Psychiatry Research: Neuroimaging 203 (2012) 237–240

Contents lists available at SciVerse ScienceDirect

Psychiatry Research: Neuroimaging

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

Brief report

Decreased leftward bias of prefrontal activity in autism spectrum disorder revealed by functional near-infrared spectroscopy

Ryu Tamura [a,b], Hideaki Kitamura [a,c,*], Taro Endo [a], Ryo Abe [a], Toshiyuki Someya [a,c]

[a] Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
[b] Niigata Psychiatric Center, Niigata, Japan
[c] Research Institute for Natural Hazards and Disaster Recovery, Niigata University, Niigata, Japan

ARTICLE INFO

Article history:
Received 17 December 2010
Received in revised form 29 November 2011
Accepted 18 December 2011

Keywords:
Pervasive developmental disorder
Imitation
Cerebral lateralization

ABSTRACT

Hemodynamic responses in rostral prefrontal cortex (RoPFC) were measured by functional near-infrared spectroscopy. Although performance level was equal, autistic patients showed a decrease in leftward bias of the balance between right and left RoPFC activity when compared with typically developing children when anatomical imitation was contrasted with mirror-image imitation.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by qualitative impairments in reciprocal interactions and communication as well as repetitive and stereotyped behaviors. As to neural substrate, subcortical structures such as the amygdala–hippocampus region (Endo et al., 2007), the thalamus (Tamura et al., 2010) and other cortical regions including the mirror neuron system (MNS) have been examined as potential foci of interest for autism spectrum disorder (ASD). However, the rostral prefrontal cortex (RoPFC) is also involved in higher cognitive processing, and willed action may also be involved (Dumontheil et al., 2008). Postmortem studies in ASD patients have shown minicolumn abnormalities in the RoPFC (Brodmann area (BA) 10) and the adjacent prefrontal cortex (PFC) (BA 9 (Casanova et al., 2006)). These findings form the basis for investigating these regions in patients with ASD (Casanova et al., 2006). Moreover, the RoPFC may be susceptible to developmental abnormalities because of its prolonged maturation period (Dumontheil et al., 2008).

In the context of ASD, the RoPFC has been investigated predominantly through the use of word fluency tasks (WFT) (Kawakubo et al., 2009). These tasks act as a common probe for executive function, which is thought to activate the RoPFC. However, WFTs are not specifically related to the psychopathology of ASD, and the RoPFC is involved in a wide range of other functions including willed action, executive control (Burgess et al., 2007) and intentional imitation (Chiavarino et al., 2007). Impairments in imitation and the associated involvement in the MNS have been implicated in ASD (Iacoboni and Dapretto, 2006; Rizzolatti et al., 2006; Williams et al., 2006; Verhoeven et al., 2010); however, there are ongoing debates regarding these findings (Southgate and Hamilton, 2008), especially on the other brain regions beyond narrowly defined MNS. Therefore, within the present study we sought to measure hemodynamic responses in the RoPFC during two kinds of intentional imitation tasks of hand motion, anatomical imitation (AI) and mirror-image imitation (MI), with functional near-infrared spectroscopy (fNIRS), a methodology that enables the subjects to freely move their hands in a natural position. To our knowledge, this is the first fNIRS study to examine the issue in detail. We assume that a remaining component by subtracting MI from AI would represent an executive process of looking from the other person's viewpoint.

It is hypothesized that functional hemispheric difference in the RoPFC may be revealed when ASD patients and typically developing individuals are examined with tasks emphasizing the above component. The rationale for investigating the hemispheric differences in the RoPFC is derived from two major fields. One is from the findings that brain regions closely connecting with the RoPFC show significant differences in structural and functional asymmetry between ASD and control subjects. Of the three brain regions densely connecting with the RoPFC (the superior temporal gyrus (STG) through the extreme capsule, the amygdala through the uncinate fasciculus, and the anterior cingulate gyrus (ACG) through the cingulate fasciculus (Petrides and Pandya, 2007)), asymmetric activation of the STG have been well documented in ASD.

The other rationale derives from findings about the size and the white matter integrity of the corpus callosum (CC). A meta-analysis found a significantly small CC in autism, with the greatest reduction

* Corresponding author at: Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Chuo-ku, Niigata 951-8510, Japan. Tel.: +81 25 227 2213; fax: +81 25 227 0777.
E-mail address: kitamura@med.niigata-u.ac.jp (H. Kitamura).

0925-4927/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2011.12.008

of the rostral body containing motor neurons from the PFC (Frazier and Hardan, 2009). Diffusion tensor imaging studies also revealed microstructural abnormalities of inter-hemispheric white matter, even in high-functioning autistic children: reduced fractional anisotropy (FA) and increased mean diffusivity of the genu of the CC (Alexander et al., 2007), and higher apparent diffusion coefficient and lower white matter density of the anterior third transcallosal fiber tracts (Hong et al., 2011). Reduced FA of the CC was found concurrently in white matter adjacent to the ventromedial PFC as well as in ACG, the STG and the temporal lobes approaching the amygdala (Barnea-Goraly et al., 2004), which are known to connect with the RoPFC as mentioned before. These studies suggest that functional lateralization may be present in the RoPFC and may play a crucial role in controlling hierarchically lower brain regions such as the ACG, the STG, and the amygdala.

2. Methods and materials

2.1. Subjects

Twenty right-handed patients (M/F 16/4; age 10.2 ± 3.4 years; Intelligence Quotient (IQ) 100.2 ± 11.5) and 20 controls (M/F 16/4; age 9.5 ± 2.5 years; IQ 102.6 ± 8.1) participated in the study. IQ was measured using the Japanese version of the Wechsler Intelligence Scale for Children (third edition). Independent two-sample *t*-tests revealed no group differences in age or IQ between the controls and patients (age: $t = -0.72$, d.f. = 38, $P = 0.47$; IQ: $t = 0.77$, d.f. = 38, $P = 0.44$). All patients were high-functioning (IQ > 70) and met the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) criteria for pervasive developmental disorders (PDD): six with autistic disorder; nine with Asperger's disorder and five with unspecified PDD, without any history of neurological disorders. The controls were recruited from the local community and screened through an interview with each subject by a child psychiatrist. Only subjects who showed no autistic traits on the Autism Screening Questionnaire (mean score 3.9) and had no family history of PDD participated in the study. All procedures were approved by the Ethics Committee of the Niigata University. Written informed consent was obtained from all subjects and their parents.

2.2. Imitation tasks

The AI and MI tasks employed were based on tasks used in a previous study (Hamilton et al., 2007), but were modified for fNIRS measurements. In the original study by Hamilton et al., individual subjects were required to do two kinds of imitation tasks with two circular targets vertically or horizontally placed on a table in front of the subjects. Task performances were also separately rated for vertical and horizontal conditions. In contrast, we simultaneously placed four targets in a rhomboid configuration (two targets were vertically positioned, while the others were horizontally positioned) because of the limited time of the NIRS experiment and the absence of any hypothesis about differences in target positions (vertical or horizontal).

In the AI task, the subjects were required to match the anatomical position of their hands to those of a model shown on a monitor (with the subject's right side corresponding to the model's right side). Four circular targets were placed on a table in a rhomboid configuration in front of the subjects. One pair of targets was vertically positioned 30 cm apart, while the other pair was horizontally positioned 50 cm apart. One-handed actions could be performed with either the right or left hand, and were directed towards the ipsilateral/contralateral target or the proximal/distal target. Two-handed movements directed to the horizontal targets could be crossed or uncrossed, while the right- and left-hand movements to vertical targets were either directed to the proximal/distal or the distal/proximal targets. The MI task followed a similar procedure whereby the participants were required to mirror the position of their own hands to those of a model, in terms of the position relative to the circular targets on the monitor (with the observer's right side corresponding to the model's left side). Our underlying assumption for these tasks is that AI and MI share common perceptual and motor components except for an additional component contained exclusively in the AI task, looking from the other person's viewpoint.

The participants were required to do one hand action trial for 5 s and repeat it 12 times for 60 s of the one task block (four trials with left hand only, four trials with right hand only and four trials with both hands). There was a 60-s task block per AI or MI in the individual participants. A 3-min resting segment was inserted between the first and second activation conditions. The order of the two task blocks was counterbalanced among the subjects. We determined the accuracy of task performance by viewing the digital videos. For both tasks touching wrong targets and delayed trials exceeding 5 s were all regarded as errors. The intra-rater reliability of scoring task performance was 0.92.

2.3. fNIRS measurements and data analysis

A NIRO-200 system (Hamamatsu Photonics K.K., Japan) with near-infrared light emitted at three different wavelengths (775, 810, and 850 nm) was used to measure the concentrations (μmol/l) of oxygenated hemoglobin ([O_2Hb]) and deoxygenated hemoglobin ([HHb]) in the PFC. Two pairs of emission and detection probes placed 3 cm apart were symmetrically attached to the forehead of the subjects. According to the 10–20 system, one detection probe was located at Fp1 and the corresponding emission probe at F7, while the other pair of probes was located at Fp2-F8. This placement of the probes allowed us to measure largely from a rostral part of the superior or middle frontal gyrus (BA 10) (Okamoto et al., 2004). Data were sampled at intervals of 0.5 s. Baseline correction was made by using linear fitting based on the two baseline data (the pre-task baseline: the mean across a 10-s period just before the activation period; the post-task baseline: the mean across a 10-s period after the 60-s activation period). In temporal smoothing, moving average methods were applied to remove short-term motion artifacts and to correct fluctuations in the analyzed data (moving average window: 5 s).

After baseline correction and temporal smoothing, we calculated the average of [O_2Hb] and [HHb] changes from baseline in each subject during AI ($\Delta[O_2Hb]_{AI}$ and $\Delta[HHb]_{AI}$) and MI ($\Delta[O_2Hb]_{MI}$ and $\Delta[HHb]_{MI}$) across the whole task segment of 60 s. We considered $\Delta[O_2Hb]_{AI}$–$\Delta[O_2Hb]_{MI}$ and $\Delta[HHb]_{AI}$–$\Delta[HHb]_{MI}$ as an index of looking from the model's point of view as mentioned before. Two-way repeated-measures analysis of variance (ANOVA), using hemisphere (left and right) as a within-subjects factor and diagnosis as a between-subjects factor (patients and controls) was performed. In case of significant interactions between both factors, post hoc analysis using independent two-samples *t*-test and paired *t*-test was applied to evaluate simple main effects of diagnosis (separately for the left and right PFC) and hemisphere (separately for the controls and patients) respectively. Correlation between demographic, clinical and task performance data, and the index defined before was evaluated with the Pearson's correlation coefficient. All statistical tests were performed by SPSS software. *P*-values less than 0.05 indicated statistical significance.

3. Results

The number of successful trials (ranging between 0 and 12) did not differ between the two groups during either the AI task (ASD, 5.7 [2.9]; controls, 5.7 [3.1]; $t = 0.00$, d.f. = 38, $P = 1.00$) or the MI task (ASD, 12 [0.0]; controls, 12 [0.0]). The waveforms of the means per 10 s of the $\Delta[O_2Hb]_{AI}$–$\Delta[O_2Hb]_{MI}$ and the $\Delta[HHb]_{AI}$–$\Delta[HHb]_{MI}$ are shown in Fig. 1. The mean values ± standard deviation (S.D.) of the $\Delta[O_2Hb]_{AI}$–$\Delta[O_2Hb]_{MI}$ and the $\Delta[HHb]_{AI}$–$\Delta[HHb]_{MI}$ in the ASD patients and the controls were as follows: right [O_2Hb], [HHb] in the patients: 0.28 ± 0.95, 0.01 ± 0.30; left [O_2Hb], [HHb] in patients: 0.19 ± 0.66, −0.04 ± 0.21; right [O_2Hb], [HHb] in controls: −0.01 ± 0.67, −0.16 ± 0.34; left [O_2Hb], [HHb] in controls: 0.26 ± 0.67, 0.02 ± 0.31 μmol/l; respectively. Note that the ASD patients seem to show an early peak particularly for O_2Hb, while the opposite seems to be true for the controls (i.e., the time course shows an additional late peak within the second half of the task block).

ANOVA demonstrated a significant interaction between diagnosis and hemisphere in both $\Delta[O_2Hb]_{AI}$–$\Delta[O_2Hb]_{MI}$ and $\Delta[HHb]_{AI}$–$\Delta[HHb]_{MI}$ ($F = 5.82$, d.f. = 1, 38, $P = 0.02$ and $F = 7.38$, d.f. = 1, 38, $P = 0.01$; Fig. 1), but there were no main effects of diagnosis and hemisphere. There was no significant difference between the control and patient groups for either the left ([O_2Hb], [HHb]: $t = 0.41$, d.f. = 19, $P = 0.68$, $t = 0.79$, d.f. = 19, $P = 0.43$) or right side ([O_2Hb], [HHb]: $t = -1.08$, d.f. = 19, $P = 0.28$, d.f. = 19, $t = -1.80$, $P = 0.08$). In contrast, a significant difference was seen between the left and right PFC in controls, but not in ASD patients (controls [O_2Hb], [HHb]: $t = 2.23$, d.f. = 19, $P = 0.03$, $t = 2.52$, d.f. = 19, $P = 0.02$; ASD patients [O_2Hb], [HHb]: $t = -1.23$, d.f. = 19, $p = 0.23$, $t = -1.09$, d.f. = 19, $P = 0.28$). Note that O_2Hb values appear to be higher on the left than the right side in controls, while HHb values seem to be more negative on the right than on the left side.

The number of successful trials with the AI task was correlated with age in both groups (ASD: $r = 0.50$, $P = 0.02$; controls: $r = 0.54$, $P = 0.01$), but only with the $\Delta[O_2Hb]_{AI}$–$\Delta[O_2Hb]_{MI}$ in the right PFC in the ASD group ($r = 0.50$, $P = 0.03$). There are no significant correlations between IQ and hemoglobin, while age is significantly correlated with left and right [O_2Hb] (left: $r = 0.32$, $P = 0.04$; right: $r = 0.49$, $P = 0.00$), but not [HHb].

4. Discussion

In the present study, individuals with ASD showed a decrease in leftward bias of the balance between right and left RoPFC activity when compared with normal subjects when [O_2Hb] change during