NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 39 (2008) 1129 – 1141

A method for multi-group inter-participant correlation: Abnormal synchrony in patients with schizophrenia during auditory target detection

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Received 9 June 2007; revised 11 September 2007; accepted 24 September 2007
Available online 4 October 2007

The general linear model (GLM) approach is the most commonly used method in functional magnetic resonance imaging analysis in predicting a particular response. Recently, a novel method of analysis, referred to as inter-participant correlation (IPC), was developed which attempts to determine the level of blood oxygen level-dependent (BOLD) synchrony among subjects. The IPC approach enables detection of changes in inter-participant BOLD synchrony in a manner that does not rely on an explicit model of the hemodynamic activity. In this paper, we extend IPC to the case of two groups and derive an approach for thresholding the resulting maps. We demonstrate our approach by comparing 35 patients with paranoid schizophrenia (DSM-IV sub-type 295.30) to 35 healthy matched controls during an auditory target detection paradigm. Results showed significantly lower inter-participant BOLD synchrony in patients versus healthy controls in areas including bilateral temporal lobes, medial frontal gyrus, anterior cingulate cortex, dorsolateral prefrontal cortex, thalamus, insula, and cerebellum. The IPC approach is straightforward to use and provides a useful complement to traditional GLM techniques. This approach may also be sensitive to underlying, but unpredictable, changes in inter-participant BOLD synchrony between patients and controls.
Published by Elsevier Inc.

Keywords: Schizophrenia; Paranoid; Neural synchrony; fMRI; Functional; Brain; Correlation; Model; Hemodynamic; GLM

Introduction

The most commonly used technique in functional magnetic resonance imaging (fMRI) analysis is based on the general linear model (GLM) (Friston et al., 1995a,c) and involves fitting the acquired fMRI data to a canonical hemodynamic response function (Friston et al., 1995b; Rajapakse et al., 1998). The GLM is an excellent tool when searching for a task-related response, but is limited by the fact that it only accounts for canonical hemodynamic activity. Recently, a novel approach to fMRI analysis, referred to as inter-participant correlation (IPC), was introduced which attempts to quantify the level of correlation of fMRI BOLD activity within a group of participants (Hejnar et al., 2006). By not making a specific assumption about the shape of the hemodynamic response, the IPC approach has proven capable of revealing regions synchronized across individuals, and thus finding activations that do not necessarily track smoothly with a given task. More specifically, it attempts to determine this correlation at the voxel level between two participants for every voxel in the brain. A correlation map is then generated that depicts areas of high BOLD correlation between two participants and repeated for all possible pairwise comparisons within a group. The statistical average of these comparisons then provides a picture of which regions in the brain are synchronized for a particular group of participants.

The previous study that developed the IPC algorithm analyzed a single group of healthy controls. Here we develop the IPC method to allow for group comparisons and to make additional changes that would more effectively account for the variances between them. Two modifications were made to the original IPC algorithm. The first modification was to utilize the fundamental theories of *U*-statistics to create valid statistical thresholds for the within-group and between-group comparisons. The motivation for this modification was because the previous algorithm divided its

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Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter. Published by Elsevier Inc.
doi:10.1016/j.neuroimage.2007.09.042

averaged correlation maps by its standard deviation and was thresholded at an arbitrary z-value. To remedy this, we took into account the dependence that would exist between individual correlation images as a result of performing an exhaustive correlation analysis between participants within a group. Our solution involved the use of U-statistics (Randles and Wolfe, 1979), a statistical method used in nonparametric statistics that accounted for the dependence between participants and provided us with true t-values that can be further thresholded using a false discovery rate correction (Genovese et al., 2002). The second modification was made to account for the variances that might exist between sessions by using an ordinary GLM regression model to regress one participant's session with another. The original IPC algorithm concatenated the sessions for a single participant as a single session and then performed its correlation afterwards. The GLM regression model allows us to treat each session individually, thus the first session for each participant would be correlated with the first session of the other participant.

After the IPC results were generated, a clustering analysis was performed at the group level to conglomerate regions that activate in a similar manner. This was performed to account for the possibility that neighboring voxels might have very different time courses from one another since the IPC does not test for inter-voxel synchrony. The clustering approach allows us to see which regions of the brain are closely linked to one another and a maximum efficiency algorithm was developed to determine the best number of clusters to use for this part of the analysis.

In order to test the between-group comparisons approach with the IPC method, we chose to compare a group of patients with schizophrenia (n=35) with a matched group of healthy controls (n=35). Participants performed an auditory target detection or 'oddball' task. This task was chosen because this paradigm elicits a robust fMRI response that reliably distinguishes patients with schizophrenia from controls (Calhoun et al., 2006; Kiehl and Liddle, 2001; Kiehl et al., 2005a; Laurens et al., 2005; Ngan et al., 2003). The auditory oddball paradigm is a task where a participant hears a combination of three distinct classes of stimuli, defined as standard (80% probability), novel (10% probability), and target (10% probability) tones. The participant is instructed to press a button during the experiment whenever they hear a target tone and to ignore everything else. Previous work utilizing this paradigm with fMRI have found attenuated activity in schizophrenia within frontal, temporal, parietal, and subcortical sites during the detection process of this specific target auditory tone (Kiehl et al., 2005b).

Our specific hypothesis was that deficits in schizophrenia that are related to abnormalities within the delicate interplay of multiple brain regions could manifest as a lack of coherence between participants. This is consistent with the hypothesis that patients with schizophrenia are characterized by abnormal interconnections between various brain regions (Breakspear et al., 2003; Friston, 1998; Job et al., 2002; Kubicki et al., 2007). Calhoun et al. (2003) used independent component analysis to show that patients with schizophrenia were characterized by aberrant patterns of connectivity in bilateral temporal lobes during performance of the auditory oddball task. We hypothesized that healthy controls would show a much stronger correlation in BOLD activity versus patients with schizophrenia in the superior temporal gyrus and in areas associated with target detection such as the anterior cingulate, dorsolateral prefrontal cortex and subcortical systems such as the thalamus and cerebellum (Calhoun et al., 2004; Kiehl et al., 2005a; Lawrie et al., 2002; Stevens et al., 2005).

Methods

Participants

Thirty-five outpatients with schizophrenia (30 males) and thirty-five matched healthy controls (30 males) provided written informed consent and volunteered for the study. Healthy controls were free from any Axis I disorder, as assessed with the SCID (Structured Clinical Interview for DSM-IV-TR) screening device. Patients met criteria for paranoid schizophrenia (sub-type 295.30) in the DSM-IV based on a structured clinical interview and review of the case file (First et al., 1995). All participants were right-handed and there were no significant group differences in age (patients, 38±11 years, range 18–59 years; controls, 37±12 years, range 18–55 years). IQ (intelligence quotient) assessments were determined from NART (National Adult Reading Test) scores where healthy controls were higher than patients (patients n=26, 35±15 points; controls n=17, 22±7 points; $t(41)=3.1323, p<.0032$). To determine the presence or absence of psychotic symptoms, the mean PANSS (Positive and Negative Syndrome Scale) for patients were determined (n=28, 66±19.6). Medication information was available for 24 patients, where 13 patients were on atypical antipsychotic medications, 4 were on typical antipsychotic medications, 2 were on both atypical and typical medications, and 3 were on no medications at all. Four participants from the patient group were omitted from analysis, as they demonstrated extremely poor performance on the auditory oddball task (more than ten total incorrect responses in either targets or novels for both sessions). Two additional participants were omitted for excessive head motion (greater than one and a half voxel-length (6 mm) in translation or rotation). All participants had normal hearing (assessed by self-report) and were able to carry out both tasks successfully during practice, and during the scanning session.

Tasks: Auditory oddball

The auditory oddball task used in this study was identical to that used in the original inter-participant correlation study (Hejnar et al., 2006). Two runs of auditory stimuli were presented to each participant by a computer stimulus presentation system (VAPP: http://nilab.psychiatry.ubc.ca/vapp/) via insert earphones embedded within 30 dB sound-attenuating MR compatible headphones. The standard stimulus was a 500-Hz tone, the target stimulus was a 1000-Hz tone, and the novel stimuli consisted of non-repeating random digital noises (e.g., tone sweeps, whistles). The target and novel stimuli each occurred with a probability of 10%; the non-target stimuli occurred with a probability of 80%. The stimulus duration was 200 ms with a random 1000, 1500, or 2000 ms inter-stimulus interval. All stimuli were presented at approximately 80 dB and all participants reported that they could hear the stimuli and discriminate them from the background scanner noise. The headphones were designed to work together with the head restraint system in order to minimize head movement.

An MRI-compatible fiber-optic response device (Lightwave Medical, Vancouver, BC) was used to acquire behavioral responses. Prior to entry into the scanning room, each participant performed a practice block of 10 trials to ensure understanding of the instructions. The participants were instructed to respond as quickly and accurately as possible with their right index finger every time they heard the target stimulus and not to respond to the non-target stimuli or to the novel stimuli.