Title

Detecting brain dysfunction in children with autism spectrum disorders when inferring the mental state of others using near-infrared spectroscopy

Authors

Ryoichiro Iwanaga Ph.D.[1)]

Goro Tanaka Ph.D.[1)]

Hideyuki Nakane MD. Ph.D.[1)]

Sumihisa Honda PhD.[1)]

Akira Imamura MD, PhD.[2)]

Hiroki Ozawa MD, Ph.D.[2)]

Affiliation

1) Division of Physical and Occupational Therapy, Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

2) Division of Neuropsychiatry, Department of Translation Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Address and E-mail address of correspond author

Ryoichiro Iwanaga,

Department Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, 852-8520, Japan,

E-mail: iwanagar@nagasaki-u.ac.jp

The number of figures: 2

The number of table: 1

The number of words in the manuscript: 4977

Specification of fields: Infant, child, and adolescent psychiatry

Running title: Detecting ASD brain dysfunction by NIRS

Abstract

Aims: The purpose of this study was to examine the usefulness of near-infrared spectroscopy (NIRS) for identifying abnormalities in prefrontal brain activity in children with autism spectrum disorders (ASD) as they inferred the mental states of others.

Methods: The subjects were 16 children with ASD aged between 8 and 14 years and 16 age-matched healthy control children. Oxygenated hemoglobin concentrations were measured in the subject's prefrontal brain region by NIRS during tasks expressing a person's mental state (MS-task) and expressing an object's characteristics (OC-task).

Results: There was a significant main effect of group (ASD group vs. control group), with the control group having more activity than the ASD group. However, there was no significant main effect of task (MS-task vs OC-task) or hemisphere (right vs left). Significant interactions of task and group were found, with the control group showing more activity than the ASD group during the MS-task relative to the OC-task.

Conclusions: It was demonstrated by NIRS that there was lower activity in the prefrontal brain area when children with ASD performed MS-tasks. Therefore, clinicians might be able to use NIRS and these tasks for conveniently detecting brain dysfunction related to inferring mental states in children with ASD in clinical settings.

Key words : autism spectrum disorders, near-infrared spectroscopy, prefrontal cortex, child, theory of mind

Introduction

Individuals with Autism Spectrum Disorder (ASD) have been shown to have a consistent deficit in their Theory of Mind (ToM), the ability to attribute an independent mental state to self and others.[1-3] A number of neuroimaging studies using functional magnetic resonance imaging (fMRI), or positron emission tomography (PET) suggest that several areas of the brain including the medial prefrontal cortex (MPFC) contribute to ToM.[4-9] Lower or abnormal activity in the MPFC during ToM tasks in individuals with ASD have also been reported.[10-12] While, activity in the MPFC during the ToM task located in the dorsal subregion in ASD subjects and ventral areas in control subjects previously was reported.[11] Therefore, lower or abnormal activity in the lower MPFC region would seem to indicate abnormalities related to impairment of ToM in individuals with ASD.

Neuroimaging data from PET and fMRI can provide information to help identify brain dysfunction associated with ASD, however, it is difficult or undesirable to apply these techniques to children in the usual clinical setting.[13,14] To investigate brain activity concerning ToM in children with ASD, neuroimaging techniques that can be used in clinical settings are necessary. Recently, several Near-infrared spectroscopy (NIRS) studies have attempted to detect changes in the hemoglobin oxygenation state in the

prefrontal region during emotional or mental tasks.[13,15,16] Because near-infrared light is noninvasive, repeated measurements are possible. Subjects are also maintained under natural conditions during examinations, can perform the tasks and move naturally, and the apparatus is small and portable.[17] NIRS, therefore, has many advantages for measuring the brain activity of children with ASD. In fact, two previous NIRS studies indicated abnormalities of prefrontal brain activity in ASD patients during a letter fluency task and a self-face recognition task.[14,17] Since NIRS could measure activities in a part of the MPFC,[18] it might useful to detect brain activities concerning ToM. Thus, the abnormal activities of the prefrontal area such as MPFC related to inferring mental states in children with ASD might be detectable by NIRS. If the usefulness of NIRS for detecting brain dysfunction related to inferring mental states could be demonstrated, clinicians would be able to use NIRS for examinations in clinical settings in order to better understand brain dysfunction and to acquire neurophysiological information to diagnose ASD. With this goal in mind, we investigated the usefulness of NIRS to detect brain activity related to inferring mental states.

The purpose of this study was to examine the usefulness of NIRS in identifying abnormalities in prefrontal brain activities concerning the inference of mental states in children with ASD that were previously identified by fMRI and PET studies.

Methods

Subjects

A total of 16 children with ASD aged between 8 and 14 years old, and 16 age-matched healthy control children participated in this study (Table 1). The children with ASD were recruited from the Nagasaki Autism Society. The subjects were diagnosed at the Nagasaki City Welfare Center or Nagasaki University Hospital. These children were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders[19] criteria by expert pediatricians or psychiatrists. Seven of them were diagnosed with autistic disorders, and 9 were diagnosed with Asperger's disorder. The diagnoses were confirmed by the first author using diagnostic instruments and screening questionnaires including the Pervasive Developmental Disorder-Autism Society Japan Rating Scale (PARS)[20] which is a diagnostic interview scale for autism spectrum disorders developed in Japan and the Japanese translation of the High Functioning Autism Spectrum Screening Questionnaire (ASSQ-R).[21,22] All respondents to the PARS and ASSQ-R were mothers. The scores of all children with ASD were above the cutoff scores of the two sub-scores of the PARS and ASSQ-R. No subjects had any other neurological or psychiatric disorders, and none of subjects were being medicated. For

the control group, healthy children were recruited from an elementary school and a junior high school in the same community. There were no significant differences between the two groups regarding age and sex. There were also no significant group differences in the full scale IQ, verbal IQ, or performance IQ on the WISC-Ⅲ (Table1). Subjects and their parents gave informed consent according to institutional guidelines of the Ministry of Welfare, Japan. This study received prior approval by the Human Investigation Committee of Nagasaki University Graduate School of Biomedical Sciences.

Tasks and Procedures

The experiment consisted of a 30 sec pre-task baseline, after which the following sequence was repeated 3 times: a 20 sec expression of a person's mental state task (MS-task), a 60 sec baseline, a 20 sec expression of an object's characteristics task (OC-task), and a 60 sec baseline.

In the MS-task, three different photographs of a person's eyes only (black and white) were shown, for example as shown in Figure 1. This task was referred to as the Eye Task in a previous study.[3] Although Baron-Cohen et al.[3] adopted a method to choose between two mental state terms printed under each picture, we used a method

where the subject could comment on the mental state of the presented eye pictures. In the OC-task, three color photographs of objects, a truck, a flower, and a church were used. While each photograph was shown on a screen, subjects were required to express the mental states of a person or to describe an object's characteristics in the photograph. During the pre-task and post-task baseline periods, the Japanese letter for the vowels /a/, /i/, /u/, /e/, and /o/ were presented on the screen, and the subjects were instructed to repeat those sounds.

The subjects sat on a comfortable chair in a dark room with their eyes open during the measurements. Each photograph was projected on a screen in front of the subject 1.5 m away with the projector (EPSON EB-1725) controlled by personal computer using Power Point 2003 (Microsoft). The size of the projected area was 80 cm (width)×60 cm (height; visual angle 29.9×22.6°; 1024 pixels×768 pixels). The photographs of the OC-task were presented in all of the projected area, while eyes only photographs were presented in an 80cm (width) ×34cm (height; visual angle 29.9 × 12.9°) area on a white background.

Before the study, in order to assess the perceived difficulty of these tasks, we asked the opinions of 33 healthy, non-subject volunteers (12 males, 21 females; mean age 21.4 ± 3 years) about the mental state of the people in the MS-task pictures and the difficulty

level of all tasks. The pictures for the MS-task were taken from a face model book published for artists.[23] The healthy volunteers' major comments about each picture were as follows: the first picture (Figure 1) was 'angry' (39%) or 'impatient (27%), the second was a 'blank stare' (38%) or 'neutral' (24%), and the third was 'happy' (79%) or 'showing pleasure' (42%). Because of these results, these pictures were called 'angry' (Figure1), 'blank stare', and 'happy', respectively. The volunteers were asked to rate the difficulties of assessing the feelings associated with each photograph on a scale of 1 (very difficult) to 9 (very easy), referring to the rating scale degree of the International Affective Picture System (IAPS).[24] The mean of the rated difficulty levels of the MS-task (angry, blank stare, happy) and the OC-task (truck, flower, church) were 4.6 ± 1.3 and 4.7 ± 1.2, respectively. There were no significant differences between the difficulty levels of the tasks (t[31]=0.092, *P*=0.927).

Evaluation of responses during tasks

We recorded all comments made by the subjects during the tasks. The words in comments were counted for the MS-task and OC-task. The first and fifth authors judged whether the responses were appropriate or inappropriate in both tasks, while also determining whether responses were emotional expression or non-emotional sentences

in the MS-task. We also counted the number of emotional expression and non-emotional sentences in the MS-task.

NIRS measurements

A 22-channel (CH) NIRS system (Hitachi ETG-4000) was used. The absorption of near-infrared light was measured, and the concentrations of oxygenated hemoglobin (oxy-Hb) and reduced hemoglobin (deoxy-Hb) were calculated. The total-Hb was calculated as the sum of oxy-Hb and deoxy-Hb. The probes measured the relative concentrations of Hb changes at 22 measurement points in a 6 × 12 cm area with 15 probes (3 × 5) on the subjects' frontal regions, with an inter probe distance of 3.0 cm. The lowest probes were positioned along the Fp1-Fp2 line, according to the international 10/20 system. According to Okamoto et al.,[25] the measurement area should include the rostral frontal cortex and dorsal medial prefrontal cortex (Brodmann Areas 9, 10). The absorption of near-infrared light was measured with a time resolution of 0.1 sec. The obtained data were analyzed with the "integral mode" which calculates average waveform. Pre-task baseline was determined by the last 10 sec of the baseline just before the task period. Moving average methods were used to exclude short-term motion artifacts in the analyzed data (moving average: 5 sec). The data that clearly

contained motion artifacts, based on observations and on the NIRS recordings, were excluded from further analyses.

Data analysis

The numbers of generated words during the MS-task and OC-task in each group, and the numbers of ‘emotional expression sentences’ and ‘non-emotional sentences’ generated in the MS-task in each group were analyzed using Two-way analysis of variance (ANOVA). If ANOVA found a main effect or a significant interaction, one-way ANOVA with a Tukey’s HSD post-hoc test was performed to identify significant differences between any combination of group and generated words, or group and expression sentences. And, the ratios of ‘non-emotional sentences’ to total number of commented sentences in the MS-task were compared between the ASD group and control group using Mann-Whitney U test. Differences in the behavioral data between children with an autistic disorder and children with Asperger disorder were analyzed using one-way ANOVA.

In this study, the value of oxy-Hb, which is the most sensitive indicator of regional cerebral blood flow[26] was analyzed. First, the average oxy-Hb waveforms of each subject were calculated by averaging each of the 3 MS-task and 3 OC-task data sets.

The region of interest (ROI) was the central frontal area on and just above the Fp1 and Fp2 line, because this area is positioned on the rostral prefrontal cortex,[25] and might reflect activation in the lower region of the MPFC. The average oxy-Hb changes in task segments in the right hemisphere CHs (CH3, CH8, CH12), and left hemisphere CHs (CH2, CH6, CH11) were calculated. We next analyzed the data with a three-way ANOVA for 'group' (ASD vs. control), 'task' (MS-task vs. OC-task) and 'hemisphere' (right vs. left). If a significant interaction was found, one-way ANOVA with a Tukey's HSD post-hoc test was performed to identify significant differences between any combination of the group, task or hemishere.

In order to determine the relationships between behavior and the brain activities in prefrontal area: the correlation between the number of words in the MS-task and OC-task; the number of emotional expression and non-emotional sentences; and oxy-Hb changes in each hemisphere were analyzed.

All statistical analyses were performed using SPSS for Windows version 19.0 (SPSS, Cicago, IL, USA), and the significance level was set at $P<0.05$.

Results

Behavioral data

The numbers of generated words in the MS-task were 5-42 (22 ±11.7) in the ASD group, and 0-32 (13.9 ± 9.9) in the control group; and 8-55 (26.8 ±12.6) in the ASD group and 4-32 (15.5 ± 9.7) in the control group for the OC-task. Two-way ANOVA revealed a significant main effects by group (F[1,60]=12.69, P=0.001) and no significant main effect by task (F[1,60]=1.381, P=0.245) and no significant interaction effects (F[1,60]=0.302, P=0.585) for the words generated during tasks. One-way ANOVA showed significant differences in the number between 'generated words' in each group and task [F(3,60)=4.791, P=0.005]. The post hoc-test revealed that the word numbers of OC-task in the ASD group were greater than MS-task and OC-task in the control group. The numbers of emotional expression and non-emotional sentences generated in the MS-task were 0-10 (3.5± 2.7) and 0-13 (3.5 ± 3.9) in the ASD group, and 0-10 (4.2 ± 2.7) and 0-4 (1.4 ± 1.2) in the control group. One ASD subject responded with inappropriate emotional responses such as 'She looks happy' for the 'angry' face photograph. Another ASD subject commented on only non-emotional things, and one control subject did not comment (but she was looking at a picture) in the MS-task. There was no significant main effect of 'expression sentences' (emotional expression sentences vs. non-emotional sentences) in the MS-task (F[1,60]=2.675, P=0.107) or 'group' (ASD vs. control) (F[1,60]=2.675, P=0.107). Meanwhile, there was

a significant interaction (F[1,60]=5.243, P=0.026) in ‘expression sentences’ and ‘group’. One-way ANOVA showed significant differences in the number between each ‘expression sentences’ in each group [F(3,60)=3.531, P=0.02]. The post hoc test revealed that ‘non-emotional sentences’ in the control group were fewer than ‘non-emotional sentences’ in the ASD group and ‘emotional expression sentences’ of the control group. The ratio of non-emotional sentences to all expression sentences in the MS-task of ASD group (median=0.473) was significantly higher than in the control group (median=0.200) (Z=-2.415, P=0.016). Subjects with ASD tended to refer to the non-emotional aspects of the images in the MS-task, for instance ‘This is a woman’, ‘She looks down’.

There were no differences in the behavioral data between children with an autistic disorder and children with Asperger disorder.

NIRS data

The top half of Figure 2 shows the grand mean oxy-Hb changes during the MS-task (black line) and the OC-task (dotted line) in the ASD group. The mean values of oxy-Hb changes in ASD group, were lower than 0 during the MS-task period in both hemispheres (right; -0.011 ± 0.028 mM-mm, left; -0.028 ± 0.033mM-mm), while

the oxy-Hb changes were higher than 0 in both hemispheres (right; 0.013 ± 0.03 mM-mm, left; 0.012 ± 0.032 mM-mm) during the OC-task period. The bottom half of Figure 2 shows the grand mean changes in oxy-Hb concentrations during the MS-task (black line) and the OC-task (dotted line) in the control group. The control group showed increasing levels of oxy-Hb changes in both hemispheres during the MS-task period (right: 0.11 ± 0.034 mM-mm, left; 0.083 ± 0.034 mM-mm) and the OC-task period (right: 0.039 ± 0.032 mM-mm, left; 0.037 ± 0.028 mM-mm). For oxy-Hb changes, significant main effects for ‘group’ were observed, where the control group had higher activity than the ASD group (F[1,120] =15.432, P<0.001). No significant effects were seen for either the ‘task’ (F[1,120]=0.534, P=0.466) or ‘hemisphere’ (F[1, 120]=0.419 , P=0.518). For oxy-Hb changes, the ANOVA showed no significant interaction of task × group × hemisphere (F[1,120]=0.013, P=0.911), task × hemisphere (F[1,120]=0.291, P=0.590), or group × hemisphere (F[1,120]=0.026, P=0.873). There was, however, a significant interaction of task × group (F[1,120]=6.368, P=0.013). One-way ANOVA showed significant differences in oxy-Hb changes between each task in each group [F(3, 60)=3.902, P=0.013]. The post-hoc tests revealed that oxy-Hb changes in the MS-task of the ASD group were lesser than the control group (P=0.01), but there were no significant differences among the others.

There were no correlations between the oxy-Hb changes in each hemisphere and behavioral data.

Discussion

This study explored the usefulness of NIRS for detecting the differences in brain activities between children with ASD and children without developmental disorders during the inference of mental states of others.

The MS-task and OC-task were the same in that they expressed opinions about photographs. In addition, there were no significant differences in difficulty levels between the tasks as rated by non-subject controls. The tasks differed, however, in that one required inference of a person's mental state and the other did not. Therefore, the differences in oxy-Hb changes between tasks would seem to indicate cortex activation related to inferring the mental state of others.

The behavioral data indicated that ASD subjects refered more to the non-emotional aspects of the person's eyes images. This might be explained by previous studies that pointed out a deficit in facial emotion recognition in individuals with ASD.[27] ASD subjects tended to comment more in the OC-task than the control group in both tasks. However, these differences were not consistent with oxy-Hb changes that was lesser in

the ASD group than the control group in the MS-task. Furthermore, behavioral data results showed no significant correlation to oxy-Hb changes in each hemisphere. These results suggested no relationship between differences in behaviors and the differences in oxy-Hb changes between both groups in the MS-task. We believe lower oxy-Hb changes in the ASD group than the control group was not caused by brain activity related to word or sentence production.

The interaction of task × group for oxy-Hb changes and post-hoc tests indicates that activation in the prefrontal region was lower in the ASD group relative to the control group during the MS-task. Lower activity in the prefrontal area during the MS-task in the ASD group might have suggest that there is a deficit in prefrontal region activity related to inferring the mental state of others in children with ASD, as reported in previous studies.[10-12] Since the CHs in ROIs were placed in the central position within 3 cm above the Fp1 and Fp2 line, oxy-Hb changes in the ROIs should reflect activation in and above Brodmann's 10 area including the lower region of the MPFC.[25] Therefore, the significant interaction of the task × group for oxy-Hb changes in ROI might reflect the differences in activity in the lower region of the MPFC related to ToM between children with ASD and controls. This result would be consistent with a previous study using fMRI in adults with ASD.[11] Although some previous studies

showed differences in activity in the prefrontal area between hemispheres during ToM tasks,[8,9] there were no hemispheric differences in this study. We had thought that the children with ASD would show lower activity in both prefrontal regions when inferring the mental state of another person while looking at the eye area only.

Therefore NIRS might be able to identify abnormal activity as reported in previous studies with ASD individuals using fMRI,[10-12] NIRS combined with our tasks, could be useful for identifying brain dysfunction related to inferring mental state and for acquiring neurophysiological information to diagnose ASD in the usual clinical settings.

This study has some limitations. The MS-tasks and OC-tasks show differences not only in ‘inferring mental state or not’, but also ‘colored or not’ and ‘facial or not’. Therefore, the results might be affected by other factors unconnected with inferring mental states. Further study excluding those possible affective factors should be conducted.

ACKNOWLEDGMENT

This study was supported by a Grant-in-aid for Young Scientists (B) no. 17790712 from the Japan Society for the Promotion of Science. All authors declare that they have no conflict of interest.

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Figure legends

Figure 1. An example of a picture in mental state task (Angry)

Figure 2. The mean changes in Hb concentrations during the verbal explanation of a mental state (black line) and of an object's characteristics (dotted line). Top half shows data in the ASD group and bottom half shows the control group. A total of 22 channels were mounted on the frontal region (see face illustration). Task periods are shown between the two vertical parallel bars in each graph.

Figure 1.

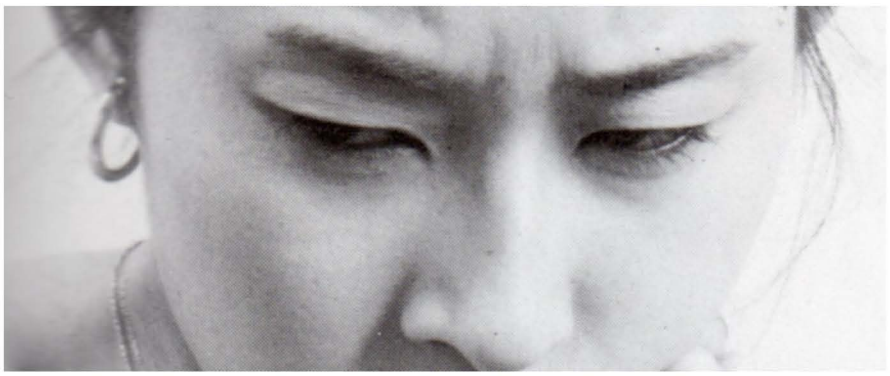

Figure 2.

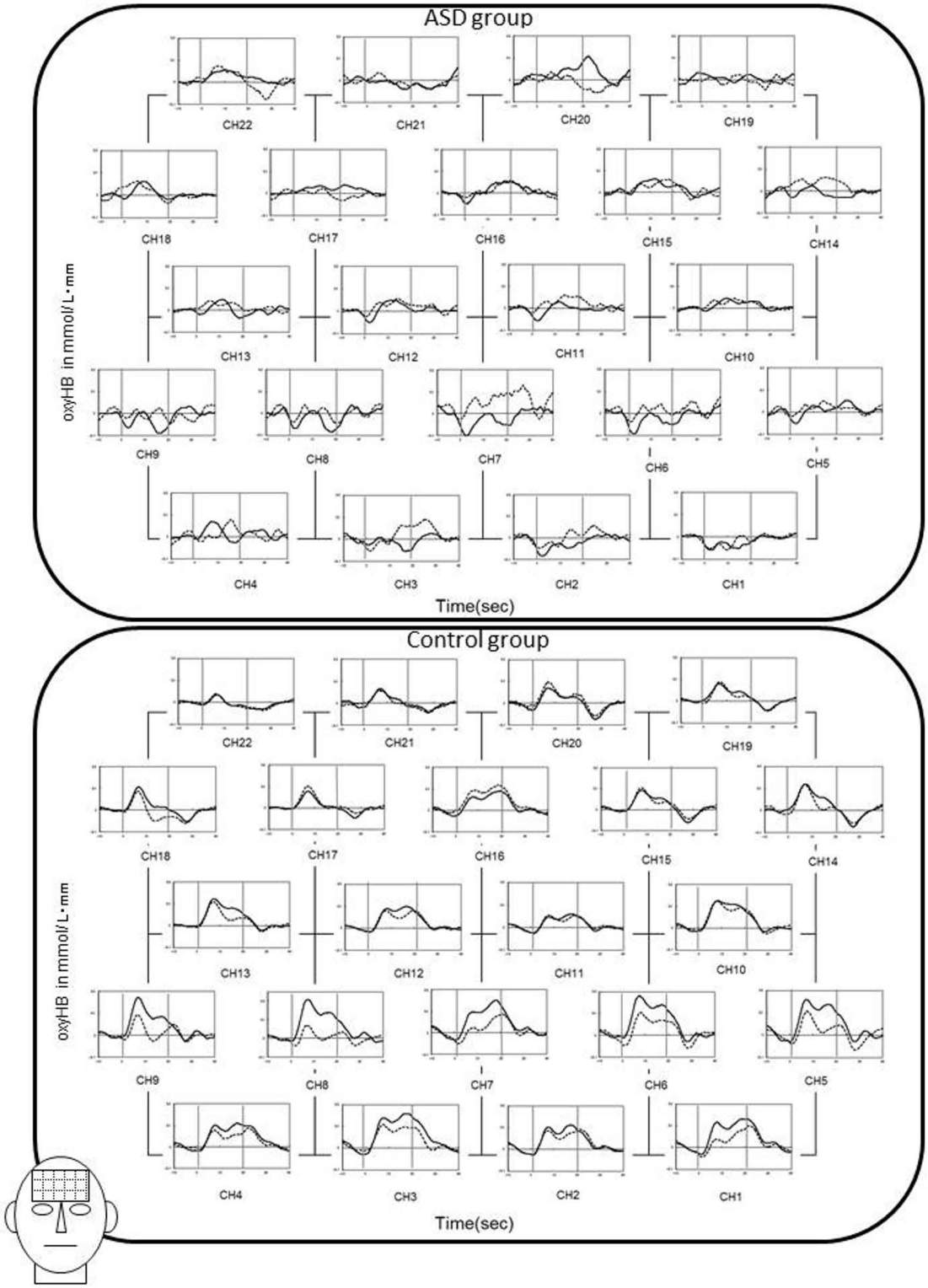
ASD group
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Table 1. Subject characteristics

	ASD	Control	Comparison between ASD and control	
n	16	16		
Sex (M : F)	14:02	12:04	$\chi^2(1) = 0.821$	$P = 0.365$
Age	11.5 ± 1.8 (8–14)	11.4 ± 1.8 (8–14)	$t(30) = 0.34$	$P = 0.736$
Dominant hand (R/L)	15/1	16/0	$\chi^2(1) = 1.032$	$P = 0.310$
WISC-IIIFIQ	100.1 ± 9.8 (86–121)	105.6 ± 5.9 (95–107)	$t(30) = 1.763$	$P = 0.089$
VIQ	99.3 ± 13.8 (83–128)	107 ± 7.2 (91–120)	$t(30) = 1.717$	$P = 0.097$
PIQ	103 ± 12.3 (78–125)	105 ± 7.8 (91–119)	$t(30) = 0.551$	$P = 0.58$
PARS-infant	13 ± 3.8 (9–19)	1.3 ± 1.4 (0–5)	$t(30) = 11.6$	$P < 0.001$
PARS-present	20.6 ± 6.3 (14–35)	1.2 ± 1.8(0–7)	$t(30) = 13.0$	$P < 0.001$
ASSQ-R	26 ± 7.3(19–46)	1.9 ± 2.2(0–9)	$t(30) = 12.5$	$P < 0.001$

ASD, autism spectrum disorder; ASSQ-R, Japanese translation of the High Functioning Autism Spectrum Screening Questionnaire; FIQ, full-scale IQ; PARS, Pervasive Developmental Disorder- Autism Society Japan Rating Scale; PIQ, performance IQ; VIQ, verbal IQ; WISC-III, Wechsler Intelligence Scale for Children–Third Edition.