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Interhemispheric transfer time in patients with auditory hallucinations: An auditory event-related potential study ☆

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Central auditory processing in schizophrenia patients with a history of auditory hallucinations has been reported to be impaired, and abnormalities of interhemispheric transfer have been implicated in these patients. This study examined interhemispheric functional connectivity between auditory cortical regions, using temporal information obtained from latency measures of the auditory N1 evoked potential. Interhemispheric Transfer Times (IHTTs) were compared across 3 subject groups: schizophrenia patients who had experienced auditory hallucinations, schizophrenia patients without a history of auditory hallucinations, and normal controls. Pure tones and single-syllable words were presented monaurally to each ear, while EEG was recorded continuously. IHTT was calculated for each stimulus type by comparing the latencies of the auditory N1 evoked potential recorded contralaterally and ipsilaterally to the ear of stimulation. The IHTTs for pure tones did not differ between groups. For word stimuli, the IHTT was significantly different across the 3 groups: the IHTT was close to zero in normal controls, was highest in the AH group, and was negative (shorter latencies ipsilaterally) in the nonAH group. Differences in IHTTs may be attributed to transcallosal dysfunction in the AH group, but altered or reversed cerebral lateralization in nonAH participants is also possible.

1. Introduction

Auditory verbal hallucinations (AHs) are a common and often incapacitating symptom of schizophrenia. Many of the defining symptoms of schizophrenia represent disturbances in language functioning (Crow, 2004a), and AHs are perhaps the most obvious of these. Although many studies have examined the phenomenology of AHs, their neural substrate remains unclear.

Imaging studies have consistently found the superior temporal gyrus, the cortical region in which Heschl's gyrus (primary auditory cortex) the planum temporale (part of the auditory association cortex) are located, to have reduced grey matter volume in schizophrenia patients (Chance et al., 2008; Shenton et al., 2010, 2001; Williams, 2008). In healthy individuals, hemispheric asymmetries of the auditory cortical areas concerned with receptive language are well documented; the left auditory area, especially the planum temporale, is larger than the right in most subjects (Geschwind and Levitsky, 1968; Shenton et al., 2001). In studies of schizophrenia, the left–right asymmetry of the planum temporale volume has been reported to be reduced (Hirayasu et al., 2000), or reversed (Barta et al., 1997). Heschl's gyrus has also been found to be reduced in volume in schizophrenia patients (Crespo-Facorro et al., 2004; Hirayasu et al., 2000), an effect which is greater in the left than the right hemisphere (Kasai et al., 2003). Furthermore, Crespo-Facorro et al. (2004) have reported that reduced planum temporale volume is associated with positive symptoms of schizophrenia including auditory hallucinations and delusions, Sumich et al. (2005) reported an association between reduction in volume of the left Heschl's gyrus and the experience of auditory hallucinations, and Hubl et al. (2010) have reported higher Heschl's gyrus volumes in the right hemisphere relative to the left hemisphere in AH patients compared with NH patients and controls.

It is well established that language processing is lateralized to the left hemisphere in most people (Kimura, 1961, 1967). Crow

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hypothesised that psychosis and the use of language in humans are intrinsically linked via their common evolutionary origin involving hemispheric specialisation (Crow, 1998), and he has referred to schizophrenia as the "price of language" (Crow, 1997a, 2004b). He has argued that cerebral asymmetry is disrupted in schizophrenia; in particular, that the degree of functional lateralization is reduced, or possibly reversed in some language areas. Furthermore, he argued that language abnormalities seen in schizophrenia may be a consequence of the abnormal cerebral lateralization of language functions; in particular a failure of left hemispheric dominance for language (Crow, 1997a, 2004b).

The transfer and integration of neural activity between the two cerebral hemispheres may also be disrupted in schizophrenia. Crow (1997b, 1998) hypothesised that schizophrenia is a "misconnection syndrome", in which connections between asymmetrical cortical regions of the cerebral hemispheres, in particular the language-specialised areas, may be disrupted. Behavioural studies have demonstrated possible evidence of interhemispheric transfer (IHT) dysfunction in patients who experience auditory hallucinations. Members of our group (McKay et al., 2000) assessed patients for auditory processing deficits using a battery of clinical audiological tests. Three subject groups were compared: normal controls; and two groups of schizophrenia patients — auditory hallucinators, and patients who did not experience auditory hallucinations. The pattern of results seen in both patient groups was most consistent with either right auditory cortex dysfunction or interhemispheric pathway deficits. The results suggested that the deficits seen in the hallucinating patient group compared to normal controls may be essentially the same as those seen in the non-hallucinating patients, but that they may be more severe (McKay et al., 2000). Additionally, Gavrilescu et al. (2010) have recently published functional MRI evidence of reduced interhemispheric connectivity of primary and secondary auditory cortices in schizophrenia patients who experience auditory hallucinations compared to both non-hallucinating patients and normal controls. Non-hallucinating patients did not show a reduction in connectivity relative to normal control participants, demonstrating a trait effect apparently specific to hallucinators.

Interhemispheric transfer in schizophrenia has been studied using auditory-evoked magnetoencephalography (MEG). Rockstroh et al. (2001) investigated an early MEG response for both tones and the syllable/ba/. All normal controls showed a larger magnitude of the MEG contralaterally in response to tones, but the asymmetry was reversed (the ipsilateral magnitude was larger) in a significant number of the schizophrenia patients. In response to syllables, however, the asymmetry was similar between groups. The authors suggested that the group differences in the ability to transfer information between hemispheres, which depended on whether the stimulus was a tone or a syllable, may be a result of an altered brain structure in schizophrenia.

Interhemispheric transfer time (IHTT) is a measure of interhemispheric transfer which is based on the electroencephalogram (EEG), and is defined as the latency difference between specified early event-related potential (ERP) peaks recorded from the contralateral and ipsilateral hemispheres (Larson and Brown, 1997). IHTT has previously been studied using visual evoked potentials in schizophrenia patients (Barnett et al., 2005; Barnett and Kirk, 2005; Endrass et al., 2002). Endrass et al. (2002) presented written words and pseudowords to the left and right visual hemifields tachistoscopically. Their normal controls showed a significantly faster IHTT from right-to-left hemispheres than from left-to-right hemispheres when words were presented, but no hemisphere advantage when pseudowords were presented. In schizophrenia patients however, there was no evidence of a faster right-to-left transmission of information for either words or pseudowords. They attributed their results to a deficit in IHT via the corpus callosum, particularly for verbal information, in schizophrenia.

Barnett and Kirk (2005) reported a study with similar methods and findings to those of Endrass et al. (2002). However they argued that dysfunctional right hemisphere activation would be more likely than callosal dysfunction to cause the IHTT asymmetry differences they observed in schizophrenia patients. They proposed that an excess of myelinated axons in the right hemisphere relative to the left may be responsible for the faster right-to-left IHTT found in normal controls. They reasoned that the pattern of reduced right-to-left IHTT (for both words and pseudo-words) in schizophrenia patients compared to normal controls should also be apparent in the left-to-right condition if it were caused by callosal dysfunction, but this was not found in their data. Rather, they argued that it supported the proposition that reduced right hemisphere white matter would lead to reduced right-to-left asymmetry in schizophrenia patients compared to healthy controls.

Auditory evoked response potentials have been extensively studied in schizophrenia, although we are unaware of any studies that have examined the IHTT of auditory ERPs. The auditory N1, the prominent vertex-negative peak which occurs approximately 100 ms post stimulus onset, has been found to have a lower amplitude and longer latency in response to pure tone stimuli in schizophrenia patients compared to healthy controls (Boutros et al., 2004). A recent review, however, has reported that the association between schizophrenia and a reduction in auditory N1 amplitude is weak (Rosburg et al., 2008). Two of the main neural sources of the auditory N1 are within the auditory cortex. The first is a source on the supratemporal plane of the temporal lobe, most likely in the primary auditory cortex, and the response is largest when recorded at the vertex using a mastoid or earlobe reference. The generator for the second main component (the T-complex) is thought to be on the superior temporal gyrus in the secondary auditory cortex. It is most easily seen when recorded from scalp electrodes sited temporally, and is larger and slightly earlier when measured in the hemisphere contralateral to the ear of stimulation (Näätänen and Picton, 1987; Tonnquist-Uhlen et al., 2003). Evidence for the importance of this generator in language processing has been reported in children with severe language impairments, in whom the T-complex response has been found to be delayed, show poor morphology or be absent altogether compared with control children (Shafer et al., 2011; Tonnquist-Uhlen, 1996).

In this study, we investigated IHTT using the auditory N1 in schizophrenia patients in response to both pure tones and word stimuli. We compared sub-groups of schizophrenia patients with recent experiences of auditory verbal hallucinations (AH) and patients with no recent experience of auditory hallucinations (nonAH), and compared both clinical groups with normal controls (NC). We hypothesised that the interhemispheric connectivity is altered in schizophrenia, and that this effect is more pronounced in hallucinating patients. Specifically, we hypothesised that the IHTT may be increased in both the AH and nonAH groups relative to the NC group following findings in visual ERPs (e.g. Endrass et al., 2002), and that transfer times would be greatest in the AH group. Word stimuli activate a large cortical network, and there is evidence from previous studies (Barnett and Kirk, 2005; Endrass et al., 2002; Rockstroh et al., 2001) that evoked responses for verbal stimuli show important interhemispheric transfer differences from those evoked in response to tones in patients with psychosis. Following Crow's (1998) hypothesis that cerebral lateralization is altered in schizophrenia, and that language processing is consequently affected in this group of patients, we further hypothesised that differences in interhemispheric transfer time may be specific to word stimuli.

2. Materials and methods

2.1. Participants

The North-Western Mental Health Research & Ethics Committee approved this study, and informed consent was obtained from each participant. Normal controls were recruited via advertising in local newspapers. Participants with schizophrenia were recruited via an