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Distinct effects of duration of untreated psychosis on brain cortical activities in different treatment phases of schizophrenia: A multi-channel near-infrared spectroscopy study

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ABSTRACT

Background: Duration of untreated psychosis (DUP) has been shown to be associated with both poor short-term and long-term outcomes in schizophrenia. Even so, few studies have used functional neuroimaging to investigate DUP in schizophrenia. In the present study, we used near-infrared spectroscopy (NIRS) to investigate the influence of DUP on brain functions during a verbal fluency test (VFT) in patients with schizophrenia.
Methods: A total of 62 patients with schizophrenia were included. They were categorized into either short treatment (≤6 months, $n = 33$) or long treatment (>6 months, $n = 29$) groups based on their duration of treatment. Hemodynamic changes over the frontotemporal regions during a VFT were measured using multi-channel NIRS. We examined the associations between DUP and hemodynamic changes in each group to explore if there were different effects of DUP on brain cortical activity at different treatment durations.
Results: In the long treatment group, we found significant associations between a longer DUP and decreased cortical activity approximately at the left inferior frontal gyrus, left middle frontal gyrus, left postcentral gyrus, right precentral gyrus, bilateral superior temporal gyrus, and bilateral middle temporal gyrus, whereas no associations between DUP and brain cortical activity were observed in the short treatment group.
Conclusions: Our results indicated that longer DUP may be associated with decreased level of cortical activities over the frontotemporal regions in the long-term. Early detection and intervention of psychosis that shortens DUP might help to improve the long-term outcomes in patients with schizophrenia.

1. Introduction

Duration of untreated psychosis (DUP) is defined as the time from the first manifestations of psychotic symptoms to the beginning of antipsychotic treatment (Marshall et al., 2005). It has been postulated that untreated psychosis might be neurotoxic to the brain (Wyatt, 1991) and result in cognitive impairments and changes in brain morphology. Indeed, DUP may have negative effects on the brain (McGlashan, 2006; Wyatt, 1991); a longer DUP has been associated with poor clinical and functional outcomes in patients with schizophrenia both at early stage (Marshall et al., 2005; Perkins et al., 2005; Schimmelmann et al., 2008) and chronic stage (Meagher et al., 2004; Tirupati et al., 2004).

Recent studies have focused on the relationships between DUP and cognitive functions or specific brain structures, but they have reported conflicting results. Some studies have shown a relationship between a longer DUP and various domains of cognitive impairments in first-episode psychosis (FEP) or chronic schizophrenia (Amminger et al., 2002; Gaynor et al., 2009; Joyce et al., 2002; Lappin et al., 2007) (Supplementary Table 1), whereas other studies have failed to find such a relationship (Barnes et al., 2008; Galderisi et al., 2009; Goldberg et al., 2009; Ho et al., 2003; Hoff et al., 2000; Leeson et al., 2010; Rapp et al., 2013; Rund et al., 2007; Townsend et al., 2002). Longitudinal studies have found that patients with FEP had few associations between cognitive function and DUP before or with minimally treatment, but obvious

Abbreviations: DOI, duration of illness; DOT, duration of treatment; DUP, duration of untreated psychosis; FEP, first episode psychosis; FDR, false discovery rate; fMRI, functional magnetic resonance image; GAF, global assessment of functioning scale; IFG, inferior frontal gyrus; IQ, intelligence quotient; LPBA, LONI probabilistic brain atlas; MFG, middle frontal gyrus; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MTG, middle temporal gyrus; NIRS, near-infrared spectroscopy; PANSS, the positive and negative syndrome scale; PET, positron emission tomography; SPECT, single-photon emission computed tomography; STG, superior temporal gyrus; VFT, verbal fluency test.

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impairments emerged after 6 months (Cuesta et al., 2012) and 2 years (Chang et al., 2012). Other longitudinal studies, however, have failed to find such associations after a 2-year follow-up period (Addington et al., 2004).

Magnetic resonance imaging (MRI) studies also have indicated a relationship between a longer DUP and brain volume reduction in patients with FEP (Crespo-Facorro et al., 2007a; Keshavan et al., 1998; Lappin et al., 2006; Malla et al., 2011) and chronic schizophrenia (Penttila et al., 2010; Takahashi et al., 2007). Region of interest-based analyses in patients with FEP have shown that a longer DUP was associated with reduced volumes in the caudate nucleus (Crespo-Facorro et al., 2007a) and the left superior temporal gyrus (Keshavan et al., 1998). Voxel-based morphometric studies also suggest that a longer DUP was associated with reduced gray matter in several cortical regions, which included the temporal (left middle and inferior temporal cortices) (Lappin et al., 2006), orbital–frontal (medial frontal and rectal gyri, bilaterally) (Malla et al., 2011), and parietal regions (postcentral gyrus and superior parietal lobule) (Malla et al., 2011). In chronic schizophrenia, reduced volumes in the left planum temporale (Takahashi et al., 2007) and reduced gray matter densities in the right hippocampus have been associated with a longer DUP (Penttila et al., 2010). In contrast, other studies have failed to find significant correlations between DUP and abnormal brain morphology (Crespo-Facorro et al., 2007b; Fannon et al., 2000; Hietala et al., 2003; Ho et al., 2003, 2005; Hoff et al., 2000).

Although numerous studies have examined associations between DUP and cognitive functions or brain morphology, few studies have used neurophysiological methods (Wang et al., 2005) or functional brain imaging (Galinska et al., 2009) to examine these relationships. Event related potential study has indicated that drug naïve patients with FEP and a short DUP can show significant recovery of the P300 amplitude in the left temporo-parietal area after medication treatment (Wang et al., 2005). On the other hand, no relationship was reported between DUP and ^{1}H-MRS measures (Galinska et al., 2009).

Even though many of these previous studies are informative, the inconsistency among their results has complicated our understanding of how DUP might affect long-term outcomes in schizophrenia. We suspect these inconsistent findings could be attributed to variability in participant sampling, cognitive battery selection, MRI methodology, and DUP measurement. Nevertheless, the question of whether or not untreated psychosis might negatively affect the brain remains unresolved.

Multi-channel near-infrared spectroscopy (NIRS) is a recently developed functional neuroimaging technology that allows non-invasive measurement of the spatio-temporal characteristics of neural activity in the frontotemporal regions (Heinzel et al., 2013; Strangman et al., 2002). NIRS has several advantages over existing imaging techniques, such as PET, SPECT, and fMRI, because it is noninvasive, is easy to administer, tolerates small movements, is inexpensive, and provides excellent time resolution and moderate spatial resolution (Ferrari and Quaresima, 2012). More important, NIRS provides a bedside measurement of oxy-hemoglobin ([oxy-Hb]) and deoxy-hemoglobin ([deoxy-Hb]) concentrations, which are considered to indicate regional cerebral blood volumes and show strong correlations with fMRI signals (Sato et al., 2013). Many schizophrenia-related studies have used NIRS (Koike et al., 2011; Suto et al., 2004; Takizawa et al., 2008, 2009a), but none of these studies have examined the effects of DUP on brain function.

In the present study, we investigated the relationship between DUP and brain cortical activity in patients with schizophrenia by performing a verbal fluency task (VFT). Because previous studies indicated the correlations between DUP and cognitive or clinical measurements may emerge after treatment initiation and become more evident with a longer duration of follow-up (Chang et al., 2012; Cuesta et al., 2012; Marshall et al., 2005), we examined patients with schizophrenia over a wide range of duration of treatment (DOT). We therefore hypothesized that the relationship between DUP and brain cortical activity might vary with different DOTs.

2. Materials and methods

2.1. Participants

This study complied with the Declaration of Helsinki, and was approved by the Research Ethics Committee of the University of Tokyo Hospital (approval No. 630-6), beginning from 2004 to 2013. All participants received a complete explanation of the study and gave written informed consent. In total, 62 patients with schizophrenia participated in this study (Table 1). All participants were native Japanese speakers and were recruited from both out- and inpatients at the University of Tokyo Hospital. Patients in this study were diagnosed by 3 experienced psychiatrists (S.K, R.T., and/or K.K.) according to the criteria defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. (American Psychiatric Association, 1994). Most of the participants were receiving antipsychotic medication (drug naïve [$n = 5$], typical [$n = 5$], atypical [$n = 39$], typical and atypical [$n = 12$], and one data was missing). Further inclusion criteria included a duration of illness (DOI) of less than 10 years (520 weeks) to minimize the confounding effects such as relapses on DUP, and due to that the disease progression appears to plateau 5–10 years after illness onset (McGlashan, 1988). The exclusion criteria were neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, a history of electroconvulsive therapy, a history of pervasive developmental disorder, or alcohol/substance abuse or addiction. Patients in the present study were categorized into 2 subgroups based on their duration of treatment (DOT) to examine the relationship between DUP and brain cortical activity. Patients with a DOT for psychosis ≤6 months (24 weeks) were included in the short DOT group, and those with a DOT >6 months were

Table 1
Basic characteristics of study participants in each group.

	Short DOT group ($N = 33$)		Long DOT group ($N = 29$)		
	Mean	SD	Mean	SD	p value
Age, year	26.3	9.0	31.3	8.6	<0.05
Age of onset, year	25.5	8.2	26.1	9.5	0.78
Gender (M/F)[a]	19/14		13/16		0.62
Premorbid IQ	105.7	8.5	103.1	14.7	0.40
Education, year	13.5	3.0	14.0	3.4	0.50
Edinburgh[b]	89.9	21.8	91.8	21.4	0.73
VFT performance	11.9	4.1	13.1	4.4	0.27
GAF	40.7	10.3	49.0	10.6	<0.05
DUP (week)[c]	55.9	89.8	29.5	46.7	0.46
DOT (week)[d]	7.3	5.8	250.4	157.8	<0.05
PANSS					
Positive	16.3	5.0	14.4	4.8	0.13
Negative	20.4	6.7	19.1	5.3	0.40
General psychopathology	36.4	8.1	36.2	7.2	0.94
Total	73.1	17.3	69.7	13.8	0.40
Medication[e]					
Chlorpromazine	462.3	461.0	754.9	692.0	0.06
Diazepam	8.0	10.3	9.5	9.5	0.57
Biperiden	1.9	3.3	2.6	2.1	0.32
No. of admissions	0.5	0.7	1.0	1.0	<0.05

Abbreviations: IQ, Intelligence Quotient; VFT, Verbal Fluency Test; GAF, Global Assessment of Functioning scale; DUP, Duration of Untreated Psychosis; DOT, Duration of Treatment; PANSS, Positive and Negative Symptom Scale; No., number.
a. Chi-square test was used for testing group difference. Otherwise, t-tests were used.
b. Right-handedness was defined as >70 points according to Oldfield's Edinburgh Inventory.
c. DUP was examined by Mann–Whitney U test due to skewed distribution (skewness, 2.18; kurtosis, 4.39). The distribution of DUP in each group: short DOT group: range = 1–326 weeks; median = 7 weeks; long DOT group: range = 1–160 weeks; median = 8 weeks.
d. The distribution of DOT in each group: short DOT group: range = 0–17 weeks; long DOT group: range = 26–499 weeks.
e. Medication data in one patient in short DOT group was missing. Therefore it was not included in the statistical analysis (missing value).