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Resting-state theta-band connectivity and verbal memory in schizophrenia and in the high-risk state

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ABSTRACT

Background: Disturbed functional connectivity is assumed to underlie neurocognitive deficits in patients with schizophrenia. As neurocognitive deficits are already present in the high-risk state, identification of the neural networks involved in this core feature of schizophrenia is essential to our understanding of the disorder. Resting-state studies enable such investigations, while at the same time avoiding the known confounder of impaired task performance in patients. The aim of the present study was to investigate EEG resting-state connectivity in high-risk individuals (HR) compared to first episode patients with schizophrenia (SZ) and to healthy controls (HC), and its association with cognitive deficits.
Methods: 64-channel resting-state EEG recordings (eyes closed) were obtained for 28 HR, 19 stable SZ, and 23 HC, matched for age, education, and parental education. The imaginary coherence-based multivariate interaction measure (MIM) was used as a measure of connectivity across 80 cortical regions and six frequency bands. Mean connectivity at each region was compared across groups using the non-parametric randomization approach. Additionally, the network-based statistic was applied to identify affected networks in patients.
Results: SZ displayed increased theta-band resting-state MIM connectivity across midline, sensorimotor, orbitofrontal regions and the left temporoparietal junction. HR displayed intermediate theta-band connectivity patterns that did not differ from either SZ or HC. Mean theta-band connectivity within the above network partially mediated verbal memory deficits in SZ and HR.
Conclusions: Aberrant theta-band connectivity may represent a trait characteristic of schizophrenia associated with neurocognitive deficits. As such, it might constitute a promising target for novel treatment applications.

1. Introduction

Since the introduction of the concept of schizophrenia as a disorder of disturbed communication across neural networks (Andreasen et al., 1998; Friston, 1999), several studies have confirmed alterations in brain functional connectivity in patients with schizophrenia (Liemburg et al., 2012; Lui et al., 2010; Woodward et al., 2011), mainly affecting connections between frontal and more posterior areas (Pettersson-Yeo et al., 2011).

Connectivity disturbances have been consistently associated with deficient performance in a variety of cognitive domains (Dauvermann et al., 2014), which represents a core feature of schizophrenia (Heinrichs and Zakzanis, 1998). Such neurocognitive deficits are already present in individuals at high risk for the disorder (Agnew-Blais and Seidman, 2013; Bora and Murray, 2013). More importantly, they have been suggested to be more severe in high-risk individuals who will later develop a psychotic disorder compared to those who will not (De Herdt et al., 2013). Identification of the neural networks involved in this core component of schizophrenia might help clarify the pathophysiological mechanisms that eventually lead to emergence of psychotic symptoms, and promote the development of interventions aiming to prevent transition into a chronic and difficult-to-treat disorder.

Most earlier studies of connectivity in schizophrenia focused on task-related connectivity indices. However, it has been shown that spontaneous, "resting-state" activity of the brain also displays discrete spatiotemporal organization patterns that carry specific functional significance (Damoiseaux et al., 2006; Engel et al., 2001, 2013; Friston, 2005). Furthermore, as spontaneous brain activity influences the processing of incoming stimuli (Britz et al., 2009; Deco and Corbetta, 2011; Hipp et al., 2011), investigation of the resting-state allows a view into the underpinnings of cognitive and perceptual disturbances in schizophrenia while at the same time avoiding the known confounder of impaired task performance in patients. As a result, more recent

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studies on connectivity in schizophrenia and in the high-risk state have increasingly focused on the interactions within and between resting-state brain networks. Overall, the findings of these studies indicate complex dysconnectivity patterns in patients and high-risk individuals, where interactions of a brain area with others might be reduced or increased depending on the network studied (Allen et al., 2010; Guo et al., 2014; Liemburg et al., 2012; Lord et al., 2011; Manoliu et al., 2014; Shim et al., 2010).

All of the aforementioned studies of resting-state connectivity have employed functional magnetic resonance imaging (fMRI). A shortcoming of fMRI-based measures is that, due to their low time resolution, they cannot capture the fast dynamics of neuronal interactions, which occur on a millisecond time-scale (Uhlhaas, 2013). These dynamics involve neuronal oscillations across a broad frequency range, which appear to correspond in a frequency-specific manner to different spatial network configurations (Hillebrand et al., 2012; Hipp et al., 2012; Marzetti et al., 2013) and different aspects of stimulus processing (Leicht et al., 2013; Marco-Pallares et al., 2008). MEG and EEG provide the opportunity to study the spectral structure of neuronal activity with excellent temporal resolution and thus to characterize brain network properties in considerably greater detail compared to fMRI. Indeed, emerging evidence suggests that certain EEG connectivity measures, notably those based on phase correlations among signals, might reveal coupling patterns that are not captured by fMRI (Engel et al., 2013).

Several studies have reported various EEG/MEG scalp-level connectivity abnormalities in schizophrenia, with results indicating reduced phase synchronization in the beta and gamma frequency range (Kam et al., 2013; Kikuchi et al., 2011; Uhlhaas and Singer, 2010), but increased connectivity in lower frequency bands (Kam et al., 2013), in patients compared to healthy controls. However, scalp-level analyses are limited in their usefulness for drawing inferences regarding the underlying sources of electrical activity in the brain, due to known methodological problems associated with reference electrode placement and volume conduction. So far, few studies have assessed EEG/MEG connectivity at the source level in schizophrenia. In the gamma-band range, reduced task-related (Mulert et al., 2004), but intact resting-state connectivity has been reported (Rutter et al., 2013). In the lower frequencies, one study (Hinkley et al., 2011) reported a complex pattern that included region-specific increases and decreases of alpha-band connectivity in patients, whereas another study (Lehmann et al., 2014) observed decreased connectivity in the alpha-band, and increased connectivity in the delta/theta band, in patients. Clearly, more work is needed until these results can be integrated into a coherent account of connectivity disturbances in schizophrenia. Critically, so far there is very little information on the networks affected at different frequency ranges, and whether abnormalities are present before illness onset.

The aim of the present study was to evaluate EEG resting-state source-level connectivity across a wide range of frequencies in high-risk individuals compared to first-episode patients with schizophrenia and healthy controls. A second aim was to investigate to what extent resting-state connectivity disturbances contribute to the cognitive deficits that characterize schizophrenia and the high-risk state. An important consideration when investigating EEG/MEG connectivity is that measures of brain interaction may be distorted by signal mixing due to volume conduction and, for EEG, to the use of a common reference (Hipp et al., 2012; Nolte et al., 2004; Stam et al., 2007). Therefore, for the present study we used a multivariate interaction measure that maximizes both invariance with respect to volume spread and the detection of true neuronal interactions (Ewald et al., 2012).

2. Materials and methods

The present study was part of a larger ongoing project investigating resting-state and task-related brain connectivity in schizophrenia by means of EEG, MEG, and simultaneous EEG–fMRI. Participant samples consisted of 28 individuals at high-risk for psychosis (HR), 19 patients with first-episode schizophrenia (SZ), and 23 healthy controls (overlapping with previous publications; Andreou et al., 2014, in press). Only first-episode patients were included in the SZ group, in order to avoid confounds related to chronicity and long-term antipsychotic drug treatment. Moreover, only stable SZ were included in analyses, in order to adequately discriminate trait effects from those of specific acute symptoms.

SZ and HR individuals were recruited through the Psychosis Center of the Department of Psychiatry of the University Medical Center Hamburg-Eppendorf. Exclusion criteria for all participants were current substance abuse or dependence, and presence of major somatic or neurological disorders. For healthy control subjects, additional exclusion criteria were any previous psychiatric disorder or treatment, and a family history of psychotic disorders. Inclusion/exclusion criteria were assessed with a semi-structured interview conducted by a clinical psychiatrist or trainee with at least 4 years of clinical experience. The study was conducted in accordance with the Declaration of Helsinki; all participants were required to sign an informed consent form prior to entering the study.

First-episode status was defined as having received the first diagnosis and psychiatric treatment less than a year prior to study participation, *and* presence of psychotic symptoms in any form for no more than five years. SZ patients were either (a) stable outpatients (defined as no change in antipsychotic treatment in the past two months) or (b) stabilized inpatients after antipsychotic treatment of at least 6-weeks' duration, shortly before discharge.

The high-risk state was defined according to criteria of the Early Detection and Intervention program of the German Research Network on Schizophrenia (GRNS) (Wolwer et al., 2006). These include (a) basic symptoms, defined as the presence of at least two subjective cognitive or perceptual disturbances with a score of ≥ 3 on the Schizophrenia Proneness Instrument (Schultze-Lutter et al., 2007); (b) presence of either a positive family history for psychotic disorders or schizotypal personality disorder, plus decline of at least 30% in the Global Assessment of Functioning scale (APA, 2000); (c) presence of attenuated positive symptoms or brief, limited and intermittent psychotic symptoms, as assessed with the Structured Interview for Prodromal Syndromes and the Scale of Prodromal Symptoms (Miller et al., 2003). In the present study, the above criteria were fulfilled in $n = 10$, $n = 3$ and $n = 23$ HR subjects, respectively (please note that more than one criterion might apply to the same subject). Demographic characteristics of the three groups, and clinical characteristics of SZ and HR groups, are presented in Table 1.

Diagnosis of schizophrenia in patients was established with the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Severity of clinical symptomatology was assessed with the Positive and Negative Syndrome Scale (Kay et al., 1987). Subjects also underwent neuropsychological testing with an extensive battery that included tests of memory, attention, and executive functioning (see Supplementary Material for a complete list of the tasks). Neurocognitive performance data were available for 20 HC, 17 SZ and 26 HR.

2.1. EEG recording and analyses

A detailed account of EEG recording, electrode placement and computation methods is provided in the Supplementary Material. Recordings took place in a sound-attenuated and electrically shielded room. Continuous EEG activity was recorded while subjects were seated comfortably with their eyes closed. Participants were monitored for electroencephalographic signs of drowsiness (Hegerl et al., 2008) for the whole duration of the recording (5 to 10 min). Recordings were conducted at a sampling rate of 1000 Hz with 64 Ag/AgCl electrodes mounted on an elastic cap (ActiCaps, Brain Products, Munich, Germany), using the Brain Vision Recorder software version 1.10 (Brain Products, Munich,

Table 1
Clinical and demographic characteristics of the three participant groups.

	Healthy controls		Schizophrenia		High-risk		F/χ2	p	post-hoc
	N		*N*		*N*				
Gender (m/f)	18/5		17/2		16/12		8.071	**0.02**	(f) HR > SZ
Comorbid psychiatric diagnoses[a]	–		13		21				
Depressive disorders			2		11				
Anxiety disorders			–		8				
Substance related disorders[b]			11		6				
Personality disorders			1		4				
Antipsychotic medication	–		16		7				
Aripiprazole			2		3				
Amisulpride			1		–				
Olanzapine			4		2				
Paliperidone			3		–				
Risperidone			4		–				
Quetiapine			2		2				
Antidepressants	–		6		5				
Benzodiazepines/anticholinergic agents	–		–		–				
	Mean	*(SD)*	*Mean*	*(SD)*	*Mean*	*(SD)*			
Age	24.95	(5.4)	23.53	(4.3)	23.13	(4.1)	0.944	0.40	
Years of education	15.33	(2.9)	13.66	(3.3)	13.69	(3.0)	2.056	0.14	
Years of parental education	14.30	(3.5)	13.61	(3.0)	14.04	(2.6)	0.200	0.82	
PANSS scores									
Total	–		54.88	(16.5)	51.36	(14.2)	0.331	0.57	
Positive	–		13.67	(6.5)	12.48	(3.9)	0.497	0.49	
Negative	–		14.07	(5.2)	11.87	(4.0)	2.175	0.15	
Disorganization	–		14.80	(3.9)	14.22	(4.3)	0.178	0.68	
Excitement	–		13.40	(4.7)	11.13	(3.4)	2.942	0.10	
Antipsychotic medication dose[c]	–		239.59	(182.4)	297.6	(327.5)			
Distress	–		17.47	(6.6)	16.04	(6.0)	0.477	0.49	
VLMT learning score	77.00	(6.6)	59.00	(9.5)	66.15	(13.4)	12.169	<**0.001**	HC > SZ = HR
VLMT delayed recall	14.15	(1.5)	10.53	(3.0)	12.37	(2.5)	10.424	<**0.001**	HC > HR > SZ
WLM immediate recall	34.50	(7.9)	23.47	(7.4)	27.17	(10.2)	8.093	**0.001**	HC > SZ = HR
WLM delayed recall	31.53	(9.0)	19.35	(9.9)	24.48	(9.4)	8.167	**0.001**	HC > SZ = HR
TMT-A (sec)	19.66	(6.3)	24.18	(7.0)	26.82	(9.1)	4.968	**0.01**	HC < SZ = HR
TMT-B (sec)	50.73	(18.4)	60.41	(21.7)	59.85	(22.9)	2.000	0.14	
Digit span forward	8.30	(1.7)	7.47	(1.9)	8.26	(1.8)	1.500	0.23	
Digit span backward	7.15	(1.7)	5.93	(1.7)	6.41	(1.7)	2.758	0.07	
Letter–number sequencing	16.20	(3.0)	15.13	(2.9)	14.59	(3.7)	1.427	0.24	
Digit symbol	66.10	(7.3)	51.82	(8.6)	58.89	(10.4)	12.938	<**0.001**	HC > HR > SZ
Letter fluency	44.82	(11.9)	38.56	(11.5)	47.93	(9.8)	2.345	0.11	

HC = healthy controls; HR = high-risk individuals; SZ = first-episode schizophrenia patients; VLMT = Verbal Learning and Memory Test; WLM = Wechsler Logical Memory; TMT-A/B = Trail Making Test, Parts A/B.
[a] More than one diagnosis per subject possible.
[b] All subjects currently abstinent.
[c] In chlorpromazine equivalents; only patients receiving antipsychotic medication were considered in the calculation of mean antipsychotic medication dose.

Germany). Eye movements were recorded with four EOG channels. Electrode impedance was always kept below 5 kΩ.

Offline preprocessing was performed with Analyzer 2.0 (Brain Products GmbH). A 0.1–70 Hz Butterworth zero-phase bandpass filter (12 dB/octave) was applied. Ocular and prominent muscle artifacts were removed by means of independent component analysis (ICA). Subsequently, the recording was divided into 2-s epochs, which were visually inspected for artifacts, recomputed against the average reference and down-sampled to 256 Hz.

All further analyses were performed in Matlab (Mathworks) using custom-made scripts. Spectral estimates were derived in successive temporal windows with 75% overlap, the length of which varied from 0.125 to 0.5 s depending on the center frequency of the wavelet such as to result in a frequency resolution of 2 Hz for the delta and theta frequency bands, 4 Hz for alpha to high beta, and 8 Hz for the gamma frequency band. The center frequencies of the wavelet were set at 3, 6, 10, 16, 25 and 40 Hz for the delta, theta, alpha, low-beta, high-beta, and gamma frequency range, respectively.

The intracortical sources of brain electrical activity were localized using exact low-resolution electromagnetic tomography (eLORETA) (Pascual-Marqui et al., 2011). Head surface EEG data were recomputed into 80 source model time series, corresponding to the centers of all cortical and hippocampal regions of the AAL atlas (40 for each hemisphere, see Table 2 for coordinates of each point). Thus, connectivity analyses were based on ($80 * 79/2 =$) 3160 pairs of sources distributed throughout the cortex, sufficient for obtaining detailed estimates of connectivity within the constraints posed by the limited spatial resolution of EEG.

As mentioned in the Introduction, EEG connectivity assessments may be distorted by signal mixing. This problem is usually addressed by excluding zero-lag interactions from connectivity analyses, based on the notion that volume conduction occurs instantaneously, while true interactions occur at variable time delays (Hipp et al., 2012; Nolte et al., 2004; Stam et al., 2007). Most of these methods are bivariate; however, one must take account that, unless source orientations are fixed (e.g., by maximizing power), data at the source level are 3-dimensional for each grid point, corresponding to three source orientations. Multivariate methods robust to volume conduction artifacts have been introduced by Pascual-Marqui (2007) and Ewald et al. (2012) to address this problem. In the present study, we used the multivariate interaction measure (MIM) proposed by the latter (Ewald et al., 2012). MIM takes into account the possibility that, due to the low spatial resolution of EEG, estimated activity at a given grid point reflects neural activation not just of that point, but also of its vicinity, which may contain activated neuronal groups that have different orientations (please see Supplementary Material for details).

Table 2
Coordinates of the 80 cortical points used for connectivity analyses.

	Left hemisphere			Right hemisphere		
	x	*y*	*z*	*x*	*y*	*z*
Medial orbitofrontal cortex	−5	55	−5	5	50	−5
Middle orbitofrontal cortex	−30	50	−10	30	55	−10
Superior frontal gyrus, medial part	−5	50	30	10	50	30
Superior frontal gyrus, orbital part	−20	50	−15	15	50	−15
Anterior cingulate cortex	−5	35	15	5	35	15
Middle frontal gyrus	−35	35	35	35	35	35
Superior frontal gyrus	−20	35	40	20	30	45
Gyrus rectus	−5	35	−20	5	35	−20
Inferior frontal gyrus, orbital part	−35	30	−10	40	30	−10
Inferior frontal gyrus, pars triangularis	−45	30	15	45	30	15
Inferior frontal operculum	−50	15	20	50	15	20
Olfactory gyrus	−5	15	−10	5	15	−10
Temporal pole, middle temporal gyrus	−35	15	−35	45	15	−30
Temporal pole, superior temporal gyrus	−40	15	−20	45	15	−15
Insula	−40	10	0	40	10	0
Supplementary motor area	−5	5	60	10	0	60
Precentral gyrus	−40	−5	50	40	−10	50
Rolandic operculum	−50	−10	15	50	−5	15
Middle cingulate cortex	−5	−15	40	5	−10	40
Parahippocampal gyrus	−20	−15	−20	20	−15	−20
Heschl gyrus	−45	−20	10	45	−15	10
Hippocampus	−25	−20	−10	25	−20	−10
Superior temporal gyrus	−55	−20	5	55	−20	5
Paracentral lobule	−5	−25	70	5	−30	70
Postcentral gyrus	−45	−25	50	40	−25	55
Inferior temporal gyrus	−50	−30	−25	55	−30	−20
Supramarginal gyrus	−55	−35	30	55	−30	35
Middle temporal gyrus	−55	−35	0	55	−35	0
Fusiform gyrus	−30	−40	−20	35	−40	−20
Posterior cingulate cortex	−5	−45	25	5	−45	20
Inferior parietal lobule	−45	−45	45	45	−45	50
Precuneus	−10	−55	50	10	−55	45
Superior parietal lobule	−25	−60	60	25	−60	60
Angular gyrus	−45	−65	40	40	−60	40
Lingual gyrus	−15	−70	−5	15	−65	−5
Calcarine sulcus	−10	−80	10	15	−75	10
Cuneus	−5	−80	25	15	−80	30
Inferior occipital gyrus	−35	−80	−10	35	−80	−10
Middle occipital gyrus	−30	−80	15	35	−85	20
Superior occipital gyrus	−20	−85	30	20	−80	30

2.2. Statistical analyses

Differences in scalp oscillatory power between Groups were assessed with a 2 (Group) × 6 (frequency band) mixed ANOVA with Group as the between-subjects factor.

Functional connectivity comparisons were conducted separately for each frequency of interest. Mean connectivity was estimated at each grid point by averaging its MIM values to all other points across the source space. The nonparametric randomization approach (Nichols and Holmes, 2002) was used to estimate critical probability thresholds for mean MIM difference score across groups, corrected for multiple comparisons (80 grid-points). Because group comparisons were conducted in a pairwise manner, Bonferroni-adjusted significance values are reported (correction for three pairwise comparisons: HC vs. SZ, HC vs. HR, SZ vs. HR).

The above analyses should identify regions that display connectivity differences between groups, but they do not allow inferences as to what these regions interact with, i.e. which networks are affected. Therefore, significant results obtained with the above single grid-point analyses were followed up with the network-based-statistic (NBS) introduced by Zalesky et al. (2010), which corresponds to an application of cluster-based thresholding of statistical parametric maps (Bullmore et al., 1999; Nichols and Holmes, 2002) to the graph model. NBS analyses were conducted using the open-source toolbox NBS Connectome v1.2 (http://www.nitrc.org/projects/nbs).

For networks displaying significant differences between any two groups, mean connectivity within the network was calculated by averaging connectivity values across all network connections ('edges') in the respective frequency band. The association between these resting-state connectivity indices and cognitive performance was investigated with the following procedure: The number of cognitive variables was reduced with factor analysis. The scores for each of the resulting three factors (verbal memory, attention/processing speed, and working memory/executive functioning, see Table S1) were compared between groups with one-way ANOVAs followed by pairwise post-hoc tests (Bonferroni correction), and were used in subsequent correlational analyses (Pearson's r). Significant correlations were followed up by mediation analyses that assessed whether connectivity disturbances mediated differences in cognitive performance. Factor analyses and correlation analyses were carried out with SPSS 21.0; for mediation analyses, the PROCESS macro for SPSS was used (Hayes, 2012). The association between functional connectivity and symptoms was not investigated, because of the very low symptom load in the clinical groups (see Table 1).

A comprehensive account of the nonparametric randomization approach and the NBS statistic, as well as details of the factor analytical procedure, are provided in Supplementary Material.

3. Results

The three groups did not differ in age, education or parental education. Because of differences in gender ratio (there were more female participants in the HR than in the SZ group, see Table 1), gender was initially included in all analyses reported below. However, as this variable did not have any significant main effects or interactions with group in any of the analyses, it was dropped and results are reported without its inclusion.

The number of artifact-free epochs did not significantly differ between groups [HC: 212.6 ± 52.3; SZ: 212.7 ± 52.3; HR: 223.0 ± 60.1, $F(2,67) = 0.286$ $p = .75$]. The main effect of group on scalp oscillatory power was not significant [$F(2,67) = 0.690$, $p = 0.54$]. The group × frequency band interaction also missed significance in the overall ANOVA [$F(10,149.001) = 1.608$, $p = 0.17$] (Fig. S1); however, there was a trend for patients with schizophrenia to display increased theta scalp oscillatory power compared to healthy controls (Bonferroni-corrected $p = 0.10$).

3.1. Connectivity differences between groups

Significant differences in mean connectivity between patients and controls were observed only in the theta frequency band, and involved grid points belonging to bilateral somatosensory and motor areas close to the midline (left paracentral lobule, left precentral gyrus, and bilateral postcentral gyrus and supplementary motor area). All of these areas exhibited higher mean MIM in SZ compared to healthy controls (maximum difference 0.038, corr. $p = 0.01$), while HR subjects did not differ from either SZ patients or healthy controls (both $p > 0.90$). No differences emerged in any of the other frequency bands (all $p > 0.18$).

Following-up the significant result in the theta frequency band, NBS revealed a network displaying increased connectivity in SZ compared to healthy controls (threshold $t = 2.67$, corr. $p = 0.035$). This network comprised 40 connections involving mainly bilateral orbitofrontal, medial frontal areas, and posterior midline regions, as well as sensorimotor areas and the temporoparietal junction in the left hemisphere (Table 3, Fig. 1). There were no significant differences between HR and either SZ or controls. Mean connectivity values within the above network are displayed in Fig. 2, where it can be seen that SZ exhibited significantly higher values than healthy controls, while HR displayed intermediate values that did not differ from either SZ or healthy controls. These results remained essentially unchanged when medication (chlorpromazine equivalent dose) was included as a covariate in the analyses.

Table 3
Brain regions comprising the network of increased theta connectivity in patients compared to controls, sorted according to their degree (number of connections) within the network.

Region	Hemisphere	Degree
Postcentral gyrus	Left	15
Precentral gyrus	Left	10
Medial obitofrontal gyrus	Left	6
Angular gyrus	Left	4
Cuneus	Left	4
Inferior frontal gyrus, pars triangularis	Left	3
Superior frontal gyrus, orbital part	Left	3
Inferior parietal gyrus	Left	3
Inferior frontal gyrus, pars opercularis	Right	2
Middle frontal gyrus, orbital part	Left	2
Supplementary motor area	Left	2
Calcarine sulcus	Left	1
Cuneus	Right	1
Inferior frontal gyrus, orbital part	Left	1
Inferior frontal gyrus, orbital part	Right	1
Inferior frontal gyrus, pars triangularis	Right	1
Medial orbitofrontal gyrus	Right	1
Superior Frontal gyrus, orbital part	Right	1
Heschl gyrus	Left	1
Insula	Left	1
Insula	Right	1
Middle occipital gyrus	Left	1
Superior occipital gyrus	Right	1
Olfactory gyrus	Left	1
Olfactory gyrus	Right	1
Paracentral gyrus	Left	1
Paracentral gyrus	Right	1
Superior parietal gyrus	Right	1
Precuneus	Left	1
Gyrus rectus	Left	1
Gyrus rectus	Right	1
Rolandic operculum	Left	1
Rolandic operculum	Right	1
Supplementary motor area	Right	1
Supramarginal gyrus	Left	1
Middle temporal gyrus	Left	1

3.2. Associations with cognitive performance

Verbal memory significantly differed between the three groups [$F(2,60) = 11.393$, $p < 0.001$], with healthy controls performing significantly better than SZ ($p < 0.001$) and HR ($p = 0.02$), who differed from each other only marginally ($p = 0.07$). There was also a significant difference in attention/processing speed scores in the overall ANOVA [$F(2,60) = 3.815$, $p = 0.03$]; the only significant post-hoc comparison was the one between healthy controls and HR ($p = 0.03$). The third cognitive factor (working memory/executive functioning) was not significantly different between groups.

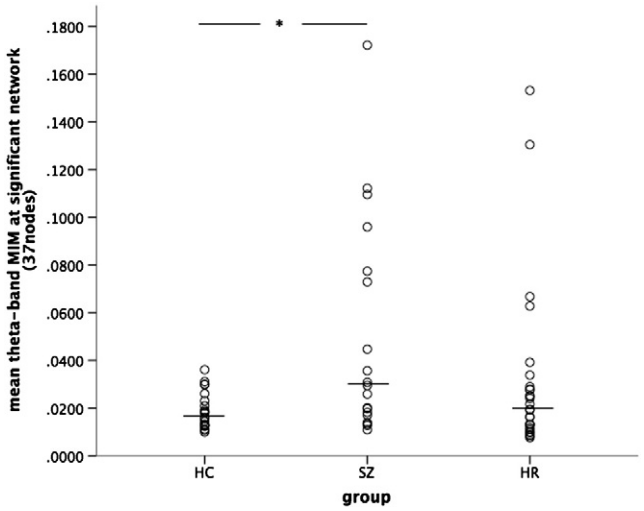

Fig. 2. Mean theta-band connectivity across the 37-node network in stable patients with schizophrenia (SZ), high-risk individuals (HR) and healthy controls (HC). The horizontal lines represent group means. *$p = 0.01$ (Bonferroni-corrected).

Mean connectivity within the above 40-edge theta-band network (log-transformed due to significant positive skew) was significantly correlated with the verbal memory factor ($r = 0.434$, $p < 0.001$). The direction of the correlation was negative, i.e. increased connectivity was associated with worse cognitive performance (Fig. 3). Controlling for chlorpromazine equivalent dose did not affect the direction or significance of these correlations.

As there were no significant differences between HR and SZ or controls in mean theta-band connectivity in the network in question (which would be a prerequisite for meaningful mediation analyses across all three groups), the HR group was clustered together with SZ for mediation analyses. Mean theta-band connectivity (log-transformed) within the 40-edge network significantly mediated differences between healthy controls and HR/SZ in verbal memory ($b = 0.19$, 95% bootstrap CI [0.04, 0.46]); the size of this effect was in the lower medium range ($\kappa^2 = 0.089$, 95% bootstrap CI [0.02,0.21]).

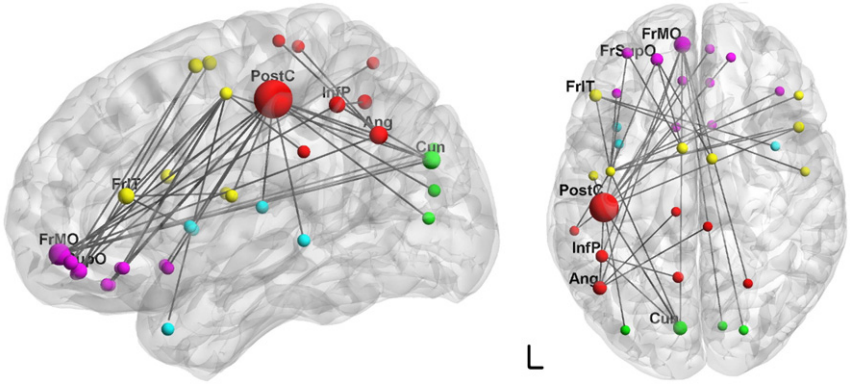

Fig. 1. Network of increased resting-state theta-band connectivity in stable SZ compared to HC. The size of each node represents its number of connections within the network (degree). Labels are provided for nodes with at least 3 connections. As shown in Table 3, these nodes are involved in more than 70% of total interactions within the network. Abbreviations: Ang = Angular gyrus; Cun = Cuneus; FrIT = Inferior frontal gyrus, pars triangularis; FrMO = Medial orbitofrontal gyrus; FSupO = Superior frontal gyrus, orbital part; InfP = Inferior parietal gyrus; PostC = Postcentral gyrus. Color coding: Inferior frontal and orbitofrontal cortex = pink; Lateral frontal cortex = yellow; Temporal cortex and insula = light blue; Parietal cortex = red; Occipital cortex = green. The figure was created using BrainNet Viewer (http://www.nitrc.org/projects/bnv/).

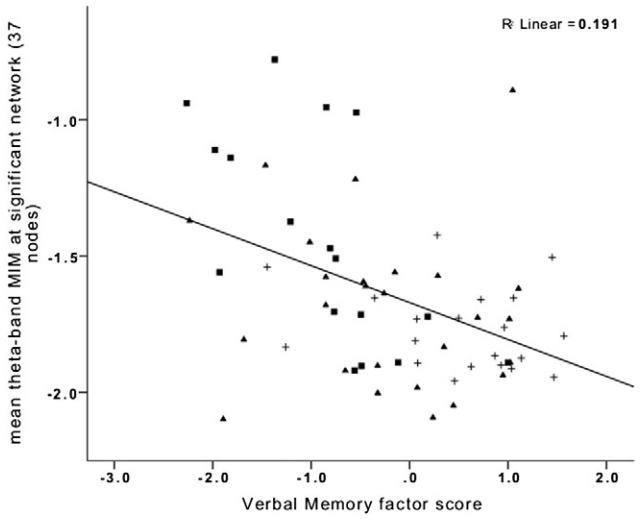

Fig. 3. Correlations between mean theta-band connectivity across the 37-node network and verbal memory factor score across groups (SZ = squares; HR = triangles; HC = crosses).

4. Discussion

The main finding of the present study was aberrant theta-band resting-state connectivity in SZ, while HR displayed intermediate connectivity patterns that did not differ from either patients or healthy controls. Increased theta-band connectivity was noted between midline, sensorimotor, orbitofrontal regions and the left temporoparietal junction. Mean connectivity within this network partially mediated verbal memory deficits in SZ and HR.

Deficits in verbal memory are known to exist long before the onset of schizophrenia (Agnew-Blais and Seidman, 2013; Bora and Murray, 2013), and have been suggested to be among the most sensitive predictors of future conversion into psychosis (Erlenmeyer-Kimling et al., 2000; Johnstone et al., 2005; Lencz et al., 2006; Lin et al., 2011; Pukrop et al., 2007; Riecher-Rossler et al., 2009; Seidman et al., 2006; Woodberry et al., 2013). So far, these deficits have been mainly investigated in connection with hippocampal damage. Indeed, hippocampal volume reductions are a consistent finding in patients with schizophrenia and in individuals at clinical or genetic high risk for the disorder (Francis et al., 2013; Walter et al., 2012; Witthaus et al., 2010; Wood et al., 2010), and have been reported to correlate with verbal memory deficits in high-risk individuals (Francis et al., 2013). However, findings regarding the association of hippocampal pathology with transition into psychosis have been inconsistent so far (Witthaus et al., 2010; Wood et al., 2010).

The present study provides an alternative, or an additional, possible pathophysiological mechanism for the emergence of verbal memory deficits: Increased resting-state theta-band connectivity within a widely distributed cortical network was associated with worse memory performance in patients and high-risk subjects. This finding is consistent with previous research implicating theta-band oscillations in neurocognitive deficits (Wichniak et al., 2014) or cognitive fatigue (Barwick et al., 2012) in general, and in mnemonic operations in particular: Successful memory encoding has been associated with changes in theta-band oscillatory power along a specific time course (Guderian et al., 2009; Long et al., 2014; Osipova et al., 2006; Sederberg et al., 2006), and theta-band oscillations are sensitive to factors affecting memory performance such as processing depth, contextual manipulations and cognitive load (Guderian et al., 2009; Hanslmayr and Staudigl, 2014; Sederberg et al., 2006). Moreover, it has been suggested that mnemonic operations might be dependent on precise modulations of theta-band synchronization within widely distributed brain networks (Burke et al., 2013; Fell and Axmacher, 2011; Sato and Yamaguchi, 2007; Summerfield and Mangels, 2005). According to this framework, increased theta-band connectivity in the resting state might interfere with appropriate modulation of theta activity during mnemonic processes, leading to memory deficits. Although the network of increased resting-state theta-band connectivity observed here did not include the hippocampal formation, it did comprise several areas of the anterior and posterior midline, the orbitofrontal cortex and the left temporoparietal junction. These regions have been consistently identified as parts of the default mode network (DMN) (Raichle et al., 2001), a set of cortical regions that show coordinated activation in the resting state and deactivation during task execution. Thus, our results parallel previous findings of fMRI studies that have reported increased resting-state connectivity both within the DMN and between its components and other cortical regions in patients with schizophrenia and high-risk individuals (Chen et al., 2013; Manoliu et al., 2014; Mingoia et al., 2012; Salvador et al., 2010) (although these findings have not been confirmed in all studies, see Bluhm et al., 2007; Repovs et al., 2011). Aberrant DMN activity and/or deficient DMN deactivation have been suggested to contribute to cognitive dysfunction in schizophrenia and in the high-risk state (Fryer et al., 2013; He et al., 2013; Wotruba et al., 2013). Our findings suggest that a specific pathophysiological mechanism, theta-band oscillations, may be underlying this hyperconnectivity. The observed link to a core trait characteristic of schizophrenia (i.e. verbal memory deficits), and the fact that high-risk individuals displayed connectivity values between those of patients and controls, raise the possibility that theta-band connectivity abnormalities constitute a stable trait of the disorder and are possibly a marker of future transition into psychosis. If this assumption is confirmed in future longitudinal studies, it has implications not only in terms of improved prognosis prediction, but also for treatment, since it provides a specific target for interventions based on electrophysiological modulation of brain circuits (e.g. repeated transcranial magnetic stimulation, or transcranial direct/alternative current stimulation).

There were no further differences between groups regarding resting-state connectivity in any other frequency band. This may appear counter-intuitive in the case of beta- and gamma-band oscillations, as previous studies have consistently reported reduced connectivity in patients with schizophrenia in these high frequency ranges (Kam et al., 2013; Kikuchi et al., 2011; Mulert et al., 2011; Uhlhaas and Singer, 2010). However, most of these studies assessed connectivity in the context of sensory tasks. Thus, it is possible that beta- and gamma-band connectivity disturbances are more relevant in the context of task-related responses to sensory stimuli than in the resting state. In support of this interpretation, a recent study that assessed resting-state gamma-band coherence at the source level in schizophrenia did not find any significant differences between patients and controls (Rutter et al., 2013). However, findings of another study by our group (Andreou et al., in press) in a sample of first-episode patients with schizophrenia (partly overlapping with the present one) indicate that the issue of gamma-band connectivity in schizophrenia might even be more complicated: Using an amplitude-based measure of connectivity (as opposed to measures based on phase synchronization used in the present and in previous studies), we observed increased resting-state gamma-band connectivity across a left-lateralized network encompassing language and memory areas in patients (Andreou et al., in press). This aberrant gamma-band connectivity was more pronounced in patients with low levels of positive and disorganization symptoms, and involved brain areas quite different from those contributing to increased theta-band connectivity in the present study. The different patterns and associations of connectivity disturbances observed in the present and our previous study thus confirm the suggestion that amplitude- and phase-based measures of connectivity represent different underlying coupling mechanisms and may have different functionalities (Engel et al., 2013).

In the alpha frequency range, our lack of a significant finding is in contrast to previous studies (Hinkley et al., 2011; Lehmann et al., 2014) that observed specific disturbances in patients with schizophrenia

using similar connectivity measures on MEG resting-state data. In both of these studies, patients were acutely (Lehmann et al., 2014) or persistently ill (Hinkley et al., 2011), and one of these reported an association between disturbed alpha-band connectivity and clinical symptoms (Hinkley et al., 2011). Since our study investigated first episode patients after sufficient clinical stabilization, it might be that alpha-band connectivity disturbances represent a state characteristic associated with symptoms. However, further studies are warranted to shed more light onto this issue.

Certain limitations of the present study need to be addressed. First, most patients and some high-risk individuals were on antipsychotic medication. Current evidence suggests that medication status affects neither neural oscillations (Uhlhaas, 2013; Uhlhaas and Singer, 2010) nor verbal memory (Keefe et al., 2007). However, and although chlorpromazine equivalent dose had no effect on results, the possibility of indirect effects of antipsychotic medication cannot be completely excluded — especially since some of the antipsychotics used to treat patients and high-risk subjects in the current sample are known to increase theta-band activity (Hubl et al., 2001; Liem-Moolenaar et al., 2011; Wetzel et al., 1995). Second, although EEG has several advantages when it comes to assessing fast neural network dynamics and the precise coordination of oscillations of different frequencies, it is limited both in its spatial resolution and in its capacity to detect sources of electrical activity at deep locations and in the cerebellum. Thus, the present results do not yield information on possible changes in structures such as the amygdala or the striatum, which have been reported to show aberrant interactions in schizophrenia (Anticevic et al., 2013; Liu et al., 2014) – among others with the DMN (Salvador et al., 2010) – , or in other brain regions such as the cerebellum or the thalamus, which have also been implicated in connectivity disturbances in patients (Argyelan et al., 2014; Chen et al., 2013; Khadka et al., 2013; Klingner et al., 2014).

In summary, the present study provides evidence for increased resting-state theta-band connectivity across orbitofrontal areas, the anterior and posterior midline and the left temporoparietal junction in patients with schizophrenia. This disturbance may already be present in the high-risk state, and appears to mediate some of the cognitive deficits that characterize schizophrenia long before the onset of psychotic symptoms. Thus, aberrant theta-band connectivity might constitute a promising target for novel, electrophysiology based, treatment applications for patients with schizophrenia or high-risk individuals.

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Contributors

C.M., G.L., I.H.-O. and A.E. designed the study and wrote the protocol. N.P., S.M. and A.K. managed literature searches and data acquisition. C.A., G.N. and S.M. conducted electroencephalographic and statistical analyses. C.A. and G.L. interpreted findings. C.A. wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

There are no conflicts of interest to declare by any of the authors.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.12.018.

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