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BRIEF REPORT

Abnormal microstructures of the basal ganglia in schizophrenia revealed by diffusion tensor imaging

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Abstract

There has been a hypothesis that deficits in the basal ganglia–thalamic system may play an important role in the dysfunctional goal-directed behaviour in schizophrenia. By using diffusion tensor imaging, we measured fractional anisotropy (FA) values in the basal ganglia–thalamic system in 42 schizophrenics and 42 matched controls to investigate microstructural tissue alterations in the basal ganglia–thalamic system in schizophrenia. Schizophrenics had significantly lower FA values in the bilateral globus pallidus and left thalamus compared to controls, suggesting that schizophrenics might have microstructural abnormalities in globus pallidus and thalamus. These data support the notion that myelination abnormalities in basal ganglia–thalamic system are related to the pathophysiology of schizophrenia.

Key words: *Schizophrenia, diffusion tensor imaging, basal ganglia, globus pallidus, MRI*

Introduction

Schizophrenia often demonstrated movement abnormalities, such as catatonia, pacing and other stereotyped behaviours considered to be associated with basal ganglia dysfunction. The basal ganglia regulates not only motor behaviours but also aspects of cognitive and limbic behaviours. There has been a hypothesis that deficits in the basal ganglia–thalamic system may play an important role in the dysfunctional goal-directed behaviour in schizophrenia (Andreasen 1999). In fact, several studies demonstrated abnormalities in the basal ganglia in schizophrenic brains, including the volume reductions of the pallidum internum of postmortem brains of patients with schizophrenia (Bogerts et al. 1985), higher volumes in the globus pallidus of previously treated patients with schizophrenia than the healthy comparison subjects and the neuroleptic-naive patients (Gur et al. 1998), fMRI evidence for basal ganglia dysfunction in subjects with schizophrenia (Menon et al. 2001), abnormality of oligodendroglial cells in caudate nucleus in schizophrenia (Uranova et al. 2001), and positive correlation between globus pallidus and the severity of global symptoms in neuroleptic-naive patients (Spinks et al. 2005).

Diffusion tensor imaging (DTI) is a relatively new technique, and it is useful for evaluating white matter abnormalities in schizophrenia. We have reported progressive changes of white matter integrity in schizophrenia using DTI (Mori et al. 2007).

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Recently, this technique was applied to investigate abnormalities of the subcortical regions in neurodegenerative diseases. Patients with Parkinson's disease had significantly decreased fractional anisotropy (FA) in the region of interest along a line between the substantia nigra and the lower part of the putamen/caudate complex, in which the nigrostriatal dopaminergic neurons are lost in Parkinson's disease, demonstrating its possibility to detect microstructural tissue alterations (Yoshikawa et al. 2004). To investigate possible microstructural abnormalities in the basal ganglia–thalamic system in schizophrenia, we measured FA values in the basal ganglia and the thalami in schizophrenics and in normal controls for comparison, as a sub-analysis of our previous study (Mori et al. 2007).

Material and methods

Subjects and clinical assessments

Forty-two patients with DSM-IV schizophrenia (26 male and 16 female, one left hander, mean age: 40.0 ± 9.3 years old, education: 13.0 ± 2.9 years, mean duration of illness; 16.8 ± 9.0 years, mean daily dose of antipsychotics (chlorpromazine equivalent): 1005.1 ± 735.3 mg/day) (Association 1994) and 42 controls (26 male and 16 female, one left hander, mean age: 39.2 ± 9.0 years old, education: 17.1 ± 3.5 years) were participated in our study. Written informed consent was obtained from all the subjects. This study has been approved by the local ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All the normal subjects were screened by a questionnaire on medical history and excluded if they had neurological, psychiatric or medical conditions that could potentially affect the central nervous system. We employed the Japanese version of National Adult Reading Test (JART) as a convenient tool to measure IQ for participants (premorbid IQ for schizophrenics). Patients had fewer years of education (two-sample t-test, $P < 0.0001$), lower scores of JART (controls: 78.8 ± 11.5, schizophrenics: 58.7 ± 25.3, two-sample t-test $P < 0.001$).

Neuroimaging analysis

MR studies were performed on a 1.5-Tesla Siemens Magnetom Vision Plus system. Axial DTI scans aligned to the plane containing anterior and posterior commissures were acquired with a pulsed-gradient, spin-echo, single-shot echo planar imaging (EPI) sequence (TR/TE = 4000/100 ms, 256 × 256 matrix, FOV 240 mm, $b = 1000$ s/mm^2, NEX = 4, 20 slices, 5 mm slice thickness, 1.5 mm gap). Diffusion was measured along six non-collinear directions, because six directions were maximum number of this Vision Plus system. For each of six gradient directions, four acquisitions were averaged. Four acquisitions without diffusion weighting ($b = 0$) were also averaged. Additionally, a three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence with a gapless series of thin sagittal sections using an MPRage sequence (TR/TE = 11.4/4.4 ms; flip angle, 15°; acquisition matrix, 256 × 256; NEX = 1, FOV 315 mm; slice thickness 1.23 mm) was acquired for evaluating the volume of grey matter (GM), WM and cerebrospinal fluid (CSF) space. Seven diffusion images acquired as above by an in-house script described previously (Mori et al. 2007) on Matlab 6.5 software (Mathworks, Inc., MA, USA). Then, the FA images were spatially normalized using high-dimensional-warping algorithm (Ashburner et al. 1999) and were matched to the FA template image (Figure 1, top). To make the FA template image, we warped FA images of four normal subjects (other than 42 control subjects) to the single-subject T1 template (skull stripped image) using spatial normalization function of SPM2 and averaged the four warped FA images. The transformed FA images were smoothed with a Gaussian kernel (the filter size, full-width half-maximum: 6 × 6 × 6 mm).

Since our interest was FA changes in the basal ganglia and thalamus, we excluded other brain areas by using an explicit mask (Figure 1, top). The resultant FA maps were analyzed using Statistical parametric mapping 2 (SPM2), which implements a 'general linear model'. To test hypotheses about regional population effects, data were analyzed by a two-sample t-test without global normalization. JART scores were treated as nuisance variables. Furthermore, we performed correlational analyses between duration of illness, age of onset, total daily dose of antipsychotic drugs (chlorpromazine equivalent) and FA value in the schizophrenics. Our a priori hypothesis is limited to the basal ganglia; however, investigation of the FA changes within this ROI is null hypothesis. Thus, we used $P < 0.05$, corrected for multiple comparisons with Family–Wise Error rate (FWE) within basal ganglia as a statistical threshold.

Results

In comparison with controls, schizophrenics had significantly lower FA values in the bilateral globus pallidus (GP) (Figure 1, bottom). Increased FA values in schizophrenics were not found in any regions (data not shown).

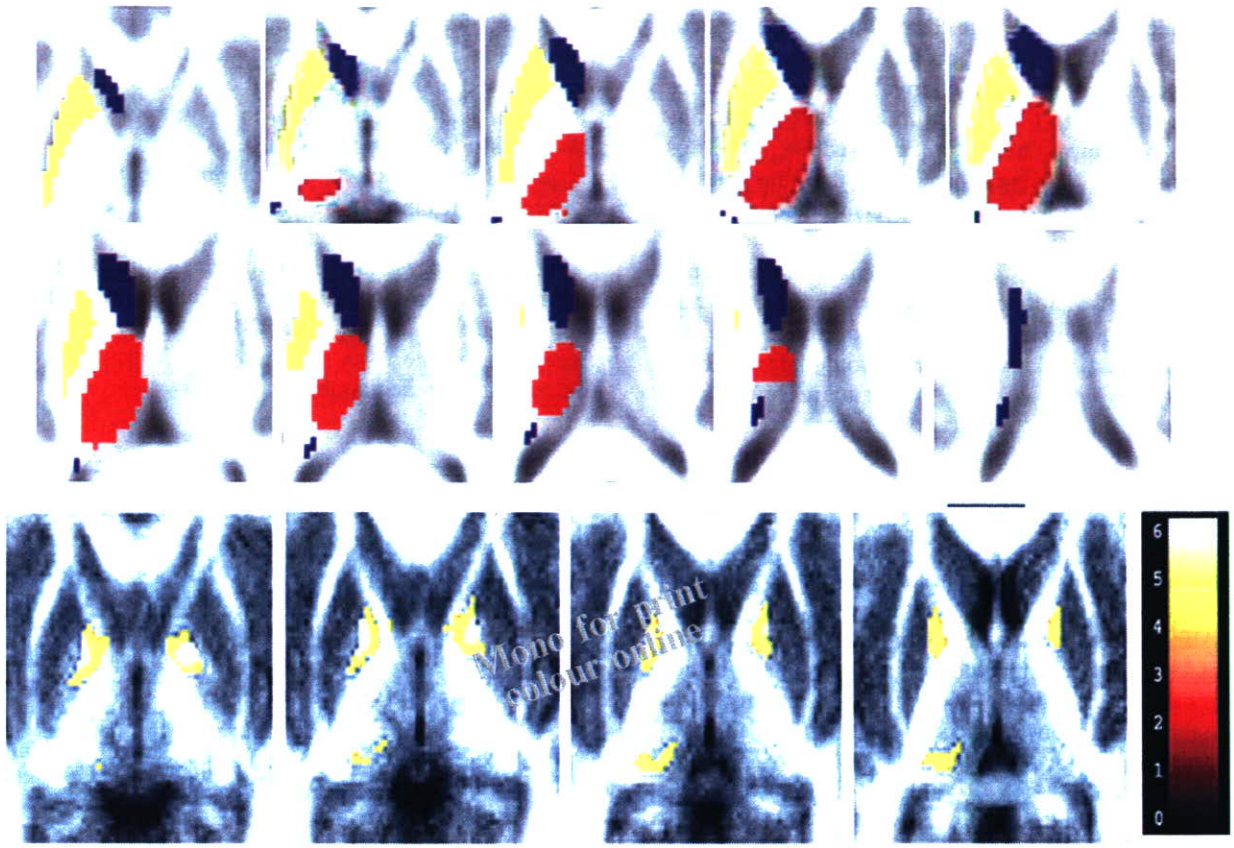

Figure 1. Top: A half of the explicit mask is displayed onto mean FA images of warped FA images obtained from 42 controls (dark blue: caudate nucleus; yellow: putamen; light blue: globus pallidus; red: thalamus). Even after averaging, the mean images are not blurred. Since globus pallidus is traversed by numerous myelinated nerve fibres, it shows higher FA value than other parts of basal ganglia. Bottom: The SPM {t} is displayed onto mean axial FA images of 42 schizophrenics. A significant reduction of FA value in schizophrenia was noted in the bilateral globus pallidus (right GP: t value = 6.52, Talairach coordinate x, y, z: 18, −2, −2, left GP: t value = 6.37, Talairach coordinate x, y, z: −18, −3, −2) and left thalamus (t value = 4.96, Talairach coordinate x, y, z: −18, −33, 10).

A correlational analysis in the schizophrenics demonstrated a significantly negative correlation between duration of illness and FA in the left head of the caudate nucleus (t value = 4.77, Talairach coordinate x, y, z: −11, −17, −6). However, there is no significant correlation between duration of illness and FA values in the GP and the thalamus. There was no significant correlation between FA values in the basal ganglia–thalamic system with age of onset or total daily dose of antipsychotic drugs.

Discussion

In this study, we found a significantly reduced FA value in the bilateral GP and left thalamus in schizophrenics compared to controls. We consider that reduced FA may reflect microstructural abnormalities in the basal ganglia–thalamic system in schizophrenia. A previous fMRI study suggested that GP itself may be the primary locus of the functional deficits in the basal ganglia and may be dysfunctional in schizophrenia (Menon et al. 2001). A postmortem study of basal ganglia morphology reported that only the GP were smaller in schizophrenics than in controls (Bogerts et al. 1985). These studies indicated functional and structural abnormalities in GP in schizophrenia. Our data, reduced FA in GP in schizophrenia, were obtained using a size-adjusted high-dimensional warping method (Ohnishi et al. 2006). Our results, microstructural abnormalities in the GP in schizophrenia, are consistent with previous reports.

Although the underlying mechanisms remain to be clarified, previous DTI studies in parkinsonism have well demonstrated ongoing pathological changes in neurodegenerative diseases, suggesting that this technique has the potential to detect microstructural alterations in the basal ganglia (Yoshikawa et al. 2004). Since pathological findings of schizophrenia are still ambiguous, the underlying pathological changes of reduced FA values in schizophrenia are unclear. However, multiple lines

of evidence now converge to implicate oligodendroglia and myelin in schizophrenia (Davis et al. 2003). We assume that damage of myelinated nerve fibres may contribute to FA reduction in the basal ganglia–thalamic system. The GP is traversed by numerous myelinated nerve fibres that give it the pale appearance for which it is named, and has rich connections to the putamen and the thalamus. These histological characteristics of the GP may contribute to its higher FA values. A qualitative electron microscopic study reported the density of concentric lamellar bodies (an indicator of damage of myelinated fibres) was dramatically increased in the caudate nucleus in schizophrenia, as compared to controls (Uranova et al. 2001). Such pathological changes seem to explain decreased FA values in the schizophrenic brain. However, there have been no data on whether GP also have alterations of myelinated fibres. Further pathological studies need to be conducted to draw a firm conclusion on this matter.

Although some studies demonstrated abnormalities of GP in neuroleptic-naïve schizophrenics (Spinks et al. 2005), abnormalities in the basal ganglia have been considered to relate to antipsychotic medication (Gur et al. 1998). In this study, FA changes in the GP and thalamus were not associated with the duration of illness or the daily dose of antipsychotic drugs, suggesting that FA changes in these regions might be independent of medication with neuroleptics. Guidelines for the biological treatment of schizophrenia developed by an international Task Force of the World Federation of Societies of Biological Psychiatry recommended atypical antipsychotics as first line drugs (Falkai et al. 2005, 2006). The differential treatment effects on brain morphology could be due to typical antipsychotics-associated toxicity or greater therapeutic effects of atypical antipsychotics (Lieberman et al. 2005). It would be interesting to compare patients treated with atypical antipsychotics to those with a history of typical antipsychotics treatment; however; the subgroup of patients that were only treated with atypical antipsychotics or the subgroup of patients that were only treated with typical antipsychotics were too small to investigate a possible difference between two groups in FA in our sample. To conclude whether observed change of FA value is a result of medication or relates to the pathophysiology of schizophrenia itself, longitudinal studies on treated schizophrenics, and studies on neuroleptic-naive schizophrenics should be conducted.

There is a limitation to our study: we used a 1.5-Tesla Siemens Magnetom Vision Plus system, which is a relatively old system. We chose six gradient directions, which is quite low, as this number is the maximum number of directions in this system. Slice thickness of 5 mm and 1.5-mm slice gaps are methodological drawbacks to this study. The reason why we used a slice thickness of 5 mm and 1.5-mm slice gaps is to cover the whole brain as in our previous study (Mori et al. 2007). There may be a partial volume effect in our mapping parameters, although we minimized the problem by using the high-dimensional warping algorithm.

Our data suggest that patients with schizophrenia might have microstructural abnormalities in globus pallidus and thalamus. The DTI study may be a promising method to investigate microstructural abnormalities in schizophrenia.

Acknowledgements/Statement of interest

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Empathy and Judging Other's Pain: An fMRI Study of Alexithymia

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Because awareness of emotional states in the self is a prerequisite to recognizing such states in others, alexithymia (ALEX), difficulty in identifying and expressing one's own emotional states, should involve impairment in empathy. Using functional magnetic resonance imaging (fMRI), we compared an ALEX group (n = 16) and a non-alexithymia (non-ALEX) group (n = 14) for their regional hemodynamic responses to the visual perception of pictures depicting human hands and feet in painful situations. Subjective pain ratings of the pictures and empathy-related psychological scores were also compared between the 2 groups. The ALEX group showed less cerebral activation in the left dorsolateral prefrontal cortex (DLPFC), the dorsal pons, the cerebellum, and the left caudal anterior cingulate cortex (ACC) within the pain matrix. The ALEX group showed greater activation in the right insula and inferior frontal gyrus. Furthermore, alexithymic participants scored lower on the pain ratings and on the scores related to mature empathy. In conclusion, the hypofunction in the DLPFC, brain stem, cerebellum, and ACC and the lower pain-rating and empathy-related scores in ALEX are related to cognitive impairments, particularly executive and regulatory aspects, of emotional processing and support the importance of self-awareness in empathy.

Keywords: anterior cingulate cortex, dorsolateral prefrontal cortex, emotion regulation, empathy, self-awareness

Introduction

The construct of empathy refers to the ability to identify with and vicariously share the feelings and thoughts of others. This naturally occurring subjective experience of similarity between the feelings of self and others is an important aspect of building interpersonal relationships. However, there are several essential aspects of empathy: 1) an affective response to another person, which often, but not always, entails sharing that person's emotional state (affective component); 2) a cognitive capacity to take the perspective of the other person (cognitive component); and 3) some regulatory mechanisms that keep track of the origins of self and other feelings (Decety and Jackson 2004). An integrative model of empathy was proposed by Preston and de Waal (2002). This model draws on that the perception of actions or emotions automatically activates the neural mechanisms that are responsible for the generation of those actions or emotions. Such a system prompts the observer to resonate with the emotional state of another individual, as a result of the observer activating the motor representations and associated autonomic and somatic responses that stem from the observed target.

In support of this perception–action integrative model, recent functional neuroimaging studies revealed shared neuronal substrates for empathy to the pain of others (Morrison et al. 2004; Singer et al. 2004; Botvinick et al. 2005; Jackson et al. 2005, 2006; Lamm et al. 2007; Saarela et al. 2006). These studies have indicated that watching others in painful situations taps into the neural mechanisms that mediate the affective-motivational component of pain processing. Notably, the anterior cingulate cortex (ACC) and anterior insula are similarly activated by the experience of pain in the self and by the observation of others in painful situations.

Self-awareness is a fundamental aspect of empathy because the individual's recognition of their own feelings is the basis for identification with the feelings of others (Gallup 1998; Decety and Jackson 2004). Individuals with alexithymia (ALEX) are typically unable to identify, understand, or describe their own emotions. Psychiatric and psychosomatic patients with ALEX are unable to talk about feelings due to a lack of emotional self-awareness (Sifneos 1972, 1996). ALEX has been repeatedly found in psychiatric disorders that have deficits in the recognition of feelings belonging to the self and identification with others, such as autism and Asperger syndrome (Frith 2004; Hill et al. 2004; Berthoz and Hill 2005), schizophrenia (Stanghellini and Ricca 1995; Cedro et al. 2001), and borderline personality disorder (Guttman and Laporte 2002). ALEX has also been found in psychopathic personality disorder, where there is a deficit in empathy (Haviland et al. 2004).

Although the concept of ALEX was originally used to describe the characteristics of psychosomatic patients, recently it has been used to refer to deficits in emotional functioning in broader populations (Taylor et al. 1997; Taylor and Bagby 2004). Some researchers hypothesized that ALEX is associated with brain abnormalities (Hoppe and Bogen 1977; Nemiah 1977; Buchanan et al. 1980). Neuroimaging studies found that ALEX may be associated with a higher level cognitive deficit in estimating emotional inputs—in which the ACC plays a crucial role—rather than a lack of neuronal response in structures representing lower level processing of emotional stimuli (Berthoz et al. 2002; Kano et al. 2003). ALEX has also been found to be related to dysfunction in the posterior cingulate cortex during various mental imagery conditions (Aleman 2005; Mantani et al. 2005). Lane et al. (1997) stressed the core feature of ALEX as a deficit in conscious awareness of emotions (e.g.,

differentiating, symbolizing emotions, and appreciating complexity in the experience of self and other). Thus, ALEX refers to an impairment in not only affective but also cognitive emotional processing.

To our knowledge, the concept of ALEX itself does not explicitly include deficits in empathy. However, the lack of knowledge of their own emotional experiences should be associated with a lack of empathy in alexithymics (e.g., Krystal 1979; see also levels of emotional awareness in Lane and Schwartz 1987). Vorst and Bermond (2001) argued that an important aspect of ALEX is "operative thinking" (i.e., preoccupation with "things" at the expense of object relations), which covers many aspects of ALEX including the lack of empathy.

The notion of "shared representations" between self and other accounts for the functional computational properties that emerge from the direct link between perception and action (Decety and Sommerville 2003; Decety and Jackson 2004, 2006; Sommerville and Decety 2006). Because empathy relies on vicarious sharing of the feelings and thoughts of others, this common representational network between the self and others in conjunction with self-other awareness provides the basic mechanism for empathy (Decety and Sommerville 2003; Decety and Jackson 2004, 2006; Decety and Grèzes 2006). From this perspective, we propose that ALEX (which is a deficit in identifying emotional states in oneself) may be associated with (or lead to) an impairment in empathy (connecting to other's emotional states). In line with this idea, some studies demonstrated that individuals with ALEX show poor performance in identifying the emotional values of facial expressions (e.g., Parker et al. 1993; Lane et al. 1996). Only a few studies, however, have focused on the relationship between ALEX and empathetic ability (Rastam et al. 1997; Guttman and Laporte 2002). Moreover, their results are not conclusive as to whether a deficit in empathetic ability is an essential component of ALEX.

The purpose of the present study was to explore whether individuals with ALEX have deficit in empathetic ability, and if so, what aspect of empathy is impaired. We measured the neurohemodynamic activity with functional magnetic resonance imaging (fMRI) in participants with ALEX as compared with non-alexithymic controls, in potentially empathic situations involving both cognitive and affective aspect of pain-processing network (response to pictures depicting human hands and feet in potentially painful situations and judging the degree of pain in those situations; cf., Jackson et al. 2005). In addition, we compared the scores assessing the empathy-related abilities in the 2 groups. We hypothesized that the ALEX group would score lower on pain- and empathy-related scores and show different neural response in pain-related regions demonstrated by previous neuroimaging studies about pain processing, for example, the primary and secondary somatosensory cortices, the posterior insula, the ACC, the middle and anterior insula, thalamus, brain stem, and lateral prefrontal cortex (for reviews, Davis 2000; Peyron et al. 2000; Rainville 2002).

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.

Subjects

Three hundred and ten college students completed the 20-item Toronto Alexithymia scale (TAS-20; Taylor et al. 2003). Individuals with high and low TAS-20 total scores (n = 20, top quartile score > 60; n = 18, bottom quartile score < 39) were selected in order to obtain a sample with as large a variance on ALEX as possible. Thirty-seven students gave informed written consent and participated in the experiment (Table 1). Participants were interviewed using the mini international neuropsychiatric interview (Sheehan et al. 1998). No subject had any history of neurological, major medical, or psychiatric disorder. All participants were right handed, as assessed by the Edinburgh handedness inventory (Oldfield 1971). The participants were the same as reported in our previous study about the association between ALEX and mentalizing (Moriguchi et al. 2006). However, the present studies were conducted in a completely different setting. In the present study, we focus only on the analyses of the other's pain perception paradigm.

The whole sample described above (n = 37) was divided into 2 groups based on the cutoff scores on the TAS-20: ALEX (TAS > 60) and non-alexithymia (non-ALEX; TAS < 39) groups. The structured interview, modified edition, of the Beth Israel hospital psychosomatic questionnaire (SIBIQ; Arimura et al. 2002) was used to further confirm the presence or absence of ALEX. Four participants with high TAS-20 and low SIBIQ scores, and 3 with low TAS-20 and high SIBIQ scores, were discarded. Table 1 gives comparative information about the resulting ALEX group (n = 16) and non-ALEX group (n = 14).

Psychological Instruments

The TAS-20 (Taylor et al. 2003; the Japanese version by Komaki et al. 2003) is a 20-item self-administered questionnaire. The items are scored on a 5-point scale from strongly disagree to strongly agree. The TAS-20 has a 3-factor structure. Factor 1 assesses difficulty in identifying feelings. Factor 2 assesses difficulty in describing feelings. Factor 3 assesses externally oriented thinking.

The SIBIQ for ALEX (Arimura et al. 2002) is based on the Beth Israel hospital psychosomatic questionnaire (Sriram et al. 1988), used mainly with psychosomatic patients. The SIBIQ was developed for patients with some physical or psychiatric symptoms, and they were asked to describe how they perceived 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 some situations that are generally supposed to cause emotional responses (similar to the Alexithymia-provoked response questionnaire [Krystal et al. 1986]) and required them to answer in terms of their own emotions. The testers rated these answers on the scale of the SIBIQ. The SIBIQ was conducted by 2 medical doctors, who were acquainted clinically with ALEX, and their 2 scores were averaged for each subject. 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.

Table 1
Appearance of TAS-20 and SIBIQ scores in the 2 groups

	Whole	Non-ALEX	ALEX
n (Male/female)	37 (7/30)	14 (2/12)	16 (3/13)
Age, mean (SD) (years)	20.4 (0.94)	20.8 (0.89)	20.2 (1.0)
TAS-20	Minimum-maximum, mean (SD)		
Total	26-74, 51.2 (16.5)	26-38, 34.1 (3.7)	61-74, 66.1 (4.5)
F1	7-32, 18.0 (8.1)	7-19, 10.6 (3.7)	19-32, 24.7 (3.9)
F2	5-25, 15.4 (6.2)	5-18, 9.6 (3.9)	15-24, 20.1 (2.4)
F3	9-30, 17.9 (5.1)	9-21, 13.9 (3.3)	13-30, 21.4 (4.0)
SIBIQ total	18-70, 42.2 (16.7)	18-56, 31.5 (11.8)	25-70, 52.2 (14.1)

Note: F1 (factor 1), difficulty in identifying feeling; F2 (factor 2), difficulty in describing feeling; F3 (factor 3), externally oriented thinking; SD, standard deviation. 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 = 14) and ALEX (n = 16) groups were obtained from this whole sample excluding the participants with discrepancy between TAS-20 and SIBIQ scores (cf., **Materials and Methods**).

The emotional empathy scale (EES; Mehrabian and Epstein 1972; Japanese version developed by Kato and Takagi 1980) is a self-administered questionnaire that measures the ability of "emotional empathy," defined as an affective response to somebody else's emotional experience. Mehrabian and Epstein (1972) had made the items of EES with expectation of multiple subscales of EES, but no subscales were extracted, although the Japanese version was subdivided into 3 components (Kato and Takagi 1980) in the Japanese population as follows: 1) Emotional warmth; a tender and compassionate attitude toward other's feelings. People with emotional warmth are impressionable in response to art, novel, and movies, as well as other's sorrow and distress, and sometimes participate in voluntary activities. 2) Emotional chill; an apathetic and sometimes disfavoring attitude toward other's feeling like sorrow, distress, and joy etc. Such people always keep others at a distance. 3) Emotional affectedness; a tendency to be easily influenced by other's feelings. It is almost the same as "emotional contagion."

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 4 scales, each measuring a distinct component of empathy: 1) empathic concern, feeling emotional concern for others and 2) perspective taking, cognitively taking the perspective of another, related to social competence. The factors (1) and (2) were characterized as desirable interpersonal styles. 3) fantasy, emotional identification with characters in books, films, etc. and 4) personal distress, negative feelings in response to the distress of others.

The stress coping inventory (SCI; Lazarus and Folkman 1984; Japanese version developed by the Japanese Institute of Health Psychology 1996) was used to investigate the participants' character and coping style in response to emotional stimuli. The SCI has 2 major factors: 1) cognitive coping strategy and 2) emotional coping strategy. There are 8 subscales on 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 version of these psychological scales (the TAS-20, EES, IRI, and SCI) were the ones that have been translated into Japanese using back-translation method, and the factor analyses of these Japanese versions showed the same factor components as the original English versions except for the EES. However, the concurrent validity and reliability in each psychological measurement have been confirmed, indicating that the Japanese version of each psychological test measures the same aspects as the original one.

Picture Stimuli

The picture stimuli had been previously developed and validated by Jackson et al. (2005) and were used with their permission. The picture stimuli consisted of a series of digital color pictures that showed right hands and right feet in painful and nonpainful situations, shot from angles that facilitate a first-person perspective (i.e., no mental rotation of the limb is required for the observer). All situations depicted familiar events that can happen in everyday life. Various types of pain (mechanical, thermal, and pressure) were represented. The target persons in the pictures varied in gender and age (between 8 and 56 years), and their limbs and arms were smoothed in order to avoid any influences of age and gender on judgments. For each painful situation, there was a corresponding neutral picture, which involved the same setting without any painful component. The 96 painful pictures used in this study were selected from a larger sample, on the basis of the pain intensity ratings of 20 independent subjects. All pictures were edited to the same size and resolution (600 × 600 pixels).

Scanning Method and Procedure

Participants took part in one fMRI session. The session consisted of 26 blocks. The participants were asked to watch and assess the pictures depicting right hands or feet in painful situations as a task condition (12 blocks) and right hands or feet in neutral situations as a control condition (12 blocks). The baseline trials showed a static cross (2 blocks at the middle and end of the session). The order of conditions was randomized within the session. No picture was presented more than once throughout the whole experiment. Each task or control block consisted of eight 4-s trials of the same condition. Each picture was shown for 2 s, followed for 2 s by a modified faces pain-rating scale (Wong and Baker 1988) that illustrated the 4-point Likert-type pain scale (no pain [0], a little pain [1], moderate pain [2], and worst possible pain [3]). In the baseline trials, subjects were asked to passively look at the central cross for 4 s and were not shown the pain-rating scale. In the task and control conditions, subjects were instructed to rate the intensity of pain they thought the person in the picture would feel in each situation. At the end of each task and control trial, they used a 4-button response box under their right hand to select the rating (thumb = 0, index = 1, middle finger = 2, and fourth finger = 3). The participants were required to press the button in every trial in the task and the control condition along the scale, thereby controlling for the motor output involved in the rating process across the 2 conditions. Participants were provided with several training trials prior to the scanning session in order to be acquainted with the rating scale and the task within the allotted time. The pictures used in the training trials were different from those used as stimuli for the fMRI measurements.

Data Acquisition and Analyses

Magnetic resonance imaging data were acquired on a 1.5-T Siemens Magnetom Vision Plus System. Changes in blood oxygenation level-dependent T_2*-weighted magnetic resonance (MR) signal (Ogawa et al. 1990) were measured using a gradient echo-planar imaging (EPI) sequence (repetition time [TR] = 4000 ms, echo time [TE] = 40 ms, field of view [FOV] = 220 mm, flip angle = 90 degree, 64 × 64 matrix, 40 slices per slab, slice thickness 3.0 mm, 0.3 mm gap, voxel size = 3.44 × 3.44 × 3.3 mm). For each scan session, a total of 213 EPI volume images were acquired along the AC–PC plane. Structural MR images were acquired with a magnetization-prepared rapid gradient echo sequence (TE/TR, 4.4/11.4 ms; flip angle, 15 degree; acquisition matrix, 256 × 256; 1 NEX FOV, 31.5 cm; slice thickness, 1.23 mm). The first 5 volumes of EPI images were discarded because of instability of magnetization; therefore, we obtained 208 volumes of EPI for analysis.

The stimuli were projected onto a screen, ~50 cm from the subject'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 subjects' T_1-weighted MR images. Then the T_1 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 a 6-mm full-width half-maximum Gaussian kernel. A first fixed level of analysis was computed subjectwise using the general linear model with hemodynamic response function modeled as a boxcar function whose length covered the 8 successive pictures of the same type.

To test the hypotheses about regionally specific effects in the painful picture condition, the estimates were compared by means of linear contrasts for each epoch (painful picture epoch as task condition versus neutral picture epoch as control). The resulting set of voxel values for each contrast constituted a statistical parametric map (SPM) of the t-statistic SPM (t). Anatomic localization was presented as MNI coordinates, and to check the localization of the Brodmann area (BA), 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 painful pictures were computed using 1-sample tests for each ALEX (n = 16) and non-ALEX group (n = 14) separately and subsequent conjunction analysis of both 1-sample tests to show overlapping activations between 2 groups. The analyses were done for each of the contrasts of interest, which yielded a SPM of the t-statistic (SPM [t]), 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 = 2.26 for non-ALEX group, 2.42 for ALEX group, 2.58 for conjunction analysis) was used to identify other pain-related regions, compared against the null hypothesis.

To compare the differences in neural activity between the ALEX group (n = 16) and the non-ALEX group (n = 14), 2-sample tests were

used. The height and extent thresholds were set at $Z = 3.09$ ($P < 0.001$ uncorrected) and $k = 20$, respectively. For the areas with an a priori pain-related hypothesis (derived from Singer et al. 2004; Jackson et al. 2005, 2006), we applied more lenient height and extent thresholds; $Z = 2.6$ ($P < 0.005$ uncorrected) and $k = 20$, respectively (adopted from Raij et al. 2005) within the regions activated in the 1-sample group tests and conjunction analysis to reduce the risk of false negatives. If the regions with significant differences were included in an a priori pain matrix confirmed by the previous studies (Peyron et al. 2000; Morrison et al. 2004; Singer et al. 2004; Jackson et al. 2005, 2006; Raij et al. 2005), we confirmed them as group effects on pain-related activations. The a priori regions were obtained from regions that had been emphasized as important components and frequently reported in the literature, that is, the primary and secondary somatosensory cortices, the posterior insula, the caudal ACC, the middle and anterior insula, thalamus, brain stem, and lateral prefrontal cortex (Davis 2000; Peyron et al. 2000). To further clarify the characteristics of regions with group differences in the a priori pain matrix, we made regions of interest (ROIs) consisted of 20 voxels centered on each peak coordinate found in the group comparisons in the present study and calculated individual mean contrast values (task minus control) for each ROI using Marsbar software (http://marsbar.sourceforge.net). The correlation coefficients between pain ratings and neural responses within pain-related regions were calculated. (ROI corrected $P < 0.05$). The correlation coefficients between these ROI mean contrast values and psychological measurement scores were also calculated to investigate the features of the regions with group differences.

Results

Behavioral Measures

In the one sample, the individual ratings of painful pictures were significantly higher than those of neutral control pictures (paired *t*-test: mean [standard deviation (SD)] score of sum of task pictures' ratings in each subject; 34.2[3.6], control pictures' ratings; 12.2[2.0], $T = 343$, $P < 10^{-28}$). Table 2 compares the scores for the pain ratings, IRI, EES, and the SCI between the ALEX ($n = 16$) and the non-ALEX groups ($n = 14$). Alexithymic participants showed lower pain ratings than non-alexithymics, indicating that they attributed lower levels of pain to the people depicted in the painful situation pictures. They scored lower on the IRI scales assessing "perspective taking" and "empathic concern," suggesting that they were less able to take the perspective of another and had less empathy. On the EES, alexithymics scored less on "warmth." Alexithymics scored lower on the SCI scales of "cognitive," "problem solving," and "positive reappraisal," indicating that they were less likely to use these approaches to manage emotional stimuli. On the other hand, alexithymics had significantly higher "personal distress" scores on the IRI.

Table 2
Comparison of psychological measurements in the ALEX and non-ALEX groups

	Mean (SD)		
	Non-ALEX ($n = 14$)	ALEX ($n = 16$)	T
Pain ratings	23.8 (3.0)	21.0 (4.3)	2.08*
IRI			
Fantasy	19.9 (6.7)	17.7 (5.6)	1.01
Perspective taking	18.5 (4.9)	14.6 (3.4)	2.61*
Empathic concern	20.0 (3.7)	16.1 (4.9)	2.48*
Personal distress	12.5 (3.7)	15.8 (4.1)	−2.31*
EES			
Warmth	58.0 (3.2)	49.2 (7.9)	3.93**
Chill	29.3 (10.2)	35.6 (8.6)	−1.89
Affectedness	21.0 (7.1)	22.0 (3.0)	−0.53
SCI			
Cognitive	36.9 (12.4)	26.3 (10.7)	2.57*
Emotional	27.7 (8.1)	23.9 (7.4)	1.30
Problem solving	10.7 (4.7)	7.4 (4.0)	2.11*
Confrontational	5.9 (2.1)	5.5 (2.5)	0.55
Seeking social support	6.9 (3.8)	4.6 (3.7)	1.74
Accepting responsibility	10.6 (3.8)	8.4 (4.4)	1.49
Self-controlling	8.1 (3.9)	6.9 (3.4)	0.91
Escape-avoidance	6.1 (2.6)	4.8 (1.7)	1.61
Distancing	4.7 (2.9)	4.9 (2.1)	−0.21
Positive reappraisal	11.6 (4.0)	7.7 (4.1)	2.63*

Note: SD, standard deviation.
*$P < 0.05$.
**$P < 0.001$.

The fMRI Data

One-Sample Analyses and Conjunction Analysis

Tables 3–5 and Figures 1–3 give the results of 1-sample tests (one for each group) throughout the whole brain related to higher activations in response to the painful pictures than the neutral pictures and conjunction analysis of both groups. Tables 3–5 give representative coordinates in pain-related regions; all the coordinates are listed in Table 1 in the Supplementary Materials. In each group and conjunction analysis, a similar activity pattern was found. Significant signal changes were detected in the dorsal ACC (Lt > Rt, BA 24/32), anterior insula (Lt > Rt, BA 13), middle/inferior lateral prefrontal cortices (Lt > Rt, BA 9/10/11/44–47), and postcentral/superior parietal cortices (Lt > Rt, BA 2; Rt > Lt, BA 1/2/3/5/7) adjacent to inferior parietal lobule (BA 40), thalamus (Rt > Lt), brain stem (dorsal pons/midbrain), and cerebellums (Rt > Lt). Additionally, activations were also found in the visual-related/fusiform areas/uncus (BA 18/19/20), superior/middle frontal gyrus (BA 6), and inferior frontal gyrus (BA 44/46). The only exception is that no significant activity was found in the pons in the ALEX group in contrast to high activity in this region in the non-ALEX group; also there was no activation in the pons in the conjunction analysis.

We calculated the correlation between neural activations in response to painful pictures and the individual pain ratings in all participants. Within the activated areas identified in the previous and present studies of perception of others in pain network, we found positive correlations between the rating scales and neural activities in the following areas: ROIs on the right caudal ACC (BA 32, center [x, y, z] [mm] = [10, 28, 40], $r = 0.44$, $P = 0.00312$), sensory association cortex (BA 7 [(28, −68, 54), $r = 0.59$, $P = 0.00006$], BA 40 [(40, −50, 50), $r = 0.63$, $P = 0.00002$]), left lateral prefrontal cortex (BA 9, [−20, 52, 34], $r = 0.41$, $P = 0.00587$), right dorsal pons ([12, −34, −40], $r = 0.52$, $P = 0.00055$), left thalamus ([−8, −12, 4], $r = 0.40$, $P = 0.00769$), and right cerebellum ([18, −60, −16], $r = 0.54$, $P = 0.00031$).

Group Comparison Analysis

We compared the ALEX ($n = 16$) group with the non-ALEX ($n = 14$) group, examining group effects on neuronal activity in response to painful pictures controlled with neutral pictures (Table 6, Fig. 4). We found lower hemodynamic activity in the ALEX group compared with non-ALEX group in the left dorsolateral prefrontal cortex (DLPFC) (BA 8/9/10) in the posterior lobes of cerebellar cortices, dorsal pons, left middle/superior frontal gyrus (BA 6/8), and right middle temporal gyrus ($P < 0.001$ uncorrected, $k = 20$). Although the ACC did not show a significant difference with the chosen threshold, we found

Table 3
Coordinates and *Z* and *T* scores for the pain-related brain areas activated in response to painful picture stimuli in a 1-sample test for the non-ALEX group

Area	BA	MNI *x*, *y*, *z* (mm)	*T*	*Z*
ACC				
Lt	24	−10, 2, 52	4.9	4.13***
	32	−8, 14, 48	5.74	4.63***
Rt	24	8, −2, 36	3.61	3.24**
	32	12, 16, 42	3.92	3.47*
Cerebellum				
Lt anterior culmen	—	−32, −34, −38	9.06	6.14****
Rt posterior declive	—	26, −64, −28	9.39	6.26****
DLPFC				
Lt inferior frontal	9	−54, 10, 32	8.3	5.85****
	10	−50, 44, 0	6.68	5.12****
	45	−56, 14, 2	4.03	3.55*
	46	−46, 36, 14	8.17	5.8****
Lt middle frontal	9	−42, 36, 40	4.56	3.91***
	10	−42, 50, 16	6.69	5.13****
	11	−44, 54, −14	5.25	4.34***
Lt superior frontal	9	−20, 56, 34	6.69	5.13****
	10	−34, 56, 20	5.95	4.74*
Rt inferior frontal	9	56, 10, 32	5.83	4.68***
	45	56, 10, 26	5.39	4.43*
Rt middle frontal	11	50, 50, −16	2.27	2.16**
	46	54, 32, 30	4.66	3.97***
	47	52, 48, −8	4.04	3.55**
Rt superior frontal	10	24, 72, 4	2.95	2.73**
Insula				
Lt anterior	13	−30, 16, 8	3.51	3.17*
	—	−40, −10, 0	2.3	2.18**
Rt anterior/inferior frontal	13	44, 24, 12	3.42	3.1*
Midbrain				
Lt	—	0, −32, 0	5.87	4.7***
Lt substantia nigra	—	−10, −20, −16	4.06	3.57*
Rt	—	6, −18, −22	2.74	2.56*
Pons	—	−2, −38, −42	5.37	4.42***
Primary somatosensory cortex				
Lt inferior parietal lobule	40	−40, −50, 58	8.06	5.75****
Lt postcentral gyrus	3	−34, −36, 48	5.03	4.21*
	1	−60, −28, 42	8.72	6.01*
Rt postcentral gyrus	5	36, −46, 58	5.47	4.48*
	2	52, −28, 44	9.54	6.32****
Secondary somatosensory cortex				
Lt postcentral gyrus	40	−62, −20, 22	3.76	3.35*
Rt inferior parietal lobule	40	68, −36, 36	2.41	2.28**
Rt postcentral gyrus	3/40	62, −20, 36	7.76	5.62****
Thalamus				
Lt/ventral lateral nucleus	—	−14, −14, 10	5.72	4.62***
Rt/ventral anterior nucleus	—	16, −6, 12	4.54	3.9***

Note: Lt, left; Rt, right.
*$P < 0.05$ false discovery rate (FDR) corrected in each ROI.
**$P < 0.05$ FDR corrected (height threshold: $t = 2.26$).
***$P < 0.001$ FDR corrected (height threshold: $t = 4.28$).
****$P < 0.05$ family wise error (FWE) corrected (height threshold: $t = 6.39$).

Table 4
Coordinates and *Z* and *T* scores for the pain-related brain areas activated in response to painful picture stimuli in a 1-sample test for the ALEX group

Area	BA	MNI *x*, *y*, *z* (mm)	*T*	*Z*
ACC				
Lt	24	0, 6, 28	4.05	3.6**
	32	−8, 24, 40	4.96	4.2***
Rt	24	6, 24, 16	2.62	2.5**
	32	6, 8, 52	4.93	4.2***
	8/32	6, 16, 48	4.98	4.2*
Cerebellum				
Lt posterior pyramis/vermis	—	0, −74, −38	5.18	4.3***
Rt posterior uvula	—	12, −74, −44	7.18	5.4****
DLPFC				
Lt inferior frontal	47	−52, 18, −6	4.1	3.6*
	45	−58, 20, 24	4.44	3.8*
	46	−46, 34, 12	6.79	5.2****
	9	−56, 8, 32	6.95	5.3****
	44	−56, 8, 20	6.98	5.3*
Lt middle frontal	11	−46, 52, −12	3.58	3.2*
	10	−32, 60, 10	5.44	4.5***
Rt inferior frontal	47	56, 22, −6	3.73	3.3*
	45	54, 28, 6	5.14	4.3***
	9	56, 8, 32	6.29	4.9***
	10	34, 40, 24	3.02	2.8*
Rt middle frontal	46	38, 28, 20	4.69	4***
Insula				
Lt	13	−30, 26, 0	3.08	2.8**
	13	−38, −6, 8	4.51	3.9*
Rt	—	36, 20, 2	4.42	3.8*
Midbrain				
Rt substantia nigra	—	18, −18, −6	4.61	3.9**
Primary somatosensory cortex				
Lt postcentral	3	−30, −38, 48	4.34	3.8*
	5	−42, −44, 66	6.84	5.2****
	1	−60, −28, 42	7.85	5.7*
	2	−68, −24, 30	8.2	5.8*
Rt inferior parietal lobule	40	38, −34, 42	6.18	4.9*
Rt postcentral	5	34, −52, 70	9.03	6.1****
	2	52, −28, 44	9.49	6.3*
Secondary somatosensory cortex				
Lt inferior parietal lobule	40	−68, −26, 30	8.27	5.8****
Lt postcentral gyrus	40	−52, −26, 20	3.57	3.2*
Rt postcentral gyrus	3/40	62, −20, 38	8.08	5.8****
Thalamus				
Lt	—	−14, −18, 10	5.08	4.2***
Rt	—	8, −26, −4	3.83	3.4*

Note: Lt, left; Rt, right.
*$P < 0.05$ false discovery rate (FDR) corrected in each ROI.
**$P < 0.05$ FDR corrected (height threshold: $t = 2.42$).
***$P < 0.001$ FDR corrected (height threshold: $t = 4.53$).
****$P < 0.05$ family wise error (FWE) corrected (height threshold: $t = 6.39$).

reduced activation for the ALEX group in the left ACC (BA 24/32) when using a more lenient threshold ($P < 0.005$, $k = 20$) within the a priori pain-related region. The ALEX group showed stronger signal change compared with the non-ALEX group in the right anterior insula (BA 13) and the inferior frontal gyrus (BA 45) within a pain matrix and additionally bilateral ventral anterior cingulate gyri, right superior frontal gyrus, and right superior/middle temporal gyrus. ALEX group also showed increased activity in the right posterior insula (BA 13) compared with non-ALEX although activation in this area was not found in the conjunction analysis. Correlation coefficients between the hemodynamic activation in each ROI and the psychological measurement scores are shown in Table 7 for the pain-related regions found in the group comparison (i.e., right DLPFC [peak] [*x*, *y*, *z*] = [-20, 56, 34]; left ACC [-12, 2, 52]; left dorsal pons [-2, 38, -42]; left cerebellum [-14, -64, -32]; right inferior frontal gyrus [Rt IFG] [54, 22, 4]; right anterior insula [38, 14, 2]; and right posterior insula [38, -30, 18]). The DLPFC did not show any significant correlations with the psychological scores. The left dorsal ACC showed a significant positive correlation coefficient with "self-controlling" on the SCI. The brain stem (dorsal pons) showed a negative correlation with "personal distress" on the IRI and a positive correlation with "cognitive" on the SCI. The left cerebellum showed a positive correlation with "warmth" on the EES and "problem solving" on the SCI. The right anterior insula correlated positively with "affectedness" on the EES and negatively with "cognitive" and "problem solving" on the SCI. The right posterior insula had positive correlation with "personal distress" on the IRI and negative correlation with "cognitive," "seeking social support," "accepting responsibility," and "positive reappraisal." The Rt IFG showed a negative correlation with "warmth" on the EES and "positive reappraisal" on the SCI.

Discussion

The results of the present experiment support previous neuroimaging studies of empathy for pain, showing selective

Table 5

Coordinates and Z and T scores for the pain-related brain areas activated in response to painful picture stimuli in conjunction analysis of 1-sample tests on both groups

Area	BA	MNI x, y, z (mm)	T	Z
ACC				
Lt	24	0, 0, 40	3.26	2.98**
	32	−8, 24, 40	4.54	3.9*
Rt	8/32	2, 18, 48	4.48	3.86*
Cerebellum				
Lt posterior tonsil	—	−30, −36, −40	3.48	3.15**
DLPFC				
Lt inferior frontal	47	−48, 44, −12	3.84	3.41*
	44	−56, 8, 22	5.43	4.45*
	46	−46, 34, 12	6.79	5.18*
	9	−56, 8, 32	6.95	5.25*
Lt middle frontal	10	−34, 60, 8	5.22	4.33*
Rt inferior frontal	44	54, 8, 20	2.76	2.58**
	9	56, 10, 32	5.64	4.57**
Rt middle frontal	46	42, 28, 20	4.14	3.63**
Insula				
Lt	13	−42, −2, 4	2.75	2.57**
	13	−32, 16, 10	3.31	3.02**
Midbrain				
Lt midbrain	—	−2, −36, −4	2.68	2.51**
Lt substantia nigra	—	−14, −22, −8	3.33	3.03**
Primary somatosensory cortex				
Lt postcentral	3	−38, −28, 58	4.36	3.78*
	5	−42, −46, 62	5.33	4.39*
	2	−62, −24, 36	7.13	5.34*
	1	−60, −28, 42	7.85	5.66*
Rt inferior parietal lobule	40	38, −34, 42	6.18	4.87*
Rt postcentral	5	38, −48, 60	4.87	4.11*
	2	52, −28, 44	9.49	6.3**
Lt inferior parietal lobule	40	−54, −32, 46	8.17	5.8*
Secondary somatosensory cortex				
Lt	40	−62, −20, 22	3.76	3.35*
Rt	3/40	62, −20, 38	7.5	5.51*
Thalamus				
Lt	—	−14, −18, 10	4.73	4.02**
Rt	—	4, −32, −4	3.29	3**

Note: Lt: left, Rt: right.

*$P < 0.05$ false discovery rate (FDR) corrected in each ROI.

**$P < 0.05$ FDR corrected (height threshold: $t = 2.58$).

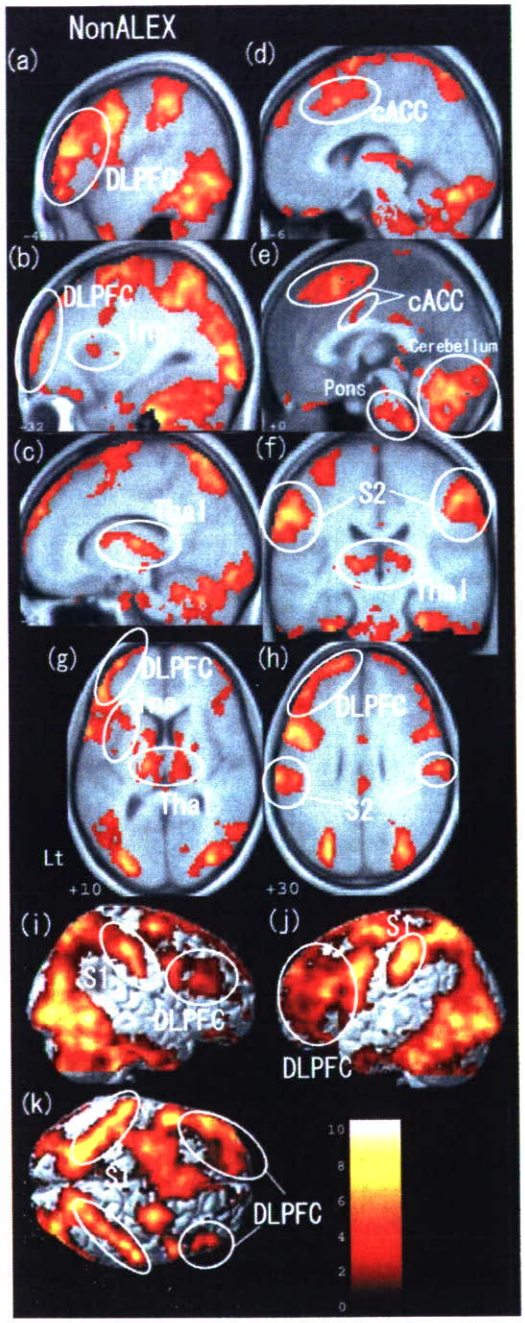

Figure 1. Brain images of the higher regional cerebral activation in response to the other's painful pictures compared with control pictures in the non-alexithymic sample. The brain images illustrate the clusters with neural activities in response to the other's pain task (contrasted with no-pain control pictures) within pain-related regions using 1-sample tests for the non-ALEX group ($n = 14$). The white circles on the brain images indicate the notable clusters related to the pain network. The bar on the lower right shows the range of t scores for SPM. The height threshold for illustrating the clusters was $P < 0.05$ corrected (false discovery rate). (*a–e*) sagittal view; (*f*) coronal view; (*g*, *h*) axial view; (*i*) right side; (*j*) left side; (*k*) top. Ins, insula; Thal, thalamus; cACC, caudal anterior cingulate cortex; S2, secondary sensory cortex; S1, primary sensory cortex.

activation of the neural network mediating the perception of other's pain (Morrison et al. 2004; Singer et al. 2004; Botvinick et al. 2005; Jackson et al. 2005, 2006; Lamm et al. 2007; Saarela et al. 2006). Interestingly, individuals with ALEX rated the painful stimuli as less painful than individuals without ALEX. Furthermore, fMRI measures showed lower signal change in the left lateral prefrontal cortex, left ACC, cerebellum, and dorsal pons in the ALEX group than in the non-ALEX group in response to viewing pictures of painful situations.

The behavioral measures revealed that the ALEX group showed lower scores for pain ratings and on questionnaires assessing empathetic qualities. This indicates that ALEX is associated with not only difficulty in representing one's own emotional state but also the emotions of others. It is worth noting that Guttman and Laporte (2002) reported behavioral results very similar to ours: alexithymic participants had higher levels of IRI personal distress and lower levels of perspective taking and fantasy. Personal distress scale has clearly different features from other scales on IRI: perspective taking and fantasy were significant and positively related to empathic concern, whereas a significant inverse relationship was found between perspective taking and personal distress (Davis 1983). Personal distress involves the experiences of another's distress as if it were one's own due to incapability of distinguishing the self-other difference. It is generally considered as a primitive form of empathic response in developmental science because the infant imitates the emotional distress of another but without an awareness of the other's situation or condition (Eisenberg 2000; Decety 2007; Lamm et al. 2007). Davis (1996) noted that personal distress as a mere reactive response to another's condition, rather than a direct representation of another's

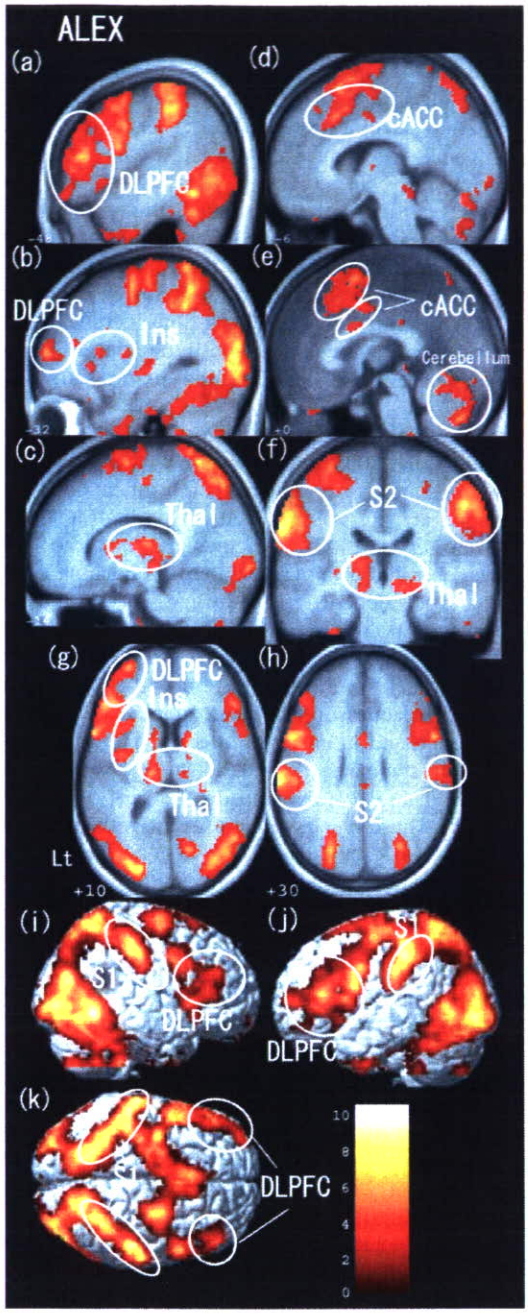

Figure 2. Brain images of the higher regional cerebral activation in response to the other's painful pictures compared with control pictures in the alexithymic sample. The brain images illustrate the clusters with neural activities in response to the other's pain task (contrasted with no-pain control pictures) within pain-related regions using 1-sample tests for the ALEX group (n = 16). The white circles on the brain images indicate the notable clusters related to the pain network. The bar on the lower right shows the range of t scores for SPM. The height threshold for illustrating the clusters was $P < 0.05$ corrected (false discovery rate). (*a–e*) sagittal view; (*f*) coronal view; (*g*, *h*) axial view; (*i*) right side; (*j*) left side; (*k*) top. Ins, insula; Thal, thalamus; cACC, caudal anterior cingulate cortex; S2, secondary sensory cortex; S1, primary sensory cortex.

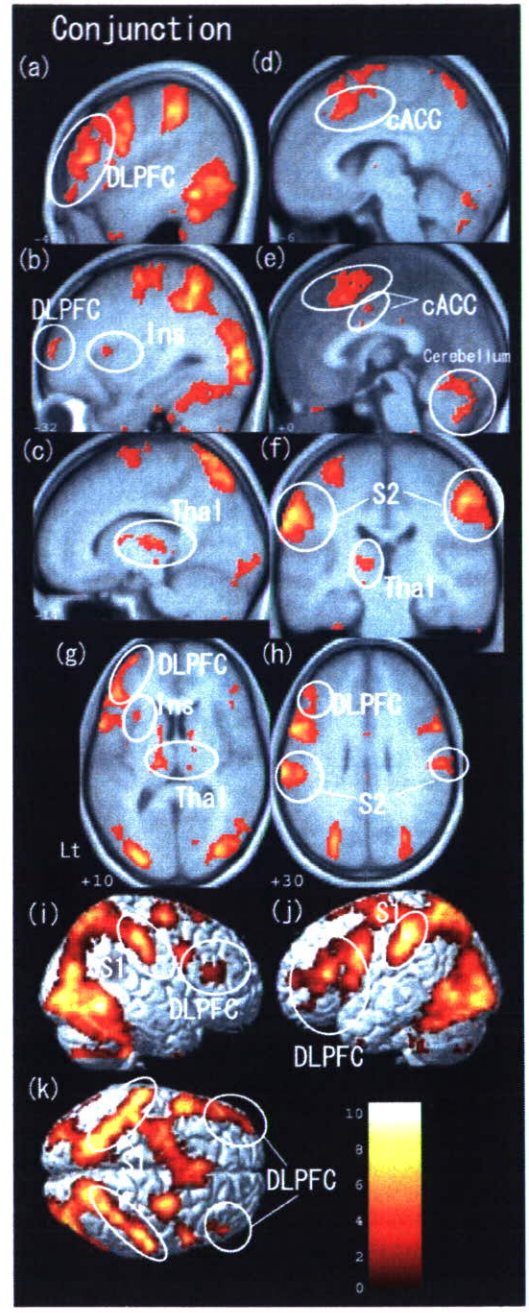

Figure 3. Brain images of the higher regional cerebral activations in response to the other's painful pictures compared with control pictures in conjunction analysis of both groups. The brain images illustrate the clusters with neural activities in response to the other's pain task (contrasted with no-pain control pictures) within pain-related regions in conjunction analysis that shows overlapping areas using two 1-sample tests (ALEX group [n = 16] and non-ALEX group [n = 14]). The white circles on the brain images indicate the notable clusters related to the pain network. The bar on the lower right shows the range of t scores for SPM. The height threshold for illustrating the clusters was $P < 0.05$ corrected (false discovery rate). (*a–e*) sagittal view; (*f*) coronal view; (*g*, *h*) axial view; (*i*) left side; (*j*) right side; (*k*) top. Ins, insula; Thal, thalamus; cACC, caudal anterior cingulate cortex; S2, secondary sensory cortex; S1, primary sensory cortex.

affect, characterized by a negative affective tone and self-oriented thought processes. Such individuals experiencing personal distress as a reaction to another's distress tend to feel more anxious and uncomfortable regardless of the state of mind of the other. Personal distress scale is associated with high levels of social dysfunction, fearfulness, uncertainty, emotional vulnerability, shyness, and social anxiety. High personal distress was characterized by their concern with how others evaluate them and with lowered concern for others (Davis 1983). Thus,

Table 6
Coordinates and Z and T scores for the brain areas differently activated between the ALEX and non-ALEX groups; group comparison using 2-sample tests

Area	BA	MNI x, y, z(mm)	T	Z	Cluster k
ALEX < non-ALEX					
Lt lateral prefrontal cortex	9	−20, 56, 34	4.73	4.02	113
	9	−12, 60, 32	4.31	3.74	
	8	−12, 52, 44	4.07	3.57	
Cerebellum					
Lt anterior dentate	—	−14, −64, −32	4.98	4.18	133
Lt anterior culmen	—	−18, −50, −24	4.95	4.16	
	—	−10, −54, −28	4.33	3.76	
Lt posterior declive	—	−4, −70, −20	4.73	4.02	115
Rt posterior declive	—	6, −76, −28	4.02	3.54	
	—	22, −70, −28	3.91	3.46	26
Lt posterior cerebellar tonsil	—	−32, −34, −40	4.6	3.94	100
Lt brain stem pons	—	−22, −32, −36	4.5	3.87	
	—	−2, −38, −42	4.34	3.76	70
Lt dorsal anterior cingulate gyrus[a]	24	−12, 2, 52	3.42	3.1	25
	24	−14, 4, 56	3.28	2.99	
Rt middle temporal gyrus	38	32, 2, −32	4.83	4.08	21
Lt superior frontal gyrus	8	−20, 12, 46	4.09	3.59	20
Lt middle frontal gyrus	6	−32, 10, 58	4.04	3.55	28
ALEX > non-ALEX					
Rt anterior insula[a]	13	38, 14, 2	3.49	3.15	65
Rt posterior insula	13	38, −30, 18	4.26	3.71	46
	40	48, −24, 16	4.08	3.58	
Rt IFG	45	54, 26, 6	5.48	4.48	40
Rt ventral anterior cingulate	24	6, 26, 14	5.33	4.39	53
Rt superior frontal gyrus	9	20, 42, 34	5.16	4.29	71
Rt middle temporal gyrus	21	62, −6, −6	4.55	3.9	100
	21	60, 2, −8	4.16	3.64	
Rt superior temporal gyrus	22	62, −26, −2	4.49	3.86	20
Lt ventral anterior cingulate	—	−8, 38, 4	4.15	3.63	22

Note: Height and extent threshold: $T = 3.41$ ($P = 0.001$ uncorrected) and $k = 20$ voxels. Lt, left; Rt, right.
[a] $T = 2.76$, ($P = 0.005$ uncorrected) and $k = 20$ voxels.

personal distress is regarded as a less mature aspect of empathy and is related to impairments in cognitive aspects of empathy. Higher levels of personal distress in alexithymics in the present study indicate that ALEX may be related to immature forms of empathy (Guttman and Laporte 2000, 2002). We also found significantly lower scores in the ALEX group on the EES for warmth and on the SCI for cognitive, "planful problem solving," and positive reappraisal, reflecting their less cognitive strategies on the occasion of coping with emotional stress. ALEX has been found to be associated with low "emotional intelligence" (Fukunishi et al. 2001), which has a factor of empathy in terms of recognizing and understanding emotions in others (Goleman 1995). Therefore, we consider that alexithymic individuals, who have difficulty in identifying their own feelings, are also poor at representing and evaluating other's mental states, especially in terms of their cognitive aspects.

The fMRI experiment showed that the main effect of watching painful stimuli was associated with activation in the somatosensory (SI/SII), thalamus, ACC, anterior insula, cerebellum, lateral prefrontal cortex, and brain stem. Consistent with previous neuroimaging studies, activation in these areas involved in empathy for pain was replicated, without physical sensation of actual pain stimulation. Furthermore, we found a relationship between the evaluation of painful pictures and activation in the lateral prefrontal cortex, pons, cerebellum, and right caudal ACC, as previously reported (Singer et al. 2004; Jackson et al. 2005). In our study, sensory inputs and motor outputs were controlled, so these activations derived from only visual input and processing these stimuli, not sensory feedback as a result of pressing the response buttons. It is possible that to accurately estimate pain in others, participants might further engage almost the whole pain matrix, not only the affective component within the pain network, notably the rostral ACC and anterior insula. Interestingly, a recent transcranial magnetic stimulation study demonstrated the sensorimotor side of empathy for pain by showing a reduction in excitability of hand muscles during the observation of painful stimuli (Avenanti et al. 2005). Together with our results, this points to the implication of regions other than those implicated in the affective component of empathy for pain.

The group comparison analyses indicated lower activation in the left lateral prefrontal cortex, dorsal pons, cerebellum, and ACC in the ALEX group as compared with the non-ALEX group. These regions have been demonstrated to be activated in association with the perception of other's pain (Singer et al. 2004; Jackson et al. 2006; Lamm et al. 2007) and in other pain-related studies (Davis 2000; Peyron et al. 2000; Raij et al. 2005). Reportedly, the interregional correlation of midbrain and medial thalamic activity was reduced during high left DLPFC activity (Lorenz et al. 2003). This indicates that the DLPFC exerts active control of pain perception by modulating cortico-subcortical and corticocortical pathways. Furthermore, the locus of the region in the present study is close to that activated by empathic and forgiveness tasks (Farrow et al. 2001), chronic facial pain contrasted with the pain-free condition after thalamic stimulation (Kupers et al. 2000), and rating the valence and intensity of affective pictures (Grimm et al. 2005). In summary, the DLPFC was associated with cognitive (especially executive and/or regulatory) processing of visual stimuli. These results are consistent with the hypothesis proposed by Taylor and Bagby (2004) of a hypofunction of the prefrontal cortex in individuals with ALEX, referring to the neuroimaging study by Hariri et al. (2000). In addition, it has been suggested that the DLPFC, reciprocally connected to many other neocortical areas, including the ACC, as well as the basal ganglia and the brain stem, regulates the functions that utilize emotional feelings for a survival function like planning and initiative. This includes the capacity to harmonize current behavior with the demands of the environment. Hence, it would be expected that selective lesions in this neural network may result in alexithymic features (Bermond 1997). Empathy requires emotional regulation (Eisenberg 2000; Decety and Jackson 2006; Decety 2007), and the DLPFC is key region implicated in this process (Ochsner and Gross 2005). It is thus logical to suggest that lateral prefrontal hypoactivity in ALEX is associated with a deficit in cognitive (particularly executive/regulating) function in empathizing and evaluating other's pain.

Moreover, the caudal ACC (cCZ [caudal cingulate zone]; Picard and Strick 1996, posterior part of 24b′; Vogt and Peters 1981, Vogt et al. 1996) showed less activation in alexithymics than in non-alexithymics. TAS-20 total scores have been reported to be correlated with the size of the normalized surface area of the right ACC (Gundel et al. 2004). The ACC has been associated with conscious awareness of emotion (Lane et al. 1997). The locus of the ACC that was less activated in ALEX in our study corresponds to the cognitive subdivision of the ACC that is involved in second-order representation or awareness (Lane 2000; Berthoz et al. 2002). Alexithymic individuals have been reported to show less activation in the ACC in response to the emotionally laden (e.g., anger) components of facial expressions (Kano et al. 2003). Interestingly, Vogt et al. (1996) argued that

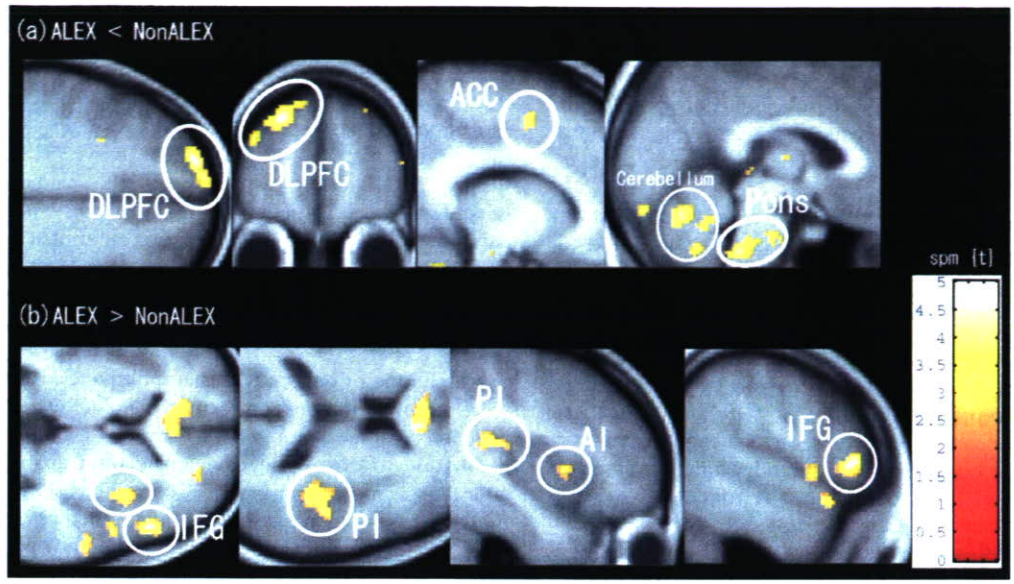

Figure 4. Brain images of the different regional cerebral activations between individuals with and without ALEX in response to the other's painful picture task. The orthogonal views of brain images illustrate the clusters with different neural activities in response to the other's pain task (contrasted with no-pain control pictures) within pain-related regions. The bar on the lower right shows the range of t scores for SPM. The height and extent threshold for illustrating were $Z = 2.6$ ($T = 3.33$), ($P < 0.005$ uncorrected) and $k = 20$, respectively. (*a*) The figures for the notable clusters with less activation in the ALEX group compared with non-ALEX group. Peak MNI coordinates (x, y, z) = (−20, 56, 34); cACC, caudal anterior cingulate cortex (−12, 2, 52); brain stem (dorsal pons) (−2, 38, −42); and cerebellum (−14, −64, −32). (*b*) The figures for the clusters with more activation in the ALEX group than the non-ALEX group. AI, anterior insula (38, 14, 2); PI, posterior insula (38, −38, 18); and IFG, inferior frontal gyrus (54, 22, 4).

Table 7

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

	Lt DLPFC	Lt cACC	Pons	Lt cerebellum	Rt AI	Rt PI	Rt IFG
EES							
Warmth	0.22	0.24	0.28	**0.36***	−0.12	−0.11	**−0.36***
Chill	−0.07	0.19	−0.14	−0.23	−0.14	−0.05	0.02
Affectedness	−0.08	−0.11	−0.18	0.1	**0.36***	0.24	0.21
IRI							
Fantasy	0.27	0.14	0	−0.02	−0.05	0.19	−0.12
Perspective taking	0.17	0.14	0.06	0.11	−0.31	−0.09	−0.14
Empathic concern	0.2	0.07	0.19	0.31	−0.14	−0.06	−0.19
Personal distress	−0.15	−0.05	**−0.44***	0.01	0.28	**0.42***	0.07
SCI							
Cognitive	0.15	0.24	**0.37***	0.3	**−0.35***	**0.48***	−0.33
Emotional	−0.07	0.18	0	0.04	−0.2	−0.32	−0.3
Problem solving	0.16	0.17	0.3	**0.37***	**−0.36***	−0.26	−0.3
Confrontational	0.02	−0.12	0.12	−0.02	−0.29	−0.11	−0.18
Seeking social support	0.09	0.04	0.14	0.23	−0.09	**−0.37***	−0.32
Accepting responsibility	0.1	0.26	0.26	0.03	−0.25	**−0.34***	−0.15
Self-controlling	−0.07	**0.35***	0.15	0.32	−0.15	−0.28	−0.02
Escape-avoidance	0.05	0.05	−0.03	−0.06	−0.1	−0.19	−0.25
Distancing	−0.15	0.09	−0.16	−0.24	−0.05	−0.12	0.02
Positive reappraisal	0.11	0.24	0.29	0.22	−0.29	**−0.53***	**−0.47***

Note: cACC, caudal anterior cingulate cortex; AI/PI, anterior/posterior insula; IFG, inferior frontal gyrus; Lt, left; Rt, right.
Bold type *$P < 0.05$.

different parts of cingulate cortex are engaged in different processing levels of nociceptive information and that area 24b′ is involved in the controlling aspect of pain processing like response selection. A meta-analysis concluded that mid-ACC hemodynamic activations detected in the first-hand experience of pain reflect the cognitive dimension of pain experience, including the awareness and response selection to pain stimuli (Peyron et al. 2000). The location of the caudal ACC activation, observed in group comparison analysis, is more posterior than the rostral ACC region associated with affective reaction to pain. Therefore, we suggest that ALEX may be related to some impairment in the cognitive–motivational aspects of pain processing. It is important to note that the motivational dimension of pain processing includes the selection and preparation of movements of aversion (Morrison et al. 2004). Reportedly, activation in the mid-ACC is related to processes regarding pain in self, such as somatic monitoring, negative stimulus evaluation, and the selection of appropriate skeletomuscular movements of aversion (Isomura and Takada 2004; Jackson et al. 2006). Considering the participants with ALEX scored lower on pain and empathy scales, they would not be concerned by other's pain, so there should be less need for them to prepare their own organisms for a negative threatening experience. That might result in the less activation in caudal ACC in alexithymics in the present study. Interestingly, neural activities in this region had a positive correlation with pain ratings, which alexithymic participants estimated as lower. Activity in this region is associated with self-control ability in response to painful picture tasks. These results are fairly consistent with the ACC deficit model of ALEX (Lane et al. 1997; Berthoz et al. 2002).

The dorsal pons and cerebellum were found to be less activated in the ALEX group in the present study. Although monoaminergic projections from the brain stem to the prefrontal cortex are well known (Porrino and Goldman-Rakic 1982), there are sizable and highly ordered inputs to the pons from the DLPFCs, which are then relayed to the cerebellum (Schmahmann and Pandya 1997). Hence, this area is an integral node in the distributed cortical–subcortical neural circuitry supporting cognitive operations (Schmahmann and Pandya 1995). In order to evaluate painful situations in others without actually experiencing pain, people probably also rely on high-order cognitive functions to access minor changes in their physical state as a tool for estimating the stimulus input. Cerebellum abnormality is related to a broad range of psychiatric

disorders (Konarski et al. 2005). Furthermore, in our study, neural activity in the pons was associated with the cognitive coping strategy scale and negatively correlated with personal distress. Neural activation in the cerebellum correlated with problem solving coping style, which suggests that the subtentorial structures may be engaged in cognitive control aspects of empathy for other's pain.

We found more activation in the anterior insula in the ALEX group. The anterior insula, known to be closely connected to the amygdala and ventral ACC, plays an important role in responding to emotional stimuli as "ventral prelimbic" areas, and these regions are often synchronized with each other (Mayberg 1997). The prelimbic areas were found to be suppressed (or biased against) during cognitively demanding tasks like a counting stroop task (Bush et al. 1998, 2000). Furthermore, reciprocal changes involving the prelimbic area and prefrontal cortex were also found. Hemodynamic increases in the prelimbic area and decreases in the prefrontal cortex were reported in response to sadness, although these 2 areas demonstrated the inverse correlation as a person recovered from a depressive state (Mayberg et al. 1999). If an individual engages less cognitive processing for the painful pictures, the suppression of activation in the anterior insula would be decreased. The ALEX group, which has more impairment in cognitive aspects, may have had more activation in the anterior insula compared with the non-alexithymics as a result of decreased suppression. In contrast to our study, Kano et al. (2003) found reduced activation in the anterior insula in response to emotional faces. The reason for this discrepancy might be that our study required participants to judge other's pain cognitively, whereas the paradigm used by Kano and colleagues involved the passive observation of emotional stimuli, less cognitively demanding. Thus, the present study might tap into more cognitive processing than the study by Kano and colleagues. Furthermore, the finding in the present study that neural activity in the insula was associated with more personal distress and emotional affectedness and less cognitive and less problem solving coping styles supports these inferences.

ALEX group also showed increased neural activity in the right posterior insula, although this region was not extracted by the conjunction analysis. Craig (2003) noted that the dorsal posterior insula involves the primary (not metarepresentational) interoceptive representation of the inputs of physiological condition from all tissues of the body, including pain, temperature, itch, sensual touch, muscular and visceral sensations, vasomotor activity, hunger, thirst, and "air hunger." Thus, the posterior insula is related to lower level representation of the physical state. Considering that neural activity in this region positively correlated with the personal distress scale and negatively with cognition-related stress coping scales, the result of stronger activity in the posterior insula in the ALEX group indicates that individuals with ALEX might be stuck in lower level representation of one's own physical state. Interestingly, a recent neuroscience research, including intracranial electrophysiological stimulations in neurological patients, indicates that distinct subregions of the insula contribute to different aspects of empathy (Decety and Lamm 2006). The posterior insula is associated with personal distress (self-oriented response), whereas the anterior insula is associated with empathy (other oriented emotional responses).

In the present study, the neural activity in the Rt IFG ($x = 54$, $y = 22$, $z = 4$) was stronger in ALEX group than non-ALEX group. Eisenberger et al. (2003) and Eisenberger Lieberman (2003, 2004) noted that the right ventral prefrontal cortex activation (RVPFC [$x = 42$, $y = 27$, $z = 11$], near the Rt IFG in the present study [$x = 42$, $y = 27$, $z = 11$]) was associated with less dorsal ACC activation and less self-reported distress across participants, suggesting that the RVPFC might serve a self-regulatory suppressive function by disrupting the pain distress. One possible interpretation is that the individuals with ALEX might try to deny and suppress the negative emotional aspects of the painful picture stimuli, resulting in their discreet evaluation about pain in the task pictures. Relationship between ALEX and a suppressive aspect of emotional processing remains to be solved.

A limitation of our study is that multiple correlation analyses were computed between hemodynamic ROI activation and psychological measurements, which might induce a significant result due to chance in each correlation analysis. However, adopting a more conservative corrected alpha level could increase false negative results. Although the present correlation study is useful to check the features of hemodynamic activation in each ROI in an exploratory way, one should acknowledge that the present results are only suggestive values and need further reconfirmations in future experiments. Another limitation is that the perception of pain in others with the use of pictures of limbs does not account for the full construct of empathy, but only part of it. According to several recent neurocognitive models of empathy, this capacity includes emotional contagion (that can lead to personal distress), sympathy, cognitive empathy, helping behavior etc., which all share aspects of their underlying process and cannot be totally disentangled (Preston and de Waal 2002; Decety and Jackson 2004, 2006; Lawrence et al. 2006). Further studies are needed in the future with the task to focus and discriminate each more specific aspect of empathy. Moreover, it has not been concluded whether the degree of ALEX does not influence thresholds for experimentally induced pain (de Zwaan et al. 1996; Nyklicek and Vingerhoets 2000; Jackson et al. 2002), so the results of the group comparisons for empathy to pain in the present study might be affected by actual tolerances for pain. Relationship between pain perception and ALEX remains to be clarified.

In conclusion, the present study demonstrates that individuals with ALEX showed diminished pain ratings, less mature empathy scores, and decreased neural activity associated with cognitive empathy to other's pain, notably in the lateral prefrontal and caudal anterior cingulate areas rather than in affective components like the anterior insula. The pain-related areas like the pons, ACC, and cerebellum showing decreased neural activities in ALEX were associated with cognitive aspects of empathy and coping style questionnaires. Empathy is comprised of a number of components such as taking others' perspectives and emotional regulation (including identifying, describing, and objectifying inner feelings) based on continuous self-awareness (Decety and Jackson 2004, 2006). Any organism capable of self-recognition would have an introspective awareness of its own mental state and the ability to ascribe mental states to others (Humphrey 1990). The emergence of a self-representation in psychological development is crucial for the empathic process (e.g., Lewis et al. 1989). Taken together with our results, the impaired cognitive (particularly executive/regulatory) aspects of empathy could be a part of the core deficit in ALEX, which is associated with impaired emotional regulation and also highlights the importance of self-awareness in empathy.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Notes

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