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Reduced default mode network connectivity in schizophrenia patients

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ABSTRACT

In the present study, we explored possible alterations in the default mode network (DMN) and its functional connectivity in 41 schizophrenia patients and 42 age-matched healthy controls. Schizophrenia patients displayed reduced activation in the ventromedial prefrontal cortex, left superior temporal gyrus including auditory cortex and temporal pole. Psychophysiological interaction analysis revealed reduced connectivity between left superior temporal gyrus including auditory cortex and the left temporal pole in schizophrenia patients compared to healthy subjects.

1. Introduction

The default mode network (DMN) describes a large-scale functional brain network, which is more active during rest periods compared to cognitively demanding tasks (Raichle et al., 2001). While regions of the DMN are involved in a wide range of psychological functions, such as cognitive control and social evaluation (Broyd et al., 2009), simultaneous activation of the DMN has been hypothesized to mediate intrinsic thought and feeling rather than extrinsic stimulus processing and has thus been associated with processing of self-related information (Mason et al., 2007). It has been proposed that misattributed self-reference may ultimately contribute to the development of positive symptoms in schizophrenia (van der Meer et al., 2010; Pankow et al., 2012).

There are several studies reporting alterations in DMN activity in schizophrenia patients (for review see Broyd et al., 2009). These studies differ in task design and methodological analysis strategies. For example, DMN activation was assessed during task-interleaved resting periods (taken from blocked designs) or during resting-state using functional magnetic resonance imaging (fMRI, Whitfield-Gabrieli and Ford, 2012). A recent meta-analysis reported reduced resting-state connectivity of medial prefrontal and temporal regions in schizophrenia and suggested that these findings are to be linked to disturbed self-reference processing (Kuhn and Gallinat, 2013).

In the present study, we compared a rest period versus a working memory challenge during fMRI to explore possible alterations in the DMN and its functional connectivity in schizophrenia patients.

2. Methods and material

2.1. Subjects

The study included 41 schizophrenia patients (SZ; ICD-10 and DSM IV; 10 females and 31 males) treated with antipsychotics and 42 age-matched healthy controls (HC; 19 females and 23 males). Based on SCID interviews, patients had no other psychiatric axis I disorder (SCID, First et al., 2001). Healthy controls had no psychiatric disorder (SCID, First et al., 2001). The sample was previously published with a focus on working memory dependent effective connectivity (Deserno et al., 2012) and its application to classification and clustering of psychiatric spectrum diseases (Brodersen et al., 2013). For a detailed group description see Supplementary Table S1.

2.2. FMRI data acquisition

Imaging was performed on a 1.5 T Scanner (Magnetom Vision Siemens®) with an Echo Planar Imaging (EPI)-sequence (TR = 2600 ms, TE = 40 ms, flip $\alpha = 90°$, matrix = 64×64, voxel size =

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4 mm × 4 mm × 5.5 mm). Head movement was minimized by using a vacuum pad. Twenty-four slices approximately parallel to the bicommissural plane were collected, covering the whole brain. Twenty fMRI volumes were acquired per block: twelve during stimulation and eight during the resting period.

2.3. FMRI paradigm

The participants performed a numeric n-back working memory task as used in previous studies (Schlagenhauf et al., 2008). The task contains the '0-back' condition, where the participants had to respond with a button press each time they saw the number zero. In the '2-back' condition the participants had to press a button when the number presented in the current trial equaled the number presented two trials before. During the rest period, the participants were instructed to fixate a cross in the center of the screen. Each block consisted of 22 stimuli containing three targets and was indicated by an instruction cue displayed for 2 s before each block. The stimuli were presented for 500 ms with an intertrial interval of 900 ms. The rest period between the blocks lasted 20.8 s. Stimulation and resting periods alternated within the experiment with a total of six '2-back'- six '0-back'- and 6 'rest'-periods.

2.4. FMRI data analysis

Functional data were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Images were motion corrected, normalized to the standard EPI template provided by the Montreal Neurological Institute (MNI), and spatially smoothed with an 8 mm Gaussian kernel.

At the first level, 'rest'-, '2-back'- and '0-back'-periods were modeled as well as the instruction cue. Realignment parameters were added as nuisance regressors to the design matrix. At the second level, group comparison between schizophrenia patients and healthy control subjects were conducted using a two-sample t-test for the contrast images 'rest > 2-back' at $p < 0.05$ FWE-corrected for the whole brain (see Table 1).

2.5. Psychophysiological interaction

The psychophysiological interaction approach (PPI, Gitelman et al., 2003) was used to assess connectivity differences between regions which displayed group differences. Based on theoretical work (Northoff and Qin, 2011; Whitfield-Gabrieli and Ford, 2012) and the observed group difference in this study, the left superior temporal gyrus including auditory cortex was defined as the seed region. Individual time-series were extracted at peak coordinates of the group difference in the left superior temporal gyrus for the contrast 'rest > 2-back' (-54/-8/6). For the PPI analysis, time series were deconvolved within a Bayesian framework to generate the neural signal. For each subject, a first-level statistical model was estimated, which included the individual's time series of the seed region, the psychological variable ('rest' vs. '2-back'), and the reconvolved interaction term. The other task conditions ('0-back', '2-back' and cue) were also modeled. Between group differences for the contrast images of the interaction term were tested using a two-sample t-test.

Based on the a-priori hypothesis, small volume correction was used. Based on previous studies (Andrews-Hanna et al., 2010; Alonso-Solis et al., 2012) the temporal pole is a region of the DMN and plays a pivotal role in self-reference processing (Pauly et al., 2013). The results of the PPI were corrected for a 20 mm sphere around the peak of the group difference in the temporal pole (-38/16/-34).

3. Results

3.1. FMRI data

Across all the participants, 'rest > 2-back' revealed the activation in the typical default mode network, containing medial prefrontal cortex and posterior cingulate as well as temporal regions (Fig. 1A, Table 1). Reduced activation in schizophrenia patients compared to controls was present in the ventromedial prefrontal cortex (2/44/-26), left superior temporal gyrus including auditory cortex (-54/-8/6) and temporal pole (-38/16/-34) (Fig. 1B, Table 1).

3.2. Psychophysiological interaction

Healthy controls showed stronger rest-related connectivity in comparison to schizophrenia patients between left superior temporal gyrus and the left temporal pole (-26/24/-30, $t = 3.86$, $p = 0.022$) (Fig. 1C, Table 1).

Table 1
Peak coordinates of all participants taken together and comparison between the two groups (HC > SZ) for the contras 'rest > 2-back' reported at $p < 0.05$ FWE corrected for the whole brain (peak and cluster-level). Results of the psychophysiological interaction for 'rest > 2-back' (HC > SZ) are corrected for 20 mm sphere around group difference peak in temporal pole (-38/16/-34).

Anatomical region	Cluster size	MNI-coordinates			R/L	Peak-level		Cluster-level
		x	y	z		T	$p_{FWE\text{-}corrected}$	$p_{FWE\text{-}corrected}$
All 'rest > 2-back'								
Ventromedial prefrontal cortex	101	2	36	−22	R	7.49	<0.001	<0.001
Superior medial gyrus	33	−6	60	30	L	6.16	<0.001	<0.001
Middle cingulate cortex	63	−2	−28	46	L	6.87	<0.001	<0.001
Posterior cingulate	145	−6	−56	6	L	8.18	<0.001	<0.001
Middle/superior temporal gyrus	82	−62	−68	22	L	8.58	<0.001	<0.001
Middle temporal gyrus	16	58	−72	22	R	5.89	≤0.001	≤0.001
Middle temporal gyrus	9	−58	−4	−22	L	5.27	0.009	0.004
Middle temporal gyrus	7	62	0	−22	R	5.19	0.012	0.006
Temporal pole	3	30	20	−38	R	5.47	0.004	0.015
Temporal pole	1	−30	16	−42	L	4.86	0.035	0.028
Superior occipital gyrus	5	−18	−96	42	L	5.03	0.020	0.009
Lingual gyrus	2	14	−68	−6	R	4.90	0.031	0.020
HC > SZ 'rest > 2-back'								
Ventromedial prefrontal cortex	32	−2	44	−26	L	4.82	0.041	0.232
Middle/superior temporal gyrus	148	−54	−8	6	L	5.38	0.006	0.002
Temporal pole	74	−38	16	−34	L	4.62	0.075	0.035
PPI, HC > SZ								
Temporal pole	2	−26	24	−30	L	3.86	0.022	0.073