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Brain volume and dysexecutive behavior in schizophrenia

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ABSTRACT

Objective: Behaviors associated with frontal/executive impairments are common in patients with schizophrenia. Our aim was to reconfirm that morphological brain abnormalities in schizophrenia patients would overlap the areas underpinning frontal systems behavior, and examine whether any specific association exists between abnormalities of brain structures and frontal behavioral deficits in schizophrenia patients.

Method: Twenty-six schizophrenia patients and 26 matched healthy controls underwent structural magnetic resonance imaging and their frontal function was assessed by a self-rating questionnaire, Frontal Systems Behavior Scale (FrSBe). We applied voxel-based morphometry (VBM) to investigate regional brain volume alternations.

Result: Compared with healthy controls, schizophrenia patients showed reduced gray matter volume in multiple frontal and temporal structures, namely, the bilateral dorsolateral prefrontal cortices (DLPFC), bilateral medial prefrontal cortices, left ventrolateral prefrontal cortex, bilateral anterior cingulate cortices, and bilateral superior temporal gyri. The scores on the executive dysfunction subscale of the FrSBe were correlated with volume reduction in the bilateral DLPFC in the patient group.

Conclusion: Our result suggests that pathology of the DLPFC could be the neural basis of real-life dysexecutive behaviors in schizophrenia patients.

1. Introduction

Behaviors associated with frontal/executive impairments have long been observed in patients with schizophrenia. Many of the behavioral symptoms reported in schizophrenia overlap with those commonly described in individuals with prefrontal damage. The negative symptoms of schizophrenia resemble the apathy often observed in patients with frontal lobe damage (Fuster, 1989). Disinhibition and poor planning and problem solving, typically known as frontal lobe syndromes, are also well documented in schizophrenia (Frith, 1992; Morice and Delahunty, 1996). In addition to the positive symptoms, these behavioral symptoms may be major causes of social dysfunction in schizophrenia patients (Velligan et al., 2002).

The neuropsychological impairments shown by schizophrenia patients also resemble those among patients with prefrontal lesions, such as working memory impairment, executive dysfunction, or impairment of attention control. Many studies have reported brain morphological abnormalities (Fornito et al., 2009; Honea et al., 2005; Shenton et al., 2001), activation abnormalities (Tan et al., 2007), and neuropathology (Iritani, 2007) in the frontal lobes of patients with schizophrenia. Furthermore, some studies also reported relationships between structural/functional frontal abnormalities and cognitive dysfunction in schizophrenia patients. For instance, by investigating monozygotic twins discordant for schizophrenia, Goldberg et al. (1994) demonstrated that reduced prefrontal blood flow correlated with perseveration errors in a set-shifting task in schizophrenia. Premkumar et al. (2008) demonstrated that reduced prefrontal volumes correlated with immediate and delayed recall in a visual reproduction test in chronic schizophrenia subjects.

Abbreviations: WCST, Wisconsin Card Sorting Test; FrSBe, Frontal Systems Behavior Scale; Sc, schizophrenia group; DSM-IV, Diagnostic and statistical manual of mental disorders, fourth edition; PANSS, Positive and Negative Syndrome Scale; SCID-P, Structural Clinical Interview for DSM-IV Axis I Disorders—Patient Edition; SCID-NP, Structural Clinical Interview for DSM-IV Axis I Disorders—Nonpatient Edition; HC, healthy control group; IQ, intelligence quotient; WAIS-R, Wechsler Adult Intelligence Scale—Revised; A, apathy; D, disinhibition; E, executive dysfunction; 3D-MPRAGE, three-dimensional magnetization-prepared, rapid-gradient echo; MRI, magnetic resonance imaging; VBM, voxel-based morphometry; SPM, statistical parametric mapping; GM, gray matter; SPMs, statistical parametric maps; FDR, false discovery rate; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; MPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; STG, superior temporal gyrus; BIS, Barratt Impulsiveness Scale; IGT, Iowa gambling task.

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However, the relationships between comprehensive frontal behavioral symptoms and frontal lobe pathology have not been directly investigated. Previous studies in frontal lobe-damaged patients show that behavioral disturbances do not always parallel neuropsychological impairments. For example, damage to the orbitofrontal lobes is known to disrupt social behavior profoundly, but leaves the patient's cognitive abilities generally well preserved, including those measured by conventional "frontal lobe" tests, such as the Wisconsin Card Sorting Test (WCST) (Bechara et al., 2000; Eslinger and Damasio, 1985).

In this study, we assessed frontal behavioral symptoms using the Frontal Systems Behavior Scale (FrSBe) (Grace et al., 1999), which captures multifaceted frontal behavioral disorder comprehensively on a questionnaire basis. The FrSBe was applied in schizophrenia patients (Velligan et al., 2002; Yoshizumi et al., 2008) as well as in other neuropsychiatric populations (Chiaravalloti and DeLuca, 2003; Stout et al, 2003; Vedejo-Garcia and Pérez-Garcia, 2008). Regarding the clinical and neuropsychological correlates of the FrSbe, Velligan et al. (2002) investigated schizophrenia subjects, and reported that each of the FrSBe subscales correlated variously with psychopathological measures (assessed by the Brief Psychiatric Rating Scale-Expanded Version), and with neuropsychological tests assessing initiation, inhibition, planning and problem-solving. In multiple sclerosis patients, correlations of FrSBe scores with working memory and executive control were reported (Chiaravalloti and DeLuca, 2003).

However, the above-mentioned studies did not explore the neuroanatomical correlates of FrSBe measures. Thus, in this study, to investigate the neural underpinnings of each domain of frontal behavioral disturbances in schizophrenia patients, a structural MRI study was performed. The possible association of FrSBe subscale scores with regional cortical volumes was investigated at a whole brain level using voxel-based analyses of gray matter volumes.

2. Method

2.1. Participants

The schizophrenia group (Sc) comprised 26 Japanese patients (11 men and 15 women), referred to the Department of Psychiatry, Kyoto University Hospital. The majority of patients were outpatients of the university hospital, and others were outpatients of regional community mental health clinics. Based on the Structural Clinical Interview for DSM-IV Axis 1 Disorders-Patient Edition (SCID-P, Version 2.0), each patient fulfilled the DSM-IV criteria for schizophrenia. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al, 1987). All patients were receiving antipsychotic medication [typical ($n=2$), atypical ($n=18$), typical and atypical ($n=6$)] and were physically healthy at the time of scanning and cognitive tests. None had a history of neurological injury or disease, or other medical diseases that may have affected brain function. None of them had any history of substance abuse, including alcohol or cannabis. All patients were on a stable regimen of antipsychotic medication. We recruited patients who could tolerate MRI examination and psychological testing. Thus, those with severe psychopathology were not included in the study. Chlorpromazine equivalents were calculated according to the practice guidelines for the treatment of patients with schizophrenia (American Psychiatric Association, 1997; Woods, 2003). Six patients were receiving antidepressants or mood stabilizers (two of them were medicated with lithium carbonate, one with lithium carbonate and carbamazepine. One of them was medicated with paroxetine, one with amitriptyline hydrochloride, and one with trazodone hydrochloride). The "dose year" formula (Miller et al., 1995) was used to measure cumulative neuroleptic exposure. Exposure was calculated over time and weighted for dose (in chlorpromazine equivalents). Exposure ranged from 16.7 to 47125.0 "dose years". Handedness was assessed by the Edinburgh Laterality Inventory (Oldfield, 1971).

The healthy control group (HC) comprised 26 healthy individuals (11 men and 15 women) recruited from the local community through advertisement, who were matched to the schizophrenia group with respect to age, gender, handedness, education level, verbal IQ, and performance IQ. These subjects were also evaluated on the basis of a non-patient version of the SCID. They had no history of neurological or psychiatric disease and no first-degree relative with psychotic episodes. Verbal and performance IQs were estimated from vocabulary and block design subtests, respectively, in the Wechsler Adult Intelligence Scale-Revised (WAIS-R), by transforming the scores corrected for age into *T* scores. Table 1 presents demographic information.

After a complete description of the study to the participants, written informed consent was obtained. The study design complied with the declaration of Helsinki and was approved by the Committee on Medical Ethics of Kyoto University in accordance with The Code of Ethics of the World Medical Association.

2.2. Tasks

We used the FrSBe self-rating version, which is a 46-item rating scale aimed at assessing three major domains of behavioral disturbances frequently associated with frontal lobe injury; namely, *apathy* (A: poor initiation, loss of energy and interest, blunted affective expression), *disinhibition* (D: problems with inhibitory control, socially inappropriate behavior, unmodulated or excessive emotional expression), and *executive dysfunction* (E: deficits of planning, working memory, mental flexibility). Raw scores can be transformed into *T* scores adjusted for age and gender. Higher scores indicate higher levels of behavioral problems. Although the scale was originally designed to assess the behaviors of patients with frontal lobe brain damage, its use has been validated in dementia (Norton et al., 2001) as well as in schizophrenia (Velligan et al. 2002). Because all the patients were Japanese, in this study we used the Japanese form of the FrSBe, the reliability and validity of which have been demonstrated to be

Table 1
Demographic, clinical and neuropsychological characteristics of subjects.

	Schizophrenia group ($N=26$)		Healthy control ($N=26$)		Statistics
	Mean	S.D.	Mean	S.D.	p
Age (years)	36.7	8.6	36.3	8.8	$p>0.05$
Gender (male/female)	11/15		11/15		
Handedness (right/left)	23/3		24/2		$p>0.05$
Education (years)	13.9	2.6	13.7	2	$p>0.05$
Estimated VIQ (Vocabulary)	101.5	17.1	98.8	17.2	$p>0.05$
Estimated PIQ (Block Design)	101.3	12.4	105	13.9	$p>0.05$
PANSS Positive	14.5	5.5			–
PANSS Negative	15.5	5.1			–
PANSS General	31.1	9.3			–
PANSS Total	61.1	18.1			–
Duration of Illness (years)	9.9	7.7			–
Drug (mg/day, chlorpromazine equivalent)	577.3	429.3			–
Number of episodes	2.8	3.0			–
Dose years	3391.8	9088.7			–
FrSBe *T*-score					
Apathy	70.0	13.4			–
Disinhibition	64.4	20.3			–
Executive dysfunction	65.6	16.2			–
Total	68.4	16.1			–
FrSBe raw score					
Apathy	40.3	7.9			–
Disinhibition	34.1	10.7			–
Executive dysfunction	44.3	12.1			–
Total	118.7	28.1			–