Aberrant functional connectivity of cortico-basal ganglia circuits in major depression

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Abstract

There is considerable evidence of functional abnormalities of the cortico-basal ganglia circuitry in affective disorders. However, it has been unknown whether this represented primary pathology within these circuits or altered activation as a result of aberrant input from other brain regions. The aim of this study was to test the hypothesis that cortico-basal ganglia circuit dysfunction represents primary pathology in unipolar depression. Eighteen male subjects with recurrent unipolar depression and eighteen controls without psychiatric illness were studied using functional MRI and functional connectivity analyses. All unipolar subjects were unmedicated and without current psychiatric comorbidity. Compared to controls, unipolar subjects exhibited altered connectivity between bilateral subcortical components of the circuitry (putamen-thalamus) and left hemisphere input and output components. Results provided evidence that functional abnormalities of these circuits represent primary pathology. Further, we found that age of onset but not duration of illness impacts circuit function. These findings suggest that the cortico-basal ganglia circuitry is likely one of several loci of primary pathology in major depression. Additionally, early age of onset is associated with greater circuit abnormality and as such may impact clinical characteristics and/or treatment response through a mechanism of decreasing functional connectivity of some circuit segments. Finally, altered cortico-basal ganglia circuit connectivity with cortical regions (anterior cingulate, inferior frontal gyrus and sensorimotor) may contribute to the emotional dysregulation, impaired emotional recognition and psychomotor symptoms associated with unipolar illness.

Key words

Major depression; striatum; anterior cingulate cortex; functional MRI; functional connectivity; basal ganglia

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Abbreviations

ACC, anterior cingulate cortex; CORE, CORE Assessment of Psychomotor Change; FDR, False Discovery Rate; fMRI, functional magnetic resonance imaging; IFG, inferior frontal gyrus; MADRS, Montgomery-Asberg Depression Rating Scale; MNI, Montreal Neurological Institute; ROI, Region-of-interest; SCID, Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Research Version; SMA, supplementary motor area; WTAR, Wechsler Test of Adult Reading

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Introduction

There is extensive evidence that aberrant function of the striatum and associated cortico-basal ganglia circuitry plays an important role in the neuropathology of affective disorders, including unipolar depression, for recent reviews see [19, 28]. However, the exact neural mechanisms remain poorly characterized [19, 28]. One important question is whether cortico-basal ganglia circuit dysfunction represents primary pathology. One possibility is that these circuits are one of several loci of primary pathology in mood disorders. However because of extensive connectivity with much of the brain, altered activation of these circuits could occur as a result of abnormal input from other areas. As we have previously reviewed [19], cortico-basal ganglia input nuclei (striatum and subthalamic nucleus) neurons fire in response to excitatory inputs from other regions. Therefore, the increased or decreased activation of the striatum and other circuit structures that has been reported in affective disorders [28] could occur as a result of changes in excitatory input from other regions rather as a result of dysfunction within the circuits themselves.

We have hypothesized [28] that primary pathology exists within the cortico-basal ganglia circuitry. The aim of this study was to test that hypothesis. The cortico-basal ganglia circuits can be divided into three basic components. These are input (cortex to striatum), subcortical (striatum to thalamus) and output (thalamus to cortex) segments. Thus, we reasoned that determining which of these segments exhibit functional abnormalities in unipolar illness would inform the question of primary pathology. Specifically, if functional connectivity of input segments was abnormal but the subcortical segments were normal, this would suggest that primary pathology did not exist within the circuitry. In contrast, aberrant connectivity within the

subcortical segments, particularly along with dysfunctional output segments, would suggest primary pathology within the circuitry.

A secondary aim was to characterize the impact of prior antidepressant treatment, age of onset and duration of illness on cortico-basal ganglia circuit function in this illness. To achieve these aims we studied eighteen unmedicated subjects with recurrent major depression and eighteen controls without psychiatric illness using functional magnetic resonance imaging (fMRI) and functional connectivity analyses.

Material and methods

Subjects

Participants were recruited from the community. Recruitment methods included flyers posted in the community as well as online, TV, radio and print media advertising. 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 Research Review Committee of the George E. Whalen Veterans Administration Medical Center.

All subjects received a study evaluation during which the SCID [4] was administered to confirm the diagnosis of unipolar depression and rule out current psychiatric comorbidity for the unipolar subjects as well as rule out lifetime psychiatric illness for control subjects. The Edinburgh Handedness Inventory [30] was given to ensure that all subjects were strongly right-handed. Subject IQ was estimated using a previously validated [2] screen, the WTAR.

Unipolar subjects were enrolled who met criteria for major depression, recurrent, as determined by the SCID evaluation. Control subjects were enrolled who did not meet criteria for a lifetime diagnosis of, or have a first-degree relative with, any psychiatric disorder. All subjects were between 21 and 45 years of age. Exclusionary criteria for all subjects included: diseases

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impacting the central nervous system; education < 12 years; WTAR-IQ scores <90; medications affecting the central nervous system; use of nicotine within the previous 30 days; history of traumatic brain injury; score < 80 on the Edinburgh Handedness Inventory. Additional exclusionary criteria for unipolar subjects included any comorbid psychiatric or substance abuse disorder within six months of the study evaluation and treatment with psychiatric medications within the previous three months.

Eighteen subjects with recurrent unipolar depression and eighteen controls without psychiatric illness were studied. These subjects were part of a larger study for which 487 potential subjects were phone screened and 45 enrolled. All subjects were male to avoid any confound secondary to gender-specific fMRI activation patterns [3]. Mean ages were 26.7 and 27.6 for unipolar and control subjects respectively. Unipolar subjects had mean estimated IQs of 114.7 versus 117.6 for controls. Mean Hollingshead socioeconomic scale scores were 44.4 for unipolar subjects and 47.4 for controls. There were no significant between group differences in regard to age ($p = 0.49$), estimated IQ ($p = 0.36$) or socioeconomic status ($p = 0.20$). For the unipolar subjects, the mean age of illness onset was 13.9 with a range from age 9 to 22. The mean duration of illness was 12.8 years with a range from 2 to 21 years. Nine of the 18 unipolar subjects (50%) had been treated with antidepressants in the past.

On the day of the scan, mood symptoms were assessed using the MADRS [29] and the CORE [31] was used to assess psychomotor symptoms. Mean scores were 26.3 and 1.3 for the MADRS and CORE respectively. Thus, all subjects were experiencing moderate to severe depression and none of the subjects were experiencing significant psychomotor agitation or retardation. All subjects had negative urine drug screens on the day of the scan. Finally, all

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structural MRI scans were read by a radiologist and determined to have no chronic or acute pathology.

Activation paradigms and experimental procedure

Subjects completed three motor activation paradigms during the scan. Results from one of these, a self-paced button-pressing task, are reported herein. The motor activation task was a self-paced paradigm during which subjects pressed a button with the index finger of the non-dominant (left) hand for blocks of 20 seconds alternating with 20-second blocks of rest. The duration of each run was four minutes and included six blocks of activity and six blocks of rest. Subjects completed two runs.

This motor task was utilized because our aim was to examine components of the cortico-basal ganglia circuitry. Therefore, we used a motor activation paradigm based on those that we have previously shown to have very good group reliability [16] and be useful for studies of striatal function in bipolar I disorder [23, 25], bipolar II disorder [19] and panic disorder [20] as well as normal brain function [21, 22, 24, 26, 27].

Visual stimuli for the tasks were presented on a translucent slide screen at the back of the magnet, which was viewed through a mirror. Stimulus presentation and response recordings were controlled by E-prime software (Psychology Software Tools, Inc., Pittsburgh, USA; www.pstnet.com/eprime). Subjects completed the motor task by pressing a button on a handheld response box. Responses were recorded in E-prime. Subjects were trained on the task immediately prior to scanning.

Functional image acquisition

Subjects were scanned on a Siemens 3T Trio MR scanner with a 12-channel head coil. Functional MRI data were acquired with a susceptibility weighted gradient echo EPI sequence

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(field-of-view 22 cm, matrix 64×64, repetition time TR=2.08s, echo time TE=30ms, slice thickness 3mm with no gap, flip angle 75º). Thirty-five slices were acquired during each repetition time. The first five image volumes of each task were discarded to ensure signal equilibrium. Distortions caused by variations in magnetic susceptibility were removed during post-processing using fieldmap data acquired with a separate sequence. Anatomical T1-weighted images were acquired using an MPRAGE sequence (field-of-view 22cm, matrix 192×192, repetition time TR=1.5s, inversion time TI=1.1s, slice thickness 2mm, slices = 80, flip angle 8º, signal averages=2). Pulse oximetry data was acquired on a finger of the subject's right hand, and respiration was recorded through a respiratory bellows.

Functional image and correlational analyses

Preprocessing and statistical analyses were carried out with SPM5 (http://www.fil.ion.ucl.ac.uk/spm). Functional MRI data were corrected for cardiac and respiratory artifacts using the RETROICOR algorithm [7] as incorporated in Aztec 1.0 software downloaded from http://www.thomasgladwin.com/files/matlab/aztec.php [33]. Data loading functions were taken from Physiological Log Extraction for Modeling Toolbox (http://sites.google.com/site/phlemtoolbox/Home). 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 anatomical image. All images were spatially normalized to the Montreal Neurological Institute (MNI) template, and voxel sizes resampled to 2×2×2mm. EPI images were smoothed using isotropic 6mm 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 128s and an autoregressive AR(1) model was fitted to the residuals to account for temporal autocorrelation.

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Between-group comparisons of whole-brain activation were made using two-sample t-tests and multiple comparisons were controlled with cluster-extent thresholding.

Anatomical regions of interest (ROIs) were taken from a probabilistic atlas [9] (© Copyright Imperial College of Science, Technology and Medicine 2007. All rights reserved.). ROIs were selected based upon components of the cortico-basal ganglia circuitry of interest. In regard to cortical components we were interested in both motor and emotional function. Therefore, we chose two regions, S1/M1 and SMA to represent sensorimotor processing. The left IFG was chosen because this area is involved with processing of language, working memory and empathy [17] as well as emotional processing [6] and social perception [13] including perception of facial affect [14]. Further, the emotional labeling deficit associated with depression was recently shown to be associated with abnormal activation of this region [34]. The ACC was chosen because this region is extensively involved in emotional regulation [10-12].

ROIs were defined by combining anatomical regions of interest with control group activation results with a voxel-wise threshold of $p<0.001$, and a cluster size shown by SPM random field theory to have a one-tailed $p<0.05$, corrected for multiple comparisons using Family Wise Error (FWE) correction [5]. Cluster sizes were determined with the CorrClusTh script (http://www.sph.umich.edu/~nichols/JG5/CorrClusTh.m).

Waveforms were extracted with Marsbar software (http://marsbar.sourceforge.net), mean corrected, quadratically detrended to correct for scanner drift and high-pass filtered > 0.01 Hz with a second order Butterworth filter. In addition, regions of interest for regressors of no interest were obtained by placing 3 mm-radius seeds in both white matter and CSF (MNI coordinates 33, -62, 24 and 1, -6, -24, respectively).

Partial correlations between pairs of ROIs were carried out using the Matlab Statistics

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Toolbox (Mathworks, Natick, Massachusetts), partialing out the influence of white matter, CSF and the six motion regressors that result from spatial realignment in SPM5. The resulting partial correlations were normalized with Fisher's z transform to produce functional connectivity values. Multiple comparisons for connectivity differences were accounted for independently for right and left sides using False Discovery Rate (FDR).

Results

Behavioral results

Functional MRI activation task completion was assessed by recording the number of button presses for each subject. The mean number of button presses was 86.1 for unipolar subjects and 92.4 for controls. This was not a significant difference ($p = 0.08$). One unipolar subject was not included in this analysis because of a data collection problem.

Functional imaging results

Between-group comparisons of whole-brain activation revealed decreased activation among the unipolar subjects in the area of the left postcentral gyrus (128 voxels) and increased activation in the areas of right middle frontal gyrus (191 voxels), bilateral cingulate (280 voxels) and left (321 voxels) and right (175 voxels) inferior parietal lobule.

A between-group comparison of cortico-basal ganglia functional connectivity revealed decreased connectivity among unipolar subjects in the left hemisphere in all input segments, the subcortical segment and three of the four output segments. These results are displayed in Table 1. Additionally, functional connectivity of the subcortical segment (putamen to thalamus) was significantly decreased among the unipolar subjects in the right hemisphere ($p = 0.003$). There were no segments where connectivity was increased among the unipolar subjects compared to controls.

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Correlational analyses of the unipolar subjects alone revealed that age of illness onset was correlated with strength of cortico-basal ganglia functional connectivity for some right hemisphere segments. In contrast, duration of illness was not correlated with strength of functional connectivity for any segments. After controlling for duration of illness, age of onset was correlated with several right hemisphere connectivities (Table 2). All correlations were positive (younger age of onset = decreased connectivity strength). History of antidepressant treatment was significantly correlated with strength of connectivity for one right input segment (Table 2). There were no significant correlations between connectivities and MADRS scores.

Discussion

Novel findings from this study will, if replicated, significantly expand our understanding of neurobiological processes underlying unipolar depression.

The first key finding is that the functional connectivity along important pathways of the left hemisphere cortico-basal ganglia circuitry is disrupted among individuals with recurrent major depression (Table 1). Furthermore, subcortical circuit components were disrupted bilaterally. Our result adds to literature [28] implicating these circuits in the neurobiology of affective illness and is consistent with a recent study that found decreased functional connectivity between the ACC and thalamus in unipolar illness [1]. While considerable previous evidence [28] suggests these circuits may be dysfunctional in unipolar illness, to our knowledge this is the first study to begin to characterize the abnormalities in terms of input, output and subcortical pathways.

If replicated, our results will have a number of important ramifications. First of all, our hypothesis that subcortical (putamen to thalamus) circuit segments would exhibit abnormal functional connectivity was confirmed. This indicates that dysfunction exists within the

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subcortical components of the circuitry and suggests that these segments may be a site of primary pathology. In contrast, aberrant input and output but normal subcortical connectivities would have indicated a different process. For example, abnormal connectivity might have been the result of deficits in white matter tracts of input or output pathways. Another possibility would have been anomalous input from a brain region that was the site of primary pathology. In the latter case, the cortico-basal ganglia circuitry might have served as a final common pathway [19]. In contrast, our findings suggest that primary pathology exists within the subcortical components of the cortico-basal ganglia circuitry in recurrent unipolar depression.

Our findings also suggest how circuit dysfunction may contribute to the expression of motor and emotional symptoms. We found abnormal left hemisphere functional connectivity in both input and output pathways involved with motor function (S1/M1) as well as regulation (ACC) and recognition (ACC and IFG) of emotion. The striatum [18] and the ACC [10-12] are extensively involved in emotional regulation. Further, the emotional labeling deficit associated with depression was recently shown to be associated with abnormal activation of the left inferior frontal gyrus and anterior cingulate cortex [34]. Therefore, our novel findings suggest that altered cortico-basal ganglia circuit connectivity with cortical regions may contribute to the emotional dysregulation, impaired emotional recognition and psychomotor symptoms associated with unipolar illness.

Another key finding of this study was that age of illness onset was associated with cortico-basal ganglia circuit functional connectivity. To our knowledge, this is the first study to report such finding. Specifically, we found that earlier age of onset was correlated with decreased functional connectivity in right hemisphere putamen-IFG and putamen-S1/M1 input and output pathways. In contrast, duration of illness was not correlated with connectivity

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strength of any circuit segment. There are two ways in which this finding could be interpreted. On the one hand, it is possible that early onset of illness may disrupt circuit function, perhaps due to disruption of normal brain maturation. Alternatively, it is possible that circuit abnormalities predate the onset of illness, and that the neurobiology of childhood onset depression differs from adult onset depression. Regardless of the interpretation, this finding is consistent with the notion that age of onset may impact clinical characteristics and/or treatment response as some studies suggest [8, 15, 32]. In contrast duration of illness did not impact the function of the circuits we studied, suggesting that, at least within the age range of our sample, the illness did not have cumulative deleterious impact on brain function. Finally, it is important to note that the strength of functional connectivity between the subcortical segments was not correlated with age of onset for either hemisphere. This supports our interpretation that dysfunction within these subcortical segments represents primary pathology and is therefore not impacted by age of onset.

History of antidepressant treatment was significantly correlated with strength of connectivity for one right hemisphere input pathway (Table 2). This result suggests that our findings were not impacted by prior treatment history, since our results in regard to input pathways were all in the left hemisphere.

Finally with the exception of left S1, between-group comparisons did not reveal aberrant activation in cortical regions relevant for this study. This is consistent with our hypothesis that dysfunction exists within the cortico-basal ganglia circuitry in contrast to abnormal cortical input, which would be expected to manifest as aberrant activation.

Some limitations of this work must be acknowledged. Only right-handed males with recurrent unipolar illness within a limited age range were studied. Thus, it is unknown whether

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these results will generalize to other populations. Also, the sample size is relatively small, however results remained significant after correcting for multiple comparisons. Further, between-group differences were found primarily in the left hemisphere, while correlations with age of onset occurred in the right hemisphere. This may represent a confound due to sample size. Alternatively, brain compensatory responses and/or prior treatment might have impacted laterality results in ways that could not be discerned in this investigation. Finally, we did not make between-group comparisons of the volumes of structures of interest. In contrast, strengths of this work include well-matched subject cohorts as well as the fact that unipolar subjects were unmedicated and without psychiatric comorbidity. This work is an important first step that will lay the groundwork for future studies that are more inclusive.

Conclusions

Our results indicate that cortico-basal ganglia dysfunction in recurrent unipolar depression represents primary rather than secondary pathology. Additional studies will be needed to determine the functional relationships between the cortico-basal ganglia circuitry and other loci of primary neuropathology. Nonetheless, aberrant function of subcortical segments of these circuits appears to represent at least one component of fundamental pathological processes underlying this condition.

We also provide the first evidence that age of onset impacts neural function in major depression. Further investigations are warranted to determine whether age of onset associated variability in functional connectivity contributes to differences in clinical characteristics or treatment response. Finally, our results indicate that our fMRI activation paradigm is a useful probe of the cortico-basal ganglia circuitry in unipolar depression.

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Table 1. Between-group comparison of left hemisphere cortico-basal ganglia functional connectivity (unipolars < controls).

Circuit segment		(p value)	t statistic
Input	Putamen-IFG	0.004*	3.14
	Putamen-SMA	0.012*	2.68
	Putamen-ACC	0.015*	2.56
	Putamen-S1/M1	0.012*	2.67
Subcortical	Putamen-thalamus	0.003*	3.24
Output	Thalamus-IFG	0.033*	2.24
	Thalamus-SMA	0.155	1.46
	Thalamus-ACC	0.004*	3.08
	Thalamus-S1/M1	0.028*	2.33

* = Significant at 0.05 (df = 34) corrected for multiple comparisons using FDR; IFG = inferior frontal gyrus; SMA = supplementary motor area; ACC = anterior cingulate cortex; S1/M1= primary sensorimotor cortex.

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Table 2. Significant correlations of clinical variables with strength of right hemisphere cortico-basal ganglia functional connectivity.

Circuit segment		Age of illness onset (after controlling for illness duration) (r)	Prior antidepressant treatment (r)
Input	Putamen-IFG	0.69**	0.05
	Putamen-SMA	0.44	0.52*
	Putamen-ACC	0.34	0.35
	Putamen-S1/M1	0.65**	0.25
Subcortical	Putamen-thalamus	0.44	0.10
Output	Thalamus-IFG	0.63**	-0.002
	Thalamus-SMA	0.38	0.24
	Thalamus-ACC	0.32	0.17
	Thalamus-S1/M1	0.57*	0.31

** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed). IFG = inferior frontal gyrus; SMA = supplementary motor area; ACC = anterior cingulate cortex; S1/M1= primary sensorimotor cortex. Prior antidepressant treatment was coded as 1=treatment and 0=no treatment; thus, positive correlation reflect higher connectivity among previously treated individuals.

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