REFERENCES

1. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol.* 1991;82:239–259.
2. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science.* 1992;256:184–185.
3. Mathis CA, Wang Y, Holt DP, Huang GF, Debnath ML, Klunk WE. Synthesis and evaluation of ^{11}C-labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents. *J Med Chem.* 2003;46:2740–2754.
4. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound-B. *Ann Neurol.* 2004;55:306–319.
5. Choi SR, Golding G, Zhuang Z, et al. Preclinical properties of ^{18}F-AV-45: a PET agent for Aβ plaques in the brain. *J Nucl Med.* 2009;50:1887–1894.
6. Johnson AE, Jeppsson F, Sandell J, et al. AZD2184: a radioligand for sensitive detection of beta-amyloid deposits. *J Neurochem.* 2009;108:1177–1186.
7. Nyberg S, Jonhagen ME, Cselenyi Z, et al. Detection of amyloid in Alzheimer's disease with positron emission tomography using [^{11}C]AZD2184. *Eur J Nucl Med Mol Imaging.* 2009;36:1859–1863.
8. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34:939–944.
9. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology.* 1993;43:2412–2414.
10. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189–198.
11. Andersson JD, Varnas K, Cselenyi Z, et al. Radiosynthesis of the candidate beta-amyloid radioligand [^{11}C]AZD2184: positron emission tomography examination and metabolite analysis in cynomolgus monkeys. *Synapse.* 2010;64:733–741.
12. Matsumoto K, Kitamura K, Mizuta T, et al. Performance characteristics of a new 3-dimensional continuous-emission and spiral-transmission high-sensitivity and high-resolution PET camera evaluated with the NEMA NU 2-2001 standard. *J Nucl Med.* 2006;47:83–90.
13. Ishikawa A, Kitamura K, Mizuta T, et al. Implementation of on-the-fly scatter correction using dual-energy window method in continuous 3D whole body PET scanning. *IEEE Nucl Sci Symp Conf Rec.* 2005;5:2497–2500.
14. Mintun MA, Raichle ME, Kilbourn MR, Wooten GF, Welch MJ. A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography. *Ann Neurol.* 1984;15:217–227.
15. Innis RB, Cunningham VJ, Delforge J, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab.* 2007;27:1533–1539.
16. Marquardt D. An algorithm for least-squares estimation of nonlinear parameters. *J Soc Ind Appl Math.* 1963;11:431–441.
17. Ito H, Ota M, Ikoma Y, et al. Quantitative analysis of dopamine synthesis in human brain using positron emission tomography with L-[β-^{11}C]DOPA. *Nucl Med Commun.* 2006;27:723–731.
18. Price JC, Klunk WE, Lopresti BJ, et al. Kinetic modeling of amyloid binding in humans using PET imaging and Pittsburgh compound-B. *J Cereb Blood Flow Metab.* 2005;25:1528–1547.
19. Kudo Y, Okamura N, Furumoto S, et al. 2-(2-[2-dimethylaminothiazol-5-yl] ethenyl)-6- (2-[fluoro]ethoxy)benzoxazole: a novel PET agent for in vivo detection of dense amyloid plaques in Alzheimer's disease patients. *J Nucl Med.* 2007;48:553–561.
20. Ito H, Hietala J, Blomqvist G, Halldin C, Farde L. Comparison of the transient equilibrium and continuous infusion method for quantitative PET analysis of [^{11}C]raclopride binding. *J Cereb Blood Flow Metab.* 1998;18:941–950.
21. Klunk WE, Wang Y, Huang GF, et al. The binding of 2-(4'-methylaminophenyl) benzothiazole to postmortem brain homogenates is dominated by the amyloid component. *J Neurosci.* 2003;23:2086–2092.
22. Klunk WE, Lopresti BJ, Ikonomovic MD, et al. Binding of the positron emission tomography tracer Pittsburgh compound-B reflects the amount of amyloid-beta in Alzheimer's disease brain but not in transgenic mouse brain. *J Neurosci.* 2005;25:10598–10606.
23. Fodero-Tavoletti MT, Rowe CC, McLean CA, et al. Characterization of PiB binding to white matter in Alzheimer disease and other dementias. *J Nucl Med.* 2009;50:198–204.
24. Stankoff B, Freeman L, Aigrot MS, et al. Imaging central nervous system myelin by positron emission tomography in multiple sclerosis using [methyl-^{11}C]-2-(4'-methylaminophenyl)- 6-hydroxybenzothiazole. *Ann Neurol.* 2011;69:673–680.
25. Ito H, Takahashi H, Arakawa R, Takano H, Suhara T. Normal database of dopaminergic neurotransmission system in human brain measured by positron emission tomography. *Neuroimage.* 2008;39:555–565.
26. Ito H, Halldin C, Farde L. Localization of 5-HT$_{1A}$ receptors in the living human brain using [carbonyl-^{11}C]WAY-100635: PET with anatomic standardization technique. *J Nucl Med.* 1999;40:102–109.
27. Zhou Y, Sojkova J, Resnick SM, Wong DF. Relative equilibrium plot improves graphical analysis and allows bias correction of standardized uptake value ratio in quantitative ^{11}C-PiB PET studies. *J Nucl Med.* 2012;53:622–628.
28. Masliah E, Terry RD, Mallory M, Alford M, Hansen LA. Diffuse plaques do not accentuate synapse loss in Alzheimer's disease. *Am J Pathol.* 1990;137:1293–1297.
29. Price JL. Diagnostic criteria for Alzheimer's disease. *Neurobiol Aging.* 1997;18:S67–S70.

Journal of Affective Disorders 165 (2014) 170–175

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Preliminary communication

Altered brain response to others' pain in major depressive disorder

Junya Fujino [a], Nobuyuki Yamasaki [a,*], Jun Miyata [a], Ryosaku Kawada [a], Hitoshi Sasaki [a], Noriko Matsukawa [a], Ariyoshi Takemura [a], Miki Ono [a], Shisei Tei [a], Hidehiko Takahashi [a], Toshihiko Aso [b], Hidenao Fukuyama [b], Toshiya Murai [a]

[a] *Department of Psychiatry, Graduate School of Medicine, Kyoto University, Shogoin-Kawaharacho 54, Kyoto 606-8507, Japan*

[b] *Human Brain Research Center, Graduate School of Medicine, Kyoto University, Shogoin-Kawaharacho 54, Kyoto 606-8507, Japan*

ARTICLE INFO

Article history:
Received 25 November 2013
Received in revised form
24 April 2014
Accepted 25 April 2014
Available online 4 May 2014

Keywords:
Depression
Empathy
fMRI
Inferior frontal gyrus
Cingulate cortex

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,

* Corresponding author. Tel.: +81 75 751 3386; fax: +81 75 751 3246.
E-mail address: yamasaki@rakunan-hosp.jp (N. Yamasaki).

http://dx.doi.org/10.1016/j.jad.2014.04.058
0165-0327/

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 derived from similar experiments of previous studies (Moriguchi et al., 2007; Lamm et al., 2010). In addition, partial correlations after adjusting for age and gender were calculated between HDRS score and the parameter estimates, which were extracted as first eigenvariate from the clusters of significant group differences in MDD patients using SPSS 21.

The MNI coordinates were converted to the Talairach coordinates using the mni2tal scripts (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). We interpreted the anatomical location of the clusters by consulting the Talairach Daemon database (http://www.talairach.org), the Anatomic Automatic Labeling toolbox (Tzourio-Mazoyer et al., 2002), and neuroanatomy atlas books (Duvernoy, 1991; Talairach and Tournoux, 1988).

3. Results

Demographic data are shown in Table 1. The MDD sample consisted of two euthymic patients (HDRS ≤ 7), four patients with mild depression (8 ≤ HDRS ≤ 16), three patients with moderate depression (17 ≤ HDRS ≤ 23), and two patients with severe depression (24 ≤ HDRS) (using the severity classification by Zimmerman et al., 2013).

MDD patients showed reduced pain ratings on the painful videos compared with healthy controls (HC, mean = 66.1, SD = 22.6; MDD, mean = 33.9 SD = 29.9, $p = 0.02$). Both groups scored non-painful videos as no pain (both groups, mean = 0.0, SD = 0.0). No significant correlation was observed between the pain rating and the HDRS score in MDD patients. Additionally, no significant differences were observed among pain ratings depending on the type of antidepressants the patients were taking (tricyclic antidepressants, selective serotonin reuptake inhibitors, or selective serotonin noradrenaline reuptake inhibitors).

Table 2 shows the results of one-sample t tests for each group throughout the whole brain related to higher activations in response to the painful videos than the non-painful videos. In the HC group, the brain response to others' pain was associated with activation in several regions that are related to cognitive, affective, and sensory processing, such as MCC, left anterior insula, bilateral postcentral gyrus, and prefrontal cortices, including left inferior frontal gyrus (IFG). Similarly, MDD patients showed significant activation in the medial frontal gyrus extending to the MCC, left anterior insula, left postcentral gyrus, and left IFG. However, in the group comparison, compared with the HC group, the MDD patients showed reduced cerebral activation in the left MCC, and the right SRC including the postcentral gyrus, supramarginal gyrus, and parietal operculum, whereas showing greater cerebral activation in the left IFG (Table 2 and Fig. 1). In the correlational analyses, no significant correlation emerged between the HDRS score and neural activation in any of these clusters in MDD patients.

Table 1
Demographic and clinical characteristics.

	HC ($n = 11$)		MDD ($n = 11$)		Statistics
	Mean	S.D.	Mean	S.D.	p
Age	32.3	10.5	37.2	9.5	0.24[a]
Gender (M/F)	2/9		3/8		0.61[b]
Handedness (R/L)	10/1		9/2		0.53[b]
Years of education	14.6	2.4	14.9	2.6	0.90[a]
HDRS	1.0	1.6	16.2	7.4	< 0.01[a]
Depressive episodes			1.7	0.6	
Duration of illness (years)			7.1	5.5	

Abbreviations: HC = healthy controls, MDD = major depressive disorder, HDRS = Hamilton Depression Rating Scale.

[a] Mann–Whitney U test.

[b] Two-tailed chi-square tests.

4. Discussion

To the best of our knowledge, this is the first study to examine brain responses to others' pain in MDD patients. We found that the MDD patients rated the painful stimuli as less painful compared with healthy subjects. Furthermore, the MDD patients showed reduced cerebral activation in the left MCC and the right SRC, whereas showing greater cerebral activation in the left IFG during empathy for others' pain.

A previous study found that MDD patients showed reduced awareness of others' emotions compared with healthy controls (Donges et al., 2005). Our behavioral results also indicate that MDD patients would have difficulty in understanding others' emotions.

Our fMRI results showed that the brain response to others' pain was associated with activation in the MCC, anterior insula, SRC, and prefrontal cortices. Consistent with previous studies (Jackson et al., 2006; Lamm et al., 2010, 2011), activation of areas involved in empathy for others' pain was replicated.

Interestingly, the MDD patients showed reduced cerebral activation in the left MCC, and the right SRC, whereas showing greater cerebral activation in the left IFG. As for the MCC, the cingulate cortex plays key roles in integrating multimodal information important for emotional, sensorimotor, and cognitive functions (Taylor et al., 2009). Among the subdivisions of the cingulate cortex, the MCC is supposed to play roles in a variety of cognitive functions such as response selection or working memory, as well as motor functions, such as skeletomotor regulations (Torta and Cauda, 2011). In addition, the MCC, as a part of the pain matrix, is involved in the processing of perceived others' pain. For instance, fMRI studies in which subjects perceived others' pain showed that pain-related MCC/ACC activation correlated with subjective pain evaluation of the subjects, and the authors propose that this area might be related to the evaluative aspect of pain processing in others (Guo et al., 2013; Jackson et al., 2005). Our current results of reduced MCC activation in patients suggest that evaluative process of pain is attenuated or suppressed in these subjects. This speculation is in line with our behavioral data that subjective evaluation of others' pain is substantially reduced in the patient group.

As for the SRC, it is considered to not only encode bodily sensations but also play a key role in using social cues to understand emotional states of others (Keysers et al., 2010). In line with this notion, the previous study reported that greater neural activity in the right SRC when predicting emotional response of other person was correlated with self-reported empathy (Hooker et al., 2008). In our subjects with depression, reduced recognition of others' pain, associated with reduced activation of the SRC, was observed. This finding could be interpreted as the neural machinery, which normally provokes empathic concern in the face of distressing state of others, being dysfunctional or suppressed in depression.

Conversely, we found elevated cerebral activation in the left IFG in MDD patients. The IFG plays a key role in regulating negative emotion (Johnstone et al., 2007). Concerning pain perception, it has also been shown that the prefrontal regions including the IFG have an important role in modulating pain processing during attentional manipulation paradigms (Petrovic et al., 2000). As to the relationship between pain and depression, emotional responses to pain were reported to be altered in patients with MDD (Bär et al., 2007; Strigo et al., 2008, 2010, 2013). Bär et al. (2007) showed increased activation in the lateral prefrontal cortex

Table 2
Activations associated with watching others' pain for the HC and MDD groups.

Brain region	H	Coordinates (mm)			t	Cluster (voxel)
		x	Y	z		
HC						
Medial frontal gyrus/MCC/ACC	L/R	−8	15	23	7.43	336
Posterior cingulate cortex	L/R	−2	−28	22	5.28	40
Anterior insula/IFG	L	−32	25	−3	5.15	31
Medial/superior frontal gyrus	L	−4	7	62	5.38	61
Precentral gyrus	L	−57	5	31	6.16	93
Precuneus/superior parietal lobule	L	−30	−60	49	5.86	136
Postcentral gyrus/supramarginal gyrus	L	−59	−19	14	8.23	59
Postcentral gyrus/supramarginal gyrus	L	−48	−32	51	4.91	44
Postcentral gyrus /supramarginal gyrus/parietal operculum	R	61	−20	27	6.89	179
Postcentral gyrus/supramarginal gyrus	R	44	−31	48	7.45	76
Occipital lobe/fusiform gyrus	L	−46	−59	−11	5.29	20
Thalamus/caudate	L/R	−8	8	5	5.52	57
MDD						
Medial frontal gyrus/MCC	L/R	4	24	45	5.17	64
Anterior insula/IFG	L	−36	19	−8	5.52	28
IFG	L	−53	16	−1	7.17	53
Middle/superior frontal gyrus	L/R	−18	−4	67	7.23	386
Middle/superior frontal gyrus	L	−38	37	35	6.63	126
Middle frontal gyrus	L	−40	53	12	6.90	22
Precentral gyrus/middle frontal gyrus	L	−48	6	48	5.85	221
Precuneus/superior parietal lobule	L	−20	−58	38	7.63	341
Postcentral gyrus/supramarginal gyrus	L	−59	−37	44	7.87	447
Postcentral gyrus	L	−53	−25	51	8.73	32
Occipital lobe	R	30	−66	11	5.89	32
Cerebellum	R	34	−50	−24	6.91	76
Cerebellum	R	26	−65	−22	5.07	30
HC > MDD						
MCC	L	−4	−10	30	4.60	23
Postcentral gyrus/supramarginal gyrus	R	63	−13	21	5.96	79
Postcentral gyrus/parietal operculum	R	40	−16	27	4.48	32
HC < MDD						
IFG	L	−51	17	−1	4.96	22

$p \leq 0.001$, Uncorrected and $k=20$ voxels.
Voxel size is $2 \times 2 \times 2$ mm.
Talairach coordinates and t-values are provided for the local voxel maximum of the respective cluster.
Abbreviations: HC=healthy controls, MDD=major depressive disorder, L=left, R=right, H=hemisphere, ACC=anterior cingulate cortex, MCC=middle cingulate cortex, IFG=inferior frontal gyrus.

during the direct own pain perception, together with reduced subjective rating of the pain, in MDD patients. Furthermore, Strigo et al. (2008) reported that MDD patients showed increased activity in several brain regions including left IFG during anticipation of pain and they suggested that altered brain responses during anticipatory processing in MDD might lead to an impaired ability to modulate not only the experience of pain but also negative affective states. In addition, a recent study on healthy subjects reported that the activation in the IFG during the direct own pain perception was increased when depressed mood was induced (Berna et al., 2010). Our study is in line with these studies, although ours applied visual presentation of others' pain, and increased IFG activation might itself be a pathological process associated with MDD, or alternatively, it might be a kind of adaptive process to suppress painful subjective experiences in patients suffering depression.

Alternatively, this result may be interpreted as follows. The IFG/anterior insula were repeatedly reported to be activated during empathy for others' pain (Jackson et al., 2006; Lamm et al., 2011; Xu et al., 2009). In addition, a previous study showed that gray matter density in the left anterior insula positively correlated with empathy in healthy participants (Mutschler et al., 2013). Further, Saarela et al. (2007) showed that the activation in the left IFG/anterior insula during observation of intensified pain was positively correlated with the levels of self-reported empathic stress in affective empathy. Recently, several studies have reported that MDD patients show deficits in cognitive aspects of empathy such as perspective taking and theory of mind, but show heightened sensitivity to empathic stress in affective components of empathy (Schreiter et al., 2013). Moreover, a recent study showed that MDD patients showed a general deficit in empathic processing of dynamic stimuli at the behavioral level, yet the number of galvanic skin responses during stimulus presentation was higher than in healthy individuals (Schneider et al., 2012). Although speculative, the present result (i.e. MDD patients showed elevated cerebral activation in the left IFG in spite of their reduced pain ratings) might support these studies and suggest that MDD patients physiologically showed elevated empathic stress, yet they might not be able to verbalize it due to their multiple cognitive impairments. Future neuroimaging studies are required to address the multidimensionality of empathic impairments in patients with MDD.

To summarize, we suggest that the above-mentioned three regions with altered activations form the pathophysiological basis of reduced others' pain recognition in MDD. Unfortunately, it remains obscure whether these altered brain functions reflect a state or a trait characteristic of MDD patients, as we did not find significant correlations of depression severity with the above-mentioned three regions. This may be because of the characteristics of the patients investigated; most patients in the present

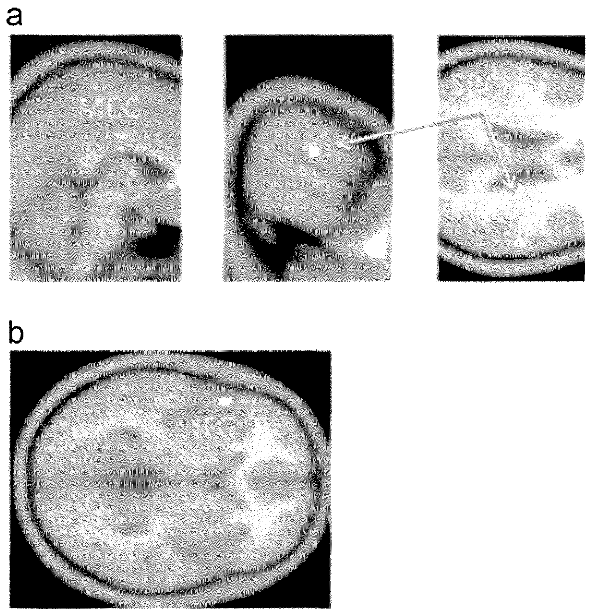

Fig. 1. The significant clusters differentially activated between the HC and MDD groups. Brain images of the different regional cerebral activations between the HC and MDD groups. (a) HC > MDD. (b) HC < MDD. The clusters with differential neural activities in response to others' pain (the contrast of painful versus non-painful conditions) are shown. The height and extent thresholds were set at $p < 0.001$, uncorrected and $k=20$ voxels. (a) The MDD group showed reduced cerebral activation in the left MCC and the right SRC compared with the HC group. (b) The MDD group showed greater cerebral activation in the left IFG compared with the HC group. *Abbreviations*: HC = healthy controls, MDD = major depressive disorder, MCC = middle cingulate cortex, SRC = somatosensory-related cortices, IFG = inferior frontal gyrus.

study had relatively mild symptoms, and the variation of HDRS scores might be too small to detect possible correlations. This is one of the major limitations of the study, and should be overcome in future studies recruiting a larger number of subjects including those with more severe symptoms. Longitudinal studies are also needed to provide a clearer view on this "state or trait" debate. Another major limitation of this study is a lack of power, with small sample sizes. In addition, two patients were in euthymic. Mixed handedness and imbalanced gender also limit the interpretation of the results. Moreover, because all patients were taking medications, we could not exclude the effects of medications. Therefore, we should interpret our findings as preliminary and caution should be exercised in generalizing the results. Future study should test larger samples including non-medicated patients to confirm our preliminary results. Concerning the task design, we did not use the pain rating in the scanner for the analyses because its purpose was to focus the participants' attention on pain while watching the videos. However, the pain ratings in the scanner were consistent with those obtained outside the scanner, that is, the pain rating of painful videos in the scanner was also low in the MDD group compared with the HC group (albeit it did not reach statistical significance). Nevertheless, despite these limitations, our preliminary study may provide an indication of this avenue of research and motivate future research on a larger scale.

In conclusion, the present study suggests that empathy for others' pain is altered in MDD patients. The MDD patients showed reduced cerebral activation in the left MCC, and the right SRC, whereas showing greater cerebral activation in the left IFG, during the empathy for others' pain. These results suggest that the functional alterations in these regions would be associated with the deficit of identification of pain in others, in MDD patients. The clinicians should note that the recognition of others' pain in MDD patients could be impaired, which might lead to their unconscious miscommunication with others. This should be taken into account when administering therapeutic interventions such as cognitive behavioral therapy in clinical settings.

Role of funding source

This work was supported by Grants-in-Aid for Young Scientists B (23791326) from the Japan Society for the Promotion of Science; SENSHIN Medical Research Foundation; Grants-in-Aid for scientific research S (22220003), and on Innovative Areas (23118004), from the Ministry of Education, Culture, Sports, Science and Technology of Japan. These agencies had no further role in the study design, collection, analysis and interpretation of data, writing of the paper, or in the decision to submit the paper for publication.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgments

The authors wish to extend their gratitude to Yusuke Tanaka, Manabu Kubota, Akihiko Sasamoto, Shiho Ubukata, Yukiko Matsumoto, Masanori Isobe, Shuraku Son, Kousuke Tsurumi, Kimito Hirose, Yasuo Mori, Naoto Yokoyama, Naho Saito, Tomomi Noda, Hideaki Takeuchi, Ema Murao and Takuro Murao for their assistance in data acquisition and processing, and, most of all, to the patients and volunteers for participating in the study. A part of this study is the result of Development of BMI Technologies for Clinical Application carried out under the Strategic Research Program for Brain Sciences by the MEXT.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2014.04.058.

References

Bär, K.J., Wagner, G., Koschke, M., Boettger, S., Boettger, M.K., Schlosser, R., Sauer, H., 2007. Increased prefrontal activation during pain perception in major depression. Biol. Psychiatry 62, 1281–1287.
Berna, C., Leknes, S., Holmes, E.A., Edwards, R.R., Goodwin, G.M., Tracey, I., 2010. Induction of depressed mood disrupts emotion regulation neurocircuitry and enhances pain unpleasantness. Biol. Psychiatry 67, 1083–1090.
Cusi, A.M., Macqueen, G.M., Spreng, R.N., McKinnon, M.C., 2011. Altered empathic responding in major depressive disorder: relation to symptom severity, illness burden, and psychosocial outcome. Psychiatry Res. 188, 231–236.
Cusi, A.M., Nazarov, A., Holshausen, K., Macqueen, G.M., McKinnon, M.C., 2012. Systematic review of the neural basis of social cognition in patients with mood disorders. J. Psychiatry Neurosci. 37, 154–169.
Decety, J., Moriguchi, Y., 2007. The empathic brain and its dysfunction in psychiatric populations: implications for intervention across different clinical conditions. Biopsychosoc. Med. 1, 22.
Donges, U.-S., Kersting, A., Dannlowski, U., Lalee-Mentzel, J., Arolt, V., Suslow, T., 2005. Reduced awareness of others??? Emotions in unipolar depressed patients. J. Nerv. Ment. Dis. 193, 331–337.
Duvernoy, H.M., 1991. The Human Brain. Surface, Three-dimensional Sectional Anatomy and MRI. Springer-Verlag, Wien.
Field, T., Diego, M., Hernandez-Reif, M., 2009. Depressed mothers' infants are less responsive to faces and voices. Infant Behav. Dev. 32, 239–244.
Fu, C.H., Williams, S.C., Cleare, A.J., Scott, J., Mitterschiffthaler, M.T., Walsh, N.D., Donaldson, C., Suckling, J., Andrew, C., Steiner, H., Murray, R.M., 2008. Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. Biol. Psychiatry 64, 505–512.
Guo, X., Zheng, L., Wang, H., Zhu, L., Li, J., Wang, Q., Dienes, Z., Yang, Z., 2013. Exposure to violence reduces empathetic responses to other's pain. Brain Cogn. 82, 187–191.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Harvey, P.O., Fossati, P., Pochon, J.B., Levy, R., Lebastard, G., Lehericy, S., Allilaire, J.F., Dubois, B., 2005. Cognitive control and brain resources in major depression: an fMRI study using the n-back task. NeuroImage 26, 860–869.
Hasselbalch, B.J., Knorr, U., Kessing, L.V., 2011. Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. J. Affect. Disord. 134, 20–31.
Hooker, C.I., Verosky, S.C., Germine, L.T., Knight, R.T., D'Esposito, M., 2008. Mentalizing about emotion and its relationship to empathy. Soc. Cogn. Affect. Neurosci. 3, 204–217.
Jackson, P.L., Brunet, E., Meltzoff, A.N., Decety, J., 2006. Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain. Neuropsychologia 44, 752–761.

Jackson, P.L., Meltzoff, A.N., Decety, J., 2005. How do we perceive the pain of others? A window into the neural processes involved in empathy. NeuroImage 24, 771–779.
Johnstone, T., van Reekum, C.M., Urry, H.L., Kalin, N.H., Davidson, R.J., 2007. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. J. Neurosci. 27, 8877–8884.
Keysers, C., Kaas, J.H., Gazzola, V., 2010. Somatosensation in social perception. Nat. Rev. Neurosci. 11, 417–428.
Lamm, C., Decety, J., Singer, T., 2011. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. NeuroImage 54, 2492–2502.
Lamm, C., Meltzoff, A.N., Decety, J., 2010. How do we empathize with someone who is not like us? A functional magnetic resonance imaging study. J. Cogn. Neurosci. 22, 362–376.
Moriguchi, Y., Decety, J., Ohnishi, T., Maeda, M., Mori, T., Nemoto, K., Matsuda, H., Komaki, G., 2007. Empathy and judging other's pain: an fMRI study of alexithymia. Cerebral Cortex 17, 2223–2234.
Mutschler, I., Reinbold, C., Wankerl, J., Seifritz, E., Ball, T., 2013. Structural basis of empathy and the domain general region in the anterior insular cortex. Front. Hum. Neurosci. 7, 177.
Petrovic, P., Petersson, K.M., Ghatan, P.H., Stone-Elander, S., Ingvar, M., 2000. Pain-related cerebral activation is altered by a distracting cognitive task. Pain 85, 19–30.
Peyron, R., Laurent, B., Garcia-Larrea, L., 2000. Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol. Clin. 30, 263–288.
Saarela, M.V., Hlushchuk, Y., Williams, A.C., Schurmann, M., Kalso, E., Hari, R., 2007. The compassionate brain: humans detect intensity of pain from another's face. Cerebral Cortex 17, 230–237.
Schneider, D., Regenbogen, C., Kellermann, T., Finkelmeyer, A., Kohn, N., Derntl, B., Schneider, F., Habel, U., 2012. Empathic behavioral and physiological responses to dynamic stimuli in depression. Psychiatry Res. 200, 294–305.
Schreiter, S., Pijnenborg, G.H., Rot, M., Aan Het, 2013. Empathy in adults with clinical or subclinical depressive symptoms. J. Affect. Disord. 150, 1–16.
Strigo, I.A., Matthews, S.C., Simmons, A.N., 2013. Decreased frontal regulation during pain anticipation in unmedicated subjects with major depressive disorder. Transl. Psychiatry 3, e239.
Strigo, I.A., Matthews, S.C., Simmons, A.N., 2010. Right anterior insula hypoactivity during anticipation of homeostatic shifts in major depressive disorder. Psychosom. Med. 72, 316–323.
Strigo, I.A., Simmons, A.N., Matthews, S.C., Craig, A.D., Paulus, M.P., 2008. Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. Arch. Gen. Psychiatry 65, 1275–1284.
Talairach, J, Tournoux, P., 1988. Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System—An Approach to Cerebral Imaging. Thieme, New York.
Taylor, K.S., Seminowicz, D.A., Davis, K.D., 2009. Two systems of resting state connectivity between the insula and cingulate cortex. Hum. Brain Mapp. 30, 2731–2745.
Torta, D.M., Cauda, F., 2011. Different functions in the cingulate cortex, a meta-analytic connectivity modeling study. NeuroImage 56, 2157–2172.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15, 273–289.
Wilbertz, G., Brakemeier, E.L., Zobel, I., Harter, M., Schramm, E., 2010. Exploring preoperational features in chronic depression. J. Affect. Disord. 124, 262–269.
Worsley, K.J., Friston, K.J., 1995. Analysis of fMRI time-series revisited—again. NeuroImage 2, 173–181.
Xu, X., Zuo, X., Wang, X., Han, S., 2009. Do you feel my pain? Racial group membership modulates empathic neural responses. J. Neurosci. 29, 8525–8529.
Zimmerman, M., Martinez, J.H., Young, D., Chelminski, I., Dalrymple, K., 2013. Severity classification on the Hamilton Depression Rating Scale. J. Affect. Disord. 150, 384–388.

Journal of Affective Disorders 174 (2015) 397–399

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Preliminary communication

Anterior cingulate volume predicts response to cognitive behavioral therapy in major depressive disorder

Junya Fujino [a], Nobuyuki Yamasaki [b,*], Jun Miyata [a], Hitoshi Sasaki [a], Noriko Matsukawa [a], Ariyoshi Takemura [a], Shisei Tei [a,c,d], Genichi Sugihara [a], Toshihiko Aso [e], Hidenao Fukuyama [e], Hidehiko Takahashi [a], Kazuomi Inoue [f], Toshiya Murai [a]

[a] Department of Psychiatry, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[b] Kyoto Prefectural Rakunan Hospital, 2, Hirookadani, Gokasho, Uji City, Kyoto 611-0011, Japan
[c] School of Human and Social Sciences, Department of Human Development and Sport Sciences, Tokyo International University, Saitama, Japan
[d] Institute of Applied Brain Sciences, Waseda University, Tokyo, Japan
[e] Human Brain Research Center, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[f] Utsumi Mental Clinic, Hyogo, Japan

ARTICLE INFO

Article history:
Received 3 December 2014
Accepted 4 December 2014
Available online 13 December 2014

Keywords:
Anterior cingulate cortex
Cognitive behavioral therapy
Depression
Magnetic resonance imaging
Voxel-based morphometry

ABSTRACT

Background: Cognitive behavioral therapy (CBT) is widely used to treat major depressive disorder (MDD). Although improved response prediction could facilitate the development of individualized treatment plans, few studies have investigated whether underlying brain structure is related to CBT response in MDD.
Methods: Ten MDD patients who received individual CBT were studied in this study. We investigated the relationship between the regional gray matter (GM) volume and subsequent responses to CBT using voxel-based morphometry.
Results: The degree of improvement in depressive symptoms was positively correlated with GM volume in the caudal portion of the anterior cingulate cortex.
Limitations: The sample size was small, and the effects of medication on the results could not be excluded.
Conclusions: Our results, although preliminary, suggest that the anterior cingulate cortex is a key structure whose volume can be used to predict responses to CBT and is thus a potential prognostic marker in MDD.

1. Introduction

Cognitive behavioral therapy (CBT) is reported to be effective for about half of people with major depressive disorder (MDD) (Hollon et al., 2002; Siegle et al., 2006). Detecting patients who are likely to benefit from CBT could increase the success rate and reduce the burden on patients. Thus, improving prediction accuracy for responses to CBT is an important goal of MDD research, and in this regard, neuroimaging data may provide useful information. Indeed, several functional neuroimaging studies indicate that CBT response is associated with activation levels in the anterior cingulate cortex (ACC) (Costafreda et al., 2009; Fu et al., 2008; Siegle et al., 2006; Ritchey et al., 2011), although localization within the ACC was mixed. For example, one study showed that CBT was more effective in MDD patients whose sustained responses to emotional stimuli were low in the subgenual ACC (Siegle et al., 2006). Additionally, another study reported that dorsal ACC activity during emotion processing of sad faces showed a significant inverse relationship with subsequent clinical response (Fu et al., 2008).

Although a number of functional imaging studies have examined the relationship between brain activation and subsequent CBT response, few studies have investigated whether underlying brain structure is related to CBT response in MDD. Here, we investigated whether there was a relationship between gray matter (GM) volume and subsequent CBT response in the disorder using voxel-based morphometry (VBM). Based on the results of previous functional imaging studies, we hypothesized that the volume of ACC would be correlated with subsequent CBT responses.

2. Methods

2.1. Participants

Fourteen consecutive MDD outpatients who participated in the CBT program in Kyoto University were recruited for the study. Patients had experienced at least one major depressive episode according to the Structured Clinical Interview for DSM-IV Axis I Disorders. Two patients

Abbreviations: ACC, anterior cingulate cortex; BDI-II, Beck depression inventory-II; CBT, cognitive behavioral therapy; GM, gray matter; MDD, major depressive disorder; MRI, magnetic resonance imaging; VBM, voxel-based morphometry

* Corresponding author. Tel./fax: +81 774 32 5900.
E-mail address: yamasaki@rakunan-hosp.jp (N. Yamasaki).

http://dx.doi.org/10.1016/j.jad.2014.12.009
0165-0327/

had current comorbid axis I diagnoses; one met the criteria for panic disorder and the other for social anxiety disorder. None had a previous history of psychosis or mania. In addition, none had a history of head trauma, any neurological illness, serious medical or surgical illness, or substance abuse. Four patients were excluded from the analyses: one could not participate in the magnetic resonance imaging (MRI) scan, one had an artificial tooth that created artifacts in the MRI scan, one was admitted to the hospital shortly after the study registration, and one developed suicidal ideation that required a substantial change in antidepressant medication during CBT. Therefore, we analyzed data from the remaining 10 patients (seven were female, mean age: 33.5 ± 9.1 years). The mean number of previous depressive episodes was 1.9 ± 1.0, and the mean duration of illness was 6.8 ± 5.7 years. 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. CBT

After scanning, patients received an individual CBT, following Beck's cognitive therapy manual (Beck et al., 1979). Sixteen sessions (45 min/session) were conducted basically once per week. All CBT sessions were performed by an experienced psychiatrist (the author N.Y.). The sessions were audiotaped and reviewed by another author (K.I.) to ensure that CBT followed the standard format. The Beck depression inventory-II (BDI-II) (Beck et al., 1996; Kojima et al., 2002) was used to assess depressive symptoms. The baseline assessment was performed on the day of the first CBT session (one patient was assessed one day before the first CBT session), and the last clinical assessment was performed on the day of the last CBT session. All patients were taking one or more antidepressants during the time of the study (one was taking a tricyclic antidepressant, five were taking a selective serotonin reuptake inhibitor, three were taking a selective serotonin noradrenalin reuptake inhibitor, and two were taking other types of antidepressants), but the doses of these medications were not increased or new antidepressants were not started during the CBT treatment.

2.3. MRI acquisition, pre-processing, and analysis

Participants were scanned with a 3-T whole-body MRI scanner equipped with an eight-channel phased-array head coil (Trio; Siemens, Erlangen, Germany). The scanning parameters of the T1-weighted, three-dimensional, magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequence were as follows: $TR = 2000$ ms, $TE = 4.38$ ms, $TI = 990$ ms, $FOV = 225 \times 240$ mm, matrix $= 240 \times 256$, resolution $= 0.9375 \times 0.9375 \times 1.0$ mm^3, and 208 total axial sections without intersection gaps.

MRI data were processed using SPM8 (Wellcome Trust Center for Neuroimaging, London, UK) and the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) in Matlab (MathWorks, Natick, MA, USA). In brief, all images were tissue classified and spatially normalized to the same stereotaxic space using the diffeomorphic anatomical registration through the exponentiated Lie algebra (DARTEL) algorithm (Ashburner, 2007). The voxel values of segmented and normalized GM images were modulated by the Jacobian determinants obtained from non-linear normalization steps. We applied the default parameters of the VBM8 toolbox, except for using the ICBM-space template for East Asian brains for affine regularization. Finally, the resultant GM images were smoothed with Gaussian kernels of 8 mm full width at half maximum.

CBT responses were calculated as follows: (baseline BDI-II score − last BDI-II score)/baseline BDI-II score. To explore the brain regions whose volumes were correlated with subsequent CBT responses, we performed a multiple regression analysis using a general linear model framework in SPM8. Age and gender were entered into the model as covariates of no interest. Because the images were modulated for nonlinear warping only, intracranial volume was not included as a nuisance covariate (http://dbm.neuro.uni-jena.de/vbm/segmentation/modulation/). Based on effect size considerations derived from previous VBM studies (Kubota et al., 2011; Sasamoto et al., 2011), a statistical threshold was set at $p < 0.001$ (uncorrected), with an extent threshold of 100 voxels. We interpreted the anatomical locations of the clusters by consulting the Talairach Client (http://www.talairach.org/client.html), and neuroanatomy atlas books (Duvernoy, 1991; Talairach and Tournoux, 1988).

3. Results

The patients varied in the degree of depressive symptom change assessed by BDI-II, but on average the depressive symptoms were improved during CBT (pre-treatment BDI-II: 21.3 ± 8.7, post-treatment BDI-II: 15.2 ± 9.5; $p = 0.04$ [paired t-test, analyzed with spss 21]).

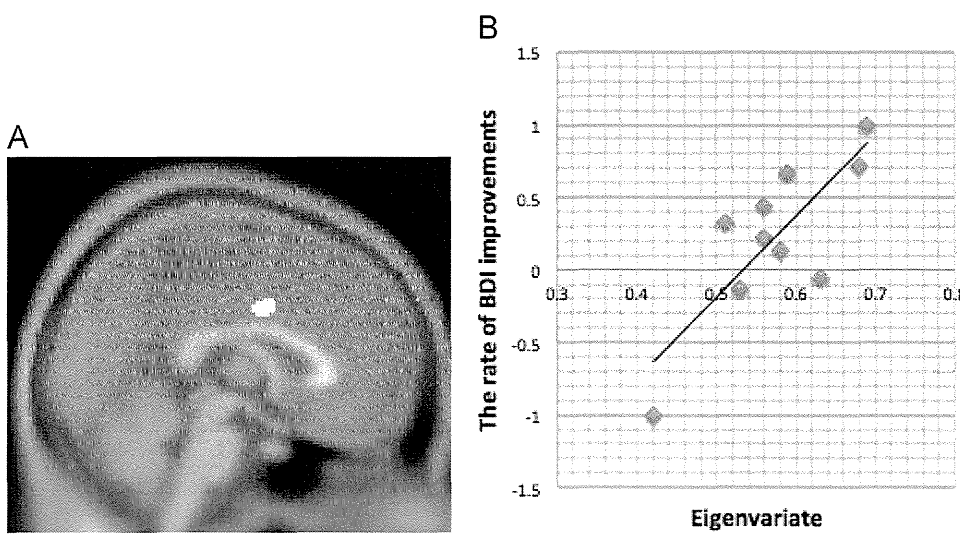

Fig. 1. Significant cluster positively correlated with the rate of BDI-II improvement. (A) The cluster positively correlated with the rate of BDI-II improvement is shown. Height and extent thresholds were set at $p < 0.001$, uncorrected and $k = 100$ voxels. The cluster including the caudal portion of ACC was positively correlated with the rate of BDI-II change, (B) correlation between the GM density data (eigenvariates extracted using the VOI function in SPM8) of the cluster seen in (A) and the rate of BDI-II change. *Abbreviations*; ACC = anterior cingulate cortex, BDI-II = Beck depression inventory-II, GM = gray matter.

Whole-brain VBM analyses showed that one cluster including the caudal portion of the ACC (peak MNI coordinates: −2, −3, 34 [Broadman area 24], T-score=6.92, k=153 voxels) was positively correlated with the rate of BDI-II improvement (Fig. 1A and B). We did not find any other clusters using the same threshold. Additionally, we did not find any significant negative correlation between regional brain volume and the rate of BDI-II improvement. The GM density data (i.e., eigenvariates extracted using the VOI function in SPM8) from the above cluster was still significantly correlated with the rate of BDI-II improvement after controlling for baseline BDI-II scores (r=0.79, p=0.01).

4. Discussion

In this study, we investigated whether there was a relationship between GM volume and subsequent CBT responses in MDD patients. We found a significant correlation between GM volume in the caudal portion of the ACC and improvements in depressive symptoms during CBT. Our results suggest that the volume in the region can predict CBT responses.

Identifying predictors of treatment efficacy is an essential goal of MDD research. Previous functional imaging studies related to emotional processing showed that activation levels in the ACC predict subsequent CBT response (Fu et al., 2008; Siegle et al., 2006). Although the cluster related to CBT responses in this study was located posterior to the regions identified in these studies, our results support the notion that the ACC is a key structure for predicting CBT responses.

The ACC is a structure that has repeatedly been reported to be altered in MDD (Fu et al., 2008; Sacher et al., 2012; Yoshimura et al., 2010), and is involved in multiple cognitive functions, such as decision making, inhibition control, and empathy (Botvinick, 2007; Decety and Moriguchi, 2007; Kuhn et al., 2012). Interestingly, the caudal portion of the ACC, which was correlated with CBT response in this study, plays a key role in regulation of behavior through performance monitoring (Haupt et al., 2009; Ursu et al., 2009). CBT addresses maladaptive behaviors through a variety of goal-oriented explicit systematic procedures (Beck et al., 1979). Our finding could be interpreted to mean that patients who have higher ACC volume may have higher capacity to effectively monitor their performance and thus receive more benefits from CBT. This speculation is in line with the notion that CBT may focus on patients' strengths, rather than compensating for their deficits (Rude and Rehm, 1991; Ritchey et al., 2011).

This study has several limitations. First, the sample size of our study was small for the prediction of clinical responses. Second, because all the patients received antidepressants during CBT, we could not exclude their effects. In addition to this, most patients included in our study were treatment-resistant because they did not respond satisfactorily to the treatment with only medications. Therefore, they may not be representative of the general population for this disorder. Our findings are preliminary and caution should be exercised in generalizing the results.

In conclusion, this study showed that ACC volume was correlated with CBT response in patients with MDD. Our result supports the notion that the ACC is a key structure for predicting the effectiveness of CBT in this population, and should further be explored as a prognostic marker of MDD.

Conflict of interest

All authors declare that they have no conflicts of interest.

Role of funding source

This work was supported by Grants-in-Aid for Young Scientists B (23791326) from the Japan Society for the Promotion of Science; SENSHIN Medical Research Foundation; Grants-in-Aid for scientific research S (22220003), scientific research A (24243061), and on Innovative Areas (23118004, 23120009), from the Ministry of Education, Culture, Sports, Science and Technology of Japan; Health and Labour Science Research Grant for Comprehensive Research on Disability Health and Welfare (H25-seishin-jitsuyouka-ippan-001) from the Ministry of Health, Labour, and Welfare. A part of this study is the result of Development of BMI Technologies for Clinical Application carried out under the Strategic Research Program for Brain Sciences by the MEXT. These agencies had no further role in the study design, collection, analysis and interpretation of data, writing of the paper, or in the decision to submit the paper for publication.

Acknowledgements

The authors wish to extend their gratitude to Ryosaku Kawada, Yusuke Tanaka, Manabu Kubota, Akihiko Sasamoto, Shiho Ubukata, Yukiko Matsumoto, Masanori Isobe, Shuraku Son, Kousuke Tsurumi, Kimito Hirose, Yasuo Mori, Naoto Yokoyama, Miki Ono, Naho Saito, Tomomi Noda, Hideaki Takeuchi, Ema Murao and Takuro Murao for their assistance in data acquisition and processing, and, most of all, to the patients and volunteers for participating in the study.

References

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. NeuroImage 38, 95–113.
Beck, A.T., Rush, J.A., Shaw, B.F., Emery, G., 1979. Cognitive Therapy of Depression. The Guilford Press, New York.
Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual for the Beck Depression Inventory-II (BDI-II). Psychological Corporation, San Antonio, TX.
Botvinick, M.M., 2007. Conflict monitoring and decision making: reconciling two perspectives on anterior cingulate function. Cogn. Affect. Behav. Neurosci. 7, 356–366.
Costafreda, S.G., Khanna, A., Mourao-Miranda, J., Fu, C.H., 2009. Neural correlates of sad faces predict clinical remission to cognitive behavioural therapy in depression. Neuroreport 20, 637–641.
Decety, J., Moriguchi, Y., 2007. The empathic brain and its dysfunction in psychiatric populations: implications for intervention across different clinical conditions. Biopsychosoc. Med 1, 22.
Duvernoy, H.M., 1991. The Human Brain. Surface, Three-dimensional Sectional Anatomy and MRI. Springer-Verlag, Wien.
Fu, C.H., Williams, S.C., Cleare, A.J., Scott, J., Mitterschiffthaler, M.T., Walsh, N.D., Donaldson, C., Suckling, J., Andrew, C., Steiner, H., Murray, R.M., 2008. Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. Biol. Psychiatry 64, 505–512.
Haupt, S., Axmacher, N., Cohen, M.X., Elger, C.E., Fell, J., 2009. Activation of the caudal anterior cingulate cortex due to task-related interference in an auditory Stroop paradigm. Hum. Brain Mapp. 30, 3043–3056.
Hollon, S.D., Thase, M.E., Markowitz, J.C., 2002. Treatment and prevention of depression. Psychol. Sci. Public Interest 3, 39–77.
Kojima, M., Furukawa, T.A., Takahashi, H., Kawai, M., Nagaya, T., Tokudome, S., 2002. Cross-cultural validation of the Beck depression inventory-II in Japan. Psychiatry Res. 110, 291–299.
Kubota, M., Miyata, J., Hirao, K., Fujiwara, H., Kawada, R., Fujimoto, S., Tanaka, Y., Sasamoto, A., Sawamoto, N., Fukuyama, H., Takahashi, H., Murai, T., 2011. Alexithymia and regional gray matter alterations in schizophrenia. Neurosci. Res. 70, 206–213.
Kuhn, S., Vanderhasselt, M.A., De Raedt, R., Gallinat, J., 2012. Why ruminators won't stop: the structural and resting state correlates of rumination and its relation to depression. J. Affect. Disord. 141, 352–360.
Ritchey, M., Dolcos, F., Eddington, K.M., Strauman, T.J., Cabeza, R., 2011. Neural correlates of emotional processing in depression: changes with cognitive behavioral therapy and predictors of treatment response. J. Psychiatr. Res. 45, 577–587.
Rude, S.S., Rehm, L.P., 1991. Response to treatments for depression: the role of initial status on targeted cognitive and behavioral skills. Clin. Psychol. Rev. 11, 493–514.
Sacher, J., Neumann, J., Funfstuck, T., Soliman, A., Villringer, A., Schroeter, M.L., 2012. Mapping the depressed brain: a meta-analysis of structural and functional alterations in major depressive disorder. J. Affect. Disord. 140, 142–148.
Sasamoto, A., Miyata, J., Hirao, K., Fujiwara, H., Kawada, R., Fujimoto, S., Tanaka, Y., Kubota, M., Sawamoto, N., Fukuyama, H., Takahashi, H., Murai, T., 2011. Social impairment in schizophrenia revealed by Autism-Spectrum Quotient correlated with gray matter reduction. Soc. Neurosci. 6, 548–558.
Siegle, G.J., Carter, C.S., Thase, M.E., 2006. Use of FMRI to predict recovery from unipolar depression with cognitive behavior therapy. Am. J. Psychiatry 163, 735–738.
Talairach, J, Tournoux, P., 1988. Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System—An Approach to Cerebral Imaging. Thieme, New York.
Ursu, S., Clark, K.A., Aizenstein, H.J., Stenger, V.A., Carter, C.S., 2009. Conflict-related activity in the caudal anterior cingulate cortex in the absence of awareness. Biol. Psychol. 80, 279–286.
Yoshimura, S., Okamoto, Y., Onoda, K., Matsunaga, M., Ueda, K., Suzuki, S., Shigetoyamawaki, 2010. Rostral anterior cingulate cortex activity mediates the relationship between the depressive symptoms and the medial prefrontal cortex activity. J. Affect. Disord. 122, 76–85.

OPEN

Citation: Transl Psychiatry (2014) **4**, e393; doi:10.1038/tp.2014.34

www.nature.com/tp

ORIGINAL ARTICLE

Can we predict burnout severity from empathy-related brain activity?

S Tei[1,2,3], C Becker[4], R Kawada[1], J Fujino[1], KF Jankowski[5], G Sugihara[1], T Murai[1] and H Takahashi[1]

Empathy cultivates deeper interpersonal relationships and is important for socialization. However, frequent exposure to emotionally-demanding situations may put people at risk for burnout. Burnout has become a pervasive problem among medical professionals because occupational burnout may be highly sensitive to empathy levels. To better understand empathy-induced burnout among medical professionals, exploring the relationship between burnout severity and strength of empathy-related brain activity may be key. However, to our knowledge, this relationship has not yet been explored. We studied the relationship between self-reported burnout severity scores and psychological measures of empathic disposition, emotional dissonance and alexithymia in medical professionals to test two contradictory hypotheses: Burnout is explained by (1) 'compassion fatigue'; that is, individuals become emotionally over involved; and (2) 'emotional dissonance'; that is, a gap between felt and expressed emotion, together with reduced emotional regulation. Then, we tested whether increased or decreased empathy-related brain activity measured by fMRI was associated with burnout severity scores and psychological measures. The results showed that burnout severity of medical professionals is explained by 'reduced' empathy-related brain activity. Moreover, this reduced brain activity is correlated with stronger emotional dissonance and alexithymia scores and also greater empathic disposition. We speculate that reduced emotion recognition (that is, alexithymia) might potentially link with stronger emotional dissonance and greater burnout severity alongside empathy-related brain activity. In this view, greater empathic disposition in individuals with higher burnout levels might be due to greater difficulty identifying their own emotional reactions. Our study sheds new light on the ability to predict empathy-induced burnout.

Translational Psychiatry (2014) **4**, e393; doi:10.1038/tp.2014.34; published online 3 June 2014

INTRODUCTION

Occupational burnout has become a pervasive problem in human services, particularly among medical professionals who are highly vulnerable to burnout.[1] Behavioral studies suggest a strong link between burnout and empathy.[2–6] Although empathic attitude and approach impact every aspect of medical care for patients and their families,[7,8] as many as 76% of medical professionals report symptoms of burnout that may lead to medical errors, substance abuse and even suicide.[9] Empathy often relates to a pro-social behavior and is essential to human life.[10] However, excessive empathy might be problematic because frequent exposure to emotionally-demanding situations may put individuals at risk of burnout.[2–6] Previous research has found that burnout severity is related to both increases and decreases in dispositional empathy scores.[11,12] There are two contradictory theories of burnout; while the conventional theory, 'compassion fatigue theory',[13] suggests that burnout relates to excessive empathy, the alternative theory, 'emotional dissonance theory',[14] suggests that burnout relates to reduced emotional regulation that causes a gap between felt and expressed emotions.

'Compassion fatigue theory' refers to one's exhaustion associated with caring for individuals who are experiencing significant emotional/physical pain and distress.[13] This theory suggests that more empathic medical professionals tend to be at greater risk of compassion fatigue and subsequent burnout.[15] Meanwhile, the 'emotional dissonance theory' denotes a conflict between experienced emotions and emotions expressed to conform to display rules.[16] Emotional dissonance may emerge when one's efforts to express socially-required, and in some instances occupationally-required, empathic emotions become too much of a burden and emotional responses become poorly regulated.[17] Related research has found that inexperienced nurses who hide negative emotion showed greater burnout symptoms than those who do not freely express their emotions.[18]

Also supporting the 'emotional dissonance theory', research suggests that burnout severity is related to difficulty in regulating negative arousal and difficulty describing/identifying one's own emotions (that is, alexithymia: reduced emotional awareness).[19] Indeed, emotional dissonance may be related to alexithymia because individuals with relatively greater alexithymic tendencies fail to match their experienced and expressed emotions. Despite having cognitive empathic abilities within the normal range, people with high levels of alexithymia may show reduced emotional reactions when observing others in pain, due to their limited emotional regulation abilities.[20,21] Therefore, it is possible that the 'emotional dissonance theory' could better explain burnout severity in medical professionals, in addition to the conventional 'compassion fatigue theory'.

Because occupational burnout in medical professionals may greatly depend on empathy levels,[2] the relationship between

[1]Department of Psychiatry, Kyoto University Graduate School of Medicine, Kyoto, Japan; [2]Institute of Applied Brain Sciences, Waseda University, Tokyo, Japan; [3]School of Human and Social Sciences, Department of Human Development and Sport sciences, Tokyo International University, Saitama, Japan; [4]Kokoro Research Center, Kyoto University, Kyoto, Japan and [5]Department of Psychology, University of Oregon, Eugene, OR, USA. Correspondence: Professor H Takahashi, Department of Psychiatry, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawara-cho Sakyo-ku, Kyoto 606-8507, Japan.
E-mail: hidehiko@kuhp.kyoto-u.ac.jp
Received 7 January 2014; revised 24 March 2014; accepted 16 April 2014

burnout severity and strength of empathy-related brain activity may be the key to understanding empathy-induced burnout. However, to our knowledge, this relationship has not yet been explored. Meanwhile, some studies have shown differences in levels of empathy-related brain activity in medical professionals compared with healthy, nonmedical individuals, further speculating on the relationship between this brain activity and burnout. However, these previous studies did not implement psychological measures of burnout severity. Using functional magnetic resonance imaging (fMRI) and electroencephalography, these studies have revealed reduced empathy-related brain activity in physicians, compared with healthy controls, when viewing photographs of others experiencing physical pain.[22,23] This included activity in the anterior insula (AI), anterior cingulate cortex (ACC) and somatosensory cortex. Although burnout level was not directly examined, this reduced brain activity was speculated to reflect an adaptive strategy for resisting burnout.[23] Specifically, this reduced brain activity may enable physicians to address their patients' symptoms without becoming too emotionally involved. Importantly, however, reduced empathy-related brain activity was associated with greater empathic capabilities in physicians. Along with some other reports (described below), these findings suggest that empathy-related brain activity is not necessarily correlated with empathic capabilities. Although fMRI studies have demonstrated a positive correlation between strength of empathy-related brain activity during the experience of vicarious pain and Interpersonal Reactivity Index (IRI) empathy scores, for example,[7,24,25] a negative correlation has also been shown among individuals with psychopathy;[26] and healthy participants.[27–30]

According to a recent review, observation of others in pain induces an empathic response that mainly involves the AI, ACC, inferior frontal gyrus (IFG) and anterior medial cingulate cortex.[24] In addition, the temporoparietal junction (TPJ) may also have an important role in empathy-processing, including perspective taking,[31] in the patient–clinician relationship. For instance, in two fMRI experiments, physicians showed stronger TPJ activation when viewing a patient receiving pain compared with a no-pain condition.[7,22] We thus hypothesized that AI, ACC, IFG and TPJ activity would be correlated with self-reported burnout severity in medical professionals.

In this study, we explored the relationship between self-reported burnout severity scores and psychological measures of empathic disposition, emotional dissonance and alexithymia to test two contradictory hypotheses in medical professionals ('compassion fatigue theory' versus 'emotional dissonance theory'). Then, we tested whether increased or decreased empathy-related brain activity measured by fMRI was associated with burnout severity scores and psychological measures.

MATERIALS AND METHODS

Participants were 25 nurses in active service with less than 11 years of experience (20 females, aged 22–34, mean = 26.0, s.d. = 3.14). All participants had worked in nursing for at least 1 year. Participants were right-handed, according to the Edinburgh handedness inventory. Exclusion criteria included a history of neurological injury or disease, medical diseases or substance abuse. None of the participants met the DSM-IV criteria for any psychiatric disorders, as assessed by structured clinical interviews. Further, all participants underwent MRI scanning to rule out cerebral anatomic abnormalities. Participants were recruited via advertising from hospitals in Kyoto. All participants provided informed written consent and were paid for their participation. The institutional review board of Kyoto University approved the study.

Psychological measures

To avoid bias towards the concept of a relationship between burnout and empathy, participants completed the following four self-report measures after the fMRI scanning session. Burnout severity was assessed by the Maslach Burnout Inventory (MBI),[32] which includes two core dimensions: (1) 'emotional exhaustion' and (2) 'depersonalization'.[33] The 'emotional exhaustion' dimension measures feelings of being emotionally over-extended and exhausted by one's work. The 'depersonalization' dimension measures emotional detachment toward the recipients of one's care. In our study, the MBI served as a standardized measure for burnout and compassion fatigue because these two symptoms largely overlap.[19,34]

Empathetic disposition was assessed by the IRI,[35] which is one of the most widely used self-report measures of dispositional empathy. Following previous studies, the 'fantasy' subscale was excluded;[11] thus, three subscales were used: (1) 'perspective taking' (the tendency to cognitively adopt the perspective of another); (2) 'empathic concern' (the tendency to feel emotional concern for others); and (3) 'personal distress' (the tendency to experience negative feelings in response to the distress of others).

Emotional dissonance was assessed by the Emotion Work Requirements Scale (EWRS).[36] In this scale, higher scores imply a greater degree of emotional dissonance. In the current study, emotional dissonance was distinctly defined by EWRS scores. EWRS measures emotional deviance as a conflict between one's own emotional experience and the expression of emotions that are socially desired.[37] It is comprised of two subscales 'hide negative emotion' and 'display positive emotion' that trigger the conflict. Previous research suggests that burnout is related, in particular, to difficulty regulating negative emotions.[19] Thus, we only focused on measuring negative emotions and used the subscale 'hide negative emotion'.

An inability to identify and describe one's own emotions (alexithymia) was assessed by the Toronto Alexithymia Scale (TAS-20).[38] This measure includes the following subscales: (1) 'difficulty in identifying feelings'; (2) 'difficulty in describing feelings'; and (3) 'externally oriented thinking'. The relationships between burnout severity (MBI) and other psychological measures were examined by Pearson's *r* correlation analyses implemented in SPSS 21.0 (Chicago, IL, USA).

fMRI & data analysis

Video clips showing a hand in painful (pain) or nonpainful (no-pain) situations were presented to participants during the fMRI scanning. Participants were asked to passively look at the stimuli. The video clips consisted of images of other people's hands being harmed by different tools (that is, knife, hammer and icepick; 2.8 s duration each). For the no-pain condition, a similar setting to the pain condition was shown, but the tool being used was a soft brush. Each scanning session consisted of pain and no-pain conditions (six blocks each) presented in a randomized order. Each block contained six video clips and lasted a total of 16.8 s. A fixation cross was displayed for 14.4 s as a baseline condition and was inserted between each stimuli block (pain and no-pain; please see a schematic of the experimental paradigm in the Supplementary Information (Supplementary Figure S1)).

All participants participated in MRI scans using a 3-T scanner equipped with an eight-channel, phased array head coil (Trio, Siemens, Erlangen, Germany). Functional images were obtained in a T2*-weighted gradient echo-planar imaging sequence with the following parameters: TE/TR: 30/2,400 ms, flip angle = 90°, FOV = 192 × 192 mm, matrix = 64 × 64; 40 interleaved axial slices of 3-mm thickness without gaps; resolution = 3 mm cubic voxels. Imaging data were preprocessed and analyzed using SPM 8 (Wellcome Department of Imaging Neuroscience, London, UK). All functional brain volumes were realigned to the first volume, spatially normalized to a standard echo-planar imaging template, and finally smoothed using an 8-mm Gaussian kernel.

At the single subject level, we conducted *a t*-test for the contrast pain>no-pain using a general linear model. This was thresholded at $P = 0.05$ (two-tailed, family-wise error corrected: FWE). Then, at the group-level, we conducted region-of-interest (ROI)-based random effects analyses to investigate activity specifically recruited within pain-related empathy regions. A pain localizer was not used during the study; however, we used predefined ROIs informed by previous research, representing AI, IFG and ACC. These regions have been discussed as major affective components of the pain matrix, and commonly recruited during empathy-for-pain.[24] ROI analyses were performed using the PickAtlas toolbox within SPM 8, and parameter estimates were extracted from group-level clusters within the AI, IFG and ACC.[39] AI and IFG clusters were included in a single ROI because they are anatomically adjacent to each other and partly overlapped in the functional ROI implemented in PickAtlas. We also included an ROI representing the TPJ, which is crucially involved in physicians' brain response for empathy-for-pain.[7,22] As TPJ is not considered a part of the pain matrix, we purposely applied a more conservative analysis when investigating neural correlates of TPJ activity. That is, TPJ parameter estimates were extracted from the cluster obtained in the whole brain analysis. Furthermore, because it is still a matter of debate whether TPJ is a precisely identifiable cortical region,[40] we selected clusters that were anatomically overlapped with the TPJ x-y-z Talairach coordinates from a meta-analysis, centered at (±50 −55 25), specifically extending from the superior temporal sulcus to the inferior parietal lobe.[41,42] Following the conventional threshold,[43] clusters smaller than 10 voxels were not considered significant in our analyses. Furthermore, because there is no clear functional laterality regarding empathic processing, parameter estimates of ROI activity in the right and left hemispheres were averaged within each participant. Subsequently, correlation analyses were conducted on the basis of this averaged result. Using Pearson's r correlation analyses implemented in SPSS, parameter estimates of the pain>no-pain contrast were correlated with psychological measures.

After the scanning session, participants were asked to rate each of the video clips on the following: (1) intensity of distress (how much distress they felt from a first-person perspective); and (2) intensity of pain (objective rating of pain from a third-person perspective). Distress and pain were each rated on a 9-point Likert scale, ranging from no-distress/pain to the most extremely imaginable distress/pain. Video clips were shown in the same order as they had been seen during the fMRI scanning. The order of the two ratings was counterbalanced among participants. Subsequently, for each of the video stimuli, the difference between these two ratings (that is, distress minus pain score) was calculated and combined to give a sum score for all stimuli for each participant. This score was also used as a representation of emotional dissonance.

RESULTS

Psychological measures

There were statistically significant relationships between burnout severity (MBI) and other psychological measures (Table 1). Burnout severity (MBI) and dispositional empathy (IRI) showed a positive correlation. In addition, burnout severity showed a positive correlation with emotional dissonance (EWRS) and alexithymia (TAS). Specifically, 'emotional exhaustion' on the MBI showed a positive correlation with 'perspective taking (PT)' on IRI ($r = 0.507$, $P = 0.010$), 'hide negative emotion (HNE)' on the EWRS ($r = 0.430$, $P = 0.032$) and 'difficulty in identifying feelings (Dif)' on the TAS-20 ($r = 0.637$, $P = 0.001$).

fMRI data

Contrasting the strength of hemodynamic activity between pain and no-pain conditions, there were statistically significant differences within our defined ROIs. Table 2 shows the results of one-sample t-tests within the defined ROIs (that is, AI/IFG and TPJ), demonstrating higher activations in the pain condition relative to the no-pain condition. ACC activity was not examined because it did not meet our cluster threshold (only one voxel remained significant).

Table 2. Pain-related brain areas activated in response to painful video stimuli

Pain>no-pain area	*Talairach atlas x-y-z (mm)*	*T*	*Z*	*P (FWE)*	*Cluster k*
Lt AI/IFG	−42, 16, 0	7.80	6.24**	0.000	237
Lt AI/IFG	−42, 30, 16	6.67	5.58**	0.000	78
Lt AI/IFG	−48, 6, 32	6.33	5.37**	0.000	293
Rt AI/IFG	42, 28, 16	5.72	4.97**	0.001	417
Rt AI/IFG	34, 26, −4	5.39	4.74**	0.003	58
Lt TPJ	−56, −32, 32	8.54	6.63**	0.000	763
Rt TPJ	56, −34, 24	8.79	6.75**	0.000	762

Abbreviations: AI, anterior insula; FWE, family-wise error corrected; IFG, inferior frontal gyrus; Lt, left; Rt, right; TPJ, temporoparietal junction. *$P < 0.05$, **$P < 0.01$. The pain effect contrast was created by comparing the signal intensity during pain, compared with no-pain conditions.

Correlations between neural activity and behavioral measures

There were statistically significant correlations between hemodynamic activity associated with the pain>no-pain contrast and psychological scores. Neural activity in AI/IFG and TPJ showed negative correlations with burnout severity. Namely, AI/IFG and TPJ activity negatively correlated with 'emotional exhaustion' on the MBI ($r = -0.590$, $P = 0.002$ and $r = -0.550$, $P = 0.004$, respectively). Figures 1 and 2 show correlations between burnout severity and hemodynamic activity in AI/IFG and TPJ across all participants.

In addition, AI/IFG and TPJ activity showed significantly negative correlations with other psychological measures (that is, empathic disposition, emotional dissonance, alexithymia and the difference between distress and pain ratings; Table 3). Namely, AI/IFG and TPJ activity negatively correlated with 'perspective taking' on the IRI ($r = -0.524$, $P = 0.007$ and $r = -0.431$, $P = 0.031$, respectively); 'hide negative emotion' on the EWRS ($r = -0.528$, $P = 0.007$ and $r = -0.504$, $P = 0.010$, respectively); 'difficulty in identifying feelings' on the TAS-20 ($r = -0.399$, $P = 0.048$ and $r = -0.581$, $P = 0.002$, respectively); and the difference between post-ratings of distress and pain ($r = -0.419$, $P = 0.037$ and $r = -0.464$, $P = 0.020$, respectively). Furthermore, AI/IFG activity showed a negative correlation with 'empathic concern' on the IRI ($r = -0.432$, $P = 0.031$), and TPJ activity showed a negative correlation with 'difficulty in describing feelings' on the TAS-20 ($r = -0.467$, $P = 0.019$).

DISCUSSION

To our knowledge, this is the first study to investigate the neural correlates of empathy in relation to burnout in medical professionals. Burnout severity was associated with 'reduced' empathy-related brain activity. In the initial correlation analysis between

Table 1. Correlation between burnout severity and other psychological measures

	Empathy PT (IRI)	*Empathy EC (IRI)*	*Empathy PD (IRI)*	*Emotional dissonance HNE (EWRS)*	*Alexithymia Dif (TAS-20)*	*Alexithymia Ddf (TAS-20)*	*Alexithymia Eot (TAS-20)*
Burnout (MBI) Emotional exhaustion	0.507**	0.135	0.237	0.430*	0.637**	0.186	−0.141
Burnout (MBI) Depersonalization	0.387	−0.022	−0.104	0.305	0.199	−0.062	0.132

Abbreviations: MBI, Maslach Burnout Inventory; Ddf, difficulty in describing feelings; Dif, difficulty in identifying feelings; EC, empathic concern; Eot, externally oriented thinking (in Toronto Alexithymia Scale: TAS-20); EWRS, Emotion Work Requirements Scale to assess emotional dissonance; HNE, hide negative emotion; IRI, Interpersonal Reactivity Index; PD, personal distress; PT, perspective taking. *$P < 0.05$, **$P < 0.01$.

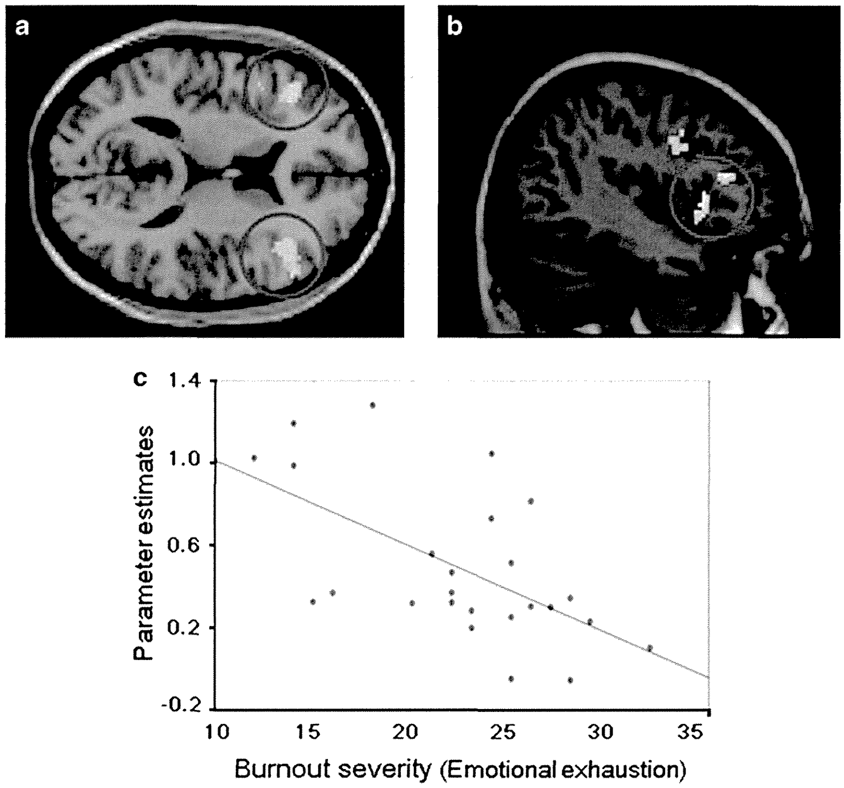

Figure 1. Correlation between burnout severity and hemodynamic activity in AI/IFG across participants. Burnout severity ('emotional exhaustion' on the MBI) was associated with decreased activation of the anterior insula and inferior frontal gyrus cluster (AI/IFG). (**a**) Image showing activation in AI/IFG within pain>no-pain contrast across participants (transverse plane). (**b**) Image showing activation in AI/IFG within pain>no-pain contrast across participants (sagittal plane). (**c**) Plots and regression line depicting the correlation between burnout severity and parameter estimates of the AI/IFG cluster activity for pain>no-pain contrast. MBI, Maslach Burnout Inventory.

self-reported psychological measures, burnout severity showed a positive correlation with empathic dispositional scores, supporting the 'compassion fatigue theory'. However, burnout severity also showed a positive correlation with trait emotional dissonance scores and alexithymia scores, which might represent a link between burnout and emotional dissonance. This positive correlation between burnout severity and emotional dissonance was no longer significant when alexithymia scores were covaried out (that is, changed from $r=0.430$, $P=0.032$ to $r=0.261$, $P=0.219$). This goes along with previous studies suggesting a link between burnout, emotional dissonance and alexithymia.[19,44–46] Meanwhile, the positive correlation between burnout severity and empathy remained significant when alexithymia scores were covaried out (changed from $r=0.507$, $P=0.010$ to $r=0.467$, $P=0.022$). Thus, the initial correlation analysis between the psychological measures supported both theories ('compassion fatigue' and 'emotional dissonance').

The brain imaging results cannot determine whether the 'compassion fatigue hypothesis' is supported or not because the relationship between empathy-related brain activity and empathic capabilities is not well understood. However, at least, the correlation between empathy-related brain activity and psychological measures showed a modest sign of emotional dissonance. Medical professionals with 'reduced' empathy-related brain activity exhibited higher burnout severity scores and greater dispositional empathy scores. This 'reduced' pain empathy-related brain activity also correlated with higher trait scores of emotional dissonance and alexithymia. We thus speculate that reduced emotion recognition (that is, alexithymia) might potentially link with stronger emotional dissonance and greater burnout severity alongside reduced empathy-related brain activity. In this view, greater empathic disposition in those with higher burnout levels may be because they have more difficulty identifying their emotional reactions. Moreover, a negative correlation between empathy-related brain activity and difference scores between post-scan ratings of the pain stimuli may also go along with higher alexithymia and emotional dissonance tendencies. Differences between distress and pain scores can be considered representations of the state of emotional dissonance; that is, participants with subjective distress scores greater than their objective ratings of pain showed weaker brain activity and stronger burnout severity.

Stronger activity in the defined ROIs (AI/IFG and TPJ) was associated with reduced severity of burnout, as measured by the MBI, emotional dissonance trait scores on the EWRS, alexithymia scores on the TAS-20 and empathy disposition scores on the IRI. IFG has been previously implicated in reducing negative arousal, inhibiting distress, facilitating response selection, encouraging optimistic thinking and supporting belief formation.[47,48] Moreover, greater activity in AI/IFG may reduce a sense of dissonance or depersonalization by enhancing ongoing awareness and sense of reality because AI/IFG contains von Economo neurons.[49] Thus, people with reduced AI/IFG activation may demonstrate relatively incomplete suppression of negative arousal and emotional conflict, thereby inducing stronger emotional dissonance, emotional exhaustion and burnout. Moreover, TPJ is involved in distinguishing between awareness of self and others during empathic behavior,[50] metalizing[51] and alexithymia.[52] Our results could imply that participants with reduced TPJ activity make a weaker distinction between one's own emotion and that of another person, thereby evoking stronger feeling of dissonance and/or reduced emotional recognition.

The relationship between burnout and empathy appears to be a more global construct than previously argued. One of the reasons

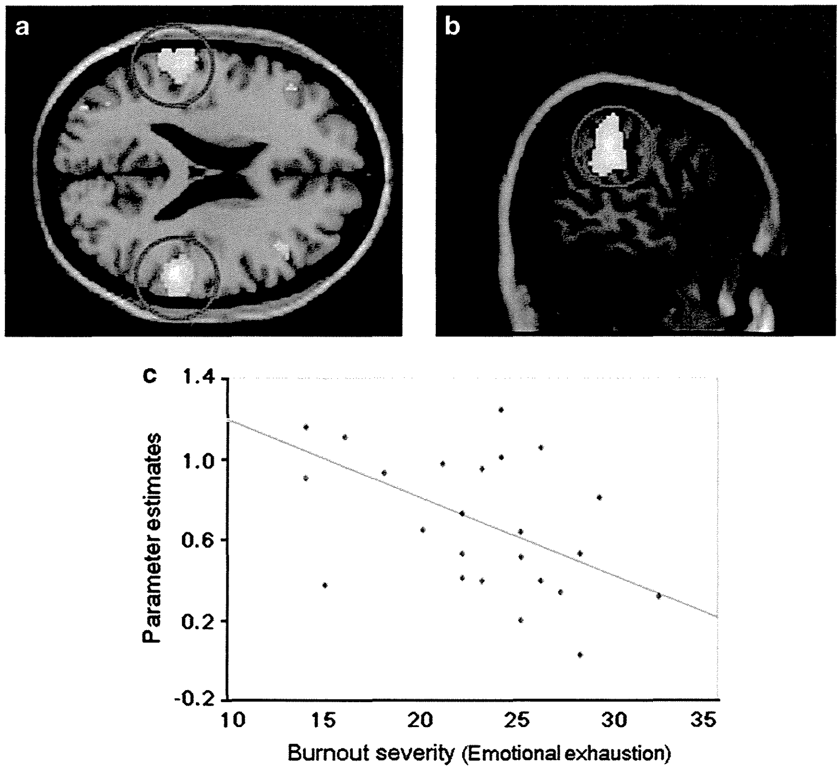

Figure 2. Correlation between burnout severity and hemodynamic activity in TPJ across participants. Burnout severity ('emotional exhaustion' on the MBI) was associated with the decreased activation of the temporoparietal junction (TPJ). (**a**) Image showing activation in TPJ within pain>no-pain contrast across participants (transverse plane). (**b**) Image showing activation in TPJ within pain>no-pain contrast across participants (sagittal plane) (**c**) Plots and regression line depicting the correlation between burnout severity and parameter estimates of the TPJ cluster activity for pain>no-pain contrast. MBI, Maslach Burnout Inventory.

Table 3. Correlation between psychological measures and mean neural activity in AI/IFG and TPJ across participants

	AI/IFG	*TPJ*
Burnout (MBI)		
Emotional exhaustion	− 0.590**	− 0.550**
Depersonalization	− 0.298	− 0.310
Empathy (IRI)		
PT	− 0.524**	− 0.431*
EC	− 0.432*	− 0.301
PD	− 0.167	− 0.378
Emotional dissonance (EWRS) HNE	− 0.528**	− 0.504*
Alexithymia (TAS-20)		
Dif	− 0.399*	− 0.581**
Ddf	− 0.017	− 0.467*
Eot	0.279	− 0.127
Post-scan rating		
Distress minus pain score	− 0.419*	−0.464*

Abbreviations: AI, anterior insula; Ddf, difficulty in describing feelings; Dif, difficulty in identifying feelings; EC, empathic concern; Eot, externally oriented thinking; EWRS, Emotion Work Requirements Scale to assess emotional dissonance; HNE, hide negative emotion; IFG, inferior frontal gyrus; IRI, Interpersonal Reactivity Index; MBI, Maslach Burnout Inventory; PD, personal distress; PT, perspective taking; TAS-20, Toronto Alexithymia Scale; TPJ, temporoparietal junction. *$P < 0.05$, **$P < 0.01$.

for the existence of the contradictory theory in burnout might be because the relationship between dispositional empathy levels and burnout severity is complex. For example, dispositional empathy scores in medical interns both increased (according to the 'personal distress' subscale of IRI) and decreased (according to other subscales of the IRI) when compared from the beginning to the end of their intern year, along with increased burnout severity.[12] Furthermore, the relationship between the strength of empathy-related brain activity and dispositional empathy is complex. Several studies have reported positive as well as negative correlations between empathy disposition measures and different brain regions.[26–30] To further distinguish this relationship, continued research is required.

Another point that warrants caution is generalizing the burnout-empathy theory to other populations. The observed relationship between burnout severity and empathy-related brain activity might only apply to inexperienced nurses because burnout can be triggered by various factors besides altered emotional regulation, such as work-life balance, salary and relationship with co-workers.[53] Moreover, the emergence of burnout symptoms may depend on occupational type. Professionals within human services are expected to manage their emotions according to occupational demands. For example, medical professionals and police officers may boost or inhibit their emotions depending on the situation, which might contribute to triggering burnout (for example, empathizing to raise a strategic smile or expressing detached reception to elicit a matter-of-fact attitude).[14,54] However, professionals from other fields, such as military service members[55] and athletes,[56] may experience burnout as a result of different psychological processes. Therefore, oversimplifying the burnout phenomenon is misleading.

In conclusion, burnout in medical professionals might be explained by reduced empathy-related brain activity. This reduced brain activity was also associated with greater difficulty in recognizing one's own emotional state, as well as with greater self-reported empathic disposition. Our results support findings from previous behavioral studies, arguing that burnout is related to weakened emotional regulation. Further, our study sheds new light on the potential to predict future burnout in medical professionals by the application of brain imaging, which may strongly complement existing psychological examinations. This approach can provide remarkable clues for understanding burnout, namely, which particular aspects of the empathic trait and state and which neuronal processes might be associated with burnout severity.

It is argued that individuals who are most vulnerable to burnout in human service work are those who are highly motivated, dedicated and emotionally involved in their work.[57] Early risk assessment of burnout in these individuals is very important because they are indispensable for providing high-quality human service.[58] Because burnout in human service has become such a critical issue,[1] further clarification of the neural mechanisms of occupational burnout is essential.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

This work was supported by grants-in-aid for scientific research A (24243061), and on Innovative Areas (23120009), from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT); Grants-in-Aid for Young Scientists A (23680045) from the Japan Society for the Promotion of Science (JSPS), and a Health and Labour Science Research Grant for Research on Applying Health Technology (H25-seishin-jitsuyouka-ippan-001) from the Ministry of Health, Labour and Welfare. A part of this study is the result of Development of BMI Technologies for Clinical Application carried out under the Strategic Research Program for Brain Sciences by the MEXT. KFJ was supported by a Japanese Society for the Promotion of Science International Research Fellowship and a National Science Foundation Graduate Research Opportunities Worldwide (GROW) Fellowship—a component of a National Science Foundation Graduate Research Fellowship (2011122786). We would like to thank Dr. Toshihiko Aso, Dr. Nobukatsu Sawamoto and Dr. Hidenao Fukuyama for their support with data collection.

REFERENCES

1 Dyrbye LN, Shanafelt TD. Physician burnout: a potential threat to successful health care reform. *JAMA* 2011; **305**: 2009–2010.
2 Pines AM, Aronson E, Kafry D. *Burnout: From Tedium to Personal Growth*. Free Press: New York, NY, USA, 1980.
3 Decety J, Ickes W (eds). *The Social Neuroscience of Empathy*. The MIT Press: Cambridge, UK, 2011.
4 West CP, Huschka MM, Novotny PJ, Sloan JA, Kolars JC, Habermann TM *et al.* Association of perceived medical errors with resident distress and empathy: a prospective longitudinal study. *JAMA* 2006; **296**: 1071–1078.
5 Krasner MS, Epstein RM, Beckman H, Suchman AL, Chapman B, Mooney CJ *et al.* Association of an educational program in mindful communication with burnout, empathy, and attitudes among primary care physicians. *JAMA* 2009; **302**: 1284–1293.
6 Williams CA. Empathy and burnout in male and female helping professionals. *Res Nurs Health* 1989; **12**: 169–178.
7 Jensen KB, Petrovic P, Kerr CE, Kirsch I, Raicek J, Cheetham A *et al.* Sharing pain and relief: neural correlates of physicians during treatment of patients. *Mol Psychiatry* 2013; **19**: 392–398.
8 Riess H. Empathy in medicine: a neurobiological perspective. *JAMA* 2010; **304**: 1604–1605.
9 Shanafelt TD, Bradley KA, Wipf JE, Back AL. Burnout and self-reported patient care in an internal medicine residency program. *Ann Intern Med* 2002; **136**: 358–367.
10 Batson CD. *Altruism in Humans*. Oxford University Press: Oxford, NY, USA, 2011.
11 Bellini LM, Baime M, Shea JA. Variation of mood and empathy during internship. *JAMA* 2002; **287**: 3143–3146.
12 Rosen IM, Gimotty PA, Shea JA, Bellini LM. Evolution of sleep quantity, sleep deprivation, mood disturbances, empathy, and burnout among interns. *Acad Med* 2006; **81**: 82–85.
13 Figley CR. Compassion fatigue: psychotherapists' chronic lack of self care. *J Clin Psychol* 2002; **58**: 1433–1441.
14 Bakker AB, Heuven E. Emotional dissonance, burnout, and in-role performance among nurses and police officers. *Int J Stress Manag* 2006; **13**: 423–440.
15 Benson J, Magraith K. Compassion fatigue and burnout: the role of Balint groups. *Aust Fam Physician* 2005; **34**: 497–498.
16 Abraham R. The impact of emotional dissonance on organizational commitment and intention to turnover. *J Psychol* 1999; **133**: 441–455.
17 Larson EB, Yao X. Clinical empathy as emotional labor in the patient-physician relationship. *JAMA* 2005; **293**: 1100–1106.
18 Erickson R, Grove W. Why emotions matter: age, agitation, and burnout among registered nurses. *Online J Issues Nurs* 2007; **13**.
19 Gleichgerrcht E, Decety J. Empathy in clinical practice: how individual dispositions, gender, and experience moderate empathic concern, burnout, and emotional distress in physicians. *PLoS One* 2013; **8**: e61526.
20 Blair RJ. Responding to the emotions of others: dissociating forms of empathy through the study of typical and psychiatric populations. *Conscious Cogn* 2005; **14**: 698–718.
21 Herpertz SC, Mueller B, Qunaibi M, Lichterfeld C, Konrad K, Herpertz-Dahlmann B. Response to emotional stimuli in boys with conduct disorder. *Am J Psychiatry* 2005; **162**: 1100–1107.
22 Cheng Y, Lin CP, Liu HL, Hsu YY, Lim KE, Hung D *et al.* Expertise modulates the perception of pain in others. *Curr Biol* 2007; **17**: 1708–1713.
23 Decety J, Yang CY, Cheng Y. Physicians down-regulate their pain empathy response: an event-related brain potential study. *Neuroimage* 2010; **50**: 1676–1682.
24 Lamm C, Decety J, Singer T. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *Neuroimage* 2011; **54**: 2492–2502.
25 Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. *Science* 2004; **303**: 1157–1162.
26 Decety J, Skelly LR, Kiehl KA. Brain response to empathy-eliciting scenarios involving pain in incarcerated individuals with psychopathy. *JAMA Psychiatry* 2013; **70**: 638–645.
27 Moriguchi Y, Decety J, Ohnishi T, Maeda M, Mori T, Nemoto K *et al.* Empathy and judging other's pain: an fMRI study of alexithymia. *Cereb Cortex* 2007; **17**: 2223–2234.
28 Lawrence EJ, Shaw P, Giampietro VP, Surguladze S, Brammer MJ, David AS. The role of 'shared representations' in social perception and empathy: an fMRI study. *Neuroimage* 2006; **29**: 1173–1184.
29 Kramer UM, Mohammadi B, Donamayor N, Samii A, Munte TF. Emotional and cognitive aspects of empathy and their relation to social cognition--an fMRI-study. *Brain Res* 2010; **1311**: 110–120.
30 Derntl B, Finkelmeyer A, Eickhoff S, Kellermann T, Falkenberg DI, Schneider F *et al.* Multidimensional assessment of empathic abilities: neural correlates and gender differences. *Psychoneuroendocrinology* 2010; **35**: 67–82.
31 Saxe R, Wexler A. Making sense of another mind: the role of the right temporo-parietal junction. *Neuropsychologia* 2005; **43**: 1391–1399.
32 Maslach C. *Burnout: The Cost of Caring*. Prentice Hall Trade: Englewood Cliffs, NJ, USA, 1982.
33 Demerouti E, Bakker AB, Nachreiner F, Schaufeli WB. The job demands-resources model of burnout. *J Appl Psychol* 2001; **86**: 499–512.
34 Deighton RM, Gurris N, Traue H. Factors affecting burnout and compassion fatigue in psychotherapists treating torture survivors: is the therapist's attitude to working through trauma relevant? *J Trauma Stress* 2007; **20**: 63–75.
35 Davis MH. Measuring individual differences in empathy: evidence for a multidimensional approach. *J Pers Soc Psychol* 1983; **44**: 113–126.
36 Brotheridge CM, Grandey AA. Emotional labor and burnout: Comparing two perspectives of "people work". *J Vocat Behav* 2002; **60**: 17–39.
37 Hochschild AR. Emotion work, feeling rules and social structure. *Am J Sociol* 1979; **85**: 551–575.
38 Taylor GJ, Bagby RM, Parker JD. The 20-Item Toronto Alexithymia Scale. IV. Reliability and factorial validity in different languages and cultures. *J Psychosom Res* 2003; **55**: 277–283.
39 Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 2003; **19**: 1233–1239.
40 Mars RB, Sallet J, Schuffelgen U, Jbabdi S, Toni I, Rushworth MF. Connectivity-based subdivisions of the human right "temporoparietal junction area": evidence for different areas participating in different cortical networks. *Cereb Cortex* 2012; **22**: 1894–1903.

41 Van Overwalle F. Social cognition and the brain: a meta-analysis. *Hum Brain Mapp* 2009; **30**: 829–858.
42 Van Overwalle F, Baetens K. Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. *Neuroimage* 2009; **48**: 564–584.
43 Lieberman MD, Cunningham WA. Type I and Type II error concerns in fMRI research: re-balancing the scale. *Soc Cogn Affect Neurosci* 2009; **4**: 423–428.
44 Bratis D, Tselebis A, Sikaras C, Moulou A, Giotakis K, Zoumakis E *et al.* Alexithymia and its association with burnout, depression and family support among Greek nursing staff. *Hum Resour Health* 2009; **7**: 72.
45 Zapf D, Seifert C, Schmutte B, Mertini H, Holz M. Emotion work and job stressors and their effects on burnout. *Psychol Health* 2001; **16**: 527–545.
46 Fox JR, Power MJ. Eating disorders and multi-level models of emotion: an integrated model. *Clin Psychol Psychother* 2009; **16**: 240–267.
47 Jarcho JM, Berkman ET, Lieberman MD. The neural basis of rationalization: cognitive dissonance reduction during decision-making. *Soc Cogn Affect Neurosci* 2011; **6**: 460–467.
48 Sharot T, Kanai R, Marston D, Korn CW, Rees G, Dolan RJ. Selectively altering belief formation in the human brain. *Proc Natl Acad Sci USA* 2012; **109**: 17058–17062.
49 Craig AD. How do you feel—now? The anterior insula and human awareness. *Nat Rev Neurosci* 2009; **10**: 59–70.
50 Lamm C, Batson CD, Decety J. The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. *J Cogn Neurosci* 2007; **19**: 42–58.
51 Moriguchi Y, Ohnishi T, Lane RD, Maeda M, Mori T, Nemoto K *et al.* Impaired self-awareness and theory of mind: an fMRI study of mentalizing in alexithymia. *Neuroimage* 2006; **32**: 1472–1482.
52 Feldmanhall O, Dalgleish T, Mobbs D. Alexithymia decreases altruism in real social decisions. *Cortex* 2013; **49**: 899–904.
53 Maslach C, Schaufeli WB, Leiter MP. Job burnout. *Annu Rev Psychol* 2001; **52**: 397–422.
54 Farrow TFD, Woodruff PWR (eds). *Empathy in Mental Illness*. Cambridge University Press: Cambridge, UK, 2007.
55 Ballenger-Browning KK, Schmitz KJ, Rothacker JA, Hammer PS, Webb-Murphy JA, Johnson DC. Predictors of burnout among military mental health providers. *Mil Med* 2011; **176**: 253–260.
56 Curran T, Appleton PR, Hill AP, Hall HK. The mediating role of psychological need satisfaction in relationships between types of passion for sport and athlete burnout. *J Sports Sci* 2013; **31**: 597–606.
57 van Dierendonck DG, Visser B, Burnout A. Prevention through personal growth. *Int J Stress Manag* 2005; **12**: 62–77.
58 Dychtwald KE, Erickson TJ, Morison R. *Workforce Crisis: How to Beat the Coming Shortage of Skills And Talent*. Harvard Business School Press: Boston, 2006.

Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp) temporo-occipital region, either in resting-state or after acoustic and visual stimulation, and a CRS-Score of 11. Thus, we decided to increase Zp dosage up to 30 mg (administered for around 3 weeks), with a further improvement of CRS-R score (i.e. 13) and EEG (presence of theta-beta rhythm over both the temporal areas), and without relevant side-effects. Our case further supports the hypothesis of a positive effect of Zp, although at higher dosage, in improving consciousness in VS. After brain injury or cerebral anoxic damage there is a change either in the levels of glutamate (resulting in neurotoxicity) or GABA neurotransmission, with reduced cell metabolism and blood flow in brain areas adjacent to the damaged area. By binding to modified $GABA_A$ receptors of the 'neurodormant cells', Zp may cause reversal of the abnormal state and associated metabolic inhibition, with a consequent arousal.[2] For the first time, we used a higher dose of Zp (30 mg) to evaluate whether the drug's response could be dose-dependent. Indeed, our patient's improvement was strictly related to the increase in Zp dosage, with a relatively good response at 30 mg. We are not able to explain this interesting finding, although a more effective action of high-dose Zp on the centrothalamic activity (by potentiating the 'mesocircuit'),[3] could be taken into account. Zp may be a valuable treatment in improving consciousness, although further studies should be fostered to confirm its efficacy, the proper dosage, and long-term safety.

REFERENCES

1. Du B, Shan A, Zhang Y, Zhong X, Chen D, Cai K. Zolpidem arouses patients in vegetative state after brain injury: Quantitative evaluation and indications. *Am. J. Med. Sci.* 2013; **347**: 178–182.
2. Ciurleo R, Bramanti P, Calabrò RS. Pharmacotherapy for disorders of consciousness: Are 'awakening' drugs really a possibility? *Drugs* 2013; **73**: 1849–1862.
3. Schiff ND. Recovery of consciousness after brain injury: A mesocircuit hypothesis. *Trend Neurosci.* 2010; **33**: 1–9.

Rocco Salvatore Calabrò, MD, PhD, Irene Aricò, MD PhD, Simona De Salvo, NPTech, Valeria Conti-Nibali, ST and Placido Bramanti, MD
IRCCS Centro Neurolesi 'Bonino-Pulejo', Messina, Italy
Email: salbro77@tiscali.it
Received 17 April 2014; revised 6 June 2014; accepted 21 June 2014.

Sense of meaning in work and risk of burnout among medical professionals

doi:10.1111/pcn.12217

MEDICAL PROFESSIONALS ARE highly vulnerable to burnout, which may lead to medical errors and even suicide. Burnout may be triggered by excessive empathic distress responses,[1] but may be mitigated by an enhanced sense of meaning in one's work,[2] which increases satisfaction and job commitment. However, the effects of sense of meaning on the correlation between empathy and burnout remain unclear.

Thirty-nine nurses (29 women, aged 22–35 years) completed the Maslach Burnout Inventory (subscales: emotional exhaustion, depersonalization),[3] the Interpersonal Reactivity Index (to assess empathy; subscales: personal distress, perspective-taking, and empathic concern),[1] and Sense of Coherence scale (SOC) to assess their sense of meaning in their work.[4] A higher score on the SOC implies a stronger sense of meaning in one's work. First, Pearson's correlations were calculated between the measures to select independent and dependent variables for subsequent multiple-regression analyses (cut-off: $P < 0.05$). Second, multiple-regression analyses were performed to evaluate the predictive effect of SOC and empathy on burnout. Finally, mediation analysis was conducted to test whether SOC mediates the correlation between empathy and burnout.

The depersonalization dimension of burnout correlated with SOC ($P < 0.001$). This dimension also related to the personal distress and perspective-taking dimensions of empathy ($P = 0.047$ and $P = 0.030$, respectively). SOC correlated negatively with personal distress ($P = 0.001$), but not with perspective-taking ($P = 0.391$). Thus, in our subsequent regression analyses, we first treated levels of empathy (personal distress and perspective-taking) as independent variables, and burnout severity (depersonalization) as the dependent variable. Next, SOC was included as an independent variable. Personal distress and perspective-taking predicted the severity of burnout. Notably, including SOC in the analysis increased the predictive power; R^2 increased from 0.23 to 0.37 after adding SOC to the independent variables. Finally, SOC had a significant mediating effect on the correlation between subscales in empathy and burnout (bias-corrected/accelerated, 95% confidence intervals: 0.149–0.691).

We found that a sense of meaning in one's work predicted burnout by a negative correlation, and sense of meaning was a significant mediator; the effect of empathy on burnout became non-significant. Our findings imply that enhanced sense of meaning may prevent burnout triggered by excessive empathic distress because medical professionals with an enhanced sense of meaning might recognize the greater purpose of their work, thus finding critical situations (e.g. alleviating patients' suffering) more fulfilling than distressing. Meanwhile, without a sufficient sense of meaning in one's work, exposure to patients' distress may induce excessive empathic distress, and thereby burnout.

As burnout has become a pervasive problem, programs to prevent it should be introduced.[2] Our findings provide evidence that enhancement of sense of meaning in one's work can have protective effects on burnout, thereby improving quality of care. To further examine the causality between strength of sense of meaning in work and burnout severity, longitudinal studies should be conducted. In this endeavor, an intervention study promoting a sense of meaning in one's work should shed more light on this issue. As well as serious clinical/economic allegations, these findings have important implications for medical administrators, academic chairs and policy-makers.

REFERENCES

1. Bellini LM, Baime M, Shea JA. Variation of mood and empathy during internship. *JAMA* 2002; **287**: 3143–3146.

2. Shanafelt TD. Enhancing meaning in work: A prescription for preventing physician burnout and promoting patient-centered care. *JAMA* 2009; **302**: 1338–1340.
3. Narumoto J, Nakamura K, Kitabayashi Y, Shibata K, Nakamae T, Fukui K. Relationships among burnout, coping style and personality: Study of Japanese professional caregivers for elderly. *Psychiatry Clin. Neurosci.* 2008; **62**: 174–176.
4. Antonovsky A. The structure and properties of the sense of coherence scale. *Soc. Sci. Med.* 1993; **36**: 725–733.

Shisei Tei, PhD,[1] Carl Becker, PhD,[3]
Genichi Sugihara, MD, PhD,[1] Ryosaku Kawada, MD,[1]
Junya Fujino, MD,[1] Takashi Sozu, PhD,[2] Toshiya Murai, MD, PhD[1]
and Hidehiko Takahashi, MD, PhD[1]
[1]*Department of Psychiatry Graduate School of Medicine,*
[2]*Department of Biostatistics School of Public Health and* [3]*Kokoro Research Center, Kyoto University, Kyoto, Japan*
Email: hidehiko@kuhp.kyoto-u.ac.jp
Received 3 March 2014; revised 9 May 2014; accepted 3 July 2014.

Headache and spontaneous glabellar ecchymosis: More than a self-injury behavior?

doi:10.1111/pcn.12220

A 33-YEAR-OLD MAN PRESENTED to our outpatient clinic for evaluation of severe headaches located at the left eye and forehead and multiple episodes of discoloration of the superior glabella. The pain was described as throbbing lasting for 30–45 min about 2–3 times per month with minimal nausea, photophobia, left eye tearing, redness, and ptosis. The erythema-like lesion developed after a severe headache episode and gradually resolved over the next few days. The patient disclosed habitually rubbing the forehead or face during pain episodes, making an 'artificial' post-traumatic skin ecchymosis unlikely.

Evaluation consisted of high-resolution brain magnetic resonance imaging, including orbital scans, angiography and paranasal computed tomography, which were unremarkable. Routine blood tests were normal. The patient's initial physical exam and the neurologic exam were also normal. The patient responded well to a brief course of subcutaneous sumatriptan and oxygen for acute attacks.

The site, severity, duration of attacks, and trigemino-autonomic symptoms as well as continuous low-grade pain between attacks of severe pain and dramatic response to subcutaneous sumatriptan appeared to be typical for trigemino-autonomic cephalgias. To our best knowledge, this is the first case reporting an association of glabellar ecchymosis with cluster-type attacks. The pathogenetic cause of this phenomenon may be related to autonomic vascular dysfunction, including the partial trigeminovascular system activation and secondary neurogenic inflammation mediated by substance P leading to dermal diapedesis of erythrocytes. In accordance with this, previous case studies suggest an activation of the trigeminovascular system as candidate mechanism of this rarely seen phenomenonon.[1–4]

It is widely known that cluster headaches not only have a cyclic pattern, but also can involve self-injury behavior to provide distraction from the severe head pain. In light of recent evidences showing that self-injury behavior and behavioral alterations are seen in both cluster headache and various cyclic psychiatric disorders associated with headache (e.g., mixed states bipolar disorder),[2] this case provides interesting evidence that some special headache types can lead to spontaneous formation of ecchymosis, which can help us to differentiate the neurological and psychiatric causes of self-injury behavior. In conclusion, bruising of the forehead associated with cluster headache is an interesting feature not only in the headache population but also in the psychiatric population with headache and should be further evaluated with functional neuroimaging (i.e. 18-Fluoro-deoxyglucose positron emission tomography, functional magnetic resonance imaging) in order to enlighten the interesting pathophysiological link between psychiatric disease, headache and spontaneous formation of ecchymosis.

REFERENCES

1. Kakisaka Y, Wakusawa K, Haginoya K, Uematsu M, Tsuchiya S. Abdominal migraine associated with ecchymosis of the legs and buttocks: Does the symptom imply an unknown mechanism of migraine? *Tohoku J. Exp. Med.* 2010; **221**: 49–51.
2. Attanasio A, D'Amico D, Frediani F *et al.* Trigeminal autonomic cephalgia with periorbital ecchymosis, ocular hemorrhage, hypertension and behavioral alterations. *Pain* 2000; **88**: 109–112.
3. Comabella M, Titus F, Huguet P. Recurrent paroxysmal headache associated with facial ecchymosis. *Cephalalgia* 1996; **16**: 341–343.
4. DeBroff BM, Spierings EL. Migraine associated with periorbital ecchymosis. *Headache* 1990; **30**: 260–263.

[Correction added on 12 November 2014, after first online publication: The journal title cited in reference no. 1 was amended.]

Burak Yulug, MD,[1] Lütfü Hanoglu, MD[1] and
Wolf Rüdiger Schabitz, MD[2]
[1]*Department of Neurology, University of Istanbul-Medipol, Istanbul, Turkey, and* [2]*Department of Neurology, Bethel-EvKB, Bielefeld, Germany*
Email: burakyulug@gmail.com
Received 11 June 2014; accepted 7 July 2014.

Successful treatment of excessive supragastric belching by combination of pregabalin and baclofen

doi:10.1111/pcn.12223

BELCHING IS FREQUENTLY seen in functional dyspepsia and gastroesophageal reflux disease. Only a minority of patients suffer from so-called 'excessive supragastric belching'

frontiers in
PSYCHOLOGY

ORIGINAL RESEARCH ARTICLE
published: 05 February 2015
doi: 10.3389/fpsyg.2014.01550

Are ambiguity aversion and ambiguity intolerance identical? A neuroeconomics investigation

Yusuke Tanaka[1†], Junya Fujino[1†], Takashi Ideno[2], Shigetaka Okubo[2,3], Kazuhisa Takemura[2], Jun Miyata[1], Ryosaku Kawada[1], Shinsuke Fujimoto[1], Manabu Kubota[1], Akihiko Sasamoto[1], Kimito Hirose[1], Hideaki Takeuchi[1], Hidenao Fukuyama[4], Toshiya Murai[1] and Hidehiko Takahashi[1]*

[1] Department of Psychiatry, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[2] Department of Psychology, Waseda University, Tokyo, Japan
[3] Research Center for Thinking and Behavioral Judgement, Keio University, Tokyo, Japan
[4] Human Brain Research Center, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Edited by:
Mitsuhiro Okada, Keio University, Japan

Reviewed by:
Satoshi Umeda, Keio University, Japan
Makiko Yamada, National Institute of Radiological Science, Japan

***Correspondence:**
Hidehiko Takahashi, Department of Psychiatry, Graduate School of Medicine, Kyoto University, Shogoin-Kawaharacho 54, Kyoto 606-8507, Japan
e-mail: hidehiko@kuhp.kyoto-u.ac.jp

† These authors have contributed equally to this work.

In recent years, there has been growing interest in understanding a person's reaction to ambiguous situations, and two similar constructs related to ambiguity, "ambiguity aversion" and "ambiguity intolerance," are defined in different disciplines. In the field of economic decision-making research, "ambiguity aversion" represents a preference for known risks relative to unknown risks. On the other hand, in clinical psychology, "ambiguity intolerance" describes the tendency to perceive ambiguous situations as undesirable. However, it remains unclear whether these two notions derived from different disciplines are identical or not. To clarify this issue, we combined an economic task, psychological questionnaires, and voxel-based morphometry (VBM) of structural brain magnetic resonance imaging (MRI) in a sample of healthy volunteers. The individual ambiguity aversion tendency parameter, as measured by our economic task, was negatively correlated with agreeableness scores on the self-reported version of the Revised NEO Personality Inventory. However, it was not correlated with scores of discomfort with ambiguity, one of the subscales of the Need for Closure Scale. Furthermore, the ambiguity aversion tendency parameter was negatively correlated with gray matter (GM) volume of areas in the lateral prefrontal cortex and parietal cortex, whereas ambiguity intolerance was not correlated with GM volume in any region. Our results suggest that ambiguity aversion, described in decision theory, may not necessarily be identical to ambiguity intolerance, referred to in clinical psychology. Cautious applications of decision theory to clinical neuropsychiatry are recommended.

Keywords: ambiguity aversion, ambiguity intolerance, agreeableness, need for closure, prefrontal cortex, voxel-based morphometry

INTRODUCTION

In recent years, there has been growing interest in understanding a person's reaction to ambiguous situations and two similar concepts related to ambiguity, "ambiguity aversion" and "ambiguity intolerance." These are described in different disciplines, economics and psychology, respectively. However, it remains unclear whether these two notions derived from different disciplines are identical or not.

In the field of economic decision-making research, ambiguity aversion represents a preference for known risks relative to unknown risks (Ellsberg, 1961; Camerer and Weber, 1992). In economics, "ambiguity" refers to situations in which outcome probabilities are unknown. On the other hand, situations in which people know the precise probabilities of each outcome are referred to as "risk" (Ellsberg, 1961; Camerer and Weber, 1992). To illustrate an example of ambiguity aversion, suppose there are two bowls filled with a mix of 24 blue and red chips each. One bowl has 12 blue and 12 red chips (risky bowl). The composition of the other bowl is unknown to the participants (ambiguous bowl). Participants are asked to select one bowl and told that if a chip with the color blue is drawn, they qualify for a predefined payoff. Most participants would choose the risky bowl, even if its payoff is lower than that of the ambiguous one. Theoretically, the winning probability of both options is the same. For the risky bowl, the probability of drawing the color blue is 0.5. For the ambiguous bowl, the probability of drawing the color blue is unknown, but the winning probability is also 0.5. Nevertheless, previous studies have shown that most individuals shy away from ambiguous options (Ellsberg, 1961; Camerer and Weber, 1992; Levy et al., 2010). Furthermore, previous studies also showed that some individuals have higher ambiguity aversion than others. For example, less optimistic people were reported to have higher ambiguity aversion compared with highly optimistic people (Pulford, 2009).

On the other hand, ambiguity intolerance is a term from the field of psychology. This construct describes the tendency to perceive ambiguous situations as undesirable (Frenkel-Brunswik, 1949), and this is seen in various psychiatric disorders in clinical