spatial coordinates of the Anatomical Automatic Labeling (AAL) atlas using the MarsBar SPM Toolbox. Peak voxel parameter estimates from interactions were examined using post-hoc Bonferroni multiple comparisons performed in SPSS version 16.0.

We conducted a psychophysiological interaction (PPI) analysis (Friston et al., 1997) to examine interactions between brain regions in relation to the experimental paradigm. This approach can capture the way in which activity in one brain region modulates activity in another region by specifically assessing responses to the active task relative to an informative baseline. To undertake PPI analysis a design matrix is established, which typically contains three columns of variables as follows: (1) a psychological variable that reflects the experimental paradigm, (2) a time series variable representing the time course of the source region; here, the source region was a 6-mm sphere with a center defined by the peak coordinate of the foregoing analysis, and (3) a variable that represents the interaction between (1) and (2). The regression coefficient for the interaction term provides a measure of PPI. In the present context, a significant effect for PPI means that the correlation (or covariance) between the source and the sink region during an emotional pain condition is significantly different from that during another emotional condition. In this regard, PPI analysis assesses differences in functional connectivity between the regions of interest. To perform PPI analyses, the first eigenvariate time series of the 6-mm sphere activated according to the previous analyses was extracted. The effect of the interaction term was then studied using the contrast [1 0 0], where the first column represents the interaction term. The extracted individual images were then taken to the second level to perform a random effects analysis, using a one-sample t-test.

The statistical threshold for all the imaging analyses described above was set at an uncorrected p value of 0.001 and at a minimum cluster size of 20 voxels, based on previous pain related fMRI studies (Ochsner et al., 2006; Yoshino et al., 2010).

Finally, we examined the correlations between the brain regions involved in modulating low pain levels within the context of sadness and the sadness-specific low-pain rating scores of patients. We also analyzed the correlations between the brain regions involved in modulating low pain levels within the context of sadness and BDI or STAI scores for all participants, and examined whether sadness-induced pain perception changes were correlated with individual differences in depressed mood or anxiety state. A correlation analysis was performed for the brain areas for which there was a significant interaction effect in the 3-way ANOVAs (the anterior/posterior insula and the hippocampus) as regions of interest (ROIs).

3. Results

3.1. Participant characteristics

Detailed demographic and clinical characteristics of the participants are presented in Tables 1 and 2. The clinical pain in the patient group was located in the head ($n = 4$), mouth ($n = 4$), chest ($n = 2$), or abdomen ($n = 1$). Patients felt more depressive and anxious prior to the study than did controls and reported more impairment in their daily activities. No significant differences in NART performance (intelligence levels) between the groups were observed.

3.2. Behavioral results

Participants reported different pain intensities across the emotional context conditions (Table 3). A 3-way ANOVA revealed a significant main effect of emotional context, $F\ (1, 20) = 7.69$, $p < 0.05$; pain intensities in the sad emotional context condition were significantly higher than in the neutral condition. No significant differences in subjective pain perception between the groups were observed.

Table 1
Demographic and psychometric variables of patients and controls.

	Patients (n = 11)	Controls (n = 11)	T_{score}
[Demographic variables]			
Age	40.9 ± 6.5	40.6 ± 6.1	0.1^{ns}
Female/male	6/5	6/5	0.0^{ns}
Pain duration (months)	91.0 ± 85.7	–	–
Rating of clinical pain (NRS)	7.6 ± 1.7/10	–	–
Psychiatric diagnosis			
Pain disorder	11/11	–	–
Current major depressive episode	0/11	–	–
Major depression in history	5/11	–	–
Generalized anxiety disorder	3/11	–	–
Other psychiatric disorders	0/11	–	–
[Psychometric variables]			
BDI	15.9 ± 11.1	4.0 ± 4.9	3.2^{**}
STAI			
State	55.3 ± 11.3	37.8 ± 8.6	4.1^{**}
Trait	55.8 ± 11.9	41.4 ± 10.7	3.0^{**}
SF-36			
Physical functioning	84.5 ± 13.7	97.3 ± 3.4	-3.0^{*}
Role physical	45.5 ± 48.5	84.1 ± 23.1	-2.4^{*}
Bodily pain	39.5 ± 28.0	92.7 ± 13.4	-5.7^{***}
General health	33.7 ± 23.9	75.2 ± 14.9	-4.9^{***}
Vitality	38.2 ± 28.6	59.5 ± 12.7	-2.3^{*}
Social functioning	63.6 ± 21.3	94.3 ± 11.7	-4.2^{***}
Role emotional	54.5 ± 45.4	81.8 ± 34.6	-1.6^{ns}
Mental health	35.3 ± 20.1	52.0 ± 10.3	-2.5^{*}
NART	110.1 ± 6.7	112.9 ± 4.3	-1.2^{ns}
SF-MPQ			
Sensory	12.5 ± 8.2	–	–
Affective	3.3 ± 2.5	–	–
PCS	35.5 ± 9.1	–	–

ns = not significant.
NRS = numeric rating scale; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; SF-36 = Short Form-36; NART = National Adult Reading Test; SF-MPQ = Short Form of the McGill Pain Questionnaire; PCS = Pain Catastrophizing Scale.
* $P_{two\text{-}sided} < 0.05$ (two sample t-test).
** $P_{two\text{-}sided} < 0.01$ (two sample t-test).
*** $P_{two\text{-}sided} < 0.001$ (two sample t-test).

Regarding the ratio for pain intensity ratings between the sad and neutral conditions, a 2-way ANOVA revealed a significant interaction between group and pain, $F\ (1, 20) = 4.96$, $p < 0.05$. Bonferroni post-hoc tests showed that the ratio for low pain levels between the sad

Table 2
Patients' characteristics.

No	Medical diagnosis	Medications
1	Somatoform pain disorder Generalized anxiety disorder Major depression in history	Tryptanol 75 mg, sulpiride 150 mg, loxoprofen 180 mg
2	Somatoform pain disorder Major depression in history	Tryptanol 75 mg, clonazepam 1.5 mg
3	Somatoform pain disorder	Mirtazapine 45 mg, pregabalin 75 mg, loxoprofen 180 mg, eperison 100 mg
4	Somatoform pain disorder	Nortriptyline 50 mg, clonazepam 0.5 mg, tizanidine 3 mg
5	Somatoform pain disorder	Tryptanol 75 mg
6	Somatoform pain disorder	Duloxetine 40 mg, tizanidine 3 mg
7	Somatoform pain disorder	Amoxapine 25 mg
8	Somatoform pain disorder Major depression in history	Tryptanol 25 mg, trazodone 25 mg Loxoprofen 180 mg
9	Somatoform pain disorder Generalized anxiety disorder	Duloxetine 20 mg, quetiapine 25 mg, clonazepam 0.5 mg, sodium valproate 400 mg
10	Somatoform pain disorder Generalized anxiety disorder Major depression in history	Nortriptyline 150 mg, tizanidine 3 mg
11	Somatoform pain disorder Major depression in history	Tryptanol 50 mg, trazodone 50 mg, carbamazepine 200 mg, clonazepam 1 mg, eletriptan 20 mg

and neutral conditions in patients was higher than the ratio for moderate pain levels in patients and for low pain levels in controls ($p < 0.05$).

3.3. fMRI data

3.3.1. Brain regions involved in pain perception (main effect of 'pain')

Significant changes in signal intensity were detected in a number of brain regions related to pain perception (Table 4), including the ACC, insula, thalamus, second somatosensory area (SII), and prefrontal cortex.

3.3.2. Differences in cerebral pain processing between groups (interaction of 'group' × 'pain' × 'emotion')

To test differences in pain-related activation between patients and controls during presentation of pain stimuli, we looked at brain activation as reflected in the interaction of 'group' × 'pain' × 'emotion' (Fig. 2A–C). There was significant activation in the anterior insula, posterior insula, and hippocampus.

3.4. Post-hoc comparisons between groups

3.4.1. Anterior insula

Activation during the low pain sad and high pain neutral conditions was significantly greater in patients than in controls ($p < 0.05$). Activation during the low pain in neutral condition was significantly greater in controls than in patients ($p < 0.05$).

3.4.2. Posterior insula

Activation during the low pain sad condition was significantly greater in patients than in controls ($p < 0.01$). Activation during the low pain neutral condition was significantly greater in controls than in patients ($p < 0.01$).

3.4.3. Hippocampus

Activation during the high pain neutral condition was significantly greater in patients than in controls ($p < 0.01$). Activation during the low pain neutral condition was significantly greater in controls than in patients ($p < 0.001$).

3.5. Psychophysiological interaction (PPI) analysis

The above whole-brain ANOVAs revealed that blood oxygenation level-dependent (BOLD) responses for the anterior/posterior insula during the presentation of low-pain stimuli were larger for the sad condition than for the neutral condition in patients. PPI analyses were performed to assess possible functional connectivity differences between patients and controls in the anterior insula [6-mm sphere centered x = 28, y = 22, z = −16], with other areas focusing primarily on the low pain sad emotional context condition, given that many studies suggest that the anterior insula is associated with the affective dimension of pain (Craig, 2002; Gu et al., 2013; Yuan et al., 2013). Considering behavioral and fMRI data results, we examined brain region connectivity for the low pain sadness condition.

The PPI analysis for the sad-specific low pain component ((low pain with sad facial images) − (low pain with neutral facial images)) revealed that anterior insula activity was accompanied by increased functional interaction with the right parahippocampus [x = 24, y = −10, z = −26; z-score 4.28, cluster extent 30] (Fig. 2D), to a greater extent in patients than in controls.

Table 3
Pain ratings by the differences of facial images.

	Patients (Mean ± SD)	Controls (Mean ± SD)	
Sad			
Moderate pain	4.2 ± 0.8	4.3 ± 0.9	*
Low pain	1.1 ± 0.7	0.8 ± 0.5	*
Neutral			
Moderate pain	4.0 ± 0.8	4.2 ± 0.7	
Low pain	0.6 ± 0.3	0.7 ± 0.3	
Sad/neutral			
Moderate pain	1.1 ± 0.3	1.0 ± 0.1	
Low pain	1.9 ± 0.6♦	1.2 ± 0.7	

SD, standard deviation.
*Statistically significant difference between emotions ($p < 0.05$).
♦Significant interaction between group and emotion ($p < 0.05$). Bonferroni's post hoc tests showed that the ratio between sad and neutral on low pain in patients was more highly rated than moderate pain in patients and low pain in controls ($p < 0.05$).

3.6. Correlation analysis

Sadness-specific lower pain level rating scores were positively correlated with sadness-specific activation during low-pain stimuli in the anterior insula ($r = 0.71$, $p = 0.019$). This finding emerged in the patient group. No regions showed negative correlations with pain rating scores.

No ROIs showed positive or negative correlations between sadness-specific activation during low-pain stimuli and BDI or STAI scores.

4. Discussion

In comparison to the matched controls, we demonstrated that the ratio for low-pain intensity ratings between the sad and neutral conditions in patients was higher than in controls. At the same time, the patients also showed stronger anterior/posterior insula activation induced by sadness-context low-pain stimuli. In patients, we found more effective connections between the parahippocampus and anterior insula during the presentation of low-pain stimuli in the sad context. This is the first fMRI study that has compared somatoform pain disorder patients with controls, in order to examine the relationship between pain perception and sad emotional context.

4.1. Subjective pain intensities

We examined changes in perceived pain intensity as influenced by sadness, using the same stimuli across sad and neutral conditions. Subjective pain intensities in the sad context were significantly greater than the subjective pain intensities in the neutral context, for both patient and control groups. The finding that sadness subjectively increased pain replicates the findings of our previous studies (Yoshino et al., 2010, 2012). However, we did not find significant differences in pain threshold between the groups. A behavioral study also reported this pain-amplifying effect for sadness both in participants with and without chronic pain, but there was no difference between the groups (van Middendorp et al., 2010). No between group differences in terms of physical pain stimulus intensity have been reported across many other fMRI studies (Baliki et al., 2006; Gündel et al., 2008; Kirsch et al., 2005; Stoeter et al., 2007).

In the present study, there was a significant difference between groups in the ratio between sad and neutral contexts for low-pain stimuli. Previous studies have identified greater pain responses associated with negative emotions in patients with chronic pain disorder than among controls (Burns, 2006; Zautra et al., 2005). Furthermore, it has also been reported that low-pain stimuli are experienced as more aversive by these patients (Morris et al., 1995). Our results suggest that patients with somatoform pain disorder may be more susceptible to the perception of low-pain stimuli in a sad emotional context, as compared to a neutral context.

4.2. Insula

Insula activation has been observed during a majority of imaging studies involving pain stimuli (Apkarian et al., 2005). Various studies have demonstrated that negative emotional states enhance pain-

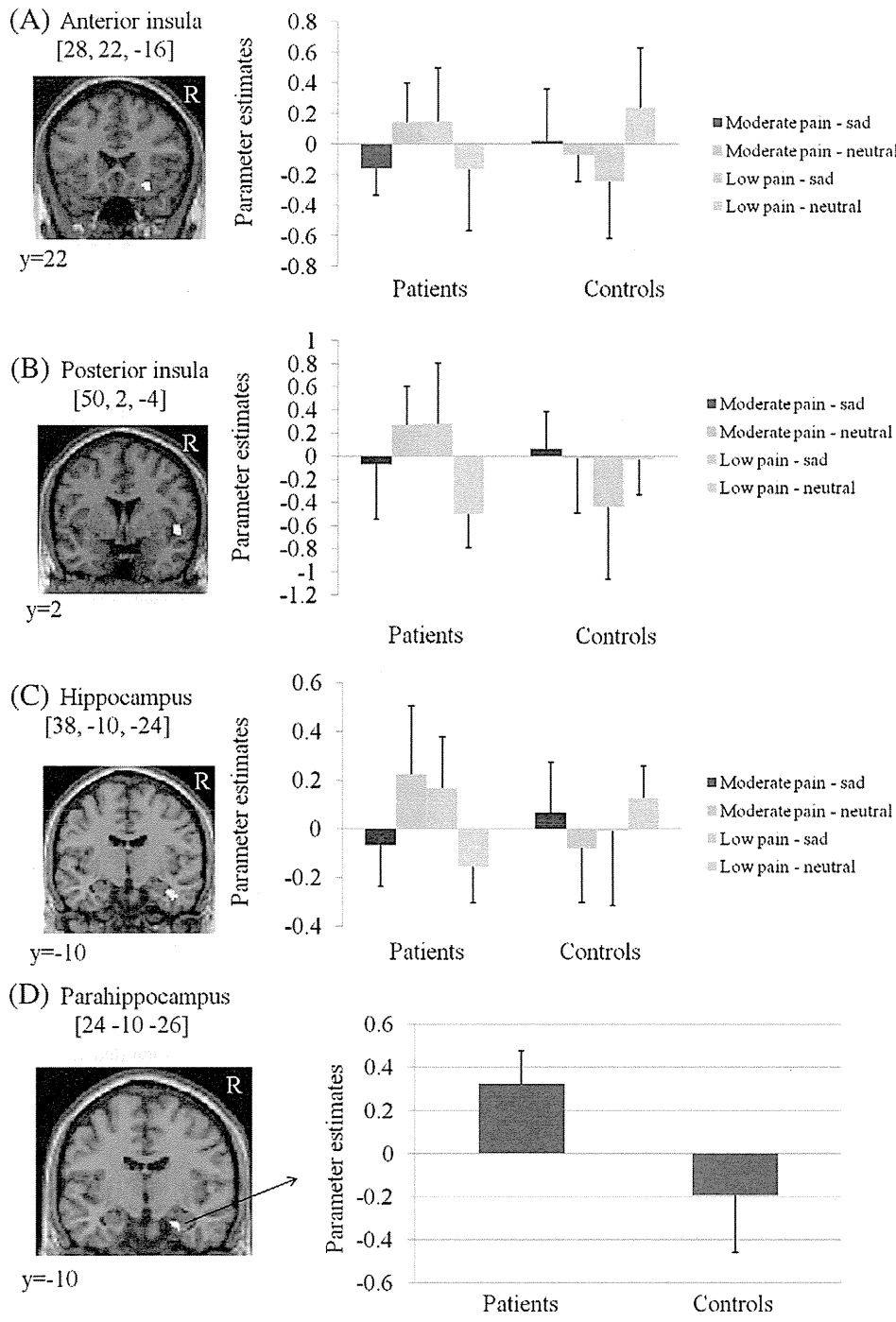

Fig. 2. BOLD-signal differences between patients with somatoform pain disorder and controls. A–C; Group × pain × emotion interactions in the insula and the hippocampus are shown (3-way-ANOVA; BDI, STAI-S, and STAI-T scores as covariates). In patients, stronger activations were found in the moderate pain neutral and low pain sad conditions. In controls, stronger activation was found in the moderate pain sad condition. D; The graph shows the parameter estimate of the peak coordinate as the difference of connectivity strength for low-pain stimuli in the sad condition. Anterior insula activity covaried more strongly with activity in the parahippocampus in patients.

related activity in the insula (Lutz et al., 2012; Terasawa et al., 2013). The present study found that activation of the anterior/posterior insula during low-pain stimuli in a sad emotional context was stronger in somatoform pain disorder patients than in controls. Previous studies also reported stronger activation of the insula for pain stimuli in patients with somatoform pain disorder as compared to controls (Gündel et al., 2008; Stoeter et al., 2007). We suggest that a vulnerability to pain perception modulated by emotional dysregulation, as well as pain perception itself, is one of the important pathophysiological factors underlying somatoform pain disorder.

Peyron et al. (2000) found that insula activation is positively correlated with pain ratings. The present study also found that anterior insula activation associated with sad-context low-pain stimuli is related to subjective ratings of such stimuli provided by patients. We suggest that the anterior insula activations we observed reflected the subjective pain ratings that we obtained.

These findings suggest the possibility that sadness is associated with more increased sensitivity to pain perception in patients with somatoform pain disorder as compared to controls, and that the insula is involved in this process.

4.3. Hippocampus and parahippocampus

Reports of pain-related responses in the hippocampus have been contradictory, but various studies have reported that the hippocampus is involved in the processing of pain stimuli (Apkarian et al., 2005; Peyron et al., 2000). The hippocampus plays a critical role in supporting the influence of context on memory encoding, storage, behavior, and the retrieval of pleasant or aversive stimuli (Rudy, 2009). Some evidence suggests that hyperalgesia induced by negative emotional states is associated with activation in the hippocampus (Berna et al., 2010; Ploghaus et al., 2001). Patients with somatoform pain disorder show altered hippocampal activation in response to pain stimuli, in comparison with controls (Gündel et al., 2008; Stoeter et al., 2007). Studies also indicate that the hippocampus is connected with pain-related brain regions such as the insula, and that hippocampus activity can enhance pain perception (Kong et al., 2008; Ploghaus et al., 2001). The present study found strong hippocampus activation in patients for low pain stimuli in a sad emotional context. We speculate that a similar mechanism may also underlie sadness-induced pain perception.

We conducted a PPI analysis to examine brain regions in relation to the insula during sadness-specific low-pain perception. Anterior insula activity was accompanied by increased functional interaction involving the parahippocampus, to a greater extent in patients than in controls. The parahippocampus plays a central role in recollection, sending information from the hippocampus to the association areas (Diederen et al., 2010). Previous studies have demonstrated effective connectivity between the parahippocampus and anterior insula in healthy controls (Ploner et al., 2011; Tanaka et al., 2008). It has been reported that stronger intensity of pain stimuli in a negative emotional context is associated with neural activity in the anterior insula, mediated by the parahippocampus (Ploner et al., 2011). Patients with somatoform pain disorder show an altered activation pattern in the parahippocampus in response to pain stimuli, in comparison to controls (Gündel et al., 2008; Stoeter et al., 2007). We therefore assume that an increased functional connectivity between the anterior insula and parahippocampus may be a distinctive feature of somatoform pain disorder in a sad emotional context. The present behavioral results suggest that the subjective experience of pain appears to be exacerbated by negative emotional states for such patients. They may perceive even relatively low pain levels as more intense during sadness, with conditioning possibly playing a role in this process. However, this interpretation may be premature, and further study is needed to elucidate the relationship between pathophysiology in somatoform pain disorder and the parahippocampus.

We also hypothesized that ACC activation would differ across patients with somatoform pain disorder and healthy controls. Although there was a main effect of pain level on ACC activity, there were no group differences, consistent with previous studies (Gündel et al., 2008; Stoeter et al., 2007). Gündel et al. (2008) described a negative correlation between intensity of patients' clinical pain and the experimental pain stimuli in terms of ACC activation, and they have explained this limited activation of the ACC in response to experimental pain in terms of increased neuronal baseline activity due to the experience of chronic pain. There is a clear need for continued research to elucidate the role of the ACC in somatoform pain disorder.

The present study has several limitations. First, the small sample size limits the robustness of our findings. Second, the display duration for the facial images (4 s) was longer than that used in previous studies (Doallo et al., 2012; Whalen et al., 2013). We must therefore consider the possibility that any context-induced emotional effects might have been attenuated *via* habituation. Third, a higher level of anxiety and depression in patients may influence the fMRI data. Previous studies have shown that somatoform patients have significantly higher depression or anxiety scores (Gündel et al., 2008; Stoeter et al., 2007). We analyzed a 3-way ANOVA using BDI, STAI-S, and STAI-T scores as covariates, and adjusted the fMRI data accordingly. Furthermore, no brain regions showed correlations between sadness-specific activation for low-pain stimuli and BDI or STAI scores across the participants. These results mean that the effects of depression and anxiety were probably limited in the present study, but nevertheless we cannot rule out such effects. Fourth, an uncertainty may remain in our experimental paradigm regarding the extent to which we adequately distinguished between pain and emotion. It has been reported that pain itself is a specific emotion (Craig, 2003), and pain and emotion show much overlap in terms of psychological and brain functional aspects although they are not necessary the same. Finally, our exclusion criteria did not include all treatments that might influence the patients' pain perception, such as antidepressants, although it included opioids, and a 24 h analgesic-free observation period prior to the fMRI was not generally fully effective. It has been reported that antidepressants have an analgesic effect in somatoform pain disorder (Luo et al., 2009) and such drugs produce clear changes in brain activity (Wiech and Tracey, 2009). We therefore cannot rule out all treatment effects on the brain activity that we observed in this study. However, it is not clear whether antidepressants influence antinociceptive effects in acute pain (Schreiber et al., 2009). Furthermore, any analgesic effects may be related to specific antidepressant effects (Luo et al., 2009). We believe that such treatment effects probably play a minor role in our findings, given that we adjusted our fMRI data to control for the presence of depressive states as described above.

Table 4
Main effect of pain.

Brain regions	L/R	x/y/z	z-score	Cluster extent
ACC (BA 32)	R	8/34/24	3.32	43
ACC (BA 24)	R	6/20/30	3.75	124
ACC (BA 24)	L	−8/6/32	4.17	152
Insula	R	42/0/−4	3.40	24
Insula	L	−40/−8/−6	4.22	50
Thalamus	R	6/−4/12	4.07	227
Thalamus	L	−8/−4/14	5.21	259
Superior frontal gyrus (BA9)	L	−18/54/26	3.96	65
Middle frontal gyrus (BA8)	L	−34/24/48	4.58	118
Inferior frontal gyrus (BA45)	L	−56/8/8	5.63	392
Caudate	L	−16/14/8	3.69	21
S1 (BA2)	L	−66/−24/34	4.12	78
S2 (BA40)	R	60/−24/20	5.82	468
S2 (BA40)	L	−60/−24/20	4.94	347
SMA (BA6)	L	−2/12/58	5.72	435
M1 (BA4)	R	50/2/44	3.99	114
M1 (BA4)	L	−38/−8/62	4.23	65
Middle temporal gyrus	L	−56/−62/6	3.99	58
Superior temporal gyrus	L	−56/4/10	5.63	81

Brain regions stated in MNI coordinates with activation maxima of experimentally induced p, thresholded at uncorrected $p < 0.001$. Minimum activation cluster size is 20 voxel.
ACC, anterior cingulate cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SMA, supplementary motor area; M1, primary motor cortex.

In summary, our results provide evidence that patients with somatoform pain disorder tend to show slightly higher pain sensitivities to low pain stimuli in contexts of sadness. The insula, hippocampus, and parahippocampus show altered activity under such conditions. These results provide some insight into sadness-induced distinctive changes in neural pain-related activity within the context of somatoform pain disorder, with interactions between brain activity and emotional context potentially playing an important role in the pathophysiology of this disorder.

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References

APA, 1994. Diagnostic and Statistical Manual of Mental Disorders: Diagnostic Criteria from DSM-IV, American Psychiatric Association Ed. American Psychiatric Association.

Apkarian, A.V., Bushnell, M.C., Treede, R.D., Zubieta, J.K., 2005. Human brain mechanisms of pain perception and regulation in health and disease. European Journal of Pain 9, 463–484.

Baliki, M.N., Chialvo, D.R., Geha, P.Y., Levy, R.M., Harden, R.N., Parrish, T.B., Apkarian, A.V., 2006. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. Journal of Neuroscience 26, 12165–12173.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Archives of General Psychiatry 4, 561–571.

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. Biological Psychiatry 67, 1083–1090.

Burns, J.W., 2006. Arousal of negative emotions and symptom-specific reactivity in chronic low back pain patients. Emotion 6, 309–319.

Craig, A.D., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. Nature Reviews Neuroscience 3, 655–666.

Craig, A., 2003. A new view of pain as a homeostatic emotion. Trends in Neurosciences 26, 303–307.

de Greck, M., Scheidt, L., Bölter, A.F., Frommer, J., Ulrich, C., Stockum, E., Enzi, B., Tempelmann, C., Hoffmann, T., Northoff, G., 2011. Multimodal psychodynamic psychotherapy induces normalization of reward related activity in somatoform disorder. The World Journal of Biological Psychiatry 12, 296–308.

Diederen, K.M.J., Neggers, S.F.W., Daalman, K., Blom, J.D., Goekoop, R., Kahn, R.S., Sommer, I.E.C., 2010. Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. The American Journal of Psychiatry 167, 427–435.

Dimsdale, J.E., Dantzer, R., 2007. A biological substrate for somatoform disorders: importance of pathophysiology. Psychosomatic Medicine 69, 850–854.

Doallo, S., Raymond, J.E., Shapiro, K.L., Kiss, M., Eimer, M., Nobre, A.C., 2012. Response inhibition results in the emotional devaluation of faces: neural correlates as revealed by fMRI. Social Cognitive and Affective Neuroscience 7, 649–659.

Ellsworth, P.C., Smith, C.A., 1988. From appraisal to emotion: differences among unpleasant feelings. Motivation and Emotion 12, 271–302.

Fayed, N., Andres, E., Rojas, G., Moreno, S., Serrano-Blanco, A., Roca, M., Garcia-Campayo, J., 2012. Brain dysfunction in fibromyalgia and somatization disorder using proton magnetic resonance spectroscopy: a controlled study. Acta Psychiatrica Scandinavica 126, 115–125.

Friston, K., Buechel, C., Fink, G., Morris, J., Rolls, E., Dolan, R., 1997. Psychophysiological and modulatory interactions in neuroimaging. NeuroImage 6, 218–229.

Fukuhara, S., Bito, S., Green, J., Hsiao, A., Kurokawa, K., 1998. Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. Journal of Clinical Epidemiology 51, 1037–1044.

Groenewold, N.A., Opmeer, E.M., de Jonge, P., Aleman, A., Costafreda, S.G., 2012. Emotional valence modulates brain functional abnormalities in depression: evidence from a meta-analysis of fMRI studies. Neuroscience and Biobehavioral Reviews 37, 152–163.

Gu, X., Liu, X., Van Dam, N.T., Hof, P.R., Fan, J., 2013. Cognition–emotion integration in the anterior insular cortex. Cerebral Cortex 23, 20–27.

Gündel, H., Valet, M., Sorg, C., Huber, D., Zimmer, C., Sprenger, T., Tölle, T., 2008. Altered cerebral response to noxious heat stimulation in patients with somatoform pain disorder. Pain 137, 413–421.

Inui, K., Kakigi, R., 2012. Pain perception in humans: use of intraepidermal electrical stimulation. Journal of Neurology, Neurosurgery & Psychiatry 83, 551–556.

Inui, K., Tran, T.D., Hoshiyama, M., Kakigi, R., 2002. Preferential stimulation of Adelta fibers by intra-epidermal needle electrode in humans. Pain 96, 247–252.

Kamachi, M., Bruce, V., Mukaida, S., Gyoba, J., Yoshikawa, S., Akamatsu, S., 2001. Dynamic properties influence the perception of facial expressions. Perception 30, 875–887.

Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., Gruppe, H., Mattay, V.S., Gallhofer, B., Meyer-Lindenberg, A., 2005. Oxytocin modulates neural circuitry for social cognition and fear in humans. Journal of Neuroscience 25, 11489–11493.

Kong, J., Gollub, R.L., Polich, G., Kirsch, I., LaViolette, P., Vangel, M., Rosen, B., Kaptchuk, T.J., 2008. A functional magnetic resonance imaging study on the neural mechanisms of hyperalgesic nocebo effect. Journal of Neuroscience 28, 13354–13362.

Lehoux, C.P., Abbott, F.V., 2011. Pain, sensory function, and neurogenic inflammatory response in young women with low mood. Journal of Psychosomatic Research 70, 241–249.

Loggia, M.L., Mogil, J.S., Bushnell, M.C., 2008. Experimentally induced mood changes preferentially affect pain unpleasantness. The Journal of Pain 9, 784–791.

Luo, Y.L., Zhang, M.Y., Wu, W.Y., Li, C.B., Lu, Z., Li, Q.W., 2009. A randomized double-blind clinical trial on analgesic efficacy of fluoxetine for persistent somatoform pain disorder. Progress in Neuro-Psychopharmacology & Biological Psychiatry 1522–1525.

Lutz, A., McFarlin, D.R., Perlman, D.M., Salomons, T.V., Davidson, R.J., 2012. Altered anterior insula activation during anticipation and experience of painful stimuli in expert meditators. NeuroImage 64, 538–546.

Matsuoka, K., Uno, M., Kasai, K., Koyama, K., Kim, Y., 2006. Estimation of premorbid IQ in individuals with Alzheimer's disease using Japanese ideographic script (Kanji) compound words: Japanese version of National Adult Reading Test. Psychiatry and Clinical Neurosciences 60, 332–339.

May, A., 2008. Chronic pain may change the structure of the brain. Pain 137, 7–15.

McEwen, B.S., Kalia, M., 2010. The role of corticosteroids and stress in chronic pain conditions. Metabolism 59, S9–S15.

Melzack, R., 1987. The short-form McGill pain questionnaire. Pain 30, 191–197.

Morris, G.C., Gibson, S.J., Helme, R.D., 1995. Capsaicin-induced flare and vasodilatation in patients with post-herpetic neuralgia. Pain 63, 93–101.

Murray, I.R., Arnott, J.L., 1993. Toward the simulation of emotion in synthetic speech: a review of the literature on human vocal emotion. Journal of the Acoustical Society of America 93, 1097–1108.

Nelson, H.E., 1982. National Adult Reading Test (NART). NFER-Nelson, Windsor, UK.

Noll-Hussong, M., Otti, A., Wohlschlaeger, A.M., Zimmer, C., Henningsen, P., Lahmann, C., Ronel, J., Subic-Wrana, C., Lane, R.D., Decety, J., 2013. Neural correlates of deficits in pain-related affective meaning construction in patients with chronic pain disorder. Psychosomatic Medicine 75, 124–136.

Ochsner, K.N., Ludlow, D.H., Knierim, K., Hanelin, J., Ramachandran, T., Glover, G.C., Mackey, S.C., 2006. Neural correlates of individual differences in pain-related fear and anxiety. Pain 120, 69–77.

Otti, A., Guendel, H., Henningsen, P., Zimmer, C., Wohlschlaeger, A.M., Noll-Hussong, M., 2013. Functional network connectivity of pain-related resting state networks in somatoform pain disorder: an exploratory fMRI study. Journal of Psychiatry & Neuroscience 38, 57–65.

Peyron, R., Laurent, B., Garcia-Larrea, L., 2000. Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiologie Clinique 30, 263–288.

Ploghaus, A., Narain, C., Beckmann, C.F., Clare, S., Bantick, S., Wise, R., Matthews, P.M., Rawlins, J.N.P., Tracey, I., 2001. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. Journal of Neuroscience 21, 9896–9903.

Ploner, M., Lee, M.C., Wiech, K., Bingel, U., Tracey, I., 2011. Flexible cerebral connectivity patterns subserve contextual modulations of pain. Cerebral Cortex 21, 719–726.

Price, D.D., 2002. Central neural mechanisms that interrelate sensory and affective dimensions of pain. Molecular Interventions 2, 392–403.

Rabkin, J.G., Klein, D.F., 1987. The Clinical Measurement of Depressive Disorders. Guilford Press, New York.

Rudy, J.W., 2009. Context representations, context functions, and the parahippocampal–hippocampal system. Learning and Memory 16, 573–585.

Schreiber, S., Frishtick, R., Volis, I., Rubovitch, V., Pick, C.G., Weizman, R., 2009. The antinociceptive properties of reboxetine in acute pain. European Neuropsychopharmacology 19, 735–739.

Seifert, F., Maihöfner, C., 2011. Functional and structural imaging of pain-induced neuroplasticity. Current Opinion in Anaesthesiology 24, 515–523.

Spielberger, C.D., 1983. Manual for the State-Trait Anxiety Inventory (STAI). Consulting Psychologists Press, Palo Alto, California.

Spitzer, R.L., Williams, J.B.W., Gibbon, M., First, M.B., 1992. The Structured Clinical Interview for DSM-III-R (SCID) I: history, rationale, and description. Archives of General Psychiatry 49, 624–629.

Stoeter, P., Bauermann, T., Nickel, R., Corluka, L., Gawehn, J., Vucurevic, G., Vossel, G., Egle, U., 2007. Cerebral activation in patients with somatoform pain disorder exposed to pain and stress: an fMRI study. NeuroImage 36, 418–430.

Sullivan, M.J.L., Bishop, S.R., Pivik, J., 1995. The pain catastrophizing scale: development and validation. Psychological Assessment 7, 524–532.

Tanaka, E., Inui, K., Kida, T., Miyazaki, T., Takeshima, Y., Kakigi, R., 2008. A transition from unimodal to multimodal activations in four sensory modalities in humans: an electrophysiological study. BMC Neuroscience 9, 116.

Terasawa, Y., Shibata, M., Moriguchi, Y., Umeda, S., 2013. Anterior insular cortex mediates bodily sensibility and social anxiety. Social Cognitive and Affective Neuroscience 8, 259–266.

van Middendorp, H., Lumley, M.A., Jacobs, J.W.G., Bijlsma, J.W.J., Geenen, R., 2010. The effects of anger and sadness on clinical pain reports and experimentally-induced pain thresholds in women with and without fibromyalgia. Arthritis Care & Research 62, 1370–1376.

Whalen, P.J., Raila, H., Bennett, R., Mattek, A., Brown, A., Taylor, J., van Tieghem, M., Tanner, A., Miner, M., Palmer, A., 2013. Neuroscience and facial expressions of emotion: the role of amygdala–prefrontal interactions. Emotion Review 5, 78–83.

Wiech, K., Tracey, I., 2009. The influence of negative emotions on pain: behavioral effects and neural mechanisms. NeuroImage 47, 987–994.

Williams, L.J., Pasco, J.A., Jacka, F.N., Dodd, S., Berk, M., 2012. Pain and the relationship with mood and anxiety disorders and psychological symptoms. Journal of Psychosomatic Research 72, 452–456.

Yoshino, A., Okamoto, Y., Onoda, K., Yoshimura, S., Kunisato, Y., Demoto, Y., Okada, G., Yamawaki, S., 2010. Sadness enhances the experience of pain *via* neural activation in the anterior cingulate cortex and amygdala: an fMRI study. NeuroImage 50, 1194–1201.

Yoshino, A., Okamoto, Y., Onoda, K., Shishida, K., Yoshimura, S., Kunisato, Y., Demoto, Y., Okada, G., Toki, S., Yamashita, H., Yamawaki, S., 2012. Sadness enhances the experience of pain and affects pain-evoked cortical activities: an MEG study. The Journal of Pain 13, 628–635.

Yuan, W., Dan, L., Netra, R., Shaohui, M., Chenwang, J., Ming, Z., 2013. A pharmaco-fMRI study on pain networks induced by electrical stimulation after sumatriptan injection. Experimental Brain Research 226, 1–10.

Zautra, A.J., Johnson, L.M., Davis, M.C., 2005. Positive affect as a source of resilience for women in chronic pain. Journal of Consulting and Clinical Psychology 73, 212–220.

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Automatic and Intentional Brain Responses during Evaluation of Face Approachability: Correlations with Trait Anxiety

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Key Words
Amygdala · Trait anxiety · Approachability judgment · Functional magnetic resonance imaging

Abstract
Background: The judgment of the approachability of others based on their facial appearance often precedes social interaction. Whether we ultimately approach or avoid others may depend on such judgments. ***Method:*** We used functional magnetic resonance imaging to determine the neural basis for such approachability judgments and the relationship between these judgments and trait anxiety. Participants viewed ambiguous (i.e. neutral) or relatively unambiguous (i.e. angry, happy) faces, assessing either the approachability or the sex of the person depicted. ***Results:*** Neutral faces elicited more inconsistent responses within participants only during approachability judgment, suggesting ambiguous property as signals. The contrast pertaining to the interaction between task and face valence demonstrated activation in several areas, such that the left amygdala and medial, middle and inferior frontal gyri were responsive to angry faces when subjects were asked to recognize the sex (implicit task) and to neutral faces when required to discern the approachability (explicit task). Moreover, the blood oxygenation level-dependent change within the left amygdala in response to neutral faces during the judgment of approachability was positively correlated with participant trait anxiety. ***Conclusions:*** These findings extend a proposed model of social cognition by highlighting the functional engagement of the amygdala in approachability judgments, which underlie an individual's sensitivity to ambiguous sources of probable threat.

Introduction

The faces of others provide a rich source of information about the individuals in question, including identity, emotionality, gender, age, trustworthiness and approachability [1–3]. We use this complex information both automatically and intentionally in our daily social lives. It seems likely that many people often judge the approachability of another individual based on his/her facial expression before communication is initiated. However, the neural processes underlying such judgment remain poorly understood, as do the relationships between the neural substrate and various psychological variables. Previous studies have investigated the neural basis of approachabil-

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ity judgments from the perspective of trustworthiness [1, 4, 5]. Evolutionally speaking, approachability judgments of faces involve primitive aspects of social functioning related to defensive responses for predators or conspecifics in mammals [1, 6]. The main purpose of our study was to investigate the neural basis underlying the relationship between approachability judgment and an individual's threat sensitivity. Following the classic theory of anxiety, we define threat sensitivity as the tendency to recognize either an ambiguous or a potential threat; in humans, this tendency is considered to be related to anxiety [7, 8].

Todorov and Engell [9] reported that a differential amygdala response to trustworthiness represents a response to differences in valence rather than trustworthiness per se. In addition, it has been observed that exaggerating the facial features that make a neutral face trustworthy produces expressions of happiness, whereas exaggerating the facial features that make a face look untrustworthy produces expressions of anger [10]. Several studies have demonstrated that negatively valenced faces such as angry ones are rated as less approachable and trustworthy [4, 10–13]. Moreover, one study has shown that angry faces trigger automatic avoidance responses [14]. Recently, Blasi et al. [15] reported the preferential amygdala reactivity to the avoidant judgment of neutral faces, suggesting the existence of neural activity for judging approachability beyond that for merely perceiving facial expression. Based on the importance of angry and happy faces as a stimulus of two poles, and the close relationship between facial expression and the judgment of approachability, angry, happy and neutral faces have been used as stimuli, in order to clarify the neural mechanisms underlying the approach-avoidance response.

The evaluation of potential threat appears to be central to the process of making an unapproachability decision [16, 17]. Recognition of facial expressions and assessing the level of potential threat based on facial recognition appear to constitute important aspects of an approachability judgment. Although the relationship between amygdala response to fearful faces and anxiety level has been investigated in healthy participants [18–22], no study has focused on the potential relationship between the participant's neural response during approachability judgments and his or her threat sensitivity. Interestingly, in previous studies, a significant relationship between neural response to fearful faces and anxiety scores emerged during a psychological task that did not require attention to or conscious awareness of the faces [18–22].

Following the approach used in previous studies [22–29], we used Spielberger's State-Trait Anxiety Inventory Trait (STAI-T) form [30]. The STAI is one of the most widely used measures of anxious emotional and cognitive reactions. STAI-T originally aimed to evaluate trait anxiety (TA), that is, the disposition to respond with anxiety to situations perceived as threatening. We used it to help us explore the relationship between the neural response during approachability judgments and the individual's threat sensitivity.

Processing of facial emotion can be implicit, occurring when participants make judgments about facial attributes that are unrelated to emotion [31, 32]. To establish whether approachability judgments might be similarly processed, we used a task in which participants viewed faces while making either an explicit judgment about whether an individual was approachable or a sex discrimination judgment. Thirty healthy adults completed an event-related functional magnetic resonance imaging (fMRI) study during which they were required to make approachability judgments (i.e. approach or avoid) about ambiguous (i.e. neutral) or relatively unambiguous (i.e. angry or happy) facial expressions. We expected that the relatively difficult task of making such judgments about neutral faces would help to elucidate the neural substrate of such judgments via a comparison with angry faces. In a different session, participants were required to make sex discrimination judgments of the same stimuli. Many studies have supported the hypothesis that the amygdala and frontal cortex mutually influence and regulate the process of making approachability judgments [12, 15, 33, 34]. We hypothesized that perceptual evaluation of neutral face stimuli might require more attention and cognitive effort to render a decision, triggering greater responses within the amygdala and frontal cortex. Given the large body of evidence supporting the role of the amygdala in the processing of emotional stimuli, we predicted that the amygdala activity would be proportional to the participant's potential-threat sensitivity.

Method and Materials

Participants

Thirty right-handed healthy volunteers with normal vision (15 women and 15 men; 20–28 years of age, mean age ± SD, 23.4 ± 2.4 years) screened for psychiatric, neurological or major medical illness were included in this study. None of the participants had a history of exposure to psychotropic medications, and all were free of psychoactive medications at the time of scanning. All participants provided their written, informed consent to participate, according to the guidelines of the institutional review board and the ethics committee of Hiroshima University Hospital, Japan. The sex/approachability judgment task was explained to the partici-

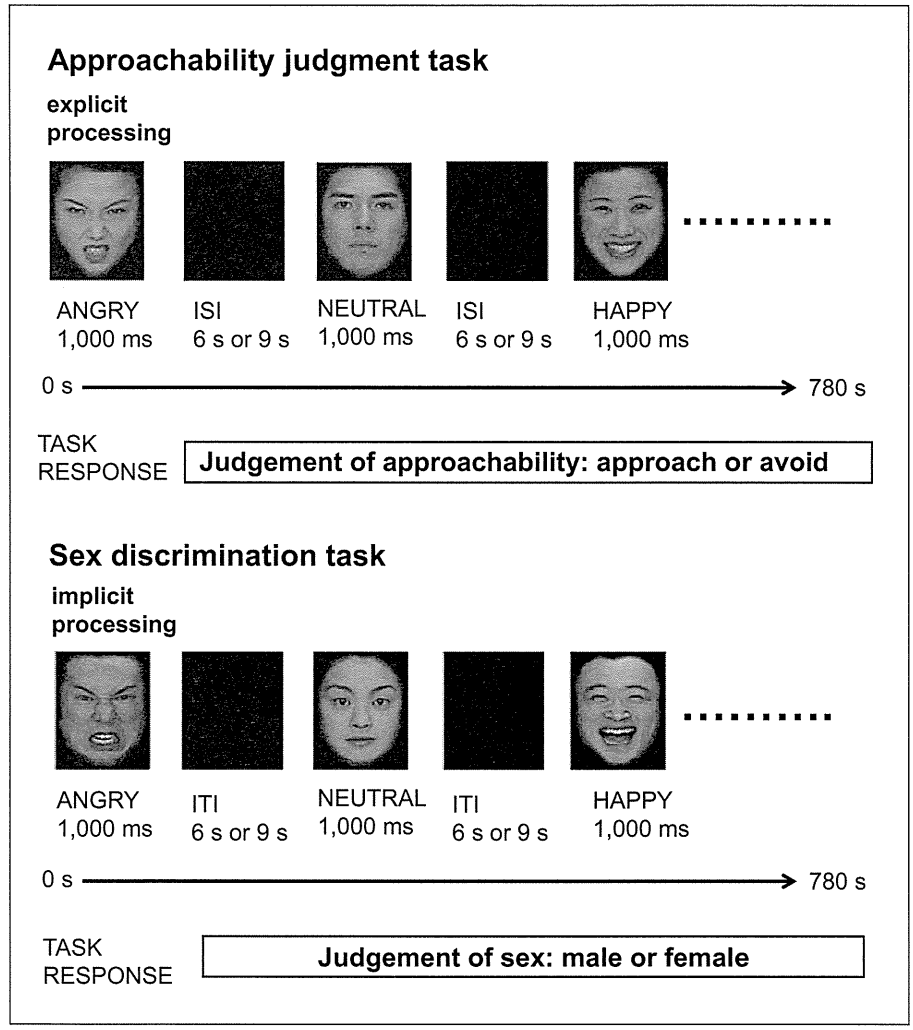

Fig. 1. Schematic of facial stimuli and task paradigm during fMRI.

pants, all of who were naïve to the facial stimuli used. Participants received course credit for their participation.

Stimuli and Task

The event-related fMRI paradigm consisted of two runs (fig. 1); each run presented people with angry, happy and neutral facial expressions derived from the standardized ATR facial expression image database [35]. A stimulus here is defined as the presentation of a face for 100 ms. The faces did not feature hair or jewelry cues, and were oriented to maximize interstimulus alignment of eyes and mouth. For each of the 30 subjects, exactly the same set of faces in exactly the same order was presented. Thirty-six stimuli were used in total: 12 angry, 12 happy and 12 neutral faces. The faces with the same identities and expressions were presented three times in one run. Stimulus order was random across the session.

Each interstimulus interval (ISI) was randomly set to between 6 and 9 s. With each stimulus being presented for 100 ms, the total run time was 13 min, on average. A black screen was presented during the ISI. All stimuli were presented using a back-projection system.

During one of the two runs, participants were instructed to decide whether they would 'approach' or 'avoid' the actor in the picture (approachability judgment task). In the other run, subjects were asked to identify the sex of each actor (sex discrimination task). Presentation order of the two runs was counterbalanced across participants. A fiber optic response box was used to record participant judgments [and reaction times (RTs)] for each stimulus: left button for approach/male response and right button for avoid/female response. After scanning, participants undertook a self-paced task in which they rated all the faces on a scale of approachability from 1 (high approachability) to 9 (high unapproachability).

Questionnaires

Volunteers had completed the Spielberger STAI-T [30] before the fMRI session. In our study, the TAs ranged from 29 to 63 (mean ± SD: 46.60 ± 10.06).

Image Acquisition

fMRI scans were performed with a MAGNEX ECLIPSE 1.5 T Power Drive 250 (Shimadzu, Japan). A time-course series of 360

volumes was acquired with T_2-weighted, gradient echo, echo planar imaging sequences. Each volume consisted of 28 slices, and the thickness of each slice was 4.0 mm with no gap, encompassing the entire brain. The interval between two successive acquisitions of the same image (repetition time, TR) was 3,000 ms, the echo time (TE) was 55 ms and the flip angle was 90°. The field of view was 256 mm and the matrix size was 64 × 64, giving voxel dimensions of 4.0 × 4.0 × 4.0 mm. After functional MRI scanning, structural scans were acquired using a T_1-weighted gradient echo pulse sequence (TR = 12 ms, TE = 4.5 ms, flip angle = 20°, field of view = 256 mm and voxel dimensions 1.0 × 1.0 × 1.0 mm), which facilitated localization and coregistration of the functional data.

Behavioral Analysis

Accuracy of sex discrimination judgments, rates of avoidance choice RTs and mean approachability scores were analyzed using one- and two-way repeated-measures analyses of variance (ANOVAs) along with the Tukey test for post hoc comparisons, using SPSS software. A probability level of $p < 0.05$ was considered statistically significant. All data presented in the text are expressed as (means ± SD). In addition, difference scores for sex discrimination, avoidance scores, RTs and mean approachability were calculated by subtracting averaged performance scores for happy trials for each participant from their corresponding angry and neutral averages. Because neutral faces tend to be recognized as threatening or ambiguous, activating neural responses within the amygdala [36–38], and happy faces are typically judged to be more approachable compared to all other emotions [13, 37, 39], we used happy faces as the baseline condition.

Item-Based Analysis

In order to elucidate the effects of facial expression on consistent response, we conducted an item-based analysis of the relationship between the facial expression and the response rate for consistent discrimination of sex and judgments of approachability over all 3 trials. For each facial stimulus, we calculated the mean rate of consistent approachability and gender decision among the thirty participants. These rates were analyzed using one-way repeated-measures ANOVA. A probability level of $p < 0.05$ was considered statistically significant. All data presented in the text are expressed as mean ± SD.

fMRI Analysis

Datasets from all 30 participants met our criteria for high quality and scan stability with minimum motion correction (<2 mm or 2 degrees displacement in any of the six motion parameters) and were subsequently included in the fMRI analyses. Residual movement was modeled as a regressor of no interest. Functional brain analysis depicting the cognitive subtraction between the presentations of angry or neutral expressions and happy expressions was performed using Statistical Parametric Mapping 5 (SPM5) software, according to standard procedures [40, 41]. After excluding the first three 'dummy' volumes, the remaining 357 volumes were used for the statistical analysis. Images were corrected for motion and realigned with the first scan of the session, which served as the reference. The T_1 anatomical images were coregistered to the first functional image for each participant and aligned to a standard stereotaxic space, using the Montreal Neurological Institute (MNI) T_1 template in SPM5. A calculated nonlinear transformation was applied to all functional images for spatial normalization. Finally, the functional MRIs were smoothed with an 8-mm full-width, half-maximum Gaussian filter. The fMRI response was temporally filtered using a high-pass filter of 128 Hz to minimize scanner drift. The result from the filtering was modeled using a canonical hemodynamic response function with its temporal and dispersion derivatives. Using both derivatives in addition to the canonical HRF allowed us to characterize HRFs with late-onset or longer duration.

Data were analyzed using a general linear model for each voxel in a two-stage random effects procedure. First, regions of activation common to all unapproachable conditions were determined using a whole-brain conjunction analysis [42] of the angry minus happy (AH) faces and neutral minus happy (NH) faces during sex discrimination as well as the AH and NH faces during approachability judgments. We used happy faces as the baseline as was done for the behavioral analysis. Second, a whole-brain ANOVA with task and emotion as within-subject factors was performed to identify differential activity between brain regions. We focused on the bilateral amygdala as a test of our hypothesis. We report predicted regions within amygdala surviving a threshold of $p < 0.005$ uncorrected with an extent threshold of 5 contiguous voxels. Consistent with the previous studies [43–46], because the activation of the amygdala has been relatively difficult to detect [47, 48], we use the less conservative threshold. In addition, we descriptively report activations outside of the amygdala regions of interest (ROIs) that survived a threshold of $p < 0.001$ uncorrected with an extent threshold of 30 contiguous voxels [49]. Moreover, small volume corrections were applied to the amygdala using an Anatomical Automatic Labeling Atlas-based mask [50]. The amygdala mask was created by the WFU PickAtlas [51]. Entire volume corrections were also applied to the significantly activated regions outside of the amygdala ROIs. We described significant results of them complementarily. Activations are reported in standard MNI space. An identification of resulting brain structures was ascertained by using Talairach Daemon client (http://www.talairach.org). The participant-specific parameter estimates at these locations were extracted for each face contrast from the significant clusters of peak activation, using the eigenvariate function in SPM5 and further examined by two-way repeated-measures ANOVA analyses, using the SPSS software package.

Correlation Analyses

To examine a possible correlation between the amygdala activity during the rating of approachability and the participant's potential-threat sensitivity, a Pearson's correlation analysis was conducted between the TA and the signal change within the amygdala. To provide data that might generate further hypotheses, we also conducted correlation analyses using the TA, sex discrimination difference, avoidance score differences, RT differences, mean approachability differences and the signal change within the amygdala and that within other activated areas. These fMRI signals were extracted from the significant clusters of the SPM ANOVA analysis. The significance level for the correlations was set at $p < 0.05$.

Results

Behavioral Data

A one-way repeated-measures ANOVA was performed on the accuracy scores for sex discrimination of

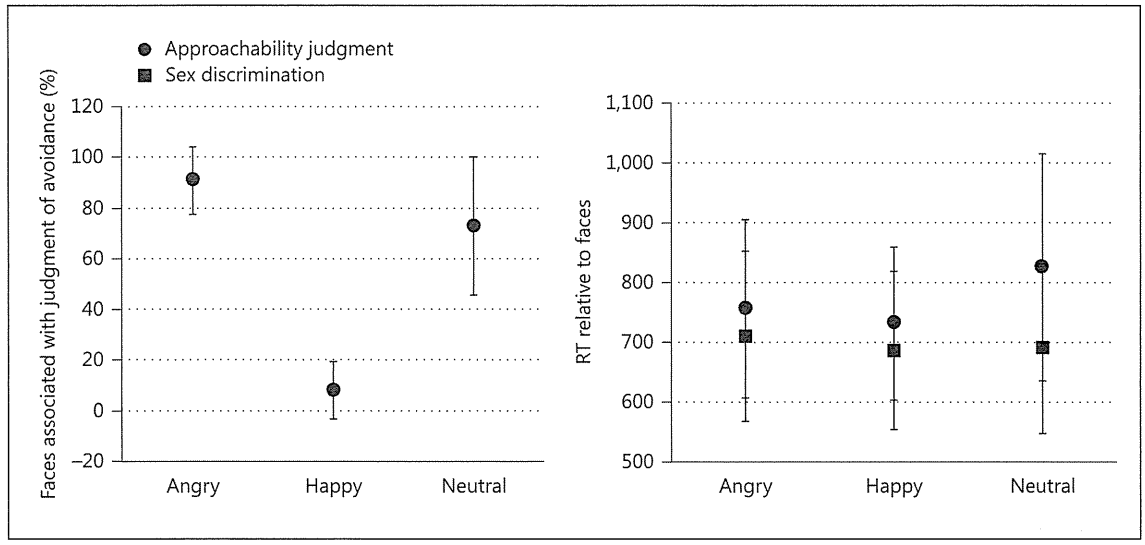

Fig. 2. Plots showing the number of faces associated with avoidance judgments (as percentage of total) during the approachability judgment task (**a**) and RT during the approachability judgment and sex discrimination tasks (**b**). See text for statistics.

faces. There was no significant main effect of face type, $F(2, 58) = 0.8$, $p = 0.423$. Accuracy scores (±SD) for each face type were 89.8 ± 11.7% for angry faces, 90.2 ± 9.8% for happy faces and 91.3 ± 10.3% for neutral faces.

There was an effect of emotional expression on the number of faces that participants judged they would avoid, $F(2, 58) = 152.0$, $p < 0.001$. Post hoc analysis showed that participants judged that they would avoid a significantly lower number of happy faces when compared to neutral and angry faces (both $p < 0.001$). The number of angry faces that participants judged they would avoid was greater than the number of neutral faces associated with a similar judgment ($p = 0.001$; fig. 2). The number of faces associated with avoidance judgments (as a percentage of the total) during the approachability judgment task was 88.6 ± 19.0% for angry faces, 11.5 ± 20.6% for happy faces and 72.8 ± 27.2% for neutral faces.

A 2 (task) × 3 (face type) repeated-measures ANOVA was performed on the RTs for face judgments. There were main effects of task and face type, and the task by face type interaction was also significant (all $p < 0.001$). Post hoc analysis indicated greater RTs during approachability judgments than during sex discrimination, for all face types (all $p < 0.01$). Furthermore, while RTs were greater for angry compared to neutral and happy faces during sex discrimination (all $p < 0.04$), RTs were greater for neutral as compared to happy and angry faces during approachability judgments (all $p < 0.001$; fig. 2).

A one-way repeated-measures ANOVA was performed on the approachability scores. There was a significant main effect of face type, $F(2, 58) = 330.4$, $p < 0.001$. Mean approachability scores (± SD) for each face type were 7.922 ± 0.822 for angry faces, 2.272 ± 0.755 for happy faces and 5.330 ± 0.787 for neutral faces.

Item-Based Analysis

A one-way repeated-measures ANOVA was performed on the rates of consistent response for sex discrimination of faces. There was no significant main effect of face type, $F(2, 22) = 0.1$, $p = 0.916$. Consistent response rates (±SD) for each face type were 83.6 ± 10.6% for angry faces, 82.5 ± 15.4% for happy faces and 83.3 ± 13.9% for neutral faces.

There was a significant main effect of face type on the rates of consistent response for approachability judgment for faces, $F(2, 22) = 15.4$, $p < 0.001$. Consistent response rates (±SD) for each face type were 86.4 ± 5.0% for angry faces, 81.9 ± 5.6% for happy faces and 68.9 ± 11.0% for neutral faces. Neutral faces elicited less consistent responses within participants, suggesting the apparent effects of ambiguity on the decision.

Brain Activation

ANOVA Analyses

Linear contrasts were performed to produce SPMs of the main effect of task (sex or approachability judg-

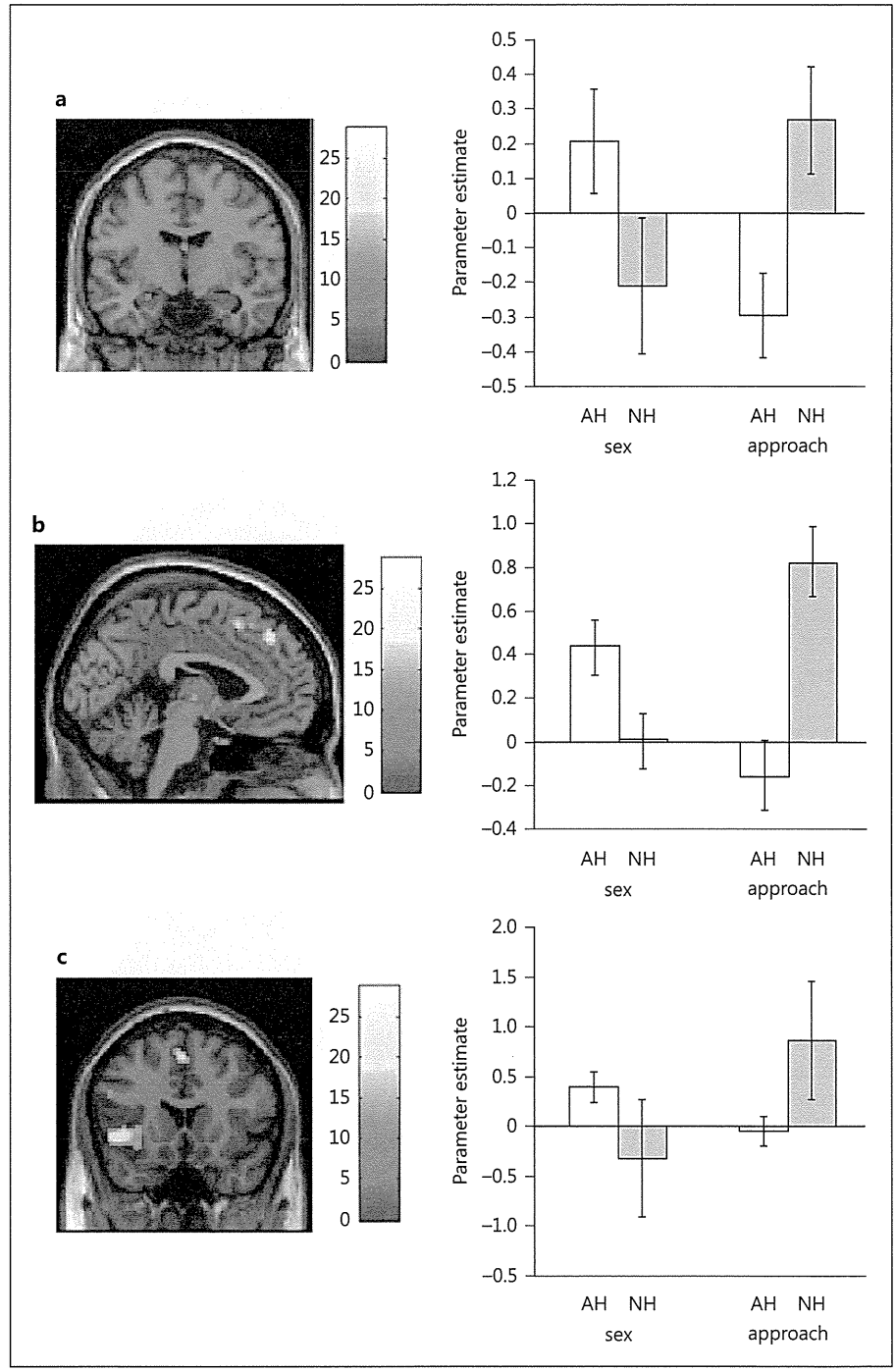

Fig. 3. a Regions showing the interaction effect of task and face on the activation magnitude within the left amygdala. **b** Regions showing the interaction effect on the activation magnitude within the left medial frontal gyrus. **c** Regions showing the interaction effect on the activation magnitude within the left inferior frontal gyrus. Mean participant-specific parameter estimates for activity in a significant cluster including the peak coordinate. AH = Angry versus happy condition; approach = approachability judgment; NH = neutral versus happy condition; sex = sex discrimination.

ment), the main effect of face type (AH or NH) and the interaction between these two factors. An ANOVA analysis revealed that the contrast pertaining to the interaction of task and face type demonstrated several areas of activation within the left amygdala (fig. 3a; table 1), the medial (fig. 3b; table 1) and inferior, middle frontal gyri (fig. 3c; table 1) and the thalamus (table 1). The interaction on amygdala activation survived FWE correction for the AAL-based amygdala mask (voxels = 1, $p < 0.05$). In addition, the interaction on medial frontal gyrus activation survived FWE correction for the entire brain (voxels = 4, $p < 0.05$). The significant main

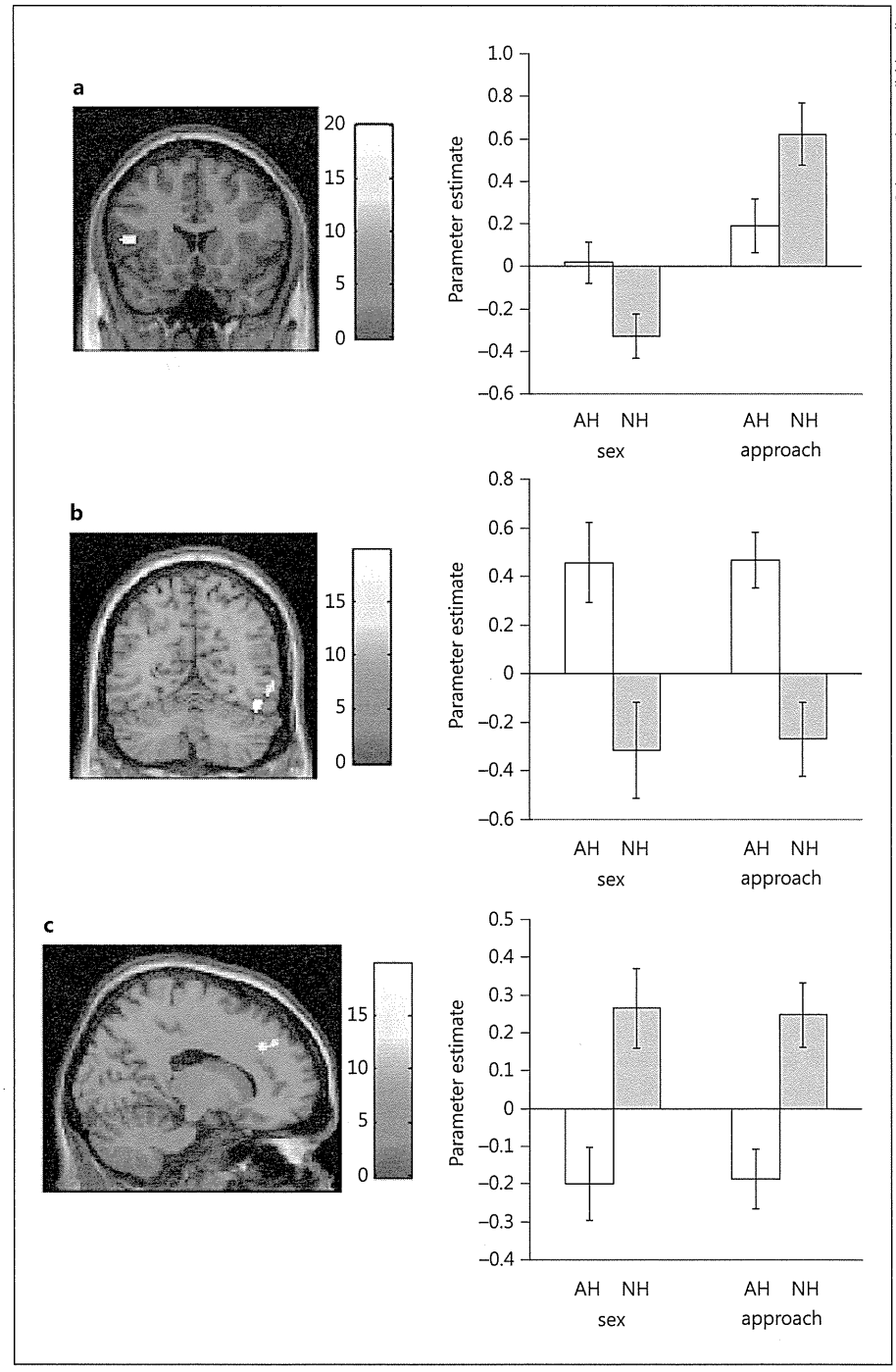

Fig. 4. a Regions showing the main effect of task on the activation magnitude within the left precentral and inferior frontal gyri. **b** Regions showing the main effect of face on the activation magnitude within the right fusiform gyrus. **c** Regions showing the main effect of face on the activation magnitude within the right inferior frontal gyrus. Mean participant-specific parameter estimates for activity in a significant cluster including the peak coordinate. AH = Angry versus happy condition; approach = approachability judgment; NH = neutral versus happy condition; sex = sex discrimination.

effect of task was present in the left prefrontal and inferior frontal gyri (fig. 4a; table 1). The significant main effect of face type was present both in the right fusiform and inferior temporal gyri (fig. 4b; table 1) and in the right medial frontal and superior frontal gyri (fig. 4c; table 1). While angry faces elicited greater fusiform gyrus activity, neutral faces elicited greater medial frontal gyrus activity.

The SPSS ANOVA analysis about neural activation within the left amygdala, the medial and inferior, middle frontal gyri and thalamus confirmed significant task by face type interactions (all $p \leq 0.002$). The ANOVA about

Table 1. ANOVA analysis of canonical HRF during judgements of sex and approachability

Brain region	Side	Voxels	x[a]	y[a]	z[a]	Z score	Effect
Task by face type interaction							
AMG*	L	5	−26	−8	−18	2.88	sex: AH>NH
MeFG	L	149	−2	40	42	4.92	approach: NH>AH
IFG	L	482	−44	18	−4	4.55	
IFG	L		−36	22	−6	4.29	
MiFG	L		−44	36	−4	3.52	
MeFG	L	100	0	18	50	4.00	
MeFG	L		−4	26	52	3.59	
Thalamus	R	33	4	−14	0	3.96	
IFG	R	44	48	24	16	3.70	
IFG	L	33	−50	20	24	3.50	
IFG	L	31	−48	32	16	3.47	
Main effect of task							
PG	L	89	−48	18	10	4.14	approach>sex
IFG	L		−48	22	−4	3.28	
Main effect of face type							
FG	R	129	46	−60	−18	4.11	AH>NH
ITG	R		56	−56	−8	3.55	
ITG	R		52	−64	−6	3.45	
MeFG	R	47	16	34	34	4.00	NH>AH
SFG	R		16	42	36	3.41	

All values $p < 0.001$. * $p < 0.005$ uncorrected.

AMG = amygdala; approach = approachability judgment; FG = fusiform gyrus; IFG = inferior frontal gyrus; ITG = inferior temporal gyrus; L = left; MeFG = medial frontal gyrus; MiFG = middle frontal gyrus; PG = precentral gyrus; R = right; sex = sex discrimination; SFG = superior frontal gyrus.

[a] MNI coordinates referring the center of gravity of the cluster.

neural activation within the left precentral and inferior frontal gyri confirmed a significant main effect of task (all $p < 0.001$). In addition, the ANOVA about neural activation within the right fusiform and right medial frontal gyri confirmed a significant main effect of face (all $p < 0.001$).

Relationships between Psychological/Behavioral Data and Activation within the Amygdala and Other Areas

Under approachability judgment, during the presentations of neutral versus happy faces, TA was positively correlated with activation in the left amygdala ($r = 0.376$, $p = 0.041$; fig. 5a). When the one outlier was removed, more robust significance was found in the correlation between TA and amygdala activity ($r = 0.437$, $p = 0.018$). During the presentations of angry versus happy faces, RT difference was positively correlated with activation in the left medial [(−2, 40, 42), $r = 0.508$, $p = 0.004$] (fig. 5b) and inferior frontal gyri [(−44, 18, −4), $r = 0.384$, $p = 0.036$].

Under sex discrimination, during the presentations of angry versus happy faces, mean approachability difference was negatively correlated with activation in the left medial frontal gyrus [(−2, 40, 42), $r = -0.481$, $p = 0.007$; fig. 5c]. Moreover, the accuracy score difference was negatively correlated with activation in the right fusiform gyrus ($r = -0.381$, $p = 0.038$; fig. 5d). For the presentations of neutral versus happy faces, there were no significant correlations among these variables.

Discussion

We investigated the neural substrates underlying implicit and explicit evaluation of approachability of faces, using faces with several different expressions. We also intended to establish whether there was a significant relationship between brain region activation, task performance and participant threat sensitivity. Ours appears to be the first study to reveal specific involvement of the amygdala in explicit approachability judgments of ambiguous stimuli and the relationship between such judgments and TA.

Participants took longer to respond during sex discrimination of angry faces, as well as during approachability judgments of neutral faces. In addition, neutral faces elicited more inconsistent responses from participants only during approachability judgment. These behavioral data suggest increased processing of angry faces due to the distracting effects of such affect on sex discrimination, and increased processing of neutral faces associated with greater ambiguity during approachability judgments. Consistent with the behavioral results, the neurobiological analysis showed that the left amygdala, the medial, inferior and middle frontal gyri and the thalamus were activated by angry faces during sex discrimination, with the same structures being activated by neutral faces during approachability judgments. Because activity in these structures has been consistently related to emotional face processing [52, 53], neural activation within this circuit may contribute to the decoding and integration of facial information, with such information being subsequently used in various judgments such as approachability.

Interestingly, we found the interaction between task and face valence within these structures including the amygdala was a stronger response to angry in the im-

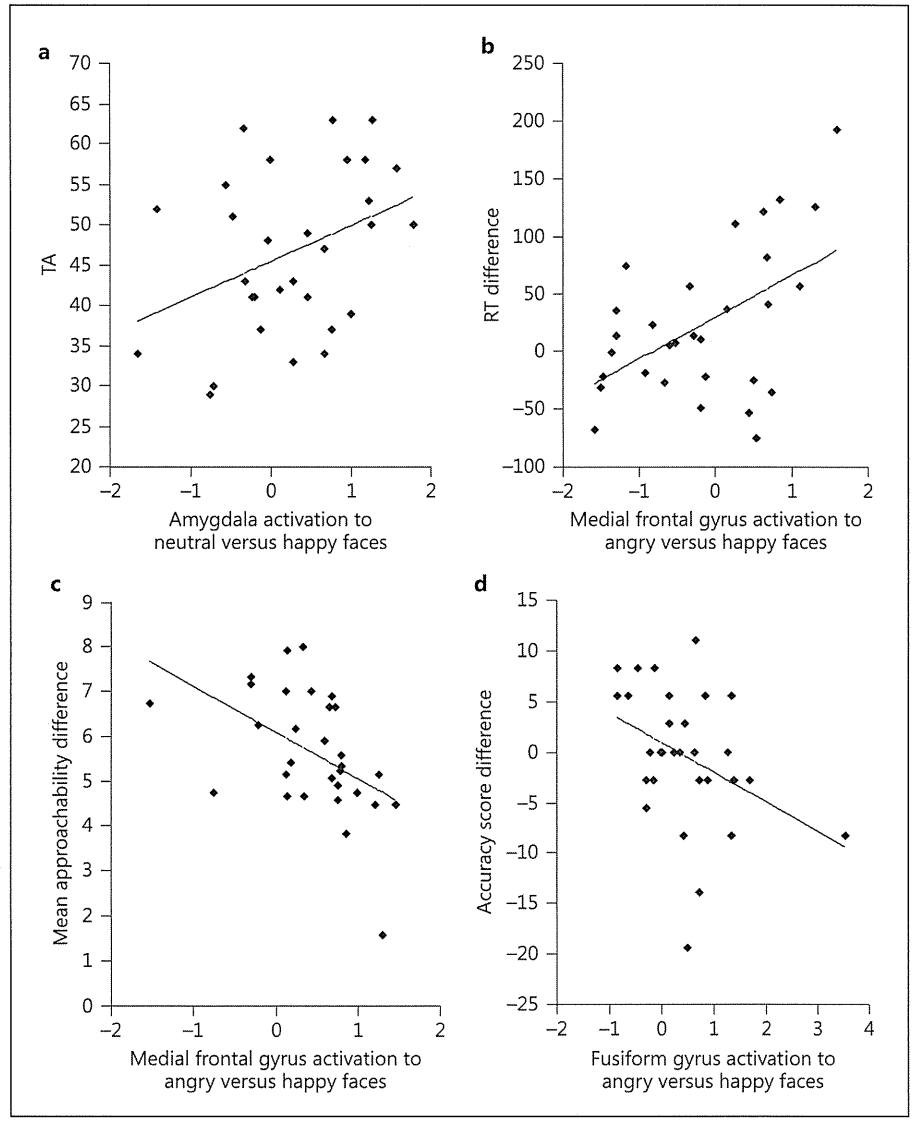

Fig. 5. a Plot showing the degree of correlation of TA with the activation magnitude within the left amygdala in response to neutral compared with happy faces during approachability judgment. **b** Plot showing the degree of correlation of RT difference with the activation magnitude within the left medial frontal gyrus in response to angry compared with happy faces during approachability judgment. **c** Plot showing the degree of correlation of mean approachability difference with the activation magnitude within the left medial frontal gyrus in response to angry compared with happy faces during gender discrimination. **d** Plot showing the degree of correlation of accuracy score difference with the activation magnitude within the right fusiform gyrus in response to angry compared with happy faces during gender discrimination.

plicit condition, but stronger to neutral in the explicit condition. The difficulty of neutral stimuli in attributing emotional significance to a facial expression may in turn lead to heightened vigilance, as well as to increased amygdala activity [15, 54, 55]. Our results were consistent with previous studies, indicating that the greater ambiguity of facial threat stimuli elicited greater amygdala activity [15, 56, 57]. Overall, we concluded that the neural response to neutral faces during approachability judgments was greater than the responses to the other face types. When judging approachability of faces, the left amygdala might take the critical role of preparing for, orienting around and evaluating the target faces. We also found an increased activation of the left precentral and inferior frontal gyri during approachability judgment compared with that during sex discrimination. Consistent with the previous study [58], this finding suggests a critical role for these structures in approachability rating that is independent of face type. These neural areas are associated with sensation integration and behavior planning [59, 60], and may play an important role in precipitating approachability decisions. Moreover, we found the main effect of face type in neural activation within the right fusiform gyrus and medial frontal gyrus. Independent of task condition, while the former responded to angry faces, the latter responded to neutral faces, suggesting the existence of expression-specific activation within both areas.

In addition, TA was positively correlated with left amygdala response to neutral faces during approachability judgment, suggesting that participants who had reported higher TA tended to have higher amygdala reactivity. Our result supports the notion that the left amygdala is more responsive to explicit evaluative processing [61–64]. That is to say, it is possible that the heightened left amygdala activity observed during approachability judgment may be due to a greater sensitivity or evaluative ability associated with explicit processing of socially ambiguous stimuli in high TA subjects. By presenting facial stimuli for 200 ms in a block design, Somerville et al. [37] observed a positive relationship between state anxiety and neural response within the bilateral amygdala to neutral faces during passive viewing. Our stimulus paradigm and task instructions might elicit more evaluative and analytical processing, leading to the observed left lateralized activation, compared with previous work. We found a significant relationship between TA and ventral amygdala activity, not for angry but for neutral faces, despite the threatening meaning of the former stimuli; this suggests the possibility that the psychological construct of TA includes not only sensitivity but also a predictive process for potential threat. This result is also consistent with earlier work that reported that the ventral amygdala is heavily involved in coding signals of ambiguity and responds more to an ambiguous or probable threat [22, 54]. Many studies found that individual levels of anxiety only influence amygdala activities to ambiguous or subthreshold threat information, but not to apparent or suprathreshold threat information [18–22]. These results parallel our findings that TA influences ventral amygdala activity in response to ambiguous, neutral stimuli. In the Introduction, according to the traditional theory of anxiety, we defined threat sensitivity as the tendency to recognize either an ambiguous or a potential threat; in humans, this tendency is considered to be related to anxiety [7, 8]. Our findings about amygdala reactivity support, at least in part, the possible link between the classic theory of anxiety and the neural functioning within the amygdala during the rating of approachability.

Beyond the relationships between amygdala activity and other variables, we found several significant correlations. During the sex discrimination task, there was a significant negative correlation between mean approachability differences between angry and happy faces and activation of the left medial frontal gyrus. Recently, it was proposed that the medial frontal cortex contains cortical relay nodes that afford the attribution of self-relevant, implicit meaning that subserves egocentric 'value' judgments, which are critical for self-control [65]. Avoidant behavioral tendencies might serve to weaken the self-relevant meaning attribution function. Moreover, the accuracy of gender discrimination in angry faces was negatively correlated with the right fusiform gyrus activation. Considering about the expression-specific activation revealed by ANOVA analysis, it is understandable that participants with higher activation of the fusiform gyrus might be more distracted by the angry expressions, resulting in lower scores in sex discrimination. During approachability judgment, there was a significant positive correlation between RT differences and activation of the left medial and inferior frontal gyri in response to angry faces. These enhanced activations might afford self-control and risk-aversion, resulting in delayed responses in assessing approachability.

Our study displays several limitations. First, it is noteworthy that TA scores were relatively high among our subjects, compared with the normative American adults in the test manual [66]. This finding has consistently emerged in Japanese samples, possibly due to the Japanese tendency toward suppressing expression of positive feelings [67, 68]. It is thus possible that TA could show a different relationship with amygdala response in European or North American participants. Such studies would provide important data for predictions concerning application of the present paradigm to the study of cultural differences in anxiety. Second, because we used no imaging method for magnetic field inhomogeneity within the medial temporal lobe, such as selection of voxel size and slice orientation [69], we cannot rule out the possibility that our results were influenced by susceptibility effects within the amygdala. Third, we investigated brain response by the slow presentation of stimuli with an ISI of 6–9 s. According to the previous technical report [70], we would maybe find stronger effects by using a more rapid presentation of stimuli; further studies using such a method could provide support for our results. Fourth, we used happy faces as a baseline. We did so because neutral faces tended to be recognized as 'threatening' or 'ambiguous'. Taking previous studies and our results together, we conclude that the amygdala response to neutral faces reflects the individual level of reactivity to an ambiguous threat. However, based on the current data only, the neurophysiological meaning of the different neural activation when a happy face is presented to the subject versus a neutral face remains unclear. We need to verify our results by using other stimuli (i.e. scrambled faces or fixation cross) as a baseline. Fifth, without correction for multiple comparisons, some of our data could reflect spurious activation

and correlation among variables. Thus, caution should be used while interpreting our findings until the results have been replicated.

In conclusion, our findings extend a proposed model of social cognition by highlighting the functional engagement of the amygdala in the explicit judgment of approachability, which is thought to reflect an individual's ambiguous threat sensitivity. Neural responses during approachability judgments varied with task instructions and facial stimuli, reflecting complex human responses to the social environment. Because fMRI does not differentiate between function-specific processing and neuromodulation, between bottom-up and top-down signals, and occasionally between excitation and inhibition [71], to support our conclusions we should conduct a multimodal study that includes electrophysiological measurements of brain activity.

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References

1 Todorov A: Evaluating faces on trustworthiness: an extension of systems for recognition of emotions signaling approach/avoidance behaviors. Ann NY Acad Sci 2008;1124:208–224.

2 Calder AJ, Young AW: Understanding the recognition of facial identity and facial expression. Nat Rev Neurosci 2005;6:641–651.

3 Tsao DY, Livingstone MS: Mechanisms of face perception. Annu Rev Neurosci 2008;31:411–437.

4 Adolphs R, Tranel D, Damasio AR: The human amygdala in social judgment. Nature 1998;393:470–474.

5 Oosterhof NN, Todorov A: The functional basis of face evaluation. Proc Natl Acad Sci USA 2008;105:11087–11092.

6 Leopold DA, Rhodes G: A comparative view of face perception. J Comp Psychol 2010;124:233–251.

7 Gray JA, McNaughton N: The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-Hippocampal System. Oxford, Oxford University Press, 2000, pp xviii, 424 p. ill. 424 cm.

8 McNaughton N, Corr PJ: A two-dimensional neuropsychology of defense: fear/anxiety and defensive distance. Neurosci Biobehav Rev 2004;28:285–305.

9 Todorov A, Engell AD: The role of the amygdala in implicit evaluation of emotionally neutral faces. Soc Cogn Affect Neurosci 2008;3:303–312.

10 Oosterhof NN, Todorov A: Shared perceptual basis of emotional expressions and trustworthiness impressions from faces. Emotion 2009;9:128–133.

11 Willis J, Todorov A: First impressions: making up your mind after a 100-ms exposure to a face. Psychol Sci 2006;17:592–598.

12 Winston JS, Strange BA, O'Doherty J, Dolan RJ: Automatic and intentional brain responses during evaluation of trustworthiness of faces. Nat Neurosci 2002;5:277–283.

13 Porter MA, Coltheart M, Langdon R: The neuropsychological basis of hypersociability in Williams and Down syndrome. Neuropsychologia 2007;45:2839–2849.

14 Marsh AA, Ambady N, Kleck RE: The effects of fear and anger facial expressions on approach- and avoidance-related behaviors. Emotion 2005;5:119–124.

15 Blasi G, Hariri AR, Alce G, Taurisano P, Sambataro F, Das S, Bertolino A, Weinberger DR, Mattay VS: Preferential amygdala reactivity to the negative assessment of neutral faces. Biol Psychiatry 2009;66:847–853.

16 Adolphs R: Recognizing emotion from facial expressions: psychological and neurological mechanisms. Behav Cogn Neurosci Rev 2002;1:21–62.

17 Adolphs R: Investigating the cognitive neuroscience of social behavior. Neuropsychologia 2003;41:119–126.

18 Bishop SJ, Jenkins R, Lawrence AD: Neural processing of fearful faces: effects of anxiety are gated by perceptual capacity limitations. Cereb Cortex 2007;17:1595–1603.

19 Bishop SJ, Duncan J, Lawrence AD: State anxiety modulation of the amygdala response to unattended threat-related stimuli. J Neurosci 2004;24:10364–10368.

20 Ewbank MP, Lawrence AD, Passamonti L, Keane J, Peers PV, Calder AJ: Anxiety predicts a differential neural response to attended and unattended facial signals of anger and fear. Neuroimage 2009;44:1144–1151.

21 Ewbank MP, Fox E, Calder AJ: The interaction between gaze and facial expression in the amygdala and extended amygdala is modulated by anxiety. Front Hum Neurosci 2010;4:56.

22 Etkin A, Klemenhagen KC, Dudman JT, Rogan MT, Hen R, Kandel ER, Hirsch J: Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. Neuron 2004;44:1043–1055.

23 Fox E: Processing emotional facial expressions: the role of anxiety and awareness. Cogn Affect Behav Neurosci 2002;2:52–63.

24 Perkins AM, Corr PJ: Reactions to threat and personality: psychometric differentiation of intensity and direction dimensions of human defensive behaviour. Behav Brain Res 2006;169:21–28.

25 Carré JM, Fisher PM, Manuck SB, Hariri AR: Interaction between trait anxiety and trait anger predict amygdala reactivity to angry facial expressions in men but not women. Soc Cogn Affect Neurosci 2012;7:213–221.

26 Indovina I, Robbins TW, Nunez-Elizalde AO, Dunn BD, Bishop SJ: Fear-conditioning mechanisms associated with trait vulnerability to anxiety in humans. Neuron 2011;69:563–571.

27 Bishop SJ: Neural mechanisms underlying selective attention to threat. Ann N Y Acad Sci 2008;1129:141–152.

28 Bishop SJ: Trait anxiety and impoverished prefrontal control of attention. Nat Neurosci 2009;12:92–98.

29 Somerville LH, Whalen PJ, Kelley WM: Human bed nucleus of the stria terminalis indexes hypervigilant threat monitoring. Biol Psychiatry 2010;68:416–424.

30 Spielberger CD: State-Trait Anxiety Inventory (STAI). Menlo Park, Mind Garden, 1983.

31 Sprengelmeyer R, Rausch M, Eysel UT, Przuntek H: Neural structures associated with recognition of facial expressions of basic emotions. Proc Biol Sci 1998;265:1927–1931.

32 Morris JS, Frith CD, Perrett DI, Rowland D, Young AW, Calder AJ, Dolan RJ: A differential neural response in the human amygdala to fearful and happy facial expressions. Nature 1996;383:812–815.

33 Baron SG, Gobbini MI, Engell AD, Todorov A: Amygdala and dorsomedial prefrontal cortex responses to appearance-based and behavior-based person impressions. Soc Cogn Affect Neurosci 2011;6:572–581.

34 Willis ML, Palermo R, Burke D, McGrillen K, Miller L: Orbitofrontal cortex lesions result in abnormal social judgements to emotional faces. Neuropsychologia 2010;48:2182–2187.
35 Kamachi M, Bruce V, Mukaida S, Gyoba J, Yoshikawa S, Akamatsu S: Dynamic properties influence the perception of facial expressions. Perception 2001;30:875–887.
36 Iidaka T, Okada T, Murata T, Omori M, Kosaka H, Sadato N, Yonekura Y: Age-related differences in the medial temporal lobe responses to emotional faces as revealed by fMRI. Hippocampus 2002;12:352–362.
37 Somerville LH, Kim H, Johnstone T, Alexander AL, Whalen PJ: Human amygdala responses during presentation of happy and neutral faces: correlations with state anxiety. Biol Psychiatry 2004;55:897–903.
38 Wright P, Liu Y: Neutral faces activate the amygdala during identity matching. Neuroimage 2006;29:628–636.
39 Willis ML, Palermo R, Burke D: Judging approachability on the face of it: the influence of face and body expressions on the perception of approachability. Emotion 2011;11:514–523.
40 Friston KJ, Ashburner J, Poline JB, Frith C, Heather J, Frackowiak RS: Spatial registration and normalization of images. Human Brain Mapping 1995;2:165–189.
41 Friston KJ, Holmes AP, Worsley K, Poline JB, Frith C, Frackowiak RS: Statistical parametric maps in functional imaging: a general approach. Human Brain Mapping 1995;5:189–201.
42 Nichols T, Brett M, Andersson J, Wager T, Poline JB: Valid conjunction inference with the minimum statistic. Neuroimage 2005;25:653–660.
43 Kim JW, Choi EA, Kim JJ, Jeong BS, Kim SE, Ki SW: The role of amygdala during auditory verbal imagery of derogatory appraisals by others. Neurosci Lett 2008;446:1–6.
44 Nomura M, Ohira H, Haneda K, Iidaka T, Sadato N, Okada T, Yonekura Y: Functional association of the amygdala and ventral prefrontal cortex during cognitive evaluation of facial expressions primed by masked angry faces: an event-related fMRI study. Neuroimage 2004;21:352–363.
45 Cremers HR, Demenescu LR, Aleman A, Renken R, van Tol MJ, van der Wee NJ, Veltman DJ, Roelofs K: Neuroticism modulates amygdala-prefrontal connectivity in response to negative emotional facial expressions. Neuroimage 2010;49:963–970.
46 Britton JC, Gold AL, Deckersbach T, Rauch SL: Functional MRI study of specific animal phobia using an event-related emotional counting Stroop paradigm. Depress Anxiety 2009;26:796–805.
47 Irwin W, Davidson RJ, Lowe MJ, Mock BJ, Sorenson JA, Turski PA: Human amygdala activation detected with echo-planar functional magnetic resonance imaging. Neuroreport 1996;7:1765–1769.
48 Schneider F, Habel U, Kessler C, Salloum JB, Posse S: Gender differences in regional cerebral activity during sadness. Hum Brain Mapp 2000;9:226–238.
49 Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC: Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn Reson Med 1995;33:636–647.
50 Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M: Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002;15:273–289.
51 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.
52 Phan KL, Wager T, Taylor SF, Liberzon I: Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 2002;16:331–348.
53 Wager TD, Phan KL, Liberzon I, Taylor SF: Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. Neuroimage 2003;19:513–531.
54 Whalen PJ: Fear, vigilance, and ambiguity: initial neuroimaging studies of the human amygdala. Curr Dir Psychol Sci 1998;7:177–188.
55 Rosen JB, Donley MP: Animal studies of amygdala function in fear and uncertainty: relevance to human research. Biol Psychol 2006;73:49–60.
56 Whalen PJ, Shin LM, McInerney SC, Fischer H, Wright CI, Rauch SL: A functional MRI study of human amygdala responses to facial expressions of fear versus anger. Emotion 2001;1:70–83.
57 Adams R, Gordon H, Baird A, Ambady N, Kleck R: Effects of gaze on amygdala sensitivity to anger and fear faces. Science 2003;300:1536.
58 Hall J, Whalley HC, McKirdy JW, Sprengelmeyer R, Santos IM, Donaldson DI, McGonigle DJ, Young AW, McIntosh AM, Johnstone EC, Lawrie SM: A common neural system mediating two different forms of social judgement. Psychol Med 2010;40:1183–1192.
59 Catani M, Dell'acqua F, Vergani F, Malik F, Hodge H, Roy P, Valabregue R, Thiebaut de Schotten M: Short frontal lobe connections of the human brain. Cortex 2012;48:273–291.
60 Fincham JM, Carter CS, van Veen V, Stenger VA, Anderson JR: Neural mechanisms of planning: a computational analysis using event-related fMRI. Proc Natl Acad Sci USA 2002;99:3346–3351.
61 Markowitsch HJ: Differential contribution of right and left amygdala to affective information processing. Behav Neurol 1998;11:233–244.
62 Morris JS, Ohman A, Dolan RJ: Conscious and unconscious emotional learning in the human amygdala. Nature 1998;393:467–470.
63 Funayama ES, Grillon C, Davis M, Phelps EA: A double dissociation in the affective modulation of startle in humans: effects of unilateral temporal lobectomy. J Cogn Neurosci 2001;13:721–729.
64 Phelps EA: Emotion and cognition: Insights from studies of the human amygdala. Annu Rev Psychol 2006;57:27–53.
65 Seitz RJ, Franz M, Azari NP: Value judgments and self-control of action: the role of the medial frontal cortex. Brain Res Rev 2009;60:368–378.
66 Spielberger C, Gorsuch R: Manual for the State-Trait Anxiety Inventory (Form Y). Palo Alto, Consulting Psychologists, 1983, p 36.
67 Iwata N, Mishima N, Shimizu T, Mizoue T, Fukuhara M, Hidano T, Spielberger CD: The Japanese adaptation of the STAI Form Y in Japanese working adults – the presence or absence of anxiety. Ind Health 1998;36:8–13.
68 Iwata N, Higuchi HR: Responses of Japanese and American university students to the STAI items that assess the presence or absence of anxiety. J Pers Assess 2000;74:48–62.
69 Chen NK, Dickey CC, Yoo SS, Guttmann CR, Panych LP: Selection of voxel size and slice orientation for fMRI in the presence of susceptibility field gradients: application to imaging of the amygdala. Neuroimage 2003;19:817–825.
70 Josephs O, Henson RN: Event-related functional magnetic resonance imaging: modelling, inference and optimization. Philos Trans R Soc Lond B Biol Sci 1999;354:1215–1228.
71 Logothetis NK: What we can do and what we cannot do with fMRI. Nature 2008;453:869–878.

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ORIGINAL ARTICLE

Comparisons of short-term efficacy between individual and group cognitive behavioral therapy for primary insomnia

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Abstract

The purpose of this study was to compare the efficacy of individual and group cognitive behavioral therapy for insomnia (CBT-I) in outpatients with primary insomnia diagnosed by DSM-IV-TR. The participants were 20 individually treated (I-CBT-I) and 25 treated in a group therapy format (three to five patients per group) (G-CBT-I), which showed no significant difference regarding demographic variables between groups. The same components of CBT-I stimulus control therapy, sleep restriction therapy, cognitive therapy, and sleep hygiene education were applied on both groups. The short-term outcome (4 weeks after treatment) was measured by sleep logs, actigraphy, the Pittsburgh Sleep Quality Index (PSQI), and the Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS), and was compared between I-CBT-I and G-CBT-I. The results indicated that CBT-I was effective in improving subjective and objective sleep parameters and subjective sleep evaluations for both individual and group treatment. However, I-CBT-I resulted in significantly better improvements over G-CBT-I, in (i) objective and subjective sleep onset latency time, (ii) objective sleep efficacy and moving time during sleeping, (iii) overall sleep quality and duration of actual sleep time in PSQI, (iv) consequences of insomnia, control and predictability of sleep, sleep requirement expectation, and sleep-promoting practices in DBAS. The present study suggested the superiority of I-CBT-I over G-CBT-I in clinical settings, and further evaluations are necessary.

Key words: behavior and cognition, cognitive behavioral therapy for insomnia, insomnia, primary insomnia, psychology.

INTRODUCTION

Primary insomnia, as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. text version (DSM-IV-TR),[1] is the most common type of chronic insomnia and is almost the same concept as psychophysiological insomnia as defined in the *International Classification of Sleep Disorders* 2nd ed. (ICSD-2).[2] Primary insomnia is characterized by morbid fear of insomnia, mental arousal, and heightened somatic tension in bed. Recently, it is been emphasized that cognitive behavioral therapy for insomnia (CBT-I) is effective for primary insomnia patients.[3–6]

The best tested and most commonly used method of delivering CBT-I had been via individualized treatment consisting of one-to-one sessions between a therapist and a single patient (I-CBT-I). As providing the I-CBT-I format is a time-consuming and cost-inefficient form of treatment delivery, the most common alternative delivery format is group therapy (G-CBT-I). However, no one established method of G-CBT-I has been used universally.[5,6] Furthermore, whether I-CBT-I and G-CBT-I are

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equally efficacious is not clear. A previous meta-analysis suggested a modest superiority of I-CBT-T over G-CBT-I.[7] On the other hand, a few clinical trials[8,9] that provided direct comparisons of I-CBT-I and G-CBT-I within the same study mentioned no different outcomes between I-CBT-I and G-CBT-I. They concluded that G-CBT-I represented a cost-effective alternative to I-CBT-I for the management of insomnia. Although G-CBT-I is a popular approach, studies directly comparing the relative efficacy of individual and group formats are limited.[10]

The purpose of this study was to compare the short-term efficacy of I-CBT-I and G-CBT-I with the same treatment components and providers in clinically referred outpatients with primary insomnia in Japan. The primary outcomes were evaluated through subjective and objective sleep parameters, along with subjective sleep evaluations.

METHODS

Study participants

The eligible subjects were sufferers of primary insomnia diagnosed by DSM-IV-TR, with chronic hypnotics use, attending Jikei University Hospital as outpatients, wishing to receive CBT-I. The participants for I-CBT-I consisted of 20 patients, and they participated in a study in 2004 to 2005.[11] From 2009, the authors switched to G-CBT-I. The participants for G-CBT-I consisted of 25 patients divided over eight groups (three to five patients per group) in 2009 to 2011.[12]

The patients were excluded if they: (i) were 20 years of age or younger, (ii) met the DSM-IV-TR criteria for an axis I diagnosis of any psychiatric disorder and/or substance abuse, (iii) required psychotropic medication for psychiatric symptoms, or (iv) had possible sleep apnea syndrome (SAS) as judged from clinical interviews and daytime polysomnography (d-PSG).[13] Each d-PSG was recorded from 14.00 hours to 04.00 hours. The respiratory tracings were evaluated for the presence of apnea (a 10-s or greater cessation of oronasal airflow) or hypopnea (a reduction in the amplitude of the thermistor signal by at least 50% for 10 s or longer, being followed by an electroencephalogram [EEG] arousal). To obtain the AHI (Apnea-Hypopnea Index), the number of apneas + hypopneas/total sleep time (TST, h) was calculated. The authors defined AHI $\geq$ 5 as the possible SAS, or (v) had symptoms suggestive of narcolepsy or restless legs syndrome as judged from clinical interviews.

The participants continued to take any medication already prescribed before enrollment, so as to avoid any effects of medication withdrawal during the treatment. The average daily dosage of hypnotics was calculated by dose equivalence of psychotropic drugs 2006-Version.[14] A total of 53 patients (I-CBT-I: 24, G-CBT-I: 29) gave written informed consent to take part in the present study. During the treatment, however, eight patients (I-CBT-I: 4, G-CBT-I: 4) dropped out at their own request or at the recommendation of their attending physicians. Data from these patients were excluded from the statistical analysis.

Treatment (Table 1)

The authors designed the CBT-I protocols with reference to the method described by Morin[5] and Edinger.[6] The four therapists (all men) conducted CBT-I, and all of them work as a clinical psychiatrist and a certified physician for a Japanese society involved in sleep research. The other authors supervised the contents of the CBT-I. The authors defined the 7 days prior to the first CBT-I session as the pre-treatment period to evaluate sleep-wake cycle of the patients for one week persistently. The post-treatment period was also defined as the first 7 days after the treatment or follow-up period (I-CBT-I: 4

Table 1 Outline of CBT-I protocol

	I-CBT-I	G-CBT-I
Treatment components	Stimulus control, sleep restriction, cognitive restructuring, sleep hygiene education	
No. sessions	Three times 1st session: 60–90 min 2nd/3rd session: 15 min	Two times (lecture and discussion, 60–90 min) plus one individual booster session (10 min)
No. patients per group	Individually	3–5
Type of provider	Psychiatric sleep physician, MD	
Post-treatment evaluation	4 weeks after 1st session	4 weeks after 2nd session

weeks after the first session, G-CBT-I: 4 weeks after second session).

The I-CBT-I protocol was as follows.[11] Just after the pre-treatment period, in the first 60–90-min session, after the introduction of CBT-I, the therapy was started for each individual patient by the same therapists. Thereafter, the patients underwent sessions of 15 min once every 2 weeks during the 4 weeks. A total of three sessions was given to each patient in this study. Four weeks after the first session, post-treatment evaluation was measured.

The G-CBT-I protocol was as follows.[12] Just after the pre-treatment period, in the two-time group sessions (60–90 min, 3–5 patients per group, the interval was one week), patients participated in a lecture by a therapist and a group discussion of CBT-I. In addition, individual booster sessions (once, 10 min) were planned in the 4-week follow-up period, at one week or 2 weeks after the second session. Four weeks after the second session, post-treatment evaluation was measured.

The components of CBT-I were the same in both treatments. These consisted of stimulus control therapy,[5,6] sleep restriction therapy,[5,6] cognitive therapy,[5,6,11,12] and sleep hygiene education.[5,6]

Stimulus control therapy

Stimulus control attempts to break the association between the sleep environment and wakefulness by teaching the patients not to be engaged in activities that might disturb their sleep. The instructions the therapists gave were as follows: (i) go to bed only when becoming sleepy; (ii) do not use the bedroom for anything except sleep or sex; and (iii) get out of bed and go to another room whenever unable to fall asleep over a period of 30 min, and return to bed only when becoming sleepy again.

Sleep restriction therapy

This treatment seeks to increase homeostatic sleep drive through partial sleep deprivation and thereby improve sleep ability. A bedtime and arising time schedule was prescribed in an attempt to improve sleep quality and decrease the time spent awake during the night. Time in bed was reduced in accordance with the total sleep time, as recorded in the sleep logs, and arising time was always fixed. The time the patient went to bed was adjusted on the basis of sleep efficiency. Though the authors were not absolutely strict in our administration of the sleep reduction therapy, combining with stimulus control therapy, the therapists emphasized the importance of spending time in bed only when sleepy.

Cognitive therapy

As mentioned below, the therapists calculated the dissociation between the patients' subjective sleep evaluation from their sleep logs and their objective sleep data measured by an actigraph during the pre-CBT-I period. To facilitate better understanding by the patients, the therapists showed them the results of dissociation between the two parameters as an indicator of sleep state misperception. Subsequently, cognitive therapy was carried out to identify patient-specific incorrect cognition about sleep so that the therapists could correct any dysfunction in this regard.

Sleep hygiene education

Sleep hygiene education included instruction about health practices and environmental factors that can be beneficial for maintaining sufficient sleep, and also details regarding homeostatic drive for sleep, circadian factors, and the effects of drugs and habits prior to sleep.

Measurements

During the pre- and post-treatment periods, the authors conducted measurements including sleep logs, actigraphy, the Pittsburgh Sleep Quality Index (PSQI),[15] and the Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS).[16,17]

Sleep logs

During the pre- and post-treatment periods, patients were asked to complete sleep logs, just after getting up in the morning, for 7 days. Then, we averaged bedtime, rising time, sleep-onset time (SONT), sleep-offset time (SOFT), sleep onset latency time (SOL), total sleep time (TST), and total time in bed (TIB). In principle, bedtime and rising time on the sleep logs were recorded by each patient's family members to increase the objectivity of the data.

Actigraphy

During the pre- and post-treatment periods, patients were required to wear an actigraph (mini motionlogger actigraph; Ambulatory Monitoring, New York, NY, USA) on their non-dominant wrist at all times for 7 days.