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Interhemispheric EEG coherence is reduced in auditory cortical regions in schizophrenia patients with auditory hallucinations

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ABSTRACT

Central auditory processing has been reported to be impaired in schizophrenia patients who experience auditory hallucinations, and interhemispheric transfer in auditory circuits may be compromised. In this study, we used EEG spectral coherence to examine interhemispheric connectivity between cortical areas known to be important in the processing of auditory information. Coherence was compared across three subject groups: schizophrenia patients with a recent history of auditory hallucinations (AH), schizophrenia patients who did not experience auditory hallucinations (nonAH), and healthy controls (HC). Subjects listened to pure tone and word stimuli while EEG was recorded continuously. Upper alpha and upper beta band coherence was calculated from six pairs of electrodes located over homologous auditory areas in the left and right cerebral hemispheres. Significant between-group differences were found on four electrode pairs (C3-C4, C5-C6, Ft7-Ft8 and Cp5-Cp6) in the upper alpha band. Relative to both the HC and nonAH groups, coherence was lower in the AH patients, consistent with the hypothesis that interhemispheric connectivity is reduced in these patients.

1. Introduction

Auditory hallucinations are a distressing symptom of schizophrenia, experienced by more than 70% of patients (Sartorius et al., 1986). Although extensively researched, the pathophysiology underlying hallucinations has not been fully explained. Alterations to auditory processing circuits may play a role in the generation of auditory hallucinations (Hoffman et al., 1999) and Crow has hypothesised that interhemispheric neural integration may be disrupted in patients who hallucinate (Crow, 1997b; Crow, 1998). This study aimed to examine interhemispheric connectivity between auditory cortical regions in schizophrenia patients who experience auditory hallucinations, using the technique of EEG spectral coherence.

Auditory verbal hallucinations are the experience of hearing voices in the absence of an external acoustic stimulus. In most healthy people, the auditory cortex is larger in the left hemisphere than in the right hemisphere (Geschwind and Levitsky, 1968), and language processing is lateralized to the left hemisphere (Kimura, 1961, 1967). Crow has hypothesised that the degree of language lateralization is reduced, or possibly reversed, in some areas of the auditory cortices in people with schizophrenia, and that

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language abnormalities, including auditory hallucinations, may be an outcome of this abnormal cerebral lateralization (Crow, 1997a; Crow, 2004). Support for this hypothesis is found in data from neuroimaging of schizophrenia patients, where it has been reported that, relative to healthy controls, Heschl's gyrus has a smaller volume (Crespo-Facorro et al., 2004; Hirayasu et al., 2000), and is more reduced on the left than the right hemisphere (Kasai et al., 2003). In the planum temporale, the left-right asymmetry has been reported to be reduced (Hirayasu et al., 2000) or reversed (Barta et al., 1997). Positive symptoms, including hallucinations and delusions, have been associated with reduced volumes in the left Heschl's gyrus (Modinos et al., 2012; Sumich et al., 2005) and Heschl's gyrus has been reported to be larger in the right hemisphere compared with the left in AH patients (Hubl et al., 2010).

Previous studies have reported evidence of dysfunctional auditory processing networks in patients with schizophrenia, and impaired interhemispheric transfer has been implicated. McKay et al. (2000) used a battery of clinical audiological (behavioural) tasks to assess two groups of schizophrenia patients: those with a history of auditory hallucinations (AH), and those who did not experience hallucinations (nonAH). The pattern of results seen in both patient groups was most consistent with dysfunction in either the right auditory cortex or in the interhemispheric pathways, but the AH group was found to be more severely affected than the nonAH group. Functional MRI comparing interhemispheric connectivity in primary and secondary auditory cortices of AH and nonAH patients has shown reduced functional connectivity specific to AH patients (Gavrilescu et al., 2010). On the other hand, fibre integrity of the interhemispheric auditory fibre tracts in the corpus callosum, measured using fractional anisotropy, has been recently been reported to be higher in AH patients compared with nonAH patients, with a trend wise increase relative to controls (Mulert et al., 2012).

EEG analysis provides fine temporal information which is unavailable from MRI, and which is an important consideration in the context of neural network dynamics. In the auditory modality, EEG studies also have the advantage of being performed in relatively quiet conditions compared with the noisy environment in an MR scanner. We have recently reported EEG data showing altered interhemispheric transfer time (IHTT) of the auditory N1 evoked potential relative to healthy controls (HC) in response to word stimuli in both AH and nonAH patients, but with differing patterns

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of results (Henshall et al., 2012). While neither group had a mean IHTT significantly different from that of HC participants when tone stimuli were presented, AH patients showed an increased mean IHTT for word stimuli compared with healthy controls, and nonAH patients showed a mean IHTT which was negative (faster transmission ipsilaterally than contralaterally) in response to word stimuli. These different IHTT patterns suggest interhemispheric transfer impairments in AH patients, and offer possible evidence of reversed or altered hemispheric lateralization in the nonAH group, in the secondary auditory cortices.

EEG spectral coherence is a frequency dependent statistical measure that can be used to estimate connectivity between two cortical regions, and has been used previously in studies of schizophrenia patients. Much of this research has examined intrahemispheric frontal-temporal lobe connectivity in affected patients, without differentiating between patients with different symptoms. Fewer studies have looked at interhemispheric connectivity, and fewer again have related their findings to whether or not patients had a history of auditory hallucinations. Interhemispheric alpha-band (8-13 Hz) coherence measured at central sites (C3-C4) has been reported to decrease relative to base-line during cognitive processing in both healthy controls and in medicated schizophrenia patients, but not unmedicated patients (Morrison-Stewart et al., 1996). Winterer and colleagues (2003) examined fronto-temporal and interhemispheric connectivity following presentation of an auditory stimulus, in order to examine possible alterations in these regions during auditory processing. They reported reduced fronto-temporal delta (0.5-4 Hz) coherence in both schizophrenia patients and unaffected siblings compared with controls, as well as an increase in interhemispheric coherence at central sites (C3-C4) in the sibling group, and suggested that both a decrease and an increase in coherence could be regarded as atypical. Higashima and co-authors (2006) have reported that an increase in beta (13-28 Hz) coherence recorded interhemispherically between frontal sites was associated with an improvement in symptom severity, following one month on medication.

Coherence studies have provided evidence that interhemispheric connectivity may be altered in schizophrenia patients depending on their symptom profile. In patients grouped according to positive and negative symptoms, increasing negative symptoms (such as blunted affect and emotional withdrawal) have been correlated with a reduction in interhemispheric alpha-coherence on electrode pair C3-C4 (Merrin and

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Floyd, 1996). More recently, Medkour et al. (2010) used a partial coherence measure of gamma activity to compare functional connectivity in positive and negative symptom patients. Interhemispherically, C3-C4 connectivity was lower in patients exhibiting positive symptoms than in either the negative symptom group or controls. At T3-T4 (alternatively known as T7-T8) connectivity was reduced in both patient groups. Overall, functional connectivity was found to be more affected in the negative symptom group. The authors concluded that patients with predominantly negative symptoms showed evidence of more pervasive changes in functional connectivity, and thus represented a more extreme pattern of abnormality in schizophrenia. Mulert and colleagues have reported that interhemispheric gamma phase synchrony of the auditory steady-state (40 Hz) response in the primary auditory cortex (BA 41) was lower in schizophrenia patients than in healthy controls. However the severity of auditory hallucinations was positively correlated with phase synchrony, that is, hallucinators were less dys-synchronous than non-hallucinators (Mulert et al., 2011).

Alpha-band coherence has been compared in schizophrenia patients who experienced auditory hallucinations, in the hallucinating and non-hallucinating states (Sritharan et al., 2005). Cortical areas known to be important in speech processing were examined, including the left and right middle and superior temporal cortices (electrodes C5, C6, T7 and T8). Alpha coherence averaged over electrodes C5 and C6 was found to be significantly increased in the hallucinating state compared with the non-hallucinating state. The authors suggested this was evidence of abnormally high synchrony of neural activity between the right and left superior temporal cortices, and thus an increase in functional interhemispheric connectivity in auditory cortex during auditory hallucinations. However as no controls were included, it is unclear which of the hallucinating or non-hallucinating states was more similar to the state found in healthy people. A recent study also comparing hallucinating and non-hallucinating patients has reported alpha-band phase synchrony was increased interhemispherically at T7-T8 during the experience of hallucinations (Angelopoulos et al., 2011).

In normal relaxed adults, alpha oscillations (8-12 Hz) are the dominant spectral components seen in scalp-recorded EEG. Alpha activity is typically recorded over widespread scalp regions, and is usually larger posteriorly (Nunez and Srinivasan, 2006). The amplitude of alpha rhythms is maximum during alert wakefulness with the eyes closed, and decreases with the processing of visual stimuli, eyes open (Klimesch,

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1999). It is also reduced in many people by performing cognitive tasks (Nunez and Srinivasan, 2006). It has been hypothesised that alpha-activity reflects long-range cortical interactions (Nunez et al., 2001; von Stein and Sarnthein, 2000) and alpha activity is typically observed to be highly correlated between homologous temporal areas (Cover et al., 2004).

Cortical neurons discharging in synchronous rhythms within the high beta and gamma frequency ranges occur in response to sensory stimuli over a range of modalities. Such activity is thought to play an important role in the co-ordination of distributed neural networks, and may be related to fundamental cognitive functions including attention and detection of novelty stimuli in the auditory system (Haenschel et al., 2000; Uhlhaas et al., 2008). Long-range sensory coding appears to be most strongly associated with activity at beta frequencies, whereas local synchronization generally occurs at gamma frequencies (von Stein and Sarnthein, 2000). In patients with schizophrenia, activity in the beta EEG band has been reported to show abnormalities including reduced amplitude during language processing in chronic patients (Hirano et al., 2008) and reduced phase synchrony during Gestalt perception (Uhlhaas et al., 2006). It has been reported that the amplitude of beta band oscillations in patients with schizophrenia increase in speech-related cortical regions during auditory hallucinations (Lee et al., 2006).

In this study, we have estimated interhemispheric connectivity using EEG coherence recorded in two frequency bands: upper alpha (9.96-11.94 Hz) and upper beta (21.91-29.88 Hz). Further details of the choice of frequencies is outlined in Section 2.5. Three participant groups were compared: healthy controls (HC), and two groups of schizophrenia patients – those with a history of auditory hallucinations (AH), and those who had not experienced hallucinations for at least 12 months (nonAH). Electrodes chosen were located at homologous sites over each cerebral hemisphere, in areas known to be important in auditory processing. Following the MRI findings reported by Gavrilescu et al. (2010), we hypothesised that interhemispheric connectivity, as measured by EEG coherence, would be altered in schizophrenia patients relative to controls; specifically, that it would be decreased in the AH patient group, measured as a decrease in EEG coherence, and that the nonAH group would show mean coherence values similar to the HC group. Following our previous findings in which the interhemispheric transfer of an auditory ERP response was

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dependent both on the participant group and the stimulus presented (Henshall et al., 2012), and assuming that beta oscillations are involved in neural network integration in central auditory processing, we also hypothesised that, in the upper beta frequency range, differences in coherence may exist between subject groups following the presentation of two auditory stimuli – pure tones and words.

2. Material and Methods

2.1 Participants

The North-Western Mental Health Research & Ethics Committee approved this study, and all subjects gave written informed consent for their participation. Patient recruitment was via an existing data-base of outpatients held by the Mental Health Research Institute, and from the Mid-West Area Mental Health Service (Melbourne, Australia). Control participants were recruited via advertising in local newspapers.

Three subject groups were included: two groups of patients with a DSM-IV diagnosis of schizophrenia, and healthy controls (HC). All participants had hearing within normal limits bilaterally, and were excluded if they had a history of major head trauma, an estimated IQ<70, or neurological disorder. Controls were excluded if they had a personal or close family history of psychiatric disorder, and patients were excluded if they had a co-morbid diagnosis of another psychiatric illness. Following interview, patients with schizophrenia were classified into an AH group, who had experienced auditory hallucinations within the last week, and the nonAH group, who had no experience of auditory hallucinations within the last year. The PANSS includes a subtest (p3) for hallucinatory behaviour, rated on the frequency and severity of hallucinations: NonAH patients scored from 0 (absent) to 2 (mild), and AH patients scored from 4 (moderate) to 7 (extreme) on the p3 subtest. Demographic details are summarised in Table 1, and further details of this same cohort of subjects is described in Henshall et al. (2012).

2.2 Stimuli

Two acoustic stimulus types were used: pure tones and single syllable words. Tones were 1 kHz pure tones of 200 ms duration, with a 10 ms rise/fall time. The words were single-syllable words, spoken by a male speaker with an average Australian accent, with a mean length of 512 ms. The stimuli (tones, words) were presented monaurally to each ear. There were 42 presentations of both stimulus types to each

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ear, and stimuli were presented in blocks of 6 stimuli, with the order (stimulus type, ear) varied using a Latin Square design. The presentation level was 70 dBSPL, and stimuli were delivered via insert earphones (E.A.R. Ear-Link) with an interstimulus interval of 2 s between stimulus onsets. Full details of the stimuli have recently been published elsewhere (Henshall et al., 2012).

2.3 Procedures

Participants sat in a comfortable arm chair in a quiet office and wore a 64 channel Ag/AgCl electrode cap (Compumedics, Quik-Cap), positioned according to the 10-20 international electrode positioning system. The ground was positioned on the forehead (FPz), a linked-ear reference was used, and eye movements were recorded using VEOG and HEOG bipolar electrodes. Continuous EEG was recorded using a 64 channel PC-based acquisition system (Neuroscan) and software (SCAN 4.3), with electrode impedances kept below 5 kΩ. The signals were amplified 20,000 times and sampled at 500 Hz with a 0.05 to 40 Hz band-pass filter. (Subjects were participating in more than one study; 64 channels of data were acquired, although a smaller number were used in this experiment – see Section 2.4).

Participants were told that they would hear a list of tones and words, and were asked to relax and with their eyes closed and listen to the stimuli, without responding in any way. They were asked to report any auditory hallucinations which occurred during the recordings, and informed that the procedure would be stopped should a hallucination occur. No participant reported AHs during testing.

The EEG data were analysed off-line. Eye-blinks were removed using the ocular artefact reduction method (Neuroscan, 2003). The data were segmented into epochs of 500 ms comprising the post-stimulus interval and the 500 ms immediately prior to each stimulus onset, and were band-pass filtered between 1 and 30 Hz (24 dB / octave). Epochs were rejected where the voltage exceeded + / - 50 μV.

Epochs for the four different stimulus conditions (right and left ears, tones and words) were sorted. Coherence was calculated for 6 electrode pairs (described below), using SCAN 4.3 software, for each participant and each condition separately. In order to provide a baseline of activity, coherence for pre-stimulus epochs of 500 ms was also calculated in the same manner.

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Coherence is a correlation coefficient computed from recordings of neural activity at two EEG sites by estimating the correlation between the activity at the selected sites, in the frequency domain (Sakkalis, 2011). It is analogous to the r^2 statistic; at frequency *f*, it measures the proportion of the variance of the signal recorded at channel *x* that can be accounted for by a best-fit linear relationship with activity recorded at channel *y*. The cross spectrum, C_{xy}, is a measure of covariance between the two signals at frequency *f*, and the power spectrum, *P*, quantifies the variance of the signals. The coherence was computed between two channels by dividing the cross spectrum, C_{xy} (squared), by the product of the power spectra of both signals, P_x, P_y :

$$Coh_{xy}^{2}(f) = \frac{|C_{xy}(f)|^2}{P_x(f) P_y(f)}$$

Coherence values range between 0 and 1; higher values indicate that neural activity at a given frequency is correlated in both phase and amplitude, and values close to zero are consistent with low correlation in relative phase and / or signal amplitude (Nunez and Srinivasan, 2006).

2.4 Choice of electrodes

Electrodes were selected based on their locations as described by Koessler and colleagues (2009). Table 2 shows the main macro-anatomical cortical projections and Brodmann area variations, as determined by Koessler et al. (2009), pertinent to the context of auditory processing.

The homologous electrode pairs chosen were C1-C2, C3-C4, C5-C6, T7-T8, Ft7-Ft8, and Cp5-Cp6. Electrode pairs C3-C4 and C5-C6 were selected as our earlier study (Henshall et al., 2012) found, using IHTT, that interhemispheric connectivity was altered at these sites in the same patients, using the same EEG data set as used here. Furthermore, Sritharan et al. (2005) reported a significant increase in coherence using electrodes C5 and C6 in a different group of patients who were hallucinating during the recordings. Coherences recorded at C3-C4 and T7-T8 (T3-T4) have been reported in several studies in psychosis patients (Angelopoulos et al., 2011; Medkour et al., 2010; Merrin and Floyd, 1996; Winterer et al., 2003). The remaining pairs (C1-C2, Ft7-Ft8 and Cp5-Cp6) were selected based on their location close to cerebral structures known to be important in the processing of auditory information, particularly speech. These were the primary auditory cortex (BA 41 and part of BA

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42) located on the superior temporal gyrus, and Wernicke's area, located on the superior temporal gyrus (BA 22) and the supramarginal gyrus (BA 39/40) (Mesulam, 1998).

2.5 Choice of Frequency Bands

Coherence was calculated in the frequency range 0 – 29.87 Hz, with 1.98-Hz-wide bins, and two frequency ranges were selected for analysis. Despite its theoretical relevance in localised perceptual processes, gamma band activity could not be included in the present study because pass-band filtering at 30 Hz was necessitated by the presence of 50 Hz mains interference.

Initial data exploration found that the maximum average coherence values were, without exception, recorded in the 9.96 – 11.94 Hz bin in each condition and electrode pair, in the healthy control group (see Figure 1). This was to be expected, as subjects were simply asked to listen passively to the stimuli with their eyes closed. As the data we report here was recorded between interhemispheric temporal electrodes in a task free condition, the high alpha 9.96 – 11.94 Hz frequency bin in the alpha-band was consequently selected for analysis.

The high beta band, comprising 21.91-29.88 Hz, was the second frequency band analysed. Because the EEG beta band is four times the width of the alpha band, four spectral bins covering the range 21.91-29.88 Hz were averaged to obtain mean high beta coherence values for each participant and condition.

2.6 Statistics

Coherence values are equivalent to squared linear correlation coefficients and consequently follow a bivariate normal distribution (Nunez and Srinivasan, 2006). The square roots of the coherence values were therefore transformed with the Fisher-z transformation prior to statistical analyses.

The transformed coherence values for the selected electrode pairs were analysed using 3 x 3 x 2 GLM ANOVA, with subject group as the between-subject factor, and stimulus type (none; i.e. the prestimulus interval, tones; words) and ear of stimulation as within-subject factors. Separate ANOVAs were performed for each pair (C1-C2, C3-C4, C5-C6, T7-T8, Cp5-Cp6 and Ft7-Ft8). Where a between-group significance level of p=0.05 was found on ANOVA, post-hoc pairwise comparisons were performed using the Tukey's HSD test with a family error rate of α=0.05.

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3. Results

3.1 Statistical analysis – Alpha coherence

Means and standard errors for the alpha coherence data are illustrated in Figure 2, panel A. Significant main effects of group on alpha band coherence values were found for electrode pairs C3-C4 ($F(2,298)=15.578$, $p<0.001$), C5-C6 ($F(2,298)=9.941$, $p<0.001$), Ft7-Ft8 ($F(2,258)=29.921$, $p<0.001$), and Cp5-Cp6 ($F(2,276)=6.692$, $p=0.001$). No significant differences were found for stimulus type or ear of stimulation in any comparison, and there were no significant group x ear or group x stimulus interactions.

Post-hoc multiple comparisons using Tukey's HSD test found different patterns of results, depending on electrode pair. These were as follows (see also Figure 3, panel A): On electrode pairs C3-C4 and C5-C6, the highest mean coherence values were found in the nonAH group, and the lowest in the AH group, while the mean values of the HC group fell in between the two patient groups. The following significant between-group differences were found: HC vs nonAH, C3-C4 ($p=0.023$); HC vs AH, C3-C4 ($p=0.013$) and C5-C6 ($p=0.009$); and nonAH vs AH patient groups, C3-C4 ($p<0.001$) and C5-C6 ($p<0.001$). On electrode pairs Cp5-Cp6 and Ft7-Ft8, the mean coherence values of the HC group were the highest, the AH group were the lowest, and the nonAH group fell between the other two groups. Post-hoc comparisons found the following significant between-group differences: HC vs nonAH, Cp5-Cp6 ($p=0.003$) and Ft7-Ft8 ($p<0.001$); HC vs AH, Cp5-Cp6 ($p=0.006$) and Ft7-Ft8 ($p< 0.001$); and nonAH vs AH on Ft7-Ft8 ($p=0.001$).

3.2 Statistical analysis – Beta coherence

Means and standard errors for the upper beta band coherence results (21.91-29.88 Hz) are illustrated in Figure 2, panel B. Significant main effects of group on beta coherence values were found for electrode pairs C1-C2 ($F(2,300)=6.88$, $p=0.001$), C3-C4 ($F(2,298)=5.69$, $p=0.004$), Ft7-Ft8 ($F(2,285)=4.04$, $p=0.019$) and Cp5-Cp6 ($F(2,276)=3.44$, $p=0.034$). No significant differences were found for stimulus type or ear of stimulation in any comparison, and there were no significant group x ear or group x stimulus interactions.

Post-hoc Tukey's testing found the following significant results (figure 3, panel B): significantly higher beta coherence values were found in the nonAH group compared

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to the HC group on electrode pair C1-C2 (HC vs nonAH; p=0.001) and Ft7-Ft8 (p=0.025). On electrode pair C3-C4, the AH group had significantly lower mean coherence than nonAH group (p=0.003). On pair Cp5-Cp6, the nonAH group was significantly lower than the HC group (p=0.025).

3.3 Gender effects – males-only analyses

There was a significant gender imbalance between groups ($\chi^2(2) = 8.01$, p=0.02), with the nonAH group having fewer females (only 1) than the other groups (see Table 1). Therefore, the ANOVAs were repeated in a "males only" condition in which female participants were excluded.

Results of ANOVA were largely consistent with the results when all participants were included. For alpha coherence results, a significant main effect of group was found on electrode pairs C3-C4 ($F(2,214)=9.41$, $p<0.001$), C5-C6 ($F(2,214)=5.07$, p=0.007) and Ft7-Ft8($F(2,186)=23.03$, $p<0.001$). For the beta coherence results, a significant group effect was found on electrode pairs C1-C2 (F(2,216)=6.67, p=0.002), C3-C4 (F(2,214)=3.18, p=0.044) and Ft7-Ft8 (F(2,186)=6.14, p=0.003). The main effect of group, for both alpha and beta coherence results, was not significant when female participants were excluded for the Cp5-Cp6 pair, where they had been when all subjects were included. Inspection of the data suggests these changes in significance were due to lower statistical power when only male participants were included, rather than a gender difference.

4. Discussion

The results presented here show significantly different interhemispheric connectivity, measured using alpha (9.96-11.94 Hz) and beta (21.91-29.88 Hz) EEG coherence, between two groups of schizophrenia patients and healthy controls, in areas of the cortex known to be important in auditory processing. Coherence was calculated under three different auditory stimulus conditions: pre-stimulus (i.e. in quiet), and following the onset of 1 kHz pure tones and single-syllable words. The assumption was made here that the EEG activity recorded for a particular scalp recording site reflects proximal cortical activity, and the cranio-cerebral correlations with the 10-10 electrode system proposed by Koessler et al. (2009) has been used to interpret the results. The limited spatial resolution of scalp EEG recordings due to volume conduction effects should be acknowledged, but the temporal resolution is very high,

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making estimation of spectral coherence possible (Nunez and Srinivasan, 2006). The results reported here show different patterns across the 6 electrode pairs considered, suggesting there was not a high degree of cross-talk between recording sites.

Current theories of the pathophysiology of schizophrenia highlight the importance of impaired connectivity between cortical regions of the brain (Andreasen, 2000; Friston, 1998; Uhlhaas et al., 2008). Uhlhaas (2008) has suggested that alterations to neural oscillatory activity found in schizophrenia patients may represent functional correlates of dysfunction in cortical network connectivity in the illness. Comparing our results for upper alpha and upper beta interhemispheric coherence, it is evident that the differences between the three subject groups were larger for the alpha band data in cerebral areas pertinent to auditory processing. Statistically different results were found for the upper beta-band analyses at the level of $p<0.05$, for four electrode pairs. However, inspection of the data (see Figure 2B) shows the between-group differences on those electrode pairs which are located closest to auditory processing regions (C3-C4, Ft7-Ft8 and Cp5-Cp6) are so small as to be potentially trivial, and these differences may not represent clinically significant group variability. According to Koessler and colleagues (2009), the remaining electrodes, C1 and C2, project principally over non-auditory areas. Here the two patient groups did not differ significantly from one another ($p=0.16$), suggesting the finding on this pair was not due to the presence or absence of auditory hallucinations.

There were no significant differences found in the coherence values recorded pre-stimulus and following the two different stimulus types (tones, words) at either frequency band analysed. This finding was unexpected. However, the null hypothesis (of no evoked response) can be rejected, as the same EEG data set showed clear temporal evoked potentials which were used to calculate IHTT measures of connectivity (Henshall et al, 2012). For alpha rhythms, with a dominant basis in long-range thalamo-cortical loop activity (Nunez and Srinivasan, 2006), the apparent absence of evoked changes in coherence implies that these ascending common-mode signals may simply mask any changes in cortico-cortical connectivity. In as much as beta rhythms may be correlated with alpha (Nunez and Srinivasan, 2006), a similar argument may be advanced for the apparent absence of evoked changes in beta coherence. Moreover, the absence of pre- and post-stimulus differences in coherence here is consistent with an earlier report suggesting that, in a passive listening task, the

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auditory evoked response is a linear transformation (specifically, an impulse response) of pre-stimulus EEG (Wright et al., 1990). Additionally, the non-significant differences in coherence measures pre- and post-stimulus recorded here demonstrates that the group differences are not attributable to systematic group differences in cognitive effects such as memory, attention or motivation – see below.

Significant differences were, however, found between subject groups, particularly in alpha band coherence, suggesting persistent underlying alterations in interhemispheric connectivity in schizophrenia patients. These global group differences are unlikely to have been due to factors unrelated to schizophrenia. The two clinical groups were matched for medication using chlorpromazine equivalents (Table 1), and it has been reported that deficits in neural oscillations are present in schizophrenia patients at illness onset, and are unlikely to be due to the effects of medication (Uhlhaas and Singer, 2010). Alpha activity has been associated with working memory engagement (Klimesch, 1999; Scheeringa et al., 2009). However, the passive listening task did not specifically engage memory processes, and the ANOVA for WMS performance showed was no difference between patient groups (Tukey HSD: nonAH vs AH p=0.929). Attention may have differed between groups and, although we lack a direct measure of attention to compare groups directly, negative symptoms could be used as a proxy-measure of attention. The two schizophrenia groups were matched on the PANSS negative symptom scale, while differing significantly in coherence results. Moreover, were attentional effects important to our results, we might expect the high beta results to show greater between-group differences. Instead, it was in the alpha band where the largest between-group differences were found. Similarly, neither do potential motivational differences fully account for our results. Finally, we have no reason to suggest that the neural substrates involved in the performance of this task would have differed between the three subject groups.

Dominant neurocognitive models of auditory hallucinations hypothesis that AHs arise from the misattribution of inner speech (David, 1994; Frith and Done, 1988; Frith et al., 1996) or of mis-remembered auditory memories of speech (eg. Copolov et al., 2003; Hoffman et al., 1994; Waters et al., 2006). The hypothesis that cortical regions involved in the processing of language are mis-connected is common to both these models. The finding of reduced mean alpha coherences on electrode pairs C3-C4 and C5-C6 in the AH group relative to controls in this study is consistent with the

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hypothesis that interhemispheric transfer may be reduced in this group of patients at these sites. This result is similar to the findings of Medkour and colleagues who reported that gamma coherence on C3-C4 was lower in positive symptom patients than in controls or patients with negative symptoms (Medkour et al., 2010). Additionally, it offers further support for the conclusion of Henshall et al. (2012) using the same electrode pairs, but different electrophysiological methods, that connectivity in interhemispheric pathways were impaired in hallucinators at these sites.

In the majority of subjects reported in Koessler et al. (2009), electrodes C3, C4, C5 and C6 projected principally to the post-central gyrus, an area important in processing somatosensory information (see Table 2). In several subjects however, these electrodes projected to Wernicke's area or its contralateral homologue (BA 22 and BA 40). As stated above, conclusions drawn from placement of electrodes must be interpreted with caution. However, the pattern of results seen here, in which mean coherence values recorded from the nonAH group were higher and the AH group lower relative to controls respectively is, at least in part, consistent with the findings of our previous study in which the IHTT (to word stimuli) was higher in nonAH patients and lower in AH patients than controls respectively, on the same electrode pairs (Henshall et al., 2012).

According to Crow's hypothesis, schizophrenia may be associated with a reduction or reversal of the normal asymmetry of cortical regions involved in language processing (Crow, 1997a; Crow, 2004). In this model, information which is normally processed in the left hemisphere could, at least in part, also be processed in the right hemisphere, and / or processed in either hemisphere differently from the normal condition. Crow has further hypothesised that the changes to lateralization of the normally asymmetrical language areas in patients with schizophrenia may lead to interhemispheric misconnections across the corpus callosum (Crow, 1997b; Crow, 1998). It could be speculated, therefore, that cortical regions with reduced asymmetry (or increased symmetry) in schizophrenia patients may appear to be more highly connected than the same typically-asymmetrical areas in healthy individuals. Evidence of such a phenomenon could potentially be observed as an increase in EEG coherence, which we found in the non-hallucinating patient group of the present study on electrode pair C3-C4.

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Previous studies investigating alpha coherence on electrode pair C3-C4 in schizophrenia patients have reported no significant differences between patients and controls (Winterer et al., 2003; Winterer et al., 2001). In the present study, significant between-group differences were found for electrode pairs C3-C4 and C5-C6 when the schizophrenia patients were dichotomised by the presence of auditory hallucinations, but results were non-significant when all patients were treated as one group: C3-C4 (p=0.79); C5-C6 (p=0.31). Thus the presence or absence of auditory hallucinations appears to be an important consideration when comparing interhemispheric alpha coherence at these sites.

A significant between-group difference was found on ANOVA between control participants and schizophrenia patients identified as a single group on electrode pairs Ft7-Ft8(F(1,264=45.36, p<0.001) and Cp5-Cp6 (F(1,282)=13.45, p<0.001) for alpha coherence. Reduced interhemispheric connectivity at these locations may therefore be present in schizophrenia patients generally. Considering three subject groups, the mean coherence on pair Ft7-Ft8 was highest in the HC group, significantly lower in the nonAH group, and further significantly reduced in the AH group. Ft7 and Ft8 both primarily projected to BA 22 in 75% of Koessler and colleagues' (2009) subjects. Mean alpha coherence values on the Cp5-Cp6 pair were significantly lower in both nonAH and AH patient groups than in control participants, but were not significantly different from one another. The predominant projections of Cp5 and Cp6 were across both BA 22 and BA 40 in most of Koessler's subjects, i.e. to the region where Wernicke's area is located. It may be that the degree of interhemispheric connectivity is reduced in both patient groups to a similar extent in BA 40, but potentially reduced more in the AH group than the nonAH group across BA 22, as suggested by the Ft7-Ft8 results.

The technique of EEG coherence quantifies a complex-domain correlation in neural activity between spatially-remote brain regions – it does not explain the cause of any observed differences between groups. However, the importance of transcallosal connectivity between bilateral superior temporal areas in speech perception has recently been demonstrated in healthy people, with a report that the size of callosal tracts which connect superior temporal areas correlated positively with speech perception performance (Westerhausen et al., 2009). In AH patients, evidence of transcallosal misconnections between auditory processing regions is increasing in the

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MR literature (Gavrilescu et al., 2010; Hubl et al., 2004; Mulert et al., 2012). The role of Wernicke's area may be conceptualised as decoding auditory stimuli in the form of words into the symbolic associations which are their meaning (Mesulam, 2000). If interhemispheric connectivity were compromised in this region in AH patients, which our aggregate results appear to suggest, the dynamic transfer of information across the corpus callosum needed to decode features of speech, such a phonology, syntax and prosody, may break down. It could be speculated that a deterioration of this relationship may contribute to the pathophysiology of auditory hallucinations, and their propensity to be experienced as speech.

5. Conclusions

Schizophrenia patients, dichotomised into two groups by the presence or absence of a recent history of auditory hallucinations, showed significantly different patterns of interhemispheric connectivity, measured using EEG alpha-band coherence, in areas of the cortex known to be important in central auditory processing. The AH patient group showed reduced alpha coherence relative to both controls and nonAH patients, consistent with the hypothesis that interhemispheric transfer of auditory information is reduced in schizophrenia patients who experience auditory hallucinations.

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Declaration of Interest.

None

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Figure Captions

Figure 1. Mean coherence values for electrode pair Ft7-Ft8, calculated at 1.98 Hz-wide bins from 0 to 29.87 Hz, following tone and word stimuli (collapsed data).

Figure 2. Coherence values for the 6 electrode pairs; means and standard errors are shown for each group and electrode pair for the 9.96-11.94 Hz band in Panel A, and for the 21.91-29.88 Hz band in Panel B.

Figure 3. Relative coherence values comparing subject groups for each electrode pair. Panel A: 9.96-11.94 Hz band; Panel B: 21.91-29.88 Hz band. See figure legend for explanation.

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Table 1 Participant Details

	NC *N = 17*	*nonAH* *N = 17*	*AH* *N = 19*
Age (years)	35.5 (9.0)	41.2 (11.4)	37.2 (9.1)
Gender*	11M / 6 F	16M / 1F	12M/7F
Education (years)	14.9 (3.5)	13.7 (3.0)	12.6 (2.8)
Predict FSIQ (NART)	109 (12)	103 (12)	104 (14)
Coren's Laterality Index	0.47 (0.53)	0.64 (0.25)	0.51 (0.45)
WMS Total**	11.2 (3.4)	7.3 (2.9)	6.9 (3.5)
Age at onset (years)	N/A	24.1 (6.5)	23.6 (5.6)
Duration of illness (years)	N/A	17.5 (9.6)	12.6 (8.9)
PANSS positive	N/A	16.9 (4.7)	18.6 (4.2)
PANSS negative	N/A	14.2 (4.9)	13.0 (5.7)
PANSS general	N/A	31.9 (8.2)	32.7 (10.3)
PANSS p3***	N/A	1.9 (0.8)	3.9 (1.3)
CPZe (mg/day)	N/A	547 (228)	453 (252)

*$p<0.05$; **$p=0.001$; Post-hoc tests: NC>nonAH, NC>AH; ***$p<0.001$
Predict FSIQ (NART); National Adult Reading Test: full-scale IQ (Nelson, 1982)
WMS; Logical Memory 1, Wechsler Memory Scale (Wechsler, 1987)
Positive, negative and general symptom scales of the Positive and Negative Syndrome Scale (PANSS) for schizophrenia (Kay et al., 1987)
PANSS p3; hallucinatory behaviour subtest of the PANSS
CPZe; chlorpromazine equivalent medication

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Table 2, after Koessler et al. (2009)

Electrode	*Main macro-anatomical structures (16 subjects)*	*Main variations relevant to auditory processing*
C1	75% Pre-central gyrus (BA 4 & 6)	
C2	56% Post-central gyrus (BA 1,2,3)	25% Supra-marginal gyrus (BA 40)
C3	62.5% Post- central gyrus (BA 1,2,3)	25% Superior temporal gyrus (BA 22)
		6% Superior temporal gyrus (BA 42)
C4	81.5% Post-central gyrus (BA 1,2,3)	6% Supra-marginal gyrus (BA 40)
C5	44% Post-central gyrus (BA 1,2,3)	37.5% Supra-marginal gyrus (BA 40)
C6	50% Post-central gyrus (BA 1,2,3)	25% Supra-marginal gyrus (BA 40)
T7	81.5% Middle temporal gyrus (BA 21)	12.5% Superior temporal gyrus (BA 22)
T8	56% Middle temporal gyrus (BA 21)	38% Superior temporal gyrus (BA 22)
Ft7	75% Superior temporal gyrus (BA 22)	
Ft8	75% Superior temporal gyrus (BA 22)	
Cp5	44% Superior temporal gyrus (BA 22)	37.5% Supra-marginal gyrus (BA 40)
Cp6	62.5% Supra-marginal gyrus (BA 40)	37.5% Superior temporal gyrus (BA 22)

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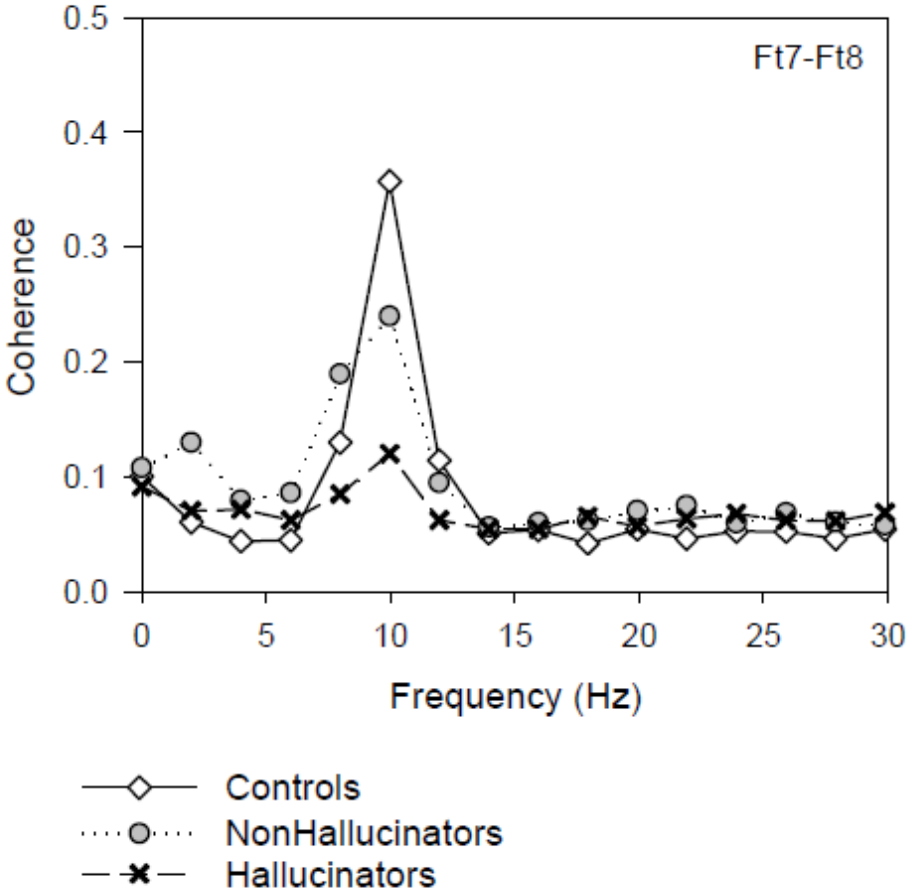

Figure 1

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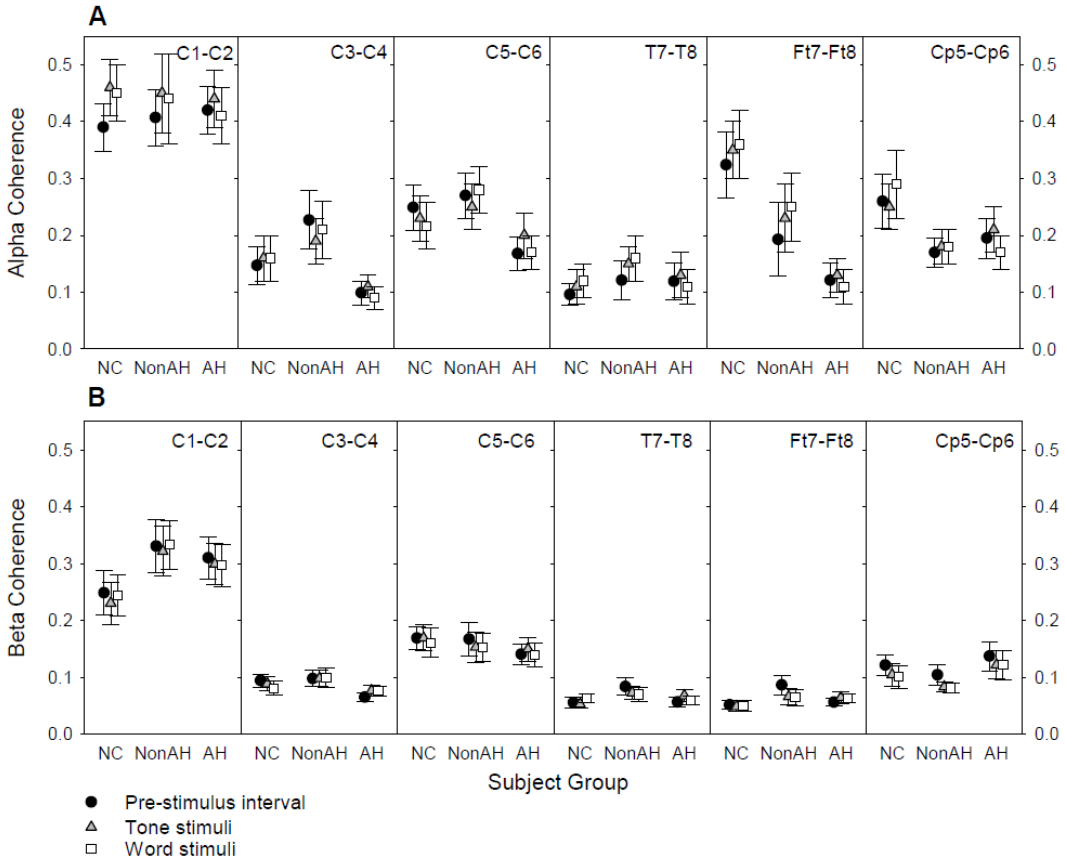

Figure 2

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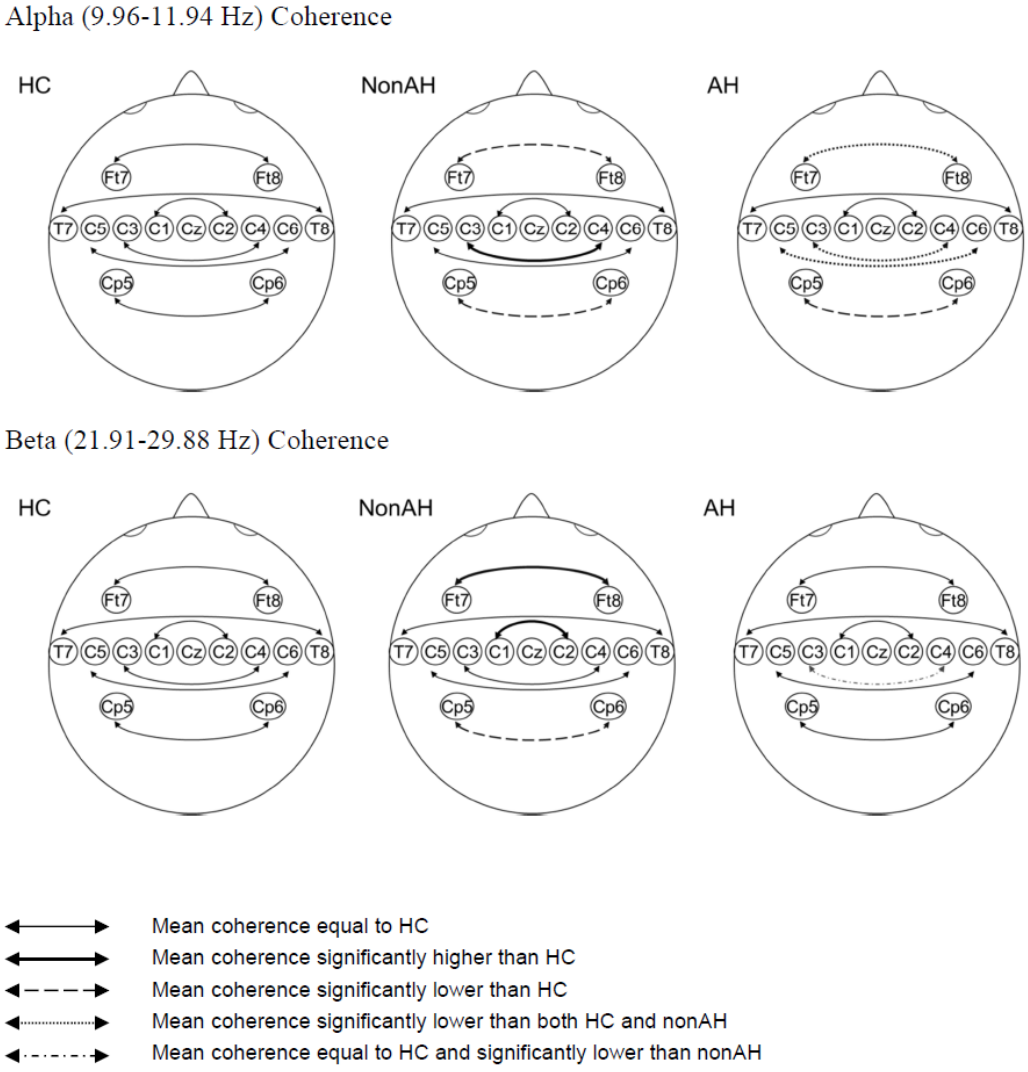
Figure 3



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Highlights

Schizophrenia patients with and without auditory hallucinations

Alpha and beta EEG spectral coherence calculated between left and right auditory cortical regions

Interhemispheric connectivity in hallucinators lower compared to controls & non-hallucinators

Interhemispheric connectivity between auditory processing regions implicated

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