progressive deficits of auditory mismatch negativity (MMN) occur concurrently with progressive brain volume reduction in the temporal cortex (Salisbury et al., 2007). Longitudinal and multi-modal studies are required to elucidate the pathophysiology of psychosis, to develop biomarkers that are easy to use in clinical settings, and finally to help with patients better prognoses (Borgwardt and Fusar-Poli, 2012).

We previously reported several neurocognitive (Suga et al., 2011; Yoshida et al., 2011), neurophysiological (Kawakubo and Kasai, 2006; Kawakubo et al., 2007; Salisbury et al., 2007), and neuroimaging studies (Kasai et al., 2003a, 2003b; Takizawa et al., 2008, 2009; Suga et al., 2010; Yamasaki et al., 2010; Koike et al., 2011b). However, most of the studies were cross-sectional and evaluated patients with chronic schizophrenia using a single modality. Since 2008, we have longitudinally evaluated ultra-high-risk (UHR) individuals and patients with first-episode psychosis (FEP) in a multi-modal fashion, and we already reported cross-sectional data from these studies (Koike et al., 2011b; Iwashiro et al., 2012). In this article, we introduce our research project, the Integrative Neuroimaging Studies in Schizophrenia Targeting for Early Intervention and Prevention (IN-STEP), aimed at exploring the pathophysiological features of the onset of psychosis and investigating possible predictive biomarkers for the clinical treatment of psychosis. We also introduce preliminary clinical assessments at baseline and at a 6-month follow-up until July 2012.

2. Methods

2.1. Research design

This research project was designed as a prospective observational cohort study to explore the pathophysiological features of psychosis, especially toward the onset, and to investigate possible predictive biomarkers of clinical outcome; therapeutic choice; early detection; and finally, the prediction of psychosis in clinical settings. The measurement protocol is illustrated in Table 1.

Table 1
The timeline of clinical assessment and measurement in the study.

		0 m	3 m	6 m	12 m	18 m	24 m	36 m
Clinical assessment	SOPS	x	x	x	x	x	x	x
	PANSS	x	x	x	x	x	x	x
	GAF	x	x	x	x	x	x	x
	SES	x			x		x	x
Subjective assessment	CAPE	x	x	x	x	x	x	x
	CES-D	x	x	x	x	x	x	x
	WHO-BREF	x	x	x	x	x	x	x
Pharmacological assessment	DIEPSS	x	x	x	x	x	x	x
	DAI-10	x	x	x	x	x	x	x
	BEMIB	x	x	x	x	x	x	x
Blood sampling		x		x	x		x	x
Neuropsychological battery	BACS-J	x		x	x		x	x
	UPSA-B	x		x	x		x	x
MRI	Structural	x			x		x	x
	Functional	x			x		x	x
ERP	MMN	x			x		x	x
	ASSR	x			x		x	x
NIRS	LFT	x		x	x		x	x
Clinical outcomes	Remission		x	x	x	x	x	x
	Recovery				x		x	x

Abbreviations: SOPS, the Scale of Prodromal Symptoms; PANSS, the Positive and Negative Syndrome Scale; GAF, the Global Assessment of Functioning; SES, socioeconomic status; CAPE, the Community Assessment of Psychic Experiences; CES-D, the Center for Epidemiologic Studies Depression Scale; WHO-BREF, the 26-item brief version of the WHO Quality of Life Scale; DIEPSS, the Drug-induced Extrapyramidal Symptoms Scale; DAI-10, the 10-item version of Drug Attitude Inventory; BEMIB, the Brief Evaluation of Medication Influences and Beliefs; BACS-J, the Brief Assessment of Cognition in Schizophrenia Japanese version; UPSA-B, the Brief UCSD Performance-Based Skills Assessment; MRI, magnetic resonance imaging; ERP, event related potential; MMN, mismatch negativity; ASSR; auditory steady state response; NIRS, near-infrared spectroscopy; LFT, letter version of verbal fluency task.

The target sample size is 100 help-seeking UHR individuals and 100 patients with FEP for the clinical evaluations. The primary outcomes are the number of transitions to psychosis in the UHR group and the number of symptomatic and functional remissions in the FEP group every year from registration. Concurrently, we collected peripheral blood in fasting to sample their genes and plasma. We also applied the Brief Assessment of Cognition in Schizophrenia Japanese Version (BACS-J) and the Brief UCSD Performance-Based Skills Assessment (UPSA-B) as neurocognitive measures, event-related potential (ERP) as brain neurophysiological measure, structural magnetic resonance imaging (sMRI) to obtain brain morphometric data, and functional MRI (fMRI) and near-infrared spectroscopy (NIRS) to measure brain activity, subject to the participants' condition. This study was approved by the ethics committee of the University of Tokyo Hospital (approval no. 2226-2) in accordance with the Declaration of Helsinki, registered in the University Hospital Medical Information Network Clinical Trials Registry of the International Committee of Medical Journal Editors (no. UMIN000008660), and written in line with the Strengthening the Reporting of Observational Studies in Epidemiology statement (von Elm et al., 2007).

2.2. Participants

The participants are help-seekers recruited from the outpatient and inpatient units of the University of Tokyo Hospital, University of Tokyo Health Service Center, psychiatry clinics, and internet referrals. All eligible participants are assessed using the Structured Interview for Prodromal Symptoms (SIPS) and evaluated using the UHR or psychosis criteria. Psychosis in SIPS criteria is the same as psychotic disorders in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association (APA), 1997).

The eligibility criteria are summarized in Table 2. The inclusion criteria are ages of 15 to 30 years for UHR and 15 to 40 years for FEP, no antipsychotic medications for psychosis for more than 16 cumulative weeks, and continuous psychotic symptoms within the past 60 months (Lieberman et al., 2005).

The exclusion criteria are neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, a history of electroconvulsive therapy, low premorbid IQ (below 70), and previous alcohol addiction. Illegal substance use (e.g., cannabis) occurs among young people all over the world, and has a crucial effect on the transition to psychosis (Cannon et al., 2008; van Os et al., 2010) and poor symptomatic and functional outcomes (Harrison et al., 2008; Schimmelmann et al., 2008). However, the incidence rate of experienced drug use in young individuals is still relatively low in Japan (Degenhardt et al., 2008). Therefore, we adopted previous continuous substance use as an exclusion criterion in this study.

Table 2
Summary of the eligibility criteria. Target condition: individuals diagnosed as ultra-high-risk or having already psychosis using the Structured Interview for Prodromal Symptoms (SIPS) criteria.

Inclusion criteria
1. Age, 15–40 years (individuals at UHR, 15–30 years)
2. No history of antipsychotic medications for psychosis for more than 16 cumulative weeks
3. Continuous psychotic symptoms within the past 60 months

Exclusion criteria
1. Neurological illness
2. Previous traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min
3. History of electroconvulsive therapy
4. Low premorbid IQ (below 70)
5. Previous alcohol addiction
6. Previous continuous substance use
7. Clearly diagnosed with an autistic disorder according to the DSM-IV criteria

In clinical assessment, the symptoms seen in pervasive developmental disorder (PDD) and dissociative disorders sometimes appear similar to the symptoms seen in schizophrenia. However, our recent findings have suggested that the differences between these disorders with respect to the development of the prefrontal cortex may clarify the pathogenesis of psychosis (Suga et al., 2010; Yamasaki et al., 2010). Therefore, we excluded participants who were clearly diagnosed with PDD and dissociative disorders according to the DSM-IV criteria to explore the specific pathophysiological features of psychosis, particularly schizophrenia.

All the participants provide written informed consent after they are given a complete explanation of the study. The registration and measurement began on July 1, 2008, and the new study protocol described here was implemented on December 1, 2011. We present the preliminary findings of the clinical assessments in the Results section.

2.3. Sample size

One-hundred help-seeking UHR individuals are considered for the clinical evaluation study, which was determined based on previous studies on the transition to psychosis with similar recruitment backgrounds (Yung et al., 2006; Woods et al., 2009) as well as the feasibility of the study, given our resources. One-hundred patients with FEP are also considered for the evaluation of clinical prognosis. The effect sizes of the rate of transition to psychosis for 6 months and 30 months were 0.32 (Yung et al., 2006) and 0.60 (Woods et al., 2009), respectively, and the estimated sample sizes (alpha error, 0.05; beta error, 0.2) were 129 and 36, respectively, as determined using G*Power 3.1.2 (Erdfelder et al., 1996).

2.4. Clinical assessment

All the clinical assessments and measurement points are summarized in Table 1. We assess the severity of symptoms and functioning using the Global Assessment of Functioning (GAF) (American Psychiatric Association (APA), 1994), Social and Occupational Functioning Assessment Scale (SOFAS), and Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) at each measurement point. The participants in the UHR group are also assessed with regard to subthreshold symptoms using the positive subscale in the Scale of Prodromal Symptoms at each measurement point. We assess the subjective depressive symptoms using the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977) and the quality of life using the 26-item brief version of the WHO Quality of Life Scale (WHO-BREF) (Tazaki and Nakane, 1997; The World Health Organization Quality of Life Group (WHOQOL Group), 1998) at each measurement point.

To evaluate symptomatic remission, we adopt a proposal from the Remission in Schizophrenia Working Group (Andreasen et al., 2005), which defined the symptomatic remission of illness as the corresponding 8 PANSS subscores (P1, P2, P3, N1, N4, N6, G5, and G9) indicating "mild" or less on all items for at least 6 months. To evaluate functional recovery, we assess 3 major domains: independent residence, productive activity, and social relationship (Harvey and Bellack, 2009; Emsley et al., 2011).

If the patients take any antipsychotic, anxiolytic, and/or antiparkinsonian agents, we calculate the chlorpromazine, diazepam, and biperiden equivalent doses, respectively. Blood sampling is performed not only for gene and plasma sampling but also for assessing the general health condition.

2.5. Data reliability of clinical assessment

Data collection by multiple raters is affected by methodological problems that result in reduced inter-rater reliability. To control the quality of data assessment, we use video interviews to ensure the scoring of PANSS, GAF, and SOFAS scores more than once a year. We also calculate the inter-rater reliability of the PANSS, GAF, and SOFAS scores provided by the raters in the video interviews and provided feedback based on the results to maintain the quality of the assessment (Cronbach alpha = 0.857).

2.6. Measurement of candidate biomarkers

We use blood sampling, BACS-J, UPSA-B, ERP, sMRI, fMRI, and NIRS as objective biomarkers, as described in detail in the following sections and summarized in Table 1. Before every measurement, we consider the participants' condition and respected their voluntary cooperation.

2.6.1. Neurocognitive batteries

Cognitive impairment is a core feature of schizophrenia and a key determinant of functional outcome; therefore, the assessment of cognitive function is important for the evaluation of patients with schizophrenia (Green et al., 2004; Keefe et al., 2004). The BACS-J is an important and sensitive tool to assess cognitive domains, especially for domains that are severely impaired in patients with schizophrenia such as verbal memory, working memory, motor speed, verbal fluency, attention, and executive function (Keefe et al., 2004; Kaneda et al., 2007). Recent neurocognitive studies suggested that individuals with UHR have relatively worse performance in verbal memory and processing speed than healthy controls; however, they show similar working memory and executive function (Seidman et al., 2010; Carrion et al., 2011). Furthermore, the severity of verbal memory impairment may predict the onset of psychosis (Brewer et al., 2005; Lencz et al., 2006; Seidman et al., 2010). The BACS-J battery is less time-consuming and easy to use in clinical settings, and it has already been used as a valid cognitive assessment tool for participants with UHR and FEP.

In the measurement of functional outcomes, the UPSA is used to assess performance in 5 real-world domains: planning/organization, finances, communication, travel, and household (Patterson, 2010; Sumiyoshi et al., 2011). The UPSA does not require specialized qualifications for administration, and it has high reliability and validity in patients with schizophrenia (Harvey et al., 2007). The UPSA-B is a brief version that consists of 2 of the 5 domains mentioned above (finances and communication). The UPSA-B requires only 10–15 min to administer and has easy instructions and high validity for the residential status of patients with schizophrenia (Mausbach et al., 2007).

2.6.2. Structural and functional MRI

MRI is well recognized for its excellent spatial resolution, lack of radioactivity, and noninvasiveness. MRI has recently made investigation of the neural correlates of pathophysiology possible in schizophrenia. Previous MRI studies in patients with schizophrenia provided quantitative evidence of structural abnormalities. Longitudinal sMRI studies demonstrated the progression of the loss of neocortical gray matter volume characteristically after the onset of psychosis (Kasai et al., 2003a, 2003b; Olabi et al., 2011). Previous longitudinal investigations of UHR individuals who later developed psychosis showed that the brain changes during the period of transition to psychosis especially in the lateral and medial temporal cortex (Pantelis et al., 2003; Velakoulis et al., 2006; Takahashi et al., 2009). These results suggest that brain morphological changes occur around the onset and sMRI is a possible biomarker for predicting the onset and identifying clinical stages of psychosis (Koutsouleris et al., 2009; Fusar-Poli et al., 2011a).

fMRI allows the imaging of brain function with high spatial resolution. Previous studies that used fMRI in UHR individuals reported significant abnormalities in the neural correlates of working memory, visual attention, and emotional processing (Fusar-Poli, 2011). Moreover, neural correlates of disrupted interpersonal cognition were reported in the previous literature (Brune et al., 2011). Patients with schizophrenia show deficits in interpersonal cognition, including abnormal performance in tasks targeting the "theory of mind"

or perspective-taking and empathy. Although impaired interpersonal cognition is considered as one of the core contributors to the poor social functioning of patients with schizophrenia (Pinkham and Penn, 2006), how and when such psychological disruptions emerge and progress have not been fully investigated. We investigated the neural correlates of disrupted interpersonal cognition in patients with schizophrenia by using a perspective-taking task and facial imitation task that were adapted from previous studies (Baron-Cohen et al., 1985; Carr et al., 2003; Lee et al., 2006; Vollm et al., 2006). The present studies may contribute to a better understanding of the pathophysiological features of schizophrenia and the development of effective and objective biomarkers for the early detection and prediction of psychosis.

2.6.3. Event-related potential

The ERP is a suitable method for investigating the neurophysiology of the brain with a high temporal resolution. We use the duration MMN, the frequency MMN, and the auditory steady-state response (ASSR) measured by a 64-channel net station in patients at different clinical stages to identify clinically useful biological markers.

To evaluate the cognitive dysfunction in schizophrenia, a promising approach involves the use of auditory MMN, which is one of the ERP components and is thought to reflect the pre-attentive deviance detection process in the early auditory function (Naatanen and Kahkonen, 2009). Primary generators for MMN have been localized to the auditory cortex (Naatanen and Kahkonen, 2009). MMN amplitude reduction observed upon the direct application of *N*-methyl-D-aspartate (NMDA) receptor antagonists suggests that the MMN reflects current influx in NMDA receptors in the primary auditory cortex (Javitt et al., 1996). Patients with chronic schizophrenia often exhibit reduced MMN amplitude. MMN deficits are specific for patients with schizophrenia, and MMN is one of the most widely replicated biomarkers of cognitive dysfunction in schizophrenia (Kawakubo and Kasai, 2006; Salisbury et al., 2007; Naatanen and Kahkonen, 2009). Several studies have suggested that deficits of MMN occur in different clinical stages according to the type of deviant stimulus. The duration MMN amplitude was reduced before the onset of psychosis (Brockhaus-Dumke et al., 2005; Bodatsch et al., 2011; Atkinson et al., 2012; Shaikh et al., 2012), whereas the frequency MMN amplitude progressively decreased after the onset (Salisbury et al., 2007; Magno et al., 2008).

Another approach to evaluate the cognitive dysfunction in schizophrenia is the measurement of the ASSR, which is one of the standard methods for the evaluation of gamma band oscillation. Cortical gamma oscillation may be associated with high-order cognitive functions such as working memory, and require inhibitory inputs to pyramidal neurons from the parvalbumin basket cell class of GABAergic neurons (Lewis et al., 2012). Several studies reported that patients with schizophrenia exhibit reduced power and coherence in response to 40-Hz click trains. This selective disturbance of ASSRs in the gamma-range frequency in schizophrenia may be caused by specific cellular neuropathological changes in gamma-aminobutyric acid-mediated neural networks in the auditory cortex (Brenner et al., 2009). Only one study showed an abnormal response in patients with FEP (Spencer et al., 2008).

2.6.4. Near-infrared spectroscopy

NIRS is a relatively new method that can measure changes in the hemodynamic oxygenated and deoxygenated hemoglobin concentrations in the cerebral cortex. NIRS offers advantages of noninvasiveness, an easy setup, minimal constraints, compactness, and quietness. Because of these advantages, NIRS can be used to measure the cortical function of patients noninvasively and repetitively in clinical settings (Takizawa et al., 2008; Koike et al., 2011b). Our multichannel NIRS study using a letter version of a verbal fluency task showed reduced activation over the prefrontal regions that showed significant positive correlations with lower GAF scores in the schizophrenia group (Takizawa et al., 2008; Koike et al., 2011b). We also found different impairment patterns in UHR, FEP, and chronic schizophrenia (Koike et al., 2011b). The verbal fluency task requires various cognitive domains such as memory recall, verbal learning and memory, inhibition, and executive function. This task is suitable because most patients can perform the task, and the impairment of verbal manipulation may be a core element for the onset of psychosis (Brewer et al., 2005; Lencz et al., 2006; Seidman et al., 2010; Carrion et al., 2011). Our major aim in this project is to determine whether these changes reflect present symptoms and/or functions and predict the transition to psychosis or symptomatic and functional outcomes.

2.6.5. Statistical analysis for clinical assessment until July 2012

In this article, we introduce the preliminary data for the clinical assessment at baseline and 6-month follow-up until July 2012 and for the transition to psychosis in the UHR group until Oct 2012. We analyzed the data by using Mann–Whitney *U*-test and Wilcoxon signed-rank test using SPSS 17.0J software (SPSS Inc., Chicago, IL, USA).

3. Results

In total, 159 individuals were assessed using SIPS, and 104 individuals fulfilled the UHR or FEP criteria (Fig. 1). Thirty-seven UHR individuals and 30 patients with FEP participated in this study. The number of diagnoses in the UHR individuals according to SIPS and in the FEP patients according to the DSM-IV is summarized in Table 3. At baseline, the GAF score was significantly different between the groups, but the other scores were not significantly different (Table 4).

Six months later, we assessed the clinical characteristics for 23 UHR individuals and 21 patients with FEP. The reasons for the lack of follow-up are summarized in Fig. 1. Although demographic characteristics of patients with FEP were not significantly different whether follow-up or not, the participants who were able to be followed-up in the UHR group were more likely to be young and have mild symptoms in the baseline assessment (age: not follow-up, 22.9 [3.6]; follow-up, 20.4 [3.3]; $p=0.032$; GAF score: 42.2 [7.6], 49.5 [11.5], $p=0.027$; PANSS general score: 42.2 [7.6], 49.5 [11.5], $p=0.027$; WHO-BREF Physical health: 2.2 [0.6], 2.8 [0.6], $p=0.009$; Psychological health: 2.0 [0.6], 2.6 [0.6], $p=0.013$; Environment: 2.8 [0.6], 3.4 [0.5], $p=0.008$; and CES-D score: 35.7 [11.7], 23.7 [10.6], $p=0.003$; respectively). The PANSS positive, general pathology, and GAF scores in the FEP group significantly changed from the baseline to the 6-month follow-up, whereas the PANSS positive and GAF scores, and the WHOQOL-BREF social relationship score significantly changed in the UHR group (Table 4). The follow-up assessment did not demonstrate significant differences between the UHR and FEP groups. Two (7.1%) of the 27 UHR individuals within 6 months, 2 (8.0%) of 24 within 12 months, and 6 (35.3%) of 17 within 24 months transitioned to psychosis according to the SIPS criteria.

4. Discussion

The goal of our research project is to explore the pathophysiological features with regard to the onset of psychosis using a longitudinal and multi-modal measurement approach and to investigate the possible predictive biomarkers of clinical outcome, therapy choice, early detection, and prediction of psychosis in clinical settings. We adopted gene, biochemical agents, neurophysiological data, brain images, and clinical features as objective biomarkers (Table 1). We have already reported cross-sectional results and now evaluate the longitudinal data (Koike et al., 2011b; Iwashiro et al., 2012).

Recent longitudinal neuroimaging investigations for UHR and FEP involved early intervention services based on community mental health services, for example, the Orygen Youth Health at Melbourne University (Pantelis et al., 2003; Brewer et al., 2005; Velakoulis et al., 2006; Takahashi et al., 2009) and LEO and OASIS at King's

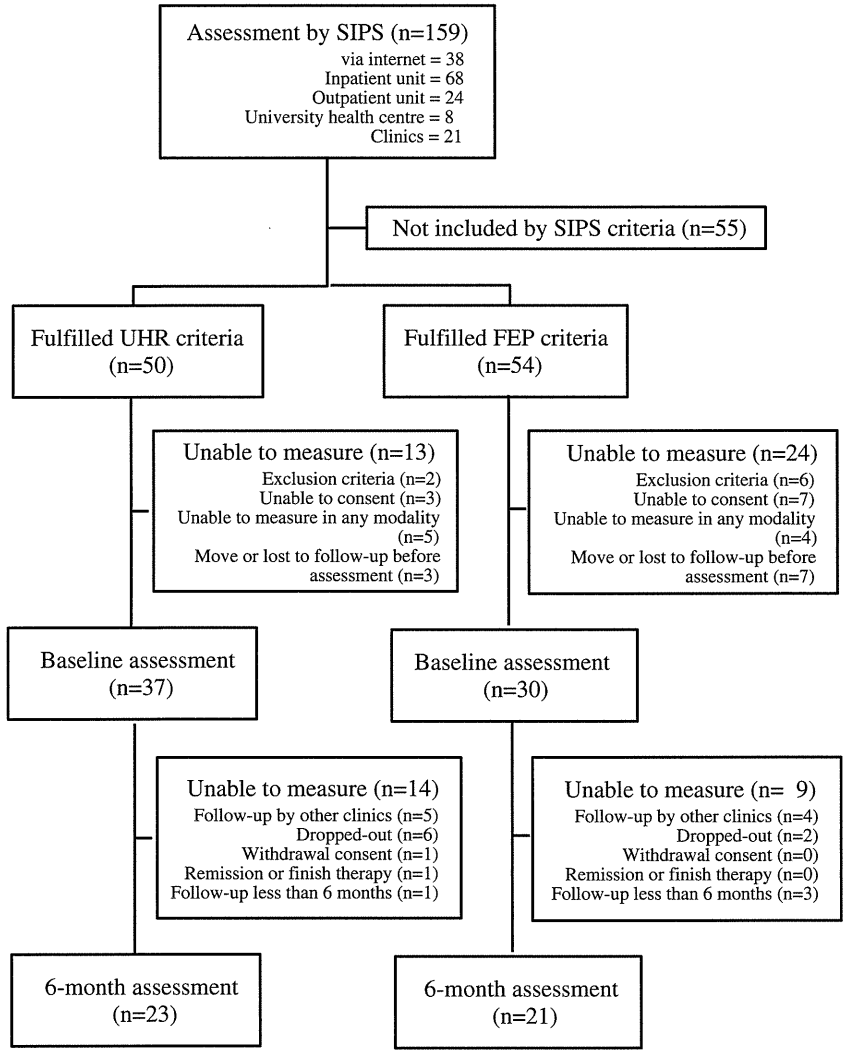

Fig. 1. Eligible individuals and participants flow in this study.

College London (Fusar-Poli et al., 2010, 2011b; Shaikh et al., 2012). In particular, several novel multi-modal approaches for UHR and FEP have been introduced by the group at King's College London (Fusar-Poli et al., 2010, 2011b). In contrast, a multi-site study with many participants in U.S., the North American Prodrome Longitudinal Study (NAPLS), especially addressed UHR individuals and proposed possible predictive clinical findings for the transition to psychosis (Cannon et al., 2008; Woods et al., 2009; Seidman et al., 2010). Recently the NAPLS-2 project was conducted to replicate possible predictors, and it also used blood sampling as well as neurocognitive batteries, ERP, sMRI, and fMRI to explore possible objective biomarkers (Addington et al., 2012). A multi-site study with many participants in Germany, the German Research Network on Schizophrenia, has conducted several pharmacological and/or psychosocial interventions for both UHR and FEP (Wölwer et al., 2006) and suggested possible biomarkers using MMN (Bodatsch et al., 2011). Differences among these research projects and the IN-STEP project include objectives, inclusion criteria, and recruitment background. The main purpose of our project was to investigate possible predictive biomarkers for the transition to psychosis as well as symptomatic and functional outcomes by using multi-level objective measurements for both UHR and FEP. Therefore, we excluded several conditions that could have affected the results such as drug abuse, PTSD, and PDD. Various genetic studies have identified substantial common risk genes between schizophrenia and autism (Stefansson et al., 2008). Neuroimaging studies have also suggested that the anatomic abnormality of the brain seen in autism also occurs in schizophrenia (Cheung et al., 2010). However, the typical clinical features and long-term outcomes are different, and also the neural basis is

Table 3
Number of diagnoses in UHR individuals according to SIPS and patients with FEP and ChSZ according to the DSM-IV.

Diagnosis	Number
UHR	
BIPS	1
APS	24
GRDS	4
BIPS + APS	2
APS + GRDS	6
FEP	
295.1 Schizophrenia, disorganized type	7
295.3 Schizophrenia, paranoid type	13
295.4 Schizophreniform disorder	7
297.1 Delusional disorder	1
298.9 Psychotic disorder not otherwise specified	2

Abbreviations: BIPS, brief intermittent psychotic symptoms; APS, attenuated psychotic symptoms; GRDS genetic risk and deterioration.

Table 4
Demographic characteristics of study participants at baseline measurement until 31 July 2012.

	UHR					FEP					Group differences	
	Baseline		6 months			Baseline		6 months			Baseline	6 months
	Ave.	SD	Ave.	SD	P value	Ave.	SD	Ave.	SD	P value	P value	P value
Participants (male)	37 (20)		23 (13)		NA	30 (18)		21 (14)		NA	NA	NA
Living with family (%)	26 (70.2)		NA		NA	23 (76.7)		NA		NA	.096	NA
Employment or Education (%)	27 (73.0)		NA		NA	20 (66.7)		NA		NA	.086	NA
Symptomatic remission (%)	NA		NA		NA	6 (20.0)		10 (47.6)		NA	NA	NA
Age (year)	21.3	3.6	NA	NA	NA	23.7	6.0	NA	NA	NA	.066	NA
Education (year)	13.2	2.3	NA	NA	NA	13.2	2.6	NA	NA	NA	.943	NA
Age at onset of illness (year)	19.1	4.1	NA	NA	NA	21.2	6.2	NA	NA	NA	.108	NA
Age at onset of psychosis (year)	NA	NA	NA	NA	NA	22.9	6.1	NA	NA	NA	NA	NA
DUP (week)	NA	NA	NA	NA	NA	37.5	71.3	NA	NA	NA	NA	NA
Premorbid IQ	106.3	9.4	NA	NA	NA	103.9	10.5	NA	NA	NA	.337	NA
GAF	46.7	10.7	55.4	15.9	**.014**	37.3	10.8	47.3	12.7	**.039**	**.001**	.069
PANSS												
Positive	14.2	3.6	12.0	3.4	**.026**	15.7	4.8	11.7	5.2	**.044**	.143	.800
Negative	18.9	6.32	16.6	6.2	.260	20.5	7.9	16.6	8.2	.061	.206	.996
General pathology	34.6	7.9	31.6	7.6	.559	36.2	9.1	27.3	9.1	**.003**	.433	.097
WHOQOL-BREF												
Physical health	2.57	0.66	2.89	0.72	.635	2.59	0.78	2.70	0.78	.202	.923	.429
Psychological health	2.36	0.70	2.68	0.75	.402	2.48	0.85	2.58	0.66	.066	.546	.693
Social relationships	2.84	0.67	3.22	0.77	**.018**	2.60	1.01	2.76	0.68	.256	.290	.061
Environment	3.13	0.60	3.51	0.51	.231	3.18	0.53	3.25	0.50	.097	.762	.125
Overall	2.21	0.85	2.53	0.75	.150	2.56	0.99	2.25	1.07	.369	.171	.363
CES-D	28.0	12.3	20.5	13.5	.488	28.4	12.1	25.8	13.5	.083	.908	.233

Abbreviation: UHR, ultra-high risk; FEP; first-episode psychosis; Ave., average; SD, standard deviation; DUI, duration of illness; DUP, duration of untreated psychosis; IQ, intelligent quotient; GAF, the Global Assessment of Functioning; SOPS, the Scale of Prodromal Symptoms; PANSS, the Positive and Negative Syndrome Scale; WHO-BREF, the 26-item brief version of the WHO Quality of Life Scale; CES-D, the Center for Epidemiologic Studies Depression Scale.
Because of minor change of measurement design, WHO-BREF (7 ARMS and 4 FEP) and CES-D (1 ARMS and 6 FEP) were not assessed at baseline.

different in genetic and neuroimaging studies among these disorders. The brain volume in patients with autism at the age of 2 to 3 years is larger than that in children with normal development at the same age and becomes smaller when these patients become older (Courchesne et al., 2001). In contrast, the brain volume of patients with schizophrenia before the onset is smaller than that in healthy controls, and a further progressive loss of brain volume then occurs (Kasai et al., 2003a, 2003b; Pantelis et al., 2003; Velakoulis et al., 2006; Salisbury et al., 2007; Takahashi et al., 2009). Through structural brain imaging studies, we have also reported that the abnormalities in schizophrenia are partially similar to but different from those in PDD and PTSD in some aspects (Kasai et al., 2003a, 2003b; Yamasue et al., 2003; Araki et al., 2005; Kasai et al., 2008; Rogers et al., 2009; Suga et al., 2010; Yamasaki et al., 2010). Our studies have shown different brain volumes in the inferior frontal gyrus between FEP and PDD, which implied that the brain functionalization related to verbal manipulation and mirror neuron system within the inferior frontal gyrus manifested the difference of characteristic symptoms between the diseases (Suga et al., 2010; Yamasaki et al., 2010; Iwashiro et al., 2012). Although patients with PDD and chronic schizophrenia showed volume reduction in the pars opercularis (corresponding to Brodmann area 44) and pars triangularis (Brodmann area 45), PDD was associated with relatively smaller volume in the pars opercularis and chronic schizophrenia in the pars triangularis. Patients with UHR and FEP have volume reduction only in the pars triangularis (Iwashiro et al., 2012). Recent studies have also suggested that brain maturation in the prefrontal cortex occurs from the caudal to rostral areas in accordance with the human evolution of verbal communication and social interaction (Badre and D'Esposito, 2009). Our study criteria may therefore be used to identify differences among several psychiatric disorders in terms of neurodevelopmental trajectory and brain maturation.

In the baseline assessment, the PANSS score in the FEP group was similar to those in the UHR group. The reason was that the clinical assessments at baseline relied on feasibility of neurocognitive batteries and/or neuroimaging instruments. The baseline assessment was performed when patients with FEP were in a relatively stable condition and therefore had similar scores on the symptom scales when compared with individuals with UHR (Koike et al., 2011b). At the 6-month follow-up, the clinical difference between the groups disappeared. It has been suggested that outcomes in schizophrenia can be roughly divided into the following three categories: symptomatic remission with little functional deficit, continuous symptoms and/or functional deficit, and severe continuous symptoms and functional deficit (van Os and Kapur, 2009). As observed for individuals at risk for psychosis, recent studies have also suggested that outcomes in UHR individuals may be classified into the following three categories: symptomatic remission and functional recovery, sustained symptoms and/or functional deficit, and transition to psychosis (Addington et al., 2011; Simon et al., 2011). These results suggest that regardless of their history of psychosis, their symptoms and functional deficits should be addressed according to the clinical stages (McGorry et al., 2006). We also plan to perform a psychological intervention for patients with FEP and to scale up intensive care for young people (Koike et al., 2011a). With regard to the transition to psychosis in the UHR group, the transition rate was similar to the previous high-risk studies, although the mean age of the participants was relatively higher than that in previous studies (Fusar-Poli et al., 2012).

Our project has possible limitations regarding the study design because our observations were mainly naturalistic and some participants have entered other psychosocial clinical trials (Koike et al., 2011a). Therefore, the number of participants who entered into these trials and their distribution must be considered. Second, selection bias must be considered as participants were recruited mainly from the university units. In addition, we have to consider participants' feasibility of measurements when registering because our project was based on neuroimaging studies. Therefore, potential selection bias according to participants' symptoms and severities also has to be considered. Third, and our naturalistic design allowed the psychiatrists to prescribe medications to the participants prior to entry. Because of free access to the medical system in Japan, it is relatively easy for patients to receive medications including

antipsychotics and benzodiazepines. Although we minimized medication and determined whether all the participants received proper medication under the guidelines for FEP after entry, it was difficult to collect blood samples and perform imaging under medication-free conditions.

In conclusion, we have introduced the research protocol for our prospective observational cohort study to explore the pathophysiological features with regard to the onset of psychosis using a multi-modal measurement approach. Our aim is also to investigate possible predictive biomarkers of clinical outcome, therapy choice, early detection, and the prediction of psychosis in clinical settings. In this research project, we expect to improve patients' prognoses applying these findings to clinical use.

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Contributors

SK, YT, MS, SY, RT, TA, and KK designed the protocol. SK wrote the entire manuscript and undertook the statistical analysis in this article. MS and SY wrote the "Neurocognitive battery" section; YT, NI, T Natsubori, NY, and HY, the "MRI" section; T Nagai, MT, and TA, the "Event-related potential" section; and SK, YS, and YN, the "Near-infrared spectroscopy" section. SK, YT, NI, YS, T Nagai, T Natsubori, MT, MS, and SY contributed to the implementation of this project. SK, MS, SY, RT, TA, and KK contributed financial resources to this project. All authors have approved the final version of the manuscript.

Conflict of interest

None.

Acknowledgment

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References

Addington, J., Cornblatt, B.A., Cadenhead, K.S., Cannon, T.D., McGlashan, T.H., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Walker, E.F., Woods, S.W., Heinssen, R., 2011. At clinical high risk for psychosis: outcome for nonconverters. Am. J. Psychiatry 168 (8), 800–805.

Addington, J., Cadenhead, K.S., Cornblatt, B., Mathalon, D.H., McGlashan, T.H., Perkins, D.O., Seidman, L.J., Tsuang, M., Walker, E.F., Woods, S.W., Addington, J.A., Cannon, T.D., 2012. North American Prodrome Longitudinal Study (NAPLS 2): overview and recruitment. Schizophr. Res. 142 (1), 77–82.

American Psychiatric Association (APA), 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Press, Washington, D.C. U.S.A.

American Psychiatric Association (APA), 1997. Practice guideline for the treatment of patients with schizophrenia. Am. J. Psychiatry 154 (4 Suppl.), 1–63.

Andreasen, N.C., Carpenter Jr., W.T., Kane, J.M., Lasser, R.A., Marder, S.R., Weinberger, D.R., 2005. Remission in schizophrenia: proposed criteria and rationale for consensus. Am. J. Psychiatry 162 (3), 441–449.

Araki, T., Kasai, K., Yamasue, H., Kato, N., Kudo, N., Ohtani, T., Nakagome, K., Kirihara, K., Yamada, H., Abe, O., Iwanami, A., 2005. Association between lower P300 amplitude and smaller anterior cingulate cortex volume in patients with posttraumatic stress disorder: a study of victims of Tokyo subway sarin attack. Neuroimage 25 (1), 43–50.

Atkinson, R.J., Michie, P.T., Schall, U., 2012. Duration mismatch negativity and P3a in first-episode psychosis and individuals at ultra-high risk of psychosis. Biol. Psychiatry 71 (2), 98–104.

Badre, D., D'Esposito, M., 2009. Is the rostro-caudal axis of the frontal lobe hierarchical? Nat. Rev. Neurosci. 10, 659–669.

Baron-Cohen, S., Leslie, A.M., Frith, U., 1985. Does the autistic child have a "theory of mind"? Cognition 21 (1), 37–46.

Bodatsch, M., Ruhrmann, S., Wagner, M., Muller, R., Schultze-Lutter, F., Frommann, I., Brinkmeyer, J., Gaebel, W., Maier, W., Klosterkotter, J., Brockhaus-Dumke, A., 2011. Prediction of psychosis by mismatch negativity. Biol. Psychiatry 69 (10), 959–966.

Borgwardt, S., Fusar-Poli, P., 2012. Third-generation neuroimaging in early schizophrenia: translating research evidence into clinical utility. Br. J. Psychiatry 200 (4), 270–272.

Brenner, C.A., Krishnan, G.P., Vohs, J.L., Ahn, W.Y., Hetrick, W.P., Morzorati, S.L., O'Donnell, B.F., 2009. Steady state responses: electrophysiological assessment of sensory function in schizophrenia. Schizophr. Bull. 35 (6), 1065–1077.

Brewer, W.J., Francey, S.M., Wood, S.J., Jackson, H.J., Pantelis, C., Phillips, L.J., Yung, A.R., Anderson, V.A., McGorry, P.D., 2005. Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. Am. J. Psychiatry 162 (1), 71–78.

Brockhaus-Dumke, A., Tendolkar, I., Pukrop, R., Schultze-Lutter, F., Klosterkötter, J., Ruhrmann, S., 2005. Impaired mismatch negativity generation in prodromal subjects and patients with schizophrenia. Schizophr. Res. 73 (2–3), 297–310.

Brune, M., Ozgurdal, S., Ansorge, N., von Reventlow, H.G., Peters, S., Nicolas, V., Tegenthoff, M., Juckel, G., Lissek, S., 2011. An fMRI study of "theory of mind" in at-risk states of psychosis: comparison with manifest schizophrenia and healthy controls. Neuroimage 55 (1), 329–337.

Cannon, T.D., Cadenhead, K., Cornblatt, B., Woods, S.W., Addington, J., Walker, E., Seidman, L.J., Perkins, D., Tsuang, M., McGlashan, T., Heinssen, R., 2008. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch. Gen. Psychiatry 65 (1), 28–37.

Carr, L., Iacoboni, M., Dubeau, M., Mazziotta, J.C., Lenzi, G.L., 2003. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. PNAS 100 (9), 5497–5502.

Carrion, R.E., Goldberg, T.E., McLaughlin, D., Auther, A.M., Correll, C.U., Cornblatt, B.A., 2011. Impact of neurocognition on social and role functioning in individuals at clinical high risk for psychosis. Am. J. Psychiatry 168 (8), 806–813.

Cheung, C., Yu, K., Fung, G., Leung, M., Wong, C., Li, Q., Sham, P., Chua, S., McAlonan, G., 2010. Autistic disorders and schizophrenia: related or remote? An anatomical likelihood estimation. PLoS One 5 (8), e12233.

Courchesne, E., Karns, C.M., Davis, H.R., Ziccardi, R., Carper, R.A., Tigue, Z.D., Chisum, H.J., Moses, P., Pierce, K., Lord, C., Lincoln, A.J., Pizzo, S., Schreibman, L., Haas, R.H., Akshoomoff, N.A., Courchesne, R.Y., 2001. Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. Neurology 57 (2), 245–254.

Degenhardt, L., Chiu, W.T., Sampson, N., Kessler, R.C., Anthony, J.C., Angermeyer, M., Bruffaerts, R., de Girolamo, G., Gureje, O., Huang, Y., Karam, A., Kostyuchenko, S., Lepine, J.P., Mora, M.E., Neumark, Y., Ormel, J.H., Pinto-Meza, A., Posada-Villa, J., Stein, D.J., Takeshima, T., Wells, J.E., 2008. Toward a global view of alcohol, tobacco, cannabis, and cocaine use: findings from the WHO World Mental Health Surveys. PLoS Med. 5 (7), e141.

Emsley, R., Chiliza, B., Asmal, L., Lehloenya, K., 2011. The concepts of remission and recovery in schizophrenia. Curr. Opin. Psychiatry 24 (2), 114–121.

Erdfelder, E., Faul, F., Buchner, A., 1996. GPOWER: a general power analysis program. Behav. Res. Methods Instrum. Comput. 28, 1–11.

Fusar-Poli, P., 2011. Voxel-wise meta-analysis of fMRI studies in patients at clinical high risk for psychosis. J. Psychiatry Neurosci. 36 (6), 110021.

Fusar-Poli, P., Howes, O.D., Allen, P., Broome, M., Valli, I., Asselin, M.C., Grasby, P.M., McGuire, P.K., 2010. Abnormal frontostriatal interactions in people with prodromal signs of psychosis: a multimodal imaging study. Arch. Gen. Psychiatry 67 (7), 683–691.

Fusar-Poli, P., Borgwardt, S., Crescini, A., Deste, G., Kempton, M.J., Lawrie, S., Mc Guire, P., Sacchetti, E., 2011a. Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis. Neurosci. Biobehav. Rev. 35 (5), 1175–1185.

Fusar-Poli, P., Stone, J.M., Broome, M.R., Valli, I., Mechelli, A., McLean, M.A., Lythgoe, D.J., O'Gorman, R.L., Barker, G.J., McGuire, P.K., 2011b. Thalamic glutamate levels as a predictor of cortical response during executive functioning in subjects at high risk for psychosis. Arch. Gen. Psychiatry 68 (9), 881–890.

Fusar-Poli, P., Bonoldi, I., Yung, A.R., Borgwardt, S., Kempton, M.J., Valmaggia, L., Barale, F., Caverzasi, E., McGuire, P., 2012. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch. Gen. Psychiatry 69 (3), 220–229.

Green, M.F., Nuechterlein, K.H., Gold, J.M., Barch, D.M., Cohen, J., Essock, S., Fenton, W.S., Frese, F., Goldberg, T.E., Heaton, R.K., Keefe, R.S., Kern, R.S., Kraemer, H., Stover, E., Weinberger, D.R., Zalcman, S., Marder, S.R., 2004. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. Biol. Psychiatry 56 (5), 301–307.

Harrison, I., Joyce, E.M., Mutsatsa, S.H., Hutton, S.B., Huddy, V., Kapasi, M., Barnes, T.R., 2008. Naturalistic follow-up of co-morbid substance use in schizophrenia: the West London first-episode study. Psychol. Med. 38 (1), 79–88.

Harvey, P.D., Bellack, A.S., 2009. Toward a terminology for functional recovery in schizophrenia: is functional remission a viable concept? Schizophr. Bull. 35 (2), 300–306.

Harvey, P.D., Velligan, D.I., Bellack, A.S., 2007. Performance-based measures of functional skills: usefulness in clinical treatment studies. Schizophr. Bull. 33 (5), 1138–1148.

Insel, T.R., 2010. Rethinking schizophrenia. Nature 468 (7321), 187–193.

Iwashiro, N., Suga, M., Takano, Y., Inoue, H., Natsubori, T., Satomura, Y., Koike, S., Yahata, N., Murakami, M., Katsura, M., Gonoi, W., Sasaki, H., Takao, H., Abe, O., Kasai, K., Yamasue, H., 2012. Localized gray matter volume reductions in the pars triangularis of the inferior frontal gyrus in individuals at clinical high-risk for psychosis and first episode for schizophrenia. Schizophr. Res. 137 (1), 124–131.

Javitt, D.C., Steinschneider, M., Schroeder, C.E., Arezzo, J.C., 1996. Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 93 (21), 11962–11967.

Kaneda, Y., Sumiyoshi, T., Keefe, R., Ishimoto, Y., Numata, S., Ohmori, T., 2007. Brief assessment of cognition in schizophrenia: validation of the Japanese version. Psychiatry Clin. Neurosci. 61 (6), 602–609.

Kasai, K., Shenton, M.E., Salisbury, D.F., Hirayasu, Y., Lee, C.U., Ciszewski, A.A., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2003a. Progressive decrease of left superior temporal gyrus gray matter volume in patients with first-episode schizophrenia. Am. J. Psychiatry 160 (1), 156–164.

Kasai, K., Shenton, M.E., Salisbury, D.F., Hirayasu, Y., Onitsuka, T., Spencer, M.H., Yurgelun-Todd, D.A., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2003b. Progressive decrease of left Heschl gyrus and planum temporale gray matter volume in first-episode schizophrenia: a longitudinal magnetic resonance imaging study. Arch. Gen. Psychiatry 60 (8), 766–775.
Kasai, K., Yamasue, H., Gilbertson, M.W., Shenton, M.E., Rauch, S.L., Pitman, R.K., 2008. Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. Biol. Psychiatry 63 (6), 550–556.
Kawakubo, Y., Kasai, K., 2006. Support for an association between mismatch negativity and social functioning in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 30 (7), 1367–1368.
Kawakubo, Y., Kamio, S., Nose, T., Iwanami, A., Nakagome, K., Fukuda, M., Kato, N., Rogers, M.A., Kasai, K., 2007. Phonetic mismatch negativity predicts social skills acquisition in schizophrenia. Psychiatry Res. 152 (2–3), 261–265.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.
Keefe, R.S., Goldberg, T.E., Harvey, P.D., Gold, J.M., Poe, M.P., Coughenour, L., 2004. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr. Res. 68 (2–3), 283–297.
Koike, S., Nishida, A., Yamasaki, S., Ichihashi, K., Maegawa, S., Natsubori, T., Harima, H., Kasai, K., Fujita, I., Harada, M., Okazaki, Y., 2011a. Comprehensive early intervention for patients with first-episode psychosis in Japan (J-CAP): study protocol for a randomised controlled trial. Trials 12, 156.
Koike, S., Takizawa, R., Nishimura, Y., Takano, Y., Takayanagi, Y., Kinou, M., Araki, T., Harima, H., Fukuda, M., Okazaki, Y., Kasai, K., 2011b. Different hemodynamic response patterns in the prefrontal cortical sub-regions according to the clinical stages of psychosis. Schizophr. Res. 132 (1), 54–61.
Koutsouleris, N., Meisenzahl, E.M., Davatzikos, C., Bottlender, R., Frodl, T., Scheuerecker, J., Schmitt, G., Zetzsche, T., Decker, P., Reiser, M., Moller, H.J., Gaser, C., 2009. Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. Arch. Gen. Psychiatry 66 (7), 700–712.
Lee, T., Josephs, O., Dolan, R.J., Critchley, H.D., 2006. Imitating expressions: emotion-specific neural substrates in facial mimicry. Soc. Cogn. Affect. Neurosci. 1 (2), 122–135.
Lencz, T., Smith, C.W., McLaughlin, D., Auther, A., Nakayama, E., Hovey, L., Cornblatt, B.A., 2006. Generalized and specific neurocognitive deficits in prodromal schizophrenia. Biol. Psychiatry 59 (9), 863–871.
Lewis, D.A., Curley, A.A., Glausie, J.R., Volk, D.W., 2012. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci. 35 (1), 57–67.
Lieberman, J.A., Tollefson, G.D., Charles, C., Zipursky, R., Sharma, T., Kahn, R.S., Keefe, R.S., Green, A.I., Gur, R.E., McEvoy, J., Perkins, D., Hamer, R.M., Gu, H., Tohen, M., 2005. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch. Gen. Psychiatry 62 (4), 361–370.
Magno, E., Yeap, S., Thakore, J.H., Garavan, H., De Sanctis, P., Foxe, J.J., 2008. Are auditory-evoked frequency and duration mismatch negativity deficits endophenotypic for schizophrenia? High-density electrical mapping in clinically unaffected first-degree relatives and first-episode and chronic schizophrenia. Biol. Psychiatry 64 (5), 385–391.
Mausbach, B.T., Harvey, P.D., Goldman, S.R., Jeste, D.V., Patterson, T.L., 2007. Development of a brief scale of everyday functioning in persons with serious mental illness. Schizophr. Bull. 33 (6), 1364–1372.
McGorry, P.D., Hickie, I.B., Yung, A.R., Pantelis, C., Jackson, H.J., 2006. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Aust. N. Z. J. Psychiatry 40 (8), 616–622.
Naatanen, R., Kahkonen, S., 2009. Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: a review. Int. J. Neuropsychopharmacol. 12 (1), 125–135.
Olabi, B., Ellison-Wright, I., McIntosh, A.M., Wood, S.J., Bullmore, E., Lawrie, S.M., 2011. Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. Biol. Psychiatry 70 (1), 88–96.
Pantelis, C., Velakoulis, D., McGorry, P.D., Wood, S.J., Suckling, J., Phillips, L.J., Yung, A.R., Bullmore, E.T., Brewer, W., Soulsby, B., Desmond, P., McGuire, P.K., 2003. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet 361 (9354), 281–288.
Patterson, P., 2010. UCSD Performance-based Skills Assessment — Brief (UPSA-B), International Version: Administration and Scoring Manual.
Pinkham, A.E., Penn, D.L., 2006. Neurocognitive and social cognitive predictors of interpersonal skill in schizophrenia. Psychiatry Res. 143 (2–3), 167–178.
Prata, D.P., Mechelli, A., Fu, C.H., Picchioni, M., Kane, F., Kalidindi, S., McDonald, C., Howes, O., Kravariti, E., Demjaha, A., Toulopoulou, T., Diforti, M., Murray, R.M., Collier, D.A., McGuire, P.K., 2009. Opposite effects of catechol-O-methyltransferase Val158Met on cortical function in healthy subjects and patients with schizophrenia. Biol. Psychiatry 65 (6), 473–480.
Radloff, L.S., 1977. The CES-D Scale: a self-report depression scale for research in the general population. Appl. Psychol. Meas. 1 (3), 385–401.
Rogers, M.A., Yamasue, H., Abe, O., Yamada, H., Ohtani, T., Iwanami, A., Aoki, S., Kato, N., Kasai, K., 2009. Smaller amygdala volume and reduced anterior cingulate gray matter density associated with history of post-traumatic stress disorder. Psychiatry Res. 174 (3), 210–216.
Salisbury, D.F., Kuroki, N., Kasai, K., Shenton, M.E., McCarley, R.W., 2007. Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. Arch. Gen. Psychiatry 64 (5), 521–529.
Schimmelmann, B.G., Huber, C.G., Lambert, M., Cotton, S., McGorry, P.D., Conus, P., 2008. Impact of duration of untreated psychosis on pre-treatment, baseline, and outcome characteristics in an epidemiological first-episode psychosis cohort. J. Psychiatr. Res. 42 (12), 982–990.
Seidman, L.J., Giuliano, A.J., Meyer, E.C., Addington, J., Cadenhead, K.S., Cannon, T.D., McGlashan, T.H., Perkins, D.O., Tsuang, M.T., Walker, E.F., Woods, S.W., Bearden, C.E., Christensen, B.K., Hawkins, K., Heaton, R., Keefe, R.S., Heinssen, R., Cornblatt, B.A., 2010. Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis. Arch. Gen. Psychiatry 67 (6), 578–588.
Shaikh, M., Valmaggia, L., Broome, M.R., Dutt, A., Lappin, J., Day, F., Woolley, J., Tabraham, P., Walshe, M., Johns, L., Fusar-Poli, P., Howes, O., Murray, R.M., McGuire, P., Bramon, E., 2012. Reduced mismatch negativity predates the onset of psychosis. Schizophr. Res. 134 (1), 42–48.
Simon, A.E., Velthorst, E., Nieman, D.H., Linszen, D., Umbricht, D., de Haan, L., 2011. Ultra high-risk state for psychosis and non-transition: a systematic review. Schizophr. Res. 132 (1), 8–17.
Spencer, K.M., Salisbury, D.F., Shenton, M.E., McCarley, R.W., 2008. Gamma-band auditory steady-state responses are impaired in first episode psychosis. Biol. Psychiatry 64 (5), 369–375.
Stefansson, H., Rujescu, D., Cichon, S., Pietilainen, O.P., Ingason, A., Steinberg, S., Fossdal, R., Sigurdsson, E., Sigmundsson, T., Buizer-Voskamp, J.E., Hansen, T., Jakobsen, K.D., Muglia, P., Francks, C., Matthews, P.M., Gylfason, A., Halldorsson, B.V., Gudbjartsson, D., Thorgeirsson, T.E., Sigurdsson, A., Jonasdottir, A., Bjornsson, A., Mattiasdottir, S., Blondal, T., Haraldsson, M., Magnusdottir, B.B., Giegling, I., Moller, H.J., Hartmann, A., Shianna, K.V., Ge, D., Need, A.C., Crombie, C., Fraser, G., Walker, N., Lonnqvist, J., Suvisaari, J., Tuulio-Henriksson, A., Paunio, T., Toulopoulou, T., Bramon, E., Di Forti, M., Murray, R., Ruggeri, M., Vassos, E., Tosato, S., Walshe, M., Li, T., Vasilescu, C., Muhleisen, T.W., Wang, A.G., Ullum, H., Djurovic, S., Melle, I., Olesen, J., Kiemeney, L.A., Franke, B., Sabatti, C., Freimer, N.B., Gulcher, J.R., Thorsteinsdottir, U., Kong, A., Andreassen, O.A., Ophoff, R.A., Georgi, A., Rietschel, M., Werge, T., Petursson, H., Goldstein, D.B., Nothen, M.M., Peltonen, L., Collier, D.A., St Clair, D., Stefansson, K., Kahn, R.S., Linszen, D.H., van Os, J., Wiersma, D., Bruggeman, R., Cahn, W., de Haan, L., Krabbendam, L., Myin-Germeys, I., 2008. Large recurrent microdeletions associated with schizophrenia. Nature 455 (7210), 232–236.
Suga, M., Yamasue, H., Abe, O., Yamasaki, S., Yamada, H., Inoue, H., Takei, K., Aoki, S., Kasai, K., 2010. Reduced gray matter volume of Brodmann's area 45 is associated with severe psychotic symptoms in patients with schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 260 (6), 465–473.
Suga, M., Uetsuki, M., Takizawa, R., Araki, T., Kasai, K., 2011. Phonological fluency is uniquely impaired in Japanese-speaking schizophrenia patients: confirmation study. Psychiatry Clin. Neurosci. 65 (7), 672–675.
Sumiyoshi, T., Sumiyoshi, C., Hemmi, C., 2011. UCSD Performance-based Skills Assessment — Brief (UPSA-B) Japanese Version: Administration and Scoring Manual.
Takahashi, T., Wood, S.J., Yung, A.R., Soulsby, B., McGorry, P.D., Suzuki, M., Kawasaki, Y., Phillips, L.J., Velakoulis, D., Pantelis, C., 2009. Progressive gray matter reduction of the superior temporal gyrus during transition to psychosis. Arch. Gen. Psychiatry 66 (4), 366–376.
Takizawa, R., Kasai, K., Kawakubo, Y., Marumo, K., Kawasaki, S., Yamasue, H., Fukuda, M., 2008. Reduced frontopolar activation during verbal fluency task in schizophrenia: a multi-channel near-infrared spectroscopy study. Schizophr. Res. 99 (1–3), 250–262.
Takizawa, R., Tochigi, M., Kawakubo, Y., Marumo, K., Sasaki, T., Fukuda, M., Kasai, K., 2009. Association between catechol-O-methyltransferase Val108/158Met genotype and prefrontal hemodynamic response in schizophrenia. PLoS One 4 (5), e5495.
Tazaki, M., Nakane, Y., 1997. WHOQOL 26 Japanese Version. Kaneko Shobo Press, Tokyo.
The World Health Organization Quality of Life Group (WHOQOL Group), 1998. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol. Med. 28 (3), 551–558.
van Os, J., Kapur, S., 2009. Schizophrenia. Lancet 374 (9690), 635–645.
van Os, J., Kenis, G., Rutten, B.P., 2010. The environment and schizophrenia. Nature 468 (7321), 203–212.
Velakoulis, D., Wood, S.J., Wong, M.T., McGorry, P.D., Yung, A., Phillips, L., Smith, D., Brewer, W., Proffitt, T., Desmond, P., Pantelis, C., 2006. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. Arch. Gen. Psychiatry 63 (2), 139–149.
Vollm, B.A., Richardson, P.C., McKie, S., Deakin, J.F.W., Elliott, R., Anderson, I., 2006. Serotonergic modulation of neuronal responses to behavioural inhibition and reinforcing stimuli: an fMRI study in healthy volunteers. Eur. J. Neurosci. 23, 552–560.
von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gotzsche, P.C., Vandenbroucke, J.P., 2007. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med. 4 (10), e296.
Wölwer, W., Baumann, A., Bechdolf, A., Buchkremer, G., Häfner, H., Janssen, B., Klosterkötter, J., Maier, W., Möller, H., Ruhrmann, S., Gaebel, W., 2006. The German Research Network on Schizophrenia — impact on the management of schizophrenia. Dialogues Clin. Neurosci. 8, 115–121.
Woods, S.W., Addington, J., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., Heinssen, R., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Walker, E.F., McGlashan, T.H., 2009. Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. Schizophr. Bull. 35 (5), 894–908.
Yamasaki, S., Yamasue, H., Abe, O., Suga, M., Yamada, H., Inoue, H., Kuwabara, H., Kawakubo, Y., Yahata, N., Aoki, S., Kano, Y., Kato, N., Kasai, K., 2010. Reduced gray matter volume of pars opercularis is associated with impaired social communication in high-functioning autism spectrum disorders. Biol. Psychiatry 68 (12), 1141–1147.
Yamasue, H., Kasai, K., Iwanami, A., Ohtani, T., Yamada, H., Abe, O., Kuroki, N., Fukuda, R., Tochigi, M., Furukawa, S., Sadamatsu, M., Sasaki, T., Aoki, S., Ohtomo, K., Asukai, N., Kato, N., 2003. Voxel-based analysis of MRI reveals anterior cingulate gray-matter

volume reduction in posttraumatic stress disorder due to terrorism. Proc. Natl. Acad. Sci. U. S. A. 100 (15), 9039–9043.
Yoshida, T., Suga, M., Arima, K., Muranaka, Y., Tanaka, T., Eguchi, S., Lin, C., Yoshida, S., Ishikawa, M., Higuchi, Y., Seo, T., Ueoka, Y., Tomotake, M., Kaneda, Y., Darby, D., Maruff, P., Iyo, M., Kasai, K., Higuchi, T., Sumiyoshi, T., Ohmori, T., Takahashi, K., Hashimoto, K., 2011. Criterion and construct validity of the CogState Schizophrenia Battery in Japanese patients with schizophrenia. PLoS One 6 (5), e20469.
Yung, A.R., Stanford, C., Cosgrave, E., Killackey, E., Phillips, L., Nelson, B., McGorry, P.D., 2006. Testing the Ultra High Risk (prodromal) criteria for the prediction of psychosis in a clinical sample of young people. Schizophr. Res. 84 (1), 57–66.

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Clinically-oriented monitoring of acute effects of methylphenidate on cerebral hemodynamics in ADHD children using fNIRS

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HIGHLIGHTS

- We explored the feasibility of using functional near-infrared spectroscopy (fNIRS) to search for a clinically implementable biological marker for the acute effect of methylphenidate (MPH) on children with attention deficit hyperactivity disorder (ADHD).
- The improved cognitive performance for a go/no-go task was associated with activation in the right lateral prefrontal cortex, which could serve as a biological marker to monitor the effect of MPH in ADHD children.
- MPH-effect assessment in ADHD children using fNIRS can be performed within a 3 h stay at a hospital during a single visit, and thus may be integrated into clinical practice.

ABSTRACT

Objective: Attention Deficit Hyperactivity Disorder (ADHD), a common developmental syndrome with inattention, hyperactivity, and impulsivity, is typically treated with the psychostimulant drug, methylphenidate (MPH). We explored the feasibility of using functional near-infrared spectroscopy (fNIRS) to search for a clinically implementable biological marker for the acute MPH effect on ADHD children.
Methods: Following an MPH washout period, twelve ADHD children performed a go/no-go task before and 1.5 h after MPH intake. fNIRS was used to monitor the lateral prefrontal cortical hemodynamics of ADHD children performing a go/no-go task.
Results: There was no significant activation in the lateral prefrontal cortices examined before MPH intake. However, after MPH intake, significant MPH-elicited activation (oxygenated hemoglobin signal increase) was detected in the right lateral prefrontal cortex (LPFC) implicated with response inhibition functions. There was a large significant correlation between increases in task performance and activation in the right LPFC.
Conclusions: The improved cognitive performance was associated with activation in the right LPFC, which might serve as a biological marker to monitor the effect of MPH in ADHD children.
Significance: MPH-effect assessment in ADHD children using fNIRS can be performed within a 3 h stay at a hospital during a single visit, and thus may be integrated into clinical practice.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a common developmental syndrome, characterized by inattention, hyperactivity and impulsivity, affecting 3–7% of school-aged children (reviewed in Wehmeier et al., 2009). The disorder often persists into adolescence and adulthood, leading to impairment in educational and vocational performance and posing an increased risk of antisocial disorders that are not directly related to ADHD (Mannuzza et al., 1997).

To confer long-term positive effects, early identification of ADHD and appropriate treatment is important. The most common treatment

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for ADHD in children is the administration of methylphenidate (MPH), a psychostimulant drug that has been shown to be effective in improving attention and behavior as well as cognition and social function (Reviewed in Spencer, 2004). The behavioral and cognitive characteristics of ADHD are considered to be partly due to a dopamine dysfunction (Wilens, 2008). MPH is believed to inhibit the reuptake of catecholamines, including dopamine, by blocking their transporters, and it acts as a dopamine agonist in the basal ganglia and cerebral cortices (Arnsten, 2006). MPH is expected to produce symptomatic improvement in 70% of ADHD children (Arnsten, 2006; Wilens, 2008). However, there are patients who do not respond to MPH (Elia et al., 1991; Spencer, 2004), and while MPH treatment confer no symptomatic benefit to such patients, side effects remain present (Rapport et al., 1994). Even to patients who do respond, the MPH dose must be appropriately controlled to prevent possible side effects including appetite loss, insomnia, headaches, and stomachaches. A small fraction of medicated children may suffer irritability, nervous mannerisms, tics, and significant weight loss (Barkley, 2003; Loeber et al., 1992; Milich et al., 2001; Murphy et al., 2001; Nigg, 1999, 2000).

Thus, the efficacy of MPH treatment in children diagnosed with ADHD should be monitored both prior to the prescription and throughout treatment. One promising approach would be an introduction of a distinct biological marker and its monitoring with a noninvasive neuroimaging instrument. A growing body of neuroimaging research has started to explore the neural basis for the clinical effectiveness of MPH in ADHD children. Functional MRI studies on ADHD children with an MPH history reported that MPH increased the activation of the frontal cortices and striatum in go/no-go tasks (Vaidya et al., 1998) and of the striatum in a divided attention task (Shafritz et al., 2004; Vaidya et al., 1998). A recent fMRI study using a rewarded continuous performance task revealed that MPH upregulated the dysfunctional networks among the frontal cortices, striatum, and cerebellum (Rubia et al., 2009).

For the clinical practice of diagnosing ADHD, fMRI poses a technical limitation: it is susceptible to body motion inherent in ADHD children. Small head motions may lead to artifacts in cortical activation patterns or reduced signal to noise ratios, complicating the detection of accurate activation (Epstein et al., 2007). Indeed, severely hyperactive children are often excluded from fMRI studies because of motion artifacts (Vaidya et al., 1998). In addition, an fMRI scan and the ensuing off-line analyses take substantial time and effort.

On the other hand, functional near-infrared spectroscopy (fNIRS) is comparatively immune to these problems. It allows for relatively more body motion and has been successfully implemented in tasks involving body movement (Herrmann et al., 2004, 2005; Hock et al., 1997; Matsuo et al., 2000, 2003; Shinba et al., 2004; Suto et al., 2004). Moreover, fNIRS entails other advantages including compact size (useful in confined experimental settings), affordable price, unrestrictiveness, and accessibility, making it a suitable choice for clinically assessing ADHD children. Indeed, a growing body of fNIRS studies has started to investigate the cortical hemodynamics of ADHD patients. Weber et al. (2005) first demonstrated differences in hemodynamic changes between normal and ADHD children using a trail-making task. There was an increase in the oxygenated hemoglobin (oxy-Hb) signal in the bilateral ventrolateral prefrontal cortex (VLPFC) of ADHD adults compared to normal controls during a working memory task (Ehlis et al., 2008) and during a verbal fluency task (Schecklmann et al., 2008b). Studies of children have also reported diminished oxy-Hb increase in the bilateral PFC of ADHD children compared to normal controls during object and spatial working memory tasks (Schecklmann et al., 2010) and the color-word Stroop task (Negoro et al., 2010). More specifically, a recent study focusing on Stroop interference revealed that the right PFC oxy-Hb increase due to Stroop interference was reduced in the right PFC of ADHD children, suggesting a dysfunction of the area (Jourdan Moser et al., 2009). Moreover, Weber et al. (2007) performed a preliminary fNIRS examination of the effect of MPH on ADHD children. They observed a tendency for a lower increase of deoxygenated and total hemoglobin signals during a trail-making task in an MPH-medicated condition than in the MPH-free condition in the right prefrontal region. However, activation in the left dorsolateral prefrontal cortex expected for the trail-making task (Moll et al., 2002; Moser et al., 2002; Segalowitz et al., 1992; Zakzanis et al., 2005) was not observed, probably due to the limited number of channels. In addition, the trail-making task, reflecting a relatively wide range of executive functions, may not be an optimal task for diagnosing ADHD children (Willcutt et al., 2005).

These studies demonstrate the potential of fNIRS neuroimaging in the clinical diagnosis of ADHD children especially in the assessment of MPH effect. Hence, as a clinically oriented extension of these studies, here we aim to explore the feasibility of using fNIRS for monitoring the effect of MPH on ADHD children with a sufficient number of channels and an appropriate neuropsychological task to detect specific activation foci reflecting MPH effect on ADHD children.

To elucidate the neural basis of MPH effects on ADHD children, experimental designs should be optimized in a neuropharmacological context. For instance, medication-naïve ADHD children undergo two scans with either an acute clinical dose of MPH or a placebo in a randomized, double-blind design with comparison to healthy control subjects (Rubia et al., 2009; Shafritz et al., 2004). An on- and off-drug design with or without an acute clinical dose of MPH after a certain washout period would be a suboptimal alternative (Vaidya et al., 1998).

On the other hand, these designs are not necessarily optimized for clinical practice where time and ease of practice are of essential importance: it would be preferable if the effect of MPH on an ADHD child could be examined within a single visit with minimum preparation. In this respect, noninvasive neuroimaging investigation may also be oriented toward clinical practice. Unlike authentic neuropharmacological studies, we designed an experiment that can be performed in a minimum amount of time with the least demand on child patients. Specifically, we selected to compare the effect of MPH before and after the medication. This experimental design would be best implemented with a double-blind placebo control. However, this may not be a practical clinical choice, first because assessment cannot be completed in a single-day hospital visit, and second because administering a placebo to an ADHD patient under MPH treatment has an additional ethical consideration. Since it has already been reported that MPH effect is attributed to MPH itself and not to a placebo, and that there is no placebo effect (Rubia et al., 2009), we chose a single-day examination omitting a placebo control. The washout period before the experiment was kept minimum (i.e., 24 h) so that deprivation of MPH would not negatively affect subjects' schoolwork. The waiting period to achieve an acute effect of MPH was determined based on previous physiological and behavioral findings that MPH (OROS-methylphenidate or Concerta) proved to have a predictable rapid onset (1–2 h) and a long duration of efficacy (10–12 h) after a single administration (Swanson et al., 2002). The necessary waiting period of 1 h has been adopted in former neuroimaging examinations on acute MPH effect (Weber et al., 2007; Rubia et al., 2009). On the other hand, a sufficient waiting period of 2 h is technically desirable, but its clinical implementation is often difficult. To balance these factors, we set the waiting period to be 1.5 h. Eventually, these efforts enabled the assessment of MPH effects on ADHD children within a 3 h stay at a hospital and in a single visit.

Regarding the experimental task, we selected a go/no-go task for the following reasons. First, impairment of response inhibition is among the most characteristic symptoms of ADHD: former fMRI

studies successfully elucidated neural substrates for ADHD using motor response inhibition tasks including go/no-go, stop signal, and Stroop tasks (Bush et al., 1999; Dillo et al., 2010; Durston et al., 2003; Rubia et al., 1999; Vaidya et al., 1998). Second, among these tasks, Stroop task performance matures latest at around 17–19 years of age (Comalli et al., 1962), followed by stop signal tasks at 13–17 years (Williams et al., 1999), and go/no-go tasks at approximately 12 years (Levin et al., 1991). Therefore, a go/no-go task is the primary choice for a study of school-aged children. Third, fMRI studies have elucidated neural substrate for go/no-go tasks including the bilateral dorsolateral prefrontal cortex (DLPFC), VLPFC, premotor cortex, inferior parietal lobe, lingual gyrus, caudate, and right anterior cingulate (Menon et al., 2001). Among these, the right VLPFC was found most responsible for response inhibition (Rubia et al., 2003), while another similar response inhibition task recruited the right DLPFC (Garavan et al., 1999). Fourth, VLPFC activation during a go/no-go task was replicated in an fNIRS study (Herrmann et al., 2005).

Another issue that needs to be determined for use of fNIRS is the region of interest (ROI). Unlike fMRI, which enables the examination of a whole brain, fNIRS measurement is limited to the lateral cortical surface. The limited size of probe holders necessitates further spatial confinement of the ROI. In the current study, we set the ROI so that it encompassed the VLPFC and DLPFC based on their integral roles in response inhibition (Garavan et al., 1999; Herrmann et al., 2004, 2005; Rubia et al., 2003).

Taken together, the aim of the current study is to confirm the clinical effectiveness of MPH in ADHD children, while introducing an experimental design oriented for clinical practice. Using fNIRS, we compare hemodynamic responses in the bilateral prefrontal cortices during a go/no-go task between pre- and post-MPH administration within a single-day hospital visit.

2. Methods

2.1. Subjects

Twelve clinically referred, right-handed Japanese children with a mean age of 9.7 (SD 2.4, range 7–14 years) who met the Diagnosis and Statistical Manuals of Mental Disorders-IV (American Psychiatric Association) criteria for ADHD participated in the study. All subjects had been taking MPH (18–45 mg/day) for between 1 week and 3.6 years. The starting dosage of MPH was 18 mg once daily for MPH-naïve patients. Dosage was increased by 9 or 18 mg/day at weekly intervals until ADHD symptoms clearly improved, with a maximum dose of 54 mg/day. MPH was administered once a day in the morning. All subjects refrained from taking MPH one day before and on the day of the experiment, and this allowed washout periods of at least 24 h. The Wechsler Intelligence Scale of Children-Third Edition (WISC-III) full IQ scores of subjects were all over 70 (mean 91.7, SD 8.1, range 77–110). Demographic and clinical characteristics of the patients are described in Table 1. Written consent was obtained from the parents of all subjects, and the study was approved by the Ethics Committee of Jichi Medical University Hospital.

2.2. Experimental design

Experimental procedure is summarized in Fig. 1. Subjects underwent two sessions, one before MPH administration, and the other at 1.5 h after MPH administration. Each session consisted of eight alternating 27 s blocks of go and go/no-go conditions. During the session, subjects viewed a series of pictures (lion, giraffe, tiger, and elephant) once every second and responded with a key press to every picture except the giraffe, to which they were instructed to withhold response. In the go (control) condition, subjects were presented a random sequence of two pictures (tiger and elephant). Subjects were to press a button for both pictures. In the go/no-go (experimental) condition, subjects were presented with the picture of a giraffe 50% of the time, thus being required to respond to half the trials (go trials, with a lion picture) and inhibit their response to the other half (no-go trials with a giraffe picture). A go/no-go ratio of 50% was selected as it has been most often used in former neuroimaging studies (Dillo et al., 2010; Herrmann et al., 2005; Liddle et al., 2001; Menon et al., 2001; Vaidya et al., 1998). In addition, it has been indicated that a high go/no-go ratio may lead to activation during no-go blocks and associated with selective attention rather than response inhibition (Dillo et al., 2010; Tamm et al., 2004). At the beginning of each block, a 3 s instruction ("press for tiger or elephant" for go conditions and "do not press for giraffe" for go/no-go conditions) appeared to inform the subject about the new task condition. Each subject performed a practice blocks to ensure their understanding of the instructions.

Stimuli were generated, and responses were collected by E-Prime 2.0 (Psychology Software Tools). They were presented to the subject on a 17" desktop computer screen. The distance between the subject's eyes and the screen was approximately 50 cm.

Table 1
Demographic, clinical, and functional profiles for patients.

Patient	Age (years)	Sex	ADHD subtype	Complication	WISC-III	MPH dose (mg)	Other medications	Increase of oxy-Hb (inter-condition contrast) (mM·mm)		Accuracy increase in no-go trials (%)
					Full IQ			Right CH10	Right CH14	
1	12	M	Combined-type	Conduct disorder	83	45	Atypical antipsychotic (Risperidone)	0.044	−0.016	3
2	11	M	Hyperactive /impulsive	None	96	27	None	0.112	0.018	1
3	8	M	Combined-type	None	97	27	None	0.092	0.041	9
4	10	M	Combined-type	Asperger s.	91	27	None	−0.062	0.034	0
5	14	M	Inattentive	Asperger s.	91	27	Atomoxetine	−0.002	−0.043	−4
6	13	M	Inattentive	Epilepsy	91	27	Carbamazepine	0.154	−0.004	3
7	8	M	Inattentive	None	90	18	None	0.041	0.034	−1
8	8	M	Combined-type	None	95	27	None	0.288	0.167	3
9	8	F	Inattentive	None	77	18	None	0.126	0.109	5
10	10	M	Inattentive	None	93	36	None	0.131	0.049	3
11	7	M	Inattentive	None	86	18	None	0.034	0.107	2
12	7	M	Inattentive	None	110	18	None	0.008	0.044	1
Mean	9.7				91.7			0.081	0.045	2.1
SD	24				81			0.091	0.058	0.032

Abbreviations: Asperger s., Asperger syndrome; SD, standard deviation.

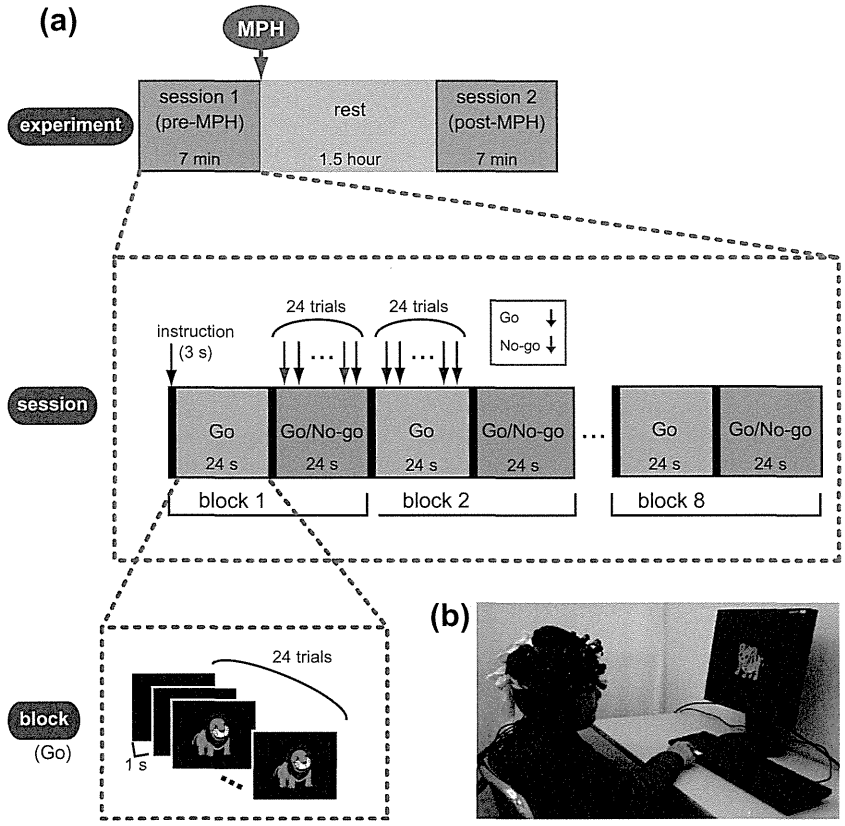

Fig. 1. Experimental design. (a) A schematic showing the flow of pre- and post-MPH sessions. (b) fNIRS measurements. Brain activity was measured while ADHD children performed the go/no-go task.

2.3. MPH treatment

After subjects performed the first session, they were administered MPH (OROS-methylphenidate or Concerta) orally. Specific acute doses were the same as the subject's daily dose as described in Table 1. Subjects underwent the second session 1.5 h after MPH intake.

2.4. Behavioral data analyses

The reaction time (RT) and number of correct responses were computed for the go/no-go condition. To examine performance difference among blocks, we performed two-way repeated-measures ANOVA with blocks and pre- or post-MPH treatment being factors for RTs and percent correct responses (accuracy). Subsequently, percent correct responses and RTs averaged across blocks for the first (pre-MPH) and second (post-MPH) sessions were compared using a Students' *t*-test. A statistical threshold of $p < 0.05$ was adopted for both analyses.

2.5. fNIRS neuroimaging instruments

We used the multichannel fNIRS optical topography system ETG-4000 (Hitachi Medical Corporation, Kashiwa, Japan), using two wavelengths of near-infrared light (695 and 830 nm) (Fig. 1b). We analyzed the optical data based on the modified Beer–Lambert Law (Cope et al., 1988) as previously described (Maki et al., 1995). This method allowed us to calculate signals reflecting the oxygenated hemoglobin (oxy-Hb), deoxygenated hemoglobin (deoxy-Hb), and total hemoglobin (total-Hb) concentration changes, calculated in units of millimolar·millimeter (mM·mm) (Maki et al., 1995; Meltzer et al., 2009). The sampling rate was set at 100 ms.

2.6. fNIRS probe placement

We set the fNIRS probes to cover the DLPFC and VLPFC in reference to previous studies (Garavan et al., 1999; Herrmann et al., 2004; Herrmann et al., 2005; Liddle et al., 2001; Rubia et al., 2003). Specifically, we used two sets of 3×5 multichannel probe holders, consisting of eight illuminating and seven detecting probes arranged alternately at an inter-probe distance of 3 cm, resulting in 22 channels (CH) per set (Fig. 2). The midpoint of a pair of illuminating and detecting probes was defined as a channel location. As shown in Fig. 2a, the bilateral probe holders were attached in the following manner: (1) their upper anterior corners, where the left and right probe holders were connected by a belt, were symmetrically placed across the sagittal midline; (2) the lower anterior corners of the probe holder were placed over the supraorbital prominence; (3) the lower edges of the probe holders were attached the upper part of the auricles.

2.7. Probabilistic registration of fNIRS channels to MNI space

For spatial profiling of fNIRS data, we employed virtual registration (Tsuzuki et al., 2007) to register fNIRS data to MNI standard brain space (Brett et al., 2002). Briefly, this method allows us to place a virtual probe holder on the scalp by simulating the holder's deformation and by registering probes and channels onto reference brains in our MRI database (Okamoto et al., 2004; Okamoto and Dan, 2005). We performed a statistical analysis of the MNI coordinate values for the fNIRS channels to obtain the most likely estimate of the location of given channels for the group of subjects,

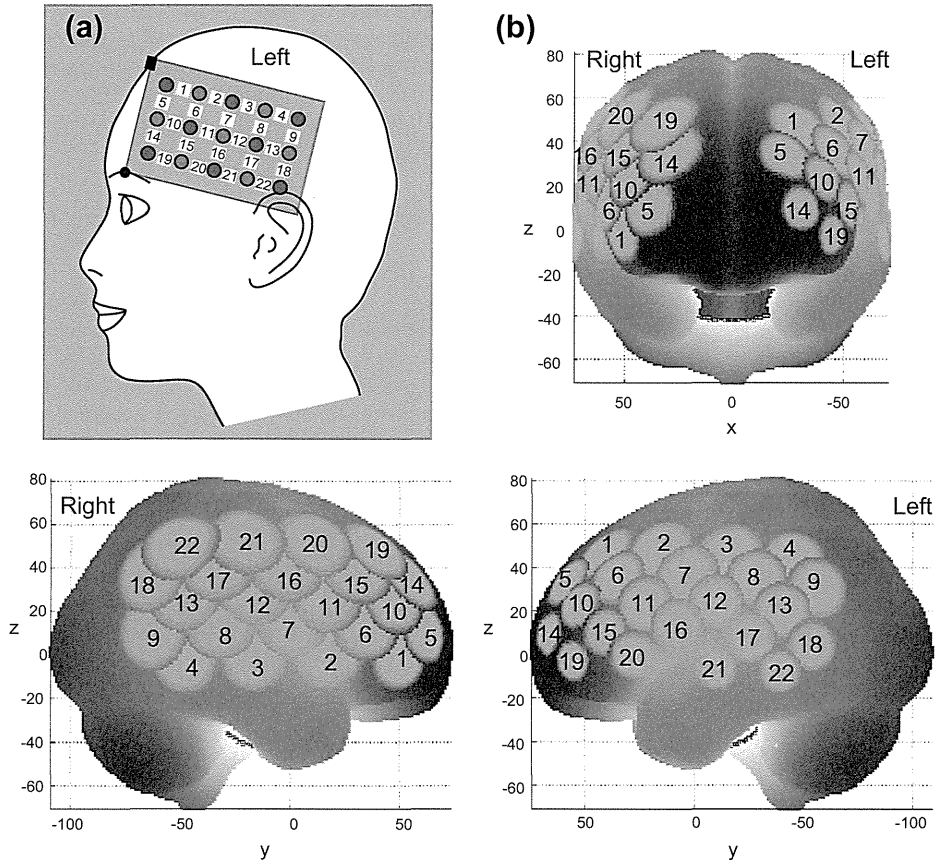

Fig. 2. Spatial profiles of fNIRS channels. (a) Left side view of the probe arrangements. fNIRS channel orientation is also illustrated. Detectors are shown as blue circles, illuminators as red circles, and channels as white squares. Corresponding channel numbers are indicated in black. (b) Channel locations on the brain. Front, right-side, and left-side views are illustrated. Statistically estimated fNIRS channel locations (centers of blue circles) for the group of subjects, and their spatial variability (SDs, radii of the blue circles) associated with the estimation are exhibited in MNI space.

and the spatial variability associated with the estimation (Fig. 2b) (Singh and Dan, 2006). Finally, we anatomically labeled the estimated locations using a Matlab function that reads anatomical labeling information coded in a macroanatomical brain atlas (LBPA40 (Shattuck et al., 2008) and Brodmann (Rorden and Brett, 2000); Table 2).

2.8. Analysis of NIRS data

When selecting which Hb signal to analyze, it is still a controversial issue whether oxy- or deoxy-Hb is more reliably related to brain activation (Schroeter et al., 2004). The fNIRS apparatus (Hitachi Medical Co., ETG-4000) used in the current study utilized two wavelengths, 695 and 830 nm, which is a configuration suitable for detecting both oxy-Hb and deoxy-Hb signals.

Individual timeline data for the oxy-Hb and deoxy-Hb signals of each channel were preprocessed with a first-degree polynominal fitting and high-pass filter using cut-off frequencies of 0.01 Hz to remove baseline drift, and a 0.8 Hz low-pass filter to remove heartbeat pulsations. From the preprocessed time series data, we obtained channel-wise and subject-wise contrasts by calculating the inter-trial mean of differences between the peak Hb signals

Table 2
Spatial profiles of the channels screened for involvement with go/no-go task.

	MNI coordinates x, y, z (SD)	Macroanatomy	Probability	Brodmann area	Probability
CH10	47, 48, 26 (17)	Middle frontal gyrus	67%	45 – Pars triangularis, part of Broca's area	56%
		Inferior frontal gyrus	33%	46 – Dorsolateral prefrontal cortex	44%
CH14	29, 55, 34 (17)	Middle frontal gyrus	100%	46 – Dorsolateral prefrontal cortex	57%
				9 – Dorsolateral prefrontal cortex	39%
				10 – Frontopolar area	4%
CH15	50, 31, 39 (18)	Middle frontal gyrus	98%	45 – Pars triangularis, part of Broca's area	37%
		Inferior frontal gyrus	2%	44 – Pars opercularis, part of Broca's area	35%
				9 – Dorsolateral prefrontal cortex	19%
				46 – Dorsolateral prefrontal cortex	8%
CH22	58, -50, 52 (19)	Angular gyrus	91%	40 – Supramarginal gyrus, part of Wernicke's area	95%
		Supramarginal gyrus	9%	39 – Angular gyrus, part of Wernicke's area	5%

All data are for the right hemisphere. For MNI coordinates, the most likely values are presented with standard deviation (SD) in units of mm. This is interpreted as 61% of the estimated channel location (midpoint of a given probe pair) among multiple subjects falling within a sphere defined by the most likely MNI coordinates as a center and SD as a radius. Macroanatomical estimation is based on LBPA40 (Shattuck et al., 2008). Brodmann area estimations are based on MRIcro (Rorden and Brett, 2000).

(4–24 s after trial onset) and baseline (0–10 s before trial onset) periods. The contrasts obtained were subjected to second level, random effects group analysis.

2.9. Statistical analyses

Hb signals analyzed in the current study do not directly represent cortical Hb concentration changes, but contain an unknown optical path length that cannot be measured. Since optical path length is known to vary among cortical regions (Katagiri et al., 2010) direct comparison of Hb signals among different channels and regions should be avoided. Therefore, we performed statistical analyses in a channel-wise manner. Specifically, the following contrasts were generated: (1) pre-MPH contrast (peak-baseline contrast for the pre-MPH condition); (2) post-MPH contrast (peak-baseline contrast for post-MPH); and (3) inter-condition contrast (post-MPH minus pre-MPH). To screen the channels involved in go/no-go tasks before and after MPH administration, pre-MPH and post-MPH contrasts were subjected to one-sample *t*-tests against zero (two-tails). For screening purposes, an uncorrected statistical threshold of $p < 0.05$ was adopted. All activated channels (channels-of-interest) were subjected to inter-condition comparison, in which inter-condition contrasts were tested by one-sample *t*-tests against zero (two-tails). The Holm method was used for family-wise error correction. The channels with significant effect of MPH were subjected to correlation analyses using the non-parametric Spearman's method. All statistical analyses were performed with PASW statistics (version 18 for Windows) (SPSS Inc., Chicago, USA) software.

3. Results

3.1. Behavioral performance

Possible differences in performance among blocks were first examined. A two-way repeated-measures ANOVA with blocks and pre- or post-MPH treatment being factors did not reveal any significant results for RTs and accuracy. Thus, they were averages to represent behavioral performance data for each subject. The average accuracy for no-go trials in the go/no-go condition was 89.33% (SD 5.57%) in the first session (pre-MPH) and 91.42% (SD 9.68%) in the second session (post-MPH). Performance was significantly improved in the post-MPH session ($t(11) = 2.253$, $p = 0.046$, Cohen's $d = -0.650$). RT for the correct go trials in the go/no-go condition was 411 ms (SD 41 ms) for the pre-MPH and 424 ms (SD 35 ms) for the post-MPH conditions. RTs of pre- and

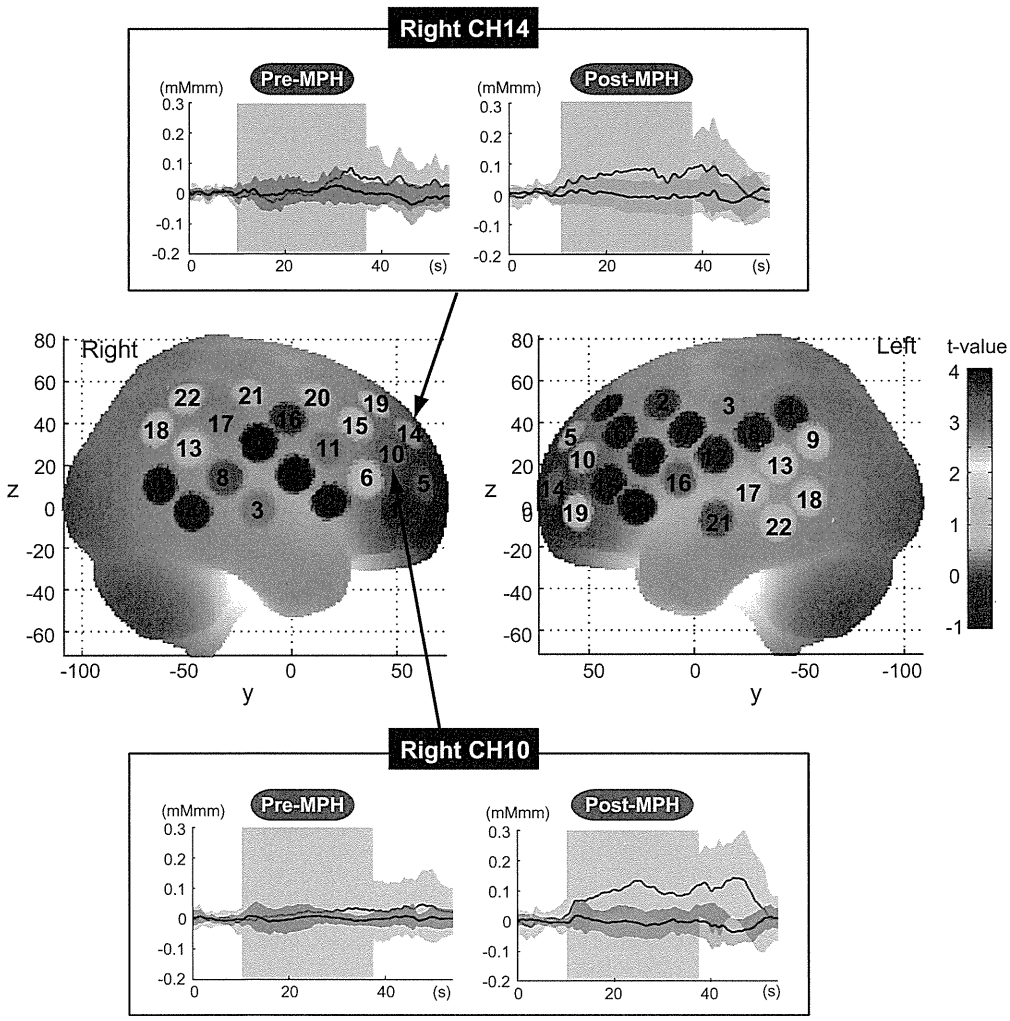

Fig. 3. Results of functional analysis. In the middle row, the differences in cortical activation patterns between pre- and post-MPH sessions (inter-condition contrast) are shown as *t*-maps of oxy-Hb signal, with *t*-values being shown according to the color bar. The graphs on the top and bottom rows show the grand average waveforms of oxy-Hb (red line) and deoxy-Hb (blue line) signals for the inter-condition contrast of CH14 and CH10 in the right hemisphere. Standard deviations among 12 subjects are exhibited as pale red (oxy-Hb) and blue (deoxy-Hb) areas. Each time line is adjusted to the average value of the baseline period. Oxy-Hb and deoxy-Hb signals are shown in units of mM·mm.

post-MPH conditions did not differ significantly ($t(11) = 0.994$, $p = 0.341$, Cohen's $d = 0.287$).

3.2. fNIRS results

Fig. 3 illustrates patterns of cortical activation in the pre-MPH and post-MPH conditions (pre-MPH and post-MPH contrasts) for the oxy-Hb signal. Examples of one-channel timeline data for oxy-Hb and deoxy-Hb signals are also exhibited. We observed more stable task-related oxy-Hb signals than deoxy-Hb signals. Thus, oxy-Hb signals are considered more appropriate for our experimental conditions.

First, we screened for any channels involved in the go/no-go task before and after MPH treatment. Analysis of pre-MPH contrasts revealed that no significant oxy-Hb increase (i.e., peak period > baseline period) was found for the pre-MPH condition. Regarding post-MPH contrasts, significant oxy-Hb increase was found in four channels on the right hemisphere (CHs 10, 14, 15, and 22, one-sample t-test, $p < 0.05$, uncorrected) in the post-MPH condition (Table 3). The activated channels were located over the right inferior frontal gyrus, the middle frontal gyrus, and the angular gyrus (Table 2). These observations led us to define CHs 10, 14, 15, and 22 as channels of interest.

We tested whether the oxy-Hb increases in post-MPH treatment in the four channels was induced by the MPH treatment. The inter-condition contrast representing oxy-Hb differences between post-MPH and pre-MPH was statistically tested. Significant MPH-effect on oxy-Hb increase (i.e., post-MPH > pre-MPH) was found in two channels (CHs 10 and 14, one-sample t-test, $p < 0.05$, Holm-corrected; see Table 3 and Fig. 3). The channels with MPH-elicited activation were located over the right middle and inferior frontal gyri (Table 2). Effect sizes of the inter-condition contrasts of the two channels were large (Cohen's $d = 0.883$) for CH10, and medium (Cohen's $d = 0.772$) for CH14. They were markedly higher than those of other channels (Supplementary Table S1), indicating that robust and focused activation were observed.

3.3. Association between performance and fNIRS results

We examined the correlation between accuracy for no-go trials in the go/no-go condition and right PFC activation induced by MPH. Increases in accuracy for no-go trials in the go/no-go condition and right PFC activation induced by MPH (inter-condition contrast) were subjected to the Spearman non-parametric test for correlation. The correlation coefficients were 0.654 (right CH10, $p = 0.021$) and 0.443 (right CH14, $p = 0.149$). There was significant correlation between increases in accuracy and oxy-Hb signals in the right CH10. This was considered a large correlation according the criteria by Cohen (1992) (Fig. 4). Thus, we concluded that the MPH-elicited right LPFC activation in CH10 during the go/no-go task was the neural correlate for the improved response inhibition function after MPH administration.

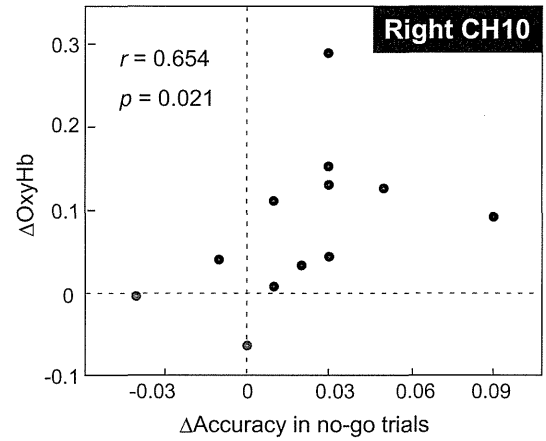

Fig. 4. Correlation between go/no-go task performance and oxy-Hb signals in right CH10. Increases in accuracy for no-go trials in the go/no-go condition and the right PFC activation induced by MPH (inter-condition contrast) were subjected to the Spearman non-parametric test for correlation. Each circle represents a subject; red circles denote the two patients who had Asperger syndrome as a complication. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.4. Notes on patient-level observations

Patient characteristics, changes in go/no-go task performance, and oxy-Hb signal change due to MPH (inter-condition contrast) in the right CHs10 and 14 are presented in Table 1. Increases in oxy-Hb between two sessions were observed for 10 of 12 patients. Neither oxy-Hb nor no-go task performance increased in the two patients who had comorbid Asperger syndrome (Fig. 4).

4. Discussion

4.1. Summary of obtained results

The key tenet of the current study was to explore the feasibility of examining the effectiveness of MPH in ADHD children in a clinically implementable manner. fNIRS monitoring of cortical hemodynamics in ADHD children performing go/no-go tasks revealed significant oxy-Hb increases in the right LPFC channel elicited by MPH intake. The right LPFC activation after intake of MPH was associated with a significantly large correlation with response inhibitory task performance.

Table 3
Functional data summary for the channels screened for involvement with go/no-go task.

	Pre-MPH						Post-MPH						Inter-condition					
	Mean	SD	t	P	Sig	ES	Mean	SD	t	P	Sig	ES	Mean	SD	t	P	Sig	ES
CH10	.024	.090	0.931	.372	ns	.269	.105	.074	4.886	.000	[3]	1.410	.081	.091	3.058	.011	*	.883
CH14	.020	.063	1.105	.293	ns	.319	.065	.059	3.839	.003	[2]	1.108	.045	.058	2.676	.022	*	.772
CH15	.015	.084	0.629	.542	ns	.181	.044	.056	2.714	.020	[1]	0.783	.028	.093	1.057	.313	ns	.305
CH22	.034	.075	1.754	.107	ns	.506	.085	.122	2.409	.035	[1]	0.695	.051	.150	1.180	.263	ns	.341

All data are for the right hemisphere. Oxy-Hb values are presented in units of mM·mm. P-values are presented as uncorrected values. Statistical significance are presented as follows: ns, not significant. Abbreviations are as follows: SD, standard deviation; t, t-value; P, p-value; Sig, statistical significance; ES, effect size (Cohen's d).

[1] $P < 0.05$ (uncorrected).
[2] $P < 0.01$ (uncorrected).
[3] $P < 0.001$ (uncorrected).
* $P < 0.05$ (Holm-corrected).

4.2. Right LPFC activation as a possible biological marker

As demonstrated in the current study, the effect of MPH in ADHD children can be made manifest using fNIRS. Before MPH administration, there was no significant cortical activation during go/no-go tasks as compared to go tasks. On the other hand, after MPH intake, the right LPFC channels were activated. Comparison between before and after MPH administration further emphasized the involvement of the two right LPFC channels (CHs 10 and 14). Among them, CH10, located at the border between the middle and inferior frontal gyri, exhibited the most significant activation as reflected in oxy-Hb signal increase.

These right lateral prefrontal regions have often been implicated with response inhibition functions most widely investigated using go/no-go tasks. Accumulating fMRI studies have reported the involvement of either or both of the middle and inferior prefrontal gyri in the right hemisphere (Garavan et al., 1999; Rubia et al., 1999, 2003). An fNIRS study also added further evidence to the involvement of the right LPFC (more exactly, F4) during go/no-go tasks (Boecker et al., 2007). The impaired right LPFC activation in ADHD children during our go/no-go task before MPH administration is in line with those former findings.

Moreover, recent fMRI studies on MPH-medicated children have provided more direct evidence for cortical activation and MPH treatment. Using a continuous performance task, Rubia et al. found that MPH treatment improved under-activation in ADHD children compared to normal children by adding activation in the right inferior frontal and middle frontal gyri along with several other regions (Rubia et al., 2009). Go/no-go and continuous performance tasks are not the same, but they are related and they are both used to measure response inhibition function. In this sense, the right LPFC activation in ADHD children during a go/no-go task after MPH administration can be considered mostly compatible with their findings.

Behavioral measurement has been known to provide an indicator for the efficacy of MPH in improving impaired response inhibition in ADHD children. A recent extensive survey on the chronic neuropsychological effects of MPH on drug-naïve ADHD boys reported a reduced error rate and shortened reaction time for a go/no-go task in an MPH-administered group compared with a placebo-treated group (Coghill et al., 2007). In the current study, MPH administration significantly reduced the error rate for go/no-go task performance and slightly, non-significantly, elongated reaction time. While error rate provided a stable measure, reaction time did not, so RT may not be useful for assessing go/no-go task performance in ADHD patients. For example, an adult ADHD study on MPH in a crossover design reported a non-significant tendency of elongated reaction time (Ohlmeier et al., 2007). A plausible reason for such apparent contradiction could be that MPH leads to enhanced cognitive performance and/or careful judgment. The latter could be expected to elongate reaction time.

Interestingly, the current study demonstrates that the increase of oxy-Hb signal between pre- and post-MPH intake was significantly and largely correlated with the decrease of error rate for the go/no-go task block in the right LPFC (CH10). Although the sample size of the current study may be regarded as small for correlation analyses, the effect size of the correlation was large according to Cohen's criteria (Cohen, 1992), suggesting that the correlation is robust. Given the functional importance of the right LPFC in response inhibition, this correlation between behavioral and neuroimaging results provides reasonable experimental evidence that the right LPFC is a neural substrate for MPH-elicited behavioral improvement in ADHD children. In addition, this behavior-neuroimaging correlation demonstrates that conventional behavioral measurement could be supplemented by fNIRS neuroimaging.

4.3. Go/no-go paradigm for fNIRS neuroimaging

The current study utilized a go/no-go paradigm, a selective attention task with a moderate load on response inhibition. Specifically, in reference to former studies, we selected a block design in which a go/no-go task requiring response inhibition was contrasted against a control go task requiring no inhibition (i.e., pre- and post-MPH contrasts) (de Zubicaray et al., 2000; Menon et al., 2001; Rubia et al., 2001). This contrast would be suitable for fNIRS neuroimaging. Since fNIRS monitors hemodynamic response transcranially, it necessarily commeasures non-cortical physiological noise such as skin hemodynamic signals (Katura et al., 2008). In order to extract task-related genuinely cortical hemodynamic signals, setting an appropriate contrast is of great technical importance. The combination of go-task and no-go-task blocks should be effective in cancelling the effects of non-cortical signals since they have similar motor requirements, and thus should allow the extraction of cognitive components.

It should be noted that this contrast does not only reflect response inhibition, but also involves other cognitive components such as decision making, conflict monitoring, and increased attentional demand in the more difficult go/no-go condition (Liddle et al., 2001; Menon et al., 2001; Rubia et al., 2001). However, the current study did not aim to extract the genuine neural substrate for response inhibition, but rather to explore a stable biological marker for assessing the effect of MPH. In this sense, the selection of a go/no-go paradigm is appropriate. Moreover, maturation for go/no-go task performance was detected at approximately 12 years of age (Levin et al., 1991). An extensive neuropharmacological study on MPH effect using behavioral parameters enrolling 7- to 15-year-old ADHD children confirmed the efficacy of the go/no-go paradigm (Coghill et al., 2007). In addition, stimuli used for the go/no-go paradigm can be easily modified for use with children. Considering these points, fNIRS monitoring with a go/no-go paradigm is a practical choice for monitoring the effects of MPH in ADHD children.

4.4. Merits of using fNIRS

Owing to several features of fNIRS exemplified by compactness, portability, tolerance to body motion, and high maneuverability in use for children, fNIRS has been applied in ADHD studies (Ehlis et al., 2008; Jourdan Moser et al., 2009; Negoro et al., 2010 Schecklmann et al., 2008b, 2010; Weber et al., 2005). Weber et al. (2007) examined the effect of MPH on ADHD children, but did not observe significant activation except for a tendency for lower increase of deoxygenated and total Hb signals in an MPH-administered condition compared to an MPH-free condition in the right prefrontal region (Weber et al., 2007).

The absence of right LPFC activation in the MPH-medicated ADHD children in their study appears to contradict to the current results. However, this may be attributed to the difference between two-channel and multi-channel systems. Among the 44 channels used to cover a substantial portion of the frontal lobe, significant MPH-elicited activation was only observed in two. Such focused activation could only be detected as significant with a multichannel system in a multi-subject group analysis. Thus, fNIRS neuroimaging investigations should be performed with a multichannel system.

4.5. Limitations

As discussed above, the current study has demonstrated that MPH-effect assessment in ADHD children using fNIRS can be feasibly incorporated into clinical practice. However, before establishing its utility in clinical practice, several issues need to be

addressed. First, the neuropharmacological basis of MPH effect on ADHD children requires further experimental evidence. Since the current study put emphasis on the technical feasibility of fNIRS neuroimaging assessment in a clinical situation, the experimental design was not optimized for neuropharmacological analyses. It should be noted that the results of the current study are limited to checking the effect of MPH on children who are already medicated with MPH. Exploration of the pharmacological effects of MPH on cortical hemodynamics, plausibly with the right LPFC activation as a biological marker, requires a double-blind placebo-controlled design or at minimum a cross-over design with naïve ADHD children not being medicated with MPH. Comparison with normal healthy children, if possible, should be incorporated. Since fNIRS neuroimaging has proven effective in assessing neuropharmacological examinations of children in a traditional double-blind placebo-controlled crossover study (Tsujii et al., 2009), its extension to ADHD children is highly feasible. In addition, although the current study presented significant MPH-elicited right LPFC activation and a high correlation with improved behavioral performance due to the large effect sizes even with a small sample size, a larger sample size would be preferable in future exploration.

Second, order and learning effect associated with go/no-go tasks cannot be excluded from the current experimental design employing comparison before and after MPH medication. For separate sessions of the same task, activation of greater magnitude has been observed for the first session for go/no-go tasks in fMRI studies (Langenecker and Nielson, 2003). Albeit language tasks, fNIRS studies have also produced a larger amplitude of oxy-Hb signal in the first session (Kakimoto et al., 2009; Kono et al., 2007; Schecklmann et al., 2008a). Since subjects underwent a practice session in the current study, the effect of novelty was assumed to be controlled. On the other hand, effects of habituation (Fischer et al., 2003; Kiehl and Liddle, 2003; Loubinoux et al., 2001) and procedural learning (Eliassen et al., 2001) could be still present. It was expected that the oxy-Hb amplitude of the second measurement would be reduced. However, in the current study, MPH administration resulted in increased oxy-Hb amplitude in the second session. This means MPH exerted pharmacological effects beyond the level needed to compensate for the expected order effects. Thus, the current findings were not likely altered by order effects, if any were present. However, if such effects are present, they could be cancelled out by appropriate experimental procedures: since there are no studies on assessing order and learning effects of the go/no-go task associated with fNIRS signals, this would be an interesting and essential area for future study.

Third, although the current study suggested a biological marker, MPH-elicited activation in the right LPFC, this was distinctly detected in a group study. At an individual level, activation cannot always be detected in such a narrow region: It can typically be found on a wider region of the right or bilateral LPFC. However, the MPH-elicited activation in the right LPFC was consistently observed among ADHD children in the current study. Quantification of the MPH-elicited activation at an individual level for clinical application should be further explored.

Fourth, the large correlation between the behavioral performance increase and MPH-elicited activation in the right LPFC necessarily suggests that a small-scale behavioral performance increase can only be reflected in small MPH-elicited activation. In such situations, it would be hard to distinguish whether the subject is a mild case or is having only a low response to the MPH. Intriguingly, in the current study, the two subjects with smallest MPH-elicited activation had Asperger syndrome as a complication. This suggests that although the association between a go/no-go paradigm and right LPFC activation as a plausible biological marker is expected to be stable in monosymptomatic ADHD cases, this may not be applicable to ADHD cases with complications. It will be necessary to explore a wider range of neuropsychological tests and relevant biological markers in the future.

Fifth, the experimental paradigm with a block design used in the current study may not yield optimum specificity and sensitivity for the response inhibition function expected to increase upon MPH treatment with ADHD children. Since the no-go block consisted of 50% no-go and 50% go trials, the cortical activation does not fully reflect inhibitory control. In order to purify cortical activation exclusively for inhibitory control, an event-related design should be explored in future studies.

Finally, the current study did not reveal a detailed mechanism of how MPH leads to improved cognitive performance and the increased cortical activation associated with it. The observation that only accuracy but not RT exhibited improvement with MPH administration implies that a certain kind of strategic shift favoring accuracy over speed might have occurred. However, we should look to future studies to clarify this issue.

5. Conclusion

In conclusion, several minutes' cortical hemodynamic monitoring using fNIRS of ADHD children performing a go/no-go task before and 1.5 h after MPH administration could confirm the neural substrate for the acute effect of MPH as a significant increase of oxy-Hb signal in the right lateral prefrontal cortex. The right LPFC activation after intake of MPH was associated with a significant, large correlation with no-go task performance. These results suggest that assessing the acute effect of MPH medication on ADHD children could be implemented by fNIRS neuroimaging investigation within a single-day hospital visit. In addition to the assessment of behavioral modulation that has been conventionally practiced, fNIRS neuroimaging can monitor the state of the neural substrate for MPH administration to provide more direct and convincing evidence for the effect of MPH in ADHD children. The current study provides the first experimental demonstration that MPH-effect assessment in ADHD children using fNIRS can be integrated into clinical practice.

The current experimental design could be easily put into clinical practice to confirm the effect of MPH in ADHD children who have already been prescribed. With small modifications, it can also be applied to assess the acute effect of MPH in naïve ADHD children. This is of great clinical importance for screening of non-responders to MPH, who make up approximately 30% of ADHD children (Cho et al., 2007). Currently, identification of the MPH non-responders requires patients to take MPH over a certain period of time, but an fNIRS neuroimaging investigation may serve as a convenient tool for screening responders and non-responders. Upon identifying non-responders, an fNIRS neuroimaging investigation would provide another clinical examination of the effect of alternative medication with atomoxetine hydrochloride.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clinph.2011.10.006.

References

Arnsten AF. Stimulants: therapeutic actions in ADHD. Neuropsychopharmacolog 2006;31:2376–83.

Barkley RA. Issues in the diagnosis of attention-deficit/hyperactivity disorder in children. Brain Dev 2003;25:77–83.

Boecker M, Buecheler MM, Schroeter ML, Gauggel S. Prefrontal brain activation during stop-signal response inhibition: an event-related functional near-infrared spectroscopy study. Behav Brain Res 2007;176:259–66.

Brett M, Johnsrude IS, Owen AM. The problem of functional localization in the human brain. Nat Rev Neurosci 2002;3:243–9.

Bush G, Frazier JA, Rauch SL, Seidman LJ, Whalen PJ, Jenike MA, et al. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop. Biol Psychiatry 1999;45:1542–52.

Cho SC, Hwang JW, Kim BN, Lee HY, Kim HW, Lee JS, et al. The relationship between regional cerebral blood flow and response to methylphenidate in children with attention-deficit hyperactivity disorder: comparison between non-responders to methylphenidate and responders. J Psychiatr Res 2007;41:459–65.

Coghill DR, Rhodes SM, Matthews K. The neuropsychological effects of chronic methylphenidate on drug-naive boys with attention-deficit/hyperactivity disorder. Biol Psychiatry 2007;62:954–62.

Cohen J. A power primer. Psychol Bull 1992;112:155–9.

Comalli Jr PE, Wapner S, Werner H. Interference effects of Stroop color-word test in childhood, adulthood, and aging. J Genet Psychol 1962;100:47–53.

Cope M, Delpy DT, Reynolds EO, Wray S, Wyatt J, van der Zee P. Methods of quantitating cerebral near infrared spectroscopy data. Adv Exp Med Biol 1988;222:183–9.

de Zubicaray GI, Andrew C, Zelaya FO, Williams SC, Dumanoir C. Motor response suppression and the prepotent tendency to respond: a parametric fMRI study. Neuropsychologia 2000;38:1280–91.

Dillo W, Goke A, Prox-Vagedes V, Szycik GR, Roy M, Donnerstag F, et al. Neuronal correlates of ADHD in adults with evidence for compensation strategies-a functional MRI study with a Go/No-Go paradigm. Ger Med Sci 2010; 8: Doc09.

Durston S, Tottenham NT, Thomas KM, Davidson MC, Eigsti IM, Yang Y, et al. Differential patterns of striatal activation in young children with and without ADHD. Biol Psychiatry 2003;53:871–8.

Ehlis AC, Bahne CG, Jacob CP, Herrmann MJ, Fallgatter AJ. Reduced lateral prefrontal activation in adult patients with attention-deficit/hyperactivity disorder (ADHD) during a working memory task: a functional near-infrared spectroscopy (fNIRS) study. J Psychiatr Res 2008;42:1060–7.

Elia J, Borcherding BG, Rapoport JL, Keysor CS. Methylphenidate and dextroamphetamine treatments of hyperactivity: are there true nonresponders? Psychiatry Res 1991;36:141–55.

Eliassen JC, Souza T, Sanes JN. Human brain activation accompanying explicitly directed movement sequence learning. Exp Brain Res 2001;141:269–80.

Epstein JN, Casey BJ, Tonev ST, Davidson M, Reiss AL, Garrett A, et al. Assessment and prevention of head motion during imaging of patients with attention deficit hyperactivity disorder. Psychiatry Res 2007;155:75–82.

Fischer H, Wright CI, Whalen PJ, McInerney SC, Shin LM, Rauch SL. Brain habituation during repeated exposure to fearful and neutral faces: a functional MRI study. Brain Res Bull 2003;59:387–92.

Garavan H, Ross TJ, Stein EA. Right hemispheric dominance of inhibitory control: an event-related functional MRI study. Proc Natl Acad Sci USA 1999;96:8301–6.

Herrmann MJ, Ehlis AC, Fallgatter AJ. Bilaterally reduced frontal activation during a verbal fluency task in depressed patients as measured by near-infrared spectroscopy. J Neuropsychiatry Clin Neurosci 2004;16:170–5.

Herrmann MJ, Plichta MM, Ehlis AC, Fallgatter AJ. Optical topography during a Go-NoGo task assessed with multi-channel near-infrared spectroscopy. Behav Brain Res 2005;160:135–40.

Hock C, Villringer K, Müller-Spahn F, Wenzel Ri, Heekeren H, Schuh-Hofer S, et al. Decrease in parietal cerebral hemoglobin oxygenation during performance of a verbal fluency task in patients with Alzheimer's disease monitored by means of near-infrared spectroscopy (NIRS) - correlation with simultaneous rCBF-PET measurements. Brain Res 1997;755:293–303.

Jourdan Moser S, Cutini S, Weber P, Schroeter ML. Right prefrontal brain activation due to Stroop interference is altered in attention-deficit hyperactivity disorder – A functional near-infrared spectroscopy study. Psychiatry Res 2009;173:190–5.

Kakimoto Y, Nishimura Y, Hara N, Okada M, Tanii H, Okazaki Y. Intrasubject reproducibility of prefrontal cortex activities during a verbal fluency task over two repeated sessions using multi-channel near-infrared spectroscopy. Psychiatry Clin Neurosci 2009;63:491–9.

Katagiri A, Dan I, Tuzuki D, Okamoto M, Yokose N, Igarashi K, et al. Mapping of optical pathlength of human adult head at multi-wavelengths in near infrared spectroscopy. Adv Exp Med Biol 2010;662:205–12.

Katura T, Sato H, Fuchino Y, Yoshida T, Atsumori H, Kiguchi M, et al. Extracting task-related activation components from optical topography measurement using independent components analysis. J Biomed Opt. 2008; 13: 054008.

Kiehl KA, Liddle PF. Reproducibility of the hemodynamic response to auditory oddball stimuli: a six-week test-retest study. Hum Brain Mapp 2003;18:42–52.

Kono T, Matsuo K, Tsunashima K, Kasai K, Takizawa R, Rogers MA, et al. Multiple-time replicability of near-infrared spectroscopy recording during prefrontal activation task in healthy men. Neurosci Res 2007;57:504–12.

Langenecker SA, Nielson KA. Frontal recruitment during response inhibition in older adults replicated with fMRI. Neuroimage 2003;20:1384–92.

Levin HS, Culhane KA, Hartmann J, Evankovich K, Mattson AJ, Harward H, et al. Developmental changes in performance on tests of purported frontal lobe functioning. Dev Neuropsychol 1991;7:377–95.

Liddle PF, Kiehl KA, Smith AM. Event-related fMRI study of response inhibition. Hum Brain Mapp 2001;12:100–9.

Loeber R, Green SM, Lahey BB, Christ MAG, Frick PJ. Developmental sequences in the age of onset of disruptive child behaviors. J Child Fam Stud 1992;1: 21–41.

Loubinoux I, Carel C, Alary F, Boulanouar K, Viallard G, Manelfe C, et al. Within-session and between-session reproducibility of cerebral sensorimotor activation: a test-retest effect evidenced with functional magnetic resonance imaging. J Cereb Blood Flow Metab 2001;21:592–607.

Maki A, Yamashita Y, Ito Y, Watanabe E, Mayanagi Y, Koizumi H. Spatial and temporal analysis of human motor activity using noninvasive NIR topography. Med Phys 1995;22:1997–2005.

Mannuzza S, Klein RG, Bessler A, Malloy P, Hynes ME. Educational and occupational outcome of hyperactive boys grown up. J Am Acad Child Adolesc Psychiatry 1997;36:1222–7.

Matsuo K, Kato T, Fukuda M, Kato N. Alteration of hemoglobin oxygenation in the frontal region in elderly depressed patients as measured by near-infrared spectroscopy. J Neuropsychiatry Clin Neurosci 2000;12:465–71.

Matsuo K, Taneichi K, Matsumoto A, Ohtani T, Yamasue H, Sakano Y, et al. Hypoactivation of the prefrontal cortex during verbal fluency test in PTSD: a near-infrared spectroscopy study. Psychiatry Res 2003;124:1–10.

Meltzer JA, Postman-Caucheteux WA, McArdle JJ, Braun AR. Strategies for longitudinal neuroimaging studies of overt language production. Neuroimage 2009;47:745–55.

Menon V, Adleman NE, White CD, Glover GH, Reiss AL. Error-related brain activation during a Go/NoGo response inhibition task. Hum Brain Mapp 2001;12:131–43.

Milich R, Balentine AC, Lynam DR. ADHD Combined Type and ADHD Predominantly Inattentive Type Are Distinct and Unrelated Disorders. Clin Psychol (New York) 2001;8:463–88.

Moll J, de Oliveira-Souza R, Moll FT, Bramati IE, Andreiuolo PA. The cerebral correlates of set-shifting: an fMRI study of the trail making test. Arq Neuropsiquiatr 2002;60:900–5.

Moser DJ, Jorge RE, Manes F, Paradiso S, Benjamin ML, Robinson RG. Improved executive functioning following repetitive transcranial magnetic stimulation. Neurology 2002;58:1288–90.

Murphy KR, Barkley RA, Bush T. Executive functioning and olfactory identification in young adults with attention deficit-hyperactivity disorder. Neuropsychology 2001;15:211–20.

Negoro H, Sawada M, Iida J, Ota T, Tanaka S, Kishimoto T. Prefrontal dysfunction in attention-deficit/hyperactivity disorder as measured by near-infrared spectroscopy. Child Psychiatry Hum Dev 2010;41:193–203.

Nigg JT. The ADHD response-inhibition deficit as measured by the stop task: replication with DSM-IV combined type, extension, and qualification. J Abnorm Child Psychol 1999;27:393–402.

Nigg JT. On inhibition/disinhibition in developmental psychopathology: views from cognitive and personality psychology and a working inhibition taxonomy. Psychol Bull 2000;126:220–46.

Ohlmeier MD, Prox V, Zhang Y, Zedler M, Ziegenbein M, Emrich HM, et al. Effects of methylphenidate in ADHD adults on target evaluation processing reflected by event-related potentials. Neurosci Lett 2007;424:149–54.

Okamoto M, Dan H, Sakamoto K, Takeo K, Shimizu K, Kohno S, et al. Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10–20 system oriented for transcranial functional brain mapping. Neuroimage 2004;21:99–111.

Okamoto M, Dan I. Automated cortical projection of head-surface locations for transcranial functional brain mapping. Neuroimage 2005;26:18–28.

Rapport MD, Denney C, DuPaul GJ, Gardner MJ. Attention deficit disorder and methylphenidate: normalization rates, clinical effectiveness, and response prediction in 76 children. J Am Acad Child Adolesc Psychiatry 1994;33: 882–93.

Rorden C, Brett M. Stereotaxic display of brain lesions. Behav Neurol 2000;12:191–200.

Rubia K, Halari R, Cubillo A, Mohammad AM, Brammer M, Taylor E. Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naive children with ADHD during a rewarded continuous performance task. Neuropharmacology 2009;57:640–52.

Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, et al. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. Am J Psychiatry 1999;156:891–6.

Rubia K, Russell T, Overmeyer S, Brammer MJ, Bullmore ET, Sharma T, et al. Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. Neuroimage 2001;13:250–61.

Rubia K, Smith AB, Brammer MJ, Taylor E. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. Neuroimage 2003;20:351–8.

Schecklmann M, Ehlis AC, Plichta MM, Fallgatter AJ. Functional near-infrared spectroscopy: a long-term reliable tool for measuring brain activity during verbal fluency. Neuroimage 2008a;43:147–55.

Schecklmann M, Ehlis AC, Plichta MM, Romanos J, Heine M, Boreatti-Hummer A, et al. Diminished prefrontal oxygenation with normal and above-average verbal fluency performance in adult ADHD. J Psychiatr Res 2008b;43:98–106.

Schecklmann M, Romanos M, Bretscher F, Plichta MM, Warnke A, Fallgatter AJ. Prefrontal oxygenation during working memory in ADHD. J Psychiatr Res 2010;44:621–8.
Schroeter ML, Zysset S, Wahl M, von Cramon DY. Prefrontal activation due to Stroop interference increases during development-an event-related fNIRS study. Neuroimage 2004;23:1317–25.
Segalowitz SJ, Unsal A, Dywan J. CNV evidence for the distinctiveness of frontal and posterior neural processes in a traumatic brain-injured population. J Clin Exp Neuropsychol 1992;14:545–65.
Shafritz KM, Marchione KE, Gore JC, Shaywitz SE, Shaywitz BA. The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder. Am J Psychiatry 2004;161:1990–7.
Shattuck DW, Mirza M, Adisetiyo V, Hojatkashani C, Salamon G, Narr KL, et al. Construction of a 3D probabilistic atlas of human cortical structures. Neuroimage 2008;39:1064–80.
Shinba T, Nagano M, Kariya N, Ogawa K, Shinozaki T, Shimosato S, et al. Near-infrared spectroscopy analysis of frontal lobe dysfunction in schizophrenia. Biol Psychiatry 2004;55:154–64.
Singh AK, Dan I. Exploring the false discovery rate in multichannel NIRS. Neuroimage 2006;33:542–9.
Spencer TJ. ADHD treatment across the life cycle. J Clin Psychiatry 2004;65(Suppl 3):22–6.
Suto T, Fukuda M, Ito M, Uehara T, Mikuni M. Multichannel near-infrared spectroscopy in depression and schizophrenia: cognitive brain activation study. Biol Psychiatry 2004;55:501–11.
Swanson JM, Lerner M, Wigal T, Steinhoff K, Greenhill L, Posner K, et al. The use of a laboratory school protocol to evaluate concepts about efficacy and side effects of new formulations of stimulant medications. J Atten Disord 2002;6(Suppl. 1):S73–88.
Tamm L, Menon V, Ringel J, Reiss AL. Event-related FMRI evidence of frontotemporal involvement in aberrant response inhibition and task switching in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2004;43:1430–40.
Tsujii T, Masuda S, Yamamoto E, Ohira T, Akiyama T, Takahashi T, et al. Effects of sedative and nonsedative antihistamines on prefrontal activity during verbal fluency task in young children: a near-infrared spectroscopy (NIRS) study. Psychopharmacology (Berl) 2009;207:127–32.
Tsuzuki D, Jurcak V, Singh AK, Okamoto M, Watanabe E, Dan I. Virtual spatial registration of stand-alone fNIRS data to MNI space. Neuroimage 2007;34:1506–18.
Vaidya CJ, Austin G, Kirkorian G, Ridlehuber HW, Desmond JE, Glover GH, et al. Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. Proc Natl Acad Sci USA 1998;95:14494–9.
Weber P, Lutschg J, Fahnenstich H. Cerebral hemodynamic changes in response to an executive function task in children with attention-deficit hyperactivity disorder measured by near-infrared spectroscopy. J Dev Behav Pediatr 2005;26:105–11.
Weber P, Lutschg J, Fahnenstich H. Methylphenidate-induced changes in cerebral hemodynamics measured by functional near-infrared spectroscopy. J Child Neurol 2007;22:812–7.
Wehmeier PM, Dittmann RW, Schacht A, Helsberg K, Lehmkuhl G. Morning and evening behavior in children and adolescents treated with atomoxetine once daily for attention-deficit/hyperactivity disorder (ADHD): findings from two 24-week, open-label studies. Child Adolesc Psychiatry Ment Health 2009;3:5.
Wilens TE. Effects of methylphenidate on the catecholaminergic system in attention-deficit/hyperactivity disorder. J Clin Psychopharmacol 2008;28:S46–53.
Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. Biol Psychiatry 2005;57:1336–46.
Williams BR, Ponesse JS, Schachar RJ, Logan GD, Tannock R. Development of inhibitory control across the life span. Dev Psychol 1999;35:205–13.
Zakzanis KK, Mraz R, Graham SJ. An fMRI study of the Trail Making Test. Neuropsychologia 2005;43:1878–86.

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Right prefrontal activation as a neuro-functional biomarker for monitoring acute effects of methylphenidate in ADHD children: An fNIRS study ☆

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ABSTRACT

An objective biomarker is a compelling need for the early diagnosis of attention deficit hyperactivity disorder (ADHD), as well as for the monitoring of pharmacological treatment effectiveness. The advent of fNIRS, which is relatively robust to the body movements of ADHD children, raised the possibility of introducing functional neuroimaging diagnosis in younger ADHD children. Using fNIRS, we monitored the oxy-hemoglobin signal changes of 16 ADHD children (6 to 13 years old) performing a go/no-go task before and 1.5 h after MPH or placebo administration, in a randomized, double-blind, placebo-controlled, crossover design. 16 age- and gender-matched normal controls without MPH administration were also monitored. Relative to control subjects, unmedicated ADHD children exhibited reduced activation in the right inferior frontal gyrus (IFG) and middle frontal gyrus (MFG) during go/no-go tasks. The reduced right IFG/MFG activation was acutely normalized after MPH administration, but not after placebo administration. The MPH-induced right IFG/MFG activation was significantly larger than the placebo-induced activation. Post-scan exclusion rate was 0% among 16 right-handed ADHD children with IQ>70. We revealed that the right IFG/MFG activation could serve as a neuro-functional biomarker for monitoring the acute effects of methylphenidate in ADHD children. fNIRS-based examinations were applicable to ADHD children as young as 6 years old, and thus would contribute to early clinical diagnosis and treatment of ADHD children.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by a behavioral phenotype of inattention, hyperactivity and impulsivity, affecting between 3 and 7% of school-aged children in the U.S. (Dittmann et al., 2009; Pietrzak et al., 2006). The symptoms of ADHD can usually be identified during their early elementary school years (Drechsler et al., 2005). Diagnosis of ADHD typically refers to the degree of the symptoms listed in the diagnostic criteria from the DSM-IV (American Psychiatric Association, 1994), which requires rating by the parents or teachers of the children, and thus often entails subjective evaluation. Thus, more objective approaches, preferably based on biomarkers, are a compelling need (Wehmeier et al., 2011; Zhu et al., 2008).

One promising approach is noninvasive functional neuroimaging in combination with neuropsychological tests. A wealth of functional neuroimaging research has started to explore the neural substrates of ADHD. The majority of such research performed thus far has used functional magnetic resonance imaging (fMRI), and many studies have reported less prefrontal activation with ADHD during performance of various cognitive tasks (e.g., Booth et al., 2005; Rubia et al., 1999, 2005; Smith et al., 2006). However, most of the fMRI studies are on adult ADHD patients with only limited implications for children. Among approximately one hundred ADHD-related fMRI studies, twenty-six included patients at the age of eight, eleven at the age of seven (Anderson et al., 2002; Bedard et al., 2010; Booth et al., 2005; Chabernaud et al., 2012; Durston et al., 2007; Fair et al., 2010; Peterson et al., 2009; Slifer et al., 2002; Solanto et al., 2009; Teicher et al., 2000; Vaidya et al., 2005) and only two at the age of six (Durston et al., 2003; Teicher et al., 2000).

The scarcity of child ADHD studies is due to technical obstacles. Severely hyperactive children could not be included in the studies because motion artifacts would have prevented successful

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