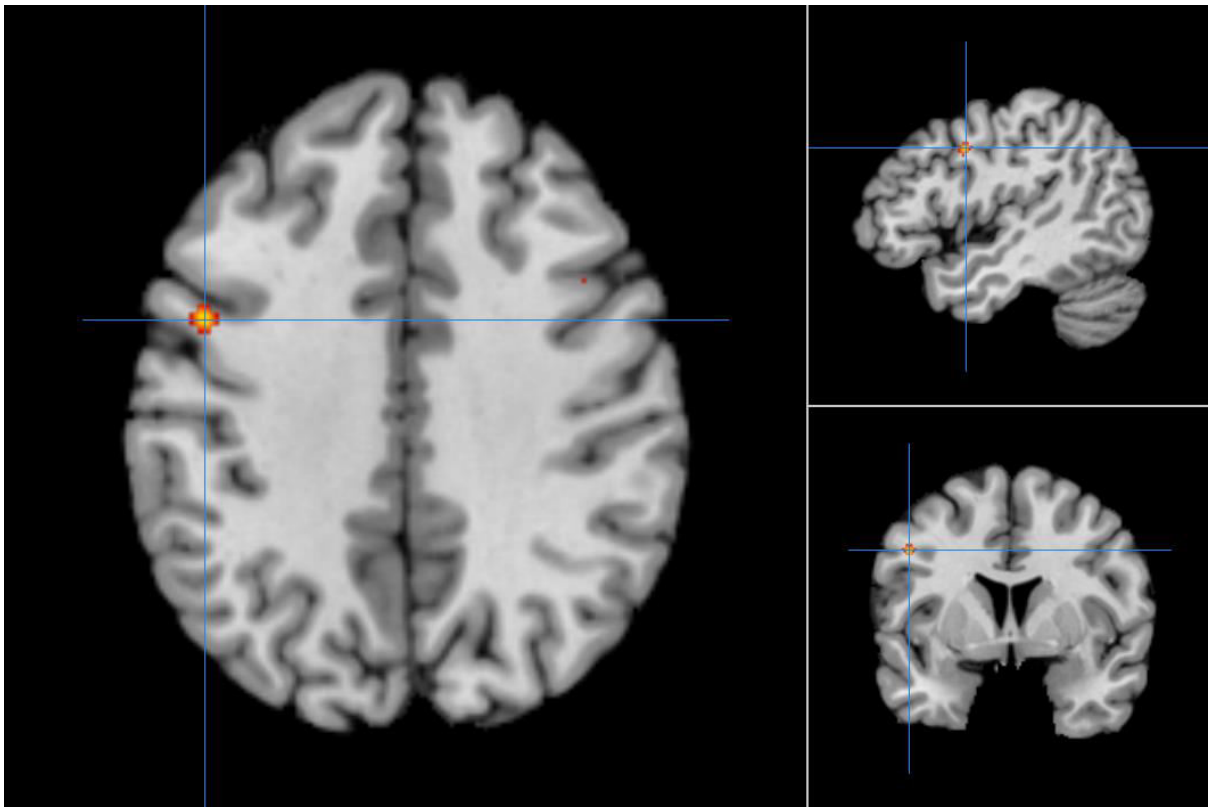

Figure 4b. Left Precentral Gyrus (Brodmann area 6) task-related activation in FEP

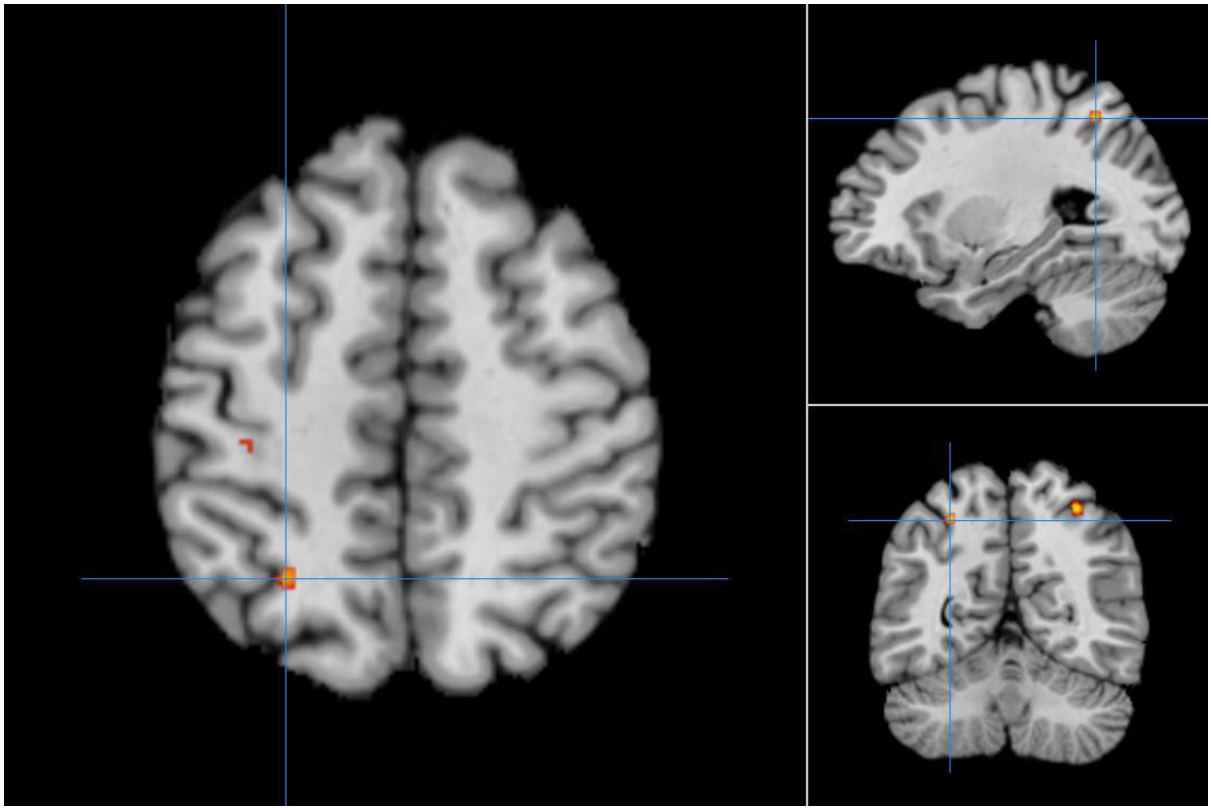

Figure 4c. Left Superior Parietal Lobule (Brodmann area 7) task-related activation in FEP

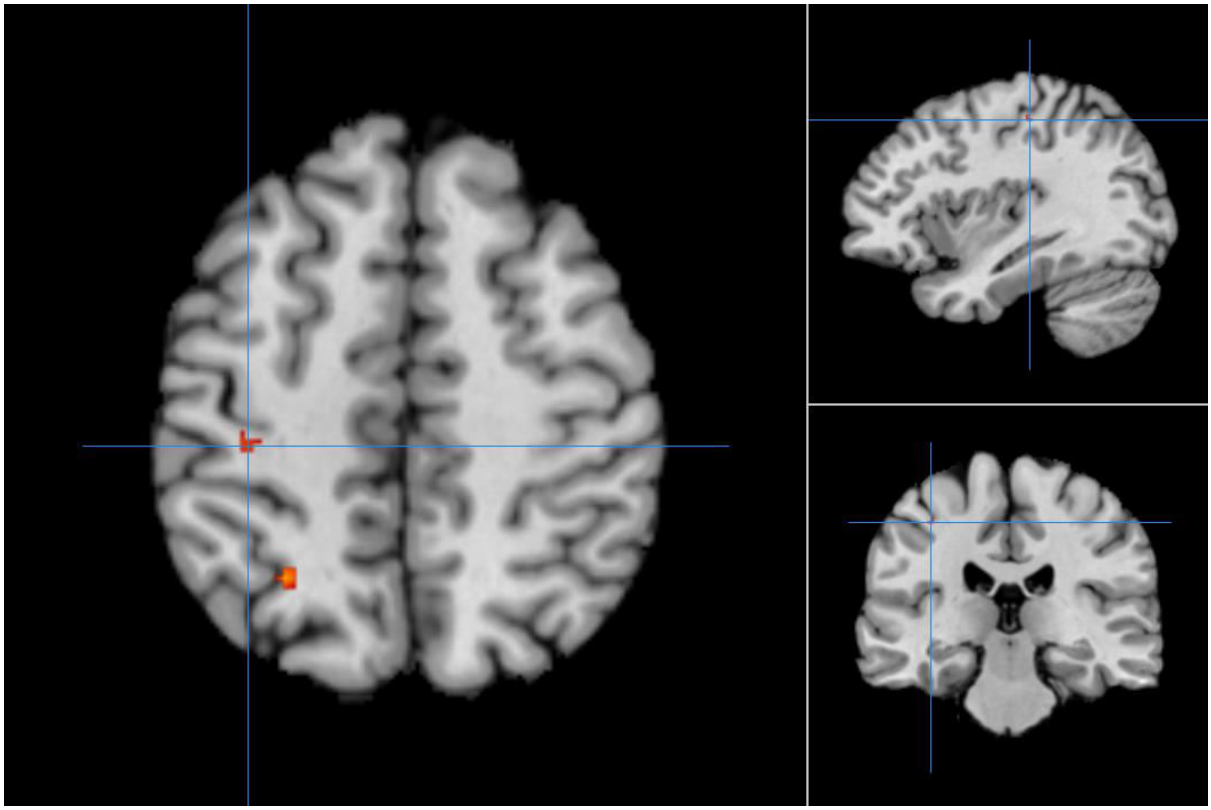

Figure 4d. Left Postcentral Gyrus (Brodmann area 3) task-related activation in FEP

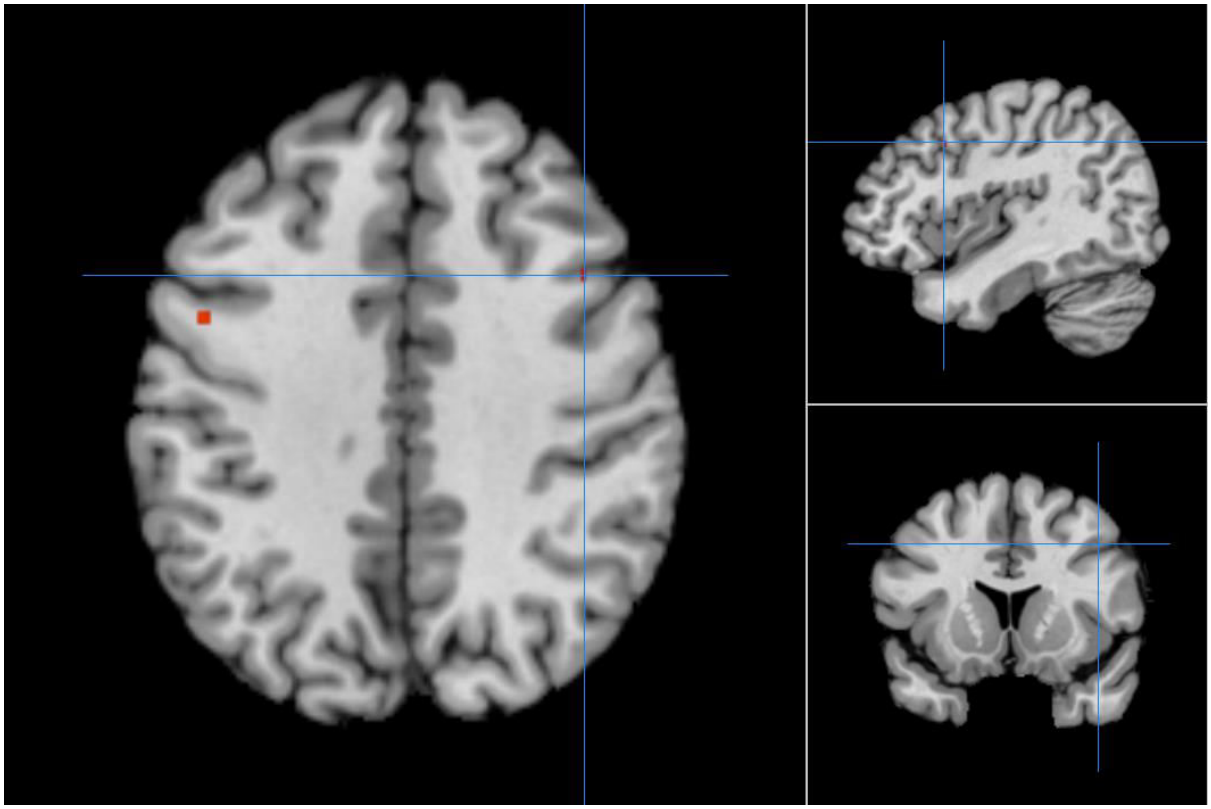

Figure 4e. Right Precentral Gyrus (Brodmann area 9) task-related activation in FEP

Contrast analyses of within-group data. Conjunction analysis (FEP activations plus CTR activations) found significant task-related activations of the left precentral gyrus (BA 6). Subtraction analyses (FEP patient activations minus CTR activations, and vice versa) did not show significant differences.

Task-segregated analyses of within-group data. This segregation has allowed us to highlight the remarkably different activations occurring in CTRs and FEP patients in relation to sensory, cognitive, emotional and language processing. Brain activations to attentional and memory-related task mainly occurred in prefrontal areas in CTRs, and in parietal areas in FEP patients; emotional task-related activations concerned the bilateral DLPFC, right parietal cortex, left cingulate cortex and right amygdala in CTRs, whereas the right fusiform gyrus in FEP patients; we found significant left-sided language task-related activations only in the CTR group, centred on the insula, DLPFC, and temporal cortex.

Between-Groups analyses. Direct comparison between CTR and FEP showed that different brain areas were significantly more active in CTR group. These areas included the right inferior parietal lobule (BA 40), left middle frontal gyrus (BA 9), right superior temporal gyrus (BA 41), right temporal sub-gyral grey matter (BA 20) (Figure 5).

The inverse comparison between FEP and CTR showed hyperactivation of the right cingulate gyrus (BA 32) in FEP patients (Figure 6).

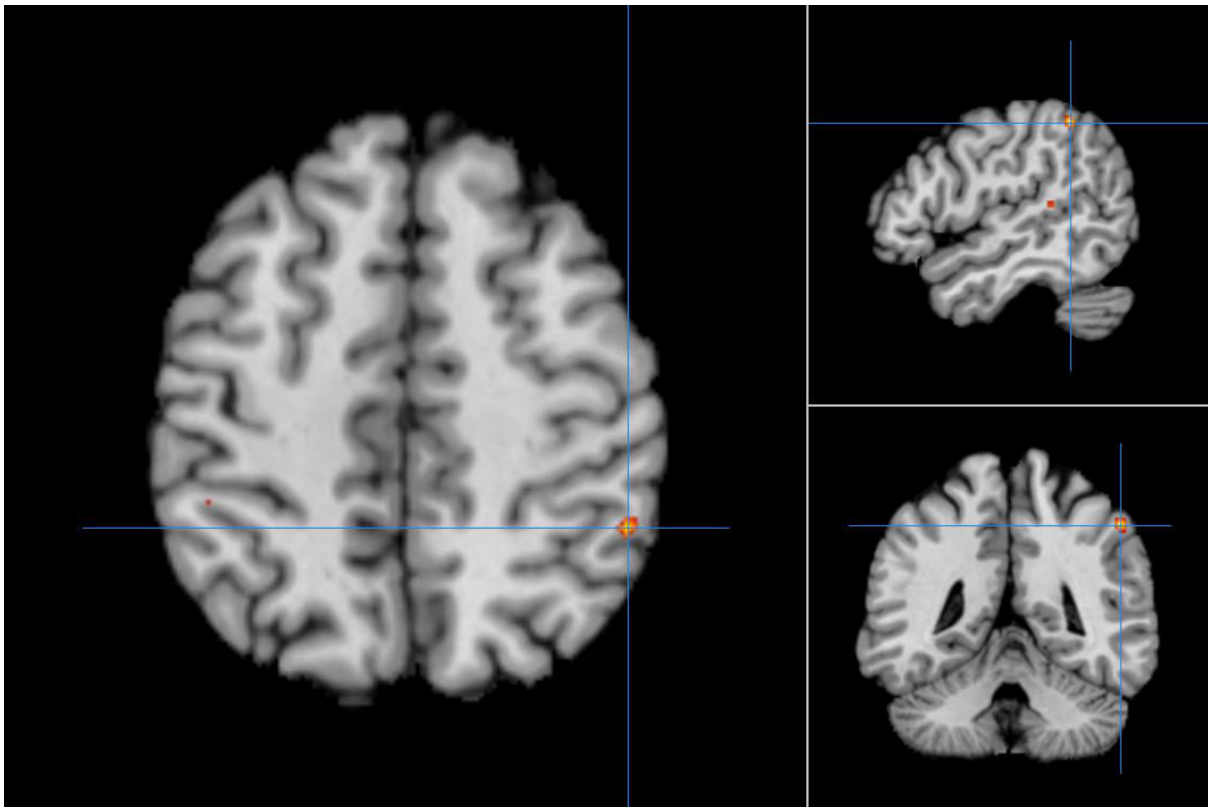

Figure 5a. Right Inferior Parietal Lobule (Brodmann area 40) hyperactivation in CTR* vs. *FEP

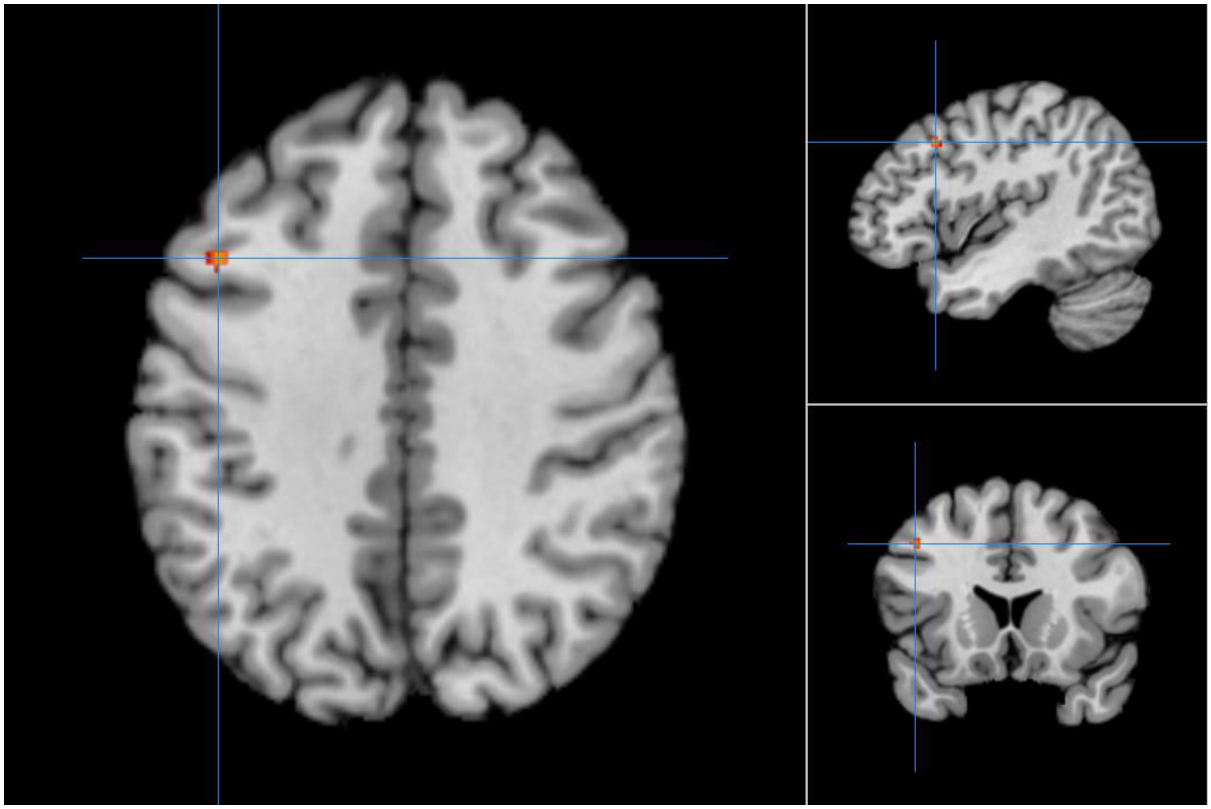

Figure 5b. Left Middle Frontal Gyrus (Brodmann area 9) hyperactivation in CTR* vs. *FEP

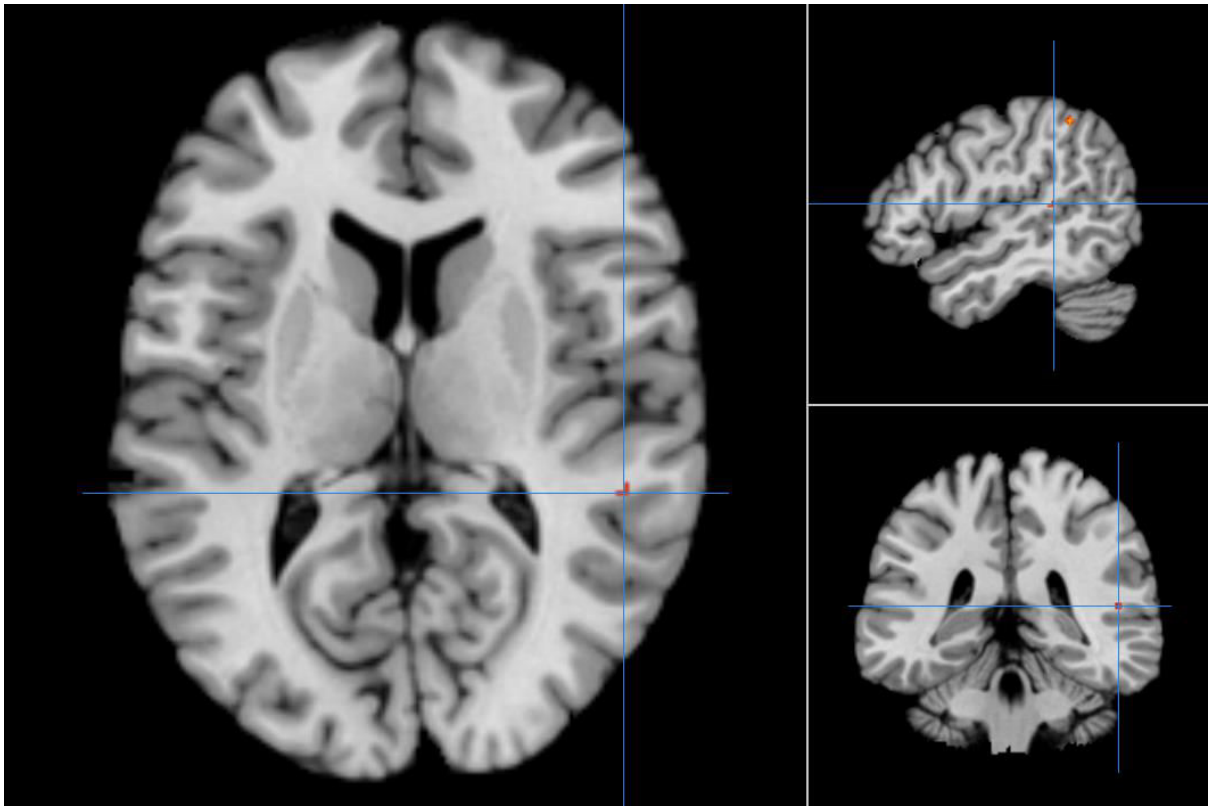

Figure 5c. Right Superior Temporal Gyrus (Brodmann area 41) hyperactivation in CTR* vs. *FEP

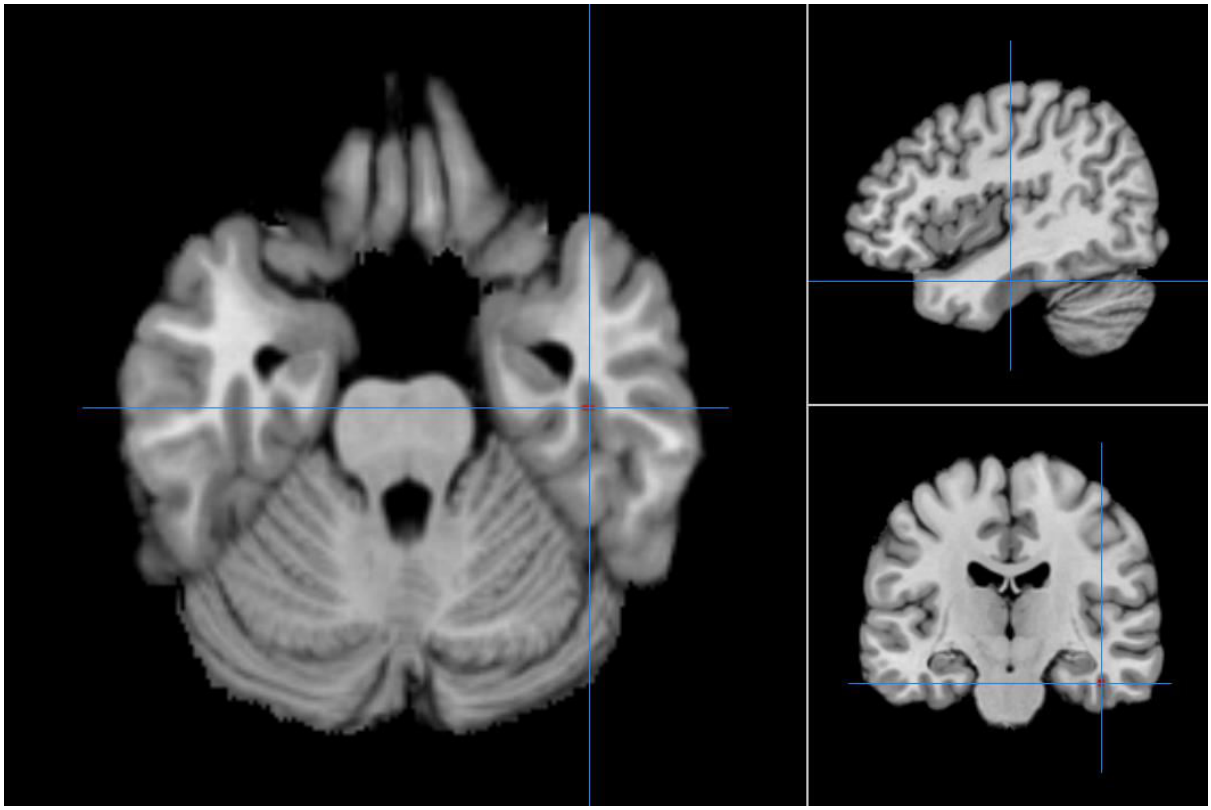

Figure 5d. Right Temporal Cortex (Brodmann area 20) hyperactivation in CTR* vs. *FEP

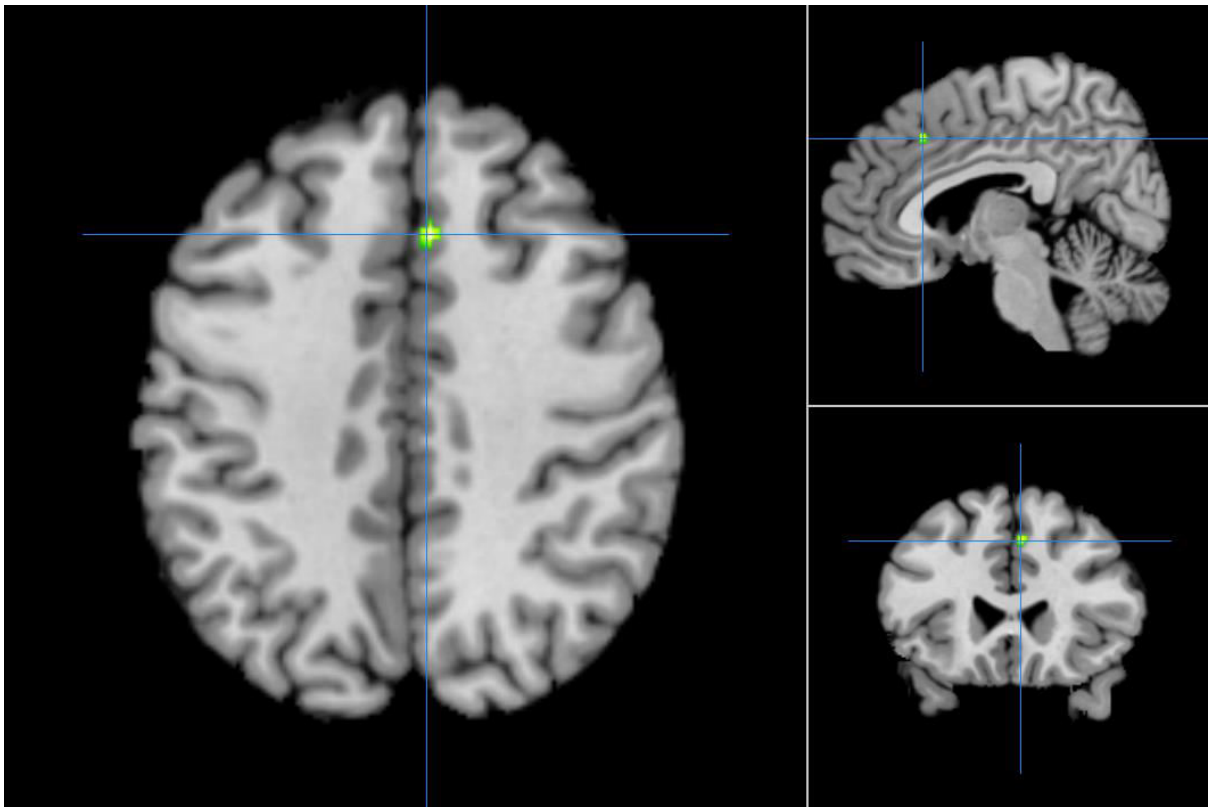

Figure 6. Right Cingulate Gyrus (Brodmann area 32) hyperactivation in FEP* vs. *CTR

DISCUSSION

This meta-analysis has shown that healthy people exhibited activation of a wide fronto-parietal cortical network that correlated with performances on the full set of tasks.

Patients with FEP showed task-related reduced activations of a similar network, which included the bilateral precentral gyrus (left BA 6 and right BA 9), bilateral superior parietal lobule (BA 7), and left postcentral gyrus (BA 3), but did not involve the bilateral middle frontal gyri (BAs 9).

Our task-segregated meta-analysis found remarkable differences in task-related brain activations occurring during cognitive, emotional and language processing. During attentional and memory-related tasks, CTRs mainly activated prefrontal areas, while FEP patients failed to activate these areas and showed extended bilateral parietal activation.

Emotional task-related activations occurred in the bilateral DLPFC, right parietal cortex, left cingulate cortex and right amygdala in CTRs, and in the right fusiform gyrus in FEP patients. These profound differences can be importantly related to difficulty in processing emotions during the psychotic onset.

Task segregation reported significant left-sided language task-related activations in the CTR group, centred on the insula, DLPFC, and temporal cortex. The lack of such activations in patients may be referred to the alterations of language, word fluency and semantic processing during psychotic onset.

The FWE algorithm confirmed the within-group left BA9 activation in CTRs during task performance.

Direct comparisons between FEP and CTR samples also reported that healthy individuals hyperactivate cortical areas (mainly parietal, prefrontal, temporal, and posterior cingulate cortices) in response to tasks, as compared to FEP patients, who conversely showed hyperactivation of the right dorsal anterior cingulate cortex (BA 32). Results of this ALE

meta-analysis confirm several findings of a previous multimodal meta-analysis that identified conjoint structural and functional differences in the insula/superior temporal gyrus and the medial frontal/anterior cingulate cortex bilaterally (Radua et al., 2012). The same results are also in line with a meta-analysis of FEP patients compared with healthy controls reporting progressive loss of whole-brain grey matter volume involving the frontal, temporal, and parietal lobes (Vita et al., 2013).

Prefrontal cortices. These areas are crucial in cognitive functioning (Frith & Dolan, 1996), and were expected to be activated by cognitive tasks. While both FEP patients and CTR subjects commonly activated the left precentral gyrus (BA 6) in response to tasks (see conjunction analysis), patients failed to activate the bilateral (mainly left-sided) middle frontal gyrus. Moreover, between-group analyses found significant task-related hypoactivation of the same bilateral BA 9 in FEP as compared to CTR group.

In brief, this meta-analysis found that BA 9 dysfunction, especially in the left hemisphere, is a major neural functional correlate of psychotic schizophrenia-spectrum onset.

The left middle frontal cortex is involved in language processing (Axelrod et al., 2015; Willems et al., 2015; Cattaneo, 2013). In particular, the left BA9 is engaged in several language functions, including syntactic processing (Wang et al., 2008), metaphor comprehension (Shibata et al., 2007), verbal fluency (Abrahams et al., 2003), semantic categorisation (Hugdahl et al., 1999), and word-stem completion (Desmond et al., 1998). Its activation also correlated with phasic and intrinsic alertness (Clemens et al., 2011), working memory (Collette et al., 2011), processing of emotions and self-reflections during decision making (Deppe et al., 2005), and REM sleep behaviour disorder (Mazza et al., 2006).

Different studies showed prefrontal structural and functional changes in FEP patients (Jardri et al., 2013; Radua et al., 2012).

Structural neuroimaging studies reported left middle frontal decreased volume, which was related to social cognitive impairments along with reduced gray-matter density in other regions within the mirror neuron system network (Bertrand et al., 2008). A follow-up diagnosis of schizophrenia in FEP patients was associated with gray matter volume deficits in the left medial and left middle frontal gyrus (Janssen et al., 2008). Cortical thickness technique revealed that poorer awareness of illness in FEP patients was associated with regional thinning in left middle frontal and inferior temporal gyri (Buchy et al., 2011). White matter deficits in the left middle frontal gyrus were also observed in drug-naïve FEP patients compared to their siblings (Lyu et al., 2015).

An important multichannel functional near-infrared spectroscopy study showed that patients with FEP had significant positive correlation between functioning scores and left middle frontal gyrus activation (Koike et al., 2016). Compared with CTRs, FEP patients showed significantly greater reaction-time interference but normal accuracy on the Stroop task. This pattern correlated with significant under-activation of the posterior left middle-frontal gyri in FEP patients (Harrison et al., 2006). Relative to CTRs, unmedicated FEP patients showed left middle frontal cortex hypoactivation during serial reaction time procedural learning (Purdon et al., 2011). Another important finding is that decreased middle frontal activity during a during verbal fluency task performances correlated with longer duration of untreated psychosis (Chou et al., 2014). Episodic memory task performance correlated with left middle frontal dysfunction in FEP patients, suggesting aberrant functioning during recollecting of information of past events when they process new items (Guimond et al., 2016). Left middle frontal gyrus aberrant function was reported in female compared to male FEP patients (Lei et al., 2015). The functional connectivity of the right superior temporal gyrus with the left middle frontal gyrus positively correlated with symptom severity (Zhang et al., 2015), confirming the correlation of the dysfunction of this area also with FEP psychopathology. In

the contrast of Fist-Edge-Palm vs. Palm-Tapping tasks, FEP patients did not show areas of significant activation, while relatives and healthy controls showed significant activation of the left middle frontal gyrus (Chan et al., 2015).

In brief, the reported BA9 hypoactivation in FEP is in line with evidence of middle frontal structural and functional alterations in FEP, which can be related to lower global functioning, longer duration of untreated psychosis, cognitive deficits, and poor awareness of illness in the context of schizophrenia onset.

Our within-group ALE meta-analyses found significant task-related activation of the BA6, which was right-sided in CTR group and left-sided in FEP. Conjunction analysis revealed a cluster of common activation of the left precentral gyrus (BA 6) in both CTR and FEP. Our between-group meta-analysis also showed left precentral gyrus hyperactivation in CTR.

BA 6 is involved in motor functions (Chouinard & Paus, 2006), and several cognitive functions, including language (Grodzinsky, 2006; Hirsch et al., 2001; Shuster & Lemieux, 2005), memory (Ranganath et al., 2003), attention (Nobre et al., 1997; Cheng et al., 1995), deductive reasoning (Reverberi et al., 2007), consciousness and others (Naghavi & Nyberg, 2005).

Differences in laterality of BA 6 task-related activations in CTR and FEP groups are in line with reported inter-hemispheric dysconnectivity in FEP (Chang et al., 2015). Precentral cortex dysconnectivity has been related to severity of positive symptoms in FEP (Guo et al., 2014a), while longer DUP showed correlation with right precentral gyrus hypoactivation in FEP (Chou et al., 2014).

From a neural morphometric point of view, FEP patients with impulsive behaviour showed altered white matter integrity of the left precentral gyrus (Wei et al., 2011a), and reduced grey matter densities in the precentral gyri correlated with neurological soft sign severity (Heuser et al., 2011), and signs of sensory integration deficits (Dazzan et al., 2004).

Compared to healthy individuals, subjects at ultra-high risk for schizophrenia showed grey matter decreases in the precentral cortex (Bohner et al., 2012), while unaffected siblings of FEP patients demonstrated left precentral cortex volume reduction (Huang et al., 2009), which correlated with genetic susceptibility (Wei et al., 2015). These findings demonstrate that this area is involved in the neuropathophysiology of schizophrenia even before the onset of the disease.

Both our within-group and between-group data are in line with the hypothesis that the precentral cortex is a key-region in the neuropathophysiology of FEP, and its structural and functional changes could be related to motor, cognitive, impulsive, and positive symptoms.

Parietal cortices. The parietal cortex is a key-region for cognitive functioning in humans (Teixeira et al., 2014; Cabeza et al., 2012; Bueti & Walsh, 2009; Sack, 2009). Our within-group meta-analyses showed cognitive task-related activations of the left postcentral gyrus (BA 3), right precuneus (BA 19), and left superior parietal lobule in CTR group, and bilateral superior parietal lobule (BAs 7) and left postcentral gyrus (BA 3) in FEP patients. Between-group data testified a major cluster of hyperactivation in the right inferior parietal lobule (BA 40) in CTR.

Left BA 7 activation in FEP could be compensation to non-activation of other fronto-temporo-parietal cortices. On the other hand, left superior parietal lobule volume reduction has been reported in individuals who subsequently developed psychosis compared to healthy subjects (Borgwardt et al., 2007).

Right BA 39/40 activity has been related to visuospatial processing (Köhler et al., 2009), reading (Ischebeck et al., 2004; Inui et al., 1998) and music reading (Schön et al., 2002), writing (Rektor et al., 2006), theory of mind (Goel et al., 1995), and many other cognitive functions that are partly mediated by integrative/associative networks (Teixeira et al., 2014).

Individuals with at-risk mental state showed reduced activation during adaptive salience (Smieskova et al., 2015) and movement generation (Broome et al., 2010b) in the right inferior parietal lobule, which was even more hypoactivated in FEP patients (Broome et al., 2010b).

FEP patients with low positive and disorganisation symptom levels showed higher gamma-band connectivity within a strongly lateralised network consisting mainly of left inferior frontal/orbitofrontal, lateral and medial temporal, and inferior parietal areas (Andreou et al., 2015). Related to our data, these findings underline the importance of changes in inter-hemispheric connectivity and neurofunctional lateralisation in patients with FEP.

Social cognitive impairment in FEP significantly correlated with reduced grey matter density in the inferior parietal lobule and other mirror neuron system network (MSN) areas, including the left middle frontal gyrus, right supplementary motor cortex, and left superior temporal gyrus (Bertrand et al., 2008).

Summarising, the inferior parietal cortex hypoactivation during cognitive tasks is involved in cognitive and social cognitive, disorganisation, motor, and positive symptoms exhibited by FEP patients. Our meta-analysis is in line with different findings that underline the involvement of the inferior parietal lobule structure and function in both psychosis-risk syndrome and first-episode psychoses.

Temporal cortices. The temporal cortices are involved in visual categorisation (ventral portion) (Grill-Spector et al., 2014), vocal expressions of emotions (superior part) (Frühholz & Grandjean, 2013), multisensory integration (superior temporal sulcus) (Beauchamp, 2015), object-related and space-related information processing, language, and other cognitive functions (Karnath, 2002). Human superior temporal cortex functions appear to be segregated between the left hemisphere (language processing), and the right hemisphere (spatial awareness and exploration) (Karnath, 2002).

Our between-group meta-analysis showed that FEP patients as compared to CTRs hypoactivate the right superior temporal gyrus (BA 41) and right sub-gyral grey matter (BA 20) during cognitive functioning.

Subjects with ultra-high risk for psychosis showed both white matter integrity (Bloemen et al., 2010), grey matter deficits (Witthaus et al., 2009; 2008), and cortical thinning (Benetti et al., 2013) in the right superior temporal cortex.

About FEP, our data are in line with existing evidence of right superior temporal gyrus volume reduction (Fusar-Poli et al., 2014; Guo et al., 2014b; Lui et al., 2009; Matsumoto et al., 2001), which correlated with severity of thought disorder and hallucinations (Matsumoto et al., 2001), and cortical thickness decrement (Scanlon et al., 2014; Zheng et al., 2014; Benetti et al., 2013; Gutiérrez-Galve et al., 2010).

Other findings reported right superior temporal cortex dysfunctional resting-state connectivity (Zhang et al., 2015), and hypoactivation related to executive attention and working memory task (Rasser et al., 2005).

Changes in the right superior temporal cortex appear to be stable in the course of the disease.

From a neural structural point of view, patients affected by schizophrenia showed significant negative correlation between hallucinations severity (Palaniyappan et al., 2012; Nenadic et al., 2011) and persistence (O'Daly et al., 2007) and grey matter right superior temporal gyrus volume. The dendritic spine density and number, and the immunoreactivity of the microtubule-associated-protein-2 have been shown to be significantly reduced in the primary auditory cortex (BA 41) of patients affected by schizophrenia (Shelton et al., 2015). Total burden of copy number deletions has been positively associated with regional volumes in the right superior temporal gyrus (Martin et al., 2014), mainly in patients with longer duration of untreated psychosis (Guo et al., 2013), and poor insight (Cooke et al., 2008). The same

area has been shown to be thinner, especially in patients with persistent negative symptoms (Bodnar et al., 2014).

From a neural functional point of view, the right superior temporal cortex also showed decreased resting-state connectivity in patients with schizophrenia (Hinkley et al., 2011). Moreover, right superior temporal cortex dysfunctions also correlated with auditory deviance processing deficit (Rissling et al., 2014), lack of calculation-related regional cerebral blood flow increase (Dirnberger et al., 2014), mentalizing/emotion recognition deficits (Lee et al., 2014; Das et al., 2012; Germine et al., 2011; Habel et al., 2010; Hirao et al., 2008), impairment in sound and spatial discriminations (Perrin et al., 2010), and decision-making (Paulus et al., 2002).

In brief, right superior temporal structural and functional changes in FEP can be related to auditory hallucinations, severity of thought disorder, mentalizing impairment, deficit in sound localisation and spatial discrimination of sounds, longer duration of untreated psychosis, poor insight, and represents one of the key neural correlates in the pathophysiology of schizophrenia.

Anterior Cingulate Cortices. Our between-group ALE meta-analysis found right dorsal ACC (BA 32) hyperactivation in FEP compared to CTR during SAMLE tasks. This area is involved in several cognitive functions, including attention and memory (Wager & Smith, 2003), language (Nathaniel-James et al., 1997), decision making and others (Bush et al., 2002), and also in motor control (Bush et al., 2002), autonomic functions, mainly including autonomic cardiovascular control (Shoemaker et al., 2015). It also has a major role in depression and anxiety (Brody et al., 2001; Liotti & Mayberg, 2001), and bipolar disorder (de Azevedo et al., 2011).

About FEP, cognitive performance of subjects with a psychotic onset has been directly correlated with right dorsal anterior cingulate grey matter volume (Minatogawa-Chang et al., 2009).

FEP patients showed more right dorsal ACC white matter alterations, compared to their siblings (Lyu et al., 2015) and to healthy individuals (Wei et al., 2011b; Moriya et al., 2010), as well as grey matter loss (Lui et al., 2009; Lopez-Garcia et al., 2006; Job et al., 2002).

Other findings showed connectivity abnormalities in FEP between the right ACC to the sensorimotor regions and decreased feedback from the sensorimotor regions to the right ACC (Guo et al., 2015), functional deficit correlated with the expression of the at risk allele (SNP 8NRG221533) of the Neuregulin-1 gene (Kircher et al., 2009), and word-fluency–related hypoactivation of the right ACC (Boksman et al., 2005).

In summary, our data confirm the existing lines of evidence of structural and functional deficits of the right dorsal ACC, which is an essential correlate of FEP. Right dorsal ACC deficits may underpin psychotic anxiety, mood dysregulation, motor symptoms, autonomic dysfunction, and cognitive impairment, especially regarding language, attention and memory.

LIMITATIONS

A major limitation is that we combined different tasks assessing different sensory, cognitive, language, and emotional functions, although task combination allowed us to examine neural functions globally. Two studies had partial overlapping samples of 15 CTRs and 14 FEP patients (Fassbender et al., 2014; Lesh et al., 2013). However, it is unlikely that 15/546 (2.7%) CTRs and 14/516 (2.7%) FEP patients could have influenced the analyses. Another limitation is that medication-free sample was lumped together with medicated sample; over 61% of FEP patients from included studies were on medication at the time of the study.

CONCLUSION

The present ALE meta-analysis of fMRI studies during SAMLE task performance showed that healthy individuals activate a fronto-parieto-temporal cortical network, while FEP patients mainly lack prefrontal task-related activations in the context of this network. The major finding of this study is the evidence of functional deficit of the left middle frontal gyrus (BA 9) in FEP (correlated with longer duration of untreated psychosis, language dysfunction, cognitive deficit, and poor awareness of illness). Our data also report right dorsal ACC hyperactivation (related to with psychotic anxiety, dysregulation of mood, motor symptoms, autonomic dysfunction, and cognitive impairment, especially regarding language, attention and memory) in FEP compared to CTRs, and indicate a role for the bilateral parietal cortices (social cognitive, disorganisation, motor, and positive symptoms) and right temporal cortex (hallucinations, severity of thought disorder, mentalizing impairment) in the neuropathophysiology of FEP, stressing that both cortical and limbic areas are dysfunctional in patients when they deal with SAMLE tasks.

This study also underlined that FEP patients failed to activate prefrontal areas, instead of which they activate the parietal cortices in response to attentional- and memory-tasks. They failed to activate a fronto-parieto-limbic network involved in emotional processing, mostly activating the right temporal cortex in response to emotional tasks. Language disturbances in FEP have important neural correlates, which mainly consisted in a lack of activation of the left insula, DLPFC, and temporal cortex.

Most of these areas have been consistently shown to be altered both in psychosis risk syndrome (with a minor impairment) and in chronic schizophrenia (major impairment), suggesting their centrality in the neuropathophysiology of schizophrenia.

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