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Neural correlates of adaptive social responses to real-life frustrating situations: a functional MRI study

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Abstract

Background: Frustrating situations are encountered daily, and it is necessary to respond in an adaptive fashion. A psychological definition states that adaptive social behaviors are "self-performing" and "contain a solution." The present study investigated the neural correlates of adaptive social responses to frustrating situations by assessing the dimension of causal attribution. Based on attribution theory, internal causality refers to one's aptitudes that cause natural responses in real-life situations, whereas external causality refers to environmental factors, such as experimental conditions, causing such responses. To investigate the issue, we developed a novel approach that assesses causal attribution under experimental conditions. During fMRI scanning, subjects were required to engage in virtual frustrating situations and play the role of protagonists by verbalizing social responses, which were socially adaptive or non-adaptive. After fMRI scanning, the subjects reported their causal attribution index of the psychological reaction to the experimental condition. We performed a correlation analysis between the causal attribution index and brain activity. We hypothesized that the brain region whose activation would have a positive and negative correlation with the self-reported index of the causal attributions would be regarded as neural correlates of internal and external causal attribution of social responses, respectively.

Results: We found a significant negative correlation between external causal attribution and neural responses in the right anterior temporal lobe for adaptive social behaviors.

Conclusion: This region is involved in the integration of emotional and social information. These results suggest that, particularly in adaptive social behavior, the social demands of frustrating situations, which involve external causality, may be integrated by a neural response in the right anterior temporal lobe.

Keywords: Adaptive social behavior, Causal attribution, Anterior temporal lobe, Integration

Background

We often encounter frustrating situations in our social lives. The following situation is an example: You are inputting data into your computer. Suddenly, the screen goes black, and soon after, your colleague holds up a plug and says, "I'm sorry; I accidently unplugged your PC" (Figure 1a, b). Rosenzweig created a model for the verbal responses to such frustrating situations, which was implemented in a widely used questionnaire, the "Picture-Frustration Study" (PF Study) [1,2]. In Rosenzweig's model, verbal responses to the frustrating situation are classified by two factors: the direction and type of aggression [1,2]. The direction of aggression involves requests towards self, another person, and nothing, and the types of aggression include attention to the frustrating event itself, to a cause of the frustrating situation, and to a solution to the frustrating situation.

Social adaptation is a crucial aspect of such social responses. Also in Rosenzweig's model, social adaptation of verbal responses is assessed by the Group Conformity Rating (GCR), which represents the degree to which these

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responses conform to common sense. However, the definition of social adaptation in this model was quite ambiguous, because "common sense" may differ across cultures. One clear definition of adaptation, drawn from coping theory [3,4], is the process used to manage environmental demands and to solve the problem that caused the frustrating situation without putting a burden on the environment. Corresponding to this definition [3,4], an adaptive response in Rosenzweig's model is one with a request to self (self-performing) that contains a solution [1]. In the above-mentioned example of a frustrating situation, verbal responses such as "You need to re-input the data" (other-performing) or "I should have saved the data" (no solution) are non-adaptive because they do not manage the environmental demand to finish the data input (containing a solution), nor do they avoid putting a burden on the environment (self-performing). In this case, a verbal response such as "I will input the data again" is an adaptive social response because it suggests self-performing behavior (i.e., action by one's self) and manages the environmental demands with a solution (i.e., to input the data again).

Causal attribution is another key dimension of adaptive social responses. Attribution theory suggests that causal attribution in social behavior has an external–internal dimension [5]. Internal causality identifies one's aptitude as causing natural responses, whereas external causality identifies environmental factors as causing less natural responses [5]. Here, we hypothesized that natural and less natural responses were related to internal and external causal attributions, respectively. Assessment of the external–internal dimension of the causal attributions in adaptive social responses is important in areas of clinical psychology such as motivational interviewing [6], where the goal is to change clients' behavior [7,8]. This technique has been used alter smoking behavior [9], alcohol consumption [10], and drug addiction [8], as well as to promote diet/exercise therapy for patients with obesity [11] and/or diabetes [12]. The goal of a motivational interview with such clients is to evoke an internal causal attribution to change counterproductive to adaptive behavior [6]. Thus, an objective assessment tool for the external–internal dimension of the causal attribution underlying adaptive social responses would be useful in the clinical setting. Recent development of a visual cortex decoding device using neuroimaging techniques, [13] indicates that neuroimaging studies have the potential to provide objective assessment tools for the clinical setting.

Although the dimension of causal attribution is a critical aspect of social adaptation, the neural correlates of causal attributions in adaptive social responses are not well understood. Several neuroimaging studies have investigated social adaptation in terms of moral cognition and social norms (for review, see [14,15]). In paticular, Moll et al. [16] reported that neural activity in the fronto–temporal areas was involved in moral judgment and moral sensitivity [17]. Berthoz et al. [18] demonstrated that the medial frontal and anterior temporal regions were activated during transgression of a social norm. In terms of causal attributions, Spitzer et al. [5] investigated the neural correlates of social norm compliance induced by punishment by others, which is thought to be associated with external causal attributions, and suggested that the bilateral orbitofrontal cortices and right dorsolateral prefrontal cortex were involved in compliance with social norms [19]. Recent fMRI studies have focused on the neural correlates of causal attributions made in social situations. Blackwood et al. [20] reported pre-motor cortex and cerebellar involvement in internal causal attributions, and Seidel et al. [21] showed that, compared with external attribution, internal causal attribution induced activation in the right temporoparietal junction (TPJ), and external attribution induced activation in the left TPJ and precuneus. Previous neuroimaging studies have investigated the neural correlates of either social adaptation or causal attribution in social situations; however, no studies have examined causal attribution in relation to social adaptation.

The present study aimed to identify the neural correlates underlying adaptive social responses to a frustrating situation by assessing causal attributions. To this end, we created an "acting task" that applied frustrating situations to Rosenzweig's model. We also used a parametric index of the self-reported social behavior causal attributions that was based on the work of Blackwood et al. and Seidel et al. [20,21]. We refer to this index as a "causality score," and applied it to the acting task to assess causal attributions related to the social responses exhibited under the experimental conditions. During the acting task, each subject was presented with a virtual frustrating situation and was asked to play the role of the protagonist by verbalizing social responses (Figure 1) that were either socially adaptive or non-adaptive (Table 1, Figure 2) while undergoing functional magnetic resonance imaging (fMRI). Following fMRI scans, subjects were asked to evaluate their own causality scores, which indicated the likelihood that they would have responded to the social situation in the same way as the protagonist in the virtual frustrating situation (i.e., internal causal attribution). The causality score was used as an index of the internal causal attribution of the described social response. We assumed that causality scores would differ across trials during the acting task. We hypothesized that the brain region whose activation would have a positive and negative correlation with the self-reported index of the causal attributions would be regarded as neural correlates of internal and external causal attribution of social responses, respectively. In other words, the brain region whose neural activity during verbalization of a more natural response (i.e., internal causality) would be

Figure 1 Example of a frustrating situation (a stimulus sequence). (**a**) Background explanation of the picture stimulus. (**b**) An example of the picture stimulus representing a frustrating situation. (**c**) An example of a verbal response as an adaptive social behavior.

associated with higher causality scores than those during verbalization of a less natural social response (i.e., external causality).

For behavioral results, we predicted that the causality scores of the adaptive social responses would correlate significantly with the results of the psychological questionnaire scales associated with character and aggressive behavior because responses to frustrating situations are affected by individual levels of social cooperation and correspond to features of aggressive behavior [1]. In particular, we predicted that the causality scores for adaptive verbal responses would correlate with the cooperativeness (C) subscale of the Temperament and Character Inventory (TCI) [22] and the anger control subscale of the State–Trait Anger Expression Inventory (STAXI) [23], which evaluates socially cooperative characteristics and self-control over angry behavior, respectively.

We predicted that the fMRI results would show involvement of the premotor cortex, cerebellum, and right TPJ in natural social responses because these areas play a role in internal causal attribution in social situations [20,21]. We expected the left TPJ and precuneus to be associated with less natural social responses because activity in these regions is associated with external causal attribution [20,21]. Furthermore, the processing underpinning social adaptation involves a wide variety of brain regions, including the medial and lateral prefrontal cortices, anterior and posterior superior temporal sulcus, and TPJ [14,15]. Thus, we predicted that the right and left TPJ would be involved in the internal and external causal attributions made about adaptive social responses to frustrating situations, respectively.

Methods

Subjects

In total, 40 healthy volunteers (eight females, 32 males; mean age 20.5 years, *SD* = 2.4, range, 18–28) participated. All participants were native Japanese speakers recruited from the Tohoku University community and all were right-handed, as assessed by the Edinburgh Handedness Inventory [24]. No subject had a history of neurological, psychiatric, or major medical disorders. Written informed consent was obtained from all subjects in accordance with the Declaration of Helsinki [25]. The current study was approved by the Ethics Committee of Tohoku University.

Stimuli

Each real-life frustrating situation was presented in text form and was followed by presentation a picture taken from the first-person perspective of the participant (Figure 1a, b). Each picture contained a message to the protagonist from the person responsible for the frustrating situation. The participant's verbal response to the frustrating situation (expressed either to the person responsible for the situation or to one's self) was then presented as a sentence on the picture (Figure 1c). This sequence was referred to as "a stimulus sequence" (Figure 1). The

Table 1 Examples of social responses

Examples of verbal responses		Adaptive	Non-adaptive		
		I will input the data again	I should have s aved the data	You need to re-input the data	You should have checked it
Factors of adaptiveness	Self-performing	+	+	-	-
	Contains solution	+	-	+	-

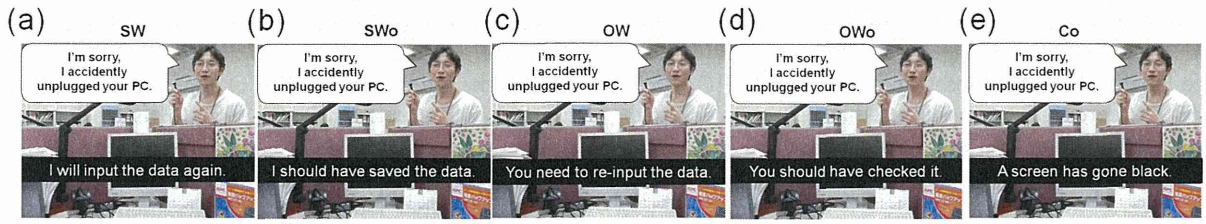

Figure 2 Example of a stimulus set. (**a**) The SW response describes the subject's own behavior in the near future. (**b**) The SWo response describes the subject's own behavior in the past. (**c**) The OW response describes another's behavior in the near future. (**d**) The OWo response describes another's behavior in the past. (**e**) The Co (control) condition only describes the situation.

individual whose photograph appears in the example provided written informed consent for publication of his photograph.

To test the specificity of a significant correlation in adaptive social behaviors, it is necessary to compare adaptive and non-adaptive verbal responses. We referred to stimulus sequences with both adaptive and non-adaptive responses to the same frustrating situation as "a stimulus set" (Figure 2). To prepare the stimulus sets for our acting task, preliminary experiments were conducted in three steps: (1) collection of stimulus sequences including frustrating situations and verbal responses in daily life; (2) categorization of adaptive and non-adaptive responses, which constituted a stimulus set; and (3) verification of the stimulus sets.

In the first step, to elicit honest verbal responses to daily frustrating situations, a separate group of subjects from the Tohoku University community, the same community from which participants in the present study were selected, anonymously completed our original questionnaire asking about daily frustrating situations in their lives as college students and possible verbal responses they would give in such situations. As a result, we identified 41 frustrating situations and seven or eight verbal responses for each situation (a total of 306 verbal responses). Then we obtained 41 pictures, either from the internet or by taking the pictures ourselves, which illustrated 41 frustrating situations.

Seventeen healthy subjects (three women, 14 men; 19–25 years old) were tested separately in the second step. Each subject looked at every stimulus sequence. They were then asked to "imagine being the protagonist in each frustrating situation and evaluate how naturally they would utter a prepared response." The evaluation of each verbal response was used as a reference for the "causality" scores. To categorize the different types of verbal responses, we performed a discriminant analysis using the SPSS software (ver. 15.0 for Windows; SPSS Inc., Chicago, IL, USA). The causality scores were used as independent variables in the discriminant analysis because the effect of the different verbal responses on the causality scores differed among individuals.

Additionally, we wanted to use an experimental approach to demonstrate that the two factors of adaptation (i.e., "self-performing" and "containing a solution") were significant explanations for the verbal responses to the frustrating situations. Based on this analysis, verbal responses were divided into four categories by two discriminant functions that accounted for 95.3% of the variance.

The functions were two types of verbal responses to the frustrating situation; these were referred to as performer (self/other-performing) and solution (with/without solution), corresponding to the direction and type of aggression in the Rosenzweig model, respectively [1]. We categorized these two factors into four types of verbal responses (Table 1): self-performing/with solution (SW), self-performing/without solution (SWo), other-performing/with solution (OW), and other-performing /without solution (OWo). In this context, the SW response satisfied the definition of adaptation as a process used to manage environmental demands [3,4] because the SW response does not suggest that a burden will be placed on the environment. As a result of dividing the verbal responses into four categories, the stimulus set contained each frustrating situation, four verbal responses for the conditions of interest (SW, SWo, OW, and OWo; Table 1), and one response as a control condition (Co; Figure 2). Under the Co condition, each subject read the description of the situation itself instead of the verbal responses.

In the third step, a preliminary psychological test conducted with 10 different healthy subjects (five women, five men, 19–29 years old) was used to verify the stimulus set. We eliminated responses understood by fewer than 90% of the subjects. Accordingly, 16 stimulus sets including four types of verbal responses met this criterion (see, Additional file 1, Appendix). The means and standard deviations of the length of the verbal responses were 11.9 ± 1.4, 13.1 ± 1.8, 12.4 ± 1.7, 13.0 ± 2.2, and 13.1 ± 1.4 moras (a prosodic unit of the Japanese language) under the SW, SWo, OW, OWo, and Co conditions, respectively. A one-way analysis of variance (ANOVA) revealed no significant difference in the average length of the responses across conditions [$F(4,75) = 1.68$]. Accordingly, we assumed that behavioral outputs, such as the speech and eye movements required for reading the verbal responses, were similar across conditions.

Task

Prior to the fMRI experiment, subjects practiced the acting task outside the scanner with four stimulus sets not used in the experiment. The subjects then viewed all the stimulus sequences without verbal responses to ensure that they could understand the frustrating situations.

During the fMRI experiment, each subject performed the acting task. Subjects acted as protagonists (i.e., as if they had been in the situation presented in the stimulus picture) by reading a verbal response with feeling. By fixing the headphones between the head coil and the temple areas, head motions were dissociated from jaw movements during reading. To record the entirety of the response, subjects were asked to press a button with their right index fingers while reading the verbal response aloud. A mixed design was applied to this fMRI experiment. To allow a parametric modulation analysis for each trial [26], the inter-trial intervals varied from 0 to 3.5 s, as in an event-related model. Because our primary objective was to have subjects act out the task, we used a block design to decrease the load involved in switching among different types of verbal responses. In brief, four trials using the same type of verbal responses were arranged in a block design. The details of the task procedure are shown in Figure 3.

Causality scores

After fMRI scanning, the subjects were presented with all of the verbal responses to the frustrating situations outside the scanner. The subjects were not informed of this task prior to scanning. They were asked to evaluate the similarity between the verbal responses given in the scanner and their natural responses to real-life situations using a nine-point scale (1: not at all natural and 9: very natural); these were referred to as causality scores. Subjects were asked to evaluate causality after the fMRI task because an evaluation during scanning may have interfered with their ability to fully immerse themselves in role playing. The causality score was defined as an index of the internal causal attribution of the described response to the hypothetical scenario. Consistent with this definition, when verbalizing a more natural response (i.e., internal causality), the subjects' causality scores would be higher than when verbalizing a less natural response (i.e., reflecting external causality).

Psychological measurements

All subjects completed the Japanese version of the STAXI [27] and the Japanese version of the TCI [28]. The STAXI assesses the intensity of feelings of anger (state anger), the disposition to experience anger (trait anger), behaviorally expressed anger (anger-out), suppressed anger (anger-in), and self-control of anger behaviors (anger-control) [23]. The TCI has four independent temperament dimensions (novelty-seeking, harm-avoidance, reward-dependence, and persistence) and three independent character dimensions (self-directedness, cooperativeness, and self-transcendence) [22]. Self-directedness refers to the ability to control one's own behavior to achieve one's own goals. Cooperativeness refers to acceptance of others, which induces socially adaptive behaviors such as social tolerance, helpfulness, and compassion. Self-transcendence is related to a kind of spirituality associated with the notion that everything is an essential and consequential part of the universe [22,29].

fMRI measurement

Transaxial gradient-echo images (number of slices = 44, echo time = 50 ms, flip angle = 90°, slice thickness = 2.2 mm, slice gap = 0.7 mm, FOV = 192 mm, and matrix = 64×64) covering the whole cerebrum were acquired at a repetition time of 4000 ms using an echo planar sequence and a Siemens Symphony (1.5 T; Siemens, Erlangen, Germany) MR scanner. To allow for T1 equilibration effects, eight dummy scans were acquired and subsequently discarded. Additionally, anatomical T1-weighted images (thickness, 1 mm; FOV, 256 mm; data matrix, 192×224; TR = 1900 ms; TE = 3.93 ms) were acquired from all participants.

Imaging data analysis

The following preprocessing procedures were performed using the Statistical Parametric Mapping (SPM2) software (Wellcome Department of Imaging Neuroscience, London, UK) and MATLAB (Mathworks, Natick, MA, USA): correction for head motion, adjustment of acquisition-timing across slices, coregistration to the anatomical image, spatial normalization using the anatomical image and the MNI template, and smoothing using a Gaussian kernel with a full-width-at-half-maximum of 10 mm. Data from eight subjects (one woman, seven men) with excessive head motion (more than 2 mm) were excluded. Thus, data from 32 subjects were analyzed.

A conventional two-level approach for fMRI data was adopted using SPM2. We designed two models of expected signal changes for each of the four types of verbal response conditions: canonical signal changes among trials (c: canonical model) and parametrically modulated signal changes correlated with the causality scores within each trial (p: parametric modulation model). The causality scores were normalized to a mean of zero under each

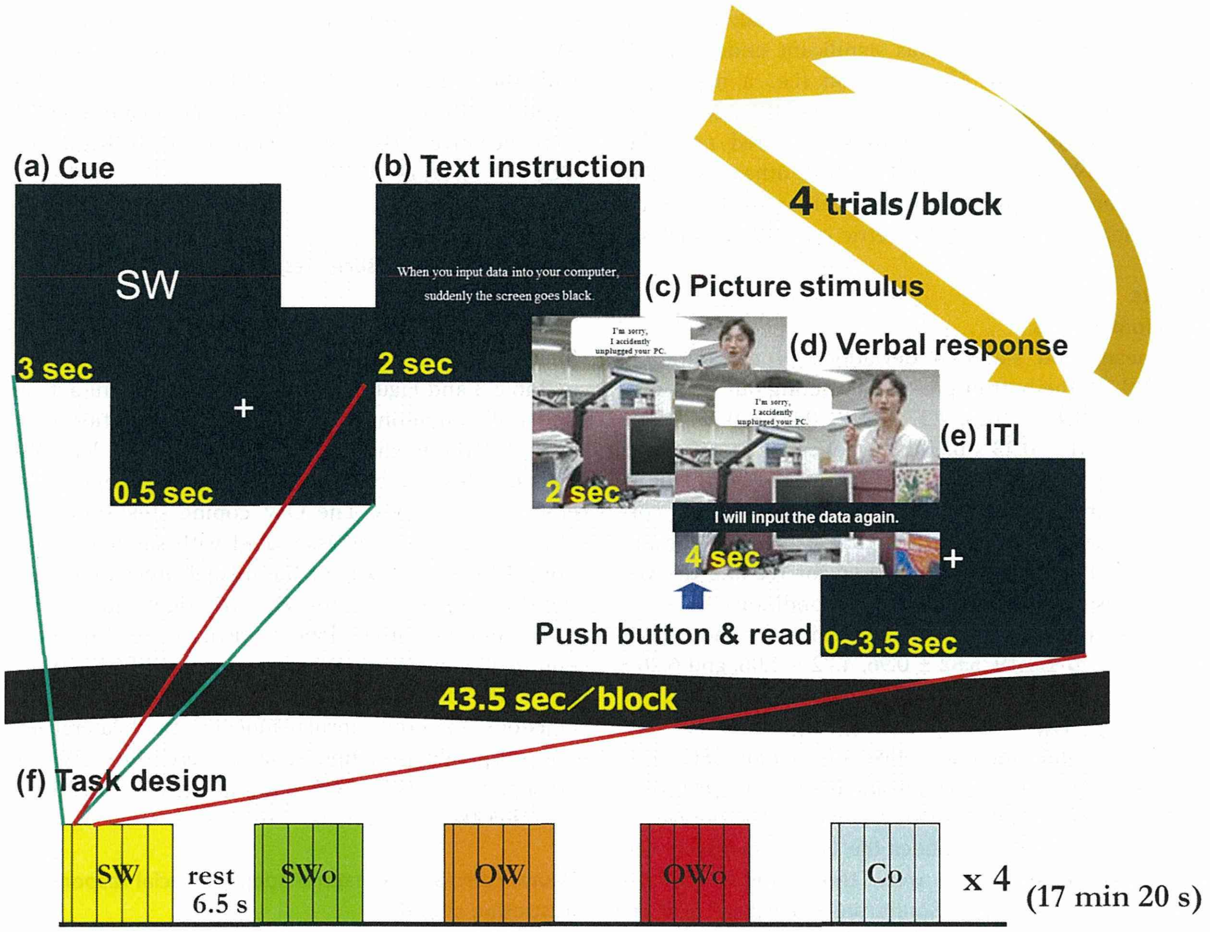

Figure 3 Task procedure. (**a**) At the start of each block, a text cue indicating which type of verbal response was to be adopted was presented for 3 s. (**b**) In each trial, a general explanation was presented for 2 s. (**c**) The picture stimulus was then shown for 2 s, and (**d**) the verbal response was elicited for 4 s. The subjects were asked to read the verbal response soon after it appeared and to press a button with their right index finger while reading. (**e**) The intertrial interval (ITI) varied from 0 to 3.5 s. (**f**) Four trials with the same types of verbal responses were presented in one block. The duration of each block was 43.5 s. The interval between blocks was 6.5 s, during which time a central fixation cross (+) was presented to signal the resting condition. Eighty stimuli (16 stimulus sets, 20 blocks) were presented while subjects underwent fMRI scanning; the order of stimuli and blocks were counterbalanced among subjects. The entire scanning time was 17 min, 20 s.

condition to orthogonalize the four conditions. Under the Co condition, we designed only a canonical model. A voxel-by-voxel multiple regression analysis of the expected signal changes for each of the nine models (SW-c, SW-p, SWo-c, SWo-p, OW-c, OW-p, OWo-c, OWo-p, and Co) was then applied to the preprocessed images for each subject. The expected signal changes were constructed using the hemodynamic response function provided by SPM2. Parameter estimates from the parametric modulation analysis appeared as the degree of correlation between the causality scores and the signal changes. Statistical inference about the contrast of parameter estimates was performed with the second-level between-subjects (random effect) model using one-sample t-tests. The height threshold of all voxel-by-voxel analyses was set at $p < 0.001$, uncorrected, and the extent threshold was set at $p < 0.05$ for multiple comparisons [30,31].

First, to identify the neural networks involved in acting out the virtual frustrating situations, we tested the contrast of the parameter estimates of the canonical model under each of the four conditions compared with the Co condition. The neural responses associated with the adaptive social response were identified by testing the contrast of SW versus each of the other three conditions. Second, to identify the neural responses related to natural and less natural social responses to the SW conditions, we used an event-related model to allow for a parametric modulation analysis of each trial [26] and tested for positive and negative correlations. To exclude the possibility of detecting deactivation correlated with the causality score, we restricted the analyses to the areas in which activation was significant under the SW conditions versus the Co condition (i.e., a mask; $p < 0.05$, uncorrected). Finally, to examine the specificity of the SW conditions, we performed a paired *t*-test between the SW condition and the three other conditions using parameter estimates of the peak activations of the cluster derived from the parametric modulation analysis.

Results

Behavioral results

The means and standard deviations of the durations recorded for the button press while acting out each condition were 2.16 ± 0.25, 2.27 ± 0.25, 2.20 ± 0.26, 2.29 ± 0.24, and 2.31 ± 0.23 s under the SW, SWo, OW, OWo, and Co conditions, respectively (Table 2). No significant difference in duration was observed among the five conditions [one-way ANOVA; $F(4,155) = 2.10$], suggesting that the behavioral output required for reading the verbal responses was controlled across conditions.

The mean values of the causality scores for each condition were 5.25 ± 1.19, 5.82 ± 0.96, 4.72 ± 1.06, and 6.26 ± 1.30 under the SW, SWo, OW, and OWo conditions, respectively. The two-way repeated measures ANOVA revealed a significant main effect of solution [$F(1,31) = 50.47$, $p < 0.05$] and a significant interaction [$F(1,31) = 12.98$, $p < 0.05$] (Table 2). *Post hoc* paired *t*-tests revealed that the causality scores under the OWo condition were significantly higher than were those under the SW [$t(31) = -2.81$, $p < 0.05$, Bonferroni correction] and the OW [$t(31) = -8.11$, $p < 0.0001$, Bonferroni correction] conditions, and that those under the SWo condition were significantly higher than were those under the OW condition [$t(31) = 5.39$, $p < 0.0001$, Bonferroni correction].

The correlation analysis between the causality scores in each condition and the psychological questionnaire scales revealed a significant positive correlation between the average causality score in the SW conditions and the Anger Control subscale of the STAXI ($r = 0.43$, $p = 0.014$), as expected. Although we did not find a significant positive correlation between the causality scores in the SW conditions and the C subscale of the TCI ($r = 0.29$, $p = 0.10$), the analysis showed the positive tendency we expected. Furthermore, the causality scores in the SWo conditions had a significant positive correlation with the C subscale of the TCI ($r = 0.37$, $p = 0.037$), whereas the causality scores in the OWo conditions were negatively correlated with the C subscale of the TCI ($r = -0.41$, $p = 0.020$).

fMRI results

Neural correlates of social responses to frustrating situations

The brain regions significantly activated in each of the four conditions, relative to the Co condition, are shown in Table 3 and Figure 4. Statistically significant activation under all conditions relative to the Co condition was observed in the medial prefrontal cortices, the left inferior frontal gyrus, the bilateral temporal lobes, and the bilateral occipital lobes. The OW coping style, but not the other conditions, was associated with significant activation of the dorsal part of the medial prefrontal cortices, the supplementary motor area, the right inferior frontal gyrus, and the parietal lobe. Statistically significant activation in all conditions, with the exception of the SWo coping style, was observed in the bilateral temporoparietal junctions, the orbito-insular junction, the bilateral hippocampus/parahippocampus, and the cerebellum. We found no significant differential activation between the SW and the other three conditions.

Neural correlates of natural adaptive social responses to frustrating situations

The parametric modulation analysis showed no significant positive correlations between the causality scores and neural responses in any condition.

Neural correlates of less natural adaptive social responses to frustrating situations

The parametric modulation analysis revealed a significant negative correlation only between the SW condition causality scores and neural responses in the right anterior temporal lobe (Table 4, Figure 5a). The parameter estimates showed significant differences between the SW condition and the other three conditions at the peak

Table 2 Behavioral data

Condition	SW	SWo	OW	OWo	Co
Duration (s)	2.16 ± 0.25	2.27 ± 0.25	2.20 ± 0.26	2.29 ± 0.24	2.31 ± 0.23
Causality score	5.25 ± 1.19	5.82 ± 0.96	4.72 ± 1.06	6.26 ± 1.30	-

The duration of the acting task is shown for each condition. No significant difference in duration was observed among the five conditions [one-way ANOVA; $F(4,155) = 2.10$]. Causality scores under the four coping conditions are shown. A two-way repeated-measures ANOVA revealed a significant main effect of solution [$F(1, 31) = 50.47$, $p < 0.05$] and a significant interaction [$F(1, 31) = 12.98$, $p < 0.05$]. *Post-hoc* paired t-tests revealed that causality scores under the OWo condition were significantly higher than those under the SW [$t(31) = -2.81$, $p < 0.05$, Bonferroni correction] and the OW conditions [$t(31) = -8.11$, $p < 0.0001$, Bonferroni correction]. Causality scores under the SWo condition were significantly higher than those under the OW condition [$t(31) = 5.39$, $p < 0.0001$, Bonferroni correction]. The values are shown as means and standard deviations. SW, self-performing/with solution; SWo, self-performing/without solution; OW, other-performing/with solution; OWo, other-performing/without solution; Co, control condition.

Table 3 Neural correlates of social responses to frustrating situations

Structure			SW–Co	SWo–Co	OW–Co	OWo–Co
Temporal lobe	Temporal pole	L	−56, 12, 22	−44, 12, −36	−48, 14, −30	−52, 16, −20
			(5.70, 6464a)	(6.05, 3992a)	(6.29, 7344a)	(6.95, 17048a)
		R	54, 16, −32	50, 16, −38	54, 10, −22	50, 14, −36
			(7.81, 10312b)	(5.69, 2304b)	(7.04, 17544b)	(7.19, 10112b)
	Anterior/posterior superior temporal sulcus	L	−46, 12, −36	−62, 0, −22	−60, 10, −18	−58, −4, −18
			(5.45, a)	(4.32, a)	(5.01, a)	(5.86, a)
				−66, −24, −2		−68, −22, −2
				(5.36, a)		(5.75, a)
		R	56, −12, −12	56, −20, −6	56, −12, −10	58, −10, −8
			(7.06, b)	(8.24, 3864c)	(8.09, b)	(7.85, 4200c)
			56, −42, 6		58, −20, −8	48, −26, −6
			(4.50, b)		(6.24, b)	(5.97, c)
	Temporoparietal junction	L	−52, −58, 20		−54, −56, 12	−52, −56, 18
			(6.15, 3880c)		(7.87, 4072c)	(4.21, 1688d)
		R	52, −54, 26		64, −54, 22	60, −54, 22
			(5.59, 2528d)		(5.63, b)	(7.21, 2552e)
	Orbitoinsular junction	L	−26, 12, −16		−28, 14, −18	(*, a)
			(3.83, a)		(4.96, a)	
		R	32, 16, −20		32, 18, −20	30, 12, −22
			(4.08, b)		(4.97, b)	(4.71, b)
	Hippocampus/ parahippocampus	L	−10, −42, −6		(*, d)	
			(5.24, 2656e)			
		R	14, −26, −12		16, −26, −14	14, −28, −14
			(6.07, 2896f)		(5.37, 15096d)	(5.85, 3512f)
Frontal lobe	Superior frontal gyrus	M	−4, 56, 24	4, 56, 18	2, 54, 24	0, 56, 26
			(5.23, 4064 g)	(5.16, 4960d)	(5.91, 7984e)	(6.28, 7584 g)
	Supplementary motor area	M			−6, 10, 64	
					(5.00, 2392f)	
	Inferior frontal gyrus	L	−52, 20, 0	−56, 22, −4	−54, 26, −6	−56, 22, 0
			(5.14, 1936 h)	(5.28, 1592e)	(6.17, 5848 g)	(6.30, a)
		R			50, 24, −8	48, 24, −10
					(4.32, b)	(4.01, b)
Parietal lobe	Precuneus	L			−4, −56, 32	
					(6.30, d)	
		R		8, −56, 36	6, −56, 18	
				(4.16, f)	(4.68, 15096d)	
Occipital lobe		L	−4, −72, 18	−12, −56, 8	−16, −62, 6	−8, −74, 10
			(4.54, 1784i)	(5.15, f)	(6.32, d)	(4.50, 1768 h)
		R	14, −38, −2	20, −62, 6	16, −80, 24	12, −52, 2
			(4.33, f)	(5.20, 2584 g)	(5.41, 5480 h)	(4.95, f)
				18, −78, 26		
				(5.20, 8120f)		

Table 3 Neural correlates of social responses to frustrating situations *(Continued)*

Cerebellum	L	−16, −82, −30	(*, i)	0, −84, −26
		(4.47, j)		(5.53, 1568i)
	R	10, −78, −30	24, −80, −36	8, −78, −18
		(4.87, 3224j)	(5.93, 3944i)	(5.12, i)

MNI coordinates (*x*, *y*, *z*) of peak activation, *t*-value at the peak, and cluster size (mm^3) in parenthesis are given for each area activated by each coping style, relative to the Co condition. The height threshold for significant activation was set at $p < 0.001$. Correction for multiple comparisons ($p < 0.05$ in cluster size) was made. L: left, R: right, M: medial. The lowercase letter given with the cluster size indicates that the peak is in the same activated cluster as are the other peaks with the same letter. (*) The region includes the activated cluster with no peak activation.

voxel in this cluster (Table 5, Figure 5b). The time-series data for the percentage signal change at the peak statistical value in this area showed larger responses for the low-causality scores compared with the medium- and high-causality scores (Figure 5c).

Discussion

The aim of the present study was to identify the neural correlates of adaptive social responses to frustrating situations by assessing causal attributions. We found a significant negative correlation between causality scores and brain activity in the right anterior temporal lobe while acting out adaptive social responses. The negative correlation indicated a less natural social response, suggesting that this region is specifically activated when an adaptive social response is driven by an external causal attribution.

Rosenzweig model and social adaptation

We revealed the neural correlates of the specificity of social adaptation based on the Rosenzweig model. In the current experiment, we combined the Rosenzweig model for social responses to frustrating situations [1,2] and social adaptation, proposed according to coping theory [3]. Through preliminary experiments, we identified two factors that contribute to social responses to frustrating situations, consistent with the Rosenzweig model. However, although the

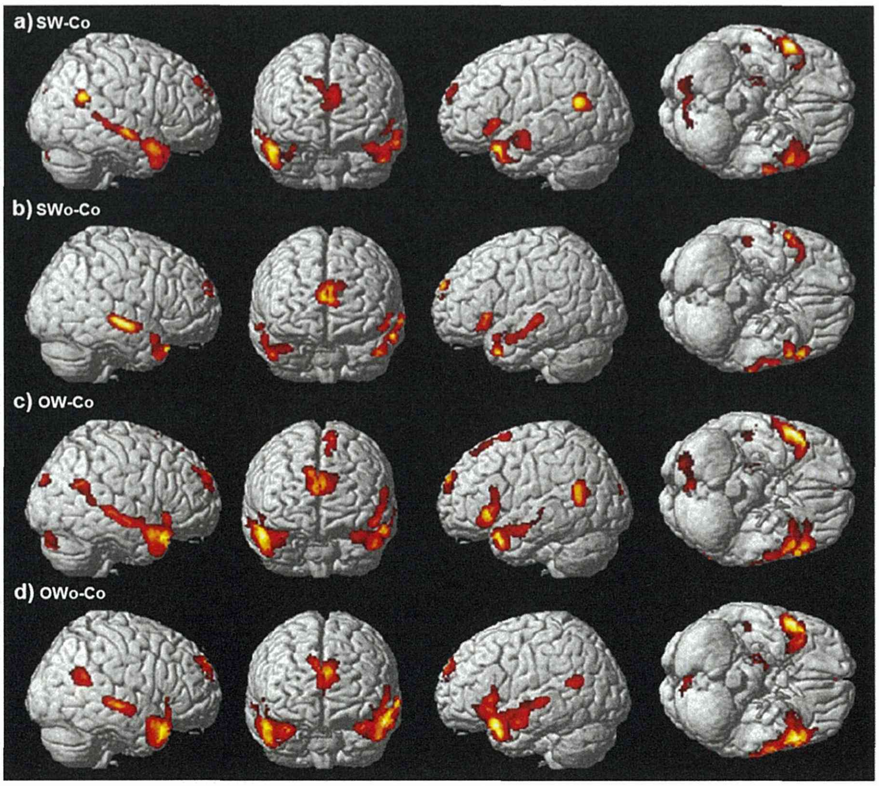

Figure 4 Neural correlates of social responses in frustrating situations. High levels of brain activity estimated from a conventional subtraction analysis of the (**a**) SW, (**b**) SWo, (**c**) OW, and (**d**) OWo conditions relative to the Co condition are overlaid on a SPM2 rendered brain. The panels show the right sagittal, anterior, left sagittal, and ventral views of the brain. The statistical threshold was set at $p < 0.001$ and corrected to $p < 0.05$ for multiple comparisons using cluster size.

Table 4 Neural correlates of less natural adaptive social responses to frustrating situations

Structure	MNI coordinate			*t*	Cluster size
	x	*y*	*z*		(mm^3)
Right temporal pole	40	20	−32	5.04	3768
Right anterior superior temporal sulcus	64	−8	−18	4.72	

The results of the significant negative correlation between the agreement scores and neural responses for the SW verbal responses masked by the SW–Co contrast inclusively. The coordinates, *t*-value of peak activation, and cluster size are shown for each activated area. The height threshold for significant activation was set at $p < 0.001$, and corrected to $p < 0.05$ for multiple comparisons using cluster size.

Rosenzweig model is a 3 × 3 factorial design (i.e., direction of aggression involving self, another person, and nothing × type of aggression, involving attention to the frustrating event itself, to the cause of the frustrating situation, and a to solution to the frustrating situation) [1,2], social responses in our results consisted of a 2 × 2 factorial design (i.e., self/other performing × containing/not containing a solution). Logical thought requires that social responses corresponding to self-/other-performing are consistent with those directing aggression toward the self and another person, respectively. However, those corresponding to the direction of aggression involving requests toward nothing were excluded from our stimuli through the discriminant analysis. The number of responses that were requests toward nothing was not sufficient to create a significant category. For the type-of-aggression factor, we could regard those with attention to the frustrating event itself and to a cause of the frustrating situation as "no solution" and regard a solution to the frustrating situation as containing a solution. Although a 3 × 3 factorial design was integrated into a 2 × 2 design, at least two factors of the Rosenzweig model were replicated in the present study.

Moreover, we found specific neural responses under SW conditions that were related to socially adaptive responses [3]. In the current study, we focused on the internal (i.e., self-performing) and external (i.e., containing a solution that implicitly responds to external demands) causality of social responses. Adaptive social responses may have a stronger association with external causal attributions than do non-adaptive social responses because the definition of social adaptation [3] refers to managing environmental demands to solve problems, which corresponds to external causality. Although other definitions of adaptation have been proposed [32,33], the

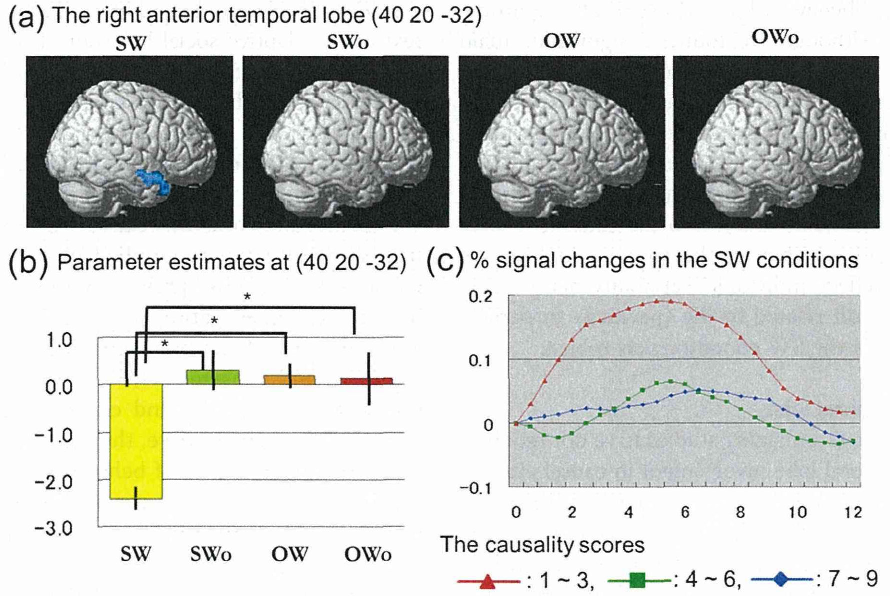

Figure 5 Neural correlates of less natural adaptive social responses. (**a**) The right anterior temporal lobe was activated only under the SW condition, as shown on the rendered brain presentation of the SPM2 from the right sagittal view. No significant correlation was found between neural activation and the causality score under the SWo, OW, or OWo conditions. The statistical threshold was set at $p < 0.001$ and corrected to $p < 0.05$ for multiple comparisons using cluster size. (**b**) The graphs show activation profiles (parameter estimates from a parametric modulation analysis and standard errors of the mean at peak activation). $*p < 0.05$, paired *t*-test. (**c**) The average percent signal changes over time are shown for trials with low (1–3; red triangles), medium (4–6; green squares), and high (7–9; blue diamonds) causality scores under the SW condition. Vertical axes represent percent signal changes; horizontal axes indicate peristimulus time (s).

Table 5 Parameter estimates at the anterior temporal lobe [40 20 -32]

Condition	SW	SWo	OW	OWo
Parameter estimates	−2.41 ± 2.71	0.31 ± 4.83	0.20 ± 2.93	0.13 ± 6.25

A significant difference was observed among the four conditions [one-way ANOVA; $F(3,124) = 2.81$, $p = 0.41$]. Significant differences between SW and the other three conditions were detected using a paired t-test ($t(31) = -2.68$, $p = 0.012$; $t(31) = -3.62$, $p = 0.001$; $t(31) = -2.51$, $p = 0.017$, respectively.

one developed by Lazarus [3] was congruent with respect to specificity. Therefore, our data showing that a specific neural response was elicited only when adaptive behavior was observed support the appropriateness of the definition proposed by Lazarus [3] for use in efforts examining the biological underpinnings of socially adaptive responses.

Causality scores and psychological measurements

We found a significant correlation between causality scores and responses to the psychological questionnaires. This finding suggests that the internal causal attribution of adaptive social responses (i.e., the SW condition) requires self-control and the ability to control anger behavior in frustrating situations. Moreover, self-performing responses (i.e., the SW and SWo conditions), which put no burden on others, were associated with a cooperative personality. This is in contrast to the OWo condition, which represents a complaining/accusing attitude and is associated with a less cooperative personality. These findings reinforce the validity of the causality scores, as we predicted.

On the other hand, we observed an apparent discrepancy between the behavioral and fMRI results regarding causality scores. Although we found a significant main effect of solution and a significant interaction in the causality scores among the four conditions, we did not detect a significant main effect or interaction among the parameter estimates derived from the parametric modulation analysis. The results of the parametric modulation model depend on within-subject variation in the causality scores under each condition, whereas the mean values of the causality scores reflect individual variability across subjects. Thus, the result related to the specificity of parameter estimates under the SW condition was robust.

Right anterior temporal lobe

Although previous neuroimaging studies have not reported right anterior temporal lobe involvement in causal attributions, the cognitive function of this region highlights the importance of integrated processing for adaptive social behavior. A previous review suggested that the lateral prefrontal cortices contributed to adaptive social reasoning because they had been shown to mediate cognitive functions, such as social exchange, simulation, integration, deductive and inductive inference, and social cognition [15]. One interpretation of our results is that adaptive social behaviors with an external causal attribution (i.e., less natural social responses) require a high cognitive load for the integration of emotional and social information. Previous studies have shown right anterior temporal lobe involvement in cognitive integration in social contexts. For example, this region was activated during the bottom-up processing of breaches occurring in social contexts, such as social norm violations [18] and social–cognitive conflicts [34]. Additionally, this region is involved in the top-down processing of comprehension in a social context, such as moral reasoning [14,16], mentalizing (understanding others' intentions) [35], irony [36], and abstract conceptual knowledge [37]. Olson et al. argued that the right anterior temporal lobe was involved in the emotional processing associated with social relationships (socio–emotional processing) [38]. Other reports have suggested that the functional role of the anterior temporal lobe can be understood in terms of its serving as a semantic hub mediating social–emotional processing [39]. In addition to these cognitive processes, the region plays a role in behavioral processes, such as producing communicative speech in a social context [40]. Thus, neural activation in this region integrates social stimuli involving the social demands of frustrating situations. Such social demands constitute the characteristics of external causal attribution, particularly in the context of an adaptive social behavior. The functional role of this region highlights the importance of integration in the performance of adaptive social behaviors.

Neural networks for social responses to frustrating situations

The neural networks associated with social responses to frustrating situations identified in the present study are consistent with those previously reported in neuroimaging studies investigating social behaviors. These brain areas are part of the brain network that mediates social cognition and behavior [41,42], such as mentalizing [35], social interaction [43], and communicative speech production [40]. Furthermore, they are related to judgments about the adaptiveness of behavior in relation to a social context with regard to considerations such as social norms [18,44] and moral judgments [14,16,45]. A comparison of our results with previous findings suggests that subjects must understand the meaning of a social situation to produce communicative speech during the acting task, and that this may be related to environmental demands.

We failed to find neural correlates of adaptive social responses via conventional subtraction analyses (i.e., contrast between adaptive and non-adaptive responses). On the other hand, after fitting the causality scores, we were able to detect adaptive-specific neural responses. The results indicate that the concept of causality is needed in attempts to identify the neural correlates of adaptive-specific neural responses under experimental conditions.

Methodological considerations and future studies

Certain methodological issues in our experiment must be considered. First, the validity of our novel methodology was supported by both psychobehavioral and fMRI results. The correlation between the causality scores and the psychological measures reinforce the validity of the causality scores. Moreover, the significant correlation between neural activation and the causality scores, together with the role of the right anterior temporal lobe in cognitive function, enabled us to interpret the fMRI results and support the validity of our novel methodology.

Second, the reason we failed to find a significant positive correlation between brain activity and causality scores in any experimental condition should be considered. We believe this was the result of the definition we used for adaptation and the characteristics of our acting task. The definition of adaptiveness, which focused on environmental demands corresponding to an external causal attribution, was taken from Lazarus' 1984 article [3]. Furthermore, our acting task was designed to emphasize a frustrating situation corresponding to external causal attributions. Thus, the subjects were likely to process an external causal attribution, derived as a negative correlation between brain activation and the causality scores, more explicitly. Separate studies optimized to highlight internal causal attribution are necessary to address natural adaptive social behaviors. To accomplish this, an alternative definition of adaptiveness, focusing on the processes used to manage environmental and internal demands [32,33], must be developed. Consistent with this definition [32,33], the internal demands were related to real-life adaptive social behaviors, which could be derived as a positive correlation.

The final issue is gender differences in the adaptive social responses to frustrating situations. Although a previous study reported a gender difference in the response to social stimuli [46], we did not examine gender differences in adaptive social behaviors. We were only able to recruit eight female subjects for the present study and found no significant differences in this subsample. We assessed the issue of mixed data from all male and female subjects and found that an analysis of the results from the male subjects alone showed the same tendency as did the results for all subjects. Thus, we believe the results are valid despite the small number of female participants.

Conclusions

This is the first reported study to investigate the neural correlates of adaptive social behaviors by assessing causal attributions using hypothetical scenarios under experimental conditions. We believe this novel approach has the potential to open up entirely new areas of research using neuroimaging methods. In particular, we believe that the recent development of a visual cortex decoding device using neuroimaging techniques gives neuroimaging studies the potential to provide objective assessment tools for clinical settings.

Additional file

Additional file 1: Appendix: List of stimuli sets.

Competing interests
We have no conflicts of interest to declare.

Authors' contributions
All authors contributed to the concept and design of the present study. AS and MS contributed to data acquisition. AS, MS, SY, YS, and RK contributed to data analysis and interpretation. AS, MS, SY, YS, and RK provided statistical expertise. AS was the primary writer of the manuscript. MS, YT, YS, and RK were the primary reviewers/revisers of the manuscript. All authors discussed the results and commented on the manuscript. All authors gave their final approval for submission of the manuscript.

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PTSDにおける扁桃体

関口　敦

はじめに

外傷後ストレス障害(post-traumatic stress disorder；PTSD)は，外傷的出来事によって引きおこされる精神障害であり，アメリカ精神医学会が定めた診断基準(Diagnostic and Statistical Manual of Mental Disorders 4th edition；DSM-Ⅳ)では不安障害に分類されており，1ヵ月以上続く再体験，回避/麻痺，過覚醒が主たる3因子として特徴づけられている(表)．PTSDの臨床症状を形成するには，恐怖反応，情動記憶の形成などの情動・認知処理が必須であると考えられ，扁桃体はこれら情動・認知処理の首座である．更に，扁桃体は視床下部を介して自律神経系の反応を司っており，PTSDの精神症状のみならず随伴する身体症状(自律神経系の過剰亢進)の病態においても重要な役割を担っている．近年，急速な発展をみせている脳画像研究の手法により，これら扁桃体を介したPTSDの病態生理が明らかになってきている．

本稿では，PTSD患者における扁桃体の脳形態・脳機能の異常を報告した脳画像研究を紹介し，更にこれら脳画像研究を基に提唱されているPTSDの病態モデル内での扁桃体の役割について解説する．

なお，2013年に発表されたDSM-Ⅴでは，PTSDは新設された疾患カテゴリーである「トラウマとストレスに関連

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PTSDの診断基準(DSM-Ⅳ)

A(外傷体験)．その人は，以下の2つが共に認められる外傷的な出来事に暴露されたことがある．
1）実際にまたは危うく死ぬまたは重症を負うような出来事を，1度または数度，または自分または他人の身体の保全に迫る危険を，その人が体験し，目撃し，または直面した．
2）その人の反応は強い恐怖，無力感または戦慄に関するものである．

B(再体験)．外傷的な出来事が，以下の1つ(またはそれ以上)の形で再体験され続けている．
1）出来事の反復的で侵入的で苦痛な想起で，それは心像，思考，または知覚を含む．
2）出来事についての反復的で苦痛な夢．
3）外傷的な出来事が再びおこっているかのように行動したり，感じたりする(その体験を再体験する感覚，錯覚，幻覚，および解離性フラッシュバックのエピソードを含む．また，覚醒時または中毒時に起こるものを含む)．
4）外傷時出来事の1つの側面を象徴し，または類似している内的または外的きっかけに暴露された場合に生じる，強い心理的苦痛．
5）外傷時出来事の1つの側面を象徴し，または類似している内的または外的きっかけに暴露された場合の生理学的反応性．

C(回避/麻痺)．以下の3つ(またはそれ以上)によって示される．(外傷以前には存在していなかった)外傷と関連した刺激の持続的回避と，全般的反応性の麻痺．
1）外傷と関連した思考，感情，または会話を回避しようという努力．
2）外傷を想起させる活動，場所，または人物を避けようとする努力．
3）外傷の重要な側面の想起不能．
4）重要な活動への関心または参加の著しい減退．
5）他の人から孤立している，または疎遠になっているという感覚．
6）感情の範囲の縮小(例：愛の感情を持つことができない)．
7）未来が短縮した感覚(例：仕事，結婚，子供，または正常な一生を期待しない)．

D(過覚醒)．(外傷以前には存在していなかった)持続的な覚醒亢進症状で，以下の2つ(またはそれ以上)によって示される．
1）入眠，または睡眠持続の困難．
2）易刺激性または怒りの爆発．
3）集中困難．
4）過度の警戒心．
5）過剰な驚愕反応．

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した障害(Trauma and stressor related disorder)」に分類され，その主症状も，侵入症状(Intrusion symptoms)，回避行動(Persistent avoidance of stimuli associated with the trauma)，認知と気分の否定的変化(Negative alterations in cognitions and mood that are associated with the traumatic event)，覚醒と反応性の変化(Alterations in arousal and reactivity that are associated with the traumatic event)の4因子に改編されている．しかし，現時点で日本語版DSM-Vの出版を待つ状況であり邦訳語が確定していないこと，加えて本稿で扱っているPTSD研究は主にDSM-Ⅳ診断基準に則り実施されていることを鑑み，本稿ではDSM-Ⅳ基準に則った記載を採用することとした．

脳形態画像研究

画像解析技術の進歩に伴い，核磁気共鳴画像(magnetic resonance imaging；MRI)を利用したvoxel-based morphometry(VBM)法により脳灰白質/白質の体積を直接測定する手法が確立され，PTSD患者を対象とした脳形態画像研究が多数報告されている．VBMとは，各個人のT1強調MR画像を用いて灰白質/白質/脳脊髄液の成分に分離し，標準脳座標上に空間的標準化をする手法であり，脳形態の個人差の影響を除外した上で，局所の脳領域の灰白質/白質密度および灰白質/白質体積を比較検討することができる．VBM法は従前に行われていた徒手的な脳局所体積の同定と異なり，コンピューターベースでほぼ自動化されたプロセスの中で大量の被験者のデータを処理することができることも大きな特長である．

Karlらのメタアナリシスによると，PTSD患者群では健常群に比して海馬，前帯状皮質，扁桃体において局所灰白質量が減少していることが明らかにされている[1]．これら脳部位は恐怖の学習や消去，情動制御に関わるネットワークを構成していることから，PTSDの病態はこれら情動・認知処理の異常であることを指示している[2]．一方で，扁桃体の灰白質量の減少を認めないというメタアナリシスの結果も散見されるが[3]，近年発表された退役軍人を対象とした大規模な横断研究によりPTSD群の扁桃体体積の減少が示されたことで，一定の見解が示されたものと評価できる[4]．局所灰白質量の減少のメカニズムは，海馬や前帯状皮質においてはストレスホルモンであるコルチゾールの過分泌状態の持続による神経細胞の減少や樹状突起の萎縮が原因と考えられているが[5]，扁桃体の体積減少については一定の見解は得られていない．

VBMと同様の手法はT1強調画像以外の画像データにも適用することができる．近年は，拡散強調画像(diffusion tensor imaging；DTI)から算出される拡散異方性(fractional anisotropy；FA)を用いた，脳白質統合性の評価が多用されている．脳白質統合性は脳白質線維束の結合性の強さを表象するとされ，脳の構造的な結合性(structural connectivity)の指標として用いられている．本手法を用いたPTSD患者研究では，PTSD群における帯状束の白質統合性の低下が報告されている[6]．帯状束は辺縁系の一部を構成し情動抑制処理の一端を担うことから，PTSDの情動抑制処理の障害を指示する結果と解釈できる．

脳機能画像研究

PTSD患者を対象とした脳機能画像研究は，1990年代のRauchらのポジトロン断層法(positron emission tomography；PET)研究が端緒を開いた．彼らはPTSD患者にトラウマに関連する記述を見せた時の局所脳血流をH_2O PETを用いて計測し，扁桃体と共に眼窩前頭皮質(orbitofrontal cortex；OFC)，島皮質，前側頭葉の活動亢進を報告した[7]．その後も多数のPET，機能的MRI(functional MRI；fMRI)研究が行われ，Etkinらのメタアナリシスの結果，PTSD患者においてはトラウマに関連した刺激のみならずトラウマとは無関係な不快情動刺激に対しても，扁桃体および島皮質の活動が亢進し，腹内側前頭前皮質，背側前帯状皮質などの脳活動が低下すると報告されている．扁桃体や島皮質の活動亢進は，PTSD以外にも社会不安障害や単一恐怖症などの他の不安障害患者にも認められる一方で，PTSD群のみが腹内側前頭前皮質や前帯状皮質の活動低下をしているとされ，恐怖刺激に対する情動抑制処理の障害という，不安障害の中でもPTSDに特異的な病態を示唆するものであった[8]．更に近年，fMRIの手法を用いた脳の機能的結合(functional connectivity)を検証する研究が盛んであり，扁桃体と背側前帯状皮質との領域間機能的結合の低下が安静時[9]および情動刺激処理時[10]において報告されており，PTSDの情動抑制処理の障害を指示する結

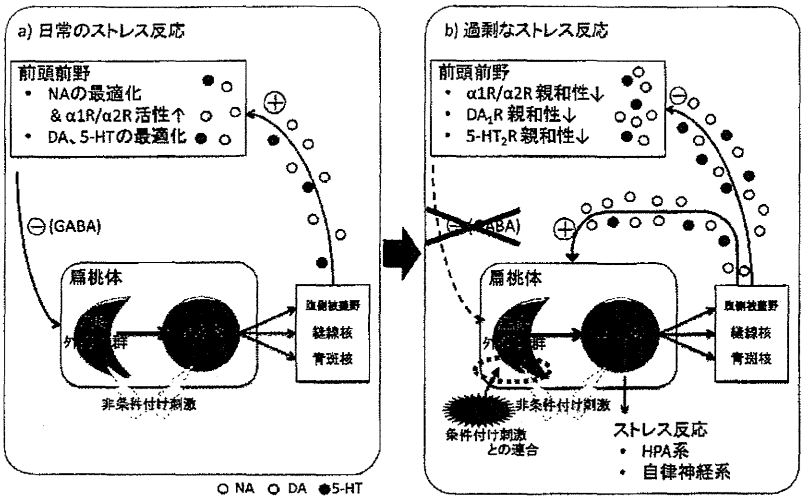

図 1　PTSD 病態の神経修飾モデル(Pitman ら[15]より改変)

a) 日常のストレス反応：　非条件付けストレス刺激が入力されると，扁桃体中心核を介して，脳幹の腹側被蓋野，青斑核，縫線核に投射し，各々ドーパミン(dopamine；DA)，ノルアドレナリン(noradrenaline；NA)，セロトニン(5-hydroxytryptamine；5-HT)などのモノアミン系神経伝達物質の分泌を促す．これら神経伝達物質は前頭前野に作用し，GABA 作動性介在ニューロンを介して扁桃体の基底外側核群の活動を抑制する．これらの機序により扁桃体の活動が制御されている．b) 過剰なストレス反応：　PTSD 患者では非条件付けストレス刺激が入力されると，扁桃体への GABA ニューロンの抑制系入力が減弱しているため扁桃体の活動が過剰に亢進する．その結果，脳幹のモノアミン作動性ニューロンが過剰に興奮し，NA，DA，5-HT の前頭前野への過剰な分泌が誘発される．前頭前野ではシナプス間のモノアミンレベルが上昇し，各モノアミン受容体への親和性が低下し，前頭前野を介した GABA ニューロンの扁桃体の抑制系入力が減弱する．更に，脳幹からのモノアミンの過剰分泌も直接的に扁桃体の活動を亢進する．更に，非条件付け刺激と過去の外傷体験で条件付けされた刺激との連合がおこり，自律神経システムと視床下部-下垂体-副腎皮質(hypothalamus-pituitary-adrenal；HPA)系を介して，再帰的なストレス反応(再体験)や自律神経系の過剰興奮(過覚醒)などの PTSD 症状を誘発する．(グレー矢印は動作性の入力，黒矢印は抑制性の入力を示す)

果と解釈できる．

PET を用いたレセプターイメージングでは，神経伝達物質の PTSD の病態に迫る研究が報告されている．Murrough らは，PTSD 患者における扁桃体におけるセロトニントランスポーター結合能の低下[11]，およびセロトニン受容体の発現量の低下[12]を報告している．Pitman らは，これら神経伝達物質の振る舞いを基に，動物実験で得られた条件付け恐怖の獲得と消去における γ-アミノ酪酸(gamma-aminobutyric acid；GABA)およびモノアミン系の神経伝達物質の知見[13,14]を併せて，PTSD の病態モデルとして扁桃体の機能的変化を中心に据えた“神経修飾モデル”を提唱している(図 1)[15]．

脳形態・脳機能変化と PTSD 症状との因果関係

数々の研究成果により，PTSD 患者における脳形態・脳機能変化の解明は進んでいるが，これらは主に横断的な研究デザインであり PTSD 症状との因果関係については未解明であった．つまり，こ

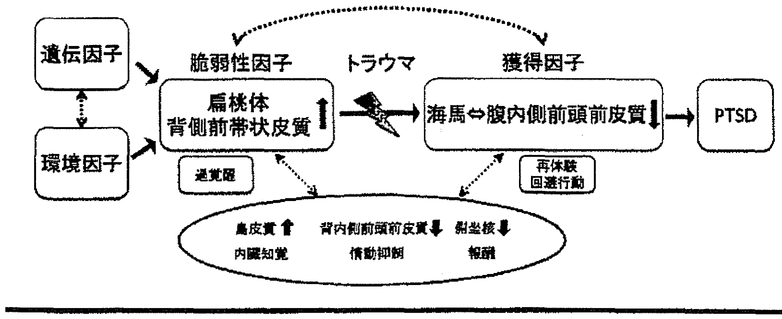

図 2　PTSD と脳形態・脳機能変化の因果モデル(Admon ら[20]より改変)

Admon らが提唱する因果モデルでは，扁桃体・背側前帯状皮質の脳活動亢進・体積増加が PTSD の脆弱性因子であり，腹内側前頭前皮質量の減少と海馬との機能的結合の減弱が PTSD の獲得因子であるとしている．扁桃体・背側前帯状皮質の変化が情動表出の亢進を来し，PTSD の主症状である過覚醒の要因となり，これら変化は遺伝的因子・環境因子(過去の外傷体験，不適な成育歴など)，およびこれら相互作用の影響を受ける．腹内側前頭前皮質と海馬の変化は恐怖反応の抑制に障害を来し，PTSD の主症状である回避行動と再体験の要因となる．脆弱性因子と獲得因子およびこれらの相互作用によって，PTSD の診断基準を満たす病態が完成する．更に，島皮質の機能亢進，背内側前頭前皮質および側坐核の機能低下に寄与し，各々内臓知覚の亢進，情動抑制機能の低下，報酬処理機能の低下など，PTSD 患者に認められる種々の認知機能変化を来すとしている．(実線矢印は因果関係を，破線矢印は相互作用を示す)

れら脳形態・脳機能の変化がPTSDに罹患する以前から存在する脆弱性因子であるのか，それともPTSDに罹患した結果としておきた変化としての獲得因子であるのかについての議論が残っていた．近年，脆弱性因子を特定する研究デザインとしては，脳形態・脳機能変化と遺伝子多型[16]や成育環境[17]などとの関連を調べる研究が，脆弱性因子と獲得因子との弁別をするための研究デザインとして，PTSDの同胞を含む一卵性双生児を対象とした研究[18]や，外傷体験前後の縦断研究[19]などが行われている．Admonらはこれら研究からPTSDと脳形態・脳機能変化の因果関係についてモデル化を試み，PTSD症状の脆弱性因子として扁桃体および背側前帯状皮質の脳活動亢進，獲得因子として腹内側前頭前皮質の機能低下および海馬との機能的結合の低下を特定し，前者がPTSD症状の過覚醒，後者が再体験と回避行動に関連するとの見解を示している(図2)[20]．

むすび

ヒトを対象としたPTSDの脳画像研究が盛んになり，その病態解明が進んできたなかで，扁桃体がPTSDの病態の中核にあることは確実視されている．他の脳部位における結果は一定しない知見も散見されるが，これらは遺伝的背景の違いや環境因子，外傷体験の性質(戦争体験，テロ，自然災害，事件・事故など)による個人差を反映しているのではないかと考えられる．これら要因を統制することで，より詳細なPTSDの病態解明が進み，将来的には個々の性質や病態に沿った予防・治療方法，すなわちオーダーメード医療の開発へと発展していくものと期待される．

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［短　報］

震災後精神症状の脆弱性・獲得因子の神経基盤の解明

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災害ストレスに起因する精神症状と脳形態変化について多数報告はあるが，災害ストレス暴露後の横断研究が主であり，災害後精神症状の脆弱性／獲得因子としての脳形態変化は未解明であった．本稿では，我々が発表した脳形態変化と震災後精神症状の脆弱性因子／獲得因子を解明した最新の研究を紹介し，複数の脳画像データが示唆する生物学的背景について文献的考察を加え，今後の災害ストレスに関わる脳画像研究の方向性を探る．

Key Words　東日本大震災，震災後精神症状，脳形態変化，脆弱性因子，獲得因子

背　景

東日本大震災による家屋の倒壊や津波の被害などは，仙台市中心部に位置する東北大学の周辺では沿岸部と比してはるかに少なかった．しかし，多くの被災者はライフラインの寸断，たび重なる余震，原発事故などの多大なストレスに晒され，心的外傷後ストレス障害（PTSD）に至らずとも，幅広い心理的ケアが必要であった[7, 13]．

ストレス暴露に関連する脳形態の変化は，海馬，扁桃体，前帯状皮質，眼窩前頭皮質などの灰白質の減少や，帯状束での白質統合性の低下が指摘されている．これら変化はPTSD患者[19]のみならず，ストレス暴露後の健常者[3, 18]にも認められる．しかし，前向き研究の困難さから[20]ストレス暴露後の脳画像評価が主であり，ストレス暴露と脳形態変化の因果関係は未解明であった．

我々の研究室では，主に東北大学の健常学生を対象とした脳画像研究を行っており，震災前の脳画像のデータを多数保有しており，これらデータベースを活用して，震災前後の縦断的な脳画像研究を行うことができた．本稿では，最近発表した脳灰白質／白質の形態変化と震災後精神症状の脆弱性因子／獲得因子に関する研究[22, 23]を紹介し，脳灰白質変化と脳白質変化の一致点・不一致点および，複数の脳画像データセットから得られる生理学的背景について文献的考察を加える．

方　法

我々の研究室では，主に健常大学生を対象とし，MRIを用いた脳画像研究を行っており，震災前の脳画像を多数保有している．今回，震災前の脳形態画像（T1強調画像）が存在する被験者に連絡をとり，42名（男／女：33／9人，年齢，21.7 ± 1.7歳）を再募集することができた．これら被験者に対して，震災後3～4カ月の時点でT1強調像を撮像した．また42名のうち，震災前の拡散強調画像が存在した30名（男／女：24／6人，年齢，21.0 ± 1.6歳）に対して，拡散強調

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＊6　東北大学　加齢医学研究所　認知機能発達寄附研究部門

画像を撮像した．MRI 撮像は Philips 社の 3.0 テスラ・インテラ・アチーバにて行った．MPRAGE（Magnetization-Prepared Rapid Acquisition with Gradient Echo）シーケンス（240 × 240 matrix, repetition time＝6.5 ms, echo time＝3 ms, field of view＝24 cm, 162 slices, 1.0 mm slice thickness）による T1 強調画像，およびスピン・エコー EPI シーケンス（TE＝55 ms, FOV＝22.4 cm, 2 × 2 × 2 mm^3 voxels, 60 slices）による拡散強調画像（32 軸，b value=1,000s/mm^2）を用いて，脳白質統合性の指標となる拡散異方性（fractional anisotropy；FA）を算出した．

心理尺度として PTSD 臨床診断面接尺度（CAPS）[1] にて PTSD 症状を，State Ttrait Anxiety Inventory（STAI）[14] を用いて状態／特性不安を評価した．さらに，精神疾患の合併の有無を精神疾患簡易構造化面接法（MINI）[17] で評価した．被験者の CAPS スコアは最大 39 点であり，MINI においても PTSD の診断基準を満たすものは認めなかった．

T1 強調画像の前処理には，VBM2[8] を使用し，脳画像統計解析には統計画像解析ソフト SPM5 を使用した．前処理では，脳灰白質，脳白質，脳脊髄液腔の各分画を作成し，脳灰白質量を算出した．さらに，空間的標準化，半値幅 8 mm で画像平滑化を行った．CAPS スコアを従属変数と，震災前の脳灰白質量および震災前後の脳灰白質変化量を独立変数とした重回帰分析解析を行った．共変量として，被験者の性別，全脳体積，震災前後の撮像間隔（日）を補正した．震災前の脳灰白質量と震災後の CAPS スコアが負相関を示す脳部位を震災後 PTSD 症状の脆弱性因子の神経基盤として，震災前後の脳灰白質量の変化量と震災後の CAPS スコアが正相関を示す脳部位を震災後 PTSD 症状の獲得因子として評価した．脳画像解析は各関心領域内（海馬，扁桃体，前帯状皮質，眼窩前頭皮質）での多重比較補正（スモール・ボリューム・コレクション；SVC）[25] を行い，統計閾値は p＝0.05 とした．

拡散強調画像により算出した FA に関しても，SPM5 を用いた脳画像統計解析を行った．空間的標準化，半値幅 10 mm で画像平滑化を行った．状態不安スコアを従属変数と，震災前の脳灰白質量および震災前後の脳灰白質変化量を独立変数とした重回帰分析解析を行った．共変量として，被験者の性別，震災前後の撮像間隔（日）を補正した．震災前の脳灰白質量と震災後の状態不安スコアが負相関を示す脳部位を震災後不安症状の脆弱性因子の神経基盤として，震災前後の脳灰白質量の変化量と震災後の状態不安スコアが正相関を示す脳部位を震災後不安症状の獲得因子として評価した．脳画像解析は，全脳での検定を行い，多重比較補正はクラスターサイズによる補正を行い[6]，統計閾値は p＝0.05 とした．

倫理的手続き

本研究は，東北大学大学院医学研究科倫理委員会の承認を得ている．また，ヘルシンキ宣言に則り，口頭および書面により実験の必要性，安全性について説明を行い，全被験者から書面による同意書を得た．また，震災前のデータの再利用に関しても，書面による同意を得ていた．

結　果

脳形態画像解析の結果，右腹側前帯状皮質において CAPS スコアと震災前の脳灰白質量が有意な負相関を（**図 1a**），左眼窩前頭皮質において震災前後の脳灰白質変化量と有意な負相関を示した（**図 1b**）．また，右前帯状束において状態不安スコアと震災前の FA が有意な負相関を（**図 2a**），左前帯状束および左鉤状束において震災前後の FA 変化量と有意な正相関を示した（**図 2b**）．

考　察

本研究により，震災後精神症状の脆弱性因子の神経基盤として，右前帯状皮質の脳灰白質体積減少および右前帯状束の脳白質統合性の低下が，震災後精神症状の獲得因子の神経基盤として左眼窩前頭皮質の減少および左帯状束・鉤状束の白質統合性の上昇が認められた．

前帯状束は前帯状皮質から延びる神経線維を含み，大脳辺縁系の一部の構成要因としても知られている[10]．その機能として，恐怖や不安の処理が知られており[5]，震災後の不安症状の病態にも

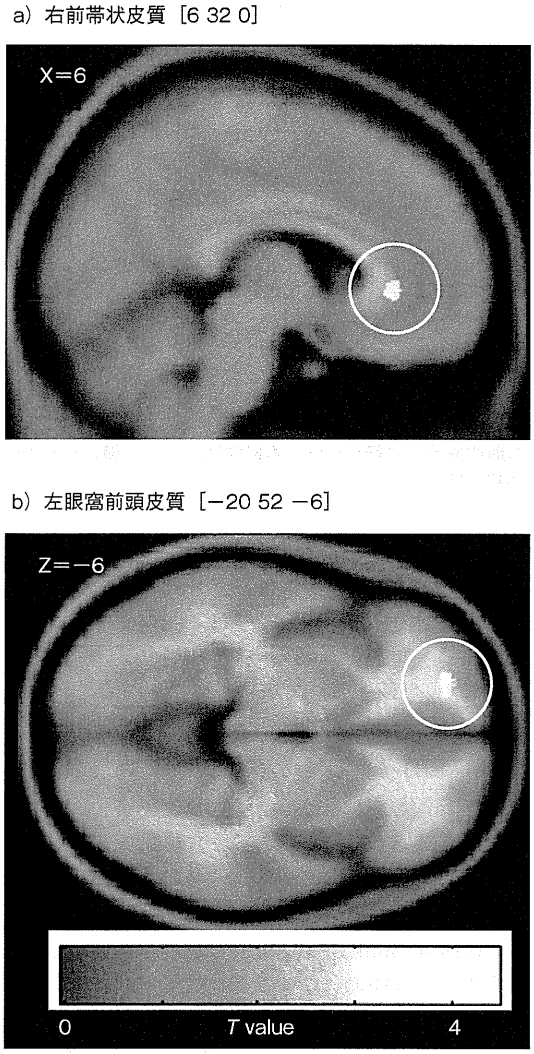

図1　震災後 PTSD 症状の脆弱性・獲得因子の神経基盤（文献[22]より改変）

a）PTSD 症状の脆弱性因子の神経基盤．震災前の右腹側前帯状皮質の局所灰白質量と震災後 CAPS スコアが有意な負相関を示した．b）PTSD 症状の獲得因子の神経基盤．震災前後の左眼窩前頭皮質の局所灰白質量の変化量と震災後 CAPS スコアが有意な負相関を示した．

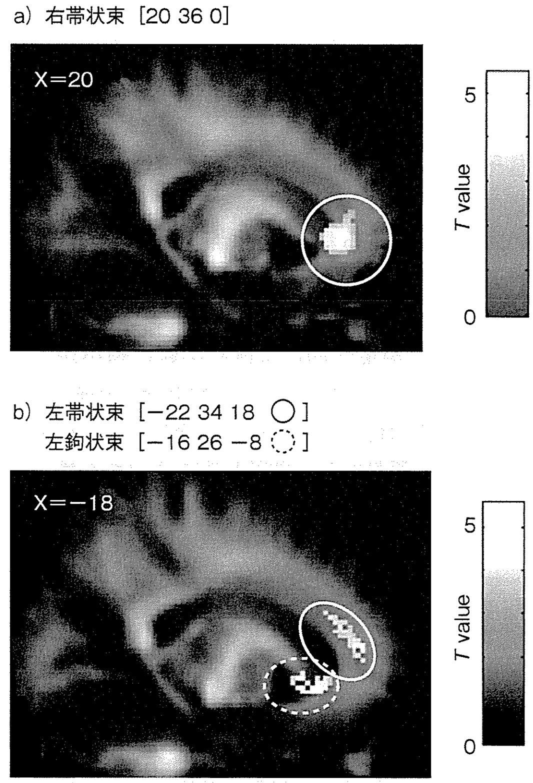

図2　震災後不安症状の脆弱性・獲得因子の神経基盤（文献[23]より改変）

a）震災後不安症状の脆弱性因子の神経基盤．震災前の右前帯状束の白質統合性と震災後の状態不安スコアが有意な負相関を示した．b）震災後不安症状の獲得因子の神経基盤．震災前後の左帯状束・鉤状束の白質統合性の変化量と震災後の状態不安スコアが有意な負相関を示した．

深く関与している[12]．本研究により，これら恐怖や不安の処理の機能不全が，震災後精神症状の脆弱性因子として関与することが示唆された．また，眼窩前頭皮質は，隣接する鉤状束を介して情動処理に関与する扁桃体の活動と協調し[9]，情動制御に重要な役割を果たしている[16]．PTSD 患者においても恐怖記憶の消去[2]や情動制御[15]の際に眼窩前頭皮質の活動が低下しているとの報告もある．さらに，左前帯状束／鉤状束の白質統合性の増加は，震災後不安症状の脆弱性因子として不安や恐怖の処理機能不全が存在し，情動制御の必要性が高まったことが震災後早期の不安症状の獲得の背景に存在していたことが示唆された[23]．

上述の脳形態変化は各々が隣接する領域であることから，解剖学的な位置関係は概ね一致していた．右前帯状皮質の灰白質量と，隣接する右帯状束の白質統合性はともに精神症状と負相関を示しており，灰白質量の減少と白質統合性の低下はともに当該領域の機能不全を示唆する所見として，震災後精神症状の脆弱性因子として解釈されている[22]．一方で，左側眼窩前頭皮質の灰白質変化