Partial Amelioration of Medial Visceromotor Network Dysfunction in Major Depression by Sertraline

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Abbreviations: ACC: anterior cingulate cortex; Amy: amygdala; BOLD: blood oxygen level dependent; CBT: cognitive behavioral therapy; dACC: dorsal anterior cingulate cortex; ECG: electrocardiogram; fMRI: functional magnetic resonance imaging; HAM-D: Hamilton Depression Inventory; HRV: heart rate variability; MADRS: Montgomery Asperg Depression Rating Scale; MDD: Major Depressive Disorder; mPFC: medial prefrontal cortex; MVN: medial visceromotor network; PAG: periaqueductal gray area; rACC: rostral anterior cingulate cortex; RSA: respiratory sinus arrhythmia; sem: standard error of the mean; sgACC: subgenual anterior cingulate cortex; SSRI: selective serotonin reuptake inhibitor

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Medial Visceromotor Network Dysfunction in Major Depression Is Partially Ameliorated by Sertraline

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Abstract

Objective: Major depression is associated with reduced cardiac vagal control, most commonly indexed by heart-rate variability. To examine the dynamics of this abnormality, we examined within-subject covariation over time between brain activity, cardiac vagal control, and depressive symptoms in depressed patients treated with sertraline and in healthy volunteers.

Methods: Patients with depression and non-depressed control participants were enrolled in a 12-week protocol. After week 0 assessment, patients began treatment with sertraline. Neural activity and vagal control were measured for all subjects at weeks 0, 2, 6 and 12 using functional magnetic resonance imaging (fMRI) and synchronized electrocardiographic (ECG) recordings. At each of the four assessments, a moving-window analysis was used to estimate vagal control as assessed by Respiratory Sinus Arrhythmia (RSA) from the ECG data, which was then regressed onto fMRI activity.

Results: At baseline, patients showed reduced BOLD-RSA covariation compared to controls within multiple a priori brain regions associated with vagal control, collectively described as the medial visceromotor network (MVN). Sertraline treatment led to significant increase in brain-RSA covariation for patients compared to controls, despite a lack of improvement in mean RSA.
**Conclusion:** These data suggest a partial normalization of MVN dysfunction in depression during sertraline treatment. Specifically, results indicate a partial recovery of MVN function. However, this recovery was insufficient to cause a significant change to RSA levels. These results may help to explain both improvements with and limitations of sertraline treatment for depression.
Introduction

Major Depressive Disorder (MDD) is commonly associated with abnormalities in subgenual anterior cingulate cortex (sgACC), rostral ACC (rACC), dorsal ACC (dACC), and subcortical regions including the hypothalamus, periaqueductal gray area (PAG) and other brainstem nuclei (1, 2). These regions participate in a larger network implementing vagal control, termed the medial visceromotor network (MVN), and are central to the regulation of autonomic and neuroendocrine responses (1, 3, 4). While MVN regions play an important role in governing mood (5, 6) and are crucial for effective emotion regulation (7, 8), the contribution of activity within the MVN to autonomic regulation in the context of depression and its treatment is not well understood (9-13).

The sgACC and rACC are two critical hubs in the MVN, and a variety of functional imaging studies implicate ACC dysfunction as a core feature of the neural basis of depression (7, 14-16). Patients with MDD tend to manifest hyperactivity in sgACC (17), and successful treatment of depression with deep brain stimulation of sgACC is associated with corresponding down-regulation of sgACC (18). The sgACC is a principal site of converging autonomic signals in neocortex and paralimbic cortex and plays a central role in autonomic regulation (19, 20). While important for autonomic regulation, rACC and dACC have stronger connections to each other and medial prefrontal cortex (mPFC) compared to sgACC suggesting that they may have a greater role in cognitive control and emotional regulation (16). Activation of dACC is associated with
regulation of negative affect and conflict resolution (21, 22), both of which are impaired in MDD (14, 21). Higher resting activity in rACC prior to treatment is predictive of successful antidepressant treatment outcomes across multiple studies (16), and failure to deactivate rACC while evaluating emotional pictures is associated with greater depressive symptoms (7).

To assess vagal control in the periphery we focused on relationships between brain activity and dynamic parasympathetic control over heart rate. Functional reductions in parasympathetic control of heart rate have been observed in depression (23-27) and anxiety (20, 28), as indexed by high frequency heart-rate variability (29) which reflects respiratory-linked changes in heart rate known as Respiratory Sinus Arrhythmia (RSA). Although normalization of RSA has been associated with successful treatment of depression (30-32), SSRI treatment is not generally associated with significant improvement in RSA (32). RSA can be assessed continuously in the fMRI environment and is a particularly useful measure for exploring the covariation of brain activity, depressive symptomatology and autonomic function over the course of antidepressant treatment.

In healthy volunteers RSA correlates positively with coincident activity of multiple structures within the MVN, including rACC, sgACC, dACC, insula, striatum, PAG and hypothalamus (33-38). Dysfunction within the MVN has been observed in the few functional neuroimaging studies that have examined RSA in relation to depression (17, 39, 40), but a neuroimaging study that
examines the association between brain activity and RSA in the context of antidepressant treatment has not been undertaken.

We conducted a preliminary study to examine the change in covariation between the time-course of the fMRI BOLD signal and RSA at each of four different visits during a 12-week treatment course. Depressed patients and non-depressed control participants were scanned at baseline and at 2, 6, and 12 weeks following baseline (week 0) assessment. We predicted that in healthy controls, the covariation between RSA and MVN regions would be positive at each assessment and remain stable across assessments. Given reduced RSA in depression, we predicted that covariation between RSA and vagal control regions would initially be reduced for patients compared to controls and that BOLD-RSA covariation would increase with successful treatment. Given the importance of the ACC regions in autonomic regulation and their known dysfunction in depression, we were particularly interested in how BOLD-RSA covariation in the sgACC, dACC and rACC evolved with treatment.

Methods and Materials

Subjects

Seventeen patients with MDD were recruited to participate in a 12-week study on the relationship between depression treatment and physiological health. Seven patients withdrew from the study prior to completing the final session, and 10 patients completed all portions of the
study. Twenty subjects (10 MDD: age = 36.8 ± 9.3, 9 female; 10 Control: age = 35.6 ± 12.3, 9 female; values represented as mean ± standard deviation here and elsewhere unless otherwise specified) participated in four separate fMRI sessions each, across 12 weeks. Of the 10 patients who completed the study, three were excluded due to artifacts in the ECG recording at baseline. Thus, the final sample contained 17 subjects (7 MDD: age = 35.6 ± 8.0, 7 female; 10 Control: age = 35.6 ± 12.3, 9 female). MDD patients were recruited from the Depression Clinic in the Department of Psychiatry as well as via newspaper and radio advertising. All patients met criteria for MDD; diagnosis was established at intake based on scores from the MINI International Neuropsychiatric Interview and the Hamilton Depression Inventory (HAM-D). All patients scored at least 16 on the HAM-D, and no controls scored more than 1. A trained clinician blind to group made weekly clinical ratings of depressive symptoms using the Montgomery Asperg Depression Rating Scale (MADRS) as well as additional Beck Depression Inventory measurements at each fMRI session (weeks 0, 2, 6, and 12). MDD patients were not taking antidepressant medication prior to study participation, nor were they currently engaged in a psychotherapy program. MDD patients with comorbidities other than anxiety (e.g. psychosis, substance abuse) were excluded. Three of the seven MDD patients included in the study also had an anxiety disorder. Control subjects were recruited via on-campus advertising at the University of Arizona. The Human Subjects Protection Program at the University of Arizona approved all procedures and protocols and all subjects provided informed consent.
Procedure

All subjects returned once per week during the full 12-week course of the study for an evaluation of depressive symptoms. Each week MDD patients also met with a study psychiatrist who, based on a pre-specified protocol, modified the daily dose of sertraline between the initial dose of 50mg up to a maximum of 200mg based on MADRS scores.

All subjects participated in the fMRI portion of the experiment on four occasions: weeks 0, 2, 6, and 12. Weeks 0 and 12 were selected to examine the effects of sertraline on BOLD-RSA interactions pre- and post-treatment. Scanning at week 2 was motivated by evidence that typically SSRIs induce neurochemical changes at this point though symptom improvement is generally absent or minimal (41). Scanning occurred at week 6 because at that point many patients who will be treatment-responsive show substantial symptom relief.

Data Acquisition

RSA: Continuous ECG was obtained in synchrony with fMRI using the In Vivo 3150M Magnitude MRI Patient Monitor, a multi-lead ECG with digital signal processing filtering for removal of MRI gradient artifact. The timing of each beat (R-spike) was first identified using QRSTool (42) then hand-edited to correct for missed, extra, or ectopic beats. The resultant interbeat interval (IBI) series was used for calculating RSA in a series of overlapping windows of 16 seconds each, offset by 3 seconds to correspond to the fMRI TR. For each window, RSA was calculated as the natural log of the variance of the bandpass
filtered (.12-.40 Hz) IBI time series (interpolated at 10 Hz). If an artifact prevented the reliable determination of a single beat, that beat was interpolated. If the artifact obscured two or more consecutive beats, the time period was truncated to the last usable beat. The result was an RSA time series, with one RSA value for each TR, reflecting the respiratory-linked variance in IBIs for the time period beginning 8 seconds prior to the TR and extending 8 seconds following the start of the TR (Figure 1). Each RSA series was high-pass filtered at 1/190 Hz to match the filtering of the fMRI data.

**Moving Window Analysis**

Figure 1. *RSA Moving Window Analysis.* The green, orange and red rectangles represent the first three time segments over which the RSA value was derived. In this example, these three values were then compared with fMRI BOLD signal recorded at 9, 12, and 15 seconds from the onset of scanning, respectively.

*fMRI:* fMRI data were acquired in the coronal plane from a 3.0 Tesla GE Signa VH/I system with an 8-channel head coil at the University of Arizona.
Scan parameters for the gradient echo spiral in-out pulse sequence were as follows: TR=3000 ms, TE=30 ms, flip angle=90°, FOV=22 cm, 64×64 matrix, 3-mm-thick slices. A structural MPRAGE scan was obtained at each session. Six functional scans were acquired during three different affective tasks that consisted of implicit processing of emotional cues (faces) (43), processing of emotion cues (words) in the attentional background (44-46), and processing of emotional cues (pictures) in the attentional foreground (47) (2 scans each: 99-106 images per scan, 620 images per week). The three tasks were designed to elicit implicit, background, and explicit emotional response, respectively. Task-related activity is being analyzed separately; the purpose of this paper was to investigate brain-RSA correlation across all tasks. All fMRI images were preprocessed using SPM8 and warped onto a standard neurological template (MNI). In the final preprocessing step, de-noised functional images were generated by removing variance in the data explained by motion parameter estimates and their squared values, gradient (derivative) values, and squared gradients, as well as any outlier volumes identified via Mahalanobis distance (48). Scanning data were collected over a three year time period, beginning with the first scan in March of 2007 and ending with the final scan in February of 2010.

**Analysis**

**RSA:** Overall differences in mean RSA values were compared across groups, and differences in the change of mean RSA over the entire study were
compared across groups using a between-groups t-test on the within-subject linear change of mean RSA over time.

**fMRI:** Each de-noised image series was correlated voxel-by-voxel with the corresponding RSA series. The first two analyses focused on 10 predetermined regions of interest (ROIs). Seven ROIs were drawn around reported functional clusters from a meta-analysis of RSA and affective states (38) and reported functional clusters correlated with RSA during non-affective working memory tasks (35). An additional three anatomical ROIs were generated for MVN regions not identified in the previous studies (dACC, PAG, hypothalamus) by searching anatomical keywords in NeuroSynth, a freely available meta-analysis tool (49) (Table 1).

**Mean ROI Analysis:** The covariation between RSA and BOLD was averaged across voxels within each ROI within each week, so that a single value represented the BOLD-RSA covariation for each subject in each ROI for each week. This method has the two-fold benefit of 1) permitting planned analyses without requiring multiple comparisons correction if all areas are specified *a priori* and reported, as they are here; and 2) reducing residual and random error in estimates of BOLD-RSA covariation within each ROI by averaging across many voxels, which improves our ability to detect between-group variation and overall changes over time. When estimating change in BOLD-RSA across weeks, we estimated the linear change within each subject and tested whether this change was different between patients and controls. These changes were analyzed across subjects using the ‘lme4’ package in R,
allowing the within-subject intercepts and slopes to vary as random effects. The planned analysis was to aggregate all data across the three tasks into a single measure. However, we also completed three post-hoc analyses in which we examined linear change in BOLD-RSA covariation within each task. Significant findings are reported at $p < .05$.

**Non-parametric analysis:** To supplement analysis of ROI averages and examine the spatial extent of BOLD-RSA covariation within each ROI at baseline and post-treatment, we used a nonparametric permutation test to estimate the distribution of null hypothesis t-values within each ROI (10,000 iterations) and applied small-volume correction to identify significant voxels. We repeated this analysis on the within subject linear contrast image of the covariation patterns across weeks to identify the spatial extent of BOLD-RSA increases over time in patients compared to controls. Additionally, we used nonparametric methods to examine relationships between MADRS scores and individual differences in BOLD-RSA covariation in patients at baseline and post-treatment. Significant results are reported at $p < .05$, small volume corrected.

**Whole-brain analysis:** The final analysis was a whole-brain analysis designed to identify other brain regions where covariation between activity and RSA may improve with treatment. We set the primary criterion threshold to $p < .001$ uncorrected, and report as significant all regions with a significant cluster corrected level of $p < .05$ (50). For completeness, we also report clusters that are significant to $p < .001$ uncorrected but fail to reach cluster-
corrected significance. While the results in these clusters cannot be fully interpreted, they may be useful in determining a priori ROIs for future studies.

Results

Behavior

At intake, patients had an average MADRS value of $21.5 \pm 7.0$ that significantly dropped to $10.9 \pm 10.5$ post-treatment (pre- vs. post-treatment $t_6 = -3.67, p = .011$). As anticipated, mean RSA was lower in patients compared to controls ($t_{15} = -1.91, p = .037$, one-tailed). This difference did not significantly change over time ($t_{15} = 1.58, p = .14$).

fMRI

Mean ROI Analysis: At baseline we observed lower BOLD-RSA covariation in patients compared to controls in L insula ($t_{15} = -2.24, p = .041$). Additionally, there was marginal evidence for lower BOLD-RSA covariation in rACC ($t_{15} = -2.09, p = .054$) and dACC ($t_{15} = -1.96, p = .069$). Post-treatment, there were no significant differences in BOLD-RSA covariation between groups within any ROI (Figure 2).
Figure 2. *Mean BOLD-RSA covariation*. Mean covariation as assessed by BOLD-RSA correlations normalizes during treatment for MDD patients (blue) and remains relatively stable for controls (red). Change in BOLD-RSA covariation is significantly greater for patients compared to controls in sgACC, dACC, PAG, L Insula, Putamen, and L Amy (* p< .05). Error bars are ± sem. ACC = anterior cingulate cortex; PFC = prefrontal cortex; sgACC = subgenual ACC; rACC = rostral ACC; dACC = dorsal ACC; vmPFC = ventromedial PFC; rmPFC = rostromedial PFC; PAG = periaqueductal gray area; Amy = amygdala; sem = standard error of the mean.

A linear increase in BOLD-RSA covariation across assessments was greater in patients compared to controls in five of the ten ROIs: L Amy (t_{15} = 2.57, p = .018), sgACC (t_{15} = 2.32, p = .035), L Putamen (t_{15} = 3.4, p = .004), L Insula (t_{15} = 2.78, p = .014), and PAG (t_{15} = 2.27, p = .038). In addition, patients showed marginally greater increases in BOLD-RSA covariation in rACC (t_{15} = 1.94, p = .074) and dACC (t_{15} = 2.11, p = .052). Linear change in BOLD-RSA covariation in rmPFC (t_{15} = 0.538, p = .60), vmPFC (t_{15} = 0.85, p = .41), and hypothalamus (t_{15} = 1.09, p = .29) was not significantly different between...
patients and controls (Figure 2). When analyzed by task, patients had significantly greater increases in BOLD-RSA covariation within L Insula ($t_{15} = -2.94, p = .011$), rmPFC ($t_{15} = -2.32, p = .035$), and L Amy ($t_{15} = -2.78, p = .015$) and marginally greater increases in dACC ($t_{15} = -1.89, p = .08$) during the pictures task, marginally greater increases within L Amy ($t_{15} = -2.07, p = .057$) during the faces task, and marginally greater increases in PAG ($t_{15} = -1.90, p = .079$) during the words task.

*Non-parametric analysis:* There was significantly less positive BOLD-RSA covariation at baseline for patients compared to controls in R rACC, R sgACC, L Putamen and L insula (Figure 3A). Post-treatment, patients had greater BOLD-RSA covariation than controls in sgACC (Figure 3B). Across the entire study, patients had greater increases compared to controls in BOLD-RSA covariation within sgACC, rACC, Putamen, Amygdala, Insula, dACC, and PAG (Figure 3C). For depressed patients, increases in BOLD-RSA covariation with treatment within PAG and hypothalamus were correlated with improvement in MADRS (Table 1)
### Table 1. Predetermined ROIs

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<th>ROI</th>
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<th>x</th>
<th>y</th>
<th>z</th>
<th>Size</th>
<th>Linear Change (t)</th>
<th>Week 0 (vox)</th>
<th>Week 12 (vox)</th>
<th>Linear Change (vox)</th>
<th>Linear MADRS (vox)</th>
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**Running title:** Medial Visceromotor Network in Depression

**Schafer 16**
Figure 3. **Voxel-wise differences in BOLD-RSA covariation within ROIs.** Green shading marks ROI extent where no differences were observed between groups. A) **Week 0 (Baseline, Patients - Controls):** Prior to treatment, patients show significantly reduced BOLD-RSA covariation compared to controls in rACC, sgACC, insula, and putamen. B) **Week 12 (Study completion, Patients - Controls):** Patients show significantly increased BOLD-RSA covariation compared to controls in sgACC following treatment. C) **Change over time (Patients - Controls):** Over the course of the study, increases in BOLD-RSA covariation are greater for patients than controls within sgACC, rACC, Putamen, amygdala, insula, dACC, and PAG. ACC = anterior cingulate cortex; sgACC = subgenual ACC; rACC = rostral ACC; dACC = dorsal ACC.

**Whole-brain analysis:** The increase in BOLD-RSA covariation over the four sessions was significantly greater for MDD patients than controls within midbrain, medial thalamus and R Putamen (cluster-corrected p< .05), indicating a shift to stronger positive brain-RSA correlations in patients over
the course of treatment (Figure 4). Group differences significant to $p < .001$ uncorrected are included for display purposes and listed in Table S1.

![Figure 4](image)

Figure 4. Whole-brain BOLD-RSA change in covariation (Patients - Controls). Whole-brain analysis showing brain regions with significantly greater linear increases over time in BOLD-RSA covariation for MDD patients compared to controls. Areas shown are significant to $p < .001$ uncorrected. Only the cluster containing the right thalamus, caudate and putamen is cluster-corrected significant at $p < .05$.

**Discussion**

This is the first study to longitudinally examine correlations between brain activity and autonomic function across the course of antidepressant treatment. In multiple brain areas, including key nodes in the MVN, a consistent pattern was observed in which the covariation between RSA and BOLD activity increased with treatment in depressed patients while largely remaining constant in healthy volunteers. These preliminary results indicate that there is a general pattern of normalization of BOLD-RSA covariation with sertraline treatment in depressed patients.

The lower baseline BOLD-RSA covariation and treatment-related increases in BOLD-RSA covariation over time in depressed subjects suggest that the depressed state is associated with an alteration in brain regulation of cardiac vagal control at baseline. The brain areas that show increased BOLD-
RSA covariation also participate in the emotion dysregulation that characterizes depression. It therefore appears that response to antidepressant treatment involves changes in regional brain function associated with both emotion and autonomic regulation.

These changes in brain-RSA relationships across sessions may be a stronger correlate of changes in depression than changes in RSA itself. A recent meta-analysis reaffirmed that RSA is lower in depression but also found that SSRI treatment is typically not associated with increased RSA despite effectively reducing symptoms of depression (32). Consistent with these findings, we observed diminished RSA in depressed patients that persisted despite effective treatment. Given that we observed significant normalization in the relationship between brain activity and RSA as depression abated, a key question is why RSA did not increase significantly during treatment. There are several potential reasons.

One hypothesis is that the SSRI-induced changes in the MVN were insufficient to induce significant change in RSA, implying that the brain-RSA changes are more sensitive to treatment than RSA changes overall. Although prominent changes were observed in the insula, and the insula is part of the MVN, the specific insula ROI drawn from the literature covers a region primarily connected to lower level viscerosensory regions (51, 52). However, positive shifts in BOLD-RSA covariation with treatment were observed in visceromotor ROIs, such as PAG and ventromedial putamen (53), as well as in sgACC and dACC, which have at least some visceromotor effects on RSA. Thus,
while some visceromotor areas were affected by SSRI treatment, the changes observed were somehow insufficient to measurably change RSA.

Within the ROIs examined, it is notable that we failed to find overall increases in covariation within the rACC. The rACC in particular possesses monosynaptic connections to hypothalamus and PAG (1) that, when stimulated, have immediate cardiovascular effects (3, 4). As both mean RSA and overall rACC activity fail to normalize following successful antidepressant treatment in this and another study (54), this suggests that the two may be related, though the failure to detect a change in the case of both variables may be due to a lack of power. While this study is unable to test that hypothesis, other therapies that improve function in rACC may be able to examine whether improvements in rACC function and RSA function are related. Some evidence is available that psychotherapy such as cognitive behavioral therapy (CBT) increases activity in cortical structures including dACC and rACC (55) and thus potentially recruits visceromotor output centers within the MVN more fully than treatment with SSRIs. To our knowledge, a longitudinal study of changes in RSA (or other indices of HRV) during CBT has not been conducted. It is possible that cognitive processes enhanced by CBT engage rACC and rmPFC to a greater degree than SSRIs and may thereby promote greater change in RSA.

The combination of medication and psychotherapy is be more effective than either modality alone (56). Perhaps this is true because the combination of treatments promotes completion of a feedback loop whereby both afferent and efferent neurotransmission is promoted in a recursive fashion. It is
possible, although not yet demonstrated, that RSA is restored when remission occurs, consistent with the observation that depression severity and RSA are inversely correlated (31).

An important implication of this research on brain mechanisms of vagal control in depression involves the 1.5-3 fold greater mortality in coronary artery disease in depressed vs. non-depressed individuals (9). The mechanisms underlying the relationship between depression and mortality are not clear. One possible mechanism is reduced vagal control, which is known to increase myocardial electrical instability and sudden cardiac death (57). Reduced vagal control could contribute to hyperarousal and the insomnia associated with depression. Reduced vagal control, as well as insomnia, is associated with elevation in inflammation (57-59), which can contribute to the progression of coronary artery disease. It is known that the somatic symptoms of depression confer increased risk for mortality, which would be consistent with these mechanisms (60). These data raise the possibility that depression treatments that normalize function within visceromotor brain regions may be cardio-protective, as they could lead to overall increased vagal control.

Limitations and Future Directions

While the findings in this study are robust, there are several limitations.

1) The sample is almost entirely composed of female subjects. Future studies should be more balanced across gender in order to generalize findings to all patients. 2) A number of patients dropped out of the study either due to response or non-response to treatment. Virtually all of the remaining
depressed subjects who completed the study (and who were included in this analysis) were treatment responders. A larger study is needed to compare the time course and extent of BOLD-RSA covariations in remitters, responders and non-responders. 3) The findings reported here may be a function of improvement in the depressed state in general rather than SSRI treatment in particular. This could be addressed in future studies by including alternative depression treatments such as CBT or other antidepressants. Placebos are also associated with significant antidepressant effects (61) that are based on changes in emotion regulatory centers in the brain (62). In future studies, comparison of the effects of antidepressants, CBT, and placebos on BOLD-RSA covariation is needed. 4) The sample size is smaller than is typically desired. However, each subject included in the study participated in four separate sessions, allowing us to test for group differences using repeated measures. This substantially increased our power to detect changes in BOLD-RSA covariation over time by accounting for more error, with an estimated 70-80% chance of detecting a moderate effect (using estimates of session-to-session variance derived from control subjects) for this within-subject design, compared to an estimated 30-40% chance of detecting an effect were each of the data points collected from separate subjects.

The concept that SSRIs do not fully normalize function within the MVN necessitates future testing of the following hypotheses: 1) Antidepressant treatment regimens that engage primary output structures of the MVN (e.g., rACC) more fully than SSRIs, such as CBT or CBT combined with SSRIs, may be
more likely to result in RSA increases than are treatments that do so to a lesser extent; 2) Greater increases in BOLD-RSA covariation in rACC and rmPFC with treatment will be correlated with greater subsequent increases in RSA and inversely correlated with the likelihood of relapse; 3) Reduced RSA may be related to cardiovascular disease risk in remitted as well as currently depressed individuals.

**Summary**

The normalization of BOLD-RSA covariation observed over 12 weeks may be an indicator of successful antidepressant treatment outcome. However, the lack of change in RSA with SSRI treatment implies that SSRI treatment only leads to partial improvement in visceromotor mechanisms. It remains untested whether improvement in RSA occurs with more effective SSRI treatment (e.g. remission rather than response) or whether improvement in RSA normalizes at some point after normalization of BOLD-RSA covariation. These findings lead to novel predictions about the mechanisms by which combined psychotherapy and pharmacotherapy may exert greater clinical effects including protection against cardiac morbidity and depressive relapse.

**Funding and Disclosure**

The authors declare no conflicts of interest.

**Acknowledgements**
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References


Schafer 25
47. Lane RD, Fink GR, Chua PM-L, Dolan RJ. Neural activation during selective attention to subjective emotional responses. NeuroReport. 1997;8:3969-72.
### Table S1. Whole brain ROIs. A table detailing all clusters where patients show greater linear increases in BOLD-RSA covariation over time compared to controls (p < .001 uncorrected). Only the cluster containing the R thalamus, caudate and putamen is cluster-corrected significant to p < .05.

<table>
<thead>
<tr>
<th>Name</th>
<th>Lat.</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>voxels</th>
<th>maxstat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus/Insula</td>
<td>L</td>
<td>-42</td>
<td>-18</td>
<td>-14</td>
<td>470</td>
<td>8.76</td>
</tr>
<tr>
<td>Insula/Putamen</td>
<td>L</td>
<td>-30</td>
<td>2</td>
<td>-6</td>
<td>133</td>
<td>12.67</td>
</tr>
<tr>
<td>Thalamus/Caudate/Putamen</td>
<td>R</td>
<td>6</td>
<td>-2</td>
<td>2</td>
<td>872</td>
<td>11.72</td>
</tr>
<tr>
<td>Superior Temporal Sulcus</td>
<td>R</td>
<td>40</td>
<td>-38</td>
<td>12</td>
<td>159</td>
<td>10.47</td>
</tr>
<tr>
<td>Putamen</td>
<td>L</td>
<td>-22</td>
<td>-4</td>
<td>14</td>
<td>153</td>
<td>8.54</td>
</tr>
<tr>
<td>Temporal/Occipital Junction</td>
<td>L</td>
<td>-20</td>
<td>-62</td>
<td>22</td>
<td>105</td>
<td>11.01</td>
</tr>
<tr>
<td>dorsomedial Prefrontal cortex</td>
<td>R</td>
<td>26</td>
<td>32</td>
<td>24</td>
<td>234</td>
<td>11.32</td>
</tr>
<tr>
<td>dorsal Frontal Pole</td>
<td>L</td>
<td>-26</td>
<td>62</td>
<td>22</td>
<td>91</td>
<td>9.1</td>
</tr>
<tr>
<td>posterior Parietal cortex</td>
<td>R</td>
<td>14</td>
<td>-58</td>
<td>38</td>
<td>121</td>
<td>10.85</td>
</tr>
<tr>
<td>primary Somatosensory cortex</td>
<td>L</td>
<td>-16</td>
<td>-30</td>
<td>66</td>
<td>279</td>
<td>11.98</td>
</tr>
</tbody>
</table>

Table S2. Mean RSA. This table shows the mean RSA values for both depressed patients and non-depressed participants for each week, ± standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 2</th>
<th>Week 6</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>4.97 ± 1.22</td>
<td>5.29 ± 0.93</td>
<td>4.61 ± 1.42</td>
<td>5.25 ± 1.07</td>
</tr>
<tr>
<td>Control</td>
<td>5.81 ± 1.13</td>
<td>5.95 ± 1.04</td>
<td>6.01 ± 1.09</td>
<td>6.15 ± 1.21</td>
</tr>
</tbody>
</table>