REVIEW

Neuroimaging in autism spectrum disorders :^{1}H-MRS and NIRS study

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Abstract : Using proton magnetic resonance spectroscopy (^{1}H-MRS), we measured chemical metabolites in the left amygdala and the bilateral orbito-frontal cortex (OFC) in children with autism spectrum disorders (ASD). The concentrations of N-acetylaspartate (NAA) in these regions of ASD were significantly decreased compared to those in the control group. In the autistic patients, the NAA concentrations in these regions correlated with their social quotient. These findings suggest the presence of neuronal dysfunction in the amygdala and OFC in ASD. Dysfunction in the amygdala and OFC may contribute to the pathogenesis of ASD. We performed a near-infrared spectroscopy (NIRS) study to evaluate the mirror neuron system in children with ASD. The concentrations of oxygenated hemoglobin (oxy-Hb) were measured with frontal probes using a 34-channel NIRS machine while the subjects imitated emotional facial expressions. The increments in the concentration of oxy-Hb in the pars opercularis of the inferior frontal gyrus in autistic subjects were significantly lower than those in the controls. However, the concentrations of oxy-Hb in this area were significantly elevated in autistic subjects after they were trained to imitate emotional facial expressions. The results suggest that mirror neurons could be activated by repeated imitation in children with ASD. J. Med. Invest. 62 : 29-36, February, 2015

1. INTRODUCTION

Recently, proton magnetic resonance spectroscopy (^{1}H-MRS) has been used to examine brain metabolism in patients. The main metabolites that can be assessed using this technique are N-acetylaspartate (NAA), creatine/phosphocreatine (Cr), and choline-containing compounds (Cho). The NAA signal, the most prominent ^{1}H spectral peak, is present at high concentrations in neurons, and might be related to mitochondrial function. Therefore, NAA is often used to assess neuronal density (1). The intensity of the Cho signal, which might indicate glial cell density (1, 2), increases with an increase in membrane synthesis and turnover (3). The Cr signal might reflect glial or overall (neurons plus glia) cell density (1, 2) ; phosphocreatine represents a key component of high-energy phosphate metabolism (4). ^{1}H-MRS studies often use Cr as an internal reference for other peaks, on the assumption that its concentration is relatively constant.

Brothers (5) proposed a network of neural regions that comprise the "social brain", which includes the amygdala−the center of limbic system−, the orbito-frontal cortex (OFC), and the superior temporal sulcus and gyrus (STG). Since the psychiatric condition of autism spectrum disorders (ASD) involves deficits in "social intelligence", it is plausible that ASD may be caused by an abnormality of these regions. We used ^{1}H-MRS to investigate metabolism in the amygdala and OFC of subjects with ASD and healthy control subjects, and compared the amounts of chemical metabolites (6). We also examined the association between these metabolic findings and intellectual and social abilities in subjects with ASD (6).

It has recently been proposed that dysfunction of the mirror neuron system (MNS) early in development could give rise to the cascade of impairments that are characteristic of ADS (7), including deficits in imitation, theory of mind and social communication. First discovered in the ventral premotor cortex (area F5) of the macaque, mirror neurons fire both while a monkey performs goal-directed actions and while it observes the same actions performed by others. This observation-execution matching system is thought to provide a neural mechanism by which others' actions and intentions can be automatically understood (8). The existence of an analogous MNS in humans has been demonstrated by a number of independent investigations (8) : MNS activity in human homolog of area F5−the pars opercularis in the inferior frontal gyrus−has been consistently reported during imitation, action observation and intention understanding (9, 10). In concert with activity in limbic centers, the MNS is considered to mediate our understanding of the emotional states of others (11, 12). Dapretto *et al.* used an event-related functional magnetic resonance imaging (fMRI) design to investigate neural activity during the imitation and observation of facial emotional expressions, in high-functioning children with ASD and typically developing children, and reported that activity in bilateral pars opercularis of the inferior frontal gyrus was seen in the typically developing group but not in the ADS group (13). We performed a near-infrared spectroscopy (NIRS) study to evaluate MNS in children with ASD (14).

¹H-MRS study

2. MATERIALS AND METHODS

2.1. Subjects

The study group included 77 autistic patients (3 to 6 years old ; mean age 4.1 ; 57 boys and 20 girls). These individuals were recruited from among outpatients at the Department of Pediatrics of Tokushima University. All subjects in this group were diagnosed with autistic disorder by two experienced pediatric neurologists according to the criteria of DSM-Ⅳ-TR. The intelligence quotient (IQ) was determined by the Tanaka-Binet intelligence scale; mean IQ$\pm$SD=61$\pm$20 (24~110). Social ability of the autistic patients was evaluated with a social maturity scale (Nihon Bunka Kagakusha) ; (S-M scale). The mean social quotient (SQ)$\pm$SD=60$\pm$17 (20~100).

The control subjects were 31 children underwent an MRI examination because of a non-specific temporal symptom such as headache or vertigo, but showed no neurological findings and were confirmed by experienced pediatricians to have no autistic traits. Ages and genders (3 to 6 years old ; mean age 4.0 ; 23 boys and 8 girls) were matched with those of autistic patients.

A routine MRI examination was conducted for all subjects to confirm the absence of organic disease, and the MRS measurement was conducted immediately afterwards. None of the nominated control subjects showed any abnormalities or symptoms during observation for more than one month and thus data from all control subjects were used as normal control data. Most of the subjects were sedated with triclofos sodium (Tricloryl, 0.5 mL/kg body weight) 30 min before the MR measurement, following the guidelines for monitoring and management of pediatric patients during and after sedation published by the American Academy of Pediatrics (15).

This study was approved by the Institutional Review Board (No. 207) and informed consent for additional MRS measurements and data analysis were obtained from the parents of all subjects, following the approved procedures. Informed consent was also obtained from the subjects who could understand the content and purpose of this study.

2.2. ¹H-MRS measurement

All ¹H-MRS studies were performed with a 1.5-tesla clinical MRI system (Signa Horizon, GE, Milwaukee, WI) with a standard head coil for both of MRI and MRS measurements. Conventional proton MR spectra were obtained using the STEAM (Stimulated Echo Acquisition Mode) sequence with parameters of TR=5 sec, TE=15 msec and sum of signals=48 to diminish the influence of the longitudinal and transverse relaxation (16). We analyzed NAA, Cr, and Cho concentrations using the external standard calibration method in LCModel (Ver. 6.1). We acquired T1 and T2 MRI images in axial and coronal views before the ¹H-MRS examination, and placed a single 3.4 ml (1.5$\times$1.5$\times$1.5 cm) volume of interest (VOI) in the left amygdala (Fig. 1). Furthermore, we also placed a single 4.5 ml (2.0$\times$1.5$\times$1.5 cm) VOI in each OFC (Fig. 1). The criteria for maintaining reliable metabolite concentrations were based on the %SD of the fit for each metabolite reflecting the Cramer-Rao lower bounds (CRLB) ; only results with S.D. below 20% were included in the analysis.

2.3. Statistical analysis

We compared autistic patients with control individuals with respect to the concentrations of NAA, Cho, and Cr. We used Student's t-test to determine statistically significant differences between autistic patients and the control group. Paired t-test was used to determine statistically significant differences between the concentrations of metabolites in the left OFC and those in the right OFC. A value of p below 0.05 was considered statistically significant. Furthermore, we examined the correlation between the concentration of NAA and IQ and SQ in autistic patients using Pearson's correlation coefficient.
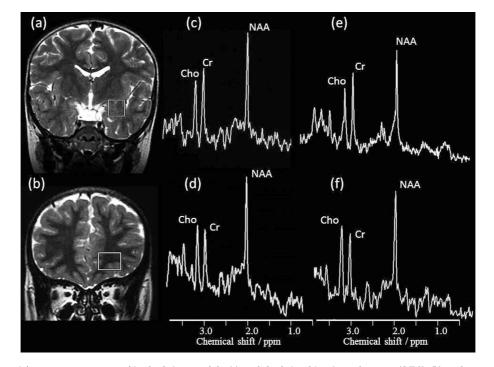

Fig. 1.　Location of the measurement voxel in the left amygdala (a) and the left orbito-frontal cortex (OFC) (b) and representative spectra obtained. (c), MR spectrum from the left amygdala in a control subject ; (d), MR spectrum from the left OFC in a control subject ; (e), MR spectrum from the left amygdala in an autistic patient ; (f), MR spectrum from the left OFC in an autistic patient.
The peaks of NAA from both regions in an autistic patient were slightly low compared to those in a control subject.
NAA, N-acetylaspartate ; Cr, creatine/phosphocreatine ; Cho, choline-containing compounds.

3. RESULTS

The baseline MRI was evaluated individually by two experienced pediatric neurologists and one neuroradiologist. No abnormal signal or distinct atrophy was detected in the brain of autistic patients or control individuals at the time when ^{1}H-MRS studies were performed.

The concentrations of NAA for the left amygdala and the bilateral OFC in autistic patients were significantly decreased compared to those in the control group (Table 1, Fig. 2).

We investigated the relationship between IQ and NAA concentration in autistic patients. NAA concentration for the left amygdala and the left and right OFC in autism was correlated with IQ. The correlation coefficient was 0.368 ($p = 0.002$), 0.415 ($p = 0.001$), 0.530 ($p < 0.0001$), respectively (Figs. 3-5).

We also investigated the relationship between SQ and NAA concentration in autistic patients. NAA concentration for the left amygdala and the left and right OFC in autism was correlated with SQ. The correlation coefficient was 0.623 ($p < 0.0001$), 0.601 ($p < 0.0001$), 0.522 ($p < 0.0001$), respectively (Figs. 3-5). The correlation coefficient between SQ and NAA concentration was higher than that between IQ and NAA concentration in the left amygdala and the left OFC.

There was no significant difference in the concentration of any metabolite between the left and right OFC in autism and control groups. There was no significant difference in the concentration of Cho and Cr for any region between autism and control groups (Table 1).

Table 1   The summarized results for the quantitative values of each metabolite.

	Left amygdala		Left OFC		Right OFC	
	autism	control	autism	control	autism	control
NAA	6.9±0.9**	7.5±1.0	7.4±1.1**	8.1±1.2	7.4±1.2**	8.3±1.3
Cr	5.9±0.9	5.9±0.8	5.5±1.2	5.5±0.8	5.6±1.0	5.8±1.0
Cho	2.1±0.3	2.2±0.4	2.1±0.4	2.0±0.4	2.1±0.5	2.1±0.5

Data are presented as mean ± standard deviation.
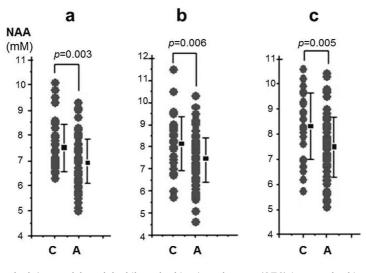OFC, orbito-frontal cortex ; **, $p < 0.01$

Fig. 2.   NAA concentrations for the left amygdala and the bilateral orbito-frontal cortex (OFC) in control subjects and autistic patients. (a), the left amygdala ; (b), the left OFC ; (c), the right OFC.
The concentrations of NAA for the left amygdala and bilateral OFC in autistic patients were significantly decreased compared to those in the control subjects.
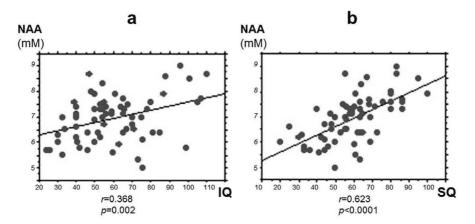C, control subjects ; A, autistic patients.

Fig. 3.   Correlation between IQ, SQ, and NAA concentration of the left amygdala in autistic patients.
(a) : A significant correlation was confirmed between intelligence quotient (IQ) and NAA concentration. (b) : A significant correlation was also confirmed between social quotient (SQ) and NAA concentration.
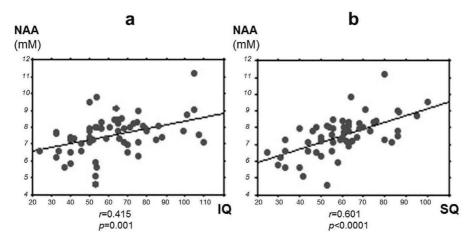
Fig. 4.   Correlation between IQ, SQ, and NAA concentration of the left orbito-frontal cortex in autistic patients.
(a) : A significant correlation was confirmed between intelligence quotient (IQ) and NAA concentration. (b) : A significant correlation was also confirmed between social quotient (SQ) and NAA concentration.
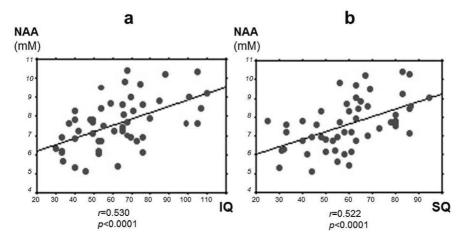

Fig. 5.   Correlation between IQ, SQ, and NAA concentration of the right orbito-frontal cortex in autistic patients.
(a) : A significant correlation was confirmed between intelligence quotient (IQ) and NAA concentration. (b) : A significant correlation was also confirmed between social quotient (SQ) and NAA concentration.

NIRS study

4. MATERIALS AND METHODS

4.1. Subjects

The subjects consisted of ten high-functioning boys with autistic disorder (9 to 14 years old ; mean age 11.5) and ten normally developing boys (9 to 14 years old ; mean age 11.8). The high-functioning boys with autistic disorder were recruited from among outpatients at the Department of Pediatrics of Tokushima University. All subjects in this group were diagnosed with autistic disorder by two experienced pediatric neurologists according to the criteria of DSM-IV-TR. The intelligence quotient (IQ) was determined by the Wechsler Intelligence Scale for Children third edition ; mean full-scale $IQ \pm SD = 82.5 \pm 9.1$ $(70 \sim 95)$. The control subjects were confirmed by experienced pediatricians to have no autistic traits. This study was approved by the Institutional Review Board (No. 1617) and informed consent for NIRS measurements and data analysis were obtained from the parents of all subjects. Informed consent was also obtained from the subjects who could understand the content and purpose of this study.

4.2. NIRS measurement

The NIRS measurement was performed using a 34-channel NIRS system (Shimazu NIRStation OMM-3000-12 ; Kyoto, Japan). Twelve probes (3×4) were set on the left and right frontal region, respectively, with an inter-probe distance of 3.0 cm. The lowest probes were positioned along the Fp1-Fp2 line in accordance with the international 10/20 Electrode Placement System for electroencephalography. The distance from the midline to the most medial probe was 3.0 cm. The position of each channel was shown on 3D-MRI by the analysis software of NIRStation⁺Fusion (Fig. 6).

The experiment consisted of a 30-s pre-task baseline, a 60-s imitation of emotional facial expression task, and a 30-s post-task baseline. This procedure was repeated five times. During the pre-task and post-task baseline periods, an asterisk was presented on the screen, and the subjects were instructed to stare the mark. The emotional facial expressions of Japanese were selected from Japanese and Caucasian Facial Expressions of Emotion and Neutral Faces (17). These stimuli consisted of six kinds of emotional facial expressions (happiness, sadness, surprise, anger, disgust and fear). During the task periods, the emotional facial expressions were presented on the screen in a random order at 5-s intervals, and the subjects were instructed to imitate the emotional facial
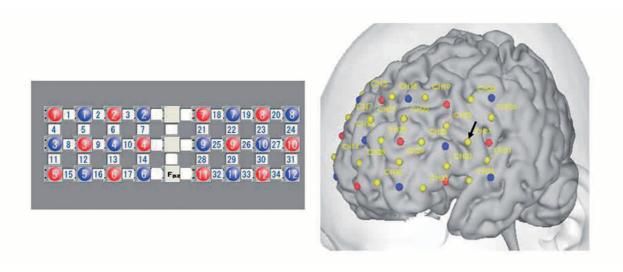
Fig. 6.   Optic probe position of a 34-channel NIRS system.
Twelve probes (3×4) were set on the left and right frontal region, respectively. The red and blue numbers indicate the position of sources and detectors, respectively. The arrow shows Ch27 on the left pars opercularis of the inferior frontal gyrus.

expressions. The obtained data were analyzed in the integral mode, which calculates average waveform. Pre-task baseline was determined by the last 10 s of the baseline just before the imitation task period.

After the first NIRS measurement, autistic patients were trained to imitate emotional facial expressions used in this NIRS experiment. The duration of the training was 30 minutes, and the training was done twice a week. The second NIRS measurement was performed after the trainings were carried out five times.

4.3. Statistical analysis

We compared autistic patients with control individuals with respect to the increments in the concentration of oxygenated hemoglobin (oxy-Hb) during the imitation task of emotional facial expressions. We used Student's t test to determine statistically significant differences between autistic patients and the control group. A value of p below 0.05 was considered statistically significant.

5. RESULTS

Representative hemoglobin concentration changes during the imitation task of emotional facial expressions in the subjects with autistic disorder and control are shown in Fig. 7. The increments in the concentration of oxy-Hb in the pars opercularis of the inferior frontal gyrus in autistic subjects were significantly lower than those in the controls (Fig. 8). However, the concentrations of oxy-Hb in this area were significantly elevated in autistic subjects after they were trained to imitate emotional facial expressions (Fig. 8).

6. DISCUSSION

The present ^{1}H-MRS study has two major findings : 1) decreased concentrations of NAA in the left amygdala and bilateral OFC in subjects with ASD ; and 2) a positive correlation between the concentrations of NAA in these regions and the SQ as determined by the S-M scale. NAA is present at high concentrations in neurons and is often used as a chemical marker of neuronal integrity (1). A decreased NAA concentration suggests abnormal neurodevelopment in this region. Therefore, our findings suggest that subjects

with ASD might have a neurodevelopmental abnormality in the left amygdala and bilateral OFC.

Unfortunately, we could only measure three regions (the left amygdala and bilateral OFC) by ^{1}H-MRS, since it was difficult to scan the subjects over a 30-min period. Although we chose the left amygdala in this study, the side of the amygdala that plays a greater role in individuals with autism is not yet clear. Schumann and Amaral reported significantly fewer neurons in the bilateral amygdalae of the postmortem autistic brain (18).

The amygdala has been implicated in the mediation of social behavior (19), face processing (20), and recognition of emotions (21) in healthy individuals and is considered to be a part of the social brain. Previous fMRI studies of ASD have reported reduced activation in the amygdala when subjects make judgments regarding the emotion expressed by the eyes (22) or when they perform a facial perception task (23). We found a positive correlation between the concentration of NAA in the amygdala and the SQ by the S-M scale. These findings suggest that the amygdala might be the primary structure that is responsible for autistic symptoms such as emotional and social impairments.

The amygdala is thought to play a central role in associating sensory cues with their motivational and emotional significance (24). Schoenbaum et al. (25) proposed models of amygdala-frontal interaction in which motivational and emotional significance, coded by the amygdala, is conveyed to the OFC for the control of action. Patients with OFC lesions show impairments in social and moral behaviors (26). Furthermore, the OFC contributes to "Theory of mind", which is impaired in ASD (27). In this study, the concentrations of NAA in the bilateral OFC were significantly decreased in subjects with ASD, and a positive correlation was observed between the concentrations of NAA in these regions and the SQ by the S-M scale. These findings suggest that abnormal neurodevelopment of the OFC may also contribute to the social impairments in ASD.

Using fMRI, Carr et al. (11) have described a neural network in which the insula acts as an interface between the frontal component of the MNS－the pars opercularis of the inferior frontal gyrus－and the limbic system, thus enabling the translation of an observed or imitated facial emotional expression into its internally felt emotional significance. Furthermore, Dapretto et al. (13) used an event-related fMRI design to investigate neural activity during the imitation and observation of facial emotional expressions, in
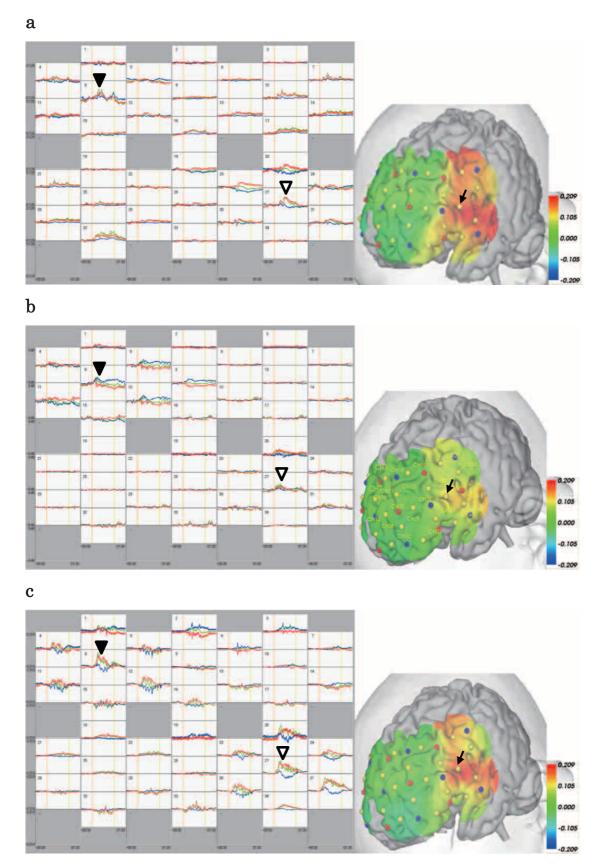
a

b

c

Fig. 7.   Hemoglobin concentration changes during the imitation task of emotional facial expressions.
a : 9-year-old typically developing boy, b : 9-year-old boy with autistic disorder, before training of the imitation task, c : 9-year-old boy with autistic disorder, after training of the imitation task.
The upper row of each graph shows hemoglobin concentration changes in the right frontal region. The lower row of each graph shows hemoglobin concentration changes in the left frontal region. Red, oxygenated hemoglobin (oxy-Hb) ; blue, deoxygenated hemoglobin (deoxy-Hb) ; green, total Hb. The arrows show Ch8 on the right pars opercularis of the inferior frontal gyrus and Ch27 on the left pars opercularis of the inferior frontal gyrus.
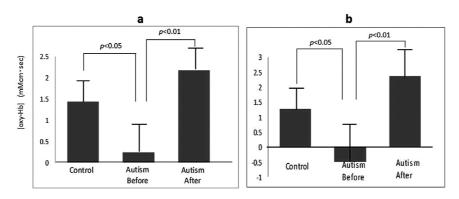
Fig. 8.   Oxygenated hemoglobin (oxy-Hb) changes of Ch27 and Ch8 during the imitation task of emotional facial expressions.
a : Ch27 on the left pars opercularis of the inferior frontal gyrus.
b : Ch8 on the right pars opercularis of the inferior frontal gyrus.
Before, before training of the imitation task ; after, after training of the imitation task.

high-functioning children with ASD and typically developing children, and reported that activity in bilateral pars opercularis of the inferior frontal gyrus and periamygdaloid regions was significantly lower in the ADS group than that in the controls.

We performed a NIRS study to evaluate MNS in children with ASD. The increments in the concentration of oxy-Hb in the pars opercularis of the inferior frontal gyrus in autistic subjects were significantly lower than those in the controls. However, the concentrations of oxy-Hb in this area were significantly elevated in autistic subjects after they were trained to imitate emotional facial expressions. These findings suggest that mirror neurons could be activated by repeated imitation in children with ASD. The lower activation in the pars opercularis of the inferior frontal gyrus in autistic subjects might be caused secondarily by human beings avoidance tendency that is brought about by neurodevelopmental abnormality of the amygdala in ASD. Individuals with ASD avoid the eye region of human beings because it heightens amygdala activation and is perceived as socially threatening (28).

The present study has some limitations. First, IQ of autistic patients was slightly low in this study. Because the difference of intellectual level between autistic patients and control individuals might influence the results of ^{1}H-MRS and NIRS study, further research with IQ matched subjects is needed. Second, we should compare the concentrations of oxy-Hb in autistic patients with those in control individuals after both of them were trained to imitate emotional facial expressions. However, the consent for the training was not obtained from the parents of control group in this NIRS study. Third, since NIRS has a comparatively low spacial resolution, we should be careful when we judge a specific anatomical region. We suppose that further research using fMRI will resolve the problem. Finally, there is some data to suggest that there might be brain changes with age (29). Because NAA concentration tends to increase with age in children (29), the age of the subjects was limited to 3 to 6 years old in ^{1}H-MRS study. Since the evolutional change in the concentration of oxy-Hb during the imitation task is unknown, additional longitudinal study with a larger sample size is needed.

CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

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