NeuroImage: Clinical 6 (2014) 171–179

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Abnormal synchrony and effective connectivity in patients with schizophrenia and auditory hallucinations

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ARTICLE INFO

Article history:
Received 23 March 2014
Received in revised form 27 August 2014
Accepted 31 August 2014
Available online 4 September 2014

Keywords:
Schizophrenia
Auditory hallucinations
Functional connectivity
Cerebellum
Synchrony
Effective connectivity

ABSTRACT

Auditory hallucinations (AH) are the most frequent positive symptoms in patients with schizophrenia. Hallucinations have been related to emotional processing disturbances, altered functional connectivity and effective connectivity deficits. Previously, we observed that, compared to healthy controls, the limbic network responses of patients with auditory hallucinations differed when the subjects were listening to emotionally charged words. We aimed to compare the synchrony patterns and effective connectivity of task-related networks between schizophrenia patients with and without AH and healthy controls.

Schizophrenia patients with AH ($n = 27$) and without AH ($n = 14$) were compared with healthy participants ($n = 31$). We examined functional connectivity by analyzing correlations and cross-correlations among previously detected independent component analysis time courses. Granger causality was used to infer the information flow direction in the brain regions.

The results demonstrate that the patterns of cortico-cortical functional synchrony differentiated the patients with AH from the patients without AH and from the healthy participants. Additionally, Granger-causal relationships between the networks clearly differentiated the groups. In the patients with AH, the principal causal source was an occipital–cerebellar component, versus a temporal component in the patients without AH and the healthy controls.

These data indicate that an anomalous process of neural connectivity exists when patients with AH process emotional auditory stimuli. Additionally, a central role is suggested for the cerebellum in processing emotional stimuli in patients with persistent AH.

Abbreviations: AH, auditory hallucinations; CCTC, cortico-cerebellar–thalamic–cortical; MRI, functional magnetic resonance imaging; BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale; PSYRATS, Psychotic Symptom Rating Scale; ICA, independent component analysis; ICA-TC, ICA-time course; SPM, statistical parametric maps; BOLD, blood oxygenation level dependent; MVAR, multivariate autoregression; CoI, component of interest; GCCA, Granger causal connectivity analysis.

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http://dx.doi.org/10.1016/j.nicl.2014.08.027

1. Introduction

Increasingly, it is hypothesized that schizophrenia reflects subtle connectivity dysfunction (Pettersson-Yeo et al., 2011). Converging neurophysiological and neuroimaging data have documented widely distributed abnormalities in brain activity and functional connectivity (Buckholtz and Meyer-Lindenberg, 2012; Friston and Frith, 1995; Pettersson-Yeo et al., 2011; Stephan et al., 2006), validating the overarching disconnection hypothesis of schizophrenia (Andreasen et al., 1998). In terms of the structural aspects, a qualitative review (Kubicki et al., 2005) and a quantitative meta-analysis (Ellison-Wright and Bullmore, 2009) have documented widespread reductions in white matter fractional anisotropy in chronic schizophrenia, which have also been observed in first-episode patients (Friedman et al., 2008). An abnormal white matter ultrastructure likely underlies abnormal cooperation among brain networks (Calhoun et al., 2009). After finding abnormal functional connectivity between the frontal and temporal regions, Friston and Frith (1995) proposed fronto-temporal disconnection as a key neurobiological feature of schizophrenia. The term "disconnection" connotes reduced connectivity. "Dysconnectivity" has been introduced to refer to abnormal integration between anatomically distinct brain regions (Stephan et al., 2006, 2009). Andreasen et al. (1998) suggested that disruption of the cortico-cerebellar–thalamic–cortical (CCTC) circuits underlies the deterioration in neural synchrony, with improper coordination of the mental processes leading to "cognitive dysmetria." Abnormal neural synchrony (Ford et al., 2007) is hypothesized to be one of the main causes of cognitive dysfunction in schizophrenia. A recent review (Uhlhaas and Singer, 2010) concluded that altered neural oscillations and synchrony are crucial elements in the pathophysiology of schizophrenia. This conclusion was based on aberrant connectivity and synchrony findings in patients with schizophrenia (Friston and Frith, 1995; Garrity et al., 2007; Jafri et al., 2008; Kim et al., 2008), as well as differences in effective connectivity in schizophrenia patients compared to controls (Demirci et al., 2008; Diaconescu et al., 2011; Kim et al., 2008). The dysconnectivity hypothesis has been extended to explain specific symptoms in schizophrenia, particularly auditory hallucinations (AH) (Rish et al., 2013) and visual hallucinations and AH in findings by Amad et al. (2014).

AH are a hallmark of the psychotic experience. Neuroimaging studies have found abnormal activation in patients with AH, particularly in cortical regions of language processing (Allen et al., 2008). Several studies have shown abnormal structural and functional connectivity in patients with AH (Benetti et al., 2013; Mechelli et al., 2007).

Most studies have found reduced functional connectivity between the temporal, limbic and frontal areas (Hoffman et al., 2011; Vercammen et al., 2010). Few studies (e.g., Mechelli et al., 2007) have analyzed synchrony and effective connectivity in a group of patients with schizophrenia and AH.

Emotional processing disturbances have been related to the origination of AH (Sanjuán et al., 2006; Aleman and Larøi, 2008). Our group has focused on understanding emotional processing in patients with AH. In a previous study, we obtained evidence of enhanced activation of the limbic and frontal brain areas in a small group of patients with persistent AH engaged in passively listening to emotional words (Sanjuán et al., 2007). These results implicated circuits subserving the processing of emotional stimuli as a neural substrate of AH. In a subsequent work, we studied functional connectivity in response to an emotional auditory paradigm in patients with AH by conducting independent component analyses (ICA) (Escartí et al., 2010). Using this approach, the activated areas could be obtained by selecting the ICA components related to the emotional auditory paradigm. Functional connectivity is then characterized by detecting statistical dependencies among the time courses of the areas activated in response to the auditory emotional stimuli (Escartí et al., 2010). In addition to the temporal, frontal and parietal networks detected in all subjects, in the schizophrenia patients with AH, we observed a specific pattern of functional connectivity involving activation of the limbic structures (predominantly the amygdala and parahippocampal gyrus). We used an emotional auditory task in this work to analyze the synchrony patterns and Granger-causal relationships to study effective connectivity and to determine which brain regions directly influence other brain regions. We predicted the following results: compared to the controls and schizophrenia patients without AH, the schizophrenia patients with AH would 1) have abnormal synchrony between the detected networks and concrete abnormalities in the frontal cortex compared with the other brain regions and 2) have different Granger-causal interactions between the frontal, parietal, temporal, limbic and cerebellar networks.

2. Materials and methods

2.1. Participants

A total of 41 male patients with schizophrenia (27 with chronic AH and 14 without AH) were recruited. All patients fulfilled the DSM-IV diagnostic criteria for schizophrenia. The patients with chronic AH fulfilled the following selection criteria for persistent hallucinations (Sanjuán et al., 2007): (a) they heard voices that were resistant to treatment for at least 1 year; (b) the voices were present at least once a day during the last year; and (c) at least two antipsychotic drugs had been tried in the last year at doses equivalent to at least 600 mg/day of chlorpromazine. Patients with a history of traumatic brain injury, epilepsy or other neurological or psychiatric history were excluded. All patients were being treated with stable doses of antipsychotic medication. The patients were clinically assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993) and the Psychotic Symptom Rating Scale (PSYRATS) for AH (Haddock et al., 1999) in the 24 h prior to scanning.

A group of 31 healthy male subjects was selected as the control group. The participants were male, right handed (as assessed with the Edinburgh Questionnaire, Oldfield, 1971) and Caucasian, and they provided written informed consent to participate in the experiment. The study was approved by the local institutional ethics committee.

The healthy controls and patients did not differ significantly in terms of sex, laterality, or ethnicity. The groups differed significantly in educational level, with a greater proportion of individuals with university and high school diplomas (or equivalence) in the control group, as expected. Table 1 shows the demographic and clinical characteristics of all participants.

2.2. Functional imaging

2.2.1. Data acquisition

A 1.5 Tesla scanner (Philips Medical Systems) was used to acquire BOLD contrasts during a stimulation paradigm (Escartí et al., 2010; Sanjuán et al., 2005). An emotional auditory paradigm was designed to evoke emotions related to the patients' hallucinatory experiences (Supplementary material 1). The participants were binaurally stimulated during two different sessions. The activation blocks in one session consisted of 13 Spanish words with high emotional content. The other session had activation blocks containing 13 words with neutral or low emotional content. Four blocks of stimuli (20 s each) were interleaved with four blocks of rest of 20 s each. The subjects were informed before the test regarding the two types of words they were going to hear and were asked to focus their attention on these words.

2.2.2. Data analysis

Pre-processing of the functional data was performed using SPM (http://www.fil.ion.ucl.ac.uk/spm) (Supplementary material 2). The ICA analysis was performed using the Group ICA approach fMRI Toolbox (GIFT, http://www.icatb.sourceforge.net). Components of interest (CoI) were selected (in terms of the individual beta values related to the