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Increased water diffusivity in the frontal and temporal cortices of schizophrenic patients

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Schizophrenia has been suggested to be the result of both macroscopic and microscopic abnormalities in the brain. Although no definitive clinico-pathological correlations have been found to reconcile the many facets inherent in this disorder, the recent development of the magnetic resonance diffusion tensor imaging (DTI) has allowed us to gather useful information regarding the microcircuitry of the brain. Specifically, the apparent diffusion coefficient (ADC) reflects the degree of diffusion barriers and heterosynaptic communication for the brain neurotransmitter. Nineteen patients with DSM-IV schizophrenia and 21 age- and sex-matched control subjects participated in DTI, and the severity of the patients' symptoms was evaluated according to the Positive and Negative Syndrome Scale (PANSS). The ADC values were determined and compared between patients and control subjects via voxel-based morphometry. The results show an increased ADC in the bilateral fronto-temporal regions of the schizophrenic patients, as compared with those of the control subjects. In addition, the ADC values in the area of the right insular were correlated with the negative syndromes from the PANSS. Our findings of increased water diffusivity in the fronto-temporal regions of schizophrenic patients and the correlation between negative symptom scales and the ADC in the right insular region indicate that damaged brain microcircuitry might contribute to the pathophysiology of schizophrenia. These findings contribute towards integrating micro and macrostructural abnormalities and syndromes of schizophrenia.

Introduction

Schizophrenia is now recognized to be a disorder characterized by abnormalities of multiple brain areas and altered connectivity of these areas rather than a disorder of any single brain region. A variety of brain regions, including the dorsolateral prefrontal cortex (DLPFC), the amygdala, hippocampus, superior temporal gyrus, the anterior cingulate and sometimes the insular region are all known to exhibit abnormalities in schizophrenia (Crespo-Facorro et al., 2000; Shenton et al., 2001, Kwon et al., 2003). Such multiple regional abnormalities are compatible with abnormalities in the neurotransmitter systems. Although the dopamine system is most intensively studied in schizophrenia, there are clear abnormalities of other neurotransmitter systems, including the serotonin, gamma-aminobutyric acid (GABA) and glutamate systems (Meltzer, 1999; Laruelle et al., 2003; Guidotti et al., 2005; Hirvonen et al., 2005). Several hypotheses and models have been advanced to account for these multiple dysfunctions in multiple domains observed in schizophrenia by linking microstructural abnormalities with symptoms. A neural network model that simulates the pruning of synaptic connections was proposed by Hoffman and McGlashan (1997). They demonstrated that abnormal dendritic arborization could be used to construct a proper model for the pathophysiology of schizophrenia. They showed that the general reduction of neuritic processes, especially in the dendrites and synapses, could account for the auditory hallucinations and could also explain some of the key clinical features of schizophrenia, including its typical age of onset and limited neurodegenerative progression profile (Hoffman and McGlashan, 1997; McGlashan and Hoffman, 2000). Hanson and Gottesman proposed that damage inflicted upon the brain's micro-vascular system might also induce the classic symptoms of schizophrenia (Hanson and Gottesman, 2005). They insisted that an inflammation of the micro-vessels in the brain

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could result in disruptions in the astroglial-mediated coupling of cerebral blood flow and that such disruptions would be responsible for many of the classic symptoms of schizophrenia, although these disruptions would be too subtle to observe without electron microscopy (Hanson and Gottesman, 2005). These hypotheses are concordant with the current view, which holds that schizophrenia can be understood most accurately in terms of a malfunction of the cortical microcircuitry (Winterer and Weinberger, 2004).

With current advancements in our understanding of interneuronal communication in the central nervous system, new features of synaptic neurotransmission have become one of the major foci of scientific investigation. The manner in which information is transferred across the neural synapses and mediated by the neurotransmitters appears not to be as unambiguous as had once been believed. The neurotransmitters appear to mediate rapid point-to-point transmission through the synapses but have also been shown to simultaneously transmit a more diffuse signal out into the perisynaptic environment (Agnati et al., 1995). The neurotransmitters diffuse through the extracellular space (ECS), binding with extrasynaptic binding sites which are located on the neurons, axons and glial cells. The glial cells, which are vital for the proper functioning of neurons, do not possess synapses, and therefore neural communication can be achieved only by the diffusion of ions and neuroactive substances throughout the ECS (Sykova, 2004). Neurotransmitters including glutamate or GABA can escape from the synaptic cleft, thereby transmitting their information to extra- and heterosynaptic receptors prior to their reuptake (Rusakov and Lehre, 2002). The importance of this form of 'fuzzy' nonsynaptic transmission, which is normally referred to as extrasynaptic transmission, has emerged in the past few years as a result of the electrophysiological recordings obtained by the microdialysis technique, which allows for in vitro diffusivity measurements of the central neurotransmitters located in the ECS of the brain (Sotak, 2004).

An alternative method for the in vivo evaluation of neurotransmitter diffusivity is the analysis of the apparent diffusion coefficient (ADC) on diffusion-weighted magnetic resonance images (Sykova, 2004). The ADC echoes the level of Brownian motion of water molecules in the tissue, thereby reflecting the ECS volume or the degree of diffusion barriers (tortuosity) for the neurotransmitters, owing to the existence of perisynaptic glial processes and/or perineuronal membranes (Rusakov and Lehre, 2002; Murakami and Ohtsuka, 2003; Sykova, 2004). Alterations in the ADC values were discovered in lesions occurring as the result of brain injuries in the mass of white matter in multiple sclerosis patients or in the hippocampi of chronic temporal lobe epilepsy patients (Babb and Brown, 1987; Maldjian and Grossman, 2001). Despite current advancements in our understanding of the ADC value in the cellular environment, as well as the findings obtained by recent studies involving the diffusion tensor magnetic resonance imaging (DTI) of the brains of schizophrenics, the implications of the ADC values have only rarely been assessed in these studies. This is especially true with regard to the degree to which the ADC value reflects cellular water homeostasis. ADC values have been, perhaps, underestimated in the literature and are often treated simply as an auxiliary parameter in fractional anisotropy for the evaluation of white matter integrity rather than as a key parameter in extrasynaptic neurotransmission (Huisman et al., 2004; Taylor et al., 2004). Extrasynaptic neurotransmission can be considered to be a 'one to many' type of communication, whereas typical synaptic transmission is clearly a 'one to one' proposition. This 'one to many' mode of communication constitutes a possible mechanism for the synchronization of neuronal activity and long-range information in functions including vigilance, memory formation and other plastic brain changes, all of which have been regarded as systems specifically affected by schizophrenia (Sykova, 2004). Here, we postulate that schizophrenia may be, in fact, a malfunction of extrasynaptic communication, either due to excessively "fuzzy" or excessively stringent communication, and that this could be determined by the altered ADC values within the brains of patients. Considering voxel-based morphometry (VBM) can provide a non-biased measure of highly localized regions with no need to define anatomical borders a priori (Ashburner and Friston, 2000), VBM was used to compare the ADC values of the brain between the patients with schizophrenia and control subjects.

Methods

Subjects

Nineteen patients, who met the DSM-IV criteria for schizophrenia, as determined by the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996), were recruited from the inpatient unit and outpatient clinic of the Seoul National University Hospital. All patients were right-handed. None of the patients had any history of traumatic brain injury, epilepsy, alcohol or substance abuse or any other neurological issues. The patients' symptoms were rated on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The patients had a mean illness duration of 7.53 (SD = 4.39) years, with a range of 1 to 17 years. The mean age of onset was 21.32 (SD = 5.32) years, and this ranged from 15 to 32. The mean values of the PANSS total scores, positive symptom scores, negative symptom scores and general psychopathology scores of these patients were as follows: 54.11 (SD = 13.24), 14.0 (SD = 5.09), 14.37 (SD = 5.95) and 25.79 (SD = 5.82), respectively. All patients were taking atypical antipsychotic medication. Ten patients were currently taking risperidone, at a daily mean dose of 2.85 mg (SD = 1.37), and 5 were on clozapine, at a mean daily dose of 305 mg (SD = 144.04). Three patients took olanzapine, with a mean daily dose of 9 mg (SD = 2.89), and one took quetiapine at a dosage of 850 mg. Twenty one sex- and age-matched healthy control subjects were recruited from the local community via newspaper advertisements and were screened by SCID-I. The exclusion criteria for the controls included any current or lifetime history of DSM-IV axis I disorders and left-handedness. Mean years of education (14.73 ± 3. 62 in patients and 16.04 ± 2.73 in control subjects respectively, $t = -0.96$, $P = 0.35$) and parental socioeconomic status (3.21 ± 0.71 and 2.86 ± 0.48 respectively, $t = 1.86$, $P = 0.07$) (Hollingshead and Redlich, 1958) between these two groups did not differ significantly (Table 1). After the subjects had been completely informed with the protocols of the study, we obtained written informed consent from all subjects. This study was conducted in accordance with the guidelines provided by the institutional review board at Seoul National University Hospital.

MRI acquisition and image processing

Imaging data were acquired using a Philips 1.5 T scanner (Philips Intera, Philips Medical System, Best, The Netherlands) at the Kangbuk Samsung Hospital (Shin et al., 2005). For coregistra-