Schizophrenia Research 206 (2019) 420–427

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Comparison of prefrontal hemodynamic responses and cognitive deficits between adult patients with autism spectrum disorder and schizophrenia

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ARTICLE INFO

Article history:
Received 12 March 2018
Received in revised form 16 July 2018
Accepted 6 October 2018
Available online 11 October 2018

Keywords:
Near-infrared spectroscopy
Working memory task
Prefrontal cortex
Brief Assessment of Cognition in Schizophrenia
Cluster analysis

ABSTRACT

Autism spectrum disorder (ASD) and schizophrenia share many phenotypic characteristics, but their association with prefrontal function have not been directly compared. The aim of this study is to compare cognitive profiles and their association with the prefrontal function between the two groups. We explored prefrontal dysfunction among adult individuals with ASD (n = 32), schizophrenia (n = 87), and healthy controls (HCs; n = 50). We assessed cognitive function in all participants using the Brief Assessment of Cognition in Schizophrenia (BACS). The BACS data of patients with schizophrenia were entered into hierarchical cluster analyses to assign subjects to a specific subgroup based on individual profiles. Using near-infrared spectroscopy, we measured hemodynamic responses in the fronto-temporal regions during a working memory task. Among the patients with schizophrenia, we defined 4 neurocognitive subgroups, including a global impairment, a mild impairment, and 2 selective impairment groups. Compared to the HCs, the ASD and schizophrenia groups had much weaker hemodynamic responses in the left DLPFC, left frontopolar cortex (FPC), and left inferior frontal gyrus. The ASD group showed a similar level of cognitive impairment with the mild level subgroup of schizophrenia. Additionally, the two groups shared reduced activity in the left DLPFC and left FPC during the task compared to HCs. Moreover, the BACS composite scores correlated positively with hemodynamic responses in a broad area involving fronto-temporal regions in the total patient sample. This research indicates considerable similarity in the left PFC dysfunction and its association with cognitive deficits between the disorders. These findings may guide future studies that investigate pathophysiological similarities between ASD and schizophrenia.

1. Introduction

Autism spectrum disorder (ASD) and schizophrenia are severe neurodevelopmental disorders characterized by considerable impairments in social and emotional function and information processing (Lewis and Levitt, 2002; Volkmar et al., 2004). They have some similar cognitive and behavioral manifestations (Kanner, 1965). Although the 2 disorders emerge at different developmental periods, both are characterized by significant impairments in social behavior and understanding (American Psychiatric Association, 2013; Eack et al., 2007; Howlin et al., 2013; Harrow et al., 2005; Macdonald et al., 2000; Mazurek, 2014; Orsmond et al., 2013). Although typically diagnosed in childhood, ASD (American Psychiatric Association, 2013) is a lifelong condition, and ASD-affected adults face significant challenges throughout life with poor long-term outcomes (Howlin, 2000).

In recent years, there has been an increasing interest in putative connections between ASD and schizophrenia (King and Lord, 2011; Nylander et al., 2008). Studies have revealed similarities in comorbidity (Unenge Hallerback et al., 2012; Waris et al., 2013), brain anatomy (Cheung et al., 2010), genetics (Burbach and van der Zwaag, 2009), and social cognition (Lugnegard et al., 2013). Eack et al. (2013) reported that the 2 disorders cause similar deficits in neurocognitive and social-cognitive functioning. On the other hand, although Cheung et al. (2010) suggested a common feature between ASD and schizophrenia in terms of brain anatomy, they also revealed unique features of each

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https://doi.org/10.1016/j.schres.2018.10.007
0920-9964/

disorder suggesting that both common and distinct etiology exist in the two clinical entities.

It is widely recognized that schizophrenia is a heterogeneous clinical entity. It is heterogeneous in the domain of cognition, which is evinced by the existence of cognitively unimpaired subgroup of patients among the majority of patients with severe cognitive impairments (Palmer et al., 1997). Previous studies have subdivided the patients with schizophrenia using cluster analyses into four subtypes in general, with two extreme subtypes, near normative and profound global impairments, and two intermediate subtypes (Goldstein et al., 1998; Hill et al., 2002; Seaton et al., 1999). Although the cognitive profiles and the relevance of the subtypes to clinical characteristics differ among each study presumably due to the difference in the neuropsychological test batteries being used, the findings support the cognitive heterogeneity of the disease.

Prefrontal cortex (PFC) dysfunctions have been consistently reported in patients with schizophrenia (Minzenberg et al., 2009; Senkowski and Gallinat, 2015) whereas they have also been reported in patients with ASD. Most neuropsychological studies have shown impairment of executive functions including planning, flexibility, and working memory (Eack et al., 2013; Happe et al., 2006), and neuroimaging studies suggest that PFC function may be abnormal in adults with ASD (Kawakubo et al., 2009; Luna et al., 2002). In functional magnetic resonance imaging (fMRI) studies, they showed abnormal PFC hemodynamic responses associated with spatial working memory (Luna et al., 2002; Ring et al., 1999), motor inhibition (Schmitz et al., 2006), and visuomotor control (Muller et al., 2003). A study by Koshino et al. (2005) using an N-back working memory task with letter stimuli revealed that, despite the absence of any performance differences, adults with ASD showed lower activation than healthy controls did in the left PFC regions, especially the DLPFC, IFG, and posterior pre-central sulcus. Similar aberrant cortical activation were observed with several other working memory tasks (Di Martino et al., 2009; Kana et al., 2007; Luna et al., 2002; Silk et al., 2006; Stigler et al., 2011).

Despite evidence of abnormal activation of cognitive neural systems in ASD and schizophrenia (Kawakubo et al., 2009; Pu et al., 2016), no studies have used NIRS to directly compare the neural substrates underlying cognitive performance between the 2 disorders. More specifically, taking into consideration the partial overlap of cognitive impairment between the two disorders, comparing the cognitive profiles and PFC neural activity between ASD and subtypes of schizophrenia subdivided by the cognitive profiles would be of interest. Such comparisons may illuminate how much they share their cognitive impairment profiles and neural mechanisms underlying cognitive deficits.

This study examined neurocognitive impairments and abnormalities in working memory-related PFC neural activity in adults with ASD or schizophrenia. We hypothesized that (1) relative to healthy controls (HC), patients with ASD and schizophrenic would have detectable abnormalities in both cognitive functioning and working memory-related PFC neural activity, (2) this neural activity would be related to cognitive ability, as we recently reported in patients with schizophrenia, and (3) ASD would show a similarity with a subtype of schizophrenia in the level and profile of cognitive impairment and these two groups may also exhibit a similar working memory-related PFC neural activity. Confirming these hypotheses would suggest that the cognitive impairment in ASD and its neural basis is common with a subtype of schizophrenia and that working memory-related PFC neural activity might be a useful biomarker for the assessment of cognition (Pu et al., 2016). It should be noted that this study is an extension of our previous study using the same data obtained for patients with schizophrenia and healthy controls as those in our previous study and added on the data of patients with ASD. In our previous study (Pu et al., 2016), we reported that whereas the hemodynamic responses in the right DLPFC, bilateral ventrolateral PFC (VLPFC), and right temporal regions decreased with increasing cognitive deficits, those of the left PFC in the higher-level-of-cognitive-function schizophrenia group were similar to those in the lower-level-of-cognitive-function schizophrenia group. In our previous study we subdivided the patients in terms of level of cognitive dysfunction but rather arbitrarily. In this study we adopted a hierarchical cluster analysis to obtain a more valid model for subgrouping.

2. Material and methods

2.1. Participants

This study was approved by the Tottori University Faculty of Medicine's Ethics Committee (approval no. 885), and the investigation was conducted in accordance with the latest revision of the Declaration of Helsinki. All participants gave written informed consent.

Table 1 presents experimental and control participant demographics. Study participants included 32 adult patients with ASD (age 28.0 ± 6.5 years, women/men 7/25, education 14.6 ± 2.9 years, estimated premorbid IQ 105.0 ± 10.2, Edinburgh handedness inventory 92.5 ± 25.4%), 87 patients with schizophrenia (age 33.6 ± 10.0 years, women/men 50/37, education 13.4 ± 2.3 years, estimated premorbid IQ 99.1 ± 7.6, Edinburgh handedness inventory 93.5 ± 14.9%), and 50 healthy controls (HCs) (age 34.4 ± 10.8 years, women/men 30/20, education 14.9 ± 2.5 years, estimated premorbid IQ 101.5 ± 9.6, Edinburgh handedness inventory 93.3 ± 12.1%). Patients with ASD or schizophrenia were recruited from the inpatient and outpatient services at the Tottori University Hospital. Diagnoses were confirmed with the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (American Psychiatric Association, 1994) criteria. The ASD sample included 25 patients with Asperger's syndrome and 7 with pervasive developmental disorder not otherwise specified. Although all subjects retrospectively met the DSM-5's ASD criteria, the DSM-IV was used in the actual assessment. Autistic symptomatology was assessed using the Pervasive Developmental Disorders Autism Society Japan Rating Scale (Adachi et al., 2006; Kamio et al., 2006). All ASD subjects were verbal and were administered the Wechsler Adult Intelligence Scale. The ASD group's mean full-scale IQ score was 100.6 ± 15.0 (verbal IQ = 105.0 ± 14.7, performance IQ = 94.8 ± 16.6). At the time of the experiments, 15 participants with ASD were using the following medications: antipsychotics [8 patients, chlorpromazine equivalent dose (Inagaki and Inada, 2006) = 56.3 ± 126.2 mg/day], antidepressants [9 patients, imipramine-equivalent dose (Inagaki and Inada, 2006) = 15.2 ± 28.4 mg/day], anticonvulsants (3 patients), hypnotics (9 patients), and anxiolytics (4 patients). The HCs and patients with schizophrenia are the same as those in our previous report (Pu et al., 2016).

Premorbid intellectual ability was estimated using the Japanese version of the National Adult Reading Test (JART) (Matsuoka et al., 2006). Inclusion criteria for all participants were: Japanese native speakers, right-handed determined by the Edinburgh Inventory (Oldfield, 1971), and adults aged 18 to 64 years old.

Patients with comorbid neurological illness, previous traumatic brain injury with any known cognitive consequences or loss of consciousness for >5 min, a history of electroconvulsive therapy, or alcohol/substance abuse or addiction (except nicotine) were excluded. Inclusion criteria for HCs were similar to those for the patient sample, although controls were also required to have no previous or current psychiatric illnesses.

2.2. Working memory task

We used a 2-back task with a blocked periodic baseline–activation–baseline design originally described by Cohen et al. (1994) to activate brain regions that maintain and manipulate components of verbal working memory. The working memory task consisted of a 60-s pre-task period, a 60-s 2-back task period, and a 60-s post-task period (for 180-s blocks, see Supplementary Fig. S1). Behavioral performance for the 2-back task was measured in terms of reaction time (RT) to target figures and sensitivity A′ (Grier, 1971).

Table 1
Demographics and clinical characteristics of participants.

	HCs group (mean ± SD)	ASD group (mean ± SD)	Schizophrenia group (mean ± SD)	*p* value	F value	Significance
n (women/men)[a]	50 (30:20)	32 (7:25)	87 (50:37)	<0.001	$X^2 = 13.93$	ASD vs HCs $p < 0.001$ ASD vs schizophrenia $p < 0.001$ HCs vs schizophrenia $p = 0.773$
Age (years)[b]	34.4 ± 10.8	28.0 ± 6.5	33.6 ± 10.0	0.009	4.84	ASD vs HCs $p = 0.004$ ASD vs schizophrenia $p = 0.002$ HCs vs schizophrenia $p = 0.903$
Education (years)[b]	14.9 ± 2.5	14.6 ± 2.9	13.4 ± 2.3	0.001	6.86	ASD vs HCs $p = 0.811$ ASD vs schizophrenia $p = 0.129$ HCs vs schizophrenia $p = 0.002$
Estimated premorbid IQ[b]	101.5 ± 9.6	105.0 ± 10.2	99.1 ± 7.6	0.005	5.55	ASD vs HCs $p = 0.278$ ASD vs schizophrenia $p = 0.012$ HCs vs schizophrenia $p = 0.274$
Edinburgh handedness inventory (%)[b]	93.3 ± 12.1	92.5 ± 25.4	93.5 ± 14.9	0.958	0.04	ASD vs HCs $p = 0.985$ ASD vs schizophrenia $p = 0.976$ HCs vs schizophrenia $p = 0.995$
PARS						
Childhood		13.6 ± 9.9				
Adolescent		17.7 ± 7.0				
PANSS						
Positive	–	–	15.4 ± 6.2	–	–	
Negative	–	–	17.5 ± 4.9	–	–	
General psychopathology	–	–	31.8 ± 6.9	–	–	
Chlorpromazine equivalent dose (mg/day)[c]	–	56.3 ± 126.2	575.1 ± 348.7	<0.001	$X^2 = 59.49$	
Task performance						
Reaction time (ms)[c]	627.5 ± 170.7	705.9 ± 173.6	761.9 ± 219.5	<0.001	$X^2 = 15.58$	
Sensitivity A′[c]	0.985 ± 0.043	0.984 ± 0.040	0.941 ± 0.134	0.014	$X^2 = 8.53$	

Note: HCs, healthy controls; ASD, autism spectrum disorder; IQ, Intelligence Quotient; PARS, Pervasive Developmental Disorders Autism Society Japan Rating Scale; PANSS, Positive and Negative Symptom Scale.
Significant group differences are shown to the right. $p < 0.05$ was considered significant.
[a] Chi-square test.
[b] One-way ANOVA and post hoc Gams-Howell tests.
[c] Kruskal-Wallis test was used for testing group differences.

2.3. NIRS methodology

A 52-channel NIRS machine (ETG-4000, Hitachi Medical Co., Tokyo, Japan) was used to measure hemoglobin concentration changes. The NIRS probe was a 3 × 11 array with 17 emitters and 16 detectors. The NIRS probes were placed on the frontotemporal region, with the probe's midcolumn located over Fpz and the lowest probes located along the T3-Fp1-Fpz-Fp2-T4 line of the electroencephalographic International 10–20 System. The inter-pair distance of source-detector probes was set at 3 cm, and each measurement area between source-detector probe pairs was defined as a "channel" (ch). The machine measures points 2 to 3 cm below the scalp, which corresponds well with the cerebral cortical surface (Okada and Delpy, 2003; Toronov et al., 2001). The correspondence between NIRS channels and cortical anatomy was confirmed in a multi-subject study (Okamoto et al., 2004; Tsuzuki et al., 2007).

NIRS measures changes in both oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) at 2 infrared wavelengths (695 and 830 nm) using the modified Beer–Lambert law (Yamashita et al., 1996). We could not measure the absolute scalp-to-cerebral-cortex path length, so we recorded hemoglobin concentrations from baseline to the activation periods. Relative hemoglobin concentration changes are reported in mM·mm.

The sampling frequency was 10 Hz. We determined changes in the task-related signal by calculating a linear fit to 2 baseline periods that included the pre-task period's last 10-s period (pre-task baseline) and the 5-s period (post-task baseline) after the 50-s post-task period (see Supplementary Fig. S1). We performed moving-averages over 5-s windows to remove any short-term motion artifacts. Additionally, we removed body-movement artifact noise (no signal, high frequency, and low frequency) using the algorithm published by Takizawa et al. (2014).

2.4. The BACS

We assessed cognitive function in all participants using the Japanese version of the BACS (Kaneda et al., 2007; Keefe et al., 2004). The BACS evaluation included tests such as the List Learning Test for verbal memory, Digit Sequencing Task for working memory, Token Motor Task for motor speed, Category Instances Test and Controlled Oral Word Association Test for verbal fluency, Symbol Coding for attention and information processing speed, and Tower of London Test for executive function. Z-scores were calculated for each subcomponent using means and standard deviations (SDs) from a dataset of 340 Japanese HCs (Kaneda et al., 2007). Composite scores were calculated by averaging the z-scores from the 6 subcomponents. Higher scores reflected higher cognitive function. The BACS and NIRS experiments were performed on the same day.

2.5. Statistical analyses

Statistical analyses were performed using SPSS Statistics 19.0 (IBM, Armonk, NY). Statistical significance was defined as $p < 0.05$.

Categorical variables were compared using the chi-square test. The normally distributed clinical variables were compared using one-way analysis of variance (ANOVA), while the non-normally distributed variables were compared using the Kruskal-Wallis nonparametric ANOVA.

Initial analyses were carried out to compare demographic, clinical characteristics, and cognitive performance of the patients with ASD, schizophrenia groups, and HCs using ANOVA and the chi-square test as appropriate (Table 1). In case there was a significant between-group difference in the demographic and clinical characteristics, we performed analyses of co-variance (ANCOVA) using the demographic, clinical characteristics as a covariate to the cognitive performance.

To identify homogeneous subgroups of patients with schizophrenia based on their cognitive performance, we conducted a hierarchical

cluster analysis. Similarities between cases were computed with the squared Euclidian distance, and the Ward linkage was used for agglomeration. Dendrogram inspections were used to establish the appropriate number of clusters to retain for the second step of the analysis. Cluster membership was used as a grouping variable. To test the clusters' validity and better understand the relationship between cognition and cluster allocation of patients with schizophrenia, we conducted a discriminant function analysis (DFA) that explored the predictive power of each of the 6 BACS domains in classifying subjects into the discrete neurocognitive groups obtained from the hierarchical cluster analysis.

We compared demographic, clinical characteristics, and cognitive performance among the patients with ASD and schizophrenia subgroups using ANOVA and the chi-square test as appropriate. In case there was a significant between-group difference in the demographic and clinical characteristics, we performed ANCOVA using the demographic, clinical characteristics as a covariate to the cognitive performance.

We compared the pre-task baselines and task period measurements of oxy-Hb changes in each channel in the HCs using *t*-tests. Since this meant performing 52 *t*-tests, we applied the false discovery rate (FDR) multiple comparisons correction method. We set the maximum FDR value, q, to 0.05 so that at most 5% of channels were falsely positive on average (Benjamini and Hochberg, 1995; Singh and Dan, 2006; Tomioka et al., 2015).

We first compared patients with ASD, schizophrenia, and HCs for oxy-Hb changes during the task period using a one-way ANOVA (or ANCOVA when appropriate) for each channel. Additionally, we compared oxy-Hb changes through a one-way ANOVA (or ANCOVA) among the schizophrenia subgroups and patients with ASD. Post-hoc Gams-Howell tests were performed on channels registering significant differences. Moreover, to examine the relationship between oxy-Hb changes and BACS scores in the total patient sample and the patients with ASD, we calculated Pearson correlation coefficients.

To elucidate the independent contributions of cognitive function to the oxy-Hb changes in the channels showing significant correlations, we performed stepwise multiple regression analyses for the total patient sample. In these analyses, the mean oxy-Hb change was the dependent variable, and we controlled for other potential confounding variables such as age, gender (dummy parameterized: male = 1, female = 0), premorbid IQ, 2-back task performance (RT and sensitivity A′), and daily dosage of antipsychotic drugs in the analyses of the all patients group, with a conservative entry F-distribution and removal criteria of 0.05 and 0.2, respectively. For significant findings, effect sizes were indicated using the standardized regression coefficient (β).

3. Results

3.1. Demographic and clinical characteristics of the study groups (Table 1)

There were significant between-group differences in sex (X^2 = 13.93, $p < 0.001$) and age (F = 4.84, $p = 0.009$), with post-hoc tests indicating significant differences between the patients with ASD and the HCs (sex: $p < 0.001$, age: $p = 0.004$) or between the patients with ASD and schizophrenia (sex: $p < 0.001$, age: $p = 0.002$) (women/men: HCs: 30/20, ASD: 7/25, schizophrenia: 50/37; age: HCs: 34.4 ± 10.8, ASD: 28.0 ± 6.5, schizophrenia: 33.6 ± 10.0).

There were significant between-group differences in education (F = 6.86, $p = 0.001$), with post-hoc tests indicating higher education level in HCs compared to the patients with schizophrenia (HCs: 14.9 ± 2.5, schizophrenia: 13.4 ± 2.3; $p = 0.002$).

The three groups significantly differed in estimated premorbid IQ (JART scores) (F = 5.55, $p = 0.005$), with post-hoc tests indicating higher estimated premorbid IQ in patients with ASD compared to schizophrenia (ASD: 105.0 ± 10.2, schizophrenia: 99.1 ± 7.6; $p = 0.012$). Moreover, the mean daily dosage level of antipsychotic drugs was significantly less in patients with ASD than schizophrenia (ASD: 56.3 ± 126.2, schizophrenia: 575.1 ± 348.7; $p < 0.0001$).

3.2. Neurocognitive profiles of ASD and schizophrenia

ANOVA revealed that the patients with ASD performed significantly worse than the HCs on the verbal memory, working memory, motor speed, attention and information processing speed (4/6) domains, as well as the BACS composite score (all *p* values < 0.05) after controlling for age, sex, education, and estimated premorbid IQ. The patients with schizophrenia performed significantly worse than the HCs did on the BACS composite score and all 6 BACS domains (all *p* values < 0.001) after controlling for age, sex, education, and estimated premorbid IQ. The patients with schizophrenia performed significantly worse than the patients with ASD did on the BACS composite score and all 6 BACS domains (all *p* values < 0.05) after controlling for age, sex, education, and estimated premorbid IQ (Table 2).

3.3. Clustering schizophrenia patients

The hierarchical cluster analysis showed that the 87 patients with schizophrenia were optimally clustered (according to BACS performance) into 4 discrete subgroups. Based on cognitive impairment levels, the subgroups were labeled as follows:

- Selective impairment groups 1 (33 subjects, 37.93%) and 2 (17 subjects, 19.54%) presented with modest deficits in specific domains, with performances ranging from normal to approximately 2.5 SD below the HC mean. Selective impairment group 1 exhibited preserved executive function but moderate to severe deficits in verbal memory, motor speed and attention/information processing speed. Selective impairment group 2 exhibited preserved verbal fluency but moderate deficits in working memory and executive function.
- The mild impairment group (18 subjects, 20.69%) presented with near-normative performance and mild dysfunction in verbal memory, verbal fluency and attention/information processing speed.
- The global impairment group (19 subjects, 21.84%) presented with diffuse and severe cognitive dysfunction, with performance falling between 1.5 and 3 SDs below the HC mean.

DFA using these 4 clusters revealed the presence of 3 discriminant functions explaining 66.8%, 28.9%, and 4.3% of the variance (Wilks' λ = 0.11, $X^2_{18} = 117.23$, $p < 0.001$; after removal of the first function: Wilk's λ = 0.40, $X^2_{10} = 73.47$, $p < 0.001$; after removal of the second function: Wilk's λ = 0.86, $X^2_4 = 12.52$, $p < 0.05$). Subject groupings into the 4 neurocognitive clusters are shown in Supplementary Fig. S2.

The subgroups' demographic and clinical characteristics are summarized in Supplementary Table S1. There was a significant main effect of subgroup in PANSS negative subscale scores ($p = 0.014$). Post-hoc tests revealed a significant difference between the mild and global impairment groups in PANSS negative subscale scores (mild: 15.7 ± 4.1, global: 20.4 ± 4.6, $p = 0.011$).

3.4. Comparison of neurocognitive profiles between the ASD and schizophrenia subgroups

Multivariate ANCOVA revealed a significant main effect of group in BACS composite scores among the ASD and the schizophrenia subgroups (F = 13.718, $p < 0.001$). After least significant difference multiple comparisons corrections, the schizophrenia global impairment group performed significantly worse than the patients with ASD on the working memory, verbal fluency, attention and information processing speed, and executive function (4/6) domains, as well as the composite score. The selective 1 group performed significantly worse than the patients with ASD did on the composite score ($p = 0.050$).

Table 2
Comparison between the ASD, schizophrenia, and HCs across neurocognitive domains (Z scores).

BACS	HCs group (mean ± SD)	ASD group (mean ± SD)	Schizophrenia group (mean ± SD)	Significance[a]
Verbal memory	0.062 ± 0.774	−0.554 ± 0.970	−1.296 ± 1.115	HCs vs ASD $p = 0.027$ HCs vs schizophrenia $p < 0.001$ ASD vs schizophrenia $p = 0.005$
Working memory	0.125 ± 0.965	−0.163 ± 1.024	−1.084 ± 1.026	HCs vs ASD $p = 0.047$ HCs vs schizophrenia $p < 0.001$ ASD vs schizophrenia $p = 0.028$
Motor speed	0.057 ± 0.909	−0.711 ± 1.258	−1.779 ± 1.480	HCs vs ASD $p = 0.006$ HCs vs schizophrenia $p < 0.001$ ASD vs schizophrenia $p = 0.009$
Verbal fluency	0.394 ± 0.817	0.158 ± 1.029	−0.741 ± 0.818	HCs vs ASD $p = 0.358$ HCs vs schizophrenia $p < 0.001$ ASD vs schizophrenia $p < 0.001$
Attention and speed of information processing	0.353 ± 0.798	−0.514 ± 0.878	−1.333 ± 0.858	HCs vs ASD $p < 0.001$ HCs vs schizophrenia $p < 0.001$ ASD vs schizophrenia $p = 0.006$
Executive function	0.350 ± 0.849	0.395 ± 0.761	−0.700 ± 1.598	HCs vs ASD $p = 0.765$ HCs vs schizophrenia $p < 0.001$ ASD vs schizophrenia $p = 0.014$
Composite score	0.224 ± 0.504	−0.231 ± 0.653	−1.156 ± 0.834	HCs vs ASD $p = 0.003$ HCs vs schizophrenia $p < 0.001$ ASD vs schizophrenia $p < 0.001$

Note: ASD, autism spectrum disorder; HCs, healthy controls; BACS, Brief Assessment of Cognition in Schizophrenia.
[a] Analyses are controlled for age, sex, education, and estimated premorbid Intelligence Quotient.

The selective 2 group performed significantly worse than the patients with ASD did on the working memory ($p = 0.049$) and executive function ($p = 0.015$) domains. The schizophrenia mild impairment group and the patients with ASD did not significantly differ on any BACS domain or the composite score (Fig. 1).

3.5. Oxy-Hb changes during the task period in the study groups

Significant between-group differences were observed in the response sensitivity A′ (2-back: Kruskal-Wallis $X^2 = 8.53$, $p = 0.014$) and RT (2-back: Kruskal-Wallis $X^2 = 15.58$, $p < 0.001$) on the working memory task during NIRS measurement (Table 1). The performance (sensitivity A′ and RT) of the patients with ASD and schizophrenia did not significantly differ (RT: $p = 0.333$, sensitivity A′: $p = 0.126$), whereas those of the HCs significantly differed from those of both the patients with ASD (RT: $p = 0.041$; sensitivity A′: $p = 0.419$) and schizophrenia (RT: $p < 0.001$; sensitivity A′: $p = 0.006$) (RT: HCs: 627.5 ± 170.7, ASD: 705.9 ± 173.6, schizophrenia: 761.9 ± 219.5; sensitivity A′: HCs: 0.985 ± 0.043, ASD: 0.984 ± 0.040, schizophrenia: 0.941 ± 0.134).

Time courses of oxy-Hb changes are shown in Fig. 2. Among the patients with ASD, schizophrenia, and HC groups, we found significant main effect of group for oxy-Hb changes in 40 channels ($F = 3.464$ to 18.274, 52 channels-FDR corrected $p < 0.038$) located in the DLPFC, VLPFC, part of the FPC, and temporal regions. Post-hoc analysis (see Supplementary Fig. S3) indicated that the increases in the task-induced oxy-Hb changes were significantly smaller in the patients with ASD than in the HCs in 4 channels (ch38, ch39, ch49, and ch50; 52 channels-FDR corrected $p < 0.004$) in the left DLPFC, left FPC, and left inferior frontal gyrus (IFG) (see Supplementary Fig. S3A). It also showed that the increases in the task-induced oxy-Hb changes were significantly smaller in the patients with schizophrenia than in the HCs in 37 channels (ch9, ch10, ch12, ch14, ch17 to ch25, ch28 to ch36, and ch38 to ch52, ch49, and 50; 52 channels-FDR corrected $p < 0.036$) in the PFC and the temporal regions (see Supplementary Fig. S3B). Moreover, the increase in the oxy-Hb changes were significantly smaller

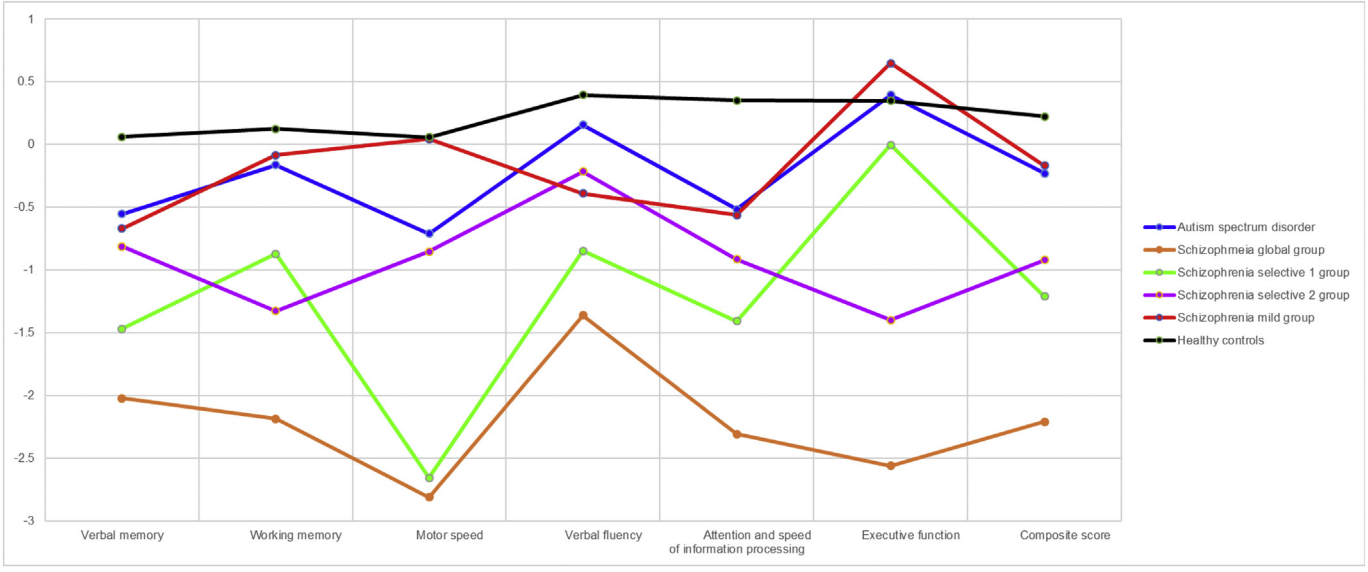

Fig. 1. Neurocognitive profiles of ASD and schizophrenia subgroups. The X-axis indicates the Brief Assessment of Cognition in Schizophrenia (BACS) domains. The Y-axis depicts a Z-score with a mean of 0 and a standard deviation of 1. Participants are divided into lines based on scoring for each cognitive domain.

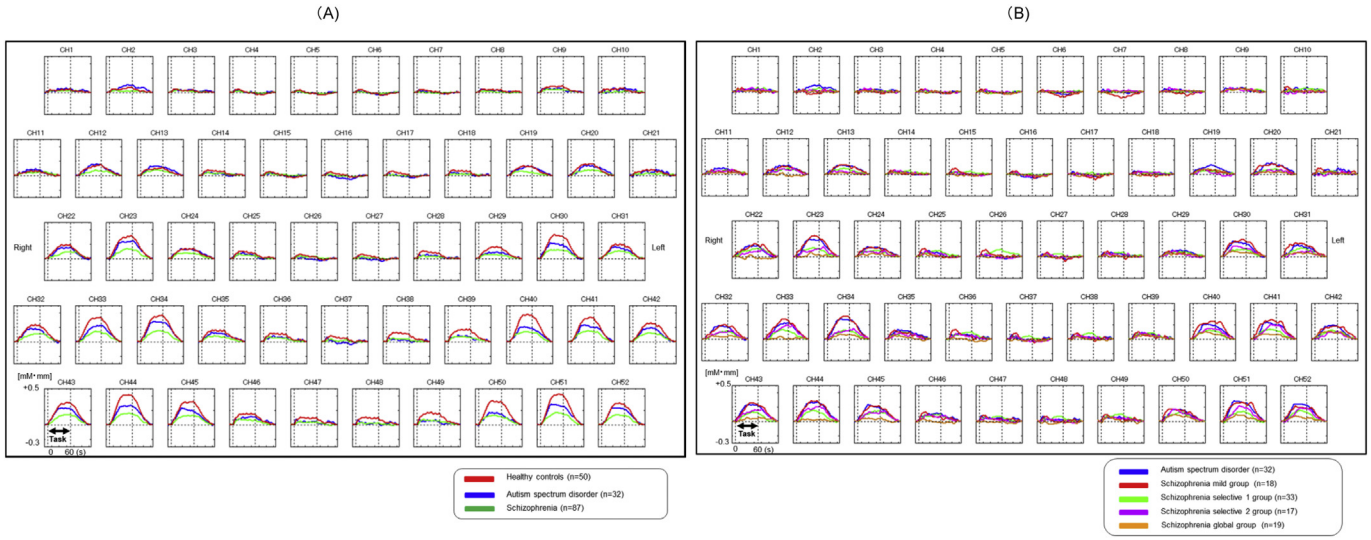

Fig. 2. Grand-averaged waveforms of oxygenated hemoglobin (oxy-Hb) changes during the 2-back task (the period between the 2 dotted vertical lines in each graph) in 52 near-infrared spectroscopy channels placed over the prefrontal and temporal regions. (A): Time-course oxy-Hb changes in the healthy control, autism spectrum disorder (ASD), and schizophrenia groups are indicated in red, blue, and light green respectively. (B): Time-course oxy-Hb changes in the ASD and schizophrenia subgroups (mild, selective 1, selective 2, and global) are indicated in blue, red, light green, pink, and orange respectively.

in the patients with schizophrenia than in the ASD in 2 channels (ch20, $p = 0.047$; and ch30, $p = 0.021$) in the left VLPFC region (see Supplementary Fig. S3C).

3.6. Comparison of oxy-Hb changes during the task period between the ASD, schizophrenia subgroups, and HCs

First, among the patients with ASD and schizophrenia subgroups, we found significant main effect of group for oxy-Hb changes in 14 channels (ch20, ch23, ch24, ch30 to ch34, ch40, ch41, ch43 to ch45, and ch51; $F = 3.360$ to 6.155, 52 channels-FDR corrected $p < 0.013$). The post hoc analysis indicated that the patients with ASD and schizophrenia mild impairment groups did not differ on any channel (see Supplementary Fig. S4A). It also indicated that in 1 channel (ch30, $p = 0.013$), the increases in the oxy-Hb changes were significantly smaller in the selective 1 group than in the patients with ASD (see Supplementary Fig. S4B, green), and that in 2 channels (ch20, $p = 0.029$; and ch31, $p = 0.031$), the increases in the oxy-Hb changes were significantly smaller in the schizophrenia selective 2 group than in the patients with ASD (see Supplementary Fig. S4B, blue). Moreover, the increases in the task-induced oxy-Hb changes were significantly smaller in the schizophrenia global impairment group than the patients with ASD in 18 channels (ch20, ch22 to ch24, ch30 to ch36, ch41, ch43 to ch46, ch51, and ch52; $p < 0.047$) (see Supplementary Fig. S4B, yellow).

As we failed to find any significant difference between the patients with ASD and schizophrenia mild impairment group in terms of both neurocognitive test scores and oxy-Hb changes during the working memory task, we additionally compared the oxy-Hb changes between HCs and the schizophrenia mild impairment group to explore whether the brain area showing attenuated activity in the mild impairment group shows an overlap with that in the ASD. The oxy-Hb changes were significantly reduced in schizophrenia mild impairment group compared to HCs in 6 channels (ch18, ch28, ch29, ch38, ch39, ch49, $p < 0.044$) (Fig. 3), 3 of which overlapped with the channels showing attenuated activity in ASD.

3.7. Correlational analyses of oxy-Hb changes and cognitive function

Including both the patients with ASD and schizophrenia, oxy-Hb changes showed a significant positive correlation with BACS composite scores in 32 channels (ch2, ch12, ch13, ch15, ch17, ch18, ch20, ch22 to ch25, ch28 to ch36, ch39 to ch46, ch48, and ch50 to ch52; $R = 0.205$ to 0.447; 52 channels FDR-corrected $p < 0.031$) in the DLPFC, VLPFC, part of the FPC, and temporal regions (see Supplementary Fig. S5).

Among those channels, multiple regression analyses revealed significant contributions of the BACS composite scores, among other confounding factors, in 31 channels ($\beta = 0.214$ to 0.457; $p < 0.05$) (see Supplementary Table S2).

4. Discussion

We hypothesized that adult patients with ASD or schizophrenia would share detectable abnormalities in both cognitive functioning and working memory-related PFC neural activity and that this neural activity would be related to cognitive abilities in both disorders. To our knowledge, this is the first NIRS study to directly compare ASD and schizophrenia. Our results show that the BACS composite scores of the patients with ASD were higher than those of schizophrenia in general but lower than those of the HCs after controlling for age, sex, education, and estimated premorbid IQ. Additionally, the 2 patient groups both exhibited reduced activity relative to the HCs in the left DLPFC, left FPC, and left IFG during the task but with a milder deficiency in the patients with ASD than in schizophrenia. Moreover, the patients' cognitive function levels, as measured with BACS composite scores, correlated positively with hemodynamic responses in a broad fronto-temporal area.

Our study showed that working memory task-induced increases in oxy-Hb changes in the left DLPFC and left FPC were significantly smaller in the patients with ASD than in the HCs (see Supplementary Fig. S3A), which is in agreement with the previously mentioned results of Koshino et al. (2005). In addition, it is also suggested that both ASD and schizophrenia at least partially share working memory-related prefrontal functional abnormalities associated with cognitive impairments.

It was interesting to find that the PFC region's cognition-induced neural activity was significantly associated with composite cognitive dysfunction in these patients with ASD and schizophrenia even after removing the effect of confounding variables such as age, gender, premorbid IQ, and 2-back task performance.

Among the patients with schizophrenia, we defined 4 neurocognitive subgroups, including a global impairment group, a mild impairment group, and 2 selective impairment groups. Besides cognition these 4 clusters significantly differed in PANSS negative

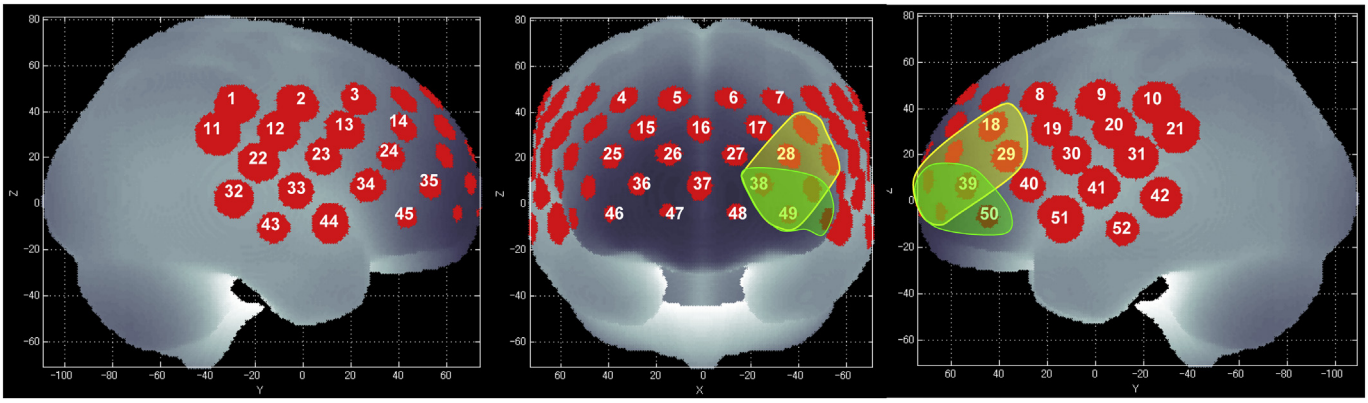

Fig. 3. Three-dimensional topographic maps of the mean oxygenated hemoglobin (oxy-Hb) changes in the prefrontal cortex sub-regions. Study groups were patients with autism spectrum disorder (ASD), healthy controls (HCs), and schizophrenia mild impairment group. The brain area in color corresponds to the near-infrared spectroscopy channels with significantly smaller oxy-Hb changes in yellow the schizophrenia mild group than in the HCs, green the ASD group than in the HCs.

subscale scores. The global impairment group in particular had significantly higher PANSS negative subscale scores than the other subgroups, which is in line with previous studies that suggest severe negative symptoms in patients with schizophrenia might increase the risk for developing more severe and generalized neurocognitive deficits (Harvey et al., 2006; Ventura et al., 2009).

Our results show that the patients with ASD exhibited a similar level of cognitive impairment to that of schizophrenia mild impairment group (Fig. 1). Additionally, the decreased activity was found similarly in the vicinity of left DLPFC and left FPC compared to HCs. These results suggest that adults with ASD and a subgroup of patients with schizophrenia share cognitive impairment profiles and working memory-related prefrontal functional abnormalities. The finding suggests some overlap in the adult populations with ASD and schizophrenia, and the commonality may reflect shared etiological mechanisms. Emerging data (Chisholm et al., 2015; Kincaid et al., 2017; Barlati et al., 2018) suggest that there is a subgroup with ASD symptoms within the group of patients with schizophrenia. We could not assure that this was the case in the present study because we did not assess ASD symptoms in patients with schizophrenia, but the possibility cannot be denied.

To advance the development of assessment of cognitive deficits associated with psychiatric illnesses, it is relevant to identify biomarkers that are applicable to cross-diagnostic entity. In neuropsychiatric research, a biomarker indicates neuronal functions hypothesized to be related to functional domains and can serve as an objective measure of therapeutic candidates' biological effects (Pu et al., 2016; Tregellas et al., 2014). Our current findings indicate that NIRS-measured, working memory-related PFC neural activity may be a useful biomarker for cognitive dysfunction across diagnoses.

Given this study's pathophysiologic implications, we must pause to carefully consider its limitations. First, multichannel NIRS has limited spatial resolution compared to fMRI due to pervasive light scattering in tissue, but unlike fMRI, NIRS is non-invasive and relatively restraint-free. Accordingly, NIRS is better suited for assessing brain function in many patients in psychiatric practice (Ishii-Takahashi et al., 2015; Takizawa et al., 2014). Second, neurocognitive measures were taken primarily from a battery of cognitive tests specifically selected for patients with schizophrenia, and the BACS battery has not been as thoroughly validated in patients with ASD, although this study suggests that it shows promise in this population. Third, the results may have limited generalizability because our ASD group included only individuals with Asperger's syndrome or pervasive developmental disorder not otherwise specified. Fourth, our data are limited by the cross-sectional study design. Longitudinal cohort studies examining the time course of the change in cognition and brain activity is warranted to strengthen our view. Finally, as this study was naturalistic and therefore uncontrolled with respect to drug usage, we cannot rule out drug effects, although we found no differences in oxy-Hb changes with respect to daily dosage level of antipsychotics.

In conclusion, this research indicates considerable similarity in left PFC dysfunction and its association with cognitive deficits between the disorders, with both having particularly marked deficits in the left DLPFC, left FPC or left IFG. These findings may guide future studies that investigate pathophysiological similarities between ASD and schizophrenia.

Conflict of interest

All the authors declare that they have no conflicts of interest with respect to this study or its publication.

Contributors

All authors have approved the final version of the manuscript.

Role of funding source

Funding agencies had no role in study delineation, data collection and analysis, decision to submit the paper to the present journal, or preparation of the manuscript.

Acknowledgement

The authors thank all the participants in this study. The authors also thank the Hitachi Medical Corporation for providing technical advice. This work has been supported by the Intramural Research Grant for Neurological and Psychiatric Disorders of the NCNP (National Center of Neurology and Psychiatry) (23-10 and 26-3 to K.K.), Takeda Science Foundation (2014 to S.P.), Suzuken Memorial Foundation (2017 to S.P.).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.10.007.

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