Gray or white matter intensity was not significantly correlated with total CAPS score in any other brain regions.

In summary, morphological analysis using VBM revealed a significant regional volume reduction in the left ACC gray matter in traumatic survivors with PTSD compared with those without PTSD. This reduced ACC gray matter volume was significantly related to the severity of the disorder in PTSD subjects. No significant structural difference was found in any other region, including the medial temporal region. These findings are consistent with several other neuroimaging studies that have suggested dysfunction or neuronal loss in ACC in patients with PTSD (Bremner et al. 1999a; De Bellis et al. 2000; Shin et al. 2001). The results of the present and previous studies support a neuroanatomic model of PTSD that posits a failure of ACC to inhibit a hyperresponsive amygdala (Bremner et al. 1999b; Rauch et al. 2000; Shin et al. 2001). These considerations suggest that the ACC may be one of the most important regions in the pathophysiology of PTSD.

3. Relationship Between Structural and Electrophysiological Abnormalities

PTSD is associated with cognitive deficits, specifically impaired attention, such as difficulty in concentrating and sustaining attention on target tasks. These attentional problems in PTSD have been evaluated using auditory event-related potentials (ERPs). The P300 has been shown to reflect the ability to allocate attentional resources and update environmental context. The existing literature suggests that the P300 is reduced in patients with PTSD (McFarlane et al. 1993; Metzger et al. 1997), although these findings have not been uniformly replicated (Kimble et al. 2000). However, no study to date has evaluated neuroanatomical correlates of P300 abnormalities in PTSD, despite many independent publications of structural MRI abnormalities in PTSD such as those in ACC (Yamasue et al. 2003) and hippocampus (Gilbertson et al. 2002), brain regions thought to be associated with P300 generation. Consequently, we coevaluated auditory P3b and MRI in never-treated, comorbidity-free patients with PTSD following the Tokyo subway sarin attack (Araki et al. 2005). The victims of the same events who did not develop PTSD served as the control group. We performed correlational analyses between ERP indices and clinical symptoms, and structural MRI abnormalities of the ACC that we have recently reported in the current sample using VBM (Yamasue et al. 2003).

Out of the 47 victims recruited, 8 victims with PTSD and 13 victims without PTSD were identified. Six subjects with PTSD and 12 subjects without PTSD overlapped with the VBM study. The subjects performed an oddball task to elicit P300 in a soundproof room. They were presented with a series of auditory stimuli with a fixed interstimulus interval of 1500 msec. Eight-five percent of the stimuli were tones of 1000 Hz, and the other 15% were tones of 2000 Hz. The subjects were instructed to press a button upon hearing the infrequent, high pitch tones. Scalp elec-

troencephalogram was recorded at Fp1, Fp2, F3, Fz, F4, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, and Oz according to the international 10-20 electrode system, referenced to linked earlobes.

Regional voxel-based analyses of the images were performed in SPM99 after covarying for global normalization in an analysis of covariance (ANCOVA) model, which removes global gray matter intensity for each subject and normalizes the segmented brain images to the same total amount of gray matter while preserving regional differences in gray matter intensity. The P300 amplitudes at Pz were treated as the covariates of interest. To test hypotheses about regionally specific covariate effects, the estimates were compared using linear contrasts (positive or negative correlation).

Groups differed significantly in P300 amplitude (main effect of group: $F[1,19] = 4.80$, $P = 0.041$), while the group-by-electrode interaction was not significant ($F[4,76] = 1.21$, $P = 0.32$, epsilon = 0.70). For P300 latency, there was no significant main effect of group ($F[1,19] = 0.49$, $P = 0.49$) or group-by-electrode interaction ($F[4,76] = 0.35$, $P = 0.80$, epsilon = 0.80). In the PTSD group, there was a significant negative correlation between present score of the cluster C of the CAPS and P300 amplitude at Pz (rho = –0.850, $n = 8$, uncorrected $P = 0.007$; corrected $P = 0.042$ after Bonferroni correction, two-tailed). Within victims with PTSD, there was a trend-level positive correlation between the amplitude of P300 at Pz and gray matter density in the left ACC (peak coordinate = [–12, 32, 22], corrected $P = 0.077$, $z = 4.08$; SVC = 0.904 ml based upon $k = 113$ obtained in the main analysis of the VBM study). This result suggests that reduced ACC gray matter volume may underlie auditory selective attention deficits as indexed by P300 in patients with PTSD. In the other regions, gray or white matter density was not significantly correlated with the amplitude of P300. In contrast, there was no voxel within the left ACC correlated with the amplitude of P300 in victims without PTSD.

In summary, we replicated a significant reduction in P300 amplitude in the oddball task in PTSD patients who were victims of Tokyo subway sarin attack compared with those victims who did not develop PTSD. We found a significant correlation between P300 amplitude and avoidance/numbing cluster score of the CAPS. Furthermore, lower P300 amplitudes showed a trend toward significant correlation with lower gray matter voxel densities of ACC in victims with PTSD, whereas such an association was not present in victims without PTSD. Although P300 has multiple generators in humans, a smaller ACC volume in the individuals with PTSD may be proportional to lower functioning of this brain region, which is one of the generators of P300, thus resulting in a tighter structure-function relationship in the PTSD group. These results provide evidence that electrophysiological deficits in controlled attention in PTSD are linked to underlying brain morphological abnormalities.

4. Functional Abnormalities in PTSD

The purpose of this functional MRI study (Sakamoto et al. 2005) was to detect dysfunctional areas common to PTSD in the whole brain at high temporal and spatial resolution, and to obtain clues to elucidate the neural mechanisms of PTSD. In previous imaging studies of brain function in PTSD, narrations, photographs, or sounds of traumatic experiences have been directly presented to subjects, and brain activity during stimulation has been measured by positron emission tomography (PET) or single photon emission computed tomography (SPECT). However, because one of the major symptoms in PTSD patients is marked fear associated with traumatic experience, explicit presentation of traumatic stimuli may cause excessive distress and be difficult to perform in many subjects. The results of earlier studies have suggested functional abnormalities in the temporal area, occipital area, amygdala, cingulate gyrus, and frontal area during exposure to symptom provocation stimuli, but findings have been inconsistent among the studies.

The disagreement between the results of previous studies may be because excessively strong stimuli induced a variety of different reactions in subjects, or because changes in blood flow not directly associated with PTSD symptoms were also detected due to the long scan intervals used in the PET or SPECT measurements. Only a small number of studies avoided explicit presentation of traumatic stimuli. In these studies, masked images were presented for a very short period, which was below the conscious perceptual threshold, and measurements were performed by functional MRI with high temporal resolution. The regions of interest (ROI) that were examined in these studies were the amygdala and anterior cingulate gyrus or the occipital lobe. However, dysfunctions associated with PTSD are not limited to these areas, and studies that examine the whole brain are necessary. Most previous functional imaging studies of PTSD have used only combat veterans or victims of sexual abuse as PTSD subjects. This limitation of subjects is advantageous regarding subject homogeneity. However, PTSD results from various causes, such as accidents, terrorism and natural disasters. Hence, the investigation of functional abnormality common to PTSD arising from various causes is also important to elucidate the underlying neural mechanisms.

Sixteen patients with PTSD and 16 healthy persons participated in the following study. Traumatic images under the conscious perceptual threshold, including scenes of earthquakes, traffic accidents, ambulances, emergency rooms, and crimes, were presented to the participants. Although the images appeared as only flowering plants, traumatic images were inserted for a very short period. Each participant viewed the images for 4 min. This period comprised eight blocks (30 s each). The first, third, fifth, and seventh blocks were REST blocks, and the second, fourth, sixth, and eighth blocks were TRAUMA blocks. In each REST block, the images were changed in the following order: an image of a red cross below the conscious perceptual threshold (0.033 s), an image of flowering plants (0.167 s), and a black blank image (0.300 s). In each TRAUMA block, images were changed in the following order: an image of a traumatic scene below the cognition threshold (0.033

s), an image of a flowering plant (0.167 s), and a black blank image (0.300 s).

Functional images of both groups were evaluated for the whole brain. Separate analyses within the PTSD and healthy groups were performed using one-sample *t*-tests employing a random-effects model in SPM99. In addition, differences in brain activation between the PTSD and healthy groups were analyzed by a two-sample *t*-test. A level of $P < 0.01$ uncorrected for multiple comparisons with a minimum cluster size of 20 was chosen for the activation threshold. Correlations between activations and CAPS score or Dissociative Experience Scale-II (DES-II) score were evaluated in the PTSD group.

The areas activated by the masked traumatic stimuli were analyzed separately by one-sample *t*-tests in SPM99 for the PTSD and the healthy groups. In the healthy group, significant activations (uncorrected $P < 0.01$) associated with the masked traumatic stimuli was observed in the right inferior parietal lobule (Talairach coordinates: [44, –56, 48]; Brodmann Area [BA] 40; $z = 3.57$), left inferior parietal lobule ([–28, –76, 42]; BA 40; $z = 3.36$), right precentral gyrus ([28, –16, 52]; BA 4; $z = 3.55$), left precentral gyrus ([–28, –18, 54]; BA 4; $z = 3.33$), and left middle frontal gyrus ([–34, 20, 44]; BA 8; $z = 3.30$; [–16, 14, 26]; BA 9; $z = 3.19$). In the PTSD group, activation was not observed in these areas, but significant marked activation (uncorrected $P < 0.01$) associated with the masked traumatic stimuli was observed in the parahippocampal region, including left parahippocampal gyrus and tail of left hippocampus ([–14, –42, –4]; BA 19; $z = 3.79$). Differences in activation between the PTSD and healthy groups were analyzed by two-sample *t*-tests. The PTSD group showed significantly greater activation (uncorrected $P < 0.01$) in the left parahippocampal gyrus ([–12, 44, –4]; BA 19, $z = 3.15$), compared with the healthy group. The healthy group showed significantly greater activations in the left superior frontal gyrus ([-8, –2, 52]; BA 6; $z = 3.84$), left cerebellum ([–18, 72, –22]; $z = 3.81$), right cerebellum ([20, –46, –12]; z = 3.67), and right precentral gyrus ([28, –18, 56]; BA 4; $z = 3.10$), compared wih the PTSD group. In the PTSD group, the percent fMRI signal change in the left parahippocampal gyrus/tail of left hippocampus (a region within a 10-mm radius from the peak of activation, [–14, –42, –4]) was significantly correlated with the dissociation symptom score on the DES-II (Pearsons $r = 0.499$, $P < 0.05$). These results imply that PTSD patients cannot inhibit hyperactivity in the limbic system associated with unconscious recollection of emotional memory induced by subliminally presented threatening stimuli. An important implication may be that our experimental design is potentially useful for clinical application, because we used both a physically and psychologically noninvasive method to detect differential activity in PTSD patients. Further sophistication of this paradigm would hopefully lead to objective diagnosis and monitoring of treatment response for PTSD.

5. Conclusions

Our studies using Japanese patients confirm that cortical abnormalities in PTSD are

located in limbic regions and in medial prefrontal cortex, which regulates the limbic system. Also, our VBM and fMRI results may be potentially useful for the clinical assay of PTSD. Future research should aim at a better convergence of knowledge from basic neuroscience and clinical studies, including: (1) further clarification of whether these abnormalities represent preexisting vulnerability factors or posttraumatic toxic changes or both; and (2) investigation of how genetic backgrounds, early environmental effects, or their interaction lead to the possible vulnerability.

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Neuroanatomy in monozygotic twins with Asperger disorder discordant for comorbid depression

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Significant genetic contributions to autism spectrum disorders (ASDs) have been reported.[1] However, specific genetic variants that contribute to ASD have not been conclusively identified. Recently, interest has centered on an approach aimed at identifying potential intermediate phenotypes such as neuroanatomic abnormalities, as such findings may facilitate the endeavor to localize specific genetic variants.[2] Here we report common and distinct neuroanatomic abnormalities of a pair of monozygotic twins concordant for Asperger disorder (ASP) but discordant for psychiatric comorbidity. The current study applied individual whole-brain voxel-based morphometry (VBM) to quantitatively identify neuroanatomic abnormalities.

Participants. A pair of 22-year-old male twins with ASP was recruited from the Department of Neuropsychiatry, Hospital of Tokyo University, Japan (see table E-1 on the *Neurology* Web site at www.neurology.org). Diagnosis of ASP was determined for each patient according to the Diagnostic and Statistical Manual for Mental Disorders-IV (DSM-IV) (reference E-1) and further confirmed according to the International Classification of Diseases-10 (reference E-2) criteria through a consensus of two trained child psychiatrists. DNA fingerprint probes were used to establish zygosity, using an eight-probe single-locus DNA profile. DNA testing was performed to rule out fragile X syndrome. Although both the twins showed normal intelligence, one of them had current major depression as a psychiatric comorbidity (for detailed clinical characteristics of each twin, see table E-1). Eighty-two Japanese men without neuropsychiatric disorder served as a comparison sample (mean [SD] age = 28.9 [4.0] years, range 22 to 39 years). The participants were interviewed by trained psychiatrists and screened for the presence or absence of DSM-IV axis I disorder (reference E-3). All subjects were right-handed based on the Edinburgh Inventory (reference E-4). The Ethical Committee of the Faculty of Medicine, University of Tokyo, approved of this study. After a complete explanation, written informed consent was obtained from all participants.

MRI acquisition and analysis. The methods of MRI acquisition and image processing have been described in detail elsewhere.[3] In brief, the MRI data with 0.9375 × 0.9375 × 1.5–mm voxels were obtained from all subjects using a 1.5 T scanner. Processing of the acquired images was similar to that described in our previous study[3] except that, rather than SPM99, the current study employed SPM2, which includes spatial normalization using study-specific customized template, tissue segmentation with extracting nonbrain voxels and smoothing with 12-mm full width at half-maximum. Furthermore, global gray matter, white matter, and CSF volumes were calculated from the optimized VBM procedure.[4] Statistical comparisons of the processed images between the twin pair (n = 2) and controls (n = 82) and between each twin (n = 1) and controls (n = 82) were performed using an analysis-of-covariance model with age and intracranial volumes as confounding covariates. For individual VBM, a statistical analysis method similar to that of a previous study[5] was employed. Significance levels were set at corrected $p < 0.05$.

Results. Significantly reduced gray matter voxel densities were found in the left superior temporal gyrus including superior temporal sulcus (STS), left fusiform gyrus, right amygdala, and right prefrontal cortex (PFC) in twins with ASP as compared with control subjects. Individual VBM revealed reduced gray matter densities in the left STS, fusiform, and right PFC commonly in both twins. In contrast, the reduced gray matter densities in the right amygdala were evident in the twin with comorbid depression but not in the co-twin without mood disorder. No significant group difference in voxel density was detected for other gray matter regions or any of the white matter regions (figure, page 492).

Discussion. Both of the monozygotic twins concordant for ASP had significantly smaller than normal left STS, left fusiform gyrus, and right PFC, regions important for social cognition and behavior (reference E-5). The current findings are generally consistent with previous structural MRI studies in persons with ASD, although some inconsistencies exist in the literature.[6] These findings further suggest a contribution of shared genetic factors to underlying the structural abnormalities in ASD. Of particular interest, however, reduction of the amygdala was evident only in the twin with comorbid depression. Here the difference in age distribution between the twins and the control group and the medication effect on the depressed twin should be considered. Taking into account the age-associated decrease in brain volume[4] and neurotrophic effects of lithium and antidepressants, (reference E-6) however, the elimination of these effects would likely only strengthen the statistical difference. Taken together with the amygdala volume reduction reported in some forms of depression and anxiety (reference E-7), our results have an important implication for the interpretation of structural abnormality of amygdala, which has been extensively demonstrated in adults with ASD (reference E-8). Our results are also in accordance with recent animal studies[7] suggesting a role of the amygdala in abnormal fear and anxiety rather than abnormal social behavior in ASD.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the August 9 issue to find the title link for this article.

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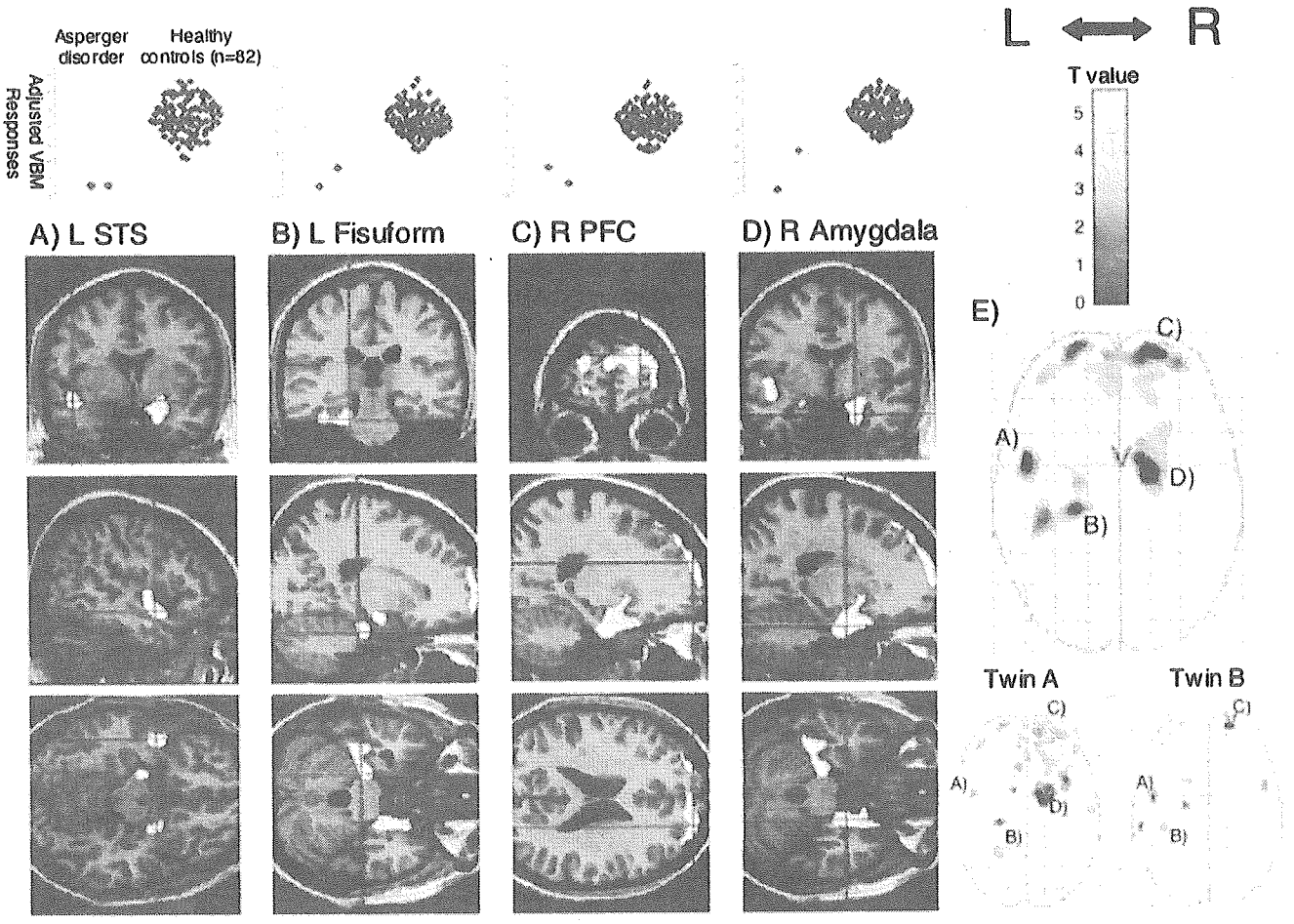

Figure. Morphological abnormalities in twins with Asperger disorder. (Left bottom, A through D) Gray matter voxels with reduced density in the twins with Asperger disorder as compared with normal control subjects (n = 2 vs n = 82) were rendered onto orthogonal slices of the normal template MR images. Voxel threshold: uncorrected p< 0.001; significantly abnormal regions: left superior temporal gyrus including superior temporal sulcus (A): peak coordinate at (x, y, z): (−49, 2, -13), spatial extent k = 1,934, Z(2,81) = 4.94, corrected p = 0.015; left fusiform gyrus (B): (−23, −23, −26), Z = 4.97, k = 3,590, corrected p = 0.013; right prefrontal cortex (C): (20, 61, 23), Z = 5.01, k = 9,617, corrected p = 0.011; right amygdala (D): (18, -3, -26), Z = 5.14, k = 6,514, corrected p = 0.006. (Left top, A through D) Plots of adjusted voxel-based morphometry responses at each brain region. (E) Statistical parametric maps in the axial projection showing gray matter voxels with reduced density in the twins (n = 2; upper map) and each twin (lower maps) as compared with normal controls (n = 82). A significant reduction in the right amygdala (D) found in Twin A was absent in Twin B. Voxel threshold: uncorrected p< 0.001.

A patient with left ventricular thrombus and recurrent stereotypic TIAs

Christine M. Bower, MD; Lola Morgan, MD; and Bruce Ovbiagele, MD

Stereotyped TIAs are presumed to occur secondary to a fixed flow-limiting stenosis of medium/large vessels in the cervicocephalic arterial tree[1] or in situ disease of small deep penetrating arteries in the brain.[2] We report the unusual case of a patient with recurrent stereotypic TIAs associated with the presence of a left ventricular thrombus and with delayed focal ischemia on the T1-weighted MRI sequence.

Case report. A 60-year-old nonsmoking Filipino man, with an unremarkable medical history, reported three distinct episodes of sudden-onset right-sided weakness and numbness and difficulty with expression. These episodes occurred every 2 hours over a 6-hour period. The first two spells lasted 10 minutes, and the third spell lasted 20 minutes.

On admission, his blood pressure was 155/90 mm Hg and pulse was 61 beats/min. Otherwise, general and neurologic exams were normal. Brain CT showed no evidence of infarct. Because of the temporal and stereotypic nature of his spells, we felt that the patient had a fixed flow-limiting stenosis in his left internal carotid or middle cerebral arteries causing hemodynamic compromise. The patient was admitted to the intensive care unit and placed on a heparin drip. MRI of the brain showed a mild hyperintensity on diffusion-weighted imaging (DWI) with corresponding apparent diffusion coefficient hypointensity in the left head and body of the caudate and a portion of the anterior internal capsule (figure, A and B). There was no corresponding signal change on T1-weighted, T2-weighted, or fluid-attenuated inversion recovery images. MR angiograms of the neck and circle of Willis were within normal limits (see the figure, C and D). Despite his stereo-

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Parahippocampal activation evoked by masked traumatic images in posttraumatic stress disorder: A functional MRI study

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Posttraumatic stress disorder (PTSD) has been widely studied, but its neural mechanism is still unclear. The purpose of this study is to identify dysfunctional areas in PTSD throughout the whole brain to help to elucidate the neural mechanisms of PTSD. Sixteen patients with PTSD and sixteen healthy controls participated in this study. Traumatic images under perceptual threshold including scenes of earthquakes, traffic accidents, ambulances, emergency rooms, and crimes were presented to the participants, and brain activation was measured using functional MRI. Functional brain images of both groups were evaluated with random effect analysis for the whole brain. In the control group, activation in the ventral frontoparietal areas correlated significantly with presentation of the masked traumatic stimuli. In the PTSD group, activation was not observed in these areas, but significant activation correlated with the masked traumatic stimuli in the parahippocampal region including the left parahippocampal gyrus and tail of the left hippocampus. These results suggest that in PTSD patients activation in the ventral frontoparietal network associated with visual attention processing is attenuated, while the left hippocampal area associated with episodic and autobiographical memory is abnormally easily activated. This pattern of activation corresponds well to the clinical characteristics of PTSD, in which even slight traumatic stimuli tend to induce intrusive recollection or flashbacks, despite a general decrease in attention and ability to concentrate.

Keywords: Posttraumatic stress disorder; Neuroimaging; Functional MRI

Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric condition characterized by a variety of symptoms associated with memory and emotion, which arises after experiencing or witnessing traumatic life-threatening events. The symptoms of PTSD include sleep disturbance, impaired memory, depression, tendency to be easily startled, and re-experiencing, which can result in decreased social and occupational function. PTSD has attracted wide attention from a mental health care perspective for victims of disasters, accidents, terrorism, and war. However, the underlying neural mechanism of the disorder is still unclear, and investigation of the pathology of PTSD and the establishment of objective diagnostic parameters are important issues.

Previous brain volumetry studies have repeatedly shown smaller hippocampal volume in patients with PTSD (Bremner et al., 1995, 1997; Gilbertson et al., 2002; Gurvits et al., 1996; Stein et al., 1997). Pitman and colleagues recently reported that PTSD patients exhibited selectively decreased anterior cingulate cortex and subcallosal cortex volumes (Rauch et al., 2003); furthermore, the presence of abnormally large cavum septum pellucidum is a familial vulnerability factor for PTSD (May et al., 2004). Concerning the relationship between hippocampal structure and function, Bremner et al. co-evaluated the structural volume of the hippocampus using MRI, and brain function using PET during hippocampal-based verbal declarative memory tasks, and observed both volume reduction and reduced function in the hippocampus in PTSD patients, compared with non-PTSD subjects (Bremner et al., 2003).

Shin et al. (2004) observed an abnormal rCBF response in the hippocampus of firefighters with PTSD during explicit recollection of nonemotional material. In the PTSD group, symptom severity was positively associated with rCBF in hippocampus and the parahippocampal gyrus. The PTSD group also had significantly smaller right (and a trend for smaller left) hippocampal volumes than the control group.

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Brain functional imaging studies of symptom provocation in PTSD have been repeatedly reported, but the results are for the most part inconsistent. Bremner et al. (1999) presented images and sounds of combat scenes to 10 Vietnam combat veterans with PTSD and to 10 veterans without PTSD and performed [^{15}O]-H_2O PET measurements. Relative to controls, the PTSD group showed decreased blood flow in the medial prefrontal cortex, middle temporal gyrus, and frontal cingulate gyrus and increased blood flow in the posterior cingulate gyrus and left precentral gyrus. Shin et al. (1999) performed CO_2 PET during narration of a traumatic experience with 8 females with PTSD who were victims of sexual abuse and 8 control females who had not suffered abuse. Blood flow increased in the orbitofrontal cortex and anterior temporal pole in both groups, but the increase was more marked in the PTSD group. In addition, compared with the healthy group, the PTSD group showed decreased blood flow in a wide area in the frontal, temporal, and occipital lobes. Lanius et al. (2001) performed functional MRI during narration of a traumatic experience to 9 PTSD patients and 9 non-PTSD controls. Compared with the control group, the PTSD group showed significantly decreased activity in the thalamus, anterior cingulate gyrus, and medial prefrontal cortex.

Rauch et al. (2000) performed functional MRI during presentation of masked visual stimuli to 8 Vietnam combat veterans with PTSD and 8 veterans without PTSD. As visual stimuli, frightening facial expressions masked by neutral facial expressions were presented using the following method. An image of a frightening face was presented to the subjects for too short a duration to be recognized (0.033 s), and immediately after this, an image of a neutral face was presented. Compared with the non-PTSD control group, the PTSD group showed marked activation of the amygdala while observing frightening images. Hendler et al. (2003) presented combat-related images for a very short duration (0.020–0.080 s) masked by mosaic images to 10 combat veterans with PTSD and 10 veterans without PTSD and observed significantly more marked activation of the visual cortex in the PTSD group than in the non-PTSD group.

The studies by Rauch et al. and Hendler et al. adopted a masked stimulus presentation method in which visual stimuli are presented for a very short period, such that subjects cannot recognize the image. There have been many studies on masked visual stimulation for non-PTSD subjects that have examined skin conductance responses (SCR) (Groeger, 1984), event-related potentials (Brazdil et al., 2001), and brain functional images (Sheline et al., 2001; Whalen et al., 1998). The minimum stimulus period that induces physiological responses is called the cognition threshold, and this is generally 0.030–0.050 s for visual stimulation.

Brazdil et al. (2001) reported interesting results using intracranial event-related potential measurements. They showed that the brain areas activated during masked visual stimulation are similar to those activated during recognizable visual stimulation but that the extent of the activation during masked stimulation is smaller than that during recognizable stimulation. This led to the conclusion that recognition of visual stimulation depends on an extensive neural network, including the prefrontal area and temporal neocortex activates.

The purpose of the present study is to detect dysfunctional areas common to PTSD in the whole brain at high temporal and spatial resolution and to obtain clues to elucidate the neural mechanisms of PTSD. In previous imaging studies of brain function in PTSD, narrations, photographs, or sounds of traumatic experiences have been directly presented to subjects, and brain activity during stimulation has been measured by PET or SPECT. However, in PTSD patients, one of the major symptoms is marked fear associated with traumatic experience and, therefore, explicit presentation of traumatic stimuli causes excessive distress and is difficult to perform in many subjects. The results of earlier studies have suggested functional abnormalities in the temporal area, occipital area, amygdala, cingulate gyrus, and frontal area during exposure to symptom provocation stimuli, but findings have been inconsistent among the studies.

The disagreement between the results of previous studies may be because excessively strong stimuli induced a variety of different reactions in subjects or because changes in blood flow not directly associated with PTSD symptoms were also detected due to the long scan intervals used in the PET or SPECT measurements. Only the studies by Rauch et al. (2000) and Hendler et al. (2003) avoided explicit presentation of traumatic stimuli. In these studies, masked images were presented for a very short period, which was below the cognition threshold, and measurements were performed by functional MRI with high temporal resolution. However, the regions of interest (ROI) that were examined in these studies were the amygdala and anterior cingulate gyrus or the occipital lobe, and not the whole brain. However, dysfunctions associated with PTSD are not limited to these areas, and studies that examine the whole brain are necessary.

Most previous functional imaging studies of PTSD have used only combat veterans or victims of sexual abuse as PTSD subjects. This limitation of subjects is advantageous regarding subject homogeneity. However, PTSD results from various causes, such as accidents, terrorism, and natural disasters. Hence, the investigation of functional abnormality common to PTSD arising from various causes is also important to elucidate the neural mechanism underlying PTSD.

Methods

Participants

Sixteen Japanese right-handed outpatients with PTSD (eight males and eight females; mean age ± standard deviation, 42.3 ± 13.6) who had visited the Kanto Medical Center NTT and the University of Tokyo Hospital participated in this study.

Diagnoses were performed according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; American Psychiatric Association) and confirmed using CAPS (Clinician-Administered PTSD Scale; National Center for Post-traumatic Stress Disorder) by two trained clinicians. Diagnoses of PTSD were reconfirmed 1 month later to fulfil all the criteria of PTSD in DSM-IV again. The comorbidity was also diagnosed using DSM-IV by the same clinicians.

Sixteen healthy right-handed volunteers (eight males and eight females; mean age ± standard deviation, 40.1 ± 11.4) were recruited as controls. They were matched with the patients for age, sex, and the dominant hand. They had no history of substance abuse or of any other medical, psychiatric, or neurological disorder that might affect brain function.

All subjects gave written informed consent to participate in the study. A structured interview using CAPS and DES-II (Dissociative Experience Scale-II; Carlson and Putnam, 1993) was performed for patients of the PTSD group to evaluate the severity of

PTSD symptoms and dissociation symptoms. CAPS is a standard clinical diagnostic scale used to evaluate the intensity and frequency of each symptom and the overall severity of PTSD in social and occupational dysfunction. DES-II is a scale for the evaluation of the severity of the dissociation experience, and its validity and reliability have been repeatedly confirmed (Carlson et al., 1993; Hansen and Gold, 1997; Ijzendoorn and Schuengel, 1996).

Stimulus presentation

The methods used in this study were approved by the Ethical Committee of Kanto Medical Center NTT and the Ethical Committee of the University of Tokyo.

The participants lay in the supine position in the MRI system. They viewed images on a semi-transparent screen through a mirror in the head coil of the MRI system. Images (90 cm in length and 120 cm in width) were presented on the semi-transparent screen placed 360 cm from the subject's eyes. Images were played using a digital video player (VLPD7, Sharp Ltd.) and projected onto the screen using a liquid crystal projector (LVP-2000, Mitsubishi Ltd.).

The images appeared to be only flowering plants, but actually traumatic images for very short period were inserted.

Each participant viewed the images for 4 min. This period comprised 8 blocks (30 s each), as shown in the center of Fig. 1. The 1st, 3rd, 5th, and 7th blocks were REST blocks, and the 2nd, 4th, 6th, and 8th blocks were TRAUMA blocks. In each REST block, the images were changed in the following order: an image of a red cross below the cognition threshold (0.033 s), an image of flowering plants (0.167 s), and a black blank image (0.300 s) (Fig. 1, upper panel). Each image appeared 60 times during a 30-s REST block. In each TRAUMA block, images were changed in the following order: an image of a traumatic scene below the cognition threshold (0.033 s), an image of a flowering plant (0.167 s), and a black blank image (0.300 s) (Fig. 1, lower panel).

A total of 20 types of traumatic images were inserted in a random order in Trauma block (Fig. 2). These images consisted of scenes associated with life-threatening crises, those coincident with criteria of PTSD in DSM-IV, such as earthquakes, fires, traffic accidents, ambulances, emergency rooms, and crimes. The images were selected from television news and dramas, and these types of images were generally avoided by PTSD patients in their daily life. The traumatic nature of these twenty images was validated by presenting them to a separate group of twelve healthy participants (six male and six female, mean age 30.7). For this validation exercise, the images were presented with a 0.5 s duration for each image so that they were consciously perceived, and Anxiety state scores of State-Trait Anxiety Inventory (STAI:Spielberger 1966) were measured before and after presentation of the images. The mean Anxiety-state score prior to presentation was 38.0 (SD = 6.51) and the mean Anxiety-state score after presentation was 45.1 (SD = 8.89). Ten subjects showed an increase in Anxiety-state scores, one subject showed no change, and another subject showed

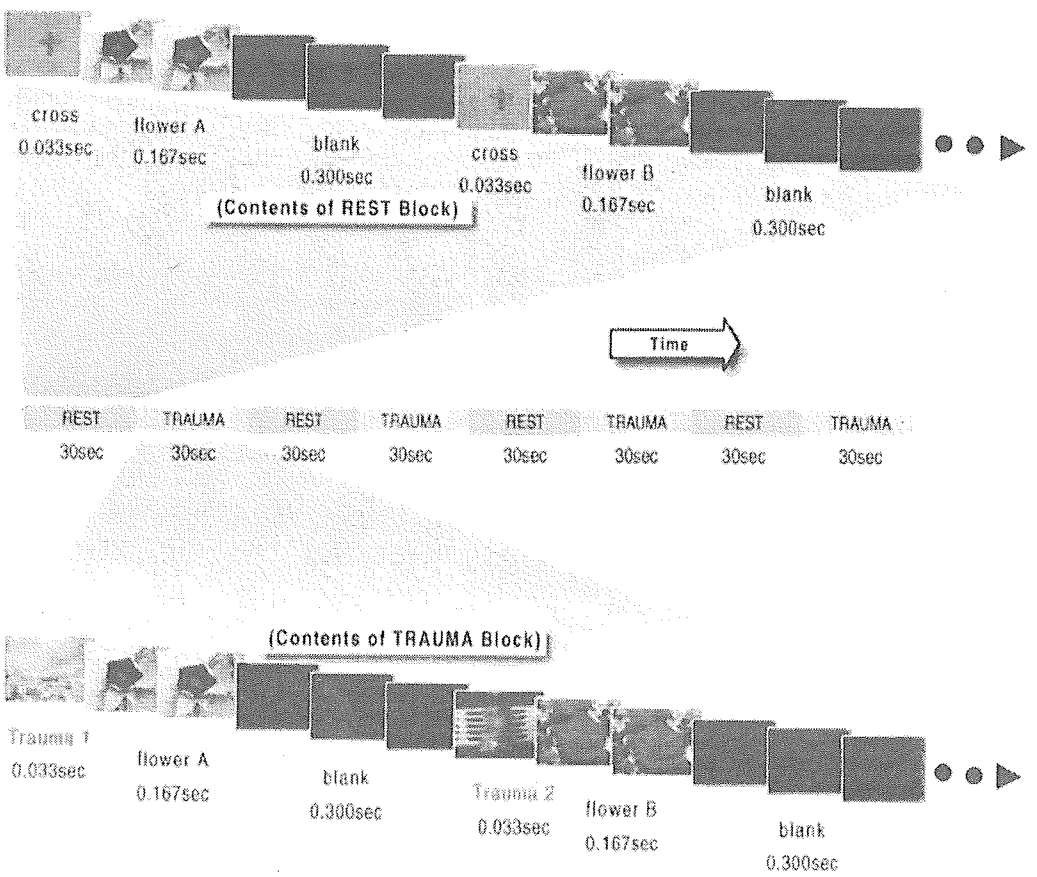

Fig. 1. Method of visual stimulation.

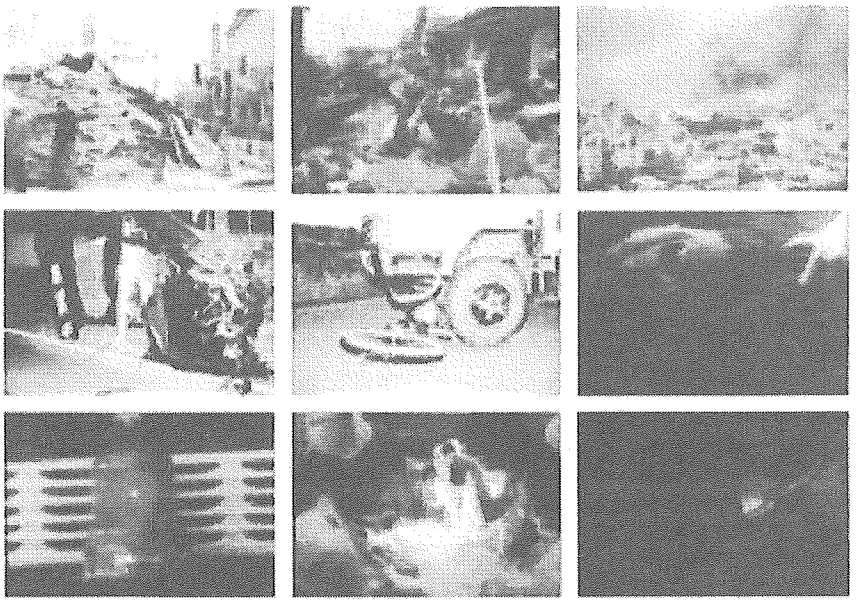

Fig. 2. Samples of images of traumatic events.

a decrease of 0.3%. It was therefore determined that the images were indeed of a traumatic nature.

A total of 20 types of flowering plant images were presented to mask the traumatic images (Fig. 3). Digital video images were composed of 30 frames per second, and insertion of a 0.033-s image was executed by replacing one video frame using digital video editing software (Premiere 6.0, Adobe Ltd.) on a Windows XP computer. In the present study, various kinds of traumatic images were used to detect dysfunctional areas common to patients with PTSD of various causes.

Data acquisition

Echo-planar images depicting blood-oxygen-level-dependent (BOLD) contrast (Cohen et al., 2002; Logothetis, 2002) were acquired using a 1.5 T Signa LX MRI system (General Electric, Milwaukee) at Kanto Medical Center NTT EC, under the following conditions: TR:3 s; TE:50 ms; flip angle: 90°; field of view: 240 mm; matrix: 64 × 64; spatial resolution: 3.75 × 3.75 × 6 mm; gap: 1 mm. 20 slices of axial images were collected to cover the whole brain, and the intercommissural line was determined to be the 9th slice from the bottom. 20 slices of T1-weighted images were simultaneously obtained as structural images for each subject.

Image analysis

Brain functional analysis depicting cognitive subtraction between the Trauma blocks and the Rest blocks was performed using SPM99 (Wellcome Department of Cognitive Neurology, London) (Friston et al., 1994, 1995a,b). Corrections were made for motion artifacts of the participants, and the images were standardized to the Talairach standard brain (Talairach and Tournoux, 1998). After smoothing with a full width half maximum (FWHM) of 10 mm, statistical parametric mapping analysis was performed, and the anatomical positions of brain activation were identified in

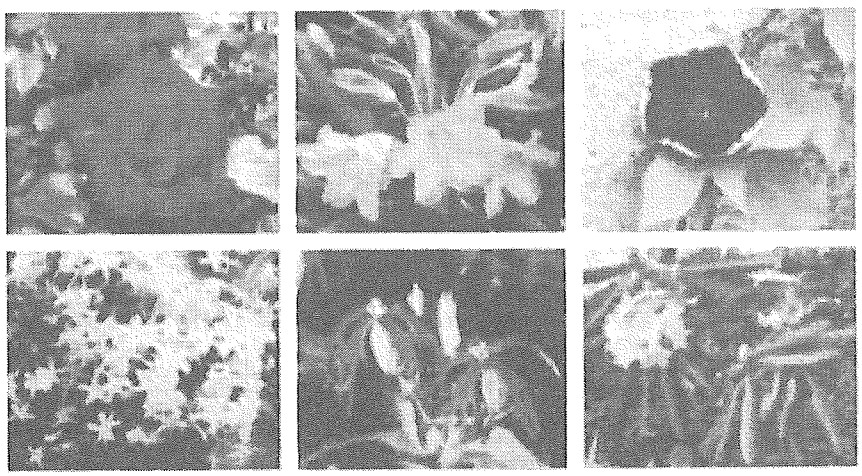

Fig. 3. Samples of images of flowering plants.

Table 1
Profiles of patients in the PTSD group

Case	Sex	Age	Present CAPS total score	DES-II score	Comorbidity	Traumatic episode	Age when the traumatic episode occurred	Length of the traumatic episode
1	M	68	106	13.6	–	A close friend of the participant was murdered and the participant himself was confined for several days and assaulted	48	1 week
2	M	26	43	29.3	Anxiety disorder	The participant was exposed to a toxic substance	26	1 day
3	F	32	75	18.6	–	The participant experienced imminent danger of violent sexual assault	31	1 day
4	F	53	56	7.1	–	A serious fire occurred at the participant's home and 2 days later a large truck crashed into the same house	53	2 days
5	F	31	60	38.6	–	The participant suffered repeated violent assaults (striking and kicking) by cohabitant	26	4 years
6	F	41	85	13.6	–	The participant's house was destroyed in the Kobe earthquake of 1995 following which her son came down with a sudden illness	34	6 months
7	M	50	58	16.1	Major depression	The participant discovered the body of a subordinate who had died several days previously of electrocution	48	1 day
8	M	35	59	22.5	–	During infancy, the participant experienced physical abuse and mistreatment from his parents repeatedly	3	6 years
9	M	25	95	8.6	–	The participant witnessed a murder and was subsequently pursued by a car driven by the murderer	24	1 day
10	M	48	79	19.6	–	The participant was thrown several meters through the air during a traffic accident	46	1 day
11	M	53	69	13.6	Anxiety disorder	The participant's wife died unexpectedly following a sudden illness	53	1 month
12	F	29	111	20.7	–	The participant was involved in a car accident in which her fellow passenger was killed and she herself suffered serious injuries	28	1 day
13	F	37	70	17.1	Major depression	The participant experienced imminent danger of violent sexual assault	36	1 day
14	F	46	85	14.3	–	The participant suffered serious injuries in an accident in which she was trapped between the vehicle and wall	45	1 day
15	F	35	76	15.0	Major depression	The participant's father died suddenly of hematemesis before her eyes	30	1 day
16	M	68	54	14.6	–	The participant's son died in a traffic accident and the participant identified the body	59	1 day

the Talairach coordinate system (Talairach and Tournoux, 1998). Data obtained from participants with head movements of 1.5 mm or more were excluded from the analysis because of the possible inadequate correction of motion artifacts. One female PTSD participant was excluded from the patient group because her head movement was more than 1.5 mm, thus leaving data from 16 PTSD patients for analysis.

Group analysis in the PTSD group and control group was performed using the one-sample t test employing random-effect model (Friston et al., 1999) of SPM99. In addition, differences in brain activation between the PTSD and control groups were analyzed by a two-sample t test. A level of $P < 0.01$ uncorrected for multiple comparisons and clustering criterion as minimum cluster size = 20 were chosen for the activation threshold. The possible correlation between the activation and the CAPS score or the DES-II score was evaluated in the PTSD group.

Results

Profiles of subjects

The profiles, CAPS score, DES-II score, and comorbidity of the subjects in the PTSD group are shown in Table 1. The traumatic episodes that had caused PTSD varied widely among the participants, and included major earthquakes, fires, crimes, traffic accidents, and abuse. Three participants had comorbid major depression and two had comorbid anxiety disorder. During stimulus presentation, 6 patients with PTSD and 3 controls felt that they momentarily saw human faces, but no participants developed discomfort or showed aggravation of symptoms.

Brain functional images

The areas activated by masked traumatic stimuli were analyzed by one sample t test of SPM99 for the PTSD group and the control group. In the control group, significant activation ($P_{\text{uncorrected}} < 0.01$) associated with the masked traumatic stimuli was observed in the right inferior parietal lobule (Talairach coordinates: 44, −56, 48; Brodmann area 40), left inferior parietal lobule (Talairach coordinates: −28, −76, 42; Brodmann area 40), right precentral gyrus (Talairach coordinates: 28, −16, 52; Brodmann area 4), left precentral gyrus (Talairach coordinates: −28, −18, 54; Brodmann area 4), and left middle frontal gyrus (Talairach coordinates: −34, 20, 44; Brodmann area 8; Talairach coordinates: −16, 14, 26; Brodmann area 9).

In the PTSD group, activation was not observed in these areas, but significant marked activation ($P_{\text{uncorrected}} < 0.01$) associated with the masked traumatic stimuli was observed in the parahippocampal region including left parahippocampal gyrus and tail of left hippocampus (Talairach coordinates: −14, −42, −4; Brodmann area 19/30). A 3-dimensional representation of this activated area superimposed on the Standard Brain Template of the Montreal Neurological Institute is shown in Fig. 4. and section images of the activation of PTSD group are shown in Fig. 5. The Talairach coordinates of the results are shown in Table 2.

Differences in activation between the PTSD and control groups were analyzed by two sample t test. The PTSD group showed significantly marked activation ($P_{\text{uncorrected}} < 0.01$) in the parahippocampal region including left parahippocampal gyrus and tail of left hippocampus (Talairach coordinates: −12, 44, −4; Brodmann area 19/30, z score: 3.15), compared to the control group. The control group showed significantly more marked activation in the left superior frontal gyrus (Talairach coordinates: −8, −2, 52; Brodmann area 6; z score: 3.84), left cerebellum (Talairach coordinates: −18, 72, −22; z score: 3.81), right cerebellum (Talairach coordinates: 20, −46, −12; z score: 3.67), and right precentral gyrus (Talairach coordinates: 28, −18, 56; Brodmann area 4; z score: 3.10), compared to the PTSD group.

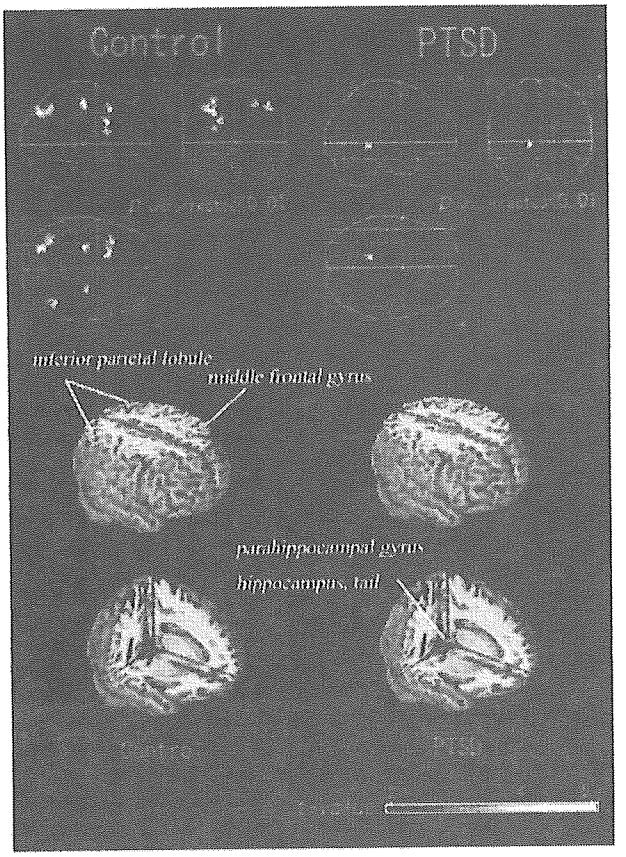

Fig. 4. The activation of the masked traumatic stimulation vs. control stimulation in control group and PTSD group. The left line indicates the control group, and the right line indicates the PTSD group. The uppermost row represents glassview images, and the middle and lower rows represent 3-dimensional overlays onto the Standard Brain Template of the Montreal Neurological Institute. Comparison at the same slice level showed significant activation of the parahippocampal gyrus in the PTSD group.

In the PTSD group, the % fMRI signal change in the parahippocampal region including left parahippocampal gyrus/tail of left hippocampus (a region within a 10 mm radius from the peak of activation; Talairach coordinates: −14, −42, −4) was significantly correlated with the dissociation symptom score on the DES-II scale (Fig. 6: correlation 0.499; $P < 0.05$). As Bonferroni correction was not applied, the correlation may not be robust, but this result suggests that there may be a relationship between activation of the parahippocampal region including the left parahippocampal gyrus/tail of left hippocampus and dissociation symptoms, such as re-experiencing and flashbacks, in PTSD. No correlation was observed between the % fMRI signal change in the parahippocampal region including the left parahippocampal gyrus/tail of left hippocampus and the severity of PTSD symptoms evaluated by the CAPS method. No significant correlations were

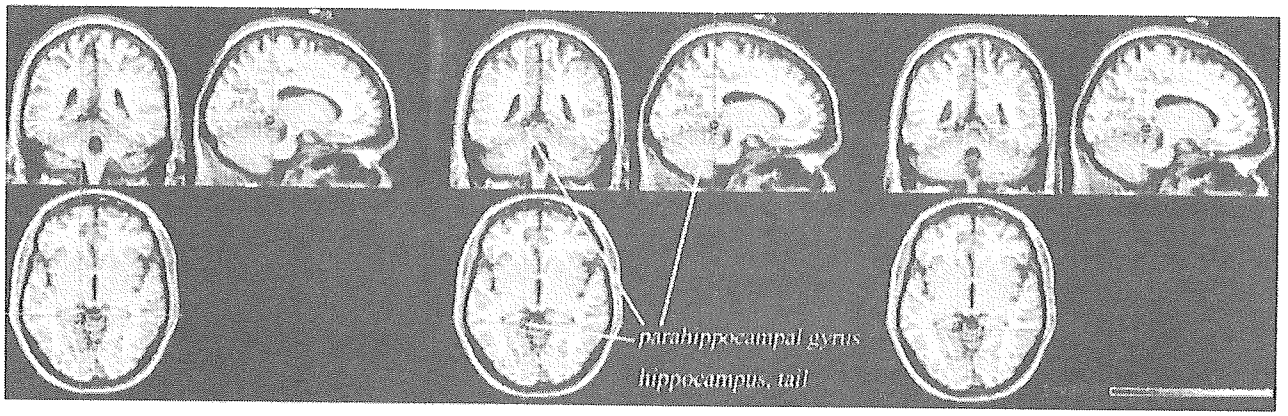

Fig. 5. Activation of PTSD group (section image).

observed between the % fMRI signal change in the same region and participant's age when the traumatic episodes occurred nor length of traumatic episode.

Discussion

During masked presentation of traumatic images, activation of the parahippocampal region including left hippocampal gyrus/tail of left hippocampus was observed in the patients with PTSD. However, activations in the bilateral inferior parietal lobules, middle frontal gyrus, and precentral gyrus, which were observed in healthy controls, were not observed in PTSD patients. Previous studies have suggested that the cooperative activation of parietal areas, including the inferior parietal lobule and the frontal association areas including the middle frontal gyrus, is generally associated with visuospatial attention (Astafiev et al., 2003; Corbetta et al., 1991, 1995, 2002; Hendler et al., 2003; McIntosh et al., 1994). Corbetta illustrated that the ventral frontoparietal network, which consists of inferior parietal lobule and the middle frontal gyrus is involved in stimulus-driven control of visual processing (Corbetta et al., 2002). Therefore, it is assumed that the neural network associated with unconscious visual attention processing was activated by the masked visual stimuli in the healthy control group in this study.

The parahippocampal area that was activated only in the PTSD group has been suggested to be related to episodic, spatial, and contextual memory and emotional responses. Niki and Luo (2002) have performed functional MRI and showed activation of the left parahippocampal gyrus during recall of recent autobiographical episodes. A preferential role for the hippocampal area in the retrieval of autobiographical events, compared with other episodic memories such as public events, has been documented previously, and often with a left hippocampal preponderance (Burgess et al., 2001; Maguire and Mummery, 1999; Maguire et al., 2000, 2001a,b; Ryan et al., 2001), but also Fink et al. and Maguire et al. reported that the activity in the left hippocampal area was not modulated by the remoteness of memories, suggesting invariant involvement in remembering autobiographical events throughout the lifespan (Fink et al., 1996; Maguire and Frith, 2003).

Our results suggest that activation in the ventral frontoparietal network associated with normal visual attention processing is attenuated in PTSD patients, while the left parahippocampal region (including parahippocampal gyrus/tail of hippocampus) associated with autobiographical memory is activated with abnormal ease. These results may be related to the clinical characteristics of PTSD, in which general ability to attend and short time memory are impaired, while traumatic memories are abnormally readily recollected. It is also possible, however that the frontoparietal inactivity may be associated with comorbidity including depression and anxiety symptoms.

Many previous studies have shown a smaller hippocampal volume in patients with PTSD, compared to healthy participants (Bremner et al., 1995, 1997; Gurvits et al., 1996; Stein et al., 1997). Gilbertson et al. (2002) evaluated the correlation between hippocampal volume and the development of PTSD in twin

Table 2
Talairach coordinates in the control group and PTSD group

Region	Brodmann area	Talairach coordinates			KE (voxels)	*z* score
		x	*y*	*z*		
Control group						
Right inferior parietal lobule	40	44	−56	48	41	3.57
Right precentral gyrus	4	28	−16	52	31	3.55
Left inferior parietal lobule	40	−28	−76	42	122	3.36
Left precentral gyrus	4	−28	−18	54	38	3.33
Left middle frontal gyrus	8	−34	20	44	25	3.30
Left middle frontal gyrus	9	−16	14	26	26	3.19
PTSD group						
Left parahippocampal gyrus/tail of left hippocampus	19/30	−14	−42	−4	25	3.79

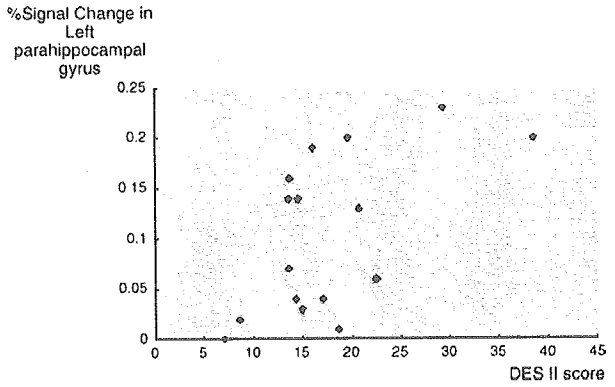

Fig. 6. Correlation of the % fMRI signal change in the left parahippocampal gyrus with the DES-II score.

Vietnam combat veterans and suggested that a congenitally small hippocampal volume is a risk factor for the development of PTSD.

Two previous functional imaging studies using masked visual stimuli have been performed in PTSD patients (Hendler et al., 2003; Rauch et al., 2000) Rauch et al. presented frightening facial expressions for a duration below the cognition threshold. Images were presented to 8 patients with PTSD and enhanced activation of the amygdala was observed. Hendler et al. similarly presented combat-related images for a duration below the cognition threshold to 10 patients with PTSD but reported enhanced activation of the lateral occipital lobe. The inconsistencies between these studies and the present study may be due to two factors: [1] The previous studies did not directly explore the hippocampal area as a region of interest. [2] There are differences in the stimulus presentation method and the nature of the participants. The PTSD participants were male combat veterans in these previous studies, whereas those in the present study are male and female patients with PTSD caused by various traumatic experiences.

In the present study, random-effect analysis was made possible by employing sixteen participants in each of the PTSD and control groups. Using this analysis method, results for the entire group are not affected by exaggerated brain activity observed in only a few participants, and more robust and consistent results can therefore be obtained. In previous functional imaging studies with masked stimuli, only limited brain regions were explored, while in this study the whole brain was analyzed using a random-effect model. Consequently, this study is the first to clearly show parahippocampal hypersensitivity specific to PTSD. Previous functional imaging studies have made focused on comparisons between PTSD caused by combat or abuse experiences and non-PTSD controls. In contrast, this study made a comparison between PTSD caused by various traumatic experiences and healthy control. Our study is disadvantageous in terms of homogeneity of PTSD participants, however, a rigorous analysis using the random-effect model was possible because the numbers of PTSD and control participants employed was about twice as large as that of previous studies. As a result, parahippocampal functional abnormality common to PTSD patients of various causes was demonstrated. Although many studies have reported hippocampal volume reduction in PTSD, few have clearly shown hippocampal dysfunction due to trauma-associated stimuli. In this study, a masked stimuli presentation method developed particularly for study of PTSD was used, and an association of parahippocampal activation with dissociation symptoms was indicated.

No participant showed short-term or long-term discomfort or aggravation of symptoms after image presentation. During CAPS diagnosis, which is a conventional structured interview method, some patients developed a transient headache or discomfort due to recall of traumatic episodes. Therefore, compared with the conventional methods, the image presentation method used here may cause participants only slight psychological pain. The brain function measurement method used in this study may be applicable as a supplementary parameter in the objective diagnosis of PTSD. In the future, it will be important to perform functional imaging studies to look for possible longitudinal changes in brain function that may correspond to improvement of PTSD symptoms.

Acknowledgments

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Delayed automatic detection of change in speech sounds in adults with autism: A magnetoencephalographic study

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Abstract

Objective: Autism is a form of pervasive developmental disorder in which dysfunction in interpersonal relationships and communication is fundamental. This study evaluated neurophysiological abnormalities at the basic level of language processing, i.e. automatic change detection of speech and non-speech sounds, using magnetoencephalographic recording of mismatch response elicited by change in vowels and tones.

Methods: The auditory magnetic mismatch field (MMF) was evaluated in 9 adults with autism and 19 control subjects using whole-head magnetoencephalography. The MMF in response to the duration change of a pure tone or vowel /a/ and that in response to across-phoneme change between vowels /a/ and /o/, were recorded.

Results: The groups were not significantly different in MMF power under any conditions. However, the autism group showed a left-biased latency prolongation of the MMF particularly under the across-phoneme change condition, and this latency delay was significantly associated with greater symptom severity.

Conclusions: These results suggest that adults with autism are associated with delayed processing for automatic change detection of speech sounds. These electrophysiological abnormalities at the earliest level of information processing may contribute to the basis for language deficits observed in autism.

Significance: These results provide the first evidence for delayed latency of phonetic MMF in adults with autism.

Keywords: Autism; Magnetoencephalography (MEG); Mismatch negativity (MMN); Phoneme; Speech sound; Tone; Vowel

1. Introduction

Autism is a pervasive developmental disorder associated with aberrant social skills, deficient language, abnormal attention, and stereotyped repetitive behaviors (American Psychiatric Association, 1994). Fundamental cognitive deficits in autism are characterized by a lack of normal attentional preference to socially relevant stimuli (Rapin, 1997). For example, individuals with autism spent more time looking at objects and less time looking at people (Swettenham et al., 1998). Moreover, children with autism

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oriented more poorly to social (both speech and non-speech) than to non-social stimuli (Dawson et al., 1998). However, brain functional basis for deficits in socially relevant auditory stimuli such as speech sounds in autism has been poorly understood. At the earliest stage, i.e. the level of auditory sensory processing, speech sound processing requires the discrimination of phonemes; a process that requires the categorization of the simplest unit of speech sounds according to their acoustic features. Such a process can be indexed by the auditory mismatch negativity (MMN) elicited by speech sounds (Näätänen et al., 2001).

The MMN or its magnetic counterpart (magnetic mismatch field; MMF) is an event-related potential (ERP) or magnetic field peaked at approximately 100–200 ms after the onset of a physically deviant auditory stimulus in identical and repeated sequence (Hari et al., 1984; Näätänen et al., 1978). Näätänen (1992) noted that MMN (MMF) reflects the detection of mismatches between the deviant stimuli and the neural trace encoding the physical features of the standard stimuli and that MMN (MMF) can be elicited even under passive conditions when subjects ignore the stimuli entirely. Thus, MMN (MMF) can be considered an index of the process of automatic detection of acoustic change in humans. A number of researchers have recently extended their investigations into MMN (MMF) in response to speech sound discrimination (reviewed in Näätänen, 2001). Magnetoencephalography (MEG) (Alho et al., 1998a; Koyama et al., 2000; Näätänen et al., 1997; Rinne et al., 1999) and positron emission tomography (PET) (Tervaniemi et al., 2000) studies have demonstrated that the left auditory cortex is predominantly activated during the automatic processing of speech sounds (vowel or consonant–vowel syllables) in normal subjects. Moreover, Kraus (1998) suggested that phonetic MMN showed an increase as a result of cognitive discrimination training; thus it may be an index of language-related plasticity in the central nervous system.

A review of the previous literature on MMN or MMF in individuals with autism, identified 5 studies that employed ERPs (MMN) (Čeponienė et al., 2003; Ferri et al., 2003; Gomot et al., 2002; Kemner et al., 1995; Seri et al., 1999) and one that employed MEG (MMF) (Tecchio et al., 2003); the results of these studies are mixed (reviewed and discussed in detail in the Discussion section). The subjects in all 5 ERP studies were children with autism, and the MEG study by Tecchio et al. employed autism individuals with a broader range of ages (8–32 years). Moreover, only two ERP studies (Čeponienė et al., 2003; Kemner et al., 1995) used speech sounds to elicit MMN: Kemner et al. (1995) reported preserved MMN amplitude in response to change between /ay/ and /oy/ sounds in children with autism; however, no analysis of latency data was reported; Čeponienė et al. (2003) reported intact MMN amplitude and latency elicited by change in vowels as well as simple and complex tones in children with autism. Thus, to date, no studies have evaluated MMN/MMF specifically in adults with autism; no studies have used MEG to record mismatch response to speech sounds in autism. Importantly, no studies have explored the relationship between MMN/MMF indices and clinical symptoms in autism. Additionally, all 5 studies that evaluated tonal MMN/MMF in autism (Čeponienė et al., 2003; Ferri et al., 2003; Gomot et al., 2002; Seri et al., 1999; Tecchio et al., 2003) measured mismatch response to frequency change (frequency MMN/MMF), with none of them assessing MMN/MMF in response to duration change of tones (duration MMN/MMF).

Accordingly, the goal of this study was to investigate, using a whole-head MEG, whether or not a reduction and/or latency prolongation in magnetic mismatch field elicited by across-category change of speech sounds is present in adults with autism. Additionally, we also measured duration MMF using tonal and vowel stimuli. The use of a whole-head MEG instead of a scalp EEG has two advantages. First, the use of a whole-head MEG enables independent investigation of left and right hemispheric functions, because, in contrast to electrical fields, magnetic fields are not influenced by intervening tissues of different conductivities. Second, MEG selectively detects electrical currents tangential to the scalp, whereas EEG is more sensitive to radially oriented currents. Thus, MMF generated in the superior temporal plane constituting the auditory cortex could be selectively detected by MEG recording, while MMF from other generators such as the frontal component (Alain et al., 1998; Alho et al., 1994; Giard et al., 1990; Kasai et al., 1999; Liasis et al., 2001; Umbricht et al., 2000), having preferentially radially oriented currents (Giard et al., 1990; Kasai et al., 1999), is largely filtered out.

2. Methods

2.1. Subjects

Nine right-handed (Edinburgh Inventory [Oldfield, 1971] with laterality index ≥ 0.8 as the cut-off for right-handedness) adults with autism were recruited from the Outpatient Clinic, Department of Neuropsychiatry, University Hospital of Tokyo, Japan. Six were male and 3 were female, and the mean age was 27.2 (SD 7.7). Nineteen age-, gender-, and handedness-matched healthy subjects (mean age 27.3; SD 7.0; 13 males and 6 females) participated in the study. Diagnosis of autism was made according to the DSM-IV (American Psychiatric Association, 1994) criteria for autistic disorder and confirmed using the Childhood Autistic Rating Scale—Tokyo Version (CARS-TV) (Kurita et al., 1989) administered by an experienced child psychiatrist (O.H.). Scores for all subjects in the patient group (mean 33.7 [SD 1.2]) were above the cut-off point of >27 for adult criteria of autism (Mesibov et al., 1989). All subjects with autism were able to construct 3 word sentences. Patient's IQs (mean 57.2 [SD 15.0]) were evaluated using the Wechsler Adult Intelligence Scale-Revised (WAIS-R)

Table 1
Subject information (autism group)

Subject no.	Gender	Age	CARS	IQ			Medication (mg/day)			EEG abnormality
				Verbal	Performance	Total	Neuroleptics	Antiepileptic drugs	Anticholinergic drugs	
1	M	33	33.5	NA[a]	NA[a]	38	Haloperidol 0.75	None	Biperiden 1	No
2	F	31	36.5	NA[a]	NA[a]	48	Haloperidol 2.25	Valproate 600	Biperiden 2	No
3	F	27	34.5	62	52	54	Haloperidol 0.75	None	Biperiden 1	No
4	M	20	33.0	73	73	68	Haloperidol 0.75	Valproate 600	Trihexyphenidyl 2	No[b]
5	F	20	34.0	NA[a]	NA[a]	37	Haloperidol 1.5	None	Biperiden 2	No
6	M	15	33.0	52	99	71	None	None	None	No
7	M	38	33.0	70	91	77	None	None	None	No
8	M	26	32.5	56	52	51	None	None	None	No
9	M	35	33.5	80	64	71	Bromperidol 3	None	Trihexyphenidyl 2	No

CARS, Childhood Autism Rating Scale; EEG, electroencephalogram; M, male; F, female.

[a] Verbal and non-verbal IQs were not available because the data were based on the Tanaka–Binet Test. Otherwise, the IQs were evaluated using the Wechsler Adult Intelligence Scale-Revised (WAIS-R).

[b] This subject had a history of generalized tonic–clonic seizures in his childhood, although no epileptiform EEG activities had been previously detected.

(Wechsler, 1981; Japanese standardized version, Shinagawa et al., 1990) or the Tanaka–Binet Intelligence Scale (Japanese standardized version of the Stanford–Binet test, Tanaka Institute for Education, 1987) (Table 1). No individuals with autism showed current electroencephalogram (EEG) abnormalities. One subject had a history of generalized tonic–clonic seizures in childhood, although no epileptiform EEG activities had been previously detected. Six of the individuals were treated with neuroleptics to reduce the occurrence of disabling self-injurious behavior. Mean haloperidol equivalent dose (Inagaki et al., 1999a) was 1.0 mg/day (SD 1.1). These 6 individuals also received anticholinergic drugs; mean biperiden equivalent dose (Inagaki et al., 1999b) of 0.89 mg/day (SD 0.78), to prevent the occurrence of Parkinsonism secondary to the neuroleptics. No symptoms of Parkinsonism were clinically observed. No individuals with autism received anxiolitics or hypnotics, but two were treated with sodium valoproate (600 mg/day) as a mood stabilizer.

The first language of all participants in both groups was Japanese. The exclusion criteria for both groups were a history of electroconvulsive therapy, neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, substance use or addiction, and presence of hearing or vision impairment. No individuals with autism showed evidence of tuberous sclerosis. An additional exclusion criterion for the control group was a history of psychiatric disease in themselves, or a family history of axis I disorder in their first-degree relatives.

This study was approved by the Ethical Committee of the Faculty of Medicine, University of Tokyo. After a complete explanation of the study, written informed consent was obtained from all the control subjects. Written informed consent was also obtained from all the autism participants as well as from their parents.

2.2. Task procedures

The subjects were presented with sequences of auditory stimuli consisting of standard (probability 90%) and deviant ($P=10\%$) stimuli delivered randomly, except that each deviant stimulus was preceded by at least one standard stimulus. The interstimulus interval (ISI) was 510 ± 20 ms. The stimuli were delivered binaurally through plastic tubes. The subjects were instructed to watch a silent film to help distract them from the stimuli.

The experiment consisted of 3 conditions. The first condition was to elicit MMF in response to a duration decrement of pure-tone stimuli (tone-duration condition; standard, 100 ms duration; deviant, 50 ms duration). The second condition was to elicit MMF in response to a duration decrement of vowel stimuli (phoneme-duration condition; standard, Japanese vowel /a/ with a 150 ms duration; deviant, /a/ with a 100 ms duration). The last condition was to elicit MMF in response to a vowel across-category change (across-phoneme condition; standard, Japanese vowel /a/ with a 150 ms duration; deviant, /o/ with a 150 ms duration). These vowel stimuli were spoken by a native-Japanese-speaking actor, digitized using the NeuroStim system (NeuroScan Inc., USA), and edited to have a duration of 100 or 150 ms, loudness of 70 dBSPL and rise/fall time of 10 ms. The frequency spectra for the vowels were as follows: /a/, formant (F) $0=140$ Hz, $F1=760$, $F2=1250$, $F3=2750$, and $F4=3600$; /o/, $F0=140$ Hz, $F1=480$, $F2=770$, $F3=2820$, and $F4=3600$. The order of the 3 conditions was counterbalanced across the subjects.