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Increased superior frontal gyrus activation during working memory processing in psychosis: Significant relation to cumulative antipsychotic medication and to negative symptoms

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Abstract

Objectives: Impairment in working memory (WM) is a core symptom in schizophrenia. However, little is known about how clinical features influence functional brain activity specific to WM processing during the development of first-episode psychosis (FEP) to schizophrenia (SZ). We compared functional WM-specific brain activity in FEP and SZ patients, including the effects of the duration of illness, psychopathological factors and antipsychotic medication.

Methods: Cross-sectional study of male FEP (n=22) and SZ (n=20) patients performing an n-back task when undergoing functional magnetic resonance imaging (fMRI). Clinical features were collected by semi-structured interviews and medical records.

Results: The SZ group performed significantly worse than the FEP group in the 2-back condition. The SZ group also showed significantly higher activation in the left superior frontal gyrus in the 2-back versus 0-back condition (2-back > 0-back). This frontal activation correlated positively with negative symptoms and with cumulative antipsychotic medication during the year before the fMRI examination. There were no significant correlations between activation and duration of illness.

Conclusion: There was greater frontal neural activation in SZ than in FEP. This indicated differences in WM processing, and was significantly related to cumulative antipsychotic exposure and negative symptoms, but not to the duration of illness.

1 Introduction

In recent decades, the clinical symptoms of schizophrenia have been precisely described and conceptualized. Besides positive (e.g., hallucinations and delusions) and negative symptoms (e.g., affective flattening, alogia and avolition) (Andreasen, 1982, 1985), cognitive impairment is a core clinical feature in the course of the illness. In particular, one of the most replicated findings in SZ is the development of deficits in working memory (WM) processing (Goldman-Rakic, 1994; Heinrichs and Zakzanis, 1998; Nuechterlein et al., 1994).

If we employ the staging model in schizophrenia, we can study *early stage* schizophrenia in the first-episode psychosis (FEP) population and *later stage* schizophrenia in chronic schizophrenia patients (SZ). The psychotic symptoms mentioned above fulfill the criteria for an acute psychotic episode and distinguish FEP individuals from chronic SZ patients (Yung, 1998), who exhibit full-blown psychotic symptoms according to the DSM-IV criteria for schizophrenia.

Both FEP and SZ exhibit comparable cognitive deficits relative to healthy controls, with a slight decrease in WM performance over the course of illness that could be associated with more severe illness or adverse medication effects (Mathes et al., 2005; Morris and DeLisi, 1992; Zanello et al., 2009). In the neural network models of WM, the prefrontal cortex (PFC) plays a critical role in functional interactions (Badre and Wagner, 2004; D'Esposito, 2007; Goldman-Rakic, 1995; Kraguljac et al., 2013) and it has been proposed that there is exaggerated and inefficient PFC activity in SZ (Callicott et al., 2000). Furthermore, a number of studies have shown normalization of brain function in patients taking antipsychotic medication (Davis et al., 2005; Honey et al., 1999; Lahti et al., 2004). However, little is known about whether this effect is only based on a change in local blood flow or is connected to the amelioration in cognitive impairment.

Additionally, WM performance seems to depend on the difficulty of the task, as well as individual performance and treatment effects such as antipsychotic medication (Ettinger et al., 2011; Forbes et al., 2009; Karlsgodt et al., 2007; Potkin et al., 2009). However, it is still

unclear whether factors such as the duration of illness (DOI) have an impact on WM processing (Elsabagh et al., 2009; Forbes et al., 2009). Furthermore, negative symptoms might be a consequence of illness or represent undesirable antipsychotic effects (Lewander, 1994). Although a recent meta-analysis confirmed that WM performance and negative symptoms are associated (Forbes et al., 2009), fMRI data revealed no significant contribution of negative symptoms to WM deficits (Perlstein et al., 2001).

Moreover, there have been comparative studies with clinical samples (SZ or FEP) and healthy controls but no fMRI studies on WM-specific changes in the early and late stages of schizophrenia, expressed as a comparison between FEP and SZ individuals.

Our first hypothesis was that we would find impaired WM performance in SZ patients relative to FEP patients. Our second hypothesis was that functional WM-specific brain activity would be impaired in SZ patients compared to FEP patients. Our third hypothesis was that the detected group differences in brain activity would be associated with effects of antipsychotic medication, duration of illness and psychopathological factors.

2 Materials and methods

2.1 Study population

Both FEP and SZ patients were recruited at the Psychiatric University Clinics (UPK), Basel, Switzerland. The patients were either recruited at the Psychiatric Outpatient Department, within an Early Detection of Psychosis (FePsy) clinic (Riecher-Rössler et al., 2006) (only FEP patients) or in the In- and Outpatient Departments at the UPK (only SZ patients). The FEP patients (N=22) fulfilled the transition criteria for a psychotic episode, as described by Yung et al. (1998). The inclusion criteria for SZ patients (N=20) were the DSM-IV criteria for schizophrenia. Inclusion and exclusion criteria are listed in Table 1. The calculation of the sample size was based on the estimates and power curves generated by Desmond and Glover (Desmond and Glover, 2002). The calculated n is comparable to other fMRI studies during working memory processing in schizophrenia (Jansma et al., 2004; Perlstein et al., 2001; Rasser et al., 2005). Furthermore, given that neural activation during working memory processing is gender-specific in schizophrenia patients (Elsabagh et al., 2009), we decided to study a homogeneous sample for gender in order to gain specificity. DOI was defined as the period of time between transition to first-episode psychosis (FEP group) and date of MRI, or the date of transition to SZ or the first psychiatric treatment of psychosis (SZ group) and date of MRI.

We assessed patients using the Brief Psychiatric Rating Scale (BPRS), the Global Assessment of Functioning (GAF), Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) (Lehrl et al., 1995) and the Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID I and II). In 3 SZ patients, SCID I and II were not available and the subsequent assessment was performed by the Operational Criteria OPCRIT checklist for psychotic and affective illness (McGuffin et al., 1991).

We collected data on current and previous doses of antipsychotic and antidepressant medication, alcohol, nicotine or other substance consumption on the basis of a semi-structured interview. In 11 of the 16 medicated SZ patients data on prescribed and actually taken antipsychotic medication were gathered from medical records. Doses of antipsychotics were converted into chlorpromazine-equivalent (CPZ-E) doses (Andreasen et al., 2010; Gardner et al., 2014). All patients provided written informed consent, and the study was awarded the research ethics committee's consent (EKBB M12/99; Amendment 189/08).

2.2 N-back task

The applied task has already been described in detail (Schmidt et al., 2014; Smieskova et al., 2012). During a baseline (0-back) condition, participants were required to press the right button when the letter “X” appeared. During 1-back and 2-back conditions, the button was pressed if the currently presented letter was the same as that previously shown (1-back condition) or as that shown two letters beforehand (2-back condition). All three conditions were presented in 10 alternating 30 s blocks, matched for the number of target letters per block in a pseudorandom order (for details see supplement). The sensitivity index d' was calculated to quantify task performance by using the formula $d' = z(\text{Hits}) - z(\text{FA})$, where FA reflects false alarms (Macmillan, 1991). Hit and false alarm rates of zero or 1 were adjusted as previously described (Macmillan and Kaplan, 1985; Schmidt et al., 2014). The d' values were subjected to the 2-sample t test.

2.3 Magnetic resonance imaging acquisition

Functional images were acquired with a 3 T scanner (Siemens Magnetom Verio, Siemens Healthcare, Germany) with a 12-channel radio frequency head coil using an echo planar sequence with a repetition time (TR) of 2.5 s, echo time (TE) of 28 ms, flip angle of 8°, matrix 76x76, 126 volumes and 38 slices with 0.5 mm interslice gap, which provided a resolution of 3x3x3 mm³, and a field of view (FOV) of 228x228 cm². Structural MRI (sMRI) scans were not

acquired within this analysis, but only clinical sMRI were acquired to exclude possible abnormalities. The n-back paradigm was presented using E-PRIME software.

2.4 fMRI analysis

We pre-processed and analyzed fMRI data using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>), as described in detail elsewhere (Smieskova et al., 2012)(see further details in supplement). In accordance with previous n-back fMRI studies, we focused our analysis on the 2b>0b contrast, in order to capture the highest possible WM load during the task (Deserno et al., 2012; Schmidt et al., 2014). We defined a minimal cluster threshold as having a size ≥ 10 voxel. Between-group differences were evaluated by using the 2-sample t-test. The groups differed with respect to age, so this variable was added as covariate in the second level analysis. Statistical significance was assessed at the cluster-level using non-stationary random field theory (Hayasaka et al., 2004). The first step of this cluster-level inference strategy consisted of identifying spatially contiguous voxels at a threshold of $P < 0.01$ without correction (cluster-forming threshold) (Petersson et al., 1999). Finally, a family-wise and error-corrected cluster-extent threshold of $P < 0.05$ was defined to infer statistical significance.

2.5 Statistical analysis

Behavioral and socio-demographic differences between groups were calculated by the 2-sample t test, or the chi-square test ($P < 0.05$). Pearson's correlation analysis was conducted to assess the relation between brain activation in the region with different between-group differences and DOI; cumulative CPZ-E dose during the last year before MRI scan; CPZ-E dose at MRI scan; negative symptoms in BPRS; and sensitivity index d' . All correlations were Bonferroni-corrected for multiple comparisons ($P = 0.05/5 = 0.01$). Brain activation from the significant between-group differences (2-back>0-back contrast) were obtained from the first eigenvariate of a sphere of 5 mm radius around the peak of activation. Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS 19.0).

3 Results

3.1 Demographic and clinical characteristics of the sample

The SZ and FEP male patients were well-matched for handedness, IQ, years of education, total BPRS score, and use of antidepressants, alcohol and cannabis at the date of the MRI ($P > 0.05$) (Table 2). The SZ patients were significantly older ($P = 0.027$), had suffered longer from SZ ($P = 0.002$) - especially from negative symptoms ($P = 0.001$) -, and smoked cigarettes more frequently ($P = 0.006$). The SZ patients had higher cumulative antipsychotic intake during the preceding year ($P < 0.0001$) and at the date of the MRI scan ($P = 0.001$). The SZ patients showed a trend for less intense positive symptoms ($P = 0.080$) and less global functioning (GAF) ($P = 0.070$), compared to FEP. 10 FEP patients and 15 of 16 medicated SZ patients were receiving atypical antipsychotics (AAP) (1 SZ patient received zuclopenthixol hydrochloride, a typical medium potency antipsychotic and 1 SZ AAP plus haloperidol) (Table 3). According to the patient histories, 2 of 20 SZ individuals and 11 of 22 FEP individuals received antipsychotic medication for less than 1 week or not at all. The average duration of antipsychotic medication in the year before the MRI scan was 37 weeks in the FEP group and 48 weeks in the SZ group.

3.2 Behavioral characteristics

Compared to FEP, the SZ patients showed a trend towards longer mean reaction times ($P = 0.084$) and worse task performance during o-back ($P = 0.058$). During the 2-back condition, SZ patients performed significantly worse than FEP patients ($P = 0.001$), but with a similar reaction time to the o-back condition ($P = 0.067$; Table 4).

3.3 fMRI data

3.3.1 Whole brain neuroimaging results

Across all 42 subjects, the main effect of task (2b > 0b) induced activity in a fronto-parietal network. In the SZ group, we observed a significantly higher blood oxygenation level-

dependent (BOLD) signal for the 2b>0b contrast in the left superior frontal gyrus (SFG) (Brodmann Area 9) compared to the FEP group ($P < 0.05$, FWE corrected) (Table 5). Additional information about WM activity for each group is provided in the supplement (Table 1 supplement).

3.3.2 Correlation analyses

Left SFG activation correlated positively with the dose of antipsychotics (as indexed by the CPZ-E during the last year before the fMRI examination) ($r = 0.489$; $P = 0.001$, $n = 40$) (Figure 1A) and with negative symptoms (as indexed by the BPRS) ($r = 0.417$, $P = 0.008$; $n = 39$) (Figure 1B). Furthermore, left SFG activation correlated negatively with the sensitivity index d' ($r = -0.433$; $P = 0.004$, $n = 42$). Correlations between the BOLD signal and duration of illness ($P = 0.042$, $n = 42$) or with the dose of CPZ-E at fMRI examination ($P = 0.015$, $n = 42$) did not survive the correction for multiple comparisons.

4 Discussion

Chronic SZ patients performed significantly worse than the FEP patients during the higher load WM task. Moreover, they showed higher activation in the left SFG. This SFG activation correlated positively with the cumulative CPZ-equivalent dose during the preceding year and with the severity of negative symptoms.

4.1 WM activation and task performance

There is considerable evidence that different PFC regions are involved during WM processing (Cornette et al., 2001; Glahn et al., 2005; Kraguljac et al., 2013; Minzenberg et al., 2009). Moreover, it has been shown that even different foci in the SFG are implicated during WM processing (Braver et al., 1997; du Boisgueheneuc et al., 2006; Owen et al., 2005). The extent of PFC activation depends on the WM load and operates on an inverted U-shape curve. In schizophrenia patients, the curve is shifted to the left side, meaning that patients reach the peak of the inverted U curve sooner and at a less difficult task level (Callicott et al., 2003). When the difficulty of the task increases further, neuronal activity may decline (Callicott et al., 2003; Karlsgodt et al., 2009).

In line with these findings and in accordance with our first hypothesis, we found significantly worse task performance at a higher WM load in the SZ group relative to the FEP group. Simultaneously we detected greater activation in the left SFG in the SZ group compared to FEP patients. Additionally, SFG activation correlated negatively with the WM performance across both groups. This finding replicates previous evidence that patients with SZ perform worse at higher levels of WM (Callicott et al., 2000; Callicott et al., 2003; Callicott et al., 1998; Stone et al., 1998). Furthermore, the greater activation in the left SFG in SZ may reflect an inefficient WM processing. Thus, different regions in the PFC, including the SFG, play a crucial role in WM and abnormal functioning of these regions in SZ reflects impairments of

the whole WM system (Callicott et al., 2000; Callicott et al., 2003; Jansma et al., 2004; Royer et al., 2009; Sabri et al., 2003)

4.2 Antipsychotic medication

Antipsychotic medication is associated with less severe positive psychotic symptoms and may ameliorate cognitive impairment, as has been shown in patients with both FEP and SZ (Davidson et al., 2009; Désaméricq et al., 2014; Harvey and Keefe, 2001; Marder and Meibach, 1994; Schooler et al., 2005). Furthermore, AAP may influence the BOLD signal in the frontal region during n-back performance, but in general this effect depends on the type of antipsychotics (Röder et al., 2013). Several fMRI studies have shown an association between antipsychotic medication and modification in regional activation (Fusar-Poli et al., 2007; Honey et al., 1999), but changes in the BOLD signal may be affected by a variety of D₂ antagonism effects (e.g., neuronal activity) and the duration of antipsychotic administration (Abbott et al., 2013). We found a positive correlation between cumulative antipsychotic medication and SFG activation. However, WM performance in SZ was worse than for FEP patients. Thus, despite the greater SFG activation, medication seems to have a negative effect on WM performance. Chronic antipsychotic medication is associated with structural modifications in neurons, e.g. reductions in the density of dendritic spines (Frost et al., 2010), a substantial increase in D₂ receptor binding and D₂ receptor upregulation (Silvestri et al., 2000), as well as an alteration in neuronal gene expression and neuronal function at the structural and ultrastructural levels, leading to effects on the BOLD signal after long-term antipsychotic administration (Abbott et al., 2013). Additionally, DA receptors are not specific for neurons and are also expressed by cerebral vessels, which might lead to a direct effect of dopamine on the local cortical blood flow via contact between dopaminergic axons and cortical microvessels, independently of cortical activity (Krimer et al., 1998; Röder et al., 2013).

Nevertheless, irrespective of the greater WM activation, SZ did not improve WM performance. This finding is in line with a previous study demonstrating that SZ patients

showed greater activation in the left ventrolateral prefrontal cortex after administration of antipsychotic medication, but without an improvement in WM performance (Meisenzahl et al., 2006). This may indicate that antipsychotic medication had an impact on positive symptoms but less so on neurocognitive impairment (Keefe et al., 2007; Meisenzahl et al., 2006).

4.3 Negative symptoms

Negative symptoms describe impairments in mental functions, such as vigilance, affectivity, motivation and motor action. Neuropsychological research has shown that negative symptoms in SZ influence WM functioning, which could be associated with undesirable antipsychotic effects (Carter et al., 1996; Lewander, 1994). Our results showed significantly more negative symptoms in the SZ than in the FEP. Furthermore, our data revealed a correlation between WM-specific SFG activation and negative symptoms. This might either be associated with the severity of illness or be caused by higher doses of AAP. This is supported by the fact that the dose of AAP medication was 7-fold higher in SZ than in FEP. Corresponding to this, the AAP risperidone caused an increase in negative signs in BPRS, but no significant motor extrapyramidal symptoms in healthy volunteers (Artaloytia et al., 2006). In our behavioral data, we did not find any significant motor retardation measured in time reaction between groups, so that the worse task performance in the SZ group cannot be explained by impairment in motor action. Thus, the well documented negative symptoms accompanying the course of schizophrenia may be enhanced by antipsychotic medication.

4.4 Duration of illness

Previous imaging studies suggested that DOI may moderate structural changes in SZ (Fusar-Poli et al., 2013), while specific effects of DOI on WM-related brain activity have hardly been investigated (Elsabagh et al., 2009). A negative correlation between PFC activity and DOI was found in older SZ patients, who had a longer DOI (and typical antipsychotic medication) than our SZ group (Elsabagh et al., 2009). We did not confirm the association between DOI

and WM-specific brain activation in SFG. An additional explanation of these results might be that 11 of our SZ patients received cognitive behavioral therapy focusing on cognitive deficits. Recent studies suggest that WM can be improved by cognitive training in association with changes in PFC activity (Klingberg, 2010). Furthermore cognitive improvement in schizophrenia leads to greater activation in PFC, without a significant improvement in the n-back task (Bor et al., 2011).

4.5 Limitations

Some limitations of this study should be considered. Firstly, our study population is a clinical sample (in- and out-patients) with different types and dosages of antipsychotic medication. Due to the small sample size, we were not able to investigate potential differences in the antipsychotics used (Vita et al., 2015). Furthermore, the information given by participants on antipsychotic medication was only reliable for the year before scanning, so that a group comparison of prescribed medication for the whole duration of the illness was not possible. Secondly, because of the block design chosen in this study, we were not able to investigate different WM components and subprocesses, although patients with psychosis exhibit different impairments during encoding and retrieval of information (Baddeley, 1992; Baddeley, 2003; Barch and Ceaser, 2012; Schlösser et al., 2008). Thirdly, in order to exclude any gender effects on signal changes and activation (Bell et al., 2006; Goldstein et al., 2005), we decided to focus on male subjects only, thus limiting the generalizability of the study. Fourthly, the available clinical data did not permit us to estimate the frequency of psychotic episodes, which might be a good predictor of SFG activation. In line with other studies (e.g. (Elsabagh et al., 2009; Honey et al., 1999)), we included DOI as an illness specific predictor of WM activation instead.

4.6 Conclusion

In conclusion, we examined WM performance in SZ compared to FEP individuals. Our findings revealed significantly poorer WM performance in SZ patients, with greater

activation in the left SFG. This was probably compensatory but inadequate. This activation correlated with the cumulative antipsychotic dose during the year preceding fMRI. Furthermore, SFG activation was correlated with the severity of negative symptoms but not to the DOI. Nevertheless, the symptoms in the course of psychosis are influenced by multidimensional interacting pathophysiological and medication factors. Therefore, our results suggest that antipsychotic medication may play a pivotal role in WM processing.

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Table 1: Inclusion and exclusion criteria

Inclusion criteria for FEP
1. Suspiciousness (BPRS ≥ 5): subject says others are maliciously talking about him/her, have negative intentions or may induce harm (incidents more than once a week OR partly delusional conviction)
2. Unusual thought content (BPRS ≥ 5): full delusion(s) with some preoccupation OR some areas of functioning disrupted (not only ideas of reference/persecution, unusual beliefs or bizarre ideas without fixed delusional conviction)
3. Hallucinations (BPRS ≥ 4): occasional hallucinations OR visual illusions > 2 /week or with functional impairment (not only hearing own name, non-verbal acoustics or formless visual hallucinations/illusions)
4. Conceptual disorganization (BPRS ≥ 5): speech difficult to understand due to circumstantiality, tangentiality, neologisms, blockings or topic shifts (most of the time OR three to five instances of incoherent phrases)
Exclusion criteria for FEP and SZ
History of previous psychotic disorders
Psychotic symptomatology secondary to an “organic” disorder
Substance abuse according to ICD-10 research criteria
Psychotic symptomatology associated with an affective psychosis or a borderline personality disorder
Age < 18 years
Inadequate knowledge of the German language
IQ ≤ 70 .

Transition criteria for a psychotic episode as described by Yung et al. (1998). At least one of the symptoms must occur at least several times a week and persist for more than one week. Inclusion criteria for SZ were the DSM-IV criteria for schizophrenia. Exclusion criteria were identical for the FEP and SZ groups, except for ‘History of previous psychotic disorder’ in the SZ group.

Abbreviations: BPRS – Brief Psychiatric Rating Scale.

Table 2: Demographic and clinical characteristics

	SZ (n=20)	FEP (n=22)	Statistics
Age in years, mean (S.D.)	33.5 (7.2)	28.4 (7.3)	P=0.027; t=-2.289
Handedness, left, n (%)	1 (5%)	2 (9.1%)	P=0.607; $\chi^2=0.264$
MWT_IQ, mean (S.D.)	109.6 (14.7)	105.6 (16.4)	P=0.469; t=-0.734
Years of education, mean (S.D.)	13.1 (2.8)	14.5 (3.3)	P=0.153; t=1.457
Duration of illness in months, mean (S.D.)	105.6 (93.8)	28.2 (38.8)	P=0.002; t=-3.432
BPRS total, mean (S.D.)	43.6 (12.6)	38.0 (8.8)	P=0.109; t=-1.640
BPRS positive symptoms, mean (S.D.)	10.5 (4.9)	13.2 (4.3)	P=0.080; t=1.802
BPRS negative symptoms, mean (S.D.)	10.8 (3.9)	7.2 (2.7)	P=0.001; t=-3.458
BPRS excited component, mean (S.D.)	4.6 (2.1)	3.9 (1.8)	P=0.252; t=-1.165
GAF at MRI scan, mean (S.D.)	48.6 (13.0)	57.4 (16.5)	P=0.070; t=1.868
Antidepressants at MRI scan, n (%)	2 (10%)	6 (27.3%)	P=0.155; $\chi^2=2.027$
Alcohol currently, n (%)			P=0.217; $\chi^2=1.527$
No	12 (60%)	9 (40.9%)	
Moderate	7 (35%)	7 (31.8%)	
Occasional drunkenness	1 (5%)	6 (27.3%)	
Cannabis currently, n (%)	2 (10%)	4 (18.2%)	P=0.413; $\chi^2=0.671$
Smoking currently, n (%)	19 (95%)	13 (59.1%)	P=0.006; $\chi^2=7.447$

Abbreviations: BPRS – Brief Psychiatric Rating Scale; FEP – first-episode psychosis group; GAF – Global Assessment of Functioning; MWT – multiple choice vocabulary test (Mehrfach-Wortschatz-Test Form B); Negative symptoms - emotional withdrawal, motor retardation, blunted affect; Positive symptoms - conceptual disorganization, grandiosity, suspiciousness, hallucinatory behavior, unusual thought content; S.D. –standard deviation; SZ – schizophrenia group.

Table 3: Characteristics of antipsychotic medication

	SZ (n=20)	FEP (n=22)	Statistics
Number of patients on antipsychotic treatment at MRI scans, n (%)	14 (70%)	9 (40.9%)	P=0.059; $\chi^2=3.579$
CPZ-equivalent dose in mg at MRI scan, mean (S.D.)	451.5 (460.9)	64.3 (99.4)	P=0.001; t=-3.680
Number of patients on antipsychotic treatment during the last year before MRI scans, n (%)	16 (80%)	10 (36.4%)	P=0.021; $\chi^2=5.301$
Cumulative CPZ-equivalent dose in mg during the last year before MRI scan, mean (S.D.)	182 660.3 (166984.1)	18 548.3 (34628.9)	P<0.0001; t=-4.304
Details of antipsychotic medication (n)	amisulpride 400mg (1)		
	aripiprazole 15 – 40mg (6)	aripiprazole 5 -7.5mg (4)	
	clozapine 450 – 600mg (2)	clozapine 300mg (1)	
	haloperidol 2mg (1)		
	olanzapine 5-25mg (4)		
	paliperidone palmitate 75mg (1)	paliperidone 3mg (2)	
	quetiapine 25 – 1500mg (4)	quetiapine 25-400mg (3)	
	risperidone 1 – 8mg (2)		
	risperidone depot 25 – 100mg (4)		
	zuclopenthixol dihydrochloride 120mg (1)		

The table presents the characteristics of antipsychotic medication. The SZ group includes patients with multiple antipsychotic prescriptions. Abbreviations: CPZ – chlorpromazine; FEP – first-episode psychosis group; n – number of prescriptions; S.D. –standard deviation; SZ – schizophrenia group.

Table 4: Behavioral data during n-back task

Characteristic mean (S.D.)	SZ	FEP	Statistics
0-back t_R (ms)	783.96 (74.16)	738.2 (86.23)	$P=0.084$; $t=-1.777$
2-back t_R (ms)	814.1 (66.42)	767.13 (76.22)	$P=0.067$; $t=-1.892$
0-back d'	2.04 (1.49)	2.79 (0.88)	$P=0.058$; $t=2.012$
2-back d'	1.81 (0.88)	2.7 (0.67)	$P=0.001$; $t=3.681$

Abbreviations: d' : the sensitivity index characterizing task performance ($d' = z(\text{hits}) - z(\text{false alarms})$); FEP – first-episode psychosis; SZ – schizophrenia; t_R – reaction time.

Table 5: Neuroimaging results

Brain Region	Cluster Size	MNI (x, y, z)	Z Score
Main effect of task across all included individuals (n=42)			
R supramarginal gyrus	1642	44, -42, 40	6.74
L inferior parietal lobule	996	-36, -48, 42	5.94
R subgyral frontal lobe	941	30, 0, 60	5.89
L subgyral frontal lobe	932	-26, 0, 60	5.82
L medial frontal gyrus	275	-4, 8, 58	5.52
L caudate	122	-16, -8, 18	5.32
R middle frontal gyrus	74	42, 38, 36	4.92
R caudate	30	18, 2, 16	5.02
SZ > FEP in 2b>ob contrast			
L SFG (BA 9)	44	-2 58 20	4.85

The upper part of the table presents the whole brain activity for the main effect of task in all 42 subjects during the 2-back>0-back contrast; activations are reported at family-wise error corrected at $P < 0.05$ and extent threshold $k=20$ voxel.

The lower part of the table presents significant differences in brain activation between SZ and FEP in 2b>ob contrast at a family-wise error-corrected threshold at $P < 0.05$ and a cluster size $k=20$ voxel. $P_{\text{FWE-corr.}}$ at cluster level was 0.002. $P_{\text{FWE-corr.}}$ at voxel level was 0.018. Abbreviations: BA–Brodman area; FEP–first-episode psychosis; MNI, coordinates x y z according to the the Montreal Neurological Institute; L–left; R–right SFG–superior frontal gyrus; SZ–schizophrenia.

Figure

Figure 1: Positive correlation between activation in the left superior frontal gyrus and cumulative CPZ-equivalent dose during the last year before scan (A) and negative symptoms (B).

(B)

Activation in the left superior frontal gyrus correlated positively with cumulative CPZ-equivalent dose (1×10^5 mg) during the last year before scan ($P=0.001$; $r=0.489$; Figure II.A) and negative psychotic symptoms indexed by BPRS item 3+13+16 ($P=0.008$; $r=0.417$, Figure II.B). In both panels, the Y-axis represents BOLD signal in the left SFG (MNI coordinates $x, y, z = -2, 58, 20$) during 2b>ob contrast.

Abbreviations

AAP – atypical antipsychotics

BA – Brodman area

BPRS – brief psychiatric rating scale

BOLD – blood oxygenation level dependent

CPZ-E – chlorpromazine equivalents

DOI – duration of illness

DSM – diagnostic and statistical manual of mental disorder

FEP – first-episode psychosis

FePsy – early detection of psychosis

FEW – family-wise error

PFC – prefrontal cortex

fMRI – functional magnetic resonance imaging

GAF – global assessment of functioning

ICD – international statistical classification of disease and related health problems

MNI – Montreal Neurological Institute

MWT-B – multiple choice vocabulary test form b

SCID – structural clinical interview of DSM

SFG – superior frontal gyrus

SZ – schizophrenia

WM – working memory