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Abnormal connectivity between attentional, language and auditory networks in schizophrenia

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ABSTRACT

Brain circuits involved in language processing have been suggested to be compromised in patients with schizophrenia. This does not only include regions subserving language production and perception, but also auditory processing and attention. We investigated resting state network connectivity of auditory, language and attention networks of patients with schizophrenia and hypothesized that patients would show reduced connectivity.
Patients with schizophrenia (n = 45) and healthy controls (n = 30) underwent a resting state fMRI scan. Independent components analysis was used to identify networks of the auditory cortex, left inferior frontal language regions and the anterior cingulate region, associated with attention. The time courses of the components where correlated with each other, the correlations were transformed by a Fisher's Z transformation, and compared between groups.
In patients with schizophrenia, we observed decreased connectivity between the auditory and language networks. Conversely, patients showed increased connectivity between the attention and language network compared to controls. There was no relationship with severity of symptoms such as auditory hallucinations.
The decreased connectivity between auditory and language processing areas observed in schizophrenia patients is consistent with earlier research and may underlie language processing difficulties. Altered anterior cingulate connectivity in patients may be a correlate of habitual suppression of unintended speech, or of excessive attention to internally generated speech. This altered connectivity pattern appears to be present independent of symptom severity, and may be suggestive of a trait, rather than a state characteristic.

1. Introduction

Problems in language processing have been consistently reported in individuals with schizophrenia (DeLisi, 2001; Crow, 2008), and also in healthy siblings (Docherty and Gordinier, 2010), albeit to a lesser degree. These deficits cover a wide range of domains including language comprehension, production and attention, and specific processes such as semantics, verbal fluency and grammar (DeLisi, 2001; Price, 2010). Language problems have been related to auditory hallucinations (Crow, 2008), formal thought disorder, disorganization and memory impairments (Docherty and Gordinier, 2010). Neuroimaging studies in schizophrenia patients have shown abnormalities in brain areas related to language processing (Price, 2010), including the auditory cortices (Li et al., 2009, 2010), language areas such as Broca's (Li et al., 2010), as well as the anterior cingulate (ACC), which is involved in attention (Sabb et al., 2010) and speech monitoring (Allen et al., 2007). Several lines of research, including postmortem and brain imaging studies suggest that schizophrenia is characterized by abnormalities in concerted action between spatially distributed networks (Shenton et al., 2001; Kubicki et al., 2002; Hubl et al., 2004). Schizophrenia has therefore been described as a dysconnectivity disorder (Peled, 1999). Aberrant connectivity between specific brain networks such as auditory, e.g. in the anterior superior temporal gyrus (STG) and language regions (Broca's and Wernicke's regions) may also underlie functional abnormalities observed in the disorder, i.e. language impairments (Li et al., 2009, 2010; Sabb et al., 2010). This study aims to study the connectivity between spatially distributed networks relevant for language processing.

Auditory verbal hallucinations (AVH) are one of the key symptoms of schizophrenia, which have been hypothesized to be related to problems in language comprehension and generation (Stephane

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et al., 2001; Crow, 2008; Wible et al., 2009). In this framework, Crow (2008) and Frith et al. (2009) hypothesized that dysfunctional connections between fronto-temporal language and auditory brain regions may lead to language processing impairments, such as the misattribution of one's own verbal thoughts as spoken words outside the head. The fronto-temporal dysconnectivity idea is supported by electrophysiological studies showing reduced fronto-temporal connectivity during talking (Ford et al., 2010), and reduced synchrony during the prespeech phase (Ford et al., 2007) in people with schizophrenia, particularly in those with AVH. Diffusion tensor imaging (DTI) studies and functional magnetic resonance imaging (fMRI) studies also showed a decreased connectivity between lateral frontal and the temporal areas in people with schizophrenia (Hubl et al., 2004; O'Daly et al., 2007; Li et al., 2010), also related to verbal learning (Karlsgodt et al., 2008; Hashimoto et al., 2010), verbal fluency capacity (Jeong et al., 2009) and hallucinations (Lawrie et al., 2002). Finally, computer simulations, verified by patient studies, showed that fronto-temporal dysconnectivity may result in erroneous word detection and spontaneous word generation (Hoffman and McGlashan, 1998; Hoffman, 1999).

In addition to abnormal fronto-temporal connectivity, decreased connectivity of auditory and language areas with the ACC may contribute to misattribution of speech, which may lead to AVH (Allen et al., 2007). DTI studies (Kubicki et al., 2002; Park et al., 2004) and functional imaging studies (Fletcher et al., 1999) support this idea by showing decreased left-sided connectivity between temporal and ventral prefrontal areas/ACC. Decreased connectivity of the ACC with other brain areas may also underlie a broad range of other language deficits, such as impairments in perception, comprehension, retrieval and production (Price, 2010). In conclusion, the literature suggest that impairments in language processing in schizophrenia may be related to aberrant connectivity between brain areas implicated in language processing and attention.

During resting state fMRI scans, the brain shows large fluctuations in the Blood Oxygen Level Dependent (BOLD) signal, which are relatively stable within brain networks consisting of functionally connected regions (Salvador et al., 2005). This coherence of BOLD fluctuations within networks is referred to as resting state functional connectivity, and may be a more natural measure of brain function than task-based fMRI (Raichle and Gusnard, 2005) as it reflects intrinsic brain interactions (Van de Ven et al., 2004). Furthermore, it has been suggested that these interactions may reflect overall brain function (Fox and Lancaster, 1994) and predict task performance or behavior (Fox and Raichle, 2007). Evaluating resting state functional connectivity may therefore be a valuable tool for the identification of dysfunctional networks in the brain associated with psychiatric disorders such as schizophrenia (Fox and Raichle, 2007; Auer, 2008). Independent component analysis (ICA) is the method of choice to study temporal fluctuations between brain networks in the resting state, i.e. in the absence of a specific cognitive task (Calhoun et al., 2001; Fox and Raichle, 2007). This data-driven method separates the BOLD signal into spatially independent networks (components) by maximizing the spatial independence between voxel time courses (Van de Ven et al., 2004; Van de Ven et al., 2005). Together with the time course, a spatial map is created per subject, which shows the contribution of every voxel in the brain to a certain network (component). Brain areas that show similar fluctuations, i.e., have a similar time course and thus belong to one network, can this way be identified (Jafri et al., 2008). Those networks show a close correspondence to networks identified by activation studies (Smith et al., 2009). Thus, ICA is a suitable tool to study the large scale connectivity between different networks.

ROI-based analysis is a widely applied technique to study functional connectivity in fMRI research. It works by taking average time courses of the raw BOLD signal based on predefined regions, and correlating these. Our aim here is to study large scale connectivity between different networks. We considered ICA more suitable for our research question than seed-based ROI connectivity as we were interested in intrinsic networks that can be identified in a model-free, data-driven way. Most importantly, Rosazza et al. (2011) showed that the largest differences in results between ICA and ROI analysis were observed for long range connections, which are the focus of our study. Moreover, ICA tends to separate signal of no interest from signal of interest (brain activation) and may give a better representation of brain activation than the raw MRI signal and contain less noise (Van de Ven et al., 2004; Fox and Raichle, 2007). Finally, it may be difficult with ROI analysis to clearly define a complete brain network, without missing certain brain areas or including areas that show different temporal patterns (Fox and Raichle, 2007; Rosazza et al., 2011). Therefore, ICA is the optimal choice to study alterations in concerted action between spatially distributed brain networks (Shenton et al., 2001; Kubicki et al., 2002; Hubl et al., 2004) as we described earlier.

Few studies have used ICA as yet to investigate brain networks in schizophrenia in auditory networks. Van de Ven et al. (2005) used ICA to investigate the cortical connectivity patterns during AVH, reporting a relationship between time courses in the auditory cortex (superior temporal gyrus; STG) and the onset of AVH's. Jafri et al. (2008) used ICA to investigate the connectivity between spatially independent brain networks of schizophrenic patients compared to healthy controls but they did not specifically investigate language and auditory networks.

Given the relevance of these networks for the neurobiology of schizophrenia, we specifically focused on language and auditory processing networks in the present study. ICA is a very suitable analysis method given the data-drive nature of ICA. The first aim was to identify complete brain networks related to language processing in the data, by investigating whether predefined language-related brain regions could be identified as an ICA component. These regions included STG, Wernicke's and Broca's area, and the anterior cingulate cortex. The second aim was to study the difference in connectivity between networks comparing schizophrenia patients and healthy controls, by comparing the correlations of the time courses of different brain networks.

2. Methods

2.1. Subjects

This study was approved by the local medical ethical committee according to the Declaration of Helsinki. The study sample consisted of a mixed sample of in- and out-patients of local psychiatric clinics diagnosed with schizophrenia by their physician (SZ; $n=45$) and a group of healthy controls (HC; $n=30$). Patients were participants in an fMRI study on neural correlates of auditory hallucinations or a study on cognitive emotional processing; in both studies a resting state scan was part of the research protocol. In patients the diagnosis of schizophrenia based on the DSM IV was confirmed by a semi-structured interview (Schedules for Clinical Assessment in Neuropsychiatry; SCAN 2.1; Giel and Nienhuis, 1996). Symptom severity was determined by the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987).

Exclusion criteria for the study consisted of MRI incompatible implants, possible pregnancy, claustrophobia and non-native Dutch speakers. All subjects gave oral and written informed consent after the study procedure had been fully explained. All subject data was handled anonymously.

Healthy controls were recruited by advertisements in local newspapers, and matched for age, gender, handedness, and education level to the patient groups. See Table 1 for demographical data. Difference in age between groups was tested with an independent samples *t*-test ($\alpha<0.05$). Educational level was determined using a six point scale of Verhage (1964) which runs from primary school (1) to university level (6) and tested with a Mann–Whitney *U* test ($\alpha<0.05$). A Chi-square test ($\alpha<0.05$) was used to test for differences in gender and handedness. Handedness was confirmed with the Edinburgh handedness inventory (Oldfield, 1971). For patients, medication status was also determined.

Table 1
Overview of the demographical data, mean values (standard deviations in parentheses) or ratios are indicated.

	Patients	Controls	p-value
Age (years)	34.7 (11.4)	33.4 (10.5)	0.67
Education (level)	3.5 (1.1)	4.1 (1.1)	0.053
Males/females	28/17	15/15	0.42
Handedness (left/right)	5/40	6/24	0.47
PANSS P3 (AVH)	3.7 (1.9)	–	–
PANSS positive	15.5 (5.0)	–	–
PANSS negative	14.4 (4.4)	–	–
PANSS general	29.1 (8.3)	–	–

2.2. Experimental procedure

All subjects underwent a resting state fMRI scan. They were instructed to close their eyes, relax, think of nothing particular, and to stay awake. A 3 T Philips Intera MRI scanner (Best, The Netherlands) equipped with a 8-channel SENSE head coil was used to acquire 200 whole brain echo-planar functional images (EPI's), TR 2.3 s and TE 28 ms. The volumes contained 39 or 43 interleaved slices ($3.8\times3.8\times3$ mm) with no gap and a 85° flip-angle ($FOV=220\times117\times220$ mm). A high-resolution, transverse T1 anatomical was also acquired for anatomical reference (160 slices; voxel size $1\times1\times1$ mm; FOV $256\times220\times256$ mm).

Participants also performed a language processing task in the same fMRI session as the resting state scan. Although the functional neuroimaging correlates of that task are beyond the scope of this paper, we present the behavioral data to provide an indication of language processing differences between groups, which may aid interpretation of our findings. The task (adapted from Aleman et al., 2005) required subjects to evaluate bisyllabic Dutch words that were presented one at a time in the middle of the screen. In one condition a valence judgment was required, by indicating whether the presented word was positive or negative to the subject (semantic condition; e.g. stimulus: “summer”; answer e.g. “positive”). In the second condition, a metrical stress judgment was required, by indicating the syllable that carried the metrical stress (phonetic condition). The task consisted of 24 trials for the semantic condition and 24 trials for the phonetic condition that were presented mixed in pseudorandom order.

2.3. Data analysis

The raw images were converted to ANALYZE format and analyzed using Statistical Parametric Mapping (SPM5; FIL Wellcome Department of Imaging Neuroscience, London, UK) running in Matlab 7.1. Images were first corrected for slice-time differences and realigned to the first functional image. All motion parameters were checked for spurious motion and all subjects that moved more than 3 mm were excluded from further analysis. The mean image created during realignment was co-registered to the anatomy, together with the functional images, and the anatomy and functional images were normalized to the T1 template of SPM (voxel size $3\times3\times3$ mm). Finally, images were smoothed with a 10 mm FWHM isotropic Gaussian kernel.

Following preprocessing, images were processed in the Group ICA FMRI Toolbox (GIFT) (http://icatb.sourceforge.net/gift/gift_startup.php; Calhoun et al., 2001). First, the mean number of independent components (IC's) was estimated using Maximum Description Length (MDL) and Akaike's criteria (Li et al., 2006), to prevent splitting or merging of components (Smith et al., 2009). Estimation showed an estimate of 30 components. Intensity normalization, which implied scaling the time courses to a mean of 100, was applied to the images before running the ICA procedure. Then, images of all subjects were decomposed into a set of 30 spatially independent components by the Infomax algorithm. Stability of the components, i.e. investigating whether a component has the tendency to split or merge with another component (Rosazza et al., 2011), was validated by running the ICASSO toolbox implemented in GIFT using twenty iterations with both random iterations and bootstrapping (Himberg and Hyvärinen, 2003; Himberg et al., 2004).

In order to exclude components with artifacts, components maps of the ICA were sorted based on the white matter and gray matter masks of SPM using the automated spatial sorting facility of GIFT. Validity of the components was further verified by visually comparing the components with previously identified networks (Beckmann et al., 2005; Damoiseaux et al., 2006; Smith et al., 2009).

Next, potential components of interests were identified by searching components that showed a substantial overlap with anatomical masks of predefined regions of key brain structures in language processing. The anatomical masks used for sorting were created by WFU pickatlas (http://www.nitrc.org/projects/wfu_pickatlas). Masks provided by WFU pickatlas are based on brain regions defined by Talairach and Tournoux (1998) that were implemented in this toolbox after conversion to MNI space (Lancaster et al., 1997, 2000; Maldjian et al., 2003). We tried to identify the auditory cortex network, language networks (Broca's and Wernicke's area), and the anterior cingulate of the attention network. The characteristics of the key regions are summarized in a table which can be found in the supplementary material. Shortly, the auditory cortex was defined as STG and the anterior cingulate cortex as ACC. Because the language areas have different definitions, Wernicke's area was both defined as Brodmann area 22 and Heschl's gyrus, and Broca's area both as BA 44/45 and inferior frontal gyrus (IFG).

Time courses of selected components were visually inspected and converted to power spectra to check for the presence of artifacts (Cordes et al., 2000). Hereafter, correlations were calculated between the time courses of all selected networks (based on Jafri et al., 2008) and converted to z-scores by a Fischer's Z transformation, where $z=1/2*\ln((1+r)/(1-r))$ where r represents the correlation. These data were loaded in Statistical Package for Social Sciences (SPSS 16). Between group comparisons were conducted using Mann–Whitney U tests ($\alpha=0.05$).

In an additional analysis, the PANSS items P2 Conceptual disorganization, P3 Hallucinations (which mainly concerned AVH) were correlated - using a non-parametric Spearman correlation ($\alpha<0.05$) - with the Z-scores, to investigate whether there was a link between symptom severity and connectivity between the auditory, language and attention networks.

With regard to the language processing task, for both groups the mean reaction times and accuracy for the phonetic and semantic condition were calculated. For the semantic condition there are no correct answers as they depend on subjective ratings. Still, the agreement of a subject's response with the opinion of independent raters (from a previous study: Aleman et al., 2005) could be judged. Finally, the percentage of positively rated words was determined, as patients may have a more negative bias toward words. These measures were compared between groups using a Mann–Whitney *U* test ($p<0.05$) because the data were non-normally distributed. The measures were tested separately because both conditions measure a distinct concept.

3. Results

3.1. Patient characteristics and language processing task

Eventually, 30 healthy controls and 45 patients with schizophrenia (after exclusion of two due to excessive movement) participated in the study. A group comparison showed no significant differences in age, education level, gender or handedness (see Table 1). Most patients had a diagnosis of schizophrenia paranoid type ($N=32$), and a few patients had another diagnosis according to the interview: schizophrenia disorganized type ($N=1$), schizophrenia undifferentiated type ($N=4$) psychotic disorder NOS ($N=4$), and some missing diagnosis ($N=4$). Possibly, the correct diagnosis was not given by the algorithm of the SCAN sometimes, because essential data were missing. The average duration of illness was 119 months, but was variable (SD = 134, min = 1, max = 480 months). The patients reported to use the following medication; antipsychotics: aripiprazole (9×), chlorprotixene (1×), clozapine (15×), haloperidol (4×), olanzapine (9×), paliperidone (1×), penfluridole (1×), perphenazine (1×), pimozide (1×), pipamperone (1×), quetiapine (7×), risperidone (10×), sulpiride (1×), and zuclopentixole (2×); antidepressants: amytriptyline (1×), bupropione (1×), citalopram (3×), clomipramine (1×), fluoxetine (2×), fluvoxamine (1×), mirtazapine (1×), paroxetine (2×), nortriptylin (1×), trazodone (1×), and venlafaxine (2×); benzodiazepines: diazepam (3×), flurazepam (1×), lorazepam (3×), oxazepam (7×), temazepam (5×); other: atenolol (1×), biperiden (6×), carbamazepine (1×), lithiumcarbonate (6×), pantaprazol (2×), promethazine (1×), and valproic acid (1×).

Performance on the valence evaluation task is shown in Fig. 1. Reaction time in the semantic condition was significantly longer for patients ($U = 307.5$, $z = -2.55$, $p = 0.011$), and showed a trend for the phonetic condition ($U = 353.0$, $z = -1.93$, $p = 0.054$). Moreover, patients performed slightly worse on the phonetic condition ($U = 347.5$, $z = -2.01$, $p = 0.045$), and in the semantic condition tended to show a lower agreement with the valence ratings of a separate control sample ($U = 361.5$, $z = -1.82$, $p = 0.069$). There was no difference however, in valence rating as expressed by the percentage positively rated (50.2% for controls and 50.1% for patients). Thus, patients rated different words as positive compared to controls.

3.2. ICA network results

Estimation of the number of independent components yielded a mean of 30 components. ICASSO showed good stability of the components with an inter-cluster similarity of >0.8 and no crosstalk with other components. After running the ICA, three different components of interest were identified (Hoffman and McGlashan, 1998; Allen et al., 2008), namely: an auditory component that mainly included STG (46% overlap with STG mask), the attention network with mainly ACC (36% overlap with ACC mask) and a language network with mainly Broca's area and also Wernicke's. This network showed overlap with both masks for Broca's area (20% overlap with the BA 44/45 mask and 57% overlap with the IFG mask). There was no substantial overlap with the masks for Wernicke. We will refer to these networks as STG network, Broca's network and ACC network respectively. Information regarding peak voxels can be found in Table 2. A stringent threshold of FWE, $p < 0.05$, $k > 50$ was applied because of the robust nature of the component maps. The language network contained Broca's area, and to a lesser degree Broca's right-sided homologue as well as Wernicke's area and its right homologue. The auditory component was constituted of the bilateral STG, encompassing the primary and secondary auditory cortex, and additionally the lingual gyrus, anterior cingulate, and medial frontal gyrus. The ACC component contained additionally some cingulate cortex, and inferior parietal lobule. Interestingly, the components also weakly contained some brain areas encompassed by another component, e.g. ACC in the language network, which may indicate a weak coherence between those networks. Visual inspection of time courses and power spectra showed no deviating pattern in one of the components. Most of the fluctuations were present in the 0.01–0.2 Hz frequency range consistent with default mode network fluctuations. Spatial maps of the components are presented in Fig. 2.

Table 2
Brain areas encompassed by the language areas identified by ICA (FWE, $p<0.05$, $k>50$).

Network	Cluster size	peak T	x,y,z {mm}			Area
ACC network	6436	34.64	−6	42	15	Anterior cingulate gyrus
	346	9.27	0	−27	30	Cingulate gyrus
	67	7.11	54	−42	54	Inferior parietal lobule
STG network	3170	28.48	−51	−18	6	Superior temporal gyrus
	1045	13.52	60	−24	6	Superior temporal gyrus
	220	10.78	−9	24	0	Anterior cingulate gyrus
	191	8.17	12	−54	−9	Lingual gyrus
	72	7.57	3	51	−6	Medial frontal gyrus
Broca's network	2135	27.18	−45	24	−6	Inferior frontal gyrus (Broca's area)
	1131	18.71	48	27	0	Inferior frontal gyrus (Broca's homologue)
	372	10.42	−6	57	27	Posterior STG (Wernicke's area)
	51	6.3	63	−36	0	Posterior STG (Wernicke's homologue)

Mann Whitney U tests comparing patients and controls revealed significant differences in the Z scores associated with the connection between ACC and Broca's networks ($M_{controls} = 0.21$, $SD = 0.30$, $M_{patients} = 0.49$, $SD = 0.32$, $p = 0.0005$), which were higher in patients, and the Z-scores associated with the connection between STG and Broca's networks ($M_{controls} = 0.52$, $SD = 0.25$, $M_{patients} = 0.37$, $SD = 0.26$, $p = 0.024$), which were lower in patients (see Fig. 3). There was no significant correlation between Z-scores and symptom severity as measured by PANSS items.

4. Discussion

In this study, we tested the hypothesis of reduced connectivity between the auditory and language networks in patients with schizophrenia. The ICA yielded three components of interest related to

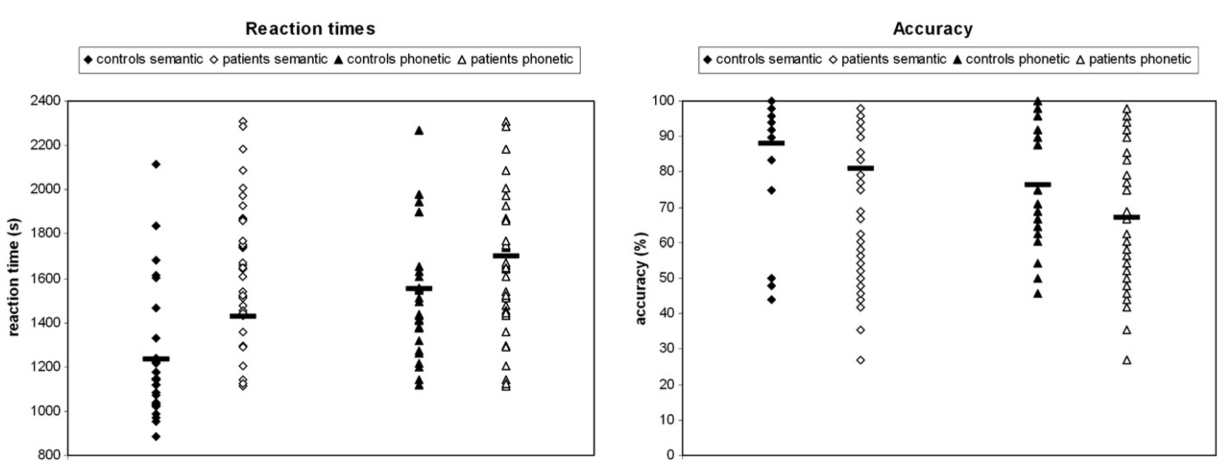

Fig. 1. Reaction times (left graph) and performance (right graph) on the valence evaluation task, for both the semantic and phonetic condition; Patients have longer reaction times and a lower accuracy compared to healthy controls.

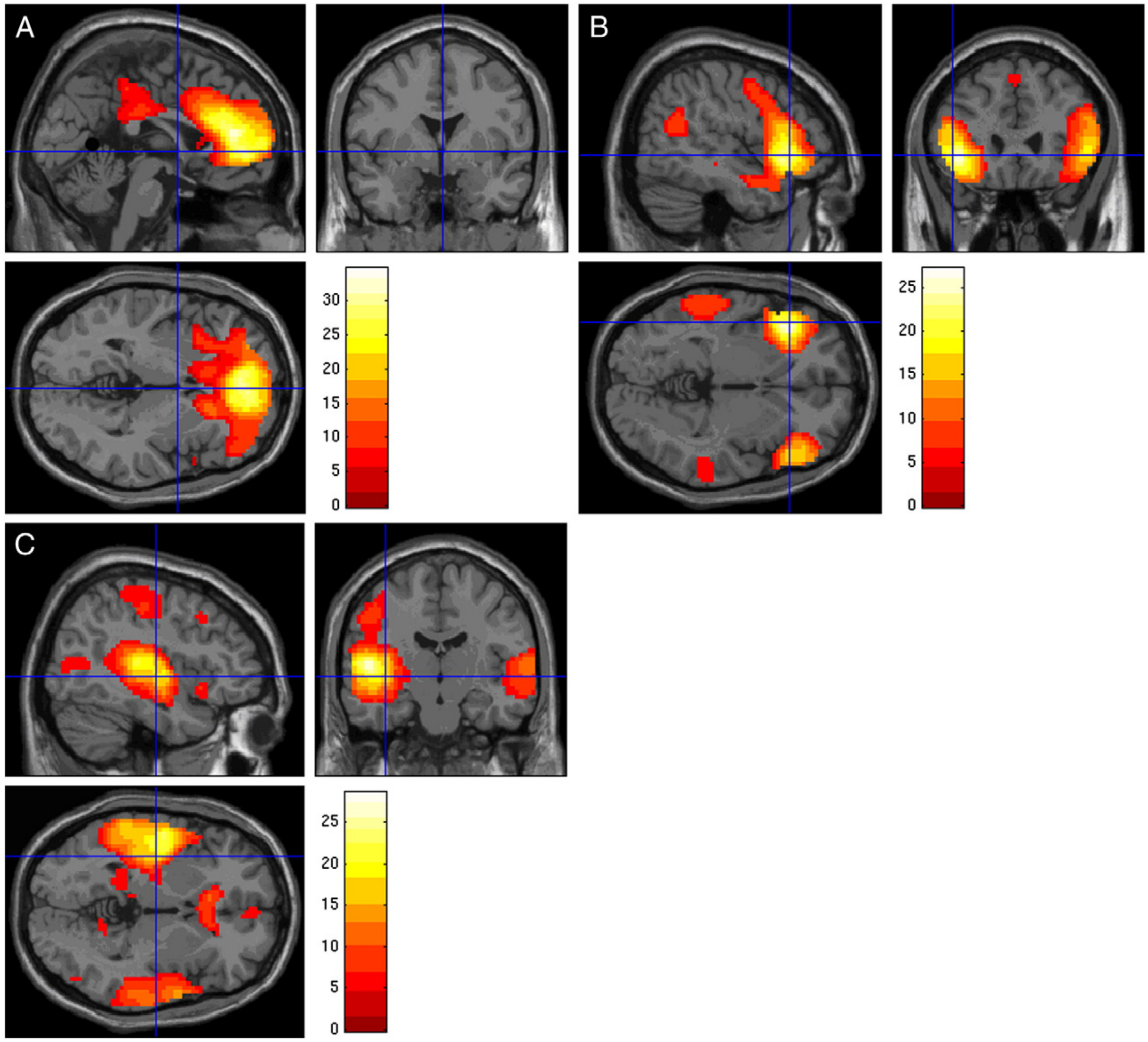

Fig. 2. The brain networks found with ICA: A: anterior cingulate network with some posterior cingulate, inferior parietal lobule and prefrontal cortex; B: language component with mainly Broca's area and it's homologue, and also Wernicke's area and it's homologue; C: auditory network with superior temporal gyrus and lingual gyrus, anterior cingulate, and medial frontal cortex.

language processing, namely the auditory cortex (STG network), fronto-temporal language regions (Broca's network) and the attention network (ACC network). Decreased connectivity was observed in patients between the auditory and language networks. However, patients showed *increased* connectivity between the attention and language network compared to controls. Fig. 4 depicts the observed connections in a model. Contrary to our expectations, we observed no relationship with severity of auditory hallucinations.

As expected, decreased connectivity between the language areas (primarily language production areas in the IFG, i.e. Broca and its homologue) and the auditory areas (mainly STG) was observed in patients with schizophrenia. This is in correspondence with the concept of reduced fronto-temporal connectivity (Kubicki et al., 2002; Shergill et al., 2002; Hubl et al., 2004; Frith et al., 2009; Vercammen et al., 2010). A number of other functional MRI studies also found evidence of reduced connectivity between these regions during different language processes, including talking, verbal learning, verbal fluency and word detection, supporting our finding (Karlsgodt et al., 2008; Jeong et al., 2009; Ford et al., 2010; Hashimoto et al., 2010). Functional changes may also be linked to reduced anatomical connectivity, as revealed by DTI studies measuring white matter integrity (Hubl et al., 2004; O'Daly et al., 2007; Li et al., 2010).

As our results concern the resting state, this is a significant extension of previous findings. That is, it suggests disconnection of language-related regions also during the default mode resting state. This finding may imply reduced control from the frontal language areas over the more receptive processing areas. Alternatively, as these regions are not exclusively involved in language processing, they may concern a broader domain of executive and auditory perception and memory functions (Stirling et al., 2001; Li et al., 2002).

More recent studies also focused on functional connectivity between brain networks in schizophrenia. Patients with schizophrenia showed a reduced global integration and functional organization of brain regions, specifically in for fronto-temporal areas (Van den Heuvel et al., 2010), or in relation to a verbal fluency task (Lynall et al., 2010). These findings show some support for our hypothesis that decreased fronto-temporal connectivity may be associated with language processing difficulties. These functional abnormalities may originate from degeneration of long range white matter tracts, including the fronto-temporal connections (Lynall et al., 2010; Van den Heuvel et al., 2010). Eventually

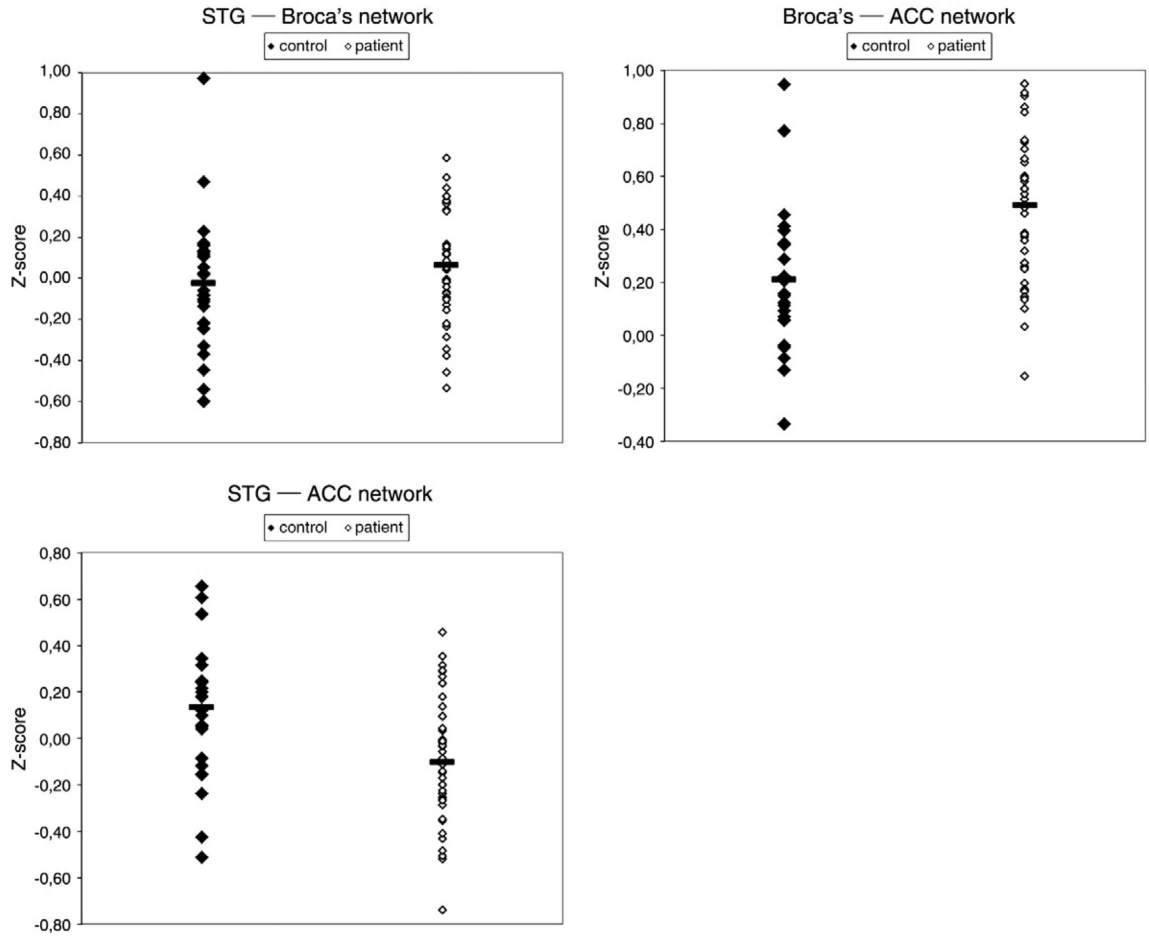

Fig. 3. Graph showing the average z-scores for all connections for the different subject groups. There was a significant difference in average Z-scores of the STG — Broca's network connection and the Broca's — ACC network connection.

these effects may result in reduced global integration of information and disturbances in cognitive processes such as language.

Contrary to our hypothesis of overall reduced connectivity in schizophrenia, we observed *increased* functional connectivity between the attention and language network in patients compared to controls. Although schizophrenia has been conceptualized as a dysconnectivity disorder, other studies have also shown increased connectivity in patients with schizophrenia (Van den Heuvel et al., 2010; Hoffman et al., 2011). In our case, increased connectivity between speech production and attention areas may be related to exaggerated attention to self-generated (inner) speech (Vercammen and Aleman, 2008), which may be related to hallucinatory predisposition often observed in schizophrenia (Evans et al., 2000). Other studies suggest that the ACC is involved in suppression of unintended (inner) speech (Price, 2010). This process may be more habitually invoked by patients with schizophrenia, as the content of their inner speech is more frequently experienced as non-desired, leading to stronger connectivity.

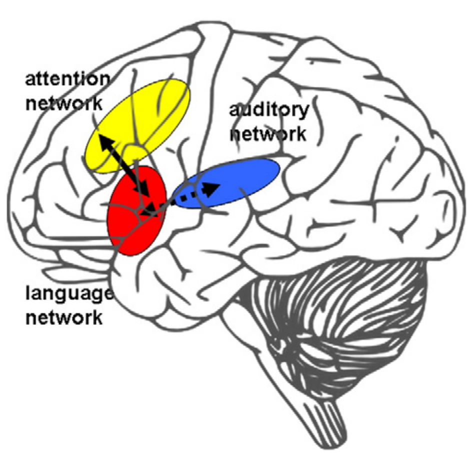

Fig. 4. The connectivity model based on the ICA data. The bold arrow indicates increased connectivity for the schizophrenia patients compared to controls; The dashed arrow indicates decreased connectivity of patients compared to controls.

We did observe a difference in performance on a language task. Patients showed a lower performance on a phonetic task, and made different semantic judgments as compared to controls. This may imply that there is indeed a link between language impairments and altered resting state connectivity, though caution is needed as larger groups would be necessary to directly compute associations between differences in connectivity and language performance, and more comprehensive testing would be in place. On the other hand, resting state fluctuations have been shown to predict individual's task performance or behavior (Fox and Raichle, 2007). Future studies could use multiple tasks measuring several language domains separately to be able to make more specific inferences.

We observed no relationships between connectivity measures and current symptom severity. Consistent with prevalence figures (Nayani and David, 1996), most of the participants in the current study in fact had a lifetime history of hallucinations, and thus regardless of their current symptoms, may have had a general disposition toward hallucinations. As previously noted, the endogenous oscillations of brain networks measured with ICA may be more indicative of stable trait characteristics, rather than a state dependent phenomena (Meyer-Lindenberg, 2009). Therefore, the absence of a relationship with current symptom severity may be due to the fact that our measurement lacked sensitivity for the more fleeting state characteristics of hallucinations. Other studies also failed to find differences between patients with and without AVH, e.g. in terms of collary discharge (Ford and Mathalon, 2005), language imagery (Simons et al., 2010) and verbal fluency (Diederen et al., 2010). Ideally, future studies would compare those without a history of hallucinations to those with a history and those with active hallucinations, in order to establish the relationships between changes in neural connectivity and symptom presence.

This is the first study that investigated regions relevant for language processing in schizophrenia using ICA in the resting state. Some previous studies have used correlation analysis (e.g. Vercammen et al., 2010). The data-driven nature of ICA has some advantages over ROI analysis, as identified brain networks may have higher biological validity than artificially defined ROI's (Van de Ven et al., 2004). Furthermore, ICA tends to separate signal of no interest (Cordes et al., 2000) into separate components (Fox and Raichle, 2007), and the signal to noise ratio of ICA time courses is probably higher than time courses of the raw BOLD signal.

Some limitations of our study should be mentioned. First of all, it is difficult to determine the correct number of components, and to prevent the splitting or merging of components (Fox and Raichle, 2007; Smith et al., 2009). We tried to reduce this risk by estimating the optimal number of components (Li et al., 2006) and running the ICASSO toolbox (Himberg and Hyvärinen, 2003; Himberg et al., 2004), which showed good stability. Moreover, we also ran ICA with more or less components (20, 25, 35 and 40), and this did not change our findings (data not shown), which is in agreement with Rosazza et al. (2011).

It should also be noted that ICA is an exploratory analysis method, and selection of components during resting state is based on criteria determined by the researcher. In addition, altered resting state connectivity analysis gives no direct evidence for disturbances in certain functions such as language. However, close inspection of the components showed that “the language network” clearly encompassed areas located in regions corresponding to Broca's and Wernicke's area (IFG and temporo-parietal junction, strongest presence on the left side) and the “STG network” (two areas, that converge with the primary and secondary auditory cortex). It has been shown that resting state networks may indeed show partial correspondence to task-related networks (Smith et al., 2009). Also, the power spectra showed that the components time courses mostly contained low-frequencies, while signal of no interest (e.g. heartbeat) also contains higher frequencies (Cordes et al., 2000). In conclusion, resting state analysis is a relevant addition method to study intrinsic connectivity of the brain besides task-induced connectivity, which may be more artificial (Van de Ven et al., 2004).

Finally, almost all subjects took antipsychotic medication. Although a recent review showed that the effect of antipsychotics on the BOLD signal is possibly limited (Röder et al., 2010), we cannot rule out that medication affected our study results.

In conclusion, patients with schizophrenia showed reduced connectivity between the auditory and language networks. Such reduced connectivity could contribute to impairments in language expression and comprehension. An abnormally increased connectivity between the attention and the language network could be related to habitual suppression of unintended speech, or to excessive attention to internally generated speech.

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Contributors

E.J. Liemburg, Msc. undertook the statistical analysis and wrote the first draft of the manuscript.

Dr. A. Vercammen helped design the study and wrote the protocol and performed data collection.

Dr. G.J. ter Horst was involved in interpretation and critically reading of the manuscript.

Dr. B. Curcic-Blake contributed to the Method section and critically reading of the manuscript.

Dr. H. Knegtering gave support during data collection and was involved in critically reading of the manuscript.

Dr. A. Aleman designed and supervised the study.

All authors contributed to and have approved the final version of the manuscript.

Conflict of interest

All other authors declare that they have no conflicts of interest.

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