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Preliminary communication

An fMRI motor activation paradigm demonstrates abnormalities of putamen activation in females with panic disorder

William R. Marchand [a,b,c,*], James N. Lee [a,b], Lindsey Healy [b], John W. Thatcher [a,b], Esther Rashkin [b], Jennifer Starr [a,b], Ed Hsu [b,c]

[a] Department of Veterans Affairs VISN 19 MIRECC, Salt Lake City, Utah, USA
[b] University of Utah, Salt Lake City, Utah, USA
[c] The Brain Institute, University of Utah, Salt Lake City, Utah, USA

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ABSTRACT

Background: The neurobiology of panic disorder is incompletely understood. The aim of this study was to determine if functional abnormalities of the putamen occur in panic disorder.
Methods: Activation patterns of 12 female subjects with panic disorder were compared to 18 female healthy controls using functional MRI at 3 T. A motor activation paradigm was used to probe putamen function.
Results: A complex motor activation paradigm for the non-dominant hand revealed decreased activation of the bilateral putamen among subjects with panic disorder.
Limitations: The sample size was a relatively small cohort of non-depressed females. Further, some panic disorder subjects were taking medications and/or had comorbid conditions. However, second-level regression analyses did not reveal any correlations between medication use or comorbidity and activation patterns demonstrated by the non-dominant hand complex task. Finally, we used a post-hoc approach to determine the magnitude of global fMRI signal as a surrogate index of the global cerebral blood flow as a means of controlling for possible confounds from reduction of BOLD signal secondary to cerebral vasoconstriction resulting from possible hyperventilation among panic subjects. A more compelling approach would have been to record the respiratory data from subjects during scanning.
Conclusions: Our findings suggest that putamen dysfunction occurs in at least some cases of panic disorder. We also provide preliminary evidence that a complex motor task for the non-dominant hand is a useful probe of putamen function in this disorder.
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1. Introduction

Currently, the neurobiology of panic disorder is incompletely understood. A primary hypothesis is that panic attacks occur as a result of an abnormally sensitive fear network, which includes the prefrontal cortex, insula, thalamus, amygdala, as well as amygdalar projections to the brainstem and hypothalamus (Gorman et al., 2000). However, some studies have also suggested abnormalities of the putamen in this condition. Specifically, bilateral decreases in putamen gray matter volumes (Yoo et al., 2005) lower GABA levels in the basal ganglia (Ham et al., 2007) and abnormalities of putamen activation (van den Heuvel et al., 2005) have been reported. The aim of this study was to determine if functional abnormalities of the putamen occur in panic disorder.

2. Materials and methods

2.1. Subjects

Thirty total subjects were studied, 12 with panic disorder and 18 controls. All subjects received a complete evaluation

* Corresponding author. VASLCHCS 116, 500 Foothill Boulevard, Salt Lake City, Utah 84148, USA. Tel.: +1 801 582 1565x2762; fax: +1 801 584 5669.
E-mail address: william.marchand@va.gov (W.R. Marchand).

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by a psychiatrist including administration of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Research Version (First, 2001), the Mini-Mental Status Examination (MMSE) (Folstein et al., 1975) and the Edinburgh Handedness Inventory (Oldfield, 1971) at study entry. The Panic Associated Symptom Scale (PASS) (Argyle et al., 1991) was given to all panic subjects at the time of the scan to quantify the severity of current panic symptoms. Subjects were all female to avoid any possible confound secondary to gender-specific activation patterns. All subjects had to be strongly right-handed, defined as score of $\geq$80 on the Edinburgh Handedness Inventory, to qualify for study entry. After a complete description of the study was given to the subjects, written informed consent was obtained, as approved by both the institutional review board at the University of Utah and the George E. Whalen Veterans Administration Medical Center.

For control subjects, exclusion criteria were: any history of head injury, any neurological disorder, any medical disorder that could impact the central nervous system, current use of any medications that impact the central nervous system, any contraindications to fMRI, as well as any past or current history of psychiatric disorders, substance abuse or treatment with psychiatric medications or any first-degree relative with any psychiatric disorder. For subjects with panic disorder, exclusion criteria were: any history of head injury, any neurological disorder, any medical disorder that could impact the central nervous system, any contraindications to fMRI and any psychiatric comorbidity other than another coexistent anxiety disorder or dysthymic disorder.

The mean age was 27.5 ± 4.9 years for the panic subjects and 26.4 ± 3.9 years for controls, which was not a statistically significant difference ($t = 0.65$, $df = 28$, $p = 0.52$) between the groups. Panic subjects had a mean Edinburgh Handedness Inventory score of 94.1 ± 8.8 as compared to 89.4 ± 7.7 for controls. This was also not a statistically significant difference ($t = 1.57$, $df = 28$, $p = 0.13$). Mean MMSE score was 29.5 ± 0.7 and 29.6 ± 0.5 for panic and control subjects respectively, which also did not represent a statistically significant difference ($t = 0.47$, $df = 28$, $p = 0.64$). For the panic subjects, the mean PASS score at the time of the scan was 10.1 ± 3.7.

Among the 12 subjects with panic disorder, six (50%) were being treated with psychiatric medications. Of these, two were taking benzodiazepines on an as needed basis, one was taking a selective serotonin reuptake inhibitor (SSRI) only and three were taking an SSRI and a benzodiazepine on an as needed basis. The two subjects taking only benzodiazepines had not taken medication within 24 h of the scan; therefore only four subjects were considered to be taking medications at the time of the scan. Three of these were SSRIs only and one was an SSRI and a benzodiazepine. Four panic subjects had psychiatric comorbidity. One had comorbid generalized anxiety disorder, one had generalized anxiety disorder and dysthymic disorder, one had social phobia and one had social phobia and posttraumatic stress disorder.

2.2. Tasks and experimental procedure

Six block design activation paradigms were used to probe brain function; three motor tasks and three cognitive/emotional tasks. Only the complex left-hand motor task (described below) and one emotional task, Ekman faces fear>neutral, revealed differences in the striatum or other basal ganglia structures in our initial analyses. Since our primary interest was to characterize striatal activation patterns in response to a motor task, we report only activation patterns in response to that task herein.

The complex motor task was a self-paced paradigm that we have previously shown to be a useful probe of putamen function in normal subjects (Marchand et al., 2008). It consisted of one four minute run repeated once for each hand with six blocks of rest and six blocks of activity presented in pseudorandom order. In this task, subjects alternated pressing buttons with the first and third fingers simultaneously and the middle finger alone. The paradigm was completed for one hand and then repeated for the opposite hand. During rest blocks the word “rest” was presented as a visual stimulus.

Visual stimuli for the tasks were presented on a translucent slide screen at the back of the magnet, which was viewed through a mirror mounted on top of the head coil. Stimulus presentation and response recordings were controlled by E-prime software (Psychology Software Tools, Inc., Pittsburgh, USA; www.pstnet.com/eprime). Subjects pressed a button in response to visual cues and responses were recorded in E-prime.

Subjects were trained on the tasks immediately prior to scanning. This was done utilizing a computer to display the visual stimuli while instructions were given. Subjects practiced each task using the actual button boxes used during the scan. Training and orientation to the scan required approximately 20 min per subject. Task compliance was confirmed during scanning by way of a remote button control box that indicated subject button presses by illuminating a light color coded for each button.

2.3. Functional imaging

Scanning was performed on a Siemens 3 T Trio MR scanner with a quadrature transverse electromagnetic (TEM) head coil (MR Instruments, Minneapolis, MN). fMRI data were acquired with a susceptibility weighted gradient echo EPI sequence (field-of-view 22 cm, matrix 64×64, repetition time TR = 2.08 s, echo time TE = 30 ms, slice thickness 3 mm with 10% gap, flip angle 75°). Thirty-five slices were acquired during each repetition time.

The first five image volumes of each task were discarded to ensure that the signal reached equilibrium. Distortions caused by variations in magnetic susceptibility were removed during post-processing using fieldmap data acquired with a separate sequence. Anatomic T1-weighted images were acquired using an MPRAGE sequence (field-of-view 24 cm, matrix 192×192, repetition time TR = 1.5 s, inversion time TI = 1.1 s, slice thickness 2 mm, flip angle 12°, signal averages = 2).

2.4. Data processing

Preprocessing and statistical analyses were carried out with SPM2 and Marsbar software (http://www.fil.ion.ucl.ac.uk/spm and http://marsbar.sourceforge.net). Images were realigned to correct for head motion, unwarped to remove susceptibility distortion, and slice-time corrected. The mean-realigned EPI image was co-registered with the anatomic image. All images were spatially normalized to the Montreal

Neurological Institute (MNI) template, and voxel sizes resampled to 2×2×2. EPI images were smoothed using isotropic 6 mm Gaussian kernels and statistically analyzed using an epoch design convolved with the hemodynamic response function. Low-frequency noise was removed with a high-pass filter with a cutoff period of 128 s and an autoregressive AR (1) model was fit to the residuals to account for temporal autocorrelation. Activation cluster location was determined with "MNI Space Utility" (http://www.ihb.spb.ru/~pet_lab).

Studies have shown that panic subjects have lower resting partial pressure of end-tidal carbon dioxide (PCO2) compared to controls, suggesting that they may hyperventilate at rest(Blechert et al., 2007; Giardino et al., 2007). The cerebral vasoconstriction resulting from hyperventilation can dramatically reduce BOLD signal (Giardino et al., 2007). To guard against this effect, a regressor of no interest was generated for each subject by extracting the mean global gray matter signal and high-pass filtering ($f<1/128$), mean-centering, and smoothing by convolution with the canonical hemodynamic response function. The gray matter mask for each subject was obtained by segmenting their anatomic MPRAGE image with SPM2.

Individual contrasts were entered into second-level random effects analyses in which within-group and between-group parametric results were assessed using one and two-sample *t*-tests. Group activation images were corrected for multiple comparisons (FWE0 and thresholded both at $p<0.05$, (whole brain main effects of condition analysis), and also at a voxelwise uncorrected threshold of $p<0.001$, combined with a cluster size threshold of 103 of the 2×2×2 mm resampled voxels (whole brain between groups analysis). This combination was shown by SPM random field theory to result in a one-tailed corrected $p<0.05$ (Friston et al., 1994). Additionally, second-level random effects analyses were carried out for specific regions of interest using Marsbar. These regions were bilateral caudate, putamen, globus pallidus, and thalamus. The models for these regions were taken from the "Automated Anatomic Modeling" library that accompanies Marsbar. Panic subjects taking medication were compared to those not taking any, by entering medication use as a covariate of interest in a second-level region-of-interest analysis. A similar analysis was done for panic subjects with and without psychiatric comorbidity.

3. Results

3.1. Behavioral performance

For the complex motor task, the number of complete cycles (one button press with the first and third finger simultaneously and one press with the second finger) per block was recorded. There were no significant differences between panic subjects and controls for either the right ($t=0.45$, $df=28$, $p=0.66$) or left-hand task ($t=0.04$, $df=28$, $p=0.97$). However, both the panic ($t=4.01$, $df=11$, $p=.002$) and control ($t=2.68$, $df=17$, $p=.016$) subjects completed significantly more cycles with the right-hand than with the left.

3.2. fMRI results

Whole brain main effect of condition analyses in response to the complex motor task for the left-hand was conducted by combining both panic and controls subjects. Significant activation ($p<0.05$, corrected for multiple comparisons) for the entire sample occurred in bilateral prefrontal, precentral, postcentral, cingulate, insular and cerebellar regions as well as right parietal, midbrain and brainstem and left temporal regions. Significant subcortical activation occurred in bilateral putamen, caudate, globus pallidus internal and external segments as well as thalamus.

Table 1
Region of interest analyses of panic subjects as compared to controls in response to the non-dominant hand motor task.

Region	Contrast	*t*	*p* (corrected)
Panic<controls			
Left caudate	0.11	1.02	0.75
Right caudate	0.17	1.61	0.39
Left globus pallidus	0.20	2.62	0.06
Right globus pallidus	0.22	2.48	0.08
Left putamen	0.28	2.87	0.03
Right putamen	0.27	2.85	0.03
Left thalamus	0.12	1.49	0.46
Right thalamus	0.10	1.34	0.55

Whole brain between group analyses revealed that in response to the complex motor paradigm for the non-dominant hand, panic subjects exhibited significantly ($p<0.05$, cluster level significance corrected for multiple comparisons) decreased activation as compared to control subjects in three clusters. One was in the right temporal/occipital region (BA 19 and 39) and the other two were in the bilateral putamen and surrounding regions. Second-level random effects analyses were carried out for specific regions of interest, which were bilateral caudate, putamen, globus pallidus, and thalamus. These analyses (Table 1) confirmed significantly ($p<0.05$, corrected for multiple for the number of regions analyzed) decreased activation in the bilateral putamen for the panic subjects as compared to controls. Neither analysis revealed any regions of greater activation for panic subjects as compared to controls.

We also completed second-level regression analyses with medication use and psychiatric comorbidity as covariants to determine if there were correlations between activation in the regions of interests specified above and these potential confounding variables. There were neither positive (all *p* values ≥ 0.9) or negative (all *p* values ≥ 0.5) correlations with comorbidity nor positive (all *p* values ≥ 0.6) or negative (all *p* values ≥ 0.9) correlations with medication use and activation in any of the regions of interest.

4. Discussion

This study adds to the literature (Ham et al., 2007; van den Heuvel et al., 2005; Yoo et al., 2005) implicating putamen dysfunction in panic disorder. Herein, we provide preliminary evidence of bilateral decreased putamen activation among subjects with panic disorder as compared to normal controls. Further, we provide preliminary evidence that a motor activation paradigm for the non-dominant hand may be useful probe of putamen function in panic disorder.

In order to begin to elucidate the effect of some clinical variables on activation patterns in response to the complex motor task, we used regression analyses to determine if

activation was either positively or negatively correlated with either psychiatric comorbidity or psychiatric medication use in the areas (bilateral basal ganglia and thalamus) used in our region of interest analyses. There were no correlations between activation in any of these regions and either variable (all p values ≥ 0.5). The numbers were small for these analyses and therefore findings must be considered preliminary. We also assessed behavioral task performance data to determine if significant between-group variability of execution occurred, which would confound our results. There were no significant differences on our measures of task completion between the panic and control group. Though these analyses did not suggest that confounding variables impacted our results, a number of limitations of this research must be considered. First, a direct measure of respiratory state of the panic patients relative to the control subjects would have provided a more compelling argument that hyperventilation among panic subjects did not introduce a confound. Also, we studied only non-depressed female subjects, thus further studies will be needed to determine if our result can be generalized to other populations. Further, we did not include a measure of state anxiety, which would have provided useful information about the level of state anxiety versus frequency/severity of panic symptoms. Subjects were not given breaks between the tasks which could have confounded results because of increasing anxiety over time in the scanner. While there were no statistically significant differences between our panic and control groups in regard to age, handedness or MMSE score; we cannot absolutely rule out the possibility that some clinical differences existed. Finally, a discussion of the significance of the laterality of temporal deactivation we found is beyond the scope of this paper, but further research into laterality of functional abnormalities in panic disorder may also contribute to our overall understanding of the neurobiology of this condition.

One possible explanation for our results involves the role of the putamen in the fear response. A recent fMRI study (Butler et al., 2007) of the normal fear response in healthy subjects revealed increased bilateral putamen and decreased cortical activation in response to a fearful situation. The authors interpreted these results as indicating that the pattern of motor cortex de-activation and basal ganglia activation during threat could be interpreted as reflecting a shift from cortical to subcortical processing during danger. They further conclude (Butler et al., 2007) that this interpretation fits with animal studies showing that cortical structures are not required for responding to threat and that fight or flight motor programs are mediated predominantly by subcortical structures. Our findings of abnormal putamen function could indicate that the subcortical mediated fight or flight response might be abnormal in panic disorder. Since the putamen is the striatal nucleus primarily associated with motor control (Cummings, 1993), this structure would likely play a role in subcortical fight or flight programs.

Models of corticostriatal circuitry (Alexander et al., 1990, 1986; Mink, 1996) suggest that as a result of information flow through one of two subcircuits, the direct or indirect pathway, either excitatory or inhibitory feedback respectively, modulates cortical activity. In normal subjects, the study described above (Butler et al., 2007) suggests predominance of indirect pathway activity (increased putamen activation is associated with decreased cortical activation). Our results provide preliminary evidence that conversely in panic disorder a preponderance of direct pathway influence might exist. In a threat condition this would suggest increased putamen activity and increased cortical (fight or flight) activity, but in a non-threat condition (as our study demonstrates) decreased putamen activation is associated with normal cortical activation.

In summary, our results suggest that further studies of putamen function in panic disorder are warranted. It may be useful to compare striatal abnormalities in panic disorder to those seen in other anxiety disorders, such as OCD (Choi et al., 2007; Olver et al., 2009). Further, it may be warranted to compare our tasks to others (Rauch et al., 1997) that are useful in the evaluation of striatal function. Finally, the role of the corticostriatal circuitry as information filters warrants further exploration in future studies.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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References

Alexander, G.E., DeLong, M.R., Strick, P.L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9, 357–381.

Alexander, G.E., Crutcher, M.D., DeLong, M.R., 1990. Basal ganglia-thalamo-cortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog. Brain Res. 85, 119–146.

Argyle, N., Deltito, J., Allerup, P., Maier, W., Albus, M., Nutzinger, D., Rasmussen, S., Ayuso, J.L., Bech, P., 1991. The Panic-Associated Symptom Scale: measuring the severity of panic disorder. Acta Psychiatr. Scand. 83, 20–26.

Blechert, J., Michael, T., Grossman, P., Lajtman, M., Wilhelm, F.H., 2007. Autonomic and respiratory characteristics of posttraumatic stress disorder and panic disorder. Psychosom. Med. 69, 935–943.

Butler, T., Pan, H., Tuescher, O., Engelien, A., Goldstein, M., Epstein, J., Weisholtz, D., Root, J.C., Protopopescu, X., Cunningham-Bussel, A.C., Chang, L., Xie, X.H., Chen, Q., Phelps, E.A., Ledoux, J.E., Stern, E., Silbersweig, D.A., 2007. Human fear-related motor neurocircuitry. Neuroscience 150, 1–7.

Choi, J.S., Kim, S.H., Yoo, S.Y., Kang, D.H., Kim, C.W., Lee, J.M., Kim, I.Y., Kim, S.I., Kim, Y.Y., Kwon, J.S., 2007. Shape deformity of the corpus striatum in obsessive-compulsive disorder. Psychiatry Res. 155, 257–264.

Cummings, J.L., 1993. Frontal-subcortical circuits and human behavior. Arch. Neurol. 50, 873–880.

First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.B., 2001. Users Guide for the Structured Clinical Interview for DSM-IV-TR Axis I Disorders — Research Version. SCID-I for DSM-IV-TR.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. psychiatr. res. 12, 189–198.

Friston, K.J., Worsley, K.J., Frackowiak, R.S.J., Mazziotta, J.C., Evans, A.C., 1994. Assessing the significance of focal activation s using their spatial extent. Hum. brain mapp. 1, 214–220.

Giardino, N.D., Friedman, S.D., Dager, S.R., 2007. Anxiety, respiration, and cerebral blood flow: implications for functional brain imaging. Compr. psychiatry 48, 103–112.

Gorman, J.M., Kent, J.M., Sullivan, G.M., Coplan, J.D., 2000. Neuroanatomical hypothesis of panic disorder, revised. Am. J. Psychiatr. 157, 493–505.

Ham, B.J., Sung, Y., Kim, N., Kim, S.J., Kim, J.E., Kim, D.J., Lee, J.Y., Kim, J.H., Yoon, S.J., Lyoo, I.K., 2007. Decreased GABA levels in anterior cingulate and basal ganglia in medicated subjects with panic disorder: a proton magnetic resonance spectroscopy (1H-MRS) study. Prog. Neuropsychopharmacol. Biol. Psychiatry 31, 403–411.

Marchand, W.R., Lee, J.N., Thatcher, J.W., Hsu, E.W., Rashkin, E., Suchy, Y., Chelune, G., Starr, J., Barbera, S.S., 2008. Putamen coactivation during motor task execution. NeuroReport 19, 957–960.

Mink, J.W., 1996. The basal ganglia: focused selection and inhibition of competing motor programs. Prog. Neurobiol. 50, 381–425.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Olver, J.S., O'Keefe, G., Jones, G.R., Burrows, G.D., Tochon-Danguy, H.J., Ackermann, U., Scott, A., Norman, T.R., 2009. Dopamine D(1) receptor binding in the striatum of patients with obsessive-compulsive disorder. J. Affect. Disord. 114 (1-3), 321–326.

Rauch, S.L., Whalen, P.J., Savage, C.R., Curran, T., Kendrick, A., Brown, H.D., Bush, G., Breiter, H.C., Rosen, B.R., 1997. Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. Hum. Brain Mapp. 5, 124–132.

van den Heuvel, O.A., Veltman, D.J., Groenewegen, H.J., Witter, M.P., Merkelbach, J., Cath, D.C., van Balkom, A.J., van Oppen, P., van Dyck, R., 2005. Disorder-specific neuroanatomical correlates of attentional bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. Arch. Gen. Psychiatry 62, 922–933.

Yoo, H.K., Kim, M.J., Kim, S.J., Sung, Y.H., Sim, M.E., Lee, Y.S., Song, S.Y., Kee, B.S., Lyoo, I.K., 2005. Putaminal gray matter volume decrease in panic disorder: an optimized voxel-based morphometry study. Eur. J. Neurosci. 22, 2089–2094.