ASD児の抑制機能課題施行時の右前頭前野の機能低下について :fNIRSを用いた検証

Hypoactivation of the Right Prefronityal Cortex Underlying Motor Related Inhibitory Deficits in Children with Autisum Spectrum Disorder : an fNIRS study

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1. Introduction

Autism spectrum disorder (ASD) refers to a group of neurodevelopmental disorders affecting 0.8–2.0% of school-aged children. According to the Diagnostic and Statistical Manual of Mental Disorders[1] the behavioral phenotype of ASD is characterized by difficulties in social interaction and communication, and stereotyped patterns of behaviors, activities, or interests. According to previous neuropsychological studies on ASD, these behavioral phenotypes, including restricted interests and repetitive behaviors, have been found to be associated with executive dysfunctions. Executive functions (EF) include broadly defined different cognitive processes that mainly involve planning, flexibility, working memory, and inhibition. Most neuropsychological studies have shown that ASD appears to be characterized by poor cognitive flexibility and planning control compared to typically developing (TD) children.

Moreover, from a neurofunctional perspective, functional atypicalities have been increasingly reported to play an important role in the development and course of ASD. Considerable studies have demonstrated that dysfunction in the frontal region would be deeply associated with selective executive dysfunctions, such as impairment of planning, flexibility, and working memory in children with ASD. This evidence collectively suggests that impairment of prefrontal function is the core pathomechanism of executive dysfunction with ASD.

Indeed, neuropsychological and neuroimaging studies performed thus far have suggested the association between ASD and cognitive dysfunction of response inhibition, a core domain of EF. However, this remains a controversial issue. On the one hand, according to a neuroimaging study and to psychological measurements, there is a great deal of evidence demonstrating that inhibitory control function is preserved in ASD. On the other hand, some neuroimaging studies and psychological studies have shown that ASD patients exhibit impairments in response inhibition. Of these neuroimaging studies on response inhibition, to our best knowledge, only two have been performed on children with ASD[2,3]. Given this limited knowledge, more attention should be paid to the neurofunction of the prefrontal cortex with regard to response inhibition in children with ASD.

In contrast to the above, prefrontal hypoactivation in children with attention-deficit hyperactivity disorder (ADHD) has been consistently demonstrated using functional magnetic resonance imaging and functional near-infrared spectroscopy.

In a series of our previous fNIRS studies, we detected neural substrates for response inhibition in TD children: a go/no-go task consistently recruited the right prefrontal cortex[4,5,6]. Furthermore, we have adopted fNIRS measurements to explore inhibition-related hemodynamic responses in children with ADHD. The activation in the right inferior frontal and middle frontal gyrus (IFG/MFG) found in TD was absent in children with ADHD[4,5,6,7]. This activation pattern is consistent with those found in previous fMRI and fNIRS studies.

Hence, in the current study, utilizing the same fNIRS-based measurement that we have thus far adopted for studies on children with ADHD[4,5,6,7], we aimed to visualize neurofunctional differences between ASD and TD children. Moreover, referring to previous results for children with ADHD, we will consider the implications of the current fNIRS study on children with ASD in light of the functional characteristics of cortical hemodynamics in the right PFC reflecting response inhibitory dysfunction in both children with ADHD and ASD.

2. Materials and methods

(1) Participants and ethics

Twenty-four clinically referred, right-handed Japanese pediatric participants with ASD (17 boys, $M_{age} \pm SD = 10.0 \pm 2.8$ years, age range: 6–15 years) were recruited from Jichi Medical University (Shimotsuke, Tochigi, Japan) and the International University of Health and Welfare (Otawara, Tochigi, Japan). The IQ scores of the participants were determined using the Japanese version of the Wechsler Intelligence Scale for Children III and IV (WISC-III and WISC-IV). The two editions contain the same material, with minor differences(correlation coefficients = 0.89 [8]). For the TD group, 24 right-handed TD children (18 boys, $M_{age} \pm SD = 9.6 \pm 1.9$ years, age range: 6–14 years) were matched with the ASD participants according to age, gender and IQ. Some TD participants had also been included in our previous studies[5,6].

Participants were diagnosed by experienced pediatric neurologists based on the DSM-5 criteria[1)]. Diagnoses were complemented by two questionnaires: the Japanese version of the Autism-Spectrum Quotient (AQ-J) and the Pervasive Developmental Disorders Autism Society Japan Rating Scale (PARS). In this study, we used the AQ-J Children's Version, and the mean score of the participants with ASD was significantly higher than that of TD participants (Table 1). The PARS is a semi-structured interview in Japanese assessing the severity of autistic symptoms, and its score correlates with that of the Autism Diagnostic Interview Revised (ADI-R; r = .41[9)]). PARS observations were missing for five ASD participants. PARS was not measured for TD participants. The mean score for the participants with ASD was 24 (*SD* = 8.2, range: 11–42). Medication-naive ASD participants, who did not have histories of other neurological/psychological problems and did not meet the DSM-5 criteria for ADHD, were included in the analyses for the present study.

We obtained written informed consent from all the parental guardians of the participants before the experiment, which was conducted in conformity with the principle of the Declaration of Helsinki and was approved by the Institutional Review Board of Jichi Medical University and the International University of Health and Welfare.

Table1
Demographic data for TD and ASD subjects.

		Gender (male/female)	Age	Full IQ WISC-Ⅲ or Ⅳ	AQ	PARS
TD	Mean	18/6	9.6	102.6	15.3	-
	SD		1.9	13.1	9.1	-
ASD	Mean	17/7	10.0	96.5	29.2	24
	SD		2.8	12.2	7.4	8.2
TD vs ASD	X^2/t	0.105	0.546	-1.663	5.814	-
	p	$0.745^{n.s.}$	$0.588^{n.s.}$	$0.103^{n.s.}$	0.000^{**}	-

t-value and p-value and statistical significance were the results of t-tests between TD and ASD. Abbreviations: SD, standard deviation; t,t-value; p, p-value. Statistical signficances are presented as follows: *, p<0.05; **,p<0.01 and ns, not signficant.

(2) Experimental design

The participants visited either of the two hospitals once and their cortical activation was measured using fNIRS during a go/no-go task. A go/no-go task consisted of six block sets, containing two sub-blocks (go and go/no-go blocks). In the go block, we presented a participant with a random sequence of two animal pictures and asked them to press the space key for both pictures. In the go/no-go block, we presented participants with a no-go picture 50% of the time, thus requesting participants to respond to half the trials (go trials) and inhibit their response to the other half (no-go trials). Pictures were displayed sequentially for 800 ms with an inter-stimulus interval of 200 ms during go and go/no-go blocks. Each sub-block lasted 24 s and was preceded by instructions displayed for 3 s, resulting in an overall block-set time of 54 s and a total session time of about 6 min. Participants responded using the forefinger of their right hand. We generated stimuli and collected responses using E-Prime. Participants were seated approximately 50 cm in front of a 17-in. screen and responded to the stimuli using a keyboard. The experimental design was identical to our previous studies.

(3) fNIRS measurement

We used the multichannel fNIRS system ETG-4000 (Hitachi, Kashiwa, Japan), utilizing two wavelengths of near-infrared light (695 nm and 830 nm). The sampling rate was set at 10 Hz.

We set the fNIRS probes to cover the lateral prefrontal cortices in reference to previous studies[4,5,6,7)], resulting in 22 channels (CH) in each hemisphere. The bilateral probe setting was identical to our previous studies[4,5,6,7)]. After the fNIRS measurement, positional data of illuminators and detectors were obtained for both the ASD and TD participants using a three-dimensional (3D)-digitizer (Fastscan, Polhemus) (Figure 1).

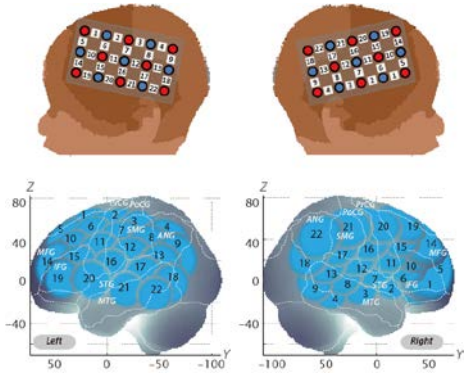

Figure 1. Spatial profiles of fNIRS channels. Left- and right-side views of probe arrangements and channel locations on the brain. Statistically estimated fNIRS channel locations (centers of blue circles) for TD and ASD, and their spatial variability (*SD*, radii of the blue circles) associated with the estimation are exhibited in MNI space.

(4) Analysis of fNIRS data

Oxy-Hb signals were used for further analysis due to their higher signal amplitude than that of deoxy-Hb. We preprocessed individual timeline raw data for the oxy-Hb signals of each channel with a linear polynomial fitting and band-pass filter with cut-off frequencies of 0.01–0.8 Hz to remove baseline drift and heartbeat pulsations in reference to previous studies[4,5,6,7,10)].

We previously reported that activation was observed in the right IFG/MFG among TD children during a go/no-go task[4,5,6,7)]. Thus, we set the right CH10, located at the right IFG/MFG, as a region-of-interest (ROI) for the rest of the study.

We removed the baseline period and go/no-go blocks with sudden, obvious, discontinuous noise based on independent visual examination by two raters.

The preprocessed time series data were transformed into z-scores based on the baseline period from −13 to −3 s after go/no-go block onset. The *z*-scores were calculated using the following formula:

$$z = \frac{\chi_{target} - \mu_{baseline}}{s}, \qquad (1a)$$

where χ_{target} represents the time series data with averaged blocks at each time point during the target period, $\mu_{baseline}$ represents the mean of averaged time series data during the baseline period, and s represents the standard deviation of the baseline period.

From the standardized time series data, we calculated channel- and participant-wise contrasts from the inter-trial mean of differences between the oxy-Hb signals for target (from 4 s to the end of the task after go/no-go block onset) and baseline (14–24 s after go block onset) periods.

(5) Statistical analysis

We performed statistical analyses in a channel-wise manner on oxy-Hb signals. To compare ROI activation for both groups, we performed one-sample t tests against zero (two-tails) with an alpha level set at .05. To examine cortical activation differences between ASD and TD participants, we performed independent two-sample t tests (two-tails) on these contrasts with an alpha level set at .05. For all statistical analyses, we used the SPSS statistics software package.

(6) Behavioral data analysis

We analyzed behavioral data for 44 participants (ASD: 20, TD: 24), excluding the data, which was insufficient, for four ASD patients. We examined the following parameters: (a) reaction time (RT) for go trials; (b) accuracy (ACC) for go trials; and (c) accuracy (ACC) for no-go trials. ACCs and RTs were averaged across go/no-go blocks and subjected to the same statistical analyses as described in the previous section. We performed independent two-sample t tests (two-tails) on ASD and TD with an alpha level set at .05.

3. Results

(1) Behavioral performance

No statistical difference was found between groups for either parameter.

(2) fNIRS analysis

We examined standardized oxy-Hb signal changes in the right CH10 for ASD and TD participants. We found no significant activation in the right CH10 during the go/no-go task period of the ASD participants (one-sample t test, $p > .05$, Cohen's $d = -0.08$), but significant activation in the TD participants (one-sample t test, $p < .05$, Cohen's $d = 0.51$, Table 2, Figure 2). Subsequently, we examined cortical activation differences between ASD and TD participants. Standardized oxy-Hb signal changes in TD participants were significantly higher than in ASD participants (independent two-sample t test, $p < .05$, Cohen's $d = 0.61$).

Table 2

Go/no-go task functional data for TD and ASD subjects.

	TD					ASD					ASD vs. TD	
	N	Mean	SD	t	p	N	Mean	SD	t	p	t	p
Oxy-Hb Changes right CH10 [Z-score]	24	1.869	3.647	2.510	0.020*	24	-0.287	3.439	-0.409	0.686*	-2.107	0.041*

Abbreviations: SD, standard deviation; t,t-value; p , p-value. Statistical signficances are presented as follows: *, p <0.05 Bonferroni-corrected; and ns, not significant.

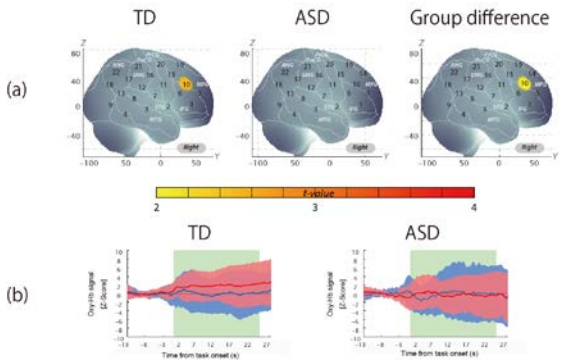

Figure 2. (a) Cortical activation patterns of both participant groups: TD, ASD, and group-level comparison between the ASD and TD groups during a go/no-go task. (b) Waveforms of standardized oxy-Hb (red lines) and deoxy-Hb (blue lines) signals for right CH 10.

4. Discussion

(1) fNIRS hemodynamic response during go/no-go task

Our results demonstrating right PFC activation in TD participants and hypoactivation in ASD participants are consistent with the results of previous fMRI and fNIRS[3] studies of ASD participants performing a go/no-go task. Our findings, together with accumulating indirect evidence, led us to postulate that the hypoactivation in the right IFG/MFG during a go/no-go task might serve as an objective neurofunctional biomarker for ASD.

Intriguingly, the current results are similar to those of our previous fNIRS studies of children with ADHD, where we also observed right prefrontal hypoactivation during a go/no-go tas[4,5,6,7]. These results suggest the possibility that ASD and ADHD share the same neurophysiological characteristics regarding inhibitory dysfunction, at least in right prefrontal response to inhibitory stimuli.

However, it should be noted that not all neural networks for response inhibition are necessarily impaired in the same manner in individuals with ASD and ADHD. Indeed, different types of network impairment have been reported for each disorder. In ADHD research, a number of fMRI studies have revealed that the frontostriatal network is considered to be the core domain of inhibition dysfunction.

In ASD, however, the inhibition network involving the right IFG/MFG, cingulate gyrus, and insula is likely associated with the neurophysiological impairment. The cingulate gyrus is considered to be involved in inhibitory control related to cognitive function, such as monitoring for the occurrence of response conflict in information processing and the detection of conflict between competing response. These findings suggest that the cingulate gyrus is related to the impairments found with ASD.

Furthermore, hypoactivation of the cingulate gyrus in ASD patients is thought to be related to the dysfunction of other EFs, such as working memory and planning, as evidenced in neuropsychological studies and neuroimaging studies, including MRI, positron-emission tomography,

and single-photon emission computed tomography. Therefore, while the right IFG/MFG may be a shared domain for inhibitory dysfunction in ASD and ADHD patients, abnormalities specific to the underlying disorder would be rooted in different functional network levels for each disorder.

Above all, the right IFG/MFG and the cingulate gyrus may both be core network domains of ASD-related inhibitory dysfunction. Further experimental exploration is necessary so as to provide a clearer overall picture of the inhibitory function in ASD and ADHD patients.

(2) Behavioral performance

In the current study, although the fNIRS results for children with ASD revealed atypical activation in the right IFG/MFG, neuropsychological tests led to no significant differences between ASD and TD children. To our knowledge, there have been five neuroimaging studies using a go/no-go task with ASD participants, including the current study. Among them, all have consistently reported reduced activation in the right PFC in ASD participants.

Conversely, no significant differences in behavioral performance between groups were found in any of the above-mentioned studies, with the exception of that by Xiao et al. (2012). Our previous fNIRS studies on children with ADHD have consistently described less activation in the right PFC region of ADHD participants than of TD participants, but we have observed inconsistency in behavioral data. Although the conventional approach aims to reveal a neurophysiological phenotype underlying changes in behavioral parameters, this may not always be possible in developmental disorders, including ASD and ADHD. Rather, brain activation patterns might visualize the mode of inhibition deficits more robustly than behavioral parameters in children with ASD.

5. Conclusion

The present study provides evidence that, relative to TD children, children with ASD exhibit reduced brain activation in the right IFG and MFG during go/no-go task blocks. These findings led us to conclude that inhibitory function is impaired in ASD and the hypoactivation of the right IFG/MFG could be a potential biomarker to assess a neurophysiological phenotype of children with ASD.

6. Notes

This manuscript was published by John Wiley & Sons Australia, Ltd. (©2018 Japanese Psychological Association[11]). The paper was authored by following authors: Tatsuya Tokuda and Drs. Takahiro Ikeda, Yukifumi Monden, Masahiro Hirai, Sakae G Mizushima, Masako Nagashima, Yasushi Kyutoku, Takamichi Taniguchi, Hideo Shimoizumi, Ippeita Dan and Takanori Yamagata. This work won the Best Paper Award, which is the top prize at the Japanese Psychological Association.

References

1) American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC: American Psychiatric Association.
2) Chantiluke, K., Barrett, N., Giampietro, V., Santosh, P., Brammer, M., Simmons, A., … Rubia K. (2015). Inverse fluoxetine effects on inhibitory brain activation in non-comorbid boys with ADHD and with ASD. Psychopharmacology, 232, 2071–2082.
3) Xiao, T., Xiao, Z., Ke, X., Hong, S., Yang, H., Su, Y., … Liu, Y. (2012). Response inhibition impairment in high functioning autism and attention deficit hyperactivity disorder: Evidence from near-infrared spectroscopy data. PLoS One, 7(10)
4) Monden, Y., Dan, H., Nagashima, M., Dan, I., Kyutoku, Y., Okamoto, M., … Watanabe, Y. (2012). Clinically-oriented monitoring of acute effects of methylphenidate on cerebral hemodynamics in ADHD children using fNIRS. Clincal Neurophysiology, 123, 1147–1157.
5) Monden, Y., Dan, H., Nagashima, M., Dan, I., Tsuzuki, D., Kyutoku, Y., … Momoi, M. Y. (2012). Right prefrontal activation as a neuro-functional biomarker for monitoring acute effects of methylphenidate in ADHD children: An fNIRS study. NeuroImage: Clinical, 1, 131–140.
6) Monden, Y., Dan, I., Nagashima, M., Dan, H., Uga, M., Ikeda, T., … Yamagata, T. (2015). Individual classification of ADHD children by right prefrontal hemodynamic responses during a go/no-go task as assessed by fNIRS. NeuroImage: Clinical, 9, 1–12.
7) Nagashima, M., Monden, Y., Dan, I., Dan, H., Tsuzuki, D., Mizutani, T., … Yamagata, T. (2014). Acute neuropharmacological effects of atomoxetine on inhibitory control in ADHD children: A fNIRS study. NeuroImage: Clinical, 6, 192–201.
8) Baron, I. S. (2005). Test review: Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV). Child Neuropsychology, 11, 471–475.
9) Ito, H., Tani, I., Yukihiro, R., Adachi, J., Hara, K., Ogasawara, M., … Tsujii, M. (2012). Validation of an interview-based rating scale developed in Japan for pervasive developmental disorders. Research in Autism Spectrum Disorders, 6, 1265–1272.
10) Nagashima, M., Monden, Y., Dan, I., Dan, H., Tsuzuki, D., Mizutani, T., … Yamagata, T. (2014). Neuropharmacological effect of methylphenidate on attention network in children with attention deficit hyperactivity disorder during oddball paradigms as assessed using functional near-infrared spectroscopy. Neurophotonics, 1, 015001.
11) Ikeda, T., Tokuda, T., Monden, Y., Hirai, M., Mizushima, S. G., … Yamagata T. (2018). Hypoactivation of the right prefrontal cortex underlying motorrelated inhibitory deficits in children with Autism Spectrum Disorder: a functional near-infrared spectroscopy study. Jpn. Psychol. Res. 60, 251–264. doi: 10.1111/jpr.12204