

ORIGINAL ARTICLE

# Investigating neural primacy in Major Depressive Disorder: multivariate Granger causality analysis of resting-state fMRI time-series data

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Major Depressive Disorder (MDD) has been conceptualized as a neural network-level disease. Few studies of the neural bases of depression, however, have used analytical techniques that are capable of testing network-level hypotheses of neural dysfunction in this disorder. Moreover, of those that have, fewer still have attempted to determine the directionality of influence within functionally abnormal networks of structures. We used multivariate GC analysis, a technique that estimates the extent to which preceding neural activity in one or more seed regions predicts subsequent activity in target brain regions, to analyze blood-oxygen-level-dependent (BOLD) data collected during eyes-closed rest from depressed and never-depressed persons. We found that activation in the hippocampus predicted subsequent increases in ventral anterior cingulate cortex (vACC) activity in depression, and that activity in the medial prefrontal cortex and vACC were mutually reinforcing in MDD. Hippocampal and vACC activation in depressed participants predicted subsequent decreases in dorsal cortical activity. This study shows that, on a moment-by-moment basis, there is increased excitatory activity among limbic and paralimbic structures, as well as increased inhibition in the activity of dorsal cortical structures, by limbic structures in depression; these aberrant patterns of effective connectivity implicate disturbances in the mesostriatal dopamine system in depression. These findings advance the neural theory of depression by detailing specific patterns of limbic excitation in MDD, by making explicit the primary role of limbic inhibition of dorsal cortex in the cortico-limbic relation posited to underlie depression, and by presenting an integrated neurofunctional account of altered dopamine function in this disorder.

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## Introduction

Over the past 15 years, research examining the neural substrates of Major Depressive Disorder (MDD) has documented a number of depression-associated anomalies in brain structure and function. With respect to brain structure, for example, meta-analytic syntheses have found reliably decreased hippocampal volume associated with depression, with volumetric decrease of the hippocampus correlating positively with chronicity of MDD.<sup>1,2</sup> Similarly, in the absence of pharmacological intervention, amygdala volume is reliably decreased in depression, more so with a longer history of depressive illness.<sup>3</sup> Although found less consistently, investigators have also noted volumetric decreases in the anterior

cingulate<sup>4–6</sup> and orbitofrontal<sup>7,8</sup> cortices and striatum<sup>9,10</sup> in depressed individuals.

Sufficient data have now accumulated from functional neuroimaging studies of MDD to permit their synthesis and systematic comparison. In the largest meta-analysis to date of functional neuroimaging data from samples of depressed individuals, Seminowicz *et al.*<sup>11</sup> compared regional brain metabolic data acquired during the initial assessment portion of three positron emission tomographic studies of the neural bases of treatment effects in depression. Compared with never-depressed controls, depressed individuals were found to be characterized by abnormal activity in the dorsolateral (DLPFC),<sup>12,13</sup> medial (MPFC)<sup>14,15</sup> and orbital/ventrolateral<sup>13,16</sup> prefrontal cortex (PFC), insular<sup>17,18</sup> and parietal<sup>18</sup> cortices, rostral<sup>19,20</sup> and ventral<sup>6,21</sup> anterior cingulate cortex (ACC), as well as in the posterior cingulate cortex,<sup>15,18</sup> hippocampus,<sup>13,22</sup> thalamus,<sup>15,23</sup> and caudate.<sup>19,23</sup> Furthermore, while activity in the amygdala has not been identified as abnormal in depression through such systematic meta-analysis, a number of

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investigators have documented anomalous amygdala activity at baseline<sup>16,22</sup> and in response to affective stimuli<sup>24,25</sup> in depression.

Results from these investigations have been integrated into neural models of MDD.<sup>11,26,27</sup> Among the most influential of these models is a formulation by Mayberg *et al.*<sup>27</sup> that specifies a reciprocal relation between the cortical structures that mediate cognition (for example, DLPFC and inferior parietal cortex) and the cortical and subcortical structures that support emotional functions (for example, anterior insular cortex and hippocampus). According to this model, activity in limbic and paralimbic structures in depression dominates activity in the dorsal cortical structures. Subsequent refinements to the original model specify that regions undergirding emotion-cognition integration (for example, MPFC and orbital PFC) act as principal mediators of this reciprocal cortico-limbic relation in depression.<sup>11</sup>

Such neural models provide a useful theoretical framework for the clinical neuroscience of depression, and have been crucial both in motivating ongoing empirical work examining the neural substrates of this disorder and in developing novel and effective neural-level interventions for MDD.<sup>15</sup> It is important to recognize, however, that these models are not yet comprehensive in their scope and require important additional characterization. Perhaps most importantly, although depression is often characterized as a network-level neural disorder, we know little about the network-level properties of the brain in MDD beyond the constellation of structures that are consistently implicated in this disease. Specifically, our current formulations regarding which structures interact in an anomalous manner in MDD and the direction of influence among them require specification beyond that informed by studies of functional co- and counter-change among these structures in mood induction and treatment paradigms,<sup>27</sup> which have relatively coarse temporal sampling, and from anterograde and retrograde tracing studies that map anatomical connectivity in non-disease model, non-human primates.<sup>26</sup> This latter approach, while justified given the limited corpus of empirical work detailing structural and functional interrelations among neural ensembles in the human brain, nevertheless suffers from crucial limitations. First, this approach often makes a 'circuit diagram' assumption regarding cross-structure communication that implies that if Structure-A sends axonal projections to Structure-B, then Structure-A, when active, *will* communicate with Structure-B. This formulation ignores a large body of research indicating that active, anatomically connected structures do not communicate in an obligatory way by virtue of their anatomical connection, but, instead, communicate dynamically in accord with task parameters and constraints.<sup>28</sup> Second, this approach tends to ignore the potential for meaningful interactions between structures that are not connected mono-synaptically; indeed, recent evidence that bi-synaptically con-

nected structures communicate in significant ways in depression<sup>29</sup> indicates that such interactions should be considered in neural models of this disorder. Finally, using anatomical connectivity data from non-disease model, non-human primates to characterize functional interactions among brain structures implicated in depression assumes that while activity in certain structures may be abnormal in depression, interaction among these structures is not; this assumption has been disconfirmed through preliminary work showing abnormal functional connectivity among structures showing abnormal function in depression.<sup>30,31</sup> The issues presented here with current multivariate, neurodynamic models of MDD suggest that the clinical neuroscience of depression will benefit from complementary model-free, multivariate analytic approaches examining functional neural network dynamics in real time in samples of depressed and non-depressed individuals.

A small handful of functional neuroimaging studies offer information about cross-structural communication and influence in depression. Lozano *et al.*,<sup>32</sup> for example, implanted and activated stimulating electrodes in white matter adjacent to the ventral ACC (vACC; Brodmann Area 25) in individuals suffering from chronic, treatment-resistant depression. In addition to significantly reducing depressive symptomatology in the majority of participants in their study, this intervention also reduced vACC activity as well as activity in the insular cortex, and in the MPFC and orbital/ventrolateral PFC; activity in the DLPFC and the dorsal ACC increased with stimulation of the vACC. These results are consistent with the formulation that modulation of vACC activity, in ameliorating depressive pathology, affects a constellation of limbic, paralimbic and dorsal cortical structures that have been consistently implicated in MDD.

Taking a different approach to examine neural interaction and influence in depression, Seminowicz *et al.*<sup>11</sup> applied structural equation modeling to positron emission tomography data from a large sample of depressed persons, assessing the stability as connections were added and removed of a connectivity model derived from anatomical connectivity data from animals. The most stable connectivity model showed that cognitive-affective integration regions, the MPFC and orbital PFC and the rostral and ventral ACC, were principal mediators of relations among other structures that have been associated with depression.

This study was designed to specify more thoroughly aberrant functional interrelations in the brain in MDD by identifying and estimating anomalous cross-structure influence in depression. To do this, we used a multivariate implementation of Granger causality (GC) analysis,<sup>33</sup> a model-free technique that has been used for estimating prior and posterior prediction between bivariate<sup>34</sup> and among multivariate<sup>35</sup> structure-specific blood-oxygen-level-dependent (BOLD) time-series data.

## Methods

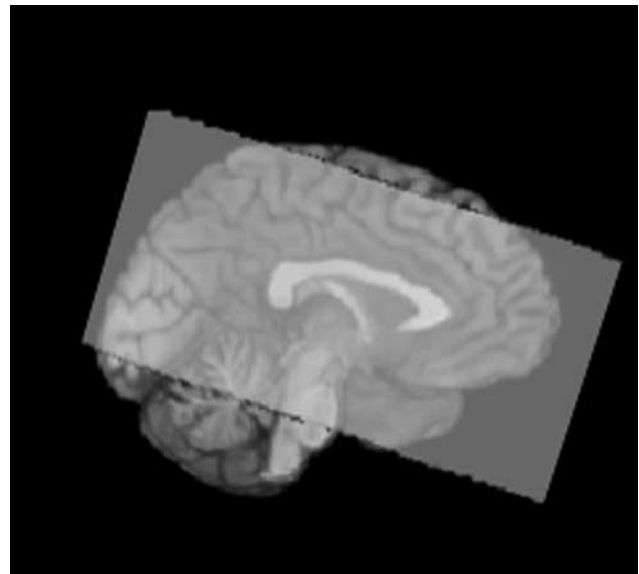
### Participants

Sixteen individuals diagnosed with MDD and 14 control subjects with no history of any DSM-IV diagnosed psychiatric disorder participated in this study. Participants were recruited from local psychiatric outpatient clinics as well as through website postings. All participants (1) were between the ages of 18 and 50; (2) had no reported history of brain injury, lifetime history of primary psychotic ideation or mania; (3) had no reported substance abuse within the past 6 months and (4) had no physical limitations that prohibited them from undergoing an MRI examination. None of the participants in either group was taking antidepressant medication at the time of the study.

All depressed participants met the criteria for a DSM-IV diagnosis of MDD on the basis of their responses to the Structured Clinical Interview for DSM (SCID; reference First *et al.*<sup>36</sup>); none of the control participants met the diagnostic criteria for any current or past Axis-I disorder. In addition, all participants completed the Beck Depression Inventory-II (BDI-II; reference Beck *et al.*<sup>37</sup>). Depressed individuals with a current comorbid diagnosis of panic or generalized anxiety disorder were excluded from the study. Informed consent was obtained from all participants, who were paid \$25 per hour for their participation in the study. All aspects of this study complied with the ethical standards for treatment of human participants from the American Psychiatric Association.

### Procedure

**fMRI data acquisition.** BOLD data were acquired with a 3.0 T General Electric Signa MR scanner. After scout scanning, two iterations of high-order shimming were performed over the whole brain to reduce signal loss arising from field inhomogeneities. For the 5-min resting-state scan, participants were instructed to lay still with their eyes closed and to avoid falling asleep. BOLD data were acquired with a single-channel, whole-head imaging coil using a spiral pulse sequence<sup>38</sup> (repetition time (TR) = 1200 ms frame<sup>-1</sup>, echo time (TE) 30 ms, flip angle = 77°, field of view (FOV) = 220 mm, number of frames = 250) that has been shown to have superior recovery of BOLD signal in the ventral prefrontal regions<sup>39</sup> of special interest to this investigation. A relatively rapid per-frame acquisition time of 1200 ms was used to increase the sensitivity of GC analysis to detect time-directed associations across the BOLD time series.<sup>34</sup> We collected 18 axial slices of BOLD data per acquisition using this short TR sequence; by using 5-mm axial slices, we were able to acquire data from the most inferior aspect of the temporal lobes to the top of the brain, excluding the most superior aspect of the somatomotor cortex (see Figure 1). Axial slices had 3.44 mm<sup>2</sup> in-plane and 5 mm through-plane resolution. A high-resolution structural scan (124



**Figure 1** Depiction of imaging volume used to collect BOLD data. BOLD, blood-oxygen-level-dependent.

axial slices, 0.859 mm<sup>2</sup> in-plane and 1.2 mm through-plane resolution, TE = min, flip angle = 15°, FOV = 220 mm) was performed after BOLD scanning. We minimized participant head movement by inserting pads between the participant's head and the functional MRI (fMRI) headcoil.

**fMRI data preprocessing.** fMRI data were pre-processed using the Analysis of Functional Neural Images (AFNI) software.<sup>40</sup> Time-series data were slice-time corrected relative to the ninth axial slice, and volume registered to correct for head translation and rotation during the scan (Fourier interpolation, two-pass). Data were spatially smoothed with a 4-mm Gaussian smoothing kernel. Functional images were then co-registered to high-resolution anatomical images and affine transformed into Talairach space.<sup>41</sup> Because GC analyses using relatively low lag orders, like those appropriate for this study, operate on high-frequency deflections in time-course data, the BOLD time series were not low-pass filtered. Low-frequency fluctuations were removed from the time-series data through regression (see section Analysis below).

### Analysis

**Description of approach.** The primary objective of the analysis was to conduct a multivariate GC analysis of a network of structures found to exhibit anomalous function in depression. Identification of this network assumed a model in which the vACC is a primary functional convergence zone of these structures, an assumption that has been confirmed in prior research.<sup>11,15</sup> This network was identified in three steps: (1) localizing a vACC region of interest (ROI) that was over-recruited in the default-mode (DMN), or task-negative, network<sup>42</sup> in depression, as

has been found in previous research;<sup>43</sup> (2) with the vACC ROI so defined, conducting both vACC-to-whole-brain and whole-brain-to-vACC *bivariate* GC analysis of data from each participant and (3) conducting voxel-wise comparisons of the resulting statistical maps from the MDD and control groups to identify both regions with abnormal advance prediction of vACC activity in depression, and regions in which activity was predicted in advance by vACC activity more strongly in depressed than in non-depressed persons. We describe each of these steps more thoroughly below.

**Identifying vACC ROI.** Greicius *et al.*<sup>43</sup> showed that the vACC is over-recruited in the DMN in MDD. We sought to replicate this finding to identify the vACC ROI for this study. First, we identified the DMN in each participant by conducting a seed region-to-whole brain time-series correlation analysis similar to that used by Fox *et al.*<sup>42</sup> We then compared the vACC involvement in this network in depressed and never-depressed persons. To identify the DMN in each participant, we regressed averaged BOLD time-series data from the medial prefrontal and posterior cingulate seed regions (12 mm diameter, centered at  $-1, 47, -4$  and  $-5, -49, 41$ , respectively;<sup>42</sup>) against preprocessed voxel time-series data from the rest of the brain. The nuisance covariates included in the regression model were three translational and three rotational head-motion estimates and four regressors modeling zeroth-through third-order polynomial trends in the BOLD time series. To remove signal artifacts in voxel time series induced by cardiac pulsatility and respiratory fluctuations, we also included as a nuisance covariate average time-series data from a gray-matter mask drawn on the Montreal Neurological Institute N27 brain. The correlation maps resulting from this regression procedure were then Fisher *Z*-transformed to ensure their statistics met the assumption of normality for conducting subsequent *t*-tests. Finally, transformed correlation maps from the MDD and control groups were compared using voxel-wise *t*-tests over the full extent of the vACC. The vACC was defined as the portion of the Talairach-defined<sup>41</sup> cingulate gyrus inferior to the most anterior aspect of the genu of the corpus callosum. The statistical threshold was set at  $P=0.05$ , corrected for multiple comparisons across vACC voxels; appropriate per-voxel significance and cluster thresholds were calculated using AFNI's AlphaSim.

**Bivariate GC analysis.** Consider the bivariate linear autoregressive model of two time-variant processes  $x$  and  $y$ :

$$x(t) = \alpha_{x,0} + \sum_{i=1}^p \alpha_{xx,i} X(t-i) + \sum_{i=1}^p \alpha_{xy,i} Y(t-i) + \sum_{j=1}^q \beta_{x,j} Z_j(t) + \varepsilon_x(t)$$

$$y(t) = \alpha_{y,0} + \sum_{i=1}^p \alpha_{yx,i} Y(t-i) + \sum_{i=1}^p \alpha_{yy,i} Y(t-i) + \sum_{j=1}^q \beta_{y,j} Z_j(t) + \varepsilon_y(t)$$

According to a definition from Granger,<sup>33</sup> one time-variant process,  $x$ , 'Granger causes' another

time-variant process,  $y$ , across up to  $p$  temporal lags if preceding information from  $x$  predicts behavior in  $y$ , uniquely, relative to what preceding information about  $y$  can predict about behavior in  $y$  itself. In this model,  $z_j(t)$  represents up to  $q$  exogenous processes (covariates, for example, head motion parameters and physiological noise) independent of the path network ( $j=1, \dots, q$ ). Contributions of each lagged variable to the prediction of its respective target are denoted by  $\alpha$ ;  $\beta$  corresponds to the covariate effect and prediction errors of individual models are denoted by  $\varepsilon$ . If  $\alpha_{yx}$  is significantly different from zero, then it is said that  $x$  Granger causes  $y$ . One of the authors (G Chen) has implemented this definition in a linear autoregressive procedure<sup>44</sup> for estimating a unique, time-directed prediction between the fMRI time series of a seed region and the rest of the brain. We used this procedure to identify both regions whose time courses predict subsequent vACC activity and regions whose activity is predicted by preceding vACC activity abnormally in depression. Nuisance covariates in the regression model were the same as those used to identify the vACC ROI: six orthogonal motion estimates, polynomial functions modeling the BOLD drifting effect and gray-matter signal. The seed region time series in the model was preprocessed BOLD data extracted from a sphere centered on the peak of the vACC ROI (5 mm diameter, centered at  $-2, 6, -7$ ) identified above. We estimated the time-directed prediction between the BOLD time series across a lag of one TR (1200 ms) to maximize the temporal resolution of our estimates of neural influence. Finally, voxel-wise comparisons of the resulting GC fit coefficients across diagnostic groups were performed using *t*-tests ( $P=0.05$ , corrected) across the whole imaging volume.

**Multivariate GC analysis.** The bivariate GC definition presented above can be extended to multivariate conditions per the following generic multivariate autoregressive model:

$$y_1(t) = \alpha_{10} + \sum_{i=1}^p \alpha_{11i} y_1(t-i) + \dots + \sum_{i=1}^p \alpha_{1ni} y_n(t-i) + \sum_{j=1}^q \beta_{1j} z_j(t) + \varepsilon_1(t)$$

$$\vdots$$

$$y_n(t) = \alpha_{n0} + \sum_{i=1}^p \alpha_{n1i} y_1(t-i) + \dots + \sum_{i=1}^p \alpha_{nni} y_n(t-i) + \sum_{j=1}^q \beta_{nj} z_j(t) + \varepsilon_n(t)$$

We implemented this definition in a multivariate autoregressive procedure for determining a unique, time-directed prediction across multiple time-variant processes. We subjected to this procedure voxel time courses from regions showing either an abnormal leading or lagging temporal relation with vACC activity in depression (We conducted quality assurance tests on these time-courses to ensure that they were stationary and that the residuals were non-skewed and non-heteroscedastic; see Supplementary Table 1.). For each participant, preprocessed time-series data were extracted from peak voxel locations in the regions that showed differential temporal



**Table 1** Participant demographic and clinical characteristics

	Control	Depressed
Age, mean (s.e.)	30.43 (2.35)	34.63 (1.60)
Education, mean (s.e.)*	17.14 (0.8)	15.44 (0.60)
% Female	43%	62%
BDI-II, mean (s.e.)*	3.79 (1.21)	37.94 (2.19)

Abbreviations: BDI-II, Beck Depression Inventory-II; s.e., standard error of the mean.

\* $P < 0.05$ .

relation with the vACC between the depressed and the control participants. These time-series data for each participant were then entered into multivariate GC analysis. The resulting GC path coefficients characterizing the strength and direction of the temporal relation among the structures, and the corresponding  $t$ -statistics, that were entered into the model were then compared between the depressed and the control groups ( $P = 0.05$ , uncorrected) using a linear mixed-effects multilevel model.

## Results

### Demographic and clinical variables

The demographic and clinical characteristics of the two groups of participants are presented in Table 1. The depressed and the control groups did not differ significantly in age ( $t(28) = 1.50$ ) or gender composition ( $\chi^2(28) = 0.50$ ;  $P < 0.05$ ). The groups did differ significantly in the years of education: the control participants had 1.5 years more education, on average, than the depressed participants ( $t(28) = 2.16$ ;  $P < 0.05$ ). As expected, the depressed participants had higher BDI-II scores than the participants in the control group ( $t(28) = 13.12$ ;  $P < 0.05$ ) (see Table 1).

### DMN comparison

The between-group, within-vACC comparison of DMN statistical maps showed a region of significantly increased contribution (peak:  $-2, 6, -7$ ; Brodmann Area 25) to the DMN in MDD (see Figure 2). Incidentally, the independent sample  $t$ -statistic value at this vACC location was the largest considering voxels outside the vACC as well.

### Bivariate GC analysis

The bivariate whole-brain-to-vACC GC analysis showed that activity in the MPFC and hippocampus predicted subsequent increases in vACC activity to a significantly greater extent in the depressed than in the control participants. This analysis also showed that increasing activity in the DLPFC predicted subsequent decreasing vACC activity in depression (see Figure 3). Finally, vACC-to-whole-brain GC analysis showed that vACC activity predicted sub-



**Figure 2** A vACC ROI derived from the comparison of the DMNs of depressed with that of the control groups. DMN, default-mode network; ROI, region of interest; vACC, ventral anterior cingulate cortex.

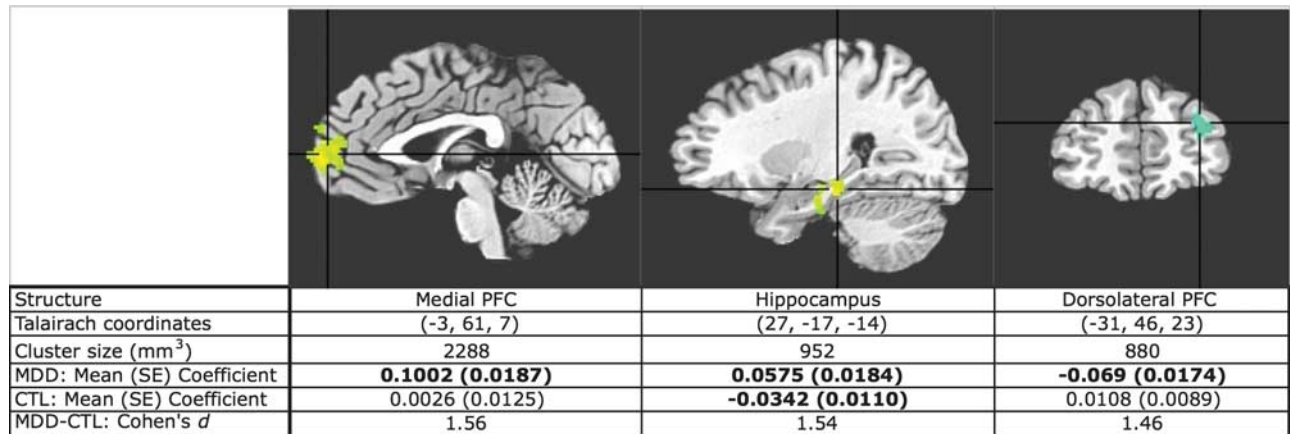
sequent decreases in activation in the posterior cingulate/cuneus (PCC), dorsomedial prefrontal cortex (DMPFC) and the ventral striatum, bilaterally, in depression (see Figure 4).

### Multivariate GC analysis

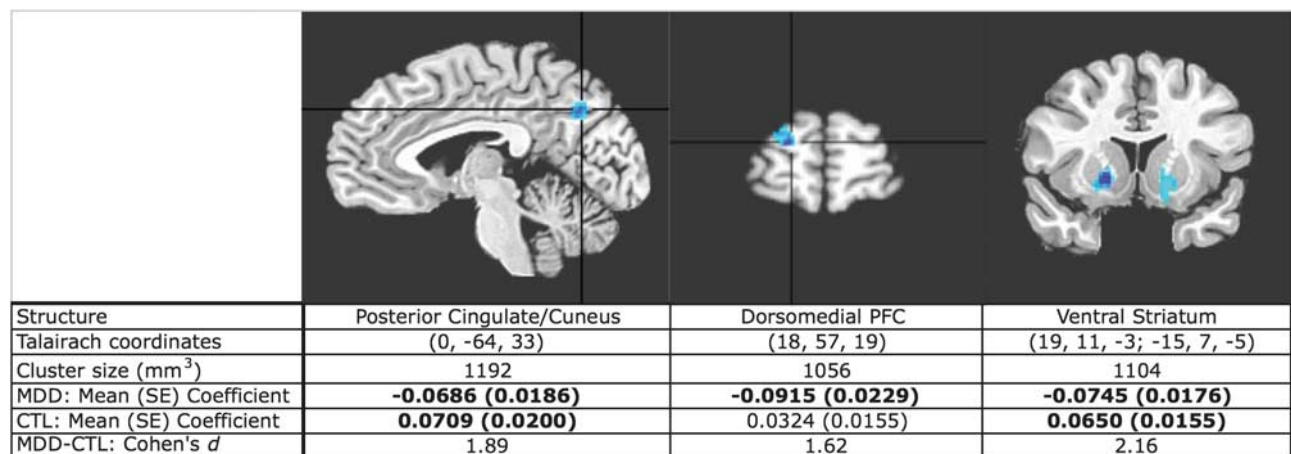
Multivariate GC analysis incorporating regions identified in the bivariate GC analyses showed unique results not noted in the bivariate analysis. We observed reciprocal augmentation of activity between the vACC and the MPFC to a significantly greater extent in the depressed than in the control participants. Further, we found evidence of dampening of the DLPFC by hippocampal activity in depression. We also noted significant dampening of the ventral striatum by DMPFC activity in MDD more than that in the control participants. Several of the functional relations identified in the bivariate analyses were maintained in the multivariate analysis: in the depressed participants, increasing hippocampal activity predicted subsequent increases in activation in the vACC, and DLPFC activity predicted decreasing activity in the vACC. Finally, activity in the vACC predicted subsequent deactivation of the DMPFC, PCC and ventral striatum in depressed more than that in the control participants (see Figure 5).

## Discussion

In this study, we used bivariate GC analysis to identify a set of structures for subsequent multivariate GC analysis in which activity precedes or follows activation in the vACC differently in depressed than in non-depressed individuals. These structures, implicated in depression in a number of functional neuroimaging studies, include the hippocampus,<sup>13,19</sup> DLPFC,<sup>13,19</sup> MPFC,<sup>45,46</sup> PCC<sup>18,47</sup> and the ventral striatum.<sup>48,49</sup> Using multivariate GC analysis, we found



**Figure 3** A *T*-statistic map of MDD-versus-control comparison of vACC-to-whole brain GC analysis fit coefficients. Increased activity in the hippocampus and in the MPFC predicts subsequent increases in vACC activity more in MDD than in the control participants. Activity increases in the DLPFC predict activity decreases in the vACC more in MDD. The group mean coefficients are averaged from a supra-threshold cluster. Group means in bold are significantly different from zero (two-tailed test; all *P*-values < 0.01, uncorrected). DLPFC, dorsolateral prefrontal cortex; GC, Granger causality; MDD, Major Depressive Disorder; MPFC, medial prefrontal cortex; vACC, ventral anterior cingulate cortex.

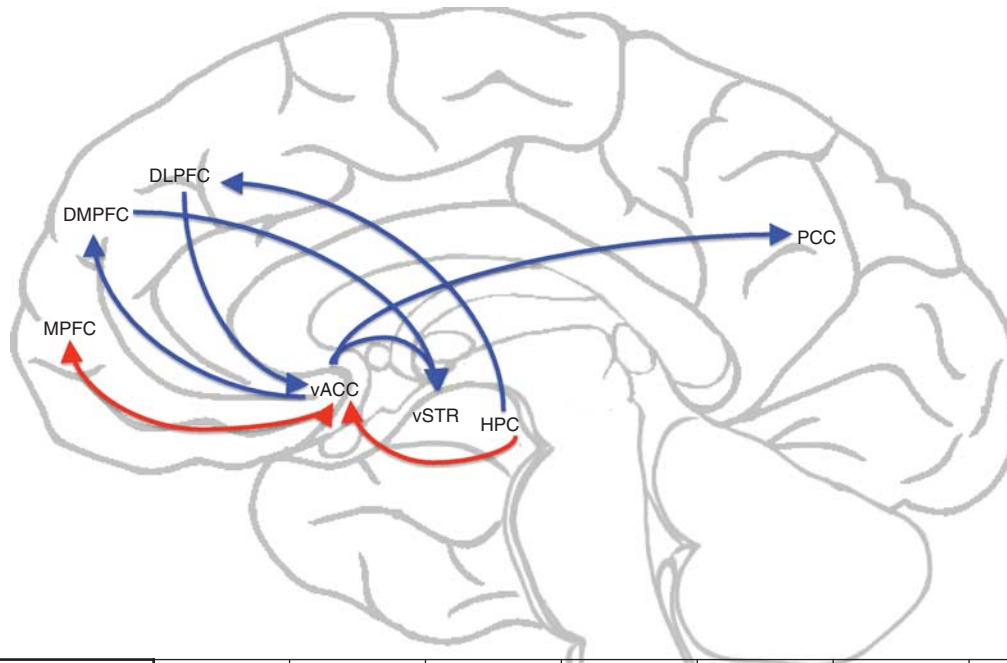


**Figure 4** A *T*-statistic map of MDD-versus-control comparison of whole brain-to-vACC GC analysis fit coefficients. Increased activity in the vACC predicts subsequent decreases in activity in the PCC, DMPFC and ventral striatum, bilaterally more in MDD than in the control participants. The group mean coefficients are averaged from a supra-threshold cluster, ventral striatum clusters averaged together. Group means in bold are significantly different from zero (two-tailed test; all *P*-values < 0.01, uncorrected). DMPFC, dorsomedial prefrontal cortex; GC, Granger causality; MDD, Major Depressive Disorder; MPFC, medial prefrontal cortex; PCC, posterior cingulate/cuneus; vACC, ventral anterior cingulate cortex.

evidence of a mutually excitatory relation between the vACC and the MPFC, and of an inhibitory relation between the hippocampus and the DLPFC in MDD. Replicating results from the bivariate analysis, we also found in the multivariate analysis subsequent dampening of activity in the PCC, DMPFC and ventral striatum by the vACC, and bolstering of activity in the vACC by the hippocampus in depressed, but not in control, participants.

The multivariate GC findings reported here represent a significant advance for current neurodynamic models of major depression. Cortico-limbic inhibition models of depression are equivocal concerning the mechanisms by which limbic and paralimbic activity

come to dominate over cortical activity in MDD; this dominance could result from attenuation of cortical-to-limbic inhibition, from strengthening of limbic-to-cortical inhibition in depression, or from these two processes working in synchrony. In showing that vACC activity predicts subsequent decreases in activity in the dorsal cortical regions (PCC and DMPFC) in depression, and that hippocampal activity predicts subsequent reduction of DLPFC activity, our data support the formulation that limbic-to-cortical inhibition is strengthened in MDD. The pattern of results that would support the formulation of decreased cortical-to-limbic inhibition in depression, that is, subsequently decreased limbic activity after



MDD - CTL	vACC	vSTR	HPC	MPFC	DLPFC	DMPFC	PCC
vACC	-0.0551	<b>-0.1552</b>	0.0308	<b>0.0913</b>	-0.0302	<b>-0.1152</b>	<b>-0.1392</b>
vSTR	-0.0465	0.0589	0.0429	-0.0530	<b>0.0864</b>	-0.0198	0.0345
HPC	<b>0.1006</b>	0.0148	-0.0553	0.0329	<b>-0.0532</b>	0.0145	0.0240
MPFC	<b>0.0970</b>	0.0260	0.0291	-0.0371	0.0176	0.0157	-0.0176
DLPFC	<b>-0.0695</b>	0.0106	-0.0465	-0.0496	-0.0877	-0.0288	-0.0138
DMPFC	0.0033	<b>-0.0584</b>	-0.0152	0.0094	-0.0081	-0.0670	-0.0223
PCC	0.0387	-0.0272	-0.0419	0.0566	0.0273	0.0054	-0.0739

MDD	vACC	vSTR	HPC	MPFC	DLPFC	DMPFC	PCC
vACC	-0.0214	<b>-0.0747</b>	0.0094	<b>0.0570</b>	-0.0188	<b>-0.0868</b>	<b>-0.0788</b>
vSTR	-0.0471	<b>0.2169</b>	<b>-0.0745</b>	<b>-0.0919</b>	0.0328	-0.0174	<b>-0.0582</b>
HPC	<b>0.0822</b>	-0.0345	<b>0.1863</b>	0.0125	<b>-0.0551</b>	0.0237	-0.0072
MPFC	<b>0.0938</b>	0.0103	0.0447	<b>0.3428</b>	-0.0051	0.0069	<b>-0.0415</b>
DLPFC	<b>-0.0560</b>	0.0095	<b>-0.0812</b>	-0.0698	<b>0.4792</b>	0.0068	<b>-0.0668</b>
DMPFC	-0.0028	<b>-0.0995</b>	-0.0334	0.0203	-0.0383	<b>0.3570</b>	-0.0323
PCC	0.0399	<b>-0.0588</b>	<b>-0.0574</b>	0.0491	-0.0378	-0.0098	<b>0.4962</b>

CTL	vACC	vSTR	HPC	MPFC	DLPFC	DMPFC	PCC
vACC	0.0336	<b>0.0804</b>	-0.0214	-0.0343	0.0119	0.0284	<b>0.0604</b>
vSTR	-0.0005	<b>0.1580</b>	<b>-0.1174</b>	-0.0388	-0.0536	0.0024	<b>-0.0927</b>
HPC	-0.0184	-0.0493	<b>0.2416</b>	-0.0204	-0.0018	0.0092	-0.0313
MPFC	-0.0032	-0.0157	0.0156	<b>0.3800</b>	-0.0227	-0.0088	-0.0239
DLPFC	0.0135	-0.0011	-0.0346	-0.0201	<b>0.5669</b>	0.0357	-0.0530
DMPFC	-0.0061	-0.0410	-0.0182	0.0109	-0.0302	<b>0.4239</b>	-0.0100
PCC	0.0011	-0.0316	-0.0155	-0.0076	<b>-0.0651</b>	-0.0152	<b>0.5700</b>

**Figure 5** A statistical map of a between-group comparison of path coefficients from multivariate GC analysis including vACC, ventral striatum (vSTR), hippocampus (HPC), MPFC, DLPFC, DMPFC and PCC. The blue/red arrows indicate significantly greater inhibition/activation of subsequent target activity in MDD versus control where a within-group effect was also present in the MDD group (two-tailed tests; all  $P$ -values  $< 0.05$ , uncorrected). The table values are group mean path coefficients with prediction going from row to column. The group means in bold are significantly different from zero. DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; GC, Granger causality; MDD, Major Depressive Disorder; MPFC, medial prefrontal cortex; PCC, posterior cingulate/cuneus; vACC, ventral anterior cingulate cortex.

dorsal cortical activation in control more than depressed persons, was not obtained. Furthermore, in documenting excitation of the vACC by the hippocampus and mutual excitation between the vACC and the MPFC in depression, the current findings suggest that dampening of dorsal cortical activity by limbic activity is a consequence of spreading excitation in depression among structures comprising limbic-paralimbic networks.

The current results that hippocampal activation precedes both increased vACC activity and decreased DLPFC activity in depression, considered together with our finding that the hippocampus itself is not differentially affected in depression by preceding activity in other structures identified in our analysis, are consistent with the formulation that the hippocampus has a principal role in affecting depressotypic neural responses. The finding that hippocampal activity predicts subsequently increased vACC activity in depression fills a gap in the body of data supporting the formulation that an overactive hippocampus-to-vACC connection has an important role in depressive pathology.<sup>50,51</sup> Research examining white-matter tractography in humans has documented direct connectivity between the hippocampus and the vACC<sup>51</sup> that is augmented in bipolar disorder.<sup>52</sup> Moreover, hippocampal subfield stimulation studies using rodents<sup>53</sup> indicate that this hippocampus-to-vACC connection is excitatory. Furthermore, using a rodent model of depression, Airan *et al.*<sup>50</sup> documented increased neural transmission from the CA1 hippocampal subfield in depression, which is decreased with administration of imipramine. Considered collectively, these results predict and underscore the significance of the finding in this study of increased effective connectivity of hippocampus-to-vACC in MDD.

The current data also show that hippocampal activity predicts subsequently decreased activation in the DLPFC in depression. That hippocampal dysfunction can have an adverse effect on DLPFC functioning is supported by animal model studies showing that lesions to the hippocampus promote subsequent DLPFC dysfunction<sup>54</sup> and affective disturbance.<sup>55</sup> An association between aberrant hippocampus–DLPFC coupling and emotional disturbance has also been documented in humans by Meyer-Lindenberg *et al.*<sup>56</sup> who reported that unmedicated schizophrenic individuals showed abnormally persistent functional connectivity between the hippocampus and the DLPFC during a working memory task. A mechanism by which this aberrant coupling may underlie affective illness is underscored by research showing that the hippocampus has a necessary mediating role in the DLPFC regulation of the striatal dopamine system.<sup>57,58</sup> Thus, hippocampus-to-DLPFC inhibition, as found in depressed persons in this study, may interfere with the DLPFC regulation of the striatal dopamine system and have a role in the anhedonic responding that characterizes major depression.

This study documents the novel neurodynamic finding of aberrant mutual excitation between the MPFC and the vACC in MDD. This co-facilitation of activity in depression between the MPFC, which is involved in representation and evaluation of the self,<sup>59</sup> and the vACC, which is postulated to subserve viscerio-affective states,<sup>60</sup> may represent a neurofunctional account of maladaptive, self-directed rumination associated with MDD. Indeed, examining the correlation between the depressive rumination subscale of the Response Style Questionnaire and the path coefficients of MPFC-to-vACC connectivity in this study supports this hypothesis: stronger the excitation of the vACC by the MPFC, the more depressive rumination reported by the depressed participants ( $r(14) = 0.55$ ;  $P < 0.05$ , two-tailed, controlling for the positive correlation between the BDI-II and Response Style Questionnaire scores).

Importantly, a growing body of work is documenting other significant associations between the vACC and the MPFC in major depression. For example, reducing activity in the vACC through electrode stimulation of adjacent white-matter tracts in depression also decreases MPFC activity.<sup>15</sup> In addition, depressed persons who respond therapeutically to sleep deprivation show greater metabolism in the vACC and the MPFC than do non-responders.<sup>61</sup> Finally, research showing that dopamine function is enhanced by sleep deprivation<sup>62</sup> suggests that elevated metabolism in the MPFC and the vACC is a consequence of disturbed dopamine function that has been hypothesized to underlie depression.<sup>63</sup> This postulation is corroborated by recent work showing that MPFC and vACC activity increases in response to catecholamine depletion in depressed but not in healthy individuals.<sup>46</sup> A unifying account of these findings that should be examined explicitly in future research is that decreased inhibitory dopaminergic input from the ventral tegmental area to the thalamus in depression disinhibits excitatory input from the thalamus to the MPFC and the vACC.<sup>61</sup>

While the results presented here are clearly relevant to formulations of neural influence in models of the pathophysiology of depression, we should note three important limitations to the methods described in this paper. First, the relatively sluggish hemodynamic response measured by fMRI in estimating brain activity does not allow us to differentiate temporally neural responses that occur less than 100 ms apart. It will be important in future research to use functional neuroimaging techniques such as magnetoencephalography that measure brain activity more directly to examine aberrant neural influence in MDD. Second, we worked from a model in which abnormal neural communication in depression is mediated through the vACC; consequently, only structures that showed abnormal activation leading or lagging that of the vACC were included in the multivariate GC model. While we functionally localized several structures that have been implicated reliably in depression, other structures, including the amygdala, orbitofrontal



cortex and insula, were not localized with the current methods. Given the consistency with which these structures have been found to be characterized by anomalous patterns of activation in depression,<sup>11</sup> it is possible either that the first-order lag examined in this study was not optimal for identifying aberrant communication between these structures and the vACC in depression, or that they are not part of an aberrantly functioning network mediated by the vACC in MDD. Finally, it is important to bear in mind that the current findings were obtained during resting-state fMRI scanning. Thus, we can infer only that the aberrant neural functioning in depression reported here is associated with depressive pathology in general, and not with a particular type of depressotypic thought or activity. Recent work has begun to identify bivariate neural causal relations during active processing of affective stimuli in depression.<sup>64</sup>

This study is the first to examine time-directed dynamic relations at the multivariate, neural-systems level in MDD. Our findings advance the neural theory of depression in specifying the short-term functional interrelations among structures implicated in this disorder. In continuing to develop a comprehensive neural theory of MDD, future work should extend this approach to include broader temporal gradients of significance to the pathophysiology of MDD, potentially incorporating multiple neurofunctional assessments as depressed persons transition from the state of acute illness to remission.

## Conflict of interest

The authors declare no conflict of interest.

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