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Regular Article

Resting state default-mode network connectivity in early depression using a seed region-of-interest analysis: Decreased connectivity with caudate nucleus

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Aim: Reports on resting brain activity in healthy controls have described a default-mode network (DMN) and important differences in DMN connectivity have emerged for several psychiatric conditions. No study to date, however, has investigated resting-state DMN in relatively early depression before years of medication treatment. The objective of the present study was, therefore, to investigate the DMN in patients seeking help from specialized mental health services for the first time for symptoms of depression.

Methods: Fourteen depressed subjects and 15 matched controls were scanned using 4-T functional magnetic resonance imaging while resting with eyes closed. All but one subject was medication free. A precuneus/posterior cingulate cortex (P/PCC) seed-region connectivity analysis was used to identify the DMN and compare study groups in regions of relevance to depression.

Results: The P/PCC analysis identified the DMN well in both study groups, consistent with prior literature. Direct comparison showed significantly reduced correlation between the P/PCC and the bilateral caudate in depression compared with controls and no areas of increased connectivity in the depressed group.

Conclusions: The present study is the first to investigate resting-state DMN in the early stages of treatment-seeking for depression. Depressed subjects had decreased connectivity between the P/PCC and the bilateral caudate, regions known to be involved in motivation and reward processing. Deficits in DMN connectivity with the caudate may be an early manifestation of major depressive disorder.

Key words: caudate nucleus, cingulate gyrus, depression, functional, magnetic resonance imaging.

RESEARCH DELINEATING LOW-FREQUENCY (<0.1 -Hz) oscillations of brain activity in the default-mode network (DMN) is increasing. The DMN is suggested to be involved in the neurophy-

siological processes of introspection and self-monitoring.¹ Many studies of the DMN involve healthy controls but investigations in clinical populations have also been conducted. These include reports on schizophrenia,^{2,3} autism,⁴ Alzheimer's disease,^{5–7} post-traumatic stress disorder⁸ and depression.^{9,10} One study has demonstrated use of resting state analyses to distinguish between schizophrenia and bipolar disorder.¹¹ Thus, this technique may eventually provide valuable clinical information not available with other approaches.

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Many functional imaging studies implicate specific brain regions involved in depression including areas of medial prefrontal cortex (mPFC),^{12–14} and the striatum.^{15–18} In a resting functional magnetic resonance imaging (fMRI) study to investigate the DMN in long-standing depressed subjects compared with controls Greicius *et al.* found greater DMN connectivity in areas long associated with depression.⁹ These included the subgenual cingulate, medial frontal cortex, thalamus, and cuneus/precuneus. The subgenual anterior cingulate differences correlated positively with length of depressive episode.⁹ The mean duration of the depressive episode of the population in that study was >3 years. No study, to date, has investigated the DMN in depressed patients early in the course of their treatment seeking, or before significant use of medications.

In the present study we used fMRI to investigate the resting-state DMN in older adolescents and adults presenting to a psychiatric clinic for the first time. Most of these individuals had never been medically treated for their psychiatric symptoms prior to scanning and all but one was medication free. Given the previous research on the DMN in chronic depression by Greicius *et al.*,⁹ we predicted that the present recently depressed subjects would show greater functional connectivity of the DMN than healthy controls in the thalamus, mPFC, and cuneus/precuneus.

METHODS

Subjects

Fourteen depressed and 15 healthy control subjects were recruited during 2006–2008. Depressed subjects were recruited from first-time psychiatric consultations at the London Health Sciences Centre and were included if their ages were between 17 and 35 years and they had a primary diagnosis of major depressive disorder (MDD). Exclusion criteria were major medical illness, history of head trauma, lifetime psychiatric medication use longer than 3 months in total, diagnosis of obsessive-compulsive disorder, current post-traumatic stress disorder, bipolar disorder, imminent danger to self or others, or pregnancy, intent to become pregnant, or other MRI exclusion criteria. Healthy controls were recruited based on matching age and gender, and were excluded if they reported a first-degree relative with a mood disorder, or for any exclusion criteria for MRI scanning. The protocol was approved by the Human-Subjects

Research Ethics Board at the University of Western Ontario. The study was fully explained to all subjects and written, informed consent was obtained and all subject identifiers were removed. The Structured Clinical Interview for DSM-IV (SCID-IV) was conducted to evaluate for axis I disorders. Subjects also completed the Beck Depression Inventory (BDI).

Functional magnetic resonance imaging

All subjects underwent a 5.5-min resting scan. They were instructed to close their eyes, relax and let their mind wander freely. Subjects were asked if they were able to comply with these directions after the resting scan. All subjects reported having been able to comply.

Images were acquired using a 4.0-T Varian Unity Inova whole-body MRI system (Varian, Palo Alto, CA, USA) equipped with Siemens Sonata actively shielded gradient coils (Siemens Medical, Erlangen, Germany). A single-tuned, ¹H quadrature hybrid birdcage volume head coil, 27 cm inner diameter, was used for transmission and signal detection (XLR Imaging, London, Ontario, Canada). Subjects' heads were immobilized with foam padding and a Plexiglass head cradle (Robarts Research Institute, London, ON, Canada). Functional images were continuously collected using a segmented (two-shot) gradient echo (T₂*-weighted) pulse sequence utilizing spiral-gradient waveforms (64 × 64 matrix size; field of view, 25.6 cm; echo time, 15 ms; volume acquisition time (relaxation time), 3 s; tip angle, 60°). Between 26 and 29 slices were acquired, depending on the number of slices needed to achieve whole-brain coverage. Slice thickness was 4 mm, resulting in 4 × 4 × 4-mm³ isotropic voxels. A total of 110 volumes was collected for each subject.

Statistical analysis

The spiral reconstruction of images utilized a regridding algorithm that incorporated a Kaiser-Bessel kernel, Jacobian weighting function, and density compensation. Image preprocessing steps and statistical analysis was conducted using Statistical Parametric Mapping (SPM2, Wellcome Department of Neurology, London, UK). Preprocessing of images followed steps previously reported in Fransson¹ and Bluhm *et al.*³ For each subject, all functional images were realigned to the first image in the series to reduce the effects of head motion. The images were then resliced

and a mean functional image was also created. Images were then coregistered to the mean functional image and normalized to the EPI template in SPM2. The functional images were smoothed using a 12-mm full-width half-maximum isotropic Gaussian filter to compensate for residual within-subject variability, decrease high spatial frequency noise and insure the applicability of Gaussian random field theory on which further statistical testing relied. Time course intensities were globally normalized.

For each subject a mean signal intensity time course, adjusted for the frequency range of 0.012–0.1 Hz, was extracted from a 10-mm sphere in the region of interest (ROI) and then used as a regressor in a correlation analysis with the resting scan data for that subject, which had been bandpass filtered to preserve only low-frequency oscillations between 0.012 and 0.1 Hz.^{3,19} Correlation analyses were conducted using a seed ROI in the precuneus/posterior cingulate cortex (P/PCC); centered at MNI coordinates $x, y, z = 0, -56, 20$. Connectivity described as follows reflects positive correlations between this seed region and other brain areas. Seed ROI analyses using the P/PCC were used to emulate previous published work on the DMN^{1,20} including our own prior work in other psychiatric sample groups,^{3,8} and because it is a central hub in functionally specialized systems.^{21,22} It was also chosen because this area was not expected to have major differences between groups at these coordinates, as would mid-line frontal regions,²³ which could have led to complications in interpretation of the results. To compare ROI connectivity within and between subject groups, second-level mixed-effects analyses, in which subjects are treated as random variables (frequently referred to as 'random effects' in the imaging literature), were conducted in SPM using contrast images from individual subjects. Reported within-group findings reflect a type 1 error threshold of $P < 0.001$ using false discovery rate correction for multiple comparisons.

Within-group comparison showed several regions that appeared in one but not both groups and several of these areas were noted to be relevant to depression from prior published studies. These included Brodmann area (BA) 10 and 32,^{24,25} the caudate^{26,27} and the parahippocampal cortex.^{28,29} We therefore conducted small volume corrected (SVC) analyses using Pickatlas³⁰ standardized BA to determine if there were significant differences between groups in these ROI. In addition, the published DMN study in chronic depression showed areas of group difference in thala-

mus, BA 25, BA 11, and cuneus/precuneus.⁹ Coordinates from the work of Greicius *et al.*⁹ were used to identify these regions. Small volume corrections using a 5-mm radius sphere were used to compare group connectivity maps in these regions. Correlation of the connectivity map with BDI scores in the depressed group was also performed.

RESULTS

Demographics and psychometrics

The age of control and depressed subjects was not significantly different at 23.5 ± 5.4 years (range, 18–34 years) and 21.9 ± 5.1 years (range, 17–35 years), respectively. Sex distribution was 11F/4M and 9F/5M for control and depressed subjects. Only one depressed subject was over 30 years of age. As expected, mean BDI score was significantly higher for depressed subjects at 24.5 ± 8 (range, 10–33) compared with healthy controls at 0.8 ± 1 (range, 0–5). Lifetime dysfunction from psychiatric illness was low. Because of the recent onset of symptoms, depressed subjects were high functioning at the time of scanning, with 13 (81%) enrolled in school.

Of 14 depressed subjects, all met DSM-IV criteria for MDD. Lifetime use of psychiatric medication in depressed subjects was low, with only three subjects having ever received any psychiatric medications in their lifetimes (two a selective serotonin norepinephrine re-uptake inhibitor, one a benzodiazepine). The maximum duration of past psychiatric medication use was 3 months. At the time of study only one subject was on a psychiatric medication, a steady dose of the selective serotonin re-uptake inhibitor escitalopram.

Three depressed subjects also met criteria for a current anxiety disorder (two social phobia, one generalized anxiety disorder). The anxiety symptoms expressed by these subjects were not easily clinically separable from their depressive symptoms. There were no current psychiatric diagnoses in control subjects.

Functional imaging

Subjects reported being able to comply with instructions for the scan session. Results of the P/PCC seed ROI connectivity analysis in each group are given in Table 1 and Fig. 1(a,b). The DMN was easily identified by the P/PCC seed-region analysis in both

Table 1. Significant clusters of DMN functional connectivity using P/PCC positive correlations

Region	Coordinates (MNI)	t-value	Voxel cluster size
Controls (<i>n</i> = 15)			
Bilateral posterior cingulate/precuneus	0, -56, 0	11.49	4721
Bilateral medial prefrontal gyrus (BA 10)	-2, 68, 12	8.97	402
Left superior temporal/angular gyrus (BA 39)	-50, -60, 30	8.83	613
Left middle frontal gyrus (BA 8)	-24, 32, 48	8.05	406
Right caudate head	12, 12, 4	7.43	427
Right superior frontal gyrus (BA 8)	26, 38, 46	6.64	164
Left caudate body	-12, 4, 16	6.06	42
Left thalamus	-20, -16, 10	5.94	38
Right medial frontal gyrus (BA 32)	6, 38, 24	5.89	12
Depressed (<i>n</i> = 14)			
Bilateral posterior cingulate/precuneus	-22, -60, 20	11.84	4239
Left precuneus/inferior parietal lobule, angular gyrus (BA 39/19)	-34, -76, 44	9.00	277
Right parahippocampal gyrus	20, -36, -8	8.83	209
Left parahippocampal gyrus	-26, -32, -14	8.57	402
Left superior/middle frontal gyrus (BA 9/8)	-22, 32, 40	7.78	234
Right inferior parietal/angular gyrus (BA 39)	36, -66, 42	7.76	134
Left superior frontal gyrus (BA 10)	-26, 60, -2	7.73	34
Left thalamus	-8, -16, 10	6.43	34
Right thalamus	8, -18, 12	6.23	10

Significance criteria of $P < 0.001$, $k \geq 10$ with false discovery rate correction for multiple comparisons; random effects analysis. BA, Brodmann area; DMN, default-mode network; MNI, Montreal Neurological Institute spatial array coordinates; P/PCC, precuneus/posterior cingulate cortex.

groups. This included the frontal pole (BA 8 and 10), angular gyrus (BA 39), and thalamus in both groups. In addition, controls showed P/PCC connectivity with the caudate, right BA 10, and right BA 32 while only depressed subjects showed connectivity in the parahippocampal cortex bilaterally.

The between-group comparisons demonstrated significantly greater connectivity with P/PCC in the bilateral caudate in controls compared to depressed subjects (Table 2; Fig. 1c). No significant differences were found in BA 10 or 32,^{24,25} parahippocampal gyri; or areas identified by Greicius *et al.*,⁹ including the thalamus, BA 25, BA 11, and cuneus/precuneus at the coordinates they identified (2, -86, 37, Talairach). There were no significant regions of greater P/PCC connectivity in the depressed subjects versus controls in any ROI. There were no correlations that survived correction between BDI and connectivity in the depressed subjects.

DISCUSSION

In the present study we investigated resting-state DMN connectivity in depression compared with

healthy controls. This was the first study to acquire such data from individuals with little to no previous treatment and only recent entry into the mental health care system. The P/PCC seed ROI analyses used here demonstrated good identification of the DMN as consistent with previous literature. It also showed significantly greater connectivity between the P/PCC and the bilateral caudate in the control group compared with the depressed subjects. Contrary to our hypothesis and the previous DMN study of depression in older and longer treated patients, there was no greater connectivity in depressed subjects between the DMN and several areas of the mPFC, subgenual anterior cingulate cortex, thalamus, parahippocampal gyri, or cuneus/precuneus.

Depressed individuals often describe anhedonia, which manifests as an inability to experience interest or pleasure in activities,³¹ and have difficulty motivating themselves to act, which may be mediated through abnormalities in the subgenual PFC and/or other limbic regions. The striatum, including the caudate, is involved in the processing of rewarding stimuli in healthy controls and is therefore intricately involved in pleasure and motivation.^{32–37} The

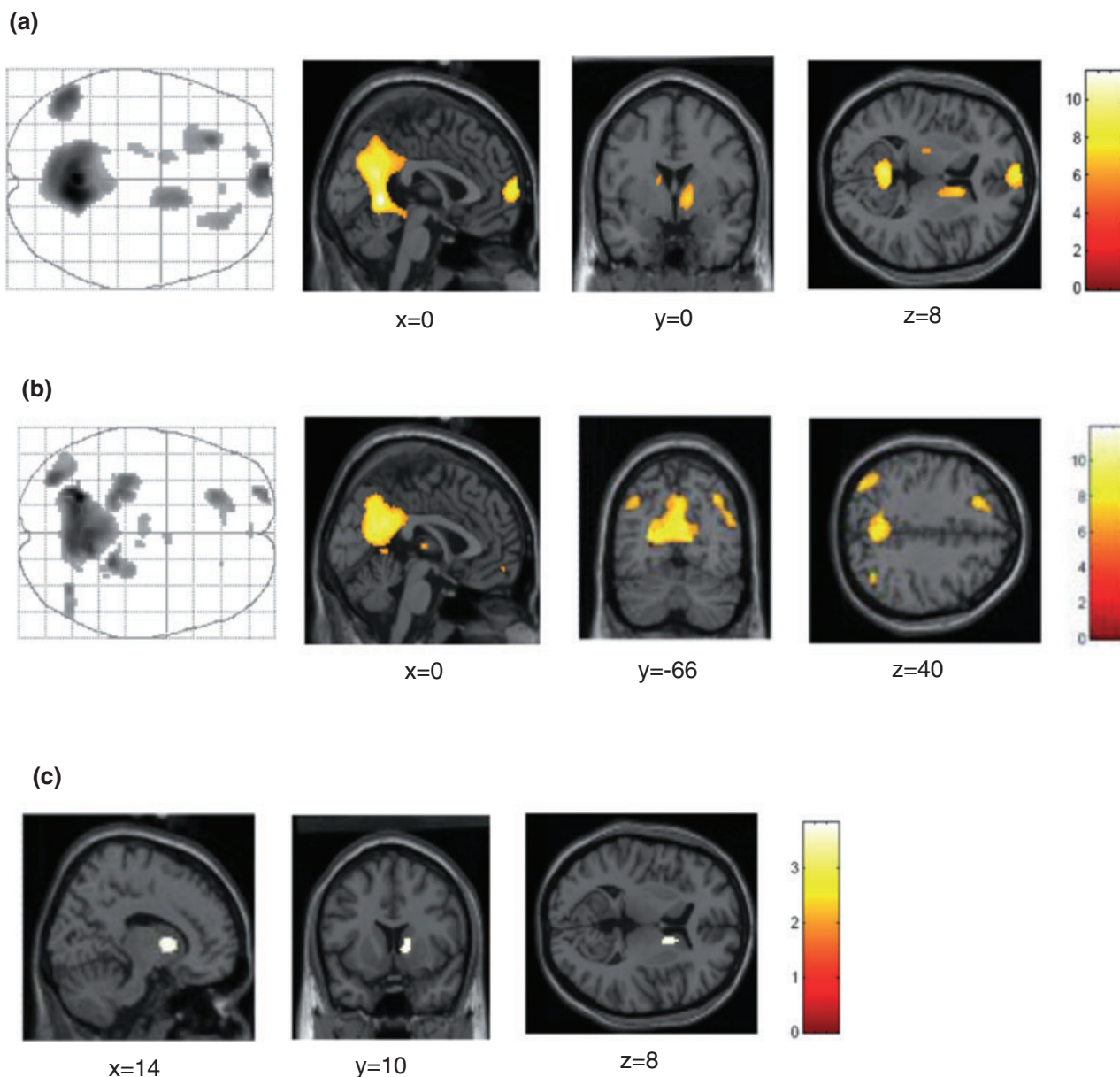


Figure 1. Connectivity SPM[T] maps of individual groups and group comparison using look-through view for full-brain results and overlays showing specific coordinates. (a) Control and (b) depressed subjects using a precuneus/posterior cingulate cortex (P/PCC) seed region-of-interest analysis within the P/PCC at coordinates $x = 0$, $y = -56$, and $z = 20$ as per the Montreal Neurological Institute spatial array coordinate system. Locations of the images are indicated by the x , y , or z as per the same coordinate system. Images reflect false discovery rate correction ($P < 0.001$). (c) Controls > depressed; right caudate. Between-group comparisons with x , y and z coordinates shown at the voxel of right caudate peak difference between groups. The threshold of significance for this whole-brain subtraction image was $P < 0.001$, uncorrected for multiple comparisons, to demonstrate the shape and extent of the right caudate finding.

striatum plays a role in conditioning and learning and is related to probability and magnitude of rewards.³⁸ Functional connectivity between the striatum and the P/PCC in the resting state has been

discovered in a previous study of healthy controls.³⁹ Previous studies of depressed individuals have found abnormalities in striatal function associated with anhedonia,^{40,41} in response to positive stimuli,⁴²

Table 2. Significant differences in DMN functional connectivity maps: controls vs depressed subjects

Region	Coordinates (MNI)	t-value
Controls > Depressed		
Right caudate body*	14, 10, 8	3.81
Left caudate body*	−14, 20, 8	3.27
Right caudate head**	12, 10, 2	3.78
Left caudate head**	−12, 20, 6	3.22
Depressed > Controls		
No significant differences		

*FDR corrected; $P = 0.03$; random-effects analysis; **FDR corrected; $P = 0.01$; random-effects analysis.

Small volume correction analyses were conducted in orbital frontal (BA 10), subgenual anterior cingulate (BA 25), medial prefrontal (BA 11), medial frontal (BA 32), thalamus, cuneus/precuneus, caudate and parahippocampal cortices as meaningful areas of possible difference. Only significant differences are shown.

BA, Brodmann area; DMN, default-mode network; FDR, false discovery rate; MNI, Montreal Neurological Institute spatial array coordinates.

positive feedback,²⁶ or with dextroamphetamine administration.⁴³ The significantly lower connectivity found here between the P/PCC and bilateral caudate in the resting state of depressed subjects compared with controls may reflect a discrepancy in reward-processing networks in these subjects even at rest and could be involved in the lack of motivation and anhedonia experienced by depressed subjects. We did not find correlations between these regions and depressive symptoms per se, however. Further investigations are warranted to determine the implications of the relationship between DMN and reward-processing neurocircuitry.

The absence of differences in the subgenual PFC between groups is in notable contrast to the other published work investigating the resting-state DMN in depression.⁹ That research showed a direct correlation between connectivity in the subgenual PFC and duration of illness. The subjects studied here were seeking their first contact with a psychiatrist and most had never been on psychiatric medications. The divergence in the present findings from those in subjects with longer duration of illness could represent differences in brain DMN connectivity that may be involved in different stages of depressive illness, or it may reflect differences between the independent components analysis and the seed ROI analysis used here. It may be important to investigate DMN

throughout the course of depressive illness to identify primary functional deficits versus compensatory deficits in this network.

There are several limitations of this study. First, we did not use physiological monitoring of respiratory or heart rate during the scans. Regions of the DMN have been found to vary with respiratory differences^{44,45} so our findings could reflect mean differences in respiratory rate, respiratory volume and/or CO₂ blood levels between the subject groups. Studies have shown no differences in respiratory function in depression itself^{46,47} but have demonstrated increased respiratory variability in panic disorder.⁴⁷ Although panic disorder was not present in any of the current patients, other anxiety disorders were and may also involve respiratory abnormalities at rest. For this and for other reasons, the presence of three subjects with anxiety disorder diagnoses may have confounded the results. Covarying for the severity of anxiety symptoms would be helpful in future studies,¹² as would monitoring of respiratory rhythm. Future studies are needed to replicate the results reported here.

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