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Association between rostral prefrontal cortical activity and functional outcome in first-episode psychosis: a longitudinal functional near-infrared spectroscopy study

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ABSTRACT

Background: Few biomarkers can be used easily and noninvasively to measure clinical condition and future outcome in patients with first-episode psychosis (FEP). To develop such biomarker using multichannel functional near-infrared spectroscopy (fNIRS), cortical function in the prefrontal cortex was longitudinally measured during a verbal fluency task.
Methods: Sixty-nine fNIRS measurements and 77 clinical assessments were obtained from 31 patients with FEP at baseline, 6-month, and 12-month follow-ups. Sixty measurements were obtained from 30 healthy controls matched for age, sex, and premorbid IQ. We initially tested signal changes for 12 months, and then investigated the relationship between fNIRS signals and clinical assessments.
Results: Signal changes from baseline to 12-month follow-up were not evident in any group. Patients with FEP had significant positive correlation coefficients between 6-month fNIRS signals and the 12-month Global Assessment of Functioning (GAF) score in the left middle frontal gyrus (FDR-corrected $p = .0016–.0052$, $r = .65–.59$). fNIRS signals at the 12-month follow-up were associated with 12-month GAF score in the bilateral superior and middle frontal gyri (FDR-corrected $p = .00085–.018$, $r = .72–.55$), and with the difference between baseline and 12-month GAF scores in the right superior frontal gyrus (FDR-corrected $p = .000067–.00012$, $r = .80–.78$). These associations were significant even after controlling for demographic variables. No association between baseline fNIRS signals and later GAF scores was found.
Discussion: fNIRS measurement can potentially be used as a biomarker to aid sequential assessment of neuroclinical conditions through the early stage of psychosis.

1. Introduction

Several epidemiological, clinical, and biological studies have explored potential markers for predicting clinical outcomes in schizophrenia. Retrospective (Marshall et al., 2005; Perkins et al., 2005) and prospective clinical cohort studies (Alvarez-Jimenez et al., 2011; Hegelstad et al., 2012) have shown that the duration of untreated psychosis (DUP) has a robust effect on symptomatic and functional outcomes. As DUP can be altered by improving the environment of treatment, special services for the early detection of, and early intervention in, patients with first-episode psychosis (FEP) have spread and led to better prognoses worldwide (Alvarez-Jimenez et al., 2011; Hegelstad et al., 2012; McGorry et al., 2006). To provide appropriate care and treatment for patients with FEP, biomarkers will be an essential part of the evaluation of patients' condition and prognosis (McGorry et al., 2006). Several neuroimaging studies have suggested potential biomarkers for predicting clinical outcomes in FEP (Andreasen et al., 2011; Palaniyappan et al., 2013; Wood et al., 2006). However, objective measurements are needed for clinical use that are easy to apply and noninvasive.

Functional near-infrared spectroscopy (fNIRS) is a candidate instrument for clinical use, as it can easily and noninvasively measure hemoglobin changes in the surface of the cortex (Koike et al., 2013a; Koike et al., 2011b; Suto et al., 2004; Takizawa et al., 2008). Moreover, fNIRS instruments are small and make very little noise; therefore, they can

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be easily moved including schools and care units. Our previous fNIRS studies demonstrated that patients with stable chronic schizophrenia showed impaired activity and characteristic waveform patterns over the prefrontal cortical regions during a letter version of verbal fluency task (LFT) (Chou et al., in press; Takizawa et al., 2008), and that the activity in the rostral part of the prefrontal cortex (PFC) was associated with the patients' present symptoms (Koike et al., 2011b; Takizawa et al., 2008). A cross-sectional fNIRS study that focused on four different clinical stages of psychosis (controls, ultra-high risk for psychosis, FEP, and chronic schizophrenia) indicated varying activity patterns among different prefrontal cortical subregions (Koike et al., 2011b). Brain activity in the superior frontal gyrus (SFG) and inferior frontal gyrus (IFG) was similar across clinical stages, whereas the activity in the middle frontal gyrus (MFG) decreased according to advancing clinical stage of psychosis (Koike et al., 2011b), which were similar to previous functional MRI studies that focused on different clinical stages (Benetti et al., 2009; Broome et al., 2009; Morey et al., 2005; Pauly et al., 2010). Large-scale cross-sectional MRI (Kubota et al., 2011) and fNIRS (Chou et al., in press) studies have suggested that patients with schizophrenia have similar age-related decline in brain volume and function compared to healthy controls, providing indication against slowly progressive brain pathology in the long-term course after the critical periods of psychosis.

As our previous studies had a cross-sectional design, a longitudinal study using fNIRS measurements and clinical assessments will be valuable for evaluating the causal relationship between fNIRS signals and clinical symptoms/functioning, and for further exploring possible biomarkers that predict patients' outcomes. In this study, we measured the functional trajectory in the prefrontal and temporal cortex using a multichannel fNIRS instrument and assessed clinical symptoms and functions at three time points (baseline, 6 months, and 12 months) in patients with FEP. Our main hypotheses (based on previous studies) were that (1) fNIRS signals in the PFC predict the future and/or reflect present clinical symptom and function, and (2) the longitudinal trajectory of fNIRS signal changes in the MFG decreases in 12-month follow-up.

2. Method and materials

2.1. Study participants

This study was part of the Integrative Neuroimaging studies in Schizophrenia Targeting for Early Intervention and Prevention (IN-STEP) research project, and the whole research setting was described in detail elsewhere (Koike et al., 2013b). In this project, we planned to obtain clinical assessments and fNIRS measurements for patients with FEP at registration, 6-month follow-up, and 12-month follow-up, considering the participants' condition. A total of 69 fNIRS measurements and clinical assessments were obtained from 31 patients with FEP (1 to 3 scans, range from baseline = 62–705 days), recruited between March 2009 and May 2013, from the outpatient and inpatient units of the University of Tokyo Hospital, University of Tokyo Health Service Center, psychiatry clinics, and internet referrals. Additionally, eight clinical outcome measures were available in follow-up clinical assessments. Thirty healthy controls matched for age, sex, and premorbid IQ ($p > .10$) underwent two fNIRS measurements (range = 94–731 days). All participants gave written informed consent to the ethical committee of the Faculty of Medicine, University of Tokyo (approval No. 630–8, 2226–4) after a complete explanation of this study and in accordance with the Declaration of Helsinki.

Members of the certificated psychiatrists in the early-intervention team (SKo, YS, YT, NI, TNag, TNat, and MT) obtained detailed clinical histories and assessed present symptoms and functions of the participants and their family members, and diagnosed FEP according to the DSM-IV criteria carefully. The inclusion criteria were age between 15 and 40 years for FEP, no intake of antipsychotic medications for more than 16 cumulative weeks, and continuous psychotic symptoms within the past 60 months (Lieberman et al., 2005). In the control group, we used the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) to rule out psychiatric disorders and excluded participants with first-degree relative(s) with psychotic disorders. The exclusion criteria for all groups were neurological illness, traumatic brain injury, a history of electroconvulsive therapy, low premorbid IQ (below 70) (Matsuoka and Kim, 2006; Uetsuki et al., 2007), previous alcohol abuse or addiction, and definite diagnosis of autistic spectrum disorders according to the DSM-IV criteria. Although illegal substance use (e.g., cannabis) has a crucial effect on the onset of psychosis (Cannon et al., 2008; van Os et al., 2010) and poor symptomatic and functional outcomes in schizophrenia (Harrison et al., 2008), the incidence rate of experienced drug use in young individuals is still relatively low in Japan (Degenhardt et al., 2008). Therefore, we regarded previous history of routine substance use as an exclusion criterion in this study (Koike et al., 2013b).

2.2. Clinical assessment

At each time point, the symptoms and functioning of the participants included in the FEP group were assessed using the Global Assessment of Functioning (GAF) (American Psychiatric Association, 1994) and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). For patients who were taking antipsychotics, anxiolytics, antiparkinsonian drugs, and/or antidepressant agents at measurement, the equivalent doses of chlorpromazine, diazepam, biperiden, and imipramine were calculated, respectively.

2.3. fNIRS instrument and measurement settings

We used a 52-channel fNIRS instrument (ETG-4000; Hitachi Medical Co., Tokyo, Japan) to measure hemoglobin changes via the procedure described in previous studies (Supplementary materials) (Koike et al., 2011a; Koike et al., 2011b; Takizawa et al., 2008). This procedure can measure hemoglobin changes mainly in the PFC (SFG, MFG, and IFG) and in the anterior and superior part of the temporal cortex (Fig. 1) (Shattuck et al., 2008; Tsuzuki et al., 2007).

We used the 160 s block-designed LFT that was reported in previous studies (Koike et al., 2011b; Takizawa et al., 2008). In the 60-s task period, the participant was instructed to say aloud as many words that started with a phonological syllable provided by a computer as possible. The task period was divided into three subperiods, and the instructed syllables changed every 20 s, to avoid silent moments and ameliorate the difference in task performance between the groups. In the 30-s pretask and 70-s post-task periods, the participant was instructed to say Japanese vowels aloud repeatedly, to extract task-specific signal changes. We recorded the total number of correct words generated by the participant during the task period as task performance.

2.4. Statistical analysis

Longitudinal signal changes were tested by two-way repeated measures analysis of covariance (ANCOVA) at each channel using Group (controls/FEP) as the between-subject factor, Time (baseline/follow-up) as the within-subject factor, and measurement interval days as the covariate. We applied the most recent fNIRS measurements as follow-up data. As we tested each channel independently, we adopted the false-discovery rate (FDR) method to correct multiple comparisons. Type I error rate was set at $\alpha < .05$, and the first step of significance was set at $p < 0{\cdot}05/52$ (channels) = .00096.(Singh and Dan, 2006).

We investigated the correlations between fNIRS signal changes and clinical assessments for each Group and Time using Pearson's correlation coefficient on the channels, which were significant difference between the group estimated in the SFG and MFG where the previous studies showed significant correlations (Koike et al., 2011b; Takizawa et al., 2008). We also adopted the FDR method within analyzed