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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 et al., 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

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.

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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).

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 ≤ 70.0

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.

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 pseudo-random 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 76 × 76, 126 volumes and 38 slices with 0.5 mm interslice gap, which provided a resolution of 3 × 3 × 3 mm^3, and a field of view (FOV) of 228 × 228 cm^2. 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.

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