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Aberrant connectivity during self–other source monitoring in schizophrenia

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ABSTRACT

Numerous investigations into schizophrenia have reported impairment in self–other source monitoring, and studies on healthy subjects have suggested that the medial prefrontal cortex (mPFC) is a critical region underlying self-monitoring abilities. In the current study, we examined the mPFC-related modulation of other brain regions in schizophrenia during self–other monitoring using a psychophysiological interaction approach. Twenty-three patients with schizophrenia and 33 healthy controls performed a self–other source monitoring task while undergoing functional magnetic resonance imaging (fMRI) scanning. Independent component analysis was used to identify the mPFC region of interest, and the averaged mPFC time course was extracted and entered into a general linear regression model for use with the psychophysiological interaction analysis, with Self vs. Other monitoring being the psychological condition of interest. Results suggested that connectivity between the mPFC and the left superior temporal gyrus (LSTG) was greater in the Other than the Self condition for the healthy subjects, but this was reversed for the schizophrenia patients, such that mPFC-LSTG connectivity was greater during Self than the Other condition. The modified functional connectivity associated with the performance of recollection of self-source information suggests that schizophrenia patients invoke circuits normally involved in retrieving other-generated information when processing self-generated information, thereby providing a possible biological basis for the self–other confusion characteristic of schizophrenia.

1. Introduction

Schizophrenia is a disorder associated with symptoms such as hallucinations, delusions, and thought disorder. Some of these symptoms (e.g., hallucinations and Schneiderian delusions) are considered to be representative of a disorder of "self," involving difficulty in discriminating between information that was self-generated and that originating from others (Bentall et al., 1991). Behavioral research indicates that schizophrenia patients display difficulty monitoring multiple aspects of their inner and outer experiences, such as self–other verbal information (Allen et al., 2007a, 2004; Ditman and Kuperberg, 2005; Laroi and Woodward, 2007), and tactile stimuli (Blakemore et al., 2000), however, the biological basis of this difficulty is not clear.

Neuroimaging studies on healthy people using various forms of self-referential processing have consistently demonstrated that the medial prefrontal cortex (mPFC, broadly corresponding to Brodmann's area [BA] 10) is a key neural correlate for the recovery and subsequent monitoring of stored information. This region has also consistently been found to be involved in reality monitoring and mentalizing tasks (Dobbins and Wagner, 2005; Frith and Frith, 2003, 2006; Simons et al., 2005a, 2005b) and is purported to play a crucial role in reallocating attentional resources to accurately process contextual information (Burgess et al., 2007; Simons et al., 2005a, 2005b). Meta-analytic studies of imaging research relevant to BA 10 revealed a great deal of

Abbreviations: mPFC, medial prefrontal cortex;STG, superior temporal gyrus;PPI, psychophysiological interaction.

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functional specialization within this region (Gilbert et al., 2006a, 2006b) and led to the proposal of a "gateway hypothesis," which posits that the mPFC influences the attentional balance between self-generated and external information (Burgess et al., 2007; Simons et al., 2005a, 2005b). Disruption in these circuits may thus be attributable to aberrant mPFC-related modulation of other brain regions during self–other monitoring.

Self–other difficulties in schizophrenia are particularly relevant to schizophrenia symptoms like hallucinations (Woodward et al., 2007), whereby patients report hearing voices while none are present. A difficulty in discriminating externally perceived information from that imagined may result from a deficit in monitoring the self-generation of thoughts (Frith and Done, 1989) or bias towards misattributing internal thoughts to external sources (Bentall et al., 1991; Woodward et al., 2007). Cognitive studies have shown that schizophrenia patients with delusions and hallucinations are impaired in judging the origin of previously encoded stimuli and show particular difficulty in identifying the source of self-generated information (Danion et al., 1999; Keefe et al., 2002; Vinogradov et al., 1997). Moreover, a recent study has indicated that abnormal medial prefrontal activation was associated with the inability to discriminate between perceived and imagined information (Simons et al., 2006).

In this functional magnetic resonance imaging (fMRI) study we developed a source monitoring task (based on previous work; Woodward et al., 2007), in which subjects were asked to distinguish between self-generated and externally generated responses. In order to control for potential confounds (e.g., arising from mentalizing, emotional content and task performance, see Gilbert et al., 2006b), a control condition was designed whereby subjects were asked to distinguish between two previously executed tasks: providing semantic associates and reading. This experimental design was similar to the contextual recollection or reality monitoring paradigms used in previous studies (Simons et al., 2005a, 2006, 2008; Turner et al., 2008; Vinogradov et al., 2006, 2008). Given that this event-related design permitted assessment of performance accuracy, the data analysis for the current study focused only on correct trials in order to focus on the abnormal functional connectivity associated with the mPFC during accurate contextual recollection.

Given that the mPFC is a key region in the default-mode network (Gusnard and Raichle, 2001; Raichle et al., 2001) and that this network is often reported to be associated with goal-oriented cognitive tasks (Buckner et al., 2008), in this study we first identify the default network and then extract subject-specific time series from the mPFC for further psychophysiological interaction (PPI) analysis. Pursuant to the gateway theory that suggests a role for the mPFC in maintaining the attentional balance between self-generated and external information, individuals with schizophrenia were expected to show abnormal mPFC functional connections when monitoring self- and other-generated items compared to healthy comparison subjects. Specifically, on the basis of previous relevant studies in functional connectivity (Mechelli et al., 2007), we hypothesized that the impaired connectivity of the mPFC would involve temporal regions sensitive to the judgments of the origin of the source. We also expected that functional connectivity to mPFC in the two cohorts would be equivalent in the task-memory control condition.

2. Materials and methods

2.1. Participants

Twenty-three patients (mean age = 27.3 years, SD = 7.6 years, eight women) were recruited from psychiatric hospitals and community health agencies in and around Vancouver, British Columbia, Canada, with schizophrenia spectrum diagnoses (i.e., schizophrenia, $n = 15$; schizoaffective disorder, $n = 8$). Diagnosis was based on a multidisciplinary team conference during the first month of admission when all sources of information are reviewed. The Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was administered on the date of MRI testing to confirm diagnosis. Participants were excluded if they had ever suffered a head injury or a concussion resulting in a loss of consciousness for 10 min or more, if they had ever been diagnosed with a neurological disease or illness, or if they had current and/or past problems with substance abuse (including alcoholism). Substance abuse was assessed by chart review and by interview, and participants were also excluded if they met the DSM IV criteria for an Axis I diagnosis of a substance-related disorder (e.g., polysubstance dependence). All patients but one were taking stable doses of antipsychotic medications at the time of testing, with the large majority taking atypical antipsychotics.

Thirty-three healthy controls (mean age = 30.0 years, SD = 9.2 years, 17 women) were recruited through advertisement and word-of-mouth. Screening with a medical questionnaire ensured that none of the healthy participants had any current or prior history of psychiatric illness. Additional exclusion criteria were the same as those employed for the patient groups. All participants gave written informed consent after a full explanation of the study and the procedures involved. All experimental procedures were approved by the University of British Columbia Clinical Research Ethics Board.

2.2. Procedure

The source monitoring task involved a non-scanned encoding session, where 120 to-be-encoded common words were presented sequentially, with 30 words presented in each of four contexts: self-generated (SG), other-generated (OG), association (AS), or reading (RD). The first two contexts (SG and OG) were termed the *source-memory conditions* and were the tasks of experimental interest in this study, whereas the latter two (AS and RD) were the control conditions termed the *task-memory conditions*. On the SG trials, a word puzzle (jumbled letters) was presented on the computer screen in conjunction with a clue about the meaning of the word, and subjects were required to say the word aloud once they had solved the puzzle; on the OG trials, subjects heard a digitized recording of the solution to the puzzle as soon as the puzzle was presented on the screen; on the AS trials, subjects used a keypress to indicate which of two possible words was a stronger semantic associate to the presented word; on the RD trials, subjects read the presented word silently.

Following this non-scanned task session, these words were used as targets during the scanned recall phase. Approximately 10 min after the end of the encoding session,