Shared Neural Activity in Panic Disorder and Undifferentiated Somatoform Disorder Compared With Healthy Controls

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Objective: In previous studies, some brain areas, including parahippocampal gyrus, were suggested to be associated with panic disorder. Both panic disorder and somatoform disorders are associated with anxiety. This study sought to determine if there are shared neural activity underlying panic disorder and undifferentiated somatoform disorder.

Method: Sixteen nonmedicated patients with panic disorder, 16 nonmedicated patients with undifferentiated somatoform disorder, and 10 healthy subjects were scanned between February 2005 and August 2006. Diagnoses were made according to the Korean version of the Structured Clinical Interview for *DSM-IV* Axis I Disorders, Research Version, Patient/Non-Patient Edition. Regional cerebral perfusion was measured by 99 m-Tc-ethyl cysteinate dimer single photon emission computed tomography (SPECT). Using statistical parametric mapping analysis, we compared the SPECT images between the groups.

Results: Significant hyperperfusion was found at the left superior temporal gyrus and the left supramarginal gyrus in the panic disorder patients when compared to the controls (family-wise error [FWE], $P < .001$). The somatoform disorder patients showed hyperperfusion in the left hemisphere at the superior temporal gyrus, inferior parietal lobule, middle occipital gyrus, precentral gyrus, postcentral gyrus, and, in the right hemisphere, at the superior temporal gyrus when compared to the controls (false discovery rate [FDR], $P < .001$). In contrast, significant hypoperfusion was found at the right parahippocampal gyrus in each of panic disorder (FWE, $P = .001$) and somatoform disorder (FWE, $P < .001$) groups compared to healthy controls. However, no significant differences were found in regional cerebral perfusion between the 2 disorder groups.

Conclusions: Both panic disorder and undifferentiated somatoform disorder showed hyperperfusion in the left superior temporal gyrus and hypoperfusion in the right parahippocampal gyrus, which suggests that the 2 disorders are likely to share neural activity.

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Anxiety is known to be closely associated with somatic symptoms in some psychiatric disorders, including somatoform disorders.[1] Somatic symptoms of anxiety are characterized by sympathetic adrenergic arousal such as tachycardia and sweating.[2] Anxiety disorders are often associated with both somatization and hypochondriasis.[3,4] Some patients with panic disorder have occasional attacks that consist only of somatic symptoms.[5] It has been reported that patients with either panic disorder or generalized anxiety disorder are more sensitive to physiologic changes than nonanxious individuals.[6]

Undifferentiated somatoform disorder is 1 subgroup of somatoform disorders that is characterized by 1 or more unexplained physical complaints lasting for at least 6 months and is below the threshold for diagnosing somatization disorder.[7] The prevalence of undifferentiated somatoform disorder is known to be quite high, ranging from 10.2% to 30.6%.[8–10]

Abnormalities in the parahippocampal gyrus, hippocampus, and temporal lobe in patients with panic disorder have been consistently reported in brain-imaging studies. A recent voxel-based morphometry study found that gray matter density in parahippocampal gyrus was decreased in subjects with panic disorder.[11] Reiman et al[12,13] reported an asymmetry of cerebral blood flow in the parahippocampal gyrus using positron emission tomography (PET). Another PET study[14] found that glucose metabolism was increased in the left hippocampus and parahippocampal area and decreased in the right inferior parietal and right superior temporal regions. Decreased blood flow in bilateral hippocampus of subjects with panic disorder was also reported in hexamethylpropylene amine oxime (HMPAO) single photon emission computed tomography (SPECT).[15] In addition, magnetic resonance imaging (MRI) studies found that panic disorder patients showed temporal lobe abnormalities.[16,17] Reduced volume of temporal lobe and amygdala was also reported in panic disorder.[18,19] In another study,[20] a decreased cerebral blood flow of temporal regions of the brain was found in patients with panic disorder under psychotropic medication.

Neuroimaging studies have also confirmed that brain areas involved in stress, memory, and emotion, play an important role in the symptomatology of anxiety disorders.[21] Functional brain-imaging studies such as PET have implicated dysregulation of cerebral blood flow. Specifically, anxiety disorders and panic attacks are associated with cerebral vasoconstriction, which may result in central nervous system symptoms such as dizziness and in peripheral

nervous system symptoms that may be induced by hyperventilation and hypocapnea.[22] It was reported that hypocapnea was associated with an increased insular and temporal cortical blood flow in panic disorder.[23]

Somatoform disorders may involve a variety of neuronal pathways, from brain-brain signals to pain pathways and perceptual pathways and from efferent signals to motor apparatus and blood vessels.[7] However, few brain-imaging studies have been performed on patients with somatoform disorders. A study using brain [^{18}F]-fluorodeoxyglucose-PET with MRI reference reported that cerebral metabolism rates of glucose were lower in both caudate nuclei, left putamen, and right precentral gyrus in somatizing women compared with healthy volunteers.[24] The researchers, using brain MRI, also later reported bilateral enlargement of caudate nuclei volumes in somatoform disorder patients compared with healthy volunteers.[25]

As mentioned earlier, both panic disorder and somatoform disorders are associated with anxiety. In the past several years, brain-imaging studies have been considered critical for advancing our understanding of pathophysiology of anxiety.[21] In particular, parahippocampal region and temporal cortex has been implicated as a pathophysiological site in anxiety disorders.[22] Therefore, comparison of regional cerebral blood flow (rCBF) between panic disorder patients, somatoform disorder patients, and healthy individuals was made to determine if there are shared neural activity underlying panic disorder and undifferentiated somatoform disorder.

METHOD

Subjects

The study was reviewed and approved by the Institutional Review Board of Yonsei University College of Medicine at Severance Hospital, Seoul, Korea. Outpatients from the Department of Psychiatry at Severance Hospital with a diagnosis of panic disorder or undifferentiated somatoform disorder were enrolled in this study. The purpose and procedures of the study were explained to all subjects, and informed consent was obtained from all who decided to participate.

During the first visit to the outpatient department, a semistructured interview was conducted using the Korean version[26,27] of the Structured Clinical Interview for *DSM-IV* Axis I Disorders, Research Version, Patient/Non-Patient Edition,[28] and the diagnosis of panic disorder or undifferentiated somatoform disorder was made by an experienced psychiatrist (K.B.K.).

The subjects included 16 patients with panic disorder and 16 with undifferentiated somatoform disorder. Both the panic disorder and undifferentiated somatoform disorder groups included 12 men and 4 women. The mean (± SD) age of the panic disorder group was 30.4 (± 8.6) years, with a range from 20 to 40 years, while the mean (± SD) age of the somatoform disorder patients was 30.7 (± 5.5) years, with a range from 20 to 39 years. In addition, 10 healthy control subjects (8 men and 2 women) were recruited from medical residents and other hospital personnel. The mean (± SD) age of the healthy control group was 29.0 (± 1.1) years (range, 27–31).

For each patient, we performed physical examinations and various laboratory examinations, including routine tests such as a complete blood count, urinalysis, serum electrolytes, liver function tests, chest X-ray, a thyroid function test, and electrocardiogram. Specific tests, such as electromyography, electroencephalography, brain magnetic resonance imaging, liver ultrasonogram, gastroscopy, or colonoscopy (if necessary), were conducted for the patients either at the Department of Psychiatry or at other departments. Only patients who had neither physical diseases nor abnormal laboratory findings were asked to participate in this study. We excluded patients who had a change in diagnosis or who developed any physical disease or additional psychiatric disorders.

The psychiatrist directly interviewed healthy control subjects and checked for the presence or absence of physical diseases and psychiatric disorders. Among these volunteers, only those who had no disorders were included in this study. Specifically, we confirmed that each healthy control had no abnormality at his or her most recent regular physical check-up.

Only right-handed subjects were chosen in order to examine the laterality of the brain. The subjects were excluded if they had taken any medication, had smoked cigarettes, or had consumed alcohol within 2 weeks of testing. Among the 24 panic disorder patients who completed the entire testing process, 8 subjects were excluded from the data analysis because they were left-handed (3 subjects), had taken antibiotics (2 subjects), or had consumed alcohol (3 subjects). Among the 21 undifferentiated somatoform disorder patients who completed the entire testing process, 5 subjects were excluded from the data analysis because they were left-handed (2 subjects), had taken antibiotics (1 subject), or had consumed alcohol (2 subjects).

Psychometric Measures

Each subject completed a self-administered questionnaire including the psychometric measures such as the Korean version[29] of the Symptom Checklist-90-Revised (SCL-90R) anxiety subscale[30] about 90 minutes before SPECT scanning. In addition, each patient and healthy subject was individually interviewed and the extent of his or her anxiety was measured by a psychiatrist using the Hamilton Anxiety Rating Scale (HARS).[31]

SPECT Scanning Procedure

The subject was placed in a quiet room with eyes closed and ears open. Scanning was performed in the resting state approximately 50 minutes after intravenous injection of 740 MBq (20 μCi) of 99 m-Tc-ethyl cysteinate dimer (ECD) (Bristol-Myers Squibb, North Billerica, Massachusetts). Brain perfusion studies were performed with a brain-dedicated annular crystal γ camera with low energy, high-resolution parallel–hole collimators (Digital Scintigraphics, Inc, Waltham, Massachusetts). Its

Table 1. The Levels of Anxiety in Panic Disorder, Undifferentiated Somatoform Disorder, and Healthy Control Groups

Measure	Panic Disorder (n = 16)	Undifferentiated Somatoform Disorder (n = 16)	Healthy Controls (n = 10)	*F*	*df*	*P*
HARS score, mean (SD)	24.5 ± 6.2[a]	21.9 ± 5.2[b]	2.1 ± 0.9	67.64	2	< .001
SCL-90-R anxiety subscale score, mean (SD)	14.8 ± 10.0[a]	13.0 ± 9.3[b]	1.8 ± 0.6	7.96	2	.001

[a]Panic disorder > healthy controls.
[b]Undifferentiated somatoform disorder > healthy controls (Scheffe test: $P < .05$).
Abbreviations: HARS = Hamilton Anxiety Rating Scale, SCL-90-R = Symptom Checklist-90-revised.

spatial resolution was 5.8 mm full-width at half-maximum (FWHM). We used a 128 × 128 matrix with 3 degree angular increment for 30 minutes to obtain axial images, using the filtered back projection method and a Butterworth filter (cut-off frequency 1.1 cycle/cm at an order no. 10). Attenuation correction was performed by Chang's method (attenuation coefficient = 0.15),[32] and sagittal, coronal, and transverse images were reconstructed. The subjects were scanned between February 2005 and August 2006.

Statistical Parametric Mapping Analysis

Statistical parametric mapping (SPM)[33,34] was used to determine differences between 99 m-Tc-ECD SPECT images of the patients and healthy controls. Using SPM 2 software (Wellcome Department of Cognitive Neurology, London, United Kingdom), we spatially normalized all images onto the 99 m-Tc-ECD SPECT standard template to remove intersubject anatomic variabilities.[33,34] Spatially normalized images were then smoothed by convolution using an isotropic Gaussian kernel with 10-mm FWHM to increase the signal-to-noise ratio and accommodate the variations in subtle anatomic structures. To minimize edge effects, voxels with values less than 80% of the whole brain mean were excluded. The count of each voxel was normalized versus the mean count of the total brain (proportional scaling in SPM) to remove global cerebral blood flow differences between the individuals.

After spatial and count normalization, significant differences between the SPECT images of the patients and healthy controls were estimated at every voxel. Then, significant increases and decreases of regional uptake were obtained using *t* statistics at every voxel from patients and healthy controls. The *t* values were transformed to *Z* scores in the standard Gaussian distribution. The false discovery rate (FDR) correction was used to control thresholds for statistical significance in multiple comparisons at voxel level.[35] Clusters consisting of a minimum of 100 contiguous voxels with either FDR or family-wise error (FWE) corrected $P < .05$ were considered to be significantly different for group comparison.

The Talairach brain coordinates were estimated with a nonlinear transformation from Montreal Neurologic Institute (McGill University, Montreal, Quebec, Canada) to Talairach space[36] and then entered into the Talairach Daemon for localization.[37] Anatomic regions were labeled as the nearest Brodmann area(s) for the most significant voxels within each cluster.

RESULTS

Demographic Data

No significant differences were found in terms of sex (Fisher exact test $P = 1.00$) or age ($t_{16} = 0.66$, $P = .52$) between the panic disorder patients and healthy controls. There were no significant differences in terms of sex (Fisher exact test $P = 1.00$) or age ($t_{17} = 1.20$, $P = .25$) between the undifferentiated somatoform disorder patients and healthy controls. No significant difference was also found in age ($t_{30} = -0.10$, $P = .92$) between the 2 disorder groups.

Comparison of Psychometric Measures Between Panic Disorder Patients, Undifferentiated Somatoform Disorder Patients, and Healthy Subjects

Panic disorder and somatoform disorder patients scored significantly higher on the HARS and SCL-90R anxiety subscale than healthy controls. However, no significant differences were found in the levels of anxiety as indicated by the HARS or SCL-90-R between the 2 disorder groups (Table 1).

Regions of Cerebral Hyperperfusion in Patients With Panic Disorder Compared With Healthy Subjects

Panic disorder patients had greater rCBF in 1 cluster. After a correction for multiple comparisons, the hyperperfusion was significant in the left hemisphere at the superior temporal gyrus (Brodmann area [BA] 39) and supramarginal gyrus (BA 40) in panic disorder patients compared to healthy controls (FWE, $P < .001$). In particular, hyperperfusion was predominantly found in the left superior temporal gyrus (Table 2, Figure 1).

Regions of Cerebral Hyperperfusion in Patients With Undifferentiated Somatoform Disorder Compared With Healthy Subjects

Undifferentiated somatoform disorder patients had significantly greater rCBF in 3 clusters. After a correction for multiple comparisons, the hyperperfusion was significant in the left hemisphere at the superior temporal gyrus (BA 39), inferior parietal lobule (BA 40), middle occipital gyrus (BA 19), precentral gyrus (BA 6), postcentral gyrus (BA 3), and, in the right hemisphere, at the superior temporal gyrus (BA 42) in undifferentiated somatoform disorder patients compared to healthy controls (FDR, $P < .001$). In particular, hyperperfusion was predominantly found in the left superior temporal gyrus (Table 2, Figure 1).

Regions of Cerebral Hypoperfusion in Patients With Panic Disorder Compared With Healthy Subjects

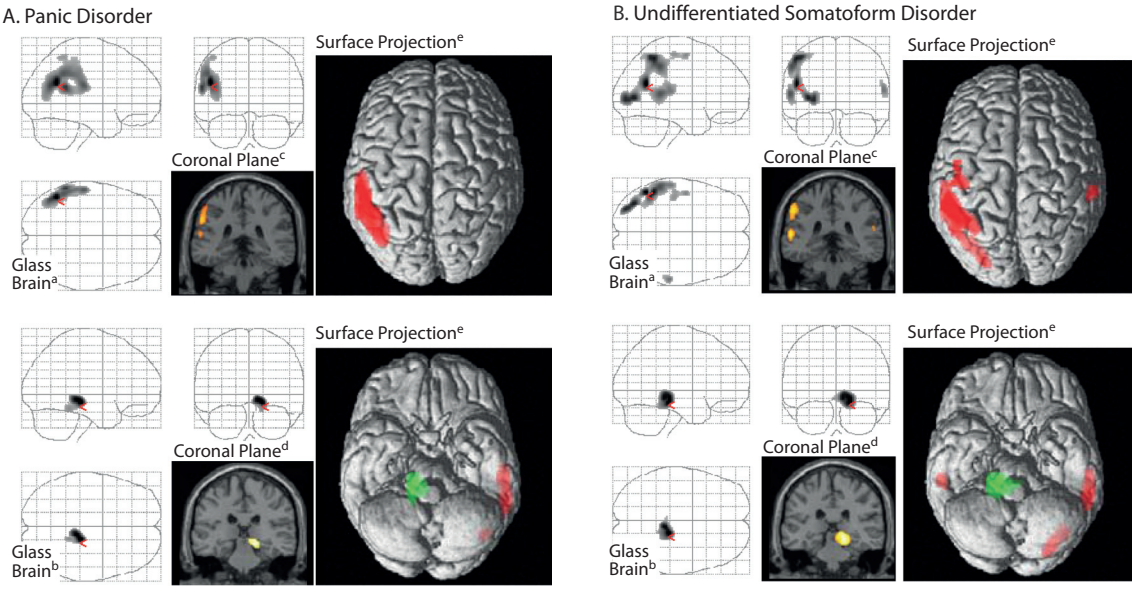
Panic disorder patients had significantly lower rCBF in 1 cluster. After a correction for multiple comparisons, the hypoperfusion was significant at the right parahippocampal

Table 2. Brain Areas With Hyperperfusion in Panic Disorder and Undifferentiated Somatoform Disorder Patients Compared With Healthy Controls

Region	Brodmann Area	*Z*	Peak Coordinates (x, y, z), mm	*P* (cluster level)	*P* (voxel level)	Extent (voxels)
Panic disorder						
Lt superior temporal gyrus	39	6.72	−48, −55, 26	< .001	FWE, < .001	1,855
Lt superior temporal gyrus	39	6.11	−58, −47, 21	< .001	FWE, < .001	1,855
Lt supramarginal gyrus	40	5.83	−41, −38, 34	< .001	FWE, < .001	1,855
Undifferentiated somatoform disorder						
Lt superior temporal gyrus	39	6.04	−49, −55, 23	< .001	FDR, < .001	1,877
Lt inferior parietal lobule	40	5.76	−49, −44, 52	< .001	FDR, < .001	1,877
Lt middle occipital gyrus	19	5.69	−34, −72, 7	< .001	FDR, < .001	1,877
Rt superior temporal gyrus	42	4.92	59, −26, 14	.001	FDR, < .001	121
Lt precentral gyrus	6	4.76	−48, −5, 54	.001	FDR, < .001	114
Lt postcentral gyrus	3	4.57	−42, −20, 56	.001	FDR, < .001	114

Abbreviations: FDR = false discovery rate, FWE = family-wise error, Lt = left, Rt = right.

Figure 1. Hyperperfused and Hypoperfused Brain Areas in Panic Disorder and Undifferentiated Somatoform Disorder Compared With Healthy Controls



[a]Hyperperfused brain areas in panic disorder and undifferentiated somatoform disorder patients compared with healthy controls (FWE, $P < .001$; FDR, $P < .001$).
[b]Hypoperfused brain areas in panic disorder and undifferentiated somatoform disorder patients compared with healthy controls (FWE, $P = .001$; FWE, $P < .001$).
[c]Hyperperfusion of the left superior temporal gyrus in panic disorder and undifferentiated somatoform disorder patients compared with healthy controls.
[d]Hypoperfusion of the right parahippocampal gyrus in panic disorder and undifferentiated somatoform disorder patients compared with healthy controls.
[e]Hyperperfused (red) or hypoperfused (green) regions in panic disorder and undifferentiated somatoform disorder patients compared with healthy controls.
Abbreviations: FDR = false discovery rate, FWE = family-wise error.

gyrus (BA 35/30) in panic disorder patients compared to healthy controls (FWE, $P = .001$) (Table 3, Figure 1).

Regions of Cerebral Hypoperfusion in Patients With Undifferentiated Somatoform Disorder Compared With Healthy Subjects

Undifferentiated somatoform disorder patients had significantly lower rCBF in 1 cluster. After a correction for multiple comparisons, the hypoperfusion was significant at the right parahippocampal gyrus (BA 35/27) in undifferentiated somatoform disorder patients compared to healthy controls (FWE, $P < .001$) (Table 3, Figure 1).

Comparison of Cerebral Perfusion Between Panic Disorder Patients and Undifferentiated Somatoform Disorder Patients

Neither regions of significant hypoperfusion (FDR, $P = .83$) nor regions of significant hyperperfusion (FDR, $P = 1.00$) were found in undifferentiated somatoform disorder patients when compared to panic disorder patients at any corrected *P* values.

DISCUSSION

This study found that significant and predominant hyperperfusion was found in the left superior temporal gyrus

Table 3. Brain Areas With Hypoperfusion in Panic Disorder and Undifferentiated Somatoform Disorder Patients Compared With Healthy Controls

Region	Brodmann Area	*Z*	Peak Coordinates (x, y, z), mm	*P* (cluster level)	*P* (voxel level)	Extent (voxels)
Panic disorder						
Rt parahippocampal gyrus	35	5.64	16, −28, −10	<.001	FWE, .001	350
Rt parahippocampal gyrus	30	5.62	10, −33, −7	<.001	FWE, .001	350
Rt parahippocampal gyrus	35	4.85	14, −34, −15	<.001	FWE, .02	350
Undifferentiated somatoform disorder						
Rt parahippocampal gyrus	35	6.04	16, −30, −10	<.001	FWE, <.001	637
Rt parahippocampal gyrus	27	5.90	8, −33, −5	<.001	FWE, <.001	637

Abbreviations: FWE = family-wise error, Rt = right.

(BA 39) in the panic disorder patients and somatoform disorder patients compared to healthy control subjects. These results suggest that the 2 disorders share increased cerebral perfusion in the left superior temporal gyrus. In contrast, the significant and predominant hypoperfusion was found only in the right parahippocampal gyrus (BA 35/30; BA 35/27) in the panic disorder patients and undifferentiated somatoform disorder patients compared to healthy control subjects, which suggests that the 2 disorders share reduced cerebral perfusion in the right parahippocampal gyrus.

However, neither regions of significant hyperperfusion nor regions of significant hypoperfusion were found between the 2 disorder patients at the corrected *P* value. Therefore, each of panic disorder patients and undifferentiated somatoform disorder patients shared increased cerebral perfusion in the left superior temporal gyrus and reduced cerebral perfusion in the right parahippocampal gyrus when compared to healthy controls. These results suggest that the 2 disorders are likely to have a common neural activity.

As already mentioned, somatoform disorders are associated with anxiety.[1] Somatic overconcern and excessive scrutiny of physiologic signals as well as some somatic symptoms are often observed not only in somatoform disorder patients but also in panic disorder patients.[2–4,6] In particular, somatic symptoms associated with anxiety involving autonomic nervous system, such as cardiovascular and respiratory systems, are shared by the 2 disorders.[22] These anxiety-related somatic symptoms may be associated with the above-mentioned neural activities.

Decreased perfusion of parahippocampal and hippocampal areas may lead to the divergence from normal learning[21] and memories.[38] Increased superior temporal perfusion is likely to be associated with emotion, such as anxiety and psychological overattachment to situations, in terms of functions of temporal lobe already reported.[21,22] Therefore, dysfunction in these areas may underlie symptoms of anxiety including autonomic arousal-related somatic symptoms in the 2 disorders.

Other studies also found that panic disorder patients showed abnormal cerebral perfusion in parahippocampal region compared with controls. Bisaga et al[14] observed hyperactivity of the left hippocampal and parahippocampal regions and hypoactivity of the right inferior parietal and right superior temporal regions in panic disorder patients as compared with controls. This finding is in contrast with our findings in which hyperactivity in the left superior temporal area and hypoactivity in the right parahippocampal area were shown. Like our findings, a study by De Cristofaro et al[15] reported a significant decrease in the blood flow in bilateral hippocampal regions (hippocampus, parahippocampal gyrus, and amygdala) in patients with panic disorder. In addition, a voxel-based morphometry study found that gray matter density in parahippocampal gyrus was decreased in patients with panic disorder, although it was in the left side.[11] However, in many other studies, hyperactivity in the parahippocampal area was reported. In particular, they found asymmetries with dominance in the left side. Therefore, superior temporal area and parahippocampal area are likely to be associated with panic disorder, but we need to further study about the asymmetry of cerebral perfusion in panic disorder patients in the future.

One intriguing finding in our study was that the hypoactivity of localized cerebral blood flow occurred predominantly on the right side in the 2 groups of patients. In particular, we could consider this hypoperfusion in the nondominant brain area likely to be associated with somatic symptoms in the somatoform disorder patients. In previous studies, there were reports that somatic symptoms, such as headache and other forms of pain, paresthesia, paralysis, and weakness, were more prevalent on the left side than on the right side of the body.[39–42] Therefore, we need to further study the relationship between asymmetry of cerebral perfusion and the laterality of somatic symptoms in somatoform disorders.

In conclusion, both panic disorder and undifferentiated somatoform disorder showed hyperperfusion in the left superior temporal gyrus and hypoperfusion in the right parahippocampal gyrus, which suggests that the 2 disorders are likely to share neural activity. Therefore, the differences between the 2 disorders could rather be explained by the psychosocial and cultural aspects relevant to the pathogenesis of the disorders.

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