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Away from home: the brain of the wandering mind as a model for schizophrenia

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ABSTRACT

Background: The notion that schizophrenia patients' (SZ) sense of being detached from external reality is a core feature of the disorder has existed since the early days of its recognition and is still largely emphasized in first person accounts of SZs; however, its etiology, neurophysiological mechanism, and significance for clinical symptoms are unclear. Mind-wandering is a ubiquitous experience of being detached from reality, the underlying neural mechanism of which closely resembles the brain in a resting-state.
Methods: The resting-state functional magnetic resonance imaging data of 33 SZs and 33 matched healthy controls (CNT) were acquired. All subjects answered the mind-wandering subscale of the Imaginal Processing Inventory Questionnaire. Functional connectivity maps were constructed using 82 regions of interest comprising default-mode, salience, and frontoparietal networks.
Results: SZs exhibit significantly higher mind-wandering frequency relative to CNT. The elevated mind-wandering frequency in SZs significantly correlated with positive and general symptom severity. The mind-wandering frequency was inversely correlated with connectivity degree in the right ventromedial prefrontal cortex, the brain region involved in self-experience in SZs.
Conclusions: Our results suggest that self-disturbances in SZs can explain SZs' disconnection to the external world, leading to the manifestation of positive psychotic symptoms. This study demonstrates strong preliminary evidence that contributes significantly to resolve the complex relationship between self, world, and the brain of SZs, which may lie at the "core" of psychotic experiences.

1. Introduction

People with schizophrenia (SZ) commonly feel "detached from [commonly shared] reality" and "away from home"(Stanghellini and Ballerini, 2007). In a recent first-person account of psychosis, Kean describes the overwhelming sense of being disconnected and disintegrated from external reality that lies behind the psychotic symptoms, but psychiatrists tend to see nothing but the symptoms alone (Kean, 2009). This notion is not new. In the 19th century, Eugene Bleuler also conceptualized SZs' psychotic despairs as mostly brought on by a lack of vital contact with reality and a withdrawal into a private world (Scarone et al., 2003; Parnas, 2011). Both in classical and modern psychiatric literatures, this trait has been considered to be the core gestalt of SZ (Parnas, 2011). The importance of the core phenomenology of psychotic experience also has been largely emphasized by recent first-person accounts of psychosis (Kean, 2009; Johnson, 2012; Payne, 2012; Humpston, 2014). Despite the fact that current diagnostic criteria revolve around the presence of psychotic symptoms (Keefe and Fenton, 2007; McGuire et al., 2008), this core phenomenology of SZs has largely escaped the mainstream topic of research (Humpston, 2014). A lack of vital studies on the phenomenology of SZs which lie beyond classical diagnosis may hinder progress in our understanding of the disorder and our ability to find adequate treatment.

Mind-wandering is a shift in attention from external circumstances toward one's personal thoughts and feelings (Smallwood et al., 2007a, b). As humans, our minds often wander from the task at hand without intention or even awareness (Giambra, 1995; Schooler, 2002; Smallwood et al., 2007b). During mind-wandering, our conscious attention is decoupled from reality and online sensory information, and focused on one's inner mental activities (Smallwood and Schooler, 2006; Kam et al., 2011; Schooler et al., 2011). It is the ubiquitous experience of being 'detached from reality,' which shares an emphasis processing information beyond the here and now (Smallwood et al., 2007b). In the brain, a set of cortical regions that increase activity during rest and reflection—the default-mode network (DMN)—were believed to underlie

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one's state of mind-wandering (Mason et al., 2007). More recently, Hasenkamp and colleagues explored the brains of people experiencing mind-wandering and proposed dissociable association of the DMN, frontoparietal (FPN), and salience networks (SN) in each cognitive element of mind-wandering (Hasenkamp et al., 2012). While possible connections between mind-wandering and resting-state brain activity were suggested in previous literature (Smallwood and Schooler, 2006; Gruberger et al., 2011), these have only lately started to be studied systematically, as one recently published study has demonstrated (Kucyi et al., 2013).

More recently, a well-known disconnection hypothesis about SZs (Friston and Frith, 1995) proposes that SZ symptomology arises from the anomalous integration of a distributed network of brain regions or a misconnection of neural circuitry (Kim et al., 2003; Rubinov et al., 2009). Advances in functional connectivity analysis of resting-state functional magnetic resonance imaging (rs-fMRI) facilitate the measurement of functional integrity within and between brain networks (Rubinov et al., 2009). Using the spontaneous resting-state neural activity, inferred on the basis of blood oxygen level dependence (BOLD) response time-series data, studies have found spatially segregated functional connectivity networks in the human brain (Fox et al., 2005). SZs' distinct symptomology is understood through impairments in fundamental resting activities of the brain regions and connections (Bassett et al., 2012; Jung et al., 2012; Kuhn and Gallinat, 2013). Specifically, SZs showed hypoactivation in the ventromedial prefrontal cortex (vmPFC), the posterior cingulated cortex (PCC), and the precuneus at rest (Kuhn and Gallinat, 2013). These brain regions have been demonstrated substantially for their anatomical deviations as well that the paralimbic system are lateralized in SZ (Honea et al., 2005; Crow et al., 2013). In the network level, SZ was associated with enhanced resting-state connectivity in DMN and reduced connectivity within SN, FPN and between SN and DMN (Lawrie et al., 2002; Whitfield-Gabrieli et al., 2009; White et al., 2010; Pu et al., 2012; Tu et al., 2012). While abnormalities in DMN and vmPFC, which are involved in self-referential and introspective processing, in SZs (Whitfield-Gabrieli et al., 2009; van Buuren et al., 2012) support the assumption that the fundamental disturbance causing psychotic symptoms is disorder of the self, a deviance in one's subjective self-experience and the external reality, it is unclear how SZs' disconnection to the world is related to their disconnectivity in the brain. Thus, we sought to examine the brain in the state of detached-from-reality mentation as neurophenomenological model for psychosis. This may provide valuable information for identifying the clinical core of SZ and its neural system that contributes to impairments that cut across traditional diagnostic boundaries.

2. Methods

2.1. Participants

Thirty-three SZ patients were recruited from the Seoul Youth Clinic at Seoul National University Hospital, all fulfilled the DSM-IV criteria for SZ using the Structured Clinical Interview for the DSM-IV AXIS-I (First et al., 1994). All SZ patients were screened by senior psychiatrists, and none of them had an affective component. Seven patients were drug-naïve, and 26 patients were receiving antipsychotic medication at the time of investigation (Table S1). We also recruited 33 comparison healthy control (CNT) subjects matched for age, sex, and handedness via Internet advertisement. Absence of axis I psychiatric disorders in CNTs was confirmed with the Structured Clinical Interview for the DSM-Non-Patient edition (SCID-NP) (First et al., 1995). None of the CNT had a positive family history for any psychiatric disorder when assessed using the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992). All participants were excluded if they had a history of substance abuse or dependence, brain lesions or head trauma history, neurological illness, or intellectual disability (IQ < 70). Demographic information is summarized in Table 1. The groups did not differ in their sex, age, handedness, education year, and parental socioeconomic status; however, the patients had significantly lower IQs than the CNTs. All subjects gave written informed consent. The study was approved by the Institutional Review Board of Seoul National University Hospital.

2.2. Clinical measures

The current psychopathology of SZ was assessed using the Positive and Negative Syndrome Scale (PANSS). The severity of depressive and anxiety symptoms of SZ was evaluated using the Hamilton Rating Scale for Depression (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A), respectively.

2.3. Mind-Wandering Questionnaire

All participants answered a 12-item mind-wandering frequency scale (Table S2) (Singer and Antrobus, 1963). It is one of the 28 scales composing the Imaginal Processes Inventory (IPI), a 344 item questionnaire designed for in-depth assessment of individuals' inner mental life. Participants were asked to rate the extent to which they experience mind-wandering in their daily life with reference to a five-point Likert-scale, ranging from 1 (not at all) to 5 (very much). An individual's subjective mind-wandering frequency was obtained by calculating the score for the mind-wandering questionnaire (MWS).

2.4. Image acquisition and preprocessing

Resting-state BOLD images of the whole-brain were acquired on a 3.0 T scanner (Siemens Magnetom Trio, Germany) using an echo-planar imaging (EPI) sequence consisting of 35 axial slices. Each functional run contained 116 image volumes. During the scan, all participants were instructed to just relax and keep their eyes closed without falling asleep.

Images are preprocessed using the SPM8 package (www.fil.ion.ucl.ac.uk/spm) after discarding the first 4 images. The remaining images were subjected to slice-timing correction, and realigned to the first image. Data were then spatially normalized to the Montreal Neurological Institute (MNI) space, resampled to $3 \times 3 \times 3$ mm^3, and spatially smoothed with a 6-mm full-width at half-maximum Gaussian kernel. Removal of the linear trend in time course and temporal band-pass filtering (0.01–0.08 Hz) was performed using a REST toolkit (http://www.restingfmri.sourceforge.net). (Song et al., 2011) The estimated six head-motion parameters and signals from the white matter, cerebrospinal fluid, and global signal activity were further regressed out to

Table 1
Demographic and clinical characteristics of the subjects.

	Control subjects n = 33	Schizophrenia n = 33	*p* value
Age (years)	24.0 ± 5.7	23.4 ± 5.0	0.637
Gender (male/female)	10/23	9/24	0.786
Handness (right/left)	30/3	30/3	1
Estimated IQ	109.0 ± 12.2	98.0 ± 14.3	0.001*
Education (years)	14.7 ± 1.8	13.8 ± 2.0	0.07
Parental SES	3.9 ± 0.9	2.7 ± 0.8	0.379
PANSS total score		65.3 ± 14.0	
Positive		15.4 ± 5.5	
Negative		16.5 ± 5.2	
General		33.3 ± 7.0	
HAM-D score		9.1 ± 5.0	
HAM-A score		7.5 ± 5.3	
Age of onset (years)		22.0 ± 5.0	
Duration of illness (years)		1.7 ± 2.6	

Data are given as mean ± SD.
Abbreviations: IQ, intelligent quotient; SES, Hollingshead socioeconomic status; HAM-D, Hamilton Rating Scale for Depression; HAM-A, Hamilton Anxiety Rating Scale; PANSS, Positive and Negative Syndrome Scale.
*$p < 0.05$.

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