Schizophrenia Research 147 (2013) 331–338

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Reduced functional connectivity and asymmetry of the planum temporale in patients with schizophrenia and first-degree relatives

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ARTICLE INFO

Article history:
Received 15 January 2013
Accepted 18 April 2013
Available online 12 May 2013

Keywords:
Resting-state fMRI
Schizophrenia
Schizophrenia spectrum
Auditory network
Planum temporale

ABSTRACT

The planum temporale (PT) is a highly lateralized brain area associated with auditory and language processing. In schizophrenia, reduced structural and functional laterality of the PT has been suggested, which is of clinical interest because of its potential role in the generation of auditory verbal hallucinations. We investigated whether resting-state functional imaging (fMRI) of the PT reveals aberrant functional connectivity and laterality in patients with schizophrenia (SZ) and unaffected relatives, and examined possible associations between altered intrinsic functional organization of auditory networks and hallucinations.

We estimated functional connectivity between bilateral PT and whole-brain in 24 SZ patients, 22 unaffected first-degree relatives and 24 matched healthy controls. The results indicated reduced functional connectivity between PT and temporal, parietal, limbic and subcortical regions in SZ patients and relatives in comparison with controls. Altered functional connectivity correlated with predisposition towards hallucinations (measured with the Revised Hallucination Scale [RHS]) in both patients and relatives. We also observed reduced functional asymmetry of the superior temporal gyrus in patients and relatives, which correlated significantly with acute severity of hallucinations in the patient group.

To conclude, SZ patients and relatives showed abnormal asymmetry and aberrant connectivity in the planum temporale during resting-state, which was related to psychopathology. These results are in line with results from auditory processing and symptom-mapping studies that suggest that the PT is a central node in the generation of hallucinations. Our findings support reduced intrinsic functional hemispheric asymmetry of the auditory network as a possible trait marker in schizophrenia.

1. Introduction

The planum temporale (PT) is a core structure of a functional network, including frontal, temporal and parietal nodes that are involved in speech processing (Hickok and Poeppel, 2007). In most healthy right-handers, the PT shows structural hemispheric asymmetry, with left PT being substantially larger in volume than its right hemispheric counterpart (Chance et al., 2008). In schizophrenia (SZ) patients, functional and anatomical brain imaging studies have shown reduced PT hemispheric asymmetry (Sommer et al., 2004; Oertel et al., 2010), which may be associated with increased auditory hallucinations (Sumich et al., 2005; Oertel et al., 2010). Indeed, several authors have suggested that auditory verbal hallucinations (AVH) in schizophrenia may be associated with a disrupted brain architecture that includes speech perception and production networks (Friston, 1998; Stephane et al., 2001; Wible et al., 2009a,b; Van de Ven, 2012).

Recently, these findings have been extended to measurements of intrinsic brain activity, which is commonly measured using functional magnetic resonance imaging (fMRI) of resting states. A handful of resting state fMRI studies has shown that AVH in schizophrenia may result from disrupted intrinsic functional connectivity of the auditory perception network (Rotarska-Jagiela et al., 2009; Gavrilescu et al., 2010; Vercammen et al., 2010). However, it is currently unknown if intrinsic PT connectivity shows a hemispheric asymmetry (i.e. tighter connections between left PT and other left hemispheric (LH) areas than between right PT and other right hemispheric [RH] areas), and if this intrinsic PT asymmetry is reduced in schizophrenia. Following our knowledge about stronger functional activity in left than in right PT, we may suggest that left PT intrinsic connectivity is stronger than right PT intrinsic connectivity.

A further issue of importance is the potential genetic impact on abnormal intrinsic connectivity in schizophrenia. First-degree relatives of SZ patients have a 5–10% risk to develop the disease compared to

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http://dx.doi.org/10.1016/j.schres.2013.04.024

the general population risk of 1% (Kendler and Gardner, 1997). A number of functional imaging studies using speech tasks showed reduced PT asymmetry in non-clinical carriers of genetic risk of schizophrenia, such as siblings or other family members (Sommer et al., 2004; Whyte et al., 2006; Oertel et al., 2010). In addition, recent resting-state fMRI studies showed changes in functional brain connectivity in relatives in a number of neural networks (Liao et al., 2012; Meda et al., 2012), but it is still unknown if PT or other nodes of the speech network are affected.

In the current study, we therefore investigated the intrinsic functional organization of bilateral PT in schizophrenia patients and first-degree relatives. We hypothesized that SZ patients and first-degree relatives show aberrant functional connectivity strength and asymmetry in distribution of PT connectivity. Decreased asymmetry may indicate altered anatomical distribution without change to function. We further hypothesized that changes in the functional architecture of left and right PT are associated with scores of state (hallucination severity) and trait (hallucination proneness) markers.

2. Methods

2.1. Participants

We included twenty-four schizophrenia patients (SZ) who were all diagnosed with paranoid schizophrenia according to DSM-IV criteria (American Psychiatric Association, 1994) (see Table 1 for demographic parameters). All patients were treated with atypical antipsychotics, and four patients additionally with typical neuroleptic medication at the time of testing (see Table 1). To ensure that the results of our study were not due to a medication effect with typical neuroleptics (Dazzan et al., 2005), we repeated the analysis for group differences on the functional measurements without the four patients with typical medication, and obtained similar results.

We further included twenty-two first-degree relatives (REL) and twenty-four healthy controls (CON) in the experiment (Table 1). Contact to the relatives was established through participating patients, from a support group for relatives of SZ patients, and through local media advertisements. The relatives were requested to provide a letter from the attending psychiatrist confirming the patient's diagnosis. The relatives and control groups were matched to the patient group in age, handedness (assessed using the Edinburgh Inventory (Oldfield, 1971)), sex and education (see Table 1). None of the participants in the control group had any positive family history of schizophrenia (up to second-degree relatives). Exclusion criteria for control and relative participants were any psychiatric disorder including Axis I and Axis II disorders according to DSM-IV, left-handedness, current drug-abuse, neurological pathology and inability to provide informed consent.

All participants were drawn from a previous experiment from our lab in which we assessed anatomical and functional PT asymmetry during active task performance (part of the study participants' results were included in the manuscript by Oertel et al. (2010)). Written informed consent was obtained from all participants individually. Experimental procedures were approved by the ethical board of the medical department of the Johann Wolfgang Goethe-University, Frankfurt, Germany. Auditory analysis by an otologist revealed normal hearing, and a neuroradiologist who did not find underlying pathology in the auditory cortex or surrounding areas. All subjects were native German speakers.

3. Assessment of psychopathology

The German version of the Structured Clinical Interview for DSM-IV (Wittchen et al., 1996) was carried out with the participants of all three groups. All patients also underwent a semi-structured interview with the Positive and Negative Symptom Scale (PANSS, (Kay et al., 1987)) within seven days of the fMRI scan. All patients reported a history of auditory hallucinations (hearing voices). The patients were debriefed by the investigators after the scan to report any hallucination experience during the measurement. None of the patients reported any hallucinations during scanning.

Furthermore, all participants filled out the Revised Hallucination Scale (RHS) self-report questionnaire that screened for the trait predisposition towards hallucinations (Morrison et al., 2002). The questionnaire contains 20 statements about hallucinatory experiences and participants rated the frequency of experiencing the statements on a four-point scale (1 = never; 4 = almost always).

4. Data acquisition and image preprocessing

Functional and anatomical images were acquired on a Siemens Magnetom Allegra 1.5 T MRI system (Siemens Medical Systems, Erlangen, Germany) at the Goethe University Brain Imaging Center, Frankfurt am Main, Germany. Each scanning session began with a resting-state functional measurement (EPI-sequence, 400 volumes,

Table 1
Demographic and illness variables of samples. Continuous variates are presented by mean (SD), nominal variates are presented as frequencies. ANOVAs of variates age and years of (parental) education, and Chi-square test of sex showed no significant differences between the groups. Predisposition to hallucinate (RHS) varied significantly between groups.

	SZ	REL	CON	F/χ^2	P	Post-hoc		
						CON > REL	CON > SZ	REL > SZ
N	24	22	24					
Age (y)	37.9 (7.84)	39.35 (10.75)	40.84(10.23)	3.05	0.78			
Gender (m/f)	12/12	10/12	13/11	0.66	0.88			
Handedness (l/r)	0/24	0/22	0/24	–	–			
Education (y)	15.08 (2.51)	15.10 (4.76)	16.14 (2.98)	2.5	0.93			
Parental education								
Mother (y)	12.87 (2.31)	12.57 (2.18)	12.92 (2.68)	2.13	0.87			
Father (y)	12.95 (2.83)	13.43 (2.98)	13.13 (2.97)	2.45	0.92			
Illness								
Onset (y)	24.12 (5.58)							
Years of illness (y)	13.52 (6.54)							
Medication								
Atypical/typical	21/4							
CZ equivalence (mg/d)	610.42 (387.3)							
PANSS								
Total	63.29 (5.24)							
Positive	15.45 (3.07)							
Negative	15.19 (1.97)							
Hallucination	3.14 (1.23)							
General	32.65 (4.01)							
RHS	33.0 (7.88)	25.67 (1.39)	23.01 (2.98)	28.12	<0.001	<0.01	<0.001	<0.01