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Preliminary communication

Altered brain response to others' pain in major depressive disorder

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ABSTRACT

Background: Empathy has a central role in successful interpersonal engagement. Several studies have reported altered empathy in major depressive disorder (MDD), which could lead to interpersonal difficulties. However, the neural basis of altered empathy in the disorder is still largely unknown. To address this, we performed functional magnetic resonance imaging that tested empathy for others' pain in MDD patients.
Methods: Eleven patients with MDD and 11 age-, gender-, handedness-, and education level-matched healthy control subjects were studied. We compared MDD patients and healthy controls for their regional hemodynamic responses to visual perception of videos showing human hands in painful situations. We also assessed subjective pain ratings of the videos in each group.
Results: The MDD patients showed lower pain ratings for the painful videos compared with the healthy controls. In addition, the MDD patients showed reduced cerebral activation in the left middle cingulate cortex, and the right somatosensory-related cortices, whereas they showed greater cerebral activation in the left inferior frontal gyrus.
Limitations: We relied on a relatively small sample size and could not exclude effects of medications.
Conclusions: These results suggest that in MDD patients the altered neural activations in these regions may be associated with a deficit in the identification of pain in others. This study adds to our understanding of the neural mechanism involved in empathy in MDD.

1. Introduction

Patients with major depressive disorder (MDD) experience significant social dysfunction, which may partly result from deficits in social cognition, involving the ability to understand and respond to the thoughts and feelings of others (Cusi et al., 2012).

Empathy is a set of constructs that enable us to understand the sensation and emotions of others by sharing their sensory and affective states, and thus has a central role in successful interpersonal engagement (Decety and Moriguchi, 2007). In recent years, functional magnetic resonance imaging (fMRI) studies during empathy for others' pain in healthy subjects have provided an avenue for investigating the neural basis of empathy. These studies showed the importance of brain regions implicated in cognitive and affective systems, such as the anterior cingulate cortex (ACC), middle cingulate cortex (MCC), anterior insula, and prefrontal cortices, and the regions for encoding the sensory dimension, such as somatosensory-related cortices (SRC) in the inferior parietal lobe, in terms of empathy processing (Jackson et al., 2006; Lamm et al., 2010, 2011). These areas overlap with the neural network of the so-called "pain matrix", which is activated in the direct experience of one's own pain (Peyron et al., 2000), thus these studies also suggest that the neural network for representing one's own subjective feeling states is crucial for understanding the emotional response in others.

In MDD patients, not only affective range is limited because of depressed mood and anhedonia, but also many of the cognitive and affective processes, for example, working memory and emotion regulation, are affected (Fu et al., 2008; Hasselbalch et al., 2011). Furthermore, the pain threshold of MDD patients is reported to be increased (Bär et al., 2007), therefore it is also possible that the sensory perception in this disorder might be altered. Accordingly, MDD patients would show altered empathic abilities (Cusi et al., 2011; Wilbertz et al., 2010). Indeed, it has been shown that depressed mothers are less responsive to crying of their newborn babies (Field et al., 2009). However, surprisingly,

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few studies have investigated the neural mechanisms underlying altered empathy in MDD patients.

To date, among many fMRI studies comparing MDD patients with healthy subjects, several studies, although not focusing on empathy, have showed differential activation in the above-mentioned brain networks that are important for empathy processing. For example, greater activation in the lateral prefrontal cortex and ACC were shown in MDD patients during a working memory task (Harvey et al., 2005). In addition, a recent study showed that neural activation in the cingulate cortex and inferior parietal cortex was reduced in MDD patients during sad facial emotion processing (Fu et al., 2008). However, to the best of our knowledge, there is no fMRI study directly investigating the neural basis of empathetic ability of MDD patients.

Here, we performed fMRI during an empathy task to test for the response to others' pain in MDD patients. We compared MDD patients and healthy subjects for their regional hemodynamic responses to visual perception of videos depicting human hands in painful situations. We hypothesized that the MDD patients would show reduced empathy for others' pain and also show different neural responses in regions related to cognitive, affective and sensory processing, such as, ACC, MCC, anterior insula, SRC, and prefrontal cortices.

2. Methods

2.1. Participants

Twelve patients who had experienced at least one episode of MDD based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) were recruited. Current comorbid axis I diagnoses were acceptable as long as the depressive episode was primary; one patient met the criteria for panic disorder and one patient for social anxiety disorder. The 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) was used to assess the severity of clinical symptoms. None had a previous history of psychosis or mania. One patient was excluded from the analyses owing to lack of compliance with task instructions, thus 11 MDD patients were analyzed. All patients were taking one or more antidepressant medications at the time of the study (two were taking tricyclic antidepressants, six were taking selective serotonin reuptake inhibitors, three were taking selective serotonin noradrenaline reuptake inhibitors, and one was taking other types of antidepressants). Eleven healthy controls (HC), matched with the patient group in age, gender, handedness, and education levels were recruited. The controls had no history of psychiatric illness, as determined by the SCID, and there was no family history of mood disorders among their first-degree relatives. Exclusion criteria for all individuals included a history of head trauma, any neurological illness, serious medical or surgical illness, and substance abuse.

This study was approved by the Committee on Medical Ethics of Kyoto University and carried out in accordance with The Code of Ethics of the World Medical Association. After a complete description of the study, written informed consent was obtained from each participant.

2.2. fMRI task

We chose to present video clips to offer a more realistic presentation than that provided by static images. Painful and non-painful control videos were presented in an event-related manner. In the painful videos, participants watched color videos showing a human's hand pricked with a needle. In the non-painful videos, the needle was covered by a protective black cap and placed next to the hand (Supplementary Fig. 1). The painful videos had 34 patterns; a needle was approaching to a man's or woman's right hand from 17 different angles. Similarly, the non-painful videos had 34 patterns in the same way. The actors in the video clips did not change facial expressions (neutral expressions). Each video was 1.1 s long and emerged twice according to a pseudo-random ordering, followed by a jittered white fixation cross on a black background in the range of 1.0–4.0 s (mean; 2.5 s). The participants were instructed to watch the videos as they would watch television. To maintain their general attention, they were required to press a button on a magnet-compatible button-box with the right thumb when each video clip (both painful and non-painful videos) appeared. Additionally, the fixation cross was sometimes interpolated with a 2-s pain-rating session (There were 12 pain rating sessions in total) so that participants could focus on the context of pain. During the pain-rating session, the participants were instructed to rate the intensity of pain of the last video from “no pain” to “very severe pain” on a 4-point scale by pressing one of four buttons with their right thumbs (for the original aim, these ratings were not included in the analysis). Stimuli were presented using the Presentation software (Neurobehavioral Systems, Albany, CA, USA). After scanning, participants were presented with the same videos as inside the scanner and were asked to rate the pain intensity they thought the person in each video would feel from 0 (no pain) to 100 (very severe pain).

2.3. fMRI data acquisition and pre-processing

fMRI images were scanned on a 3 T Trio (Siemens, Erlangen, Germany) equipped with an 8-channel phased-array head coil and preprocessed using SPM8 (Wellcome Trust Center for Neuroimaging, London, UK) (see Appendix 1).

2.4. Statistical analyses

2.4.1. Demographic and behavioral data

Demographic and behavioral data were analyzed using SPSS 21. Because some of our continuous measures were not normally distributed (Shapiro–Wilk test, $p < 0.05$), we chose the Mann–Whitney U test to compare the group differences. Results were considered statistically significant at $p < 0.05$.

2.4.2. fMRI data

After preprocessing, we fitted a general linear model (Worsley and Friston, 1995) to the fMRI data. In the first-level analyses, the design matrix contained two task-related regressors (painful and non-painful conditions). To minimize the motion-related artifacts, six movement parameters (three displacements and three rotations) were also included as additional regressors of no interest. Data were high-pass filtered at 128 s. Pain-related activation was identified using the contrast of painful versus non-painful conditions. The comparison produced a contrast image for each participant, and these contrast images were used for the second-level fMRI analyses.

In the second-level analyses, we used a random-effects model to make inferences at the population level. First, main effects of watching others' pain were computed using one-sample t-tests separately for the HC and MDD groups. The resulting set of voxel values constituted an SPM of the t statistic [SPM{t}]. The height and extent thresholds were set at $p < 0.001$, uncorrected and $k = 20$ voxels.

Next, to compare the differences in neural activity between the HC group and the MDD group, two-sample t-tests were used. The height and extent thresholds were also set at $p < 0.001$, uncorrected and $k = 20$ voxels. The choice of these thresholds was based on exploratory data analyses and on effect size considerations