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Alterations in cortical activity of male methamphetamine abusers performing an empathy task: fMRI study†

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Objectives We investigate possible differences in neural correlates of empathy processing between abstinent methamphetamine (MA) abusers and healthy subjects using functional magnetic resonance imaging (fMRI).
Methods Nineteen abstinent MA abusers (mean age of 36.06 years, range 31–52 years) and 19 healthy subjects (mean age of 37.05 years, range 33–42 years) participated in this study. A visual fMRI activation paradigm was used, comprising a series of cartoons, each depicting a short story. There were two categories of stories: empathy (Empathy) and Physical causality (Physical). fMRI images were acquired using a 3.0 T whole-body scanner. All fMRI data were analyzed using MATLAB v. 7.2 and SPM5.
Results Both MA subjects and controls exhibited activation in the dorsomedial prefrontal cortex. Despite this similarity in activation patterns, we found that the two groups differed in the activation of several cortical regions associated with the processing of empathy information. Hypoactivations of the orbitofrontal cortex, temporal poles, and hippocampus in MA abusers relative to healthy subjects suggests that the ability of empathic response could be compromised in abstinent MA abusers ($p < 0.05$, corrected for a small volume).
Conclusions Functional impairments in the empathic neural network caused by MA may contribute to the misunderstanding of others and to the erosion of social interactions in MA abusers. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — methamphetamine; empathy; fMRI

INTRODUCTION

There has been a worldwide increase in the use and abuse of methamphetamine (MA) (Shaw, 1999). In 2004, the US National Survey on Drug Use and Health found that 1.4 million people (0.6% of the population) had used MA in the past 12 months, and 600 000 (0.2%) had used it in the previous month (Office of Applied Studies, 2005). The admissions to substance abuse treatment programs with MA as the primary substance increased 182% from 1994 to 2004 (Office of Applied Studies, 2006). Because MA, a highly addictive cationic lipophilic molecule, causes euphoria, increased energy, and decreased social inhibition by stimulating the mesolimbic reward pathway, the onset of MA use has been linked to the desire to have social interaction (Homer *et al.*, 2008). During early abstinence, however, MA abusers often show mood disturbances such as depression and anxiety (London *et al.*, 2004; Newton *et al.*, 2004).

Furthermore, chronic neurotoxic effects lead to hostility, unmotivated interpersonal violence, and aggressive behavior for MA abusers (Cohen *et al.*, 2003). These behaviors are related to high rates of assault, weapons charges (Zweben *et al.*, 2004), trauma center visits for physical attacks and intentional injuries (Tominaga *et al.*, 2004; Zweben *et al.*, 2004), and death from homicidal violence in MA abusers (Logan *et al.*, 1998). Therefore, although the original intention of MA use is to facilitate and enhance social interaction, MA abuse commonly erodes social connections. Impairments in social interactions in MA abusers can contribute to stress, which may increase negative mood states and the risk of relapse (Shaham

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et al., 2000). Therefore, investigation of the socio-emotional behavior and of the neural systems underlying them could help elucidate potential mechanism of relapse and sustainment for MA abuse.

When we interact with others socially, we constantly make attributions and inferences regarding their emotional states. Thus, empathy plays a pivotal role in interpersonal relations because these abilities enable us to understand the thoughts of others and to predict their future actions. Recently, researchers in social neuroscience have investigated the neural mechanisms underlying empathy (Blakemore *et al.*, 2004; Lawrence *et al.*, 2006; Akitsuki and Decety, 2009). There exists sound evidence that the prefrontal cortex is an important neural substrate of empathy. Berthoz *et al.* (2002) found activations in the orbitofrontal cortex and medial prefrontal cortex when participants responded to aversive emotional expressions, especially anger. Using affective pictures evoking empathy, Moll *et al.* (2002) reported that the orbitofrontal, medial frontal, and superior temporal gyri are involved in the processing of moral emotions. Sabbagh (2004) demonstrated that orbitofrontal activity is related to the decoding of emotional states. Furthermore, two recent neuroimaging studies were performed to elucidate the distinct regions for empathy relative to theory of mind. Using verbal stories, Hynes *et al.* (2006) demonstrated that the medial orbitofrontal lobe was preferentially involved in emotional rather than cognitive perspective-taking. Vollm *et al.* (2006) reported enhanced activations in the paracingulate, anterior and posterior cingulate, and amygdala when participants made inferences regarding the protagonist's feelings versus thoughts in nonverbal cartoons.

There exists a growing body of evidence to suggest that the prefrontal cortex is dysfunctional in MA abusers. Using magnetic resonance spectroscopy, several previous studies demonstrated reduced concentration of *N*-acetylaspartate in the frontal area (Ernst *et al.*, 2000a) and lower *N*-acetyl-aspartate/creatine in the anterior cingulum (Nordahl *et al.*, 2002) in MA abusers. Lower levels of dopamine D2 receptor availability in the orbitofrontal cortex (Volkow *et al.*, 2001a) and decreased dopamine transporter density in the orbitofrontal cortex and the dorsolateral prefrontal cortex (Sekine *et al.*, 2003) have been previously reported in MA abusers. Paulus *et al.* (2003) used functional magnetic resonance imaging (fMRI) to demonstrate low activation of both the orbitofrontal and dorsolateral prefrontal cortex during a decision-making task in MA abusers. In addition, MA abusers showed less activation in anterior cingulate cortex and dorsolateral prefrontal cortex during delay discounting task (Hoffman *et al.*, 2008) and reduced activation in the right prefrontal cortex during variant stroop task (Salo *et al.*, 2009). Finally, MA abusers had low regional cerebral glucose metabolism in the right superior frontal white matter (Kim *et al.*, 2005), low density in the right middle frontal gray matter (Kim *et al.*, 2006).

Taken together, these abnormalities of the prefrontal cortex could represent the neural basis for impairments in social-cognitive functioning, which lead to socially problematic behaviors such as mood disturbances, aggressiveness, and social isolation. To the best of our knowledge, however, few studies have directly examined socioemotional processing, especially empathy, in MA abusers. Therefore, the aim of the present study is to investigate the differences in neural correlates of empathy between MA abusers and healthy subjects, using fMRI. We employed a visual cartoon task in which participants were asked to make inferences regarding the protagonist's emotional states (Vollm *et al.*, 2006). We hypothesized that MA abusers would show prefrontal abnormality not observed in non-drug users, reflecting neurotoxicity caused by long-term MA use. Specifically, we expected the prefrontal systems to be less active in MA abusers than in healthy individuals.

MATERIALS AND METHODS

Subjects

Nineteen abstinent MA abusers and 19 healthy subjects participated in this study. All MA abusers were recruited from the Drug Abuse Center, Bugok National Hospital, Korea, based on consensus diagnoses obtained by two licensed psychiatrists based on DSM-IV criteria. Healthy subjects were recruited as volunteers from Kyungpook National University Hospital in a neighboring town. To control for gender bias, all subjects were male. Ages ranged from 31 to 52 years (mean, 36.06 years) in MA abusers and from 33 to 42 years (mean, 37.05 years) in control subjects. Exclusion criteria included past neurological illness or traumatic brain injury, mental retardation, other substance use other than caffeine or nicotine, and lifetime axis I psychiatric diagnoses other than MA dependence.MA abusers who had above 9 points on the Beck Depression Inventory (BDI; Beck *et al.*, 1961) were excluded so as to minimize confounding effects of abstinence-related depression, anxiety, and fatigue. In the MA abusers group, the total cumulative dose of MA was 441.3 ± 429.8 g, the duration of MA use was 13.6 ± 7.3 years, and the mean period of abstinence was 20.5 ± 8.3 days. Abstinance in MA abusers strated from admission day. Thus, abstinance period is as same

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as duration of admission. Withdrawal symptoms from MA usually subsided within one week from admission day. The Institutional Review Board (IRB) of Bugok National Hospital approved all experimental procedures for the study. After receiving a detailed explanation of the research and experimental procedures, all subjects from both groups gave written informed consent approved by the IRB.

Activation paradigm

The fMRI task was derived from Vollm *et al.* (2006). A visual activation paradigm was used, comprising a series of cartoons, each depicting a short story. There were two categories of stories: empathy (Empathy) and Physical causality (Physical). Stimuli were projected from a computer onto a screen. The participants viewed the rear-projected stimuli via a mirror attached to the top of the head coil. Introductory questions given at the beginning of each block of cartoons were designed to engage the corresponding mental construct in the participant. In the empathy condition, the question was: ''what will make the main character feel better?''. Scenarios involved interaction between story characters; the correct answer required the volunteer to empathize with the protagonist. The physical conditions that relied on comprehension of the physical causalities alone were introduced with the prompt: ''what is most likely to happen next?''. To match the control and active conditions for the number of characters and complexity, two characters were depicted for both empathy stimuli and physical causality.

Each condition was presented twice, meaning that the task consisted of four blocks in total. Each block consisted of five different comic strips depicting a short story (Figure 1). Upon the second presentation of a condition, a new set of cartoons was used; hence, each cartoon was only viewed once. Each comic strip was shown for 4 s on the upper half of the screen. Two pictures showing possible outcomes of the scenario were then superimposed on the bottom half of the screen for a further 4 s. Participants were required to choose between these two story endings using a two-button box to indicate their choice. Only one of the outcomes represented a plausible story ending (correct ending). At the top of each block, a short selection question was shown with the strip. The total block length was therefore 212 s; hence, the task lasted 3 min and 32 s in total.

Functional imaging procedure, data acquisition and analysis

fMRI images were acquired using a 3.0 T whole-body scanner equipped with an 8-channel head array coil (Signa Excite HD, General Electric, Milwaukee, WI, USA). The fMRI parameters were as follows: echo planar imaging, repetition time (TR) = 4 s, echo time (TE) = 40 ms, field of view (FOV) = 240 mm, matrix = 64 × 64, 31 slices with 4 mm slice thickness and no slice gap. Anatomic T1-weighted images were obtained using the following parameters: 3D FSPGR, TR = 7.8 ms, TE = 3.0 ms, FOV = 240 mm, matrix = 256 × 256, 120 slices with 1.3 mm slice thickness.

All fMRI data were analyzed using MATLAB v. 7.2 (The Mathworks Inc., Natick, MA, USA) and SPM5 (SPM; Wellcome Department of Imaging Neuroscience, London, UK; online at http://www.fil.ion.ucl.ac.uk). All functional images were realigned to the first image of the each series for movement correction and normalized to the Montreal Neurological Institue (MNI) brain (Collins *et al.*, 1994). The normalized images were smoothed using an 8 mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. After preprocessing of raw fMRI data, statistical analysis was performed using a general linear model with boxcar design to model blood-oxygenation-level-dependent signal changes to the Empathy condition relative to the Physical condition. Functional data from each individual were entered into a random effects model using two regressors convolved with a hemodynamic response function provided by SPM5: one for Empathy blocks and one for Physical blocks. In group analysis, contrast images from the analysis of individual subjects were analyzed byo

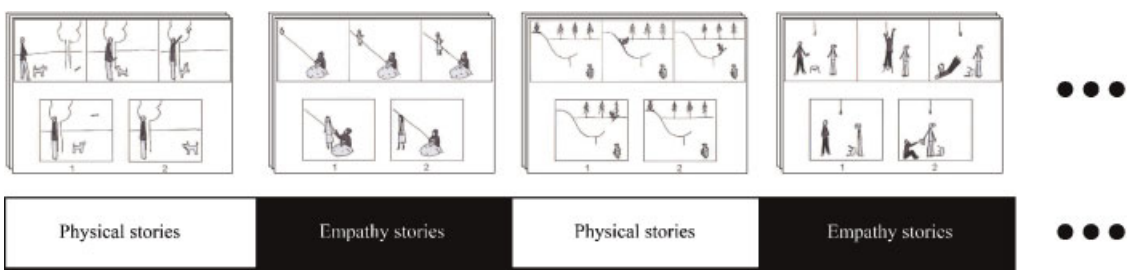

Figure 1. Block fMRI paradigm of a story stimuli. During ''Empathy'' task block, cartoons of empathy story were presented. For each empathy story, Cartoon 2 represents the ''correct'' answer. During ''Physical'' task block, cartoons of physical causality story were presented. For each physical story, Cartoon 2 represents the ''correct'' answer

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one-sample *t*-tests, thereby generating a random-effects model, allowing inference to the general population. The SPM{t}s were thresholded at $p < 0.005$ for 64 contiguous voxels, uncorrected for multiple comparisons across the whole brain. Significant regional responses are reported at $p < 0.05$, corrected for a small spherical search volume (SVC). We used a 10 mm –radius volume for cortical regions. The volumes were centered on previously published maxima, or maxima from orthogonal contrasts within our study. Finally, activation maps were created and displayed by projection onto the anatomically standardized mean T1 image of all subjects to identify the anatomical correlates of the activity.

Statistical analysis

An independent t-test was used to examine group differences using SPSS statistical package. Statistical significance was defined at $p < 0.05$. We used Pearson correlation analyses to determine the correlations between the number of activation voxel and performance of empathy task.

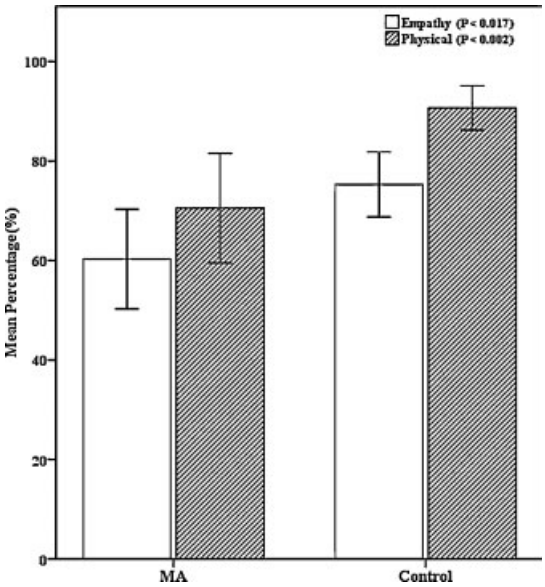

Figure 2. The mean percentage of correct answers of ''Empathy'' and ''Physical'' tasks in MA subjects and healthy control subjects

RESULTS

Demographics and empathy task performance

There were no significant differences in age ($p = 0.48$) between MA abusers and control subjects, although there was a significant difference in educational level ($p < 0.01$). It was impracticable to recruit healthy subjects with similar educational levels to those of the MA abusers. Task performance was recorded during the Empathy and Physical tasks. As shown in Table 1, most tasks were answered within the allowed response times. The percentages of 'correct' answers as a proportion of the total given answers are shown in Figure 2. Independent t-tests revealed significant difference between MA and healthy subjects for the Empathy ($p = 0.017$) and Physical ($p = 0.002$) tasks.

Functional MRI activation study

For the healthy subjects, neural responses in the Physical blocks were subtracted from those in the Empathy blocks to reveal activation areas associated with empathy processing. Significant activations were shown in the bilateral inferior part of the orbitofrontal cortex, bilateral temporal pole, right hippocampus, dorsomedial prefrontal cortex, and left cerebellum (Figure 3a, b). In MA subjects, the same comparison revealed activation regions as the inferior frontal gyrus, middle occipital gyrus, dorsomedial prefrontal cortex, and middle temporal gyrus bilaterally (Figure 3c, d). Table 2 lists the detailed areas of activation for MA subjects and healthy subjects, and the Z-score.

Comparing brain activation patterns between MA subjects and healthy subjects, the orbitofrontal cortex in the inferior frontal gyrus showed greater activation in the healthy subjects than in MA subjects; however, the dorsolateral prefrontal cortex showed greater activation in MA subjects than in healthy subjects. The temporal poles and hippocampus also showed greater activation in healthy subjects than in MA subjects during the Empathy task. Pearson correlation analysis demonstrated that in MA subjects the activation voxels of the dorsolateral prefrontal cortex did not correlate with task performance during the empathy task ($p = 0.103$).

Table 1. Task performance between MA and control subjects in the behavioral empathy and physical task

Group	Task	Mean of answers given (maximum 10)	Correct answers(%)
MA	Empathy	9.00 (SD 1.00)	60.26 (SD 21.80)
	Physical	8.42 (SD 1.30)	70.53 (SD 24.04)
Control	Empathy	8.89 (SD 2.37)	75.26 (SD 14.21)
	Physical	8.42 (SD 2.27)	90.68 (SD 9.68)

DISCUSSION

To the best of our knowledge, this study is the first to investigate the neural correlates related to empathy in MA abusers. Analysis of task-related brain activation

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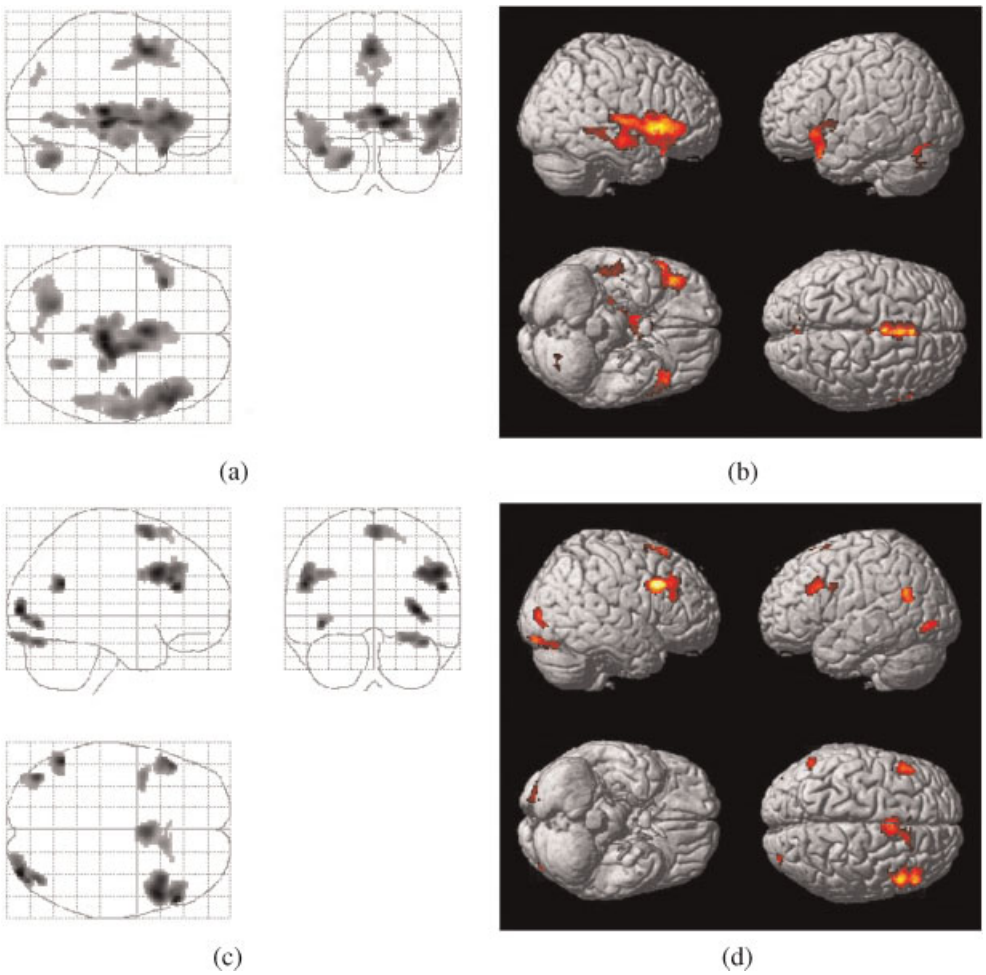

Figure 3. SPM{t} results from the within group analysis by means of one sample *t*-test for control group (a) and MA group (c). Areas of activation represent ("Empathy" — "Physical"). For illustration purpose, activation is displayed on 3D SPM template brain for control group (b) and MA group (d)

showed that both MA and control subjects exhibited common activation in the dorsomedial prefrontal cortex, which is linked to mental representations regarding the internal states of others (Frith and Frith, 2001; Ochsner *et al.*, 2004) and the triadic relationship between two minds and an object (Saxe, 2006). Our finding is therefore consistent with a previous study that reported comparable dorsomedial prefrontal cortex activations in two groups while performing a facial affect matching task (Payer *et al.*, 2008).

Although the medial prefrontal cortex is mainly engaged in social judgments, there exist functional differences between the dorsal and ventral parts of the medial prefrontal cortex. Whereas the ventromedial prefrontal cortex is involved in inferences for mental representations regarding familiar others or the self, mental representations regarding the internal states of unfamiliar others selectively engage the dorsomedial prefrontal cortex (Van Overwalle, 2009). In the present study, therefore, the common activation of the dorsomedial prefrontal cortex in both the controls and MA abusers probably occurred because all subjects were required to empathize with an unfamiliar protagonist in the cartoon.

We also found that the groups differed in the activation of several cortical regions associated with the processing of socio-emotional information. First, the healthy controls showed greater activation in the orbitofrontal cortex than did MA subjects. The occurrence of greater task-related activity in the orbitofrontal cortex in healthy subjects than in MA abusers is commonly implicated in social cognition. Activation of the orbitofrontal cortex is consistently found, particularly in empathy studies (Farrow *et al.*, 2001; Moll *et al.*, 2002; Sabbagh, 2004; Hynes *et al.*, 2006). According to Rolls' model of orbitofrontal

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Table 2. Brain regions showing significant activations associated with empathy task

Region	Side	MNI coordinates			z score	Small volume correction (FDR corrected)	
		x	y	z		*p*-value	Voxels
Control							
Orbitofrontal cortex	L	−44	22	−10	3.75	0.009	173
	R	44	28	−10	3.68	0.003	243
Temporal pole	L	−50	16	−20	3.47	0.008	81
	R	50	12	−14	3.43	0.011	136
Dorsomedial prefrontal cortex	R	2	8	52	3.87	0.003	412
Hippocampus	R	24	−26	−14	3.42	0.02	117
Cerebellum	L	−22	−64	−30	3.50	0.006	306
Methamphetamine							
Dorsolateral frontal cortex	L	−50	26	28	3.54	0.008	123
	R	50	16	32	3.73	0.002	288
Middle occipital cortex	L	−40	−76	−6	2.83	0.016	118
	R	38	−86	4	3.41	0.009	99
Dorsomedial prefrontal cortex	L	−2	8	64	3.44	0.011	101
	R	2	8	64	3.44	0.008	177
Middle temporal cortex	L	−52	−58	24	3.29	0.014	151
	R	52	−70	14	2.80	0.041	42

functioning (Rolls, 2004), this cortex facilitates social cognition by mapping the changing reward properties of a social interaction as well as instigating the inhibition of no-longer-useful behavior. It has been demonstrated that MA abusers have various kinds of orbitofrontal abnormalities, including lower levels of dopamine D2 receptor availability (Volkow *et al.*, 2001a), decreased dopamine transporter density (Sekine *et al.*, 2003), reduced serotonin transporter density (Sekine *et al.*, 2006), and less activation during a two-choice prediction task (Paulus *et al.*, 2003). Therefore, the ability of subjects to have an empathic response to the cartoons presented in the empathy condition could be compromised in MA abusers because of these neurochemical and functional deficits of the orbitofrontal cortex.

Second, the temporal poles and hippocampus were also more active in healthy subjects than in MA abusers during the empathy condition. Functional imaging studies of humans have reported activation of the temporal poles and hippocampus in relation to the broader context of episodic memory retrieval (Gallagher and Frith, 2003). It is possible that we draw on past experience to imagine ourselves in the situation of another person and thereby simulate their experience (Harris, 1992). It is also possible that episodic memory co-activates during empathizing, as episodic memory retrieval is potentially useful for empathizing. Taken together, the abilities to recall episodic memory and to show empathic response to others during social interaction are important social skills. Previous neurobehavioral studies have demonstrated that abstinent MA abusers were substantially impaired relative to controls on measures of cognitive tests including episodic memory (Simon *et al.*, 2004; Hoffman *et al.*, 2006). An experimental animal study also demonstrated that MA-treated rats showed marked impairments in long-term memory (Schroder *et al.*, 2003). Thus, the present finding of less activation in the temporal poles and hippocampal regions of MA abusers compared with healthy controls, suggesting a possible functional impairment of episodic memory in MA abusers, is in agreement with the results of previous studies. This impairment may in turn lead MA abusers to empathize inappropriately, thereby resulting in the impairment of interpersonal communication.

Another interesting finding of the current study is that the dorsolateral prefrontal cortex showed greater task-related activity in MA abusers than in healthy subjects, in disagreement with a previous finding that MA abusers have various kinds of dorsolateral abnormalities, including lower density in the gray matter (Kim *et al.*, 2006). A previous study reported that dorsolateral dysfunction resulted in MA-dependent subjects showing less dorsolateral prefrontal cortex activation during the two-choice prediction task compared with the two-choice response task (Paulus *et al.*, 2003). These results suggest that MA-dependent subjects exhibit cognitive deficits during decision-making that are consistent with both orbitofrontal and dorsolateral prefrontal dysfunction. In the present study, however, our finding of greater activation of the dorsolateral prefrontal cortex in MA abusers appears to demonstrate that the dorsolateral prefrontal cortex plays a different role during an empathy task than during the two-choice prediction task. In other words, a possible explanation for the greater activation of the dorsolateral prefrontal cortex in MA abusers may be related to inefficiency in processing empathy.

The functioning of the orbitofrontal cortex, temporal pole, and hippocampus may not be as efficient in MA abusers as in control subjects. Therefore, the dorsolateral prefrontal cortex, which is not implicated in processing empathy in healthy subjects, appears to be recruited in MA subjects to compensate for the deficit of episodic memory due to dysfunction of the temporal poles and hippocampus. Previous non-human primate studies demonstrated that the dorsolateral prefrontal cortex has projections to the hippocampus, temporal lobe, and orbitofrontal cortex (Goldman-Rakic *et al.*, 1984; Morecraft *et al.*, 2004). The results of neuroimaging studies show that the dorsolateral prefrontal areas are involved during tasks requiring

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organization of items in working memory and episodic long-term memory (Petrides, 2000; Ranganath *et al.*, 2003). In the MA subjects in the present study, however, activity in the dorsolateral prefrontal cortex measured in terms of activation voxels showed no correlation with the number of ''correct'' answers, suggesting that this dorsolateral prefrontal activity is insufficient to compensate for the neural dysfunction in the orbitofrontal cortex, temporal poles, and hippocampus. Taken together, we speculate that overactivation of the dorsolateral prefrontal cortex may occur in MA abusers through the neural networks to compensate for inefficiency in the orbitofrontal cortex and other brain areas, in an attempt to meet the demands of the empathy task. Even so, recruitment of the dorsolateral prefrontal cortex in MA subjects provides insufficient compensation for the deficit of empathic ability that results from dysfunction in the brain regions involved in the empathy neural network.

Some limitations of the current study should be considered. First, although this study revealed functional impairments in brain response during the empathy task in MA abusers, the cause of these deficits is unknown yet. A future study will be needed to clarify whether these functional impairments in MA abusers reflect a predisposition or consequence of neurotoxic effect of MA. Second, there was a significant difference in educational levels between the MA abusers and the control subjects. Thus, educational levels may have confounded our findings of altered cortical activity in MA abusers compared to the control subjects. However, there were no significant correlations between educational levels and the activity in orbitofrontal, temporal, and hippocampus within MA abusers. Therefore, it is unlikely that educational level could be a potential confounder in this study. Finally, the task response time was not measured during task. Therefore, it was difficult to reveal the potential difference in task response between MA abusers and controls although visual inspection by observer showed no difference in task response.

In summary, we used fMRI to compare differences in the neural networks related to empathy between MA abusers and healthy subjects. Except for common activation of the dorsomedial prefrontal cortex in both groups, the healthy participants showed greater task-related activity than the MA abusers for a set of cortical regions consisting of the orbitofrontal cortex, temporal pole, and hippocampus. The dorsolateral prefrontal cortex showed greater task-related activity in MA abusers than in healthy subjects to compensate for inefficiency of the orbitofrontal cortex and other brain areas, although the recruitment of the dorsolateral prefrontal cortex is insufficient to compensate for the deficit of empathic ability. Thus, functional impairments in the empathy neural network may contribute to the misunderstanding of others and unempathic response in social interactions in MA abusers. These alterations of socio-emotional behaviors could lead to increased negative mood and stress, which are related to relapse and sustainment of MA abuse.

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