Decreased blood flow of temporal regions of the brain in subjects with panic disorder

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Abstract

Object: The purpose of the current study was to investigate alterations of regional cerebral blood flow (rCBF) in subjects with panic disorder.

Methods: Twenty-two subjects with panic disorder who were under psychotropic medications and 25 age and gender-matched healthy comparison subjects were assessed regarding the rCBF of using Tc-99m-hexamethyl propylenamino oxime single photon emission tomography (SPECT). Using statistical parametric mapping, the rCBF was compared between panic disorder and healthy comparison groups.

Results: Decreased rCBF flow in right superior temporal lobe was observed in subjects with panic disorder (p < 0.05 after correction for multiple comparisons). The rCBF in right superior temporal gyrus negatively correlated with the duration of illness, scores of panic disorder severity scale (PDSS), Hamilton anxiety rating scale (HARS) and Zung self-rating anxiety scale (Z-SAS).

Conclusion: We report that there is a decreased cerebral blood flow of temporal regions of the brain in panic disorder and that this decrease may, in part, reflect the clinical severity of panic disorder.

Keywords: Panic disorder; Temporal lobe; SPECT

1. Introduction

Panic disorder is a common psychiatric disorder with a lifetime prevalence of 1.7% (Weissman et al., 1997). In an effort to better understand the neurobiological etiology, there have been a number of brain imaging studies in panic disorder, including magnetic resonance (MR) imaging (Fontaine et al., 1990; Ontiveros et al., 1989; Vythilingam et al., 2000; Massana et al., 2003a; Massana et al., 2003b; Bystritsky et al., 2001), positron emission tomography (PET) (Reiman et al., 1984; Reiman et al., 1986; Reiman, 1987; Bisaga et al., 1998; Nordahl et al., 1990) and single photon emission computed tomography (SPECT) (Stewart et al., 1988; De Cristofaro et al., 1993; Eren et al., 2003).

Temporal structural abnormalities in subjects with panic disorder have been consistently reported (Fontaine et al., 1990; Ontiveros et al., 1989; Vythilingam et al., 2000; Massana et al., 2003a; Massana et al., 2003b). Temporal lobe abnormalities on quantitative MR readings have been reported in panic disorder (Ontiveros...
et al., 1989; Fontaine et al., 1990). In addition, reduced volumes of temporal lobe and amygdala have also been reported in panic disorder (Vythilingam et al., 2000; Massana et al., 2003b). A recent voxel-based morphometry study has reported that gray matter density in parahippocampal gyrus was decreased in subjects with panic disorder (Massana et al., 2003a).

In addition to structural abnormalities, metabolic and hemodynamic changes have also been reported in temporal lobes of subjects with panic disorder. Reiman et al. (1984, 1986) have reported an asymmetry of cerebral blood flow in the parahippocampal gyrus using PET. They later reported an increased blood flow in various brain areas including bilateral temporal poles during a lactate-induced panic attack (Reiman et al., 1989). Bisaga et al. (1998) have showed an increased glucose metabolism in left hippocampus and parahippocampal area and a decreased glucose metabolism in the right inferior parietal and right superior temporal regions in a PET study. There have also been a few SPECT studies with subjects with panic disorder. Stewart et al. (1988) have reported the cerebral blood flow changes in subjects with panic disorder with Xenon-133 SPECT (Stewart et al., 1988). Decreased blood flow in bilateral hippocampus of subjects with panic disorder was also reported in hexamethylpropylene amine oxime (HMPAO) SPECT (De Cristofaro et al., 1993). Recently, Eren et al. (2003) have reported a positive correlation between the asymmetry of temporal and parietal blood flow and the severity of panic symptoms in drug-naïve subjects with panic disorder.

All the above SPECT studies were conducted in drug-naïve subjects with panic disorder. There has been only one recent preliminary SPECT study with a small sample size comparing cerebral blood flow between before and after mirtazapine treatment in panic subjects (Carli et al., 2002). Abnormal, i.e., decreased, cerebral blood flow was normalized after mirtazapine treatment in the above study. However, it is unclear whether altered cerebral blood flow can also be observed in subjects with panic disorder under psychotropic medications, when compared to healthy comparison subjects. In order to address, in part, these issues, we compared regional cerebral blood flow (rCBF) between panic subjects under medication and healthy comparison subjects using HMPAO SPECT.

Based on previous studies reporting both structural and functional temporal abnormalities in panic disorder, we hypothesized that changes in the rCBF in temporal lobes would also be observed in subjects with panic disorder after treatment, relative to healthy comparison subjects. In addition, we hypothesized that changes in the rCBF of the temporal lobe would correlate with severity of panic disorder. This study would, in part, address whether the abnormal pattern of the rCBF is primarily state-dependent or both state and trait-dependent.

2. Materials and methods

2.1. Subjects and clinical ratings

Twenty-two subjects with panic disorder have been recruited through consecutive visits at psychiatric outpatient and inpatient units at Seoul National University Hospital, Seoul, South Korea. Inclusion criteria of study participants were (1) ages: 19–50 years and (2) panic disorder with or without agoraphobia, as determined by structured clinical interview for DSM-IV (SCID-IV) administered by an experienced psychiatrist. Exclusion criteria were (1) any current or past serious medical or neurological illness, (2) current history of major psychiatric disorder of schizophrenia, bipolar disorder and other psychotic disorders, and any current axis I disorder requiring psychotropic medications, as identified by SCID-IV, (3) antisocial or borderline personality disorders, as identified by the personality disorder questionnaire-4, and (4) lifetime exposure to any other DSM-IV dependence- or abuse-related drugs except nicotine, caffeine, social drinking of alcohol, or prescribed medications.

Out of the consecutively screened 128 subjects with a potential diagnosis of panic disorder, 59 subjects met the diagnostic criteria for panic disorder. Out of these 59 panic subjects, 4 subjects with psychotic disorders, 18 non-psychotic psychiatric disorders requiring psychotropic medications, 5 antisocial or borderline personality disorder, 7 subjects with current or past history of substance abuse, and 9 subjects with cardiovascular and hepatic comorbidities were excluded from the study (the numbers are not mutually exclusive), leaving 29 panic subjects. Twenty-two subjects gave consent to the participation in the study.

Twenty-five healthy comparison subjects were recruited through advertisements at local newspapers. Study protocol was approved by the Institutional Review Board at Seoul National University Hospital. After complete description of the study to the subjects, written informed consent was obtained.

Duration of illness were defined as the time period from the age of onset. All subjects were evaluated with Hamilton depression rating scale (HAM-D) (Hamilton, 1960). Subjects with panic disorder were evaluated with panic disorder severity scale (PDSS) (Shear and Maser, 1994) and Hamilton anxiety rating scale (HARS) (Hamilton, 1959) by a clinical psychologist. Zung self-rating anxiety scale (Z-SAS) (Wang, 1978; Zung, 1971) and a questionnaire for basic demographic information were completed by subjects.

Panic disorder severity scale (PDSS) is a clinician-administered, 7-item scale for tapping the overall severity of panic disorder (Shear and Maser, 1994). Seven areas include the frequency of panic attacks, distress during panic attacks, anticipatory anxiety, agoraphobic
fear/avoidance, interoceptive fear/avoidance, impairment of work functioning and impairment of social functioning. Each item is rated on a 0–4 Likert scale, with higher ratings indicating greater degrees of symptom severity. Cronbach’s α was 0.86. The cut-off score in the PDSS for defining the clinically significant panic state has been 8 for Caucasian population (Shear et al., 2001) and 10 for the Asian population (Yamamoto et al., 2004).

Hamilton anxiety rating scale (HARS) is also, a clinician-administered 14-item scale for assessing anxiety symptom, both somatic and cognitive. Each item is rated on a 5-point Likert scale (Hamilton, 1959).

Zung self-rating anxiety scale (Z-SAS) is a self-reporting 20-item scale for assessing anxiety-associated symptoms, related to the symptom frequency. Each item is measured on a 4-point Likert scale (Wang, 1978; Zung, 1971).

Clinical rating has been conducted on the same day of the SPECT scanning, typically two hours before the scans.

2.2. Single photon emission computed tomography (SPECT) imaging acquisition and statistical parametric mapping (SPM) analysis

All subjects were laid in the supine, with their eyes closed, in a quiet room with dimmed lights. 555 MBq Tc-99m-HMPAO was administered and the SPECT image was acquired using a tri-head gamma camera (Prism 3000; Picker International, Cleveland, OH) with a low energy, high-resolution parallel hole collimator. The energy window was set at 140 keV with a 15% width. One hundred and twenty frames were acquired, in the step-and-shoot mod, with each frame acquired for 20 s. Frames were 128 × 128 pixels in size, transaxial images were reconstructed as 64 × 64 matrices and filtered with a Metz filter (x = 1.5–2.0); all images were corrected for attenuation using Chang’s method. Finally, 40–50 images from the top of the cerebral cortex to the bottom of the cerebellum perpendicular to the orbito-meatal line were reconstructed.

Statistical parametric mapping (SPM) (Friston et al., 1991) was used to determine the quantitative difference between the Tc-99m-HMPAO SPECT images of panic subjects and healthy comparison subjects. Using SPM99 (statistical parametric mapping 99, Wellcome Department of Cognitive Neurology, London, UK) software, all images were spatially normalized SPM software to remove inter-subject anatomical variability (Friston et al., 1991).

Images were spatially normalized using linear and nonlinear transformations (7 × 8 × 7 basis functions, medium regularization, reslicing with bilinear interpolation to 2 × 2 × 2 mm³) onto the standard SPECT template in SPM99.

Spatially normalized images were smoothed by convolution using an isotropic Gaussian kernel with 16-mm full width half maximum (FWHM). The aim of smoothing was to increase the signal-to-noise ratio and to account the variations in subtle anatomical structures. The count of each voxel was normalized versus the total count for the brain (proportional scaling in SPM99 with a global mean of 50 and a threshold of 0.8) to remove global CBF differences between the individuals.

After spatial and count normalization differences between the SPECT images of panic patients and controls subjects were estimated at every voxel in an ANOVA and ANCOVA (gender as covariate) model and tested using signed t-tests for independent groups. Correction for multiple comparisons was performed by using the family-wise error (FWE) option of the SPM99. Voxels with a corrected p-value of less than 0.05 were considered to be significantly different.

2.3. Statistical analyses of demographic and clinical variables

To evaluate for differences involving dimensional data between groups, independent t-test (age, duration of illness, clinical ratings of PDSS, HARS and Z-SAS, duration of treatment, cerebral blood flow of significant cluster). For the subgroup analyses of the rCBF in the patients with panic disorder, we used the non-parametric Mann–Whitney U-test as raw values were not normally distributed.

Between-group comparisons involving categorical data were assessed using Fisher’s exact test for 2 × k table (gender and handedness). Associations between continuous variables (clinical ratings and raw values of the rCBF, i.e., mean values of the significant cluster) were calculated using Pearson correlation analysis. Statistical significance was defined at an α level less than 0.05 using two-tailed tests. All analyses were performed using Statistica version 6 for windows.

3. Results

Demographic and clinical characteristics (PDSS, HAM-D, HARS and Z-SAS) of subjects with panic disorder and healthy comparison subjects are presented in Table 1. All subjects with panic disorder had been treated with combination of antidepressants and anxiolytics for a mean duration of 11.2 weeks. Details of medications usage are described in Table 1. Mean duration of treatment was 11.2 weeks. All subjects with panic disorder had been treated with combination of antidepressants and anxiolytics. Details of medications usage were described in Table 1.

Decreased rCBF was found on the right superior temporal lobe (Talairach coordinates [x, y, z]: 54, 8, −4;
Table 1
Demographic and clinical characteristics of subjects with panic disorder and healthy comparison subjects

<table>
<thead>
<tr>
<th></th>
<th>Subjects with panic disorder (n = 22)</th>
<th>Healthy comparison subjects (n = 25)</th>
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<tbody>
<tr>
<td><strong>Demographic variables</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>33.6 (6.2)</td>
<td>31.8 (6.9)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>12/10</td>
<td>18/7</td>
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<tr>
<td>Duration of illness</td>
<td>3.5 (2.0)</td>
<td></td>
</tr>
<tr>
<td>HAM-D score</td>
<td>4.9 (5.6)</td>
<td>5.3 (4.4)</td>
</tr>
<tr>
<td>PDSS score</td>
<td>9.2 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Z-SAS score</td>
<td>42.9 (9.4)</td>
<td>2.3 (1.9)</td>
</tr>
<tr>
<td>HARS score</td>
<td>10.2 (8.5)</td>
<td>1.3 (1.6)</td>
</tr>
<tr>
<td>Duration of treatment (weeks)</td>
<td>11.2 (2.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>8 (36.4%)</td>
<td>–</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>7 (31.8%)</td>
<td>–</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>6 (27.3%)</td>
<td>–</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1 (4.5%)</td>
<td>–</td>
</tr>
<tr>
<td>Bupropion</td>
<td>1 (4.5%)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Benzodiazepine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>14 (63.6%)</td>
<td>–</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>5 (22.7%)</td>
<td>–</td>
</tr>
<tr>
<td>Both</td>
<td>1 (4.5%)</td>
<td>–</td>
</tr>
<tr>
<td>No benzodiazepine</td>
<td>2 (9.1%)</td>
<td>–</td>
</tr>
</tbody>
</table>

**Abbreviations:** HAM-D: Hamilton depression rating scale; HARS: Hamilton anxiety rating scale; PDSS: panic disorder severity scale. –, not applicable.

* One subject taking fluoxetine had a concurrent medication of mirtazapine.

Brodmann area 22, superior temporal gyrus, 5.4% decrease in mean values of significant cluster) in subjects with panic disorder compared to healthy comparison subjects (corrected $p$ value < 0.05, $t > 4.97$) (Fig. 1). The same set of SPM analyses was repeated controlling for gender in order to assess potential gender differences. Similar results were produced. In order to assess the potential gender influence on the current findings, we have conducted additional analyses in post hoc style, i.e., male panic subjects vs. male comparison subjects and female panic subjects vs. female comparison subjects. Similar results were produced although at a less stringent $z$ level.

There were no regions with increased rCBF in subjects with panic disorder at the same level of significance.

Group differences in the rCBF were also calculated based on mean values of significant cluster. There were significant differences by 5.4% in the rCBF between panic and healthy comparison groups (independent $t$-test, df = 45, $p < 0.001$). After controlling for gender using an ANCOVA model, this group difference stayed (ANCOVA, $F(1,44) = 38.2, p < 0.001$).

The rCBF in the area with significant differences between groups (i.e., right temporal lobe) negatively correlated the duration of illness ($r = -0.326, p < 0.05$) and with scores of PDSS, HARS and Z-SAS ($r = -0.473, p < 0.05$; $r = -0.482, p < 0.05$; $r = -0.450, p < 0.05$, respectively). There were no significant correlation between the rCBF in the right temporal lobe and HAM-D score (see Fig. 2).

When subjects with panic disorder were classified into two groups depending on PDSS scores, i.e., subjects with scores 10 or above and subjects with scores below 10, there were significant differences in the rCBF of the right temporal lobe between two groups (Mann–Whitney $U$ test; $73.4 \pm 3.2$ vs. $75.8 \pm 2.2$, $U = 29.0$, df = 20, $p < 0.05$).

### 4. Discussion

In the current study, we reported decreased rCBF in right superior temporal regions of subjects with panic disorder relative to healthy comparison subjects. In addition, this decrease correlated with the symptom severity of panic disorder.

Our findings of a decreased rCBF by 5.4% in right temporal region were in line with prior studies reporting structural abnormalities of temporal lobes in panic disorder (Ontiveros et al., 1989; Fontaine et al., 1990; Vythilingam et al., 2000; Massana et al., 2003b). Volume decreases in these regions ranged from 8.5% to 20%. Subjects with panic disorder have been reported to have more structural abnormalities in the right temporal lobe, which were associated with an earlier onset and frequent panic attacks (Ontiveros et al., 1989). Atrophy as well as increased white matter hyperintensities in the right, than the left, temporal lobe has also been reported to be more common in subjects with panic disorder (Fontaine et al., 1990). Reduced volume of bilateral temporal lobes has been reported in panic disorder (Vythilingam et al., 2000). These discrepancies between studies may stem from differences in patient selection criteria and clinical status including symptom severity and medications.

In addition to the relevance of our findings to temporal structural abnormalities, our findings were also consistent with a prior study reporting decreased metabolism in right superior temporal region of subjects with panic disorder (Bisaga et al., 1998). Bisaga et al. (1998) have assumed that their results would be caused by the fact that the temporal lobe played a mediating role between affect and behavioral responses with input from the limbic system. They have also suggested that decreased metabolism in right superior temporal region would be associated with elevated of the $\gamma$-amino-butyric acid (GABA) activity receptor system in the right prefrontal cortex. Elevated GABA receptor system in the right prefrontal cortex may cause a decreased activation in right temporal cortex which is functionally related with right prefrontal cortex (Kuikka et al., 1995; Bisaga et al., 1998). In line with these reports, there have been reports of right frontal activation in subjects with panic disorder (Clark et al., 1988; Ehlers and Breuer, 1992).
In the current study, there was an inverse relationship between the duration of illness and the decrease in the rCBF in right superior temporal region. We also found the inverse relationship between right superior temporal blood flow and the panic disorder severity. Moreover, the rCBF in right superior temporal lobe in panic subjects with PDSS score 10 or above were significantly lower than that in panic subjects with PDSS score below 10. In brief, our findings suggested that the severity of panic disorder correlates with the level of decreased in right superior temporal blood flow. The patterns of the rCBF in anxiety disorders and depressive disorders have been relatively diverse at baseline not to mention its changes after treatment (De Cristofaro et al., 1993; Eren et al., 2003; Perico et al., 2005; Ohgami et al., 2005). Findings of the current study suggest that the rCBF in superior temporal gyrus may have components of a trait marker for panic disorder, as indicated by the rCBF differences between panic and healthy comparison groups, and a state marker for anxiety levels, as indicated by correlations of the rCBF and panic severities.

In contrast, there was only one study that found correlation between panic and agoraphobia scale scores and calculated asymmetry index of cerebral blood flow (Eren et al., 2003). However, there have been no prior studies in panic disorder that reported a direct correlation between the rCBF and symptom severity. In the current study, scores of HARS and Z-SAS negatively correlated with the rCBF in same region. Findings of the current study suggested that abnormal blood flow in temporal regions would be associated with specific panic symptoms as well as objective or subjective anxiety symptoms, as measured by a number of inventories. Consequently, we supposed that the level of decrease in temporal blood flow reflects the severity of panic disorder.

There have been reports of the left to right asymmetry in parahippocampal and hippocampal blood flow (Massana et al., 2003a; Bisaga et al., 1998; Nordahl et al., 1990; Reiman et al., 1986), and frontal and temporal regions (Eren et al., 2003; Massana et al., 2002), with a greater cerebral blood flow in the right side. In contrast, there was a decrease in cerebral blood flow of the right superior temporal region in our panic subjects. This discrepancy regarding the asymmetry may stem from differences in clinical characteristics of our panic subjects. Most possible explanation for discrepancies between studies may be differences in clinical status including medications among panic populations. While prior studies were conducted on drug-naïve panic subjects, our panic subjects were under medication for mean
In a recent preliminary study, a lower cerebral blood flow of various brain areas in panic subjects before treatment were normalized following treatment with mirtazapine (Carli et al., 2002). Analogy can be found in cases of depression. Cerebral perfusion changes after drug treatment, which were related to clinical recovery, have been reported also in depressed patients (Bench et al., 1995; Passero et al., 1995). In contrast, even after treatment for mean 11.2 weeks (at least 9.2 weeks), our panic subjects still have decreased blood flow in right temporal regions of the brain significantly. Considering that our panic subjects had been under treatment for mean 11.2 weeks, it is possible that these panic subjects before treatment may have a more profound decrease in right temporal blood flow. Therefore, it might be suggested that subjects with panic disorder might show partial recovery of blood flow as a result of treatment or clinical improvement. Since antidepressants and benzodiazepines have been reported to influence the rCBF (Vlassenko et al., 2004; Van der Linden et al., 2000; Veselis et al., 1997; Roy-Byrne et al., 1993), the fact that our subjects were on these medications should be taken into consideration while interpreting the current findings.

Conservative significance threshold, i.e., corrected $p$ value of 0.05, was used in our study, while in panic disorder uncorrected $p$ value for significant has been used in most prior imaging studies (Eren et al., 2003; Bisaga et al., 1998). In addition, while a prior SPECT study in panic disorder has used a region-of-interest (ROI) method in assessing the rCBF (Eren et al., 2003), we conducted a whole-brain wise comparison of cerebral blood flow using the SPM method. To the best of our knowledge, the current study is the first SPECT report that evaluated a cerebral blood flow by SPM method in subjects with panic disorder.

The current study had several limitations. Our study was a cross-sectional study. Consequently, the comparison of drug-naïve panic subjects with medicated panic subjects or healthy comparison subjects cannot be provided in the present study. To explore medication- or clinical state-related changes of cerebral blood flow in subjects with panic disorder, a prospective study, assessing cerebral blood flow before and after medication (or clinical improvement), is recommended.

In conclusion, we reported a decreased cerebral blood flow in right superior temporal region in subjects with panic disorder, which correlated with the severity of panic disorder. Abnormalities in cerebral blood flow on temporal region might be involved in the neurobiological cause of panic disorder.

References


