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The Human Mirror Neuron System in a Population With Deficient Self-Awareness: An fMRI Study in Alexithymia

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Abstract: The mirror neuron system (MNS) is considered crucial for human imitation and language learning and provides the basis for the development of empathy and mentalizing. Alexithymia (ALEX), which refers to deficiencies in the self-awareness of emotional states, has been reported to be associated with poor ability in various aspects of social cognition such as mentalizing, cognitive empathy, and perspective-taking. Using functional magnetic resonance imaging (fMRI), we measured the hemodynamic signal to examine whether there are functional differences in the MNS activity between participants with ALEX ($n = 16$) and without ALEX ($n = 13$), in response to a classic MNS task (i.e., the observation of video clips depicting goal-directed hand movements). Both groups showed increased neural activity in the premotor and the parietal cortices during observation of hand actions. However, activation was greater for the ALEX group than the non-ALEX group. Furthermore, activation in the left premotor area was negatively correlated with perspective-taking ability as assessed with the interpersonal reactivity index. The signal in parietal cortices was negatively correlated with cognitive facets assessed by the stress coping inventory and positively correlated with the neuroticism scale from the NEO five factor personality scale. In addition, in the ALEX group, activation in the right superior parietal region showed a positive correlation with the severity of ALEX as measured by a structured interview. These results suggest that the stronger MNS-related neural response in individuals scoring high on ALEX is associated with their insufficient self-other differentiation. *Hum Brain Mapp 30:2063–2076, 2009.* ©2008 Wiley-Liss, Inc.

Key words: emotional disturbances; premotor cortex; parietal cortex; mentalizing; self and other; hand action

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INTRODUCTION

Alexithymia (ALEX) [Sifneos, 1972] is a construct that describes people who appear to have deficiencies in understanding, processing, or describing their emotions. This includes problems in identifying, describing, and working with one's own feelings as well as difficulty in distinguishing between the feelings and the bodily sensations of emotional arousal [Taylor et al., 1997]. ALEX is considered as a personal trait, which is prevalent not only among general healthy people but also in broad spectrum of psychiatric and psychosomatic patients, and involved in onset and aggravation of these disorders [Taylor and Bagby, 2004; Taylor et al., 1997].

Even though there have been many arguments about the etiology of ALEX, a widely-accepted theory suggests an association with developmental matters. A 31-year prospective study with a large sample of children found that ALEX in adulthood was associated with being an unwanted child, being born into a family with many children, a rural upbringing, and the ability to speak words at 1-year of age [Joukamaa et al., 2003; Kokkonen et al., 2003; Taylor and Bagby, 2004]. According to current evidence, it is worth probing ALEX in relationship to relevant topics such as developmental psychology or some developmental disorders.

Although ALEX itself refers to deficiencies in emotional self-awareness, it is often marked by a lack of understanding of the feelings of others [Taylor et al., 1997]. ALEX has been repeatedly found in broad spectrum of psychiatric disorders (e.g., substance use disorder [Cleland et al., 2005; Haviland et al., 1988, 1994; Mann et al., 1995; Taylor et al., 1990], posttraumatic stress disorder [Alvarez and Shipko, 1991; Frewen et al., 2008a,b; Hyer et al., 1990; Krystal et al., 1986b], and dissociative disorders [Elzinga et al., 2002; Irwin and Melbin-Helberg, 1997; Sayar et al., 2005; Zlotnick et al., 1996]). At the same time, it is noteworthy that there is a considerable group of psychiatric disorders characterized by ALEX involving deficits in the recognition of feelings belonging to the self and identification with others, such as autism and Asperger syndrome (AS) [Berthoz and Hill, 2005; Frith, 2004; Hill et al., 2004], schizophrenia [Cedro et al., 2001; Stanghellini and Ricca, 1995], and borderline personality disorder [Guttman and Laporte, 2002]. These disorders are characterized by reduced self-other distinction and immature empathy, such as higher self-oriented personal distress or emotional contagion [Decety and Moriguchi, 2007; Moriguchi et al., 2006; Preston and de Waal, 2002]. Furthermore, recent studies utilizing functional neuroimaging [Moriguchi et al., 2006, 2007a] revealed that individuals with ALEX have reduced mentalizing capability, cognitive empathy, and perspective-taking ability. These results point to common components in the recognition of the self and others; therefore, ALEX involves impairments both in self-awareness and also in understanding the perspective of others at a higher cognitive level.

The basic neural mechanisms underlying our understanding of the mental states of others may well involve the mirror neuron system (MNS). A mirror neuron is a sensory-motor neuron that fires both when an animal performs an action and when it observes the same action performed by another individual [Gallese et al., 1996; Rizzolatti et al., 1996a]. Thus, the neuron "mirrors" the behavior of another, as if the observer was itself performing the action, and these neurons have been directly recorded in primates [Rizzolatti and Craighero, 2004]. In humans, neuroimaging studies have demonstrated brain activity consistent with mirror neurons in the premotor cortex and the inferior parietal cortex [Rizzolatti and Craighero, 2004] (for a review). The MNS provides a primitive yet critical stepping stone for understanding other minds via covert motor simulation. Indeed, the MNS has been put forth as important mechanism for social cognition in general [Blakemore and Frith, 2005; Ohnishi et al., 2004].

One functional magnetic resonance imaging (fMRI) study reported reduced hemodynamic activity in the MNS when autistic children observed or imitated facial expressions, though they performed the tasks as well as typically developing children [Dapretto et al., 2006]. Interestingly, autistic individuals have been shown to exhibit high ALEX scores [Berthoz and Hill, 2005; Bush et al., 1998; Frith, 2004; Hill et al., 2004; Tani et al., 2004]. Furthermore, autism and ALEX are considered to overlap to some extent [Berthoz and Hill, 2005; Fitzgerald and Bellgrove, 2006; Fitzgerald and Molyneux, 2004]. However, Hamilton et al. [2007] recently demonstrated that the ability to understand and imitate the goals of hand actions is intact in children with autism. Thus, it is unclear whether ALEX involves changes in the MNS that appears to act as a prerequisite for developing the ability to comprehend others' mind. To our knowledge, no investigation to date has examined the relation between the MNS and ALEX or deficits in self-awareness.

The purpose of this study was to explore the difference in the motor MNS activity between individuals with and without ALEX. We measured hemodynamic responses with fMRI while participants watched video clips depicting goal-directed actions [Ohnishi et al., 2004].

METHODS AND MATERIALS

The study was approved by the local Ethics Committees (National Center of Neurology and Psychiatry in Japan, National Institute of Mental Health) and conducted in accordance with the Declaration of Helsinki.

Participants

Three hundred and ten college students completed the 20-item Toronto Alexithymia Scale (TAS) [Moriguchi et al., 2007b; Taylor et al., 2003]. Individuals with preferably high and low TAS-20 total scores ($n = 20$, score >60; $n = 17$, score <39, respectively) were selected in order to obtain

TABLE I. Appearance of TAS-20 and SIBIQ scores in the two groups

	Whole	Non-ALEX	ALEX
n (Male/female)	37 (7/30)	14 (2/11)	16 (3/13)
Age; mean (SD) years	20.4 (0.92)	20.9 (0.76)	20.1 (1.0)
TAS-20	Min-max, mean (SD)		
Total	26–74, 51.3 (16.6)	26–38, 33.9 (3.8)	61–74, 66.3 (4.6)
F1	7–32, 18.0 (8.1)	7–19, 10.5 (3.8)	19–32, 24.7 (4.0)
F2	5–25, 15.5 (6.1)	5–18, 9.5 (4.1)	15–24, 20.1 (2.4)
F3	9–30, 17.9 (5.3)	9–21, 13.8 (3.5)	13–30, 21.5 (4.1)
SIBIQ			
Total	18–70, 42.3 (17.2)	18–56, 32.1 (12.1)	25–70, 52.7 (14.4)

The whole sample (*n* = 37) is introduced to analysis of main effect of painful picture tasks and correlation analysis between neural activations and psychological measurements. Non-ALEX (*n* = 13) and ALEX (*n* = 16) groups were obtained from this whole sample excluding the participants with discrepancy between TAS-20 and SIBIQ scores (cf. Method).

F1 (Factor 1), difficulty in identifying feeling; F2 (Factor 2), difficulty in describing feeling; F3 (Factor3), externally oriented thinking; Non-ALEX, non-alexithymic group; ALEX, alexithymic group.

two samples with a wide range of ALEX scores as possible. Thirty-seven students gave informed written consent and participated in the experiment. Pertinent demographic variables of the participants are shown in Table I. All participants who agreed to participate to the fMRI study were interviewed using the Mini-International Neuropsychiatric Interview [Sheehan et al., 1998] by two medical doctors specialized in psychiatry and psychosomatic medicine. All participants had no history of neurological, major medical, or psychiatric disorder, and no one was excluded from the study. All participants were right-handed, as assessed by the Edinburgh handedness inventory [Oldfield, 1971]. The participants were almost the same as reported in our previous studies examining the association between ALEX and mentalizing [Moriguchi et al., 2006] and ALEX and empathy [Moriguchi et al., 2007a]. However, this study was conducted in a completely different setting, and here we focus only on the analyses of the MNS paradigm.

The whole sample described earlier (*n* = 37) was divided into two groups based on the cutoff scores on the TAS-20: ALEX (TAS >60) and non-ALEX (TAS <39) group. The structured interview, modified edition, of the Beth Israel hospital psychosomatic questionnaire (SIBIQ) [Arimura et al., 2002; Sriram et al., 1988] was used to further confirm the presence or absence of ALEX. Four participants with high TAS-20 and low SIBIQ scores and four with low TAS-20 and high SIBIQ scores were discarded. Comparative scores for the resulting ALEX group (*n* = 16) and non-ALEX group (*n* = 13) are shown in Table I.

Psychological Instruments

The TAS-20 [Bagby et al., 1994a,b; Parker et al., 2003; Taylor et al., 2003]; the Japanese version by Moriguchi et al. [2007b], is a 20-item self-administered questionnaire. The items are scored on a five-point scale ranging from strongly disagree to strongly agree. The TAS-20 has a three-factor structure. Factor 1 assesses difficulty in identifying feelings. Factor 2 assesses difficulty in describing feelings. Factor 3 assesses externally oriented thinking.

The structured interview by Beth Israel hospital psychosomatic questionnaire for alexithymia (SIBIQ [Arimura et al., 2002]) is based on the Beth Israel hospital psychosomatic questionnaire [Sriram et al., 1988] that is mainly used with psychosomatic patients. The SIBIQ was developed for patients with some physical or psychiatric symptoms and asks patients to describe how they perceive their own symptoms. For interviewing nonpatients with no symptoms, we modified the SIBIQ by adding questions about their feelings in response to bad/sad/difficult (negative) or happy/good/satisfying (positive) events they had experienced. If they replied that they had no equivalent life events, we added "if" questions in which they were asked to imagine situations that were designed to cause emotional responses (similar to the Alexithymia Provoked Response Questionnaire; APRQ [Krystal et al., 1986a]) and required them to answer in terms of their own emotions. The testers rated these answers as per the scale of the SIBIQ. The SIBIQ was conducted by two qualified physicians, who were acquainted clinically with ALEX, and their two scores were averaged for each participant. The two testers were blind to the initial classification of the participants based on their TAS-20 score. There is no standard cutoff point on the SIBIQ. We set the thresholds as the top quartile of the SIBIQ scores (equivalent to >47) as "high" SIBIQ and the lowest quartile (<25) as "low" SIBIQ.

The NEO five-factor inventory (NEO-FFI) [Costa and McCrae, 1992] is one of the standard measures of the five-factor model (big five model) of personality traits and is an abridged version of the NEO personality inventory [Costa and McCrae, 1992], a widely used measure designed to provide a general description of normal personality. It uses a five-point Likert-type scale, ranging from 0 (strongly disagree) to 4 (strongly agree). This scale is comprised of 60 items designed to measure the five major domains (factors) of personality: neuroticism (N), extraversion (E), openness to experience (O), agreeableness (A), and conscientiousness (C). Scores are summed totals and have a range of 0–48 for each of the five personality domains. The Japanese version of NEO-FFI has been cross-validated and its reliability has been confirmed in the general population [Shimonaka et al., 1997].

The interpersonal reactivity index (IRI) [Davis, 1983]; Japanese version developed by Aketa [1999], was another self-administered questionnaire measuring the empathetic ability of the participants. The IRI consists of four scales, each measuring a distinct component of empathy. (1)

Empathic concern measures the feeling of emotional concern for others. (2) Perspective-taking assesses the ability to cognitively take the perspective of another and is related to social competence. (3) Fantasy measures the degree of emotional identification with characters in books, films, etc., and (4) Personal distress determines the level of negative self-focused feelings in response to the distress of others that may motivate a person to act egoistically. Factors (1) and (2) are characterized as desirable interpersonal styles and predict positive behaviors such as good communication, warmth, even temperedness, and a positive outlook. Personal distress is negatively related to these behaviors, but positively related to untrustworthiness, insensitivity, and possessiveness [Davis and Oathout, 1987].

The stress coping inventory (SCI) [Lazarus and Folkman, 1984]; Japanese version developed by Japanese Institute of Health [1996], was used to investigate the character and coping style of participants in response to emotional stimuli. The SCI has two major factors: (1) cognitive coping strategy and (2) emotional coping strategy. There are eight subscales derived from the SCI: (1) confrontational, (2) distancing, (3) self-controlling, (4) seeking social support, (5) accepting responsibility, (6) escape-avoidance, (7) problem solving, and (8) positive reappraisal.

The Japanese versions of the psychological scales used in this study and described earlier (the TAS-20, IRI, and SCI) have been translated into Japanese using a back-translation method, and factor analyses of these Japanese versions has demonstrated the same factors as the original English versions. The concurrent validity and reliability of each psychological measure have been confirmed, indicating that the Japanese version of each psychological test measures the same constructs as the original versions.

Video Clips

Video stimuli were recorded clips of another individual performing goal-directed hand actions (e.g., reaching and grasping a cup, picking up a hammer, manipulating a telephone) directed toward one of 52 objects typically used on a daily basis (e.g., an eraser, a pencil, a fork, etc.). The objects were positioned at the horizontal center of the video camera's view. Each video clip consisted of a hand reaching in from the top right-hand corner of the screen and picking up and/or manipulating the object. Each clip lasted 4 s; subjects watched five stimuli during each task epoch. The observation of object-related hand actions was contrasted with a control condition consisting of a reaching movements made by an artificial hand above the same objects used during the task period. The speed and extent of the artificial hand movement was controlled such that is matched with that during the task hand movement. Each control stimulus clip also lasted 4 s; thus, like the task epochs, subjects watched five stimuli per each control epoch. The stimuli were the same as those used in a previous fMRI study examining the MNS in children [Ohnishi et al., 2004].

Scanning Method and Procedure

Participants took part in one fMRI session consisting of 24 blocks. Each task or control block consisted of five 4-s trials of the same condition. The participants were instructed to passively but carefully observe the video clips depicting object-related hand actions during task conditions (eight blocks) and the artificial hand movements during control conditions (eight blocks). During baseline trials, participants were asked to fixate the central cross for 4 s and were not shown the MNS task (eight blocks). The order of conditions was randomized within the session. No objects in the clips were presented more than once in each condition throughout the whole experiment.

Data Acquisition and Analyses

MRI data were acquired on a 1.5-T Siemens Magnetom Vision Plus System, Erlangen, Germany. Changes in blood-oxygenation-level-dependent (BOLD) T2* weighted MR signal [Ogawa et al., 1990] were measured using a gradient echo-planar imaging (EPI) sequence (repetition time TR = 4,000 ms, echo time TE = 55 ms, FoV = 220 mm, flip angle 90°, 64 × 64 matrix, continuous 30 slices/slab, slice thickness 4.0 mm, voxel size = 3.44 mm × 3.44 mm × 4 mm). For each scan session, a total of 125 EPI volume images were acquired along the AC-PC plane. Structural MR images were acquired with a MPRAGE sequence (TE/TR, 4.4/11.4 ms; flip angle, 15°; acquisition matrix, 256 × 256; 1NEX field of view, 31.5 cm; slice thickness, 1.23 mm). The first five volumes of EPI images were discarded because of instability of magnetization; therefore, we obtained 120 volumes of EPI for analysis.

The stimuli were projected onto a screen ~50 cm from the participant's head. The participants viewed the screen through a mirror attached to the head coil.

Image processing was carried out using statistical parametric mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London, UK). The EPI images were realigned and coregistered to the participants' T1-weighted MR images. Then, the T1 images were transformed to the anatomical space of a template brain whose space is based on the MNI (Montreal Neurological Institute) stereotactic space. The parameters for the transformation were applied to the coregistered EPI images. The normalized images were smoothed by an 8-mm FWHM Gaussian kernel. A first fixed level of analysis was computed subject-wise using the general linear model with the hemodynamic response function modeled as a boxcar function whose length covered the five successive video clips of the same type.

To test the hypotheses about regionally specific effects in the MNS task condition, the estimates were compared by means of linear contrasts for each epoch (object-related hand movement epoch as task condition versus artificial hand movement epoch as control). The resulting set of voxel values for each contrast constituted a statistical parametric map of the t statistic SPM(t). Anatomic localiza-

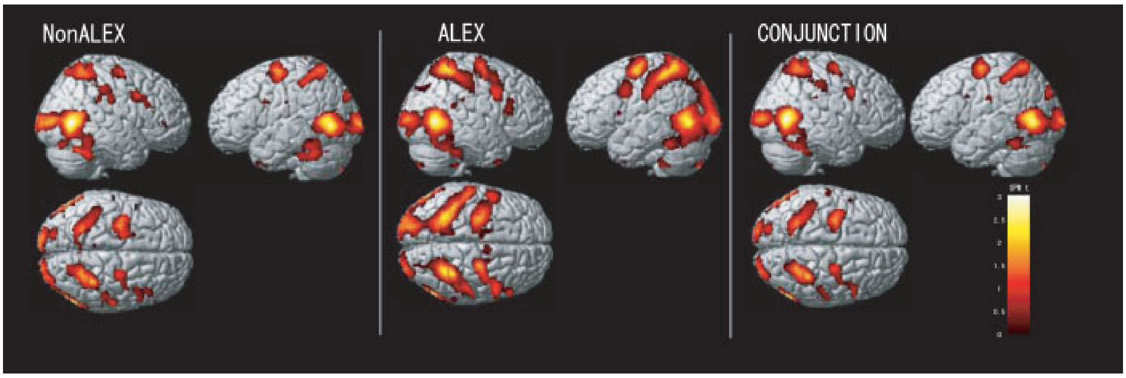

Figure 1.

Brain images of neural activity in response to the observation of object-related hand movement compared to control task using one-sample tests for the (**a**) non-alexithymia group ($n = 13$) and (**b**) alexithymia group ($n = 16$). The bar on the right shows the range of *t* scores for statistical parametric mapping. The height threshold for illustrating the clusters was $P < 0.05$ corrected (false discovery rate). (**c**) Brain images of greater activity in response to the observation of object-related hand movement compared to control task for the conjunction analysis of both groups, which shows overlapping areas using two one-sample tests {alexithymia group ($n = 16$) and non-alexithymia group ($n = 13$)}. The bar on the right shows the range of *t* scores for statistical parametric mapping. The height threshold for illustrating the clusters was $P < 0.05$ corrected (false discovery rate). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

tion was presented as MNI coordinates, and to check the localization of the Brodmann area, the Talairach coordinates [Talairach and Tournoux, 1988] were used. First-level contrasts were introduced in a second-level random-effect analysis [Friston et al., 1999] to allow for population inferences.

Main effects for watching the video clips were computed using one-sample tests separately for the ALEX and non-ALEX group, and a subsequent conjunction analysis of both one-sample tests was conducted to show overlapping areas of activation between the two groups. The analyses were done for each of the contrasts of interest, which yielded a statistical parametric map of the *t*-statistic, subsequently transformed to the unit normal distribution (SPM Z). A voxel and cluster level threshold of $P < 0.05$ corrected for multiple comparisons (false discovery rate; $t = 2.94$ for the non-ALEX group, 2.76 for the ALEX group, and 2.77 for the conjunction analysis) was used to identify MNS-related regions compared to the null hypothesis.

Two-sample tests were used to compare the difference in neural activity related to the MNS between the ALEX group ($n = 16$) and the non-ALEX group ($n = 13$). The height and extent thresholds were set at $P < 0.05$ corrected for family-wise error. For the areas with an a priori MNS-related hypothesis (bilateral dorsal/ventral premotor cortex and inferior/superior parietal cortex as the core MNS related areas, derived from a number of studies [i.e., Buccino et al., 2004a,b; Iacoboni and Dapretto, 2006; Rizzolatti and Craighero, 2004] and middle/superior temporal gyrus as an additional MNS related area [Gazzola et al., 2007; Iacoboni and Dapretto, 2006; Rizzolatti et al., 1996b; Tettamanti et al., 2005]), we applied a region of interest (ROI) analysis. To explore group differences in these MNS-related regions, we used lenient height and extent thresholds ($T = 1.70$ and $k = 10$, respectively) within the regions activated in the conjunction analysis to reduce the risk of false negatives. If the regions that showed significant differences were found in a priori regions based on both the present and previous studies, we conducted an additional ROI analysis, which consisted of 20 voxels centered on each peak coordinate found in this first-step group comparison. Individual mean contrast values (task minus control) were calculated for each ROI using Marsbar software (http://marsbar.sourceforge.net). These mean contrast values were assessed by *t*-tests ($P < 0.05$ corrected). From these ROI analyses, we confirmed regions with significant group effects for MNS activations.

To further clarify the characteristics of regions showing group differences for MNS-related activities, the correlation coefficients between these ROI mean contrast values and psychological measurement scores were also calculated to investigate the features of the regions that demonstrated between-group differences. Additionally, we tested homogeneity of covariate-dependent variable slopes, where the neural activity in each ROI as a dependent variable, existent or nonexistent of ALEX as categorical levels, and each psychological score as a covariance to see if there is an interaction between each psychological measure and categorical levels of ALEX. We also confirmed the significance of correlations in each categorical level separately.

RESULTS

One-Sample Analyses and Conjunction Analysis

Figure 1 shows the significant hemodynamic changes in response to the observation of hand movement task versus the control task (artificial hand movement) as well as for the

TABLE II. Coordinates and Z and T scores for the MNS-related brain areas activated in response to object-related hand movement stimuli in conjunction analysis of one-sample tests on both groups

	MNI x, y, z {mm}	BA	T	Z	Cluster k
Rt middle temporal gyrus	58, −66, 4	37	9.30	6.18	3454
Rt middle occipital gyrus	24, −98, 2	18	5.77	4.62	
Rt cerebellum anterior lobe	42, −52, −28	37	3.79	3.36	
Lt middle temporal gyrus	−46, −70, 4	37	7.68	5.54	1957
	−56, −64, 6	39	6.34	4.92	
Lt middle occipital gyrus	−56, −66, −14	37	2.88	2.66	
Rt cerebellum posterior lobe	10, −80, −42		3.95	3.48	470
Lt cerebellum posterior lobe	−22, −70, −50		3.76	3.34	
Lt occipital lobe cuneus	−10, −102, 4	18	6.01	4.75	783
	−16, −96, 6	18	5.17	4.27	
Lt precentral gyrus	−32, −12, 62	6	5.96	4.72	774
Rt inferior parietal lobule	34, −46, 58	5	5.75	4.61	1425
Rt subgyral	26, −52, 58	7	5.53	4.48	
Rt superior parietal lobule	30 −54 66	7	5.36	4.39	
Lt superior parietal lobule	−28, −56, 64	7	5.06	4.20	1122
Lt inferior parietal lobule	−36, −42, 54	40	4.37	3.76	
	−14, −62, 68	7	3.28	2.98	
Rt middle frontal gyrus	28, −14, 62	6	4.97	4.15	394
	42, −4, 58	6	3.19	2.91	
Lt cuneus	−20, −90, 36	19	4.79	4.04	179
Lt fusiform gyrus	−46, −48, −20	37	4.47	3.83	263
Rt inferior frontal gyrus	42, 8, 34	9	3.73	3.32	271
	54, 10, 34	9	3.31	3.00	
Rt middle frontal gyrus	56, 10, 46	8	3.05	2.80	
Lt uncus	−22, 4, −44	38	3.73	3.32	22
Rt cerebellum posterior lobe	24, −60, −50		3.71	3.31	78
Rt cerebellum posterior lobe	16, −66, −50		3.58	3.21	
Lt cerebellum posterior lobe	−14, −72, −28		3.46	3.12	72
Lt postcentral gyrus	−62, −18, 30	1	3.09	2.84	36
Lt fusiform gyrus	−34, −56, −28	37	3.07	2.81	38
Rt inferior parietal lobule	56, −32, 28	40	3.06	2.81	8
Lt inferior frontal gyrus	−54, 6, 32	9	2.99	2.76	13
Rt Inferior Frontal Gyrus	60, 28, 18	45	2.97	2.74	3
Rt cerebellum posterior lobe	24, −46, −50		2.90	2.68	4
Lt lingual gyrus	−10, −72, −4	18	2.89	2.67	5
Lt superior frontal gyrus	−16, −6, 78	6	2.87	2.66	2
Rt inferior frontal gyrus	54, 26, 24	45	2.87	2.66	5
Lt superior frontal gyrus	−16, −10, 78	6	2.80	2.60	1
Lt cerebellum posterior lobe	−4, −76, −34		2.77	2.58	1

Statistical threshold: $P < 0.05$ corrected with false discovery rate, $t = 2.94$ for non-alexithymia group, 2.76 for alexithymia group, 2.77 for conjunction analysis.

BA, brodmann area; MNI, montreal neurological Institute coordinates; Lt, left; Rt, right.

conjunction analysis of both groups. Table II summarizes the MNS-related regions and their representative coordinates for the conjunction analysis. A similar pattern of activity was found for each group and in the conjunction analysis. Significant signal change was detected bilaterally in the superior/middle frontal gyri (BA6/8), inferior frontal gyri (BA9/45), superior (BA7) and inferior parietal (BA40/5) lobules, middle temporal/occipital and in the fusiform gyri (BA37/18). Additional areas of activation were also found in the cerebellum, left uncus (BA38), and the cuneus (BA19).

Group Comparison Analysis

We compared the ALEX group with the non-ALEX group, by examining neuronal activity in response to the MNS task (Table III, Fig. 2). Initially, we found no between-group difference using a relatively strict statistical threshold ($P < 0.05$, corrected for family-wise error without an a priori hypothesis). However, when a more lenient height and extent threshold ($T = 1.70$ and $k = 10$, respectively) were set for the regions based on an a priori hypothesis within the activated areas found in the conjunction analysis, stronger activity was seen in the ALEX group when compared with non-ALEX group in the bilateral superior parietal lobules (BA7/5/3), left inferior parietal lobule (BA40), bilateral superior frontal gyri (BA6), and middle temporal and occipital visual-related regions (BA37/22/19). Within the MNS-related areas, there were no locations in which the non-ALEX group showed greater activation than the ALEX group (Table III and Fig. 2).

TABLE III. Coordinates and *Z* and *T* scores for the brain areas differentially activated by the MNS task between the alexithymia and non-alexithymia groups; exploratory group comparison using two-sample tests within activated regions found in conjunction analysis

	MNI *x*, *y*, *z* {mm}	BA	*T*	*Z*	Cluster *k*	
ALEX > non-ALEX						
Rt superior parietal lobule	**36, −54, 68**	7	3.08	2.82	169	*
Lt parietal postcentral gyrus	**−32, −52, 72**	5	2.75	2.56	254	*
	−56, −34, 54	40	2.33	2.21		*
	−40, −48, 68	5	2.20	2.09		
Rt superior frontal gyrus	**30, −10, 72**	6	2.27	2.16	20	*
Lt frontal precentral gyrus	**−24, −18, 68**	6	2.14	2.04	16	*
Rt middle temporal gyrus	**50, −50, −2**	22	2.13	2.04	75	*
	56, −60, −2	37	2.03	1.94		
	58, −48, −2	22	1.91	1.84		
Lt parietal postcentral gyrus	**−62, −24, 44**	3	2.09	2.00	18	*
Lt occipital lobe cuneus	−20, −94, 24	19	1.98	1.90	35	
ALEX < non-ALEX						
None						

Height threshold: $T = 1.70$, Extent threshold $k = 10$ voxels. **Bold type:** selected center coordinate of ROI with a priori hypothesis. $^*P < 0.05$, corrected with ROI analysis.Non-ALEX, non-alexithymic group; ALEX, alexithymic group; BA, brodmann area; MNI, montreal neurological institute coordinates; Lt, left; Rt, right.

We subsequently centered the seven ROIs on the coordinates found in the exploratory group comparison study (see bold typed coordinates in Table III). The loci of these ROIs have been put forth as MNS-related areas in humans [Buccino et al., 2001, 2004b; Decety et al., 1994, 2002; Gazzola et al., 2007; Grafton et al., 1996; Grezes et al., 1998, 2001, 2003; Iacoboni and Dapretto, 2006; Iacoboni et al., 1999; Koski et al., 2002, 2003; Manthey et al., 2003; Nishitani and Hari, 2000, 2002; Perani et al., 2001; Rizzolatti et al., 1996b; Tettamanti et al., 2005]. All seven analyses showed that the mean intensity of neural activity in each ROI in response to the MNS task was significantly increased for the ALEX group when compared with the non-ALEX group in superior premotor and superior/middle/inferior parietal cortices (Fig. 3, $P < 0.05$, ROI corrected).

Correlation Analysis

Correlation coefficients calculated between the hemodynamic activation in each ROI and the psychological measurement scores are shown in Table IV for the MNS-related ROIs found in the between-group comparison. Bilateral activation in the superior/middle/inferior parietal lobules was negatively correlated with the cognitive stress-coping scales (“cognitive,” “problem solving,” “confrontational,” “seeking social support,” “self-controlling,” and “positive reappraisal”) and the NEO-FFI factors of “extraversion,” “openness to experience,” and “conscientiousness.” The left middle/inferior parietal lobules were positively correlated with the NEO-FFI factor of “neuroticism.” The left superior premotor area was negatively correlated with the IRI perspective-taking scale (see Fig. 4). The right middle temporal region showed no correlation with any scales. Further, we tested whether there is an interaction between ALEX -based grouping and each psychological factor (covariance) for hemodynamic activity in each ROI as a dependent variable. We could find an interaction of ALEX grouping with several psychological factors in ROIs in the left middle parietal (NEO-neuroticism; $F = 5.01$, $P = 0.035$), left middle/inferior parietal (NEO-neuroticism; $F = 9.89$, $P = 0.004$, SCI-positive reappraisal; $F = 4.55$, $P = 0.035$), and right middle temporal (SCI-Emotional; $F = 6.31$, $P = 0.019$, accepting responsibility; $F = 8.83$, $P = 0.007$, distancing; $F = 8.95$, $P = 0.006$, self-controlling; $F = 5.98$, $P = 0.022$). To confirm the significances of correlations in each categorical level, we calculated correlation coefficients in ALEX and non-ALEX group separately within the pairs of psychological factor and ROI showing significant interaction with categorization on ALEX described earlier (see Fig. 5). Overall, hemodynamic change was positively correlated with NEO-neuroticism and negatively (but not significantly) with SCI factors in ALEX group. In non-ALEX group, neural activities in the right middle temporal area were positively correlated with SCI factors (emotional, accepting responsibility, and self-controlling).

For the ALEX -related scales, we conducted correlation analyses separately for the ALEX group and the non-ALEX group. The TAS-20 factor and total scores had no significant correlations with the activity in each ROI. The SIBIQ scores showed a positive correlation only with neural activity in a ROI located in the right superior parietal cortex (Spearman’s rho = 0.50, $P = 0.048$; see Fig. 6) in the ALEX group, but not in the non-ALEX group (Spearman’s rho = −0.14, $P = 0.65$).

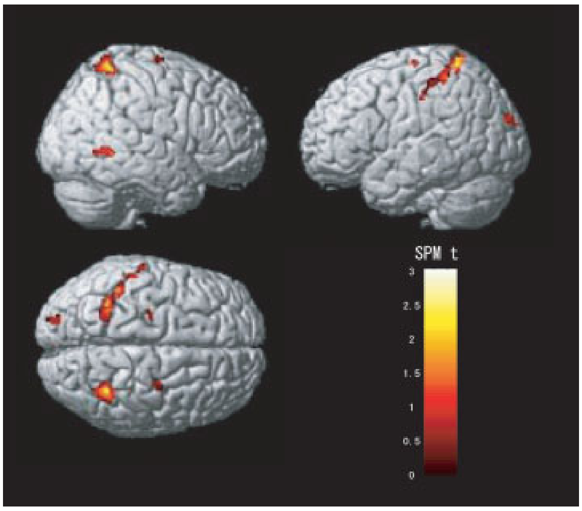

Figure 2.
Brain images of clusters differentially activated by the MNS task between the alexithymia and non-alexithymia groups; exploratory group comparison using two-sample tests within activated regions found in conjunction analysis. The bar on the right shows the range of *t* scores for statistical parametric mapping. The height and extent threshold for illustrating were $T = 1.70$ ($P < 0.05$ uncorrected) and $k = 10$, respectively. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

DISCUSSION

This study examined the difference in the neural response during the passive observation of object-related goal-directed hand movements (MNS task) between individuals with and without ALEX.

First, the conjunction analysis examining the one-sample analysis from each group confirmed an increased BOLD response in premotor and parietal cortices during observation of the MNS task. This result is consistent with findings reported by Buccino et al. [2001, 2004a] who reported that, as in the actual execution of actions, action observation leads to the selective activation of somatotopically organized frontoparietal circuits.

The between-groups comparison revealed that the ALEX group showed greater activation than the non-ALEX group in parietal and premotor areas. One recent neuroimaging study of ALEX showed that participants with ALEX activated more parts of their sensory and motor cortices (i.e., "bodily" regions) than control participants in response to emotional video clips, including the left precentral gyrus (BA4), temporal subgyral lobe, right parietal lobe (BA7), and medial/superior frontal gyrus (BA6), which suggests their over-activated sensorimotor components [Karlsson et al., 2008]. This study is consistent with our finding in terms of the overactivity in motor-related system in individuals with ALEX.

Furthermore, neural activation in the left premotor cortex was negatively correlated with the scores assessing perspective-taking ability. In addition, activation in the right superior parietal region in the ALEX group was positively correlated with severity of ALEX as measured by the structured interview.

Importantly, a recent functional MRI study [Moriguchi et al., 2006] found that individuals with ALEX performed more poorly on theory of mind (ToM) tasks and showed reduced perspective-taking ability. Lower neural activity was detected in right medial prefrontal cortex (MPFC) during the ToM task. The authors proposed that self-other discrimination capabilities as well as self-recognition may be disturbed in ALEX. Considering that the MNS enables us to automatically map others' actions to oneself through a covert neural simulation mechanism, this is essentially opposite to self-other differentiation. One explanation for this results demonstrating increased MNS-related activity in

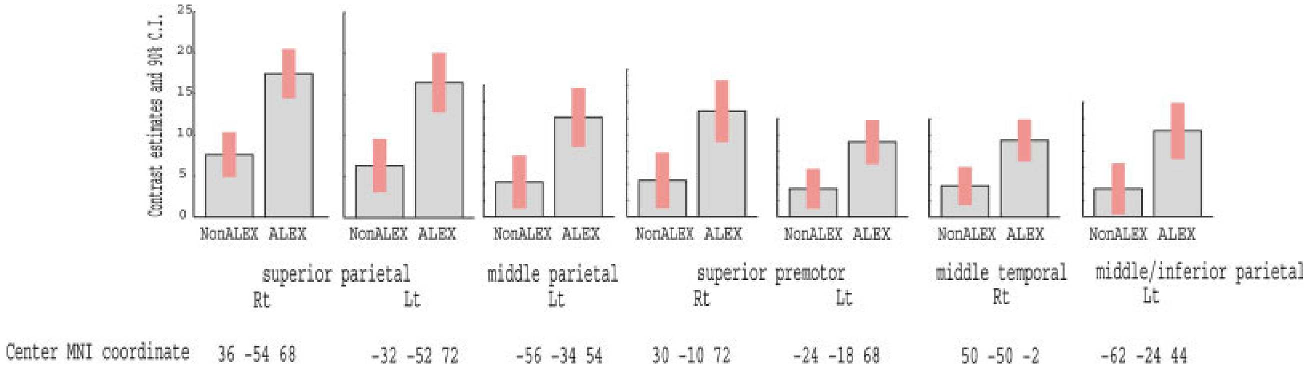

Figure 3.
ROI analysis of differential neural activity between the alexithymia and non-alexithymia groups. The graph shows the contrast estimates and 90% CI of mean activity for the two groups in response to the MNS task for each ROI. All ROI analyses show that a significant increase of MNS-related activity in superior premotor and superior/middle/inferior parietal cortices ($P < 0.05$) for the alexithymia group (ALEX) compared to the non-alexithymia group (non-ALEX). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE IV. Correlation coefficients between the mean neural activity in ROIs found in group comparisons for each psychological measurement

	Superior parietal		Middle parietal	Middle/inferior parietal	Superior premotor		Middle temporal
	Rt	Lt	Lt	Lt	Rt	Lt	Rt
Center MNI coordinate (x, y, z) mm	36, −54, 68	−32, −52, 72	−56, −34, 54	−62, −24, 44	30, −10, 72	−24, −18, 68	50, −50, −2
Interpersonal reactivity index (IRI)							
Fantasy	−0.16	−0.22	0.01	−0.12	−0.19	−0.11	0.06
Perspective taking	0.02	−0.11	−0.04	−0.25	−0.09	**−0.36***	−0.17
Empathic concern	−0.12	−0.04	−0.01	0.13	−0.12	−0.25	−0.17
Personal distress	0.20	−0.12	−0.01	0.02	0.01	0.11	0.03
Stress coping inventory (SCI)							
Cognitive	**−0.47*****	**−0.37***	**−0.40***	**−0.39***	−0.16	−0.24	0.04
Emotional	−0.26	−0.30	−0.26	−0.28	−0.12	−0.16	−0.06
Problem solving	**−0.51*****	−0.31	−0.30	−0.22	−0.12	−0.21	0.09
Confrontational	**−0.39***	−0.29	−0.32	−0.16	−0.19	−0.16	0.07
Seeking social support	−0.29	**−0.44****	**−0.47*****	**−0.49*****	−0.28	−0.29	−0.17
Accepting responsibility	−0.24	−0.22	−0.14	−0.25	−0.08	0.04	0.11
Self-controlling	**−0.36***	−0.14	−0.01	0.07	−0.06	−0.19	−0.02
Escape–avoidance	−0.14	−0.17	−0.21	−0.17	−0.14	0.03	−0.19
Distancing	0.11	0.09	0.23	−0.02	−0.04	−0.06	−0.09
Positive reappraisal	**−0.41***	**−0.42***	**−0.46*****	**−0.48*****	−0.12	−0.27	−0.02
NEO–FFI							
Neuroticism	0.18	0.12	**0.40***	**0.38***	0.04	0.12	0.04
Extraversion	**−0.49*****	−0.23	−0.28	−0.25	−0.25	−0.05	0.01
Openness to experience	−0.29	−0.18	−0.20	**−0.38***	−0.33	−0.23	−0.28
Agreeableness	−0.06	0.02	0.12	0.08	−0.08	−0.28	−0.23
Conscientiousness	**−0.47*****	−0.21	−0.19	−0.10	−0.05	−0.21	−0.10

Spearman's ρ. **Bold type** *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.005$.
Lt, left; Rt, right.

the ALEX group is that these individuals have lowered self-other discrimination abilities, and they are inclined to simulate the actions of others, and they tend to overlap the action of others onto their self. This explanation is in line with findings demonstrating that individuals with ALEX have lower perspective-taking ability and higher self-oriented personal distress scores [Guttman and Laporte, 2002; Moriguchi et al., 2006].

Interestingly, a recent study by Gazzola et al. [2006] reported that the left premotor, Broca, and SI/SII areas responded both during motor execution and when individuals listened to the sound of actions made by the same effector, thus demonstrating a human auditory mirror system. This study also found that participants with high perspective-taking scores showed more activation in this auditory mirror system. Although this appears opposite to the results of this study, the conditions of two studies are different; with one focused on visual and the other auditory stimulation. This discrepancy in the relationship between activation and perspective-taking scores across the two studies suggests that the visual motor-related MNS observed in this study might operate at a lower level of cognitive ability in perspective-taking and self-other distinction, whereas the auditory MNS might include more meta-representational contextual processes than the classical motor-related MNS. This notion is supported by our results demonstrating negative correlations between activation in the parietal cortices and various cognitive aspects of coping measured by the SCI (cognitive, problem solving, confrontational, seeking social support, self-controlling, and positive reappraisal) as well as with personality traits measured by the NEO (extraversion, openness to experience, and conscientiousness). Interestingly, SCI-positive reappraisal scores were negatively correlated with the hemodynamic activity in the parietal cortex specifically in the ALEX group. Furthermore, neuroticism was positively correlated with the left middle/inferior parietal activity, and these correlations were greater in ALEX group than in non-ALEX group. Previous findings have noted that people with a greater degree of neuroticism are intensely self-conscious and have decreased emotional regulation, motivation, and interpersonal skills; they may also have trouble controlling urges and delaying gratification [Goleman, 1995]. High neuroticism has been reported to correlate positively with the likelihood that an individual will have a negative affective reaction to a face threat (face threat sensitivity; FTS) as well as with the IRI personal distress scale, which has a significant inverse relationship with perspective-taking [Davis, 1983], and is also positively correlated with the FTS [White et al., 2004]. Hence, the MNS-related activity in parietal cortex could be associated with a tendency to be easily affected by the negative emotional cues of others. Saarela et al. [2007] reported that the inferior frontal gyrus (IFG), which has an important role in the

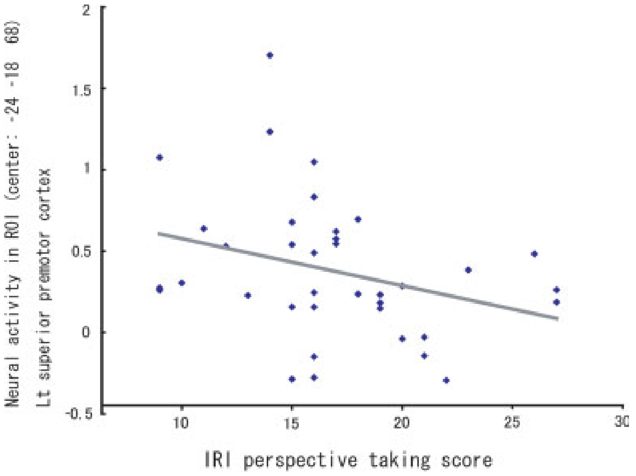

Figure 4.

The significant negative correlation between perspective-taking scores of the interpersonal reactivity index (IRI) and mean activity of the ROI in the left superior premotor region in response to the MNS task vs. control stimuli in one-sample ($n = 37$). The correlation coefficient (Spearman's rho) was -0.36. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

motor mirror-neuron system supporting understanding and imitation of action, was activated in response to observation of facial expressions of provoked pain. Also, the activation of the left IFG region was positively correlated with the IRI measure of personal distress, but it was not significantly correlated with a perspective-taking scale. These findings are in line with the supposition that there may be a variety of MNS [c.f., Hamilton et al., 2007], with one that is more associated with a tendency toward personal distress or emotional contagion rather than perspective-taking. Indeed, recent studies have pointed to plasticity in the MNS. For example, expert pianists were reported to show significantly stronger activations than nonmusicians in MNS-related areas including premotor areas in response to the sound/sight of piano playing [Bangert et al., 2006; Haslinger et al., 2005], and the MNS was found to be modulated by the motivational state of the observer such as hunger [Cheng et al., 2007]. These studies, considered together with the results of this study, indicate that the MNS is not an unmalleable architecture, rather, it can be modulated by acquired conditions and learning.

Autistic spectrum disorders including AS are supposed to be psychiatric disorders with more pervasive and severe disturbance in both the MNS and ToM than is typically seen in a healthy population with ALEX; autism appears to include impairment on a more biological level. However, the concepts of AS and ALEX overlap [Berthoz and Hill, 2005; Fitzgerald and Bellgrove, 2006; Fitzgerald and Molyneux, 2004]. Thus, studies examining the MNS in autistic people should provide clues to the understanding of the MNS in ALEX. From a developmental perspective, the MNS is considered to be important for reading the goals

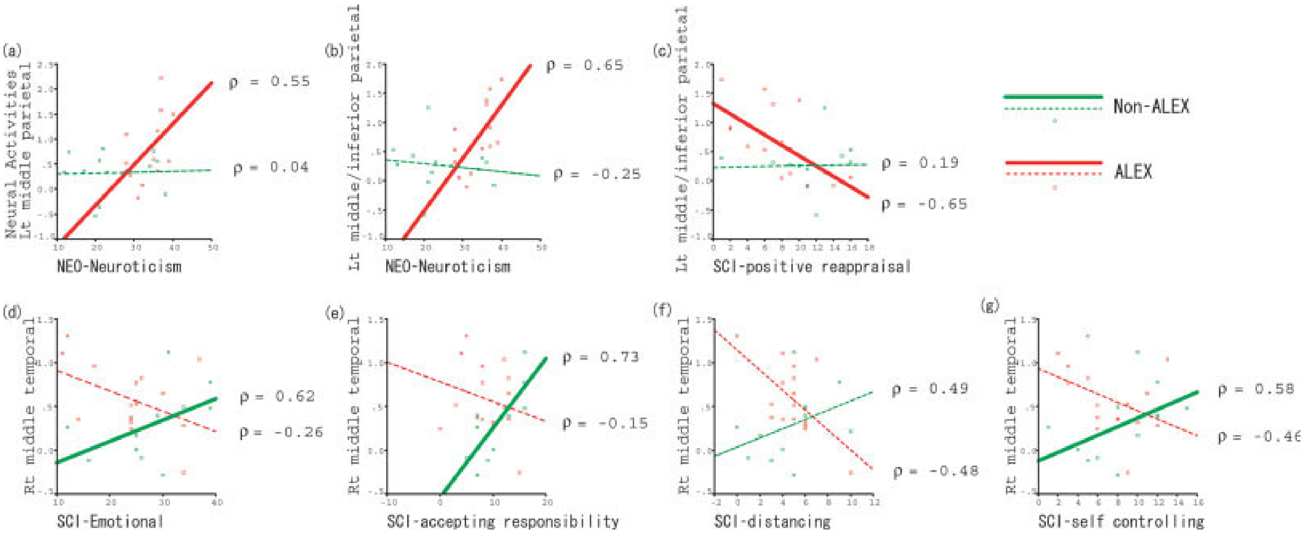

Figure 5.

Correlations between psychological scores and mean activity of the ROIs in response to the MNS task vs. control stimuli for the alexithymia group ($n = 16$; red square and line) and the non-alexithymia group ($n = 13$; green square and line), among the areas showing significant interaction between psychological scores and category levels (with/without alexithymia). The correlation coefficients (Spearman's rho) were calculated and a regression lines were fitted in each group separately. Heavy regression lines indicate correlations with statistical significance ($P < 0.05$). The vertical axes in the graphs indicate the neural activity of the ROI in the left middle parietal cortex (**a**), middle/inferior parietal cortex (**b**, **c**), and right middle temporal cortex (**d**–**g**). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

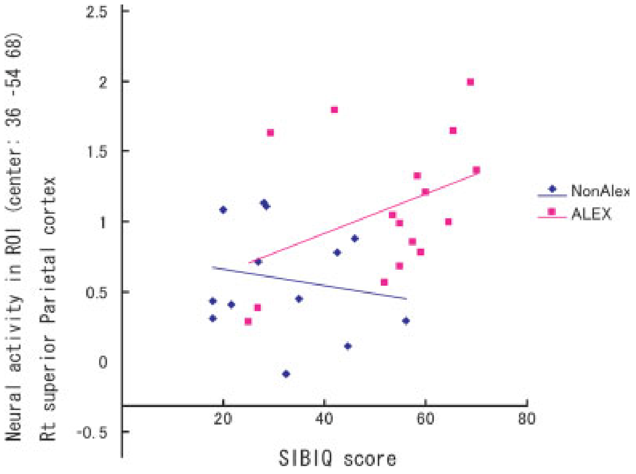

Figure 6.

The correlation between the structured interview for alexithymia (SIBIQ) scores and mean activity of the ROI in the right superior parietal region in response to the MNS task vs. control stimuli for the alexithymia group (*n* = 16; red dots and line) and the non-alexithymia group (*n* = 13; blue dots and line). For the alexithymia group, the correlation coefficient (Spearman's rho) was 0.50 (*P* = 0.048). For the non-alexithymia group, no significant correlation was found. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

and intentions of others' behaviors [Sommerville and Decety, 2006]. It is also involved in the development of language and is thought to be a primitive simulative version of more cognitive mind reading or ToM [Frith and Frith, 2006]. However, Hamilton et al. [2007] recently reported that children with autistic spectrum disorders, despite their deficit in ToM tasks, showed no impairments on an imitation task and even what was described as "superior" performance on a gesture recognition task, even though all of these tasks are thought to rely on the classical motor MNS in typical adults. In addition, autistic people showed lowered MNS-related neural activity than normative controls when observing emotional facial expressions [Dapretto et al., 2006] and meaningless hand movements [Williams et al., 2006] as well as lower neural activity on a ToM task [Brambilla et al., 2004; Castelli et al., 2002; Frith, 2003; Happe et al., 1996; Nieminen-von Wendt et al., 2003]. Indeed, Hamilton et al. [2007] proposed that the classical MNS involved in object-directed hand movements is intact in autistic people, though other MNS components (e.g., regarding emotional recognition) are impaired. The results in studies examining people with autism can be compared with studies of ALEX. Specifically, in people with ALEX, findings have pointed to reduced neural activity in the right IFG (BA44/45) and the inferior parietal lobe (BA40) when observing emotional facial expressions [Kano et al., 2003] as well as reduced activity in the right MPFC in response to a ToM task [Moriguchi et al., 2006]. In this study, classical object-related hand action observation and MNS activation in ALEX was intact and in fact stronger in the ALEX when compared with the non-ALEX group. Thus, the results of this study seem to indicate that people with ALEX, like those with autistic disorders, are fixed at this basic level of comprehension of others, relying on this primitive motor MNS function. Further, higher-level cognitive ToM function does not seem to originate in the motor MNS [Hamilton et al., 2007]. More studies are necessary to clarify the polysemy of the MNS and the functional relationships between the MNS and ToM.

We also found additional MNS related activity and group difference in the posterior middle temporal cortex. Fronto-parietal MNS regions formulate the core of the MNS, which received main visual input from superior/middle temporal areas, and these areas together form the core imitation circuit [Iacoboni and Dapretto, 2006]. Reportedly, listening to action-related sentences and observation of other's body action activate a fronto-parieto-temporal network including the posterior middle temporal gyrus [Tettamanti et al., 2005], the middle/medial superior temporal area (MT/MST), and superior temporal sulcus [Wright and Jackson, 2007], respectively. This study also showed that the neural activity in this posterior middle temporal area was significantly correlated positively with proactive and voluntary stress-coping abilities (emotional, accepting responsibility, and self-control) in the non-ALEX group, contrary to the ALEX group inclining to rather negative correlation. This suggests that, in non-ALEX individuals, visual processing system is correlated with these proactive and voluntary coping abilities, whereas in ALEX population this function is over-activated due to their different mode of visual-related processing. Interestingly, patients with multiple sclerosis, who were also reported to show alexithymic tendency [Bodini et al., 2007], showed increased activation compared to healthy controls in response to mirror neuron task in the right middle occipitotemporal region very similar to the locus found in our study [Rocca et al., 2008]. This finding supports the supposition of altered mode of visual processing in individuals with ALEX.

A limitation of this study was that multiple correlational analyses were computed between hemodynamic ROI activation and psychological measurements, thereby increasing the possibility of a significant result due to chance with each correlational analysis. However, a more conservative corrected threshold would raise the risk of false negative results. Importantly, although the present correlational results provide useful information on the features of hemodynamic activation in each ROI in an exploratory manner, this results are only suggestive values and need to be replicated in future studies.

One should also note that we compared neural/behavioral data of individuals with ALEX with those scoring very low on ALEX in healthy college student participants. Although there has been no evidence that low ALEX scores are associated with any psychiatric characteristics, the detailed features in individuals with low ALEX scores should be cleared in future research. Further, we will have to compare the present data to the data from the patient sample with the same protocol, because the concept of ALEX was originally observed in the patients and we know little about high ALEX in healthy population. Another caveat is that the present sample is composed of a group of young college students, some of whom might be typified as "super-normals," which might affect the generalizability of this findings. Samples with broad spectrum of age and state of life would be needed in the future studies.

In conclusion, our study demonstrated that ALEX is related to greater activation in MNS-related brain areas; namely in the premotor and parietal cortices, which were associated with reduced cognitive empathy and perspective-taking ability. The classic motor MNS, which responds to hand-object interactions, is intact (or stronger) in ALEX, though other MNS processing emotional recognition may not be, as is the case with autistic disorders. Our results also suggest that individuals with ALEX may stagnate in a basic and primitive level of mentalizing, and that ALEX is related to an immature state of inferring the mental state of others without sufficient self-other differentiation. This may leave individuals with ALEX to be prone to being affected by others, leading to deficiencies in emotional regulation.

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