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Pretreatment cerebral metabolic activity correlates with antidepressant efficacy of vagus nerve stimulation in treatment-resistant major depression: a potential marker for response?

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Abstract

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Conflicts of Interest

CRC has previously received grant funding for research from Cyberonics, the maker of the VNS device. He did not receive any funding from Cyberonics for this study. CRC is on the speaker's bureau for Merck and Bristol-Myers Squibb. CRC is receiving research grant funding from Bristol-Myers Squibb. MAM is an employee of Avid Radiopharmaceuticals. RDB receives royalty interest from Medtronic for licensing intellectual property in the manufacture of the StealthStation. YIS, JJC, JLP, JTC, LAG, SG, and TH have no financial relationships to disclose.

Contributors

CRC is the primary investigator and was responsible for all aspects of this study including: research design, overseeing the execution of the study, data collection, processing, analysis, and interpretation, as well as manuscript preparation and editing.

JTC contributed to all aspects of the study including research design, data analysis and interpretation, as well as manuscript preparation and editing.

SG contributed to data collection, processing and analysis and manuscript preparation.

MAM contributed to the research design, data analysis and interpretation, and manuscript preparation.

JLP contributed to the neuroanatomical verification of brain structures and assisted with manuscript preparation.

TH contributed to data analysis and interpretation as well as manuscript preparation.

LAG contributed significantly to selection of subjects, data analysis and interpretation, and manuscript preparation.

RDB contributed to research design, neurosurgical consultation and implantation of VNS devices, and manuscript preparation.

JJC contributed to research design, image processing and analysis, and manuscript preparation.

YIS is the senior investigator in this study and contributed to all aspects of this study including data analysis, interpretation, and manuscript preparation.

Background—Pretreatment brain activity in major depressive disorder correlates with response to antidepressant therapies, including pharmacotherapies and transcranial magnetic stimulation. The purpose of this trial was to examine whether pretreatment regional metabolic activity in selected regions of interest (ROIs) predicts antidepressant response following 12 months of vagus nerve stimulation (VNS) in 15 patients with treatment-resistant major depression (TRMD).

Methods—Fluorodeoxyglucose positron emission tomography (FDG PET) was used to assess regional mean relative cerebral metabolic rate for glucose (CMRGlu) in four ROIs (anterior insular, orbitofrontal, anterior cingulate, and dorsolateral prefrontal cortices) at baseline (prior to VNS activation). Depression severity was assessed at baseline and after 12 months of VNS using the Hamilton Depression Rating Scale (HDRS), with response defined as 50% reduction in HDRS from baseline.

Results—Baseline CMRGlu in the anterior insular cortex differentiated VNS responders ($n = 11$) from nonresponders ($n = 4$) and correlated with HDRS change ($r = .64$, $p = .01$). In a regression analysis, lower anterior insular cortex CMRGlu ($p = .004$) and higher orbitofrontal cortex CMRGlu ($p = .047$) together predicted HDRS change ($R^2 = .58$, $p = .005$). In a whole brain, voxel-wise analysis, baseline CMRGlu in the right anterior insular cortex correlated with HDRS change ($r = .78$, $p = .001$).

Limitations—Sample size was small, limiting statistical power; patients remained on their psychiatric medications; study was open-label and uncontrolled.

Conclusions—This preliminary study suggests that pretreatment regional CMRGlu may be useful in predicting response to VNS in TRMD patients.

Keywords

Vagus nerve stimulation; Depression; Positron emission tomography; Treatment-resistant depression; Fluorodeoxyglucose PET; Treatment response

1. Introduction

Treatment-resistant major depression (TRMD), defined as failure to respond to successive adequate dose-duration antidepressant trials, remains a significant clinical challenge. Naturalistic studies in TRMD patients receiving “treatment as usual” (i.e., any antidepressant treatment) have shown poor response rates (~12%) (Dunner et al., 2006; George et al., 2005). In 2005, the United States Food and Drug Administration approved adjunctive vagus nerve stimulation (VNS) for TRMD. Several studies have found VNS effective in a subset of TRMD patients (27-53% response rates) (Bajbouj et al., 2010; Marangell et al., 2002; Nahas et al., 2005; Rush et al., 2000, 2005). Unlike other TRMD treatments (e.g., electroconvulsive therapy, ECT), a large subset (~65%) of VNS responsive patients at one year maintain response at two years (Nahas et al., 2005; Sackeim et al., 1990). Long-term studies of VNS in TRMD demonstrate that the antidepressant effects in most patients are delayed (>6 months); in one study, 15% of patients responded to VNS at 3 months, 18% at 6 months, 23% at 9 months, and 30% at 12 months (Rush et al., 2005).

The mechanism of action of VNS is poorly understood. Current depression models hypothesize dysregulation of interconnected brain structures in the frontal and limbic circuitry (Mayberg et al., 1997a; Mayberg, 1997b, 2003; Price and Drevets, 2010). Primary regions in this network include the prefrontal, cingulate, and insular cortices, amygdala, hippocampus, striatum, dorsal thalamus, hypothalamus, and brainstem nuclei. Studies demonstrate that pretreatment brain activity in these regions correlates with antidepressant response to several treatment modalities, including pharmacotherapies, transcranial magnetic stimulation, and sleep deprivation (Brannan et al., 2000; Goldapple et al., 2002;

Kennedy et al., 2001; Little et al., 2005; Martinot et al., 2011; Mayberg et al., 1997a; Mayberg, 2003; Pizzagalli, 2011; Wu et al., 1992). The afferent vagal pathway provides numerous intersections with these mood circuits including brainstem nuclei (Beckstead and Norgren, 1979; Henry, 2002; Kalia and Sullivan, 1982; Rhoton et al., 1966), thalamus (Beckstead et al., 1980; Krout and Loewy, 2000), insular cortex (Saleem et al., 2008), orbitofrontal cortex and indirectly with the cingulate cortex (Ongür and Price, 2000; Saleem et al., 2008).

Several VNS TRMD neuroimaging studies have assessed the effects of immediate vagal stimulation (Bohning et al., 2001; Conway et al., 2006, 2011; Lomarev et al., 2002; Mu et al., 2004; Nahas et al., 2007), with significant VNS-induced changes in metabolic activity noted in the orbitofrontal, anterior cingulate, dorsolateral prefrontal, and insular cortices, as well as the striatum, cerebellum, and brainstem. However, associations of these changes with antidepressant response have not been reported. Other studies assessed chronic VNS effects on brain activity (Kosel et al., 2011; Nahas et al., 2007; Pardo et al., 2008; Zobel et al., 2005). These studies vary widely in VNS duration (1-20 months). Although results are somewhat inconsistent, decreased activity has been noted in medial frontal and limbic regions at 4 weeks (Zobel et al., 2005), in insular and precuneus regions at 10 weeks (Kosel et al., 2011), and in subgenual cingulate and ventromedial prefrontal regions at one year (Pardo et al., 2008).

Thus far, however, VNS neuroimaging studies have not examined associations between pretreatment brain activity and antidepressant response over time. This was the purpose of the present preliminary study. Fifteen TRMD patients implanted with the VNS system underwent pretreatment/baseline (i.e., prior to VNS activation) fluorodeoxyglucose positron emission tomography (FDG PET), from which measures of mean relative cerebral metabolic rate for glucose (CMRGlu) were obtained in four pre-selected regions of interest (ROI): bilateral orbitofrontal cortex (OFC), anterior insular cortex (AIC), anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (DLPFC). These ROIs were selected because they are components of the VNS afferent pathway (Henry 2002; Ongür and Price, 2000; Saleem et al., 2008), have previously been identified in VNS TRMD neuroimaging studies (Bohning et al., 2001; Conway et al., 2006, 2011; Kosel et al., 2011; Lomarev et al., 2002; Mu et al., 2004; Nahas et al., 2007; Pardo et al., 2008; Zobel et al., 2005), and are established regions in depression models (Mayberg, 1997b, 2003; Price and Drevets, 2010). Depression severity was assessed at baseline (i.e., at pretreatment FDG PET) and after 12 months of VNS therapy. Baseline CMRGlu was compared between 12-month responders and nonresponders, and univariate and multivariate associations were examined between CMRGlu and change in depression severity over time. A whole brain, voxel-wise analysis was also performed to explore other regions that might be associated with antidepressant change.

2. Methods

2.1. Participants and inclusion/exclusion criteria

Written informed consent was obtained following institutional review board approval of the study. Participants (N = 15) were recruited from the community (n = 10) or as participants in the VNS dose-finding efficacy trial (n = 5) occurring simultaneously at Saint Louis University. TRMD was defined as: (a) current diagnosis of major depressive disorder, unipolar or bipolar, as defined by DSM-IV and confirmed by Structured Clinical Interview for DSM-IV (First et al., 1995); (b) 2 adequate dose-duration medication trial failures in the current depressive episode; and (c) 4 lifetime medication trial failures. Medication trial failure was defined using the Antidepressant Treatment History Form (Prudic et al., 1990, 1996; Sackeim et al., 1990, 2001), modified to require eight week medication trials (rather

than four weeks). Participants were required to score ≥ 18 at baseline on the 24-item version of the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967) and be 18-85 years of age. Exclusion criteria included other active DSM-IV axis I diagnoses, personality disorder, recent serious suicide attempt, acute suicidal ideation, recent (within 12 months) substance abuse/dependence, stroke history, traumatic/closed head injury or brain malformation, MRI contraindications, and pregnancy. Personality disorder screening was extensive, including medical record review and telephone/in-person interviews with potential participants and their primary psychiatrists.

2.2. Study procedures

Participants underwent FDG PET at baseline (within two weeks of VNS implantation prior to VNS activation). Following FDG PET, VNS was activated. Initially, all stimulation cycles were set to 30 seconds of stimulation every 5 minutes (30/5). Other VNS parameters were set to the participant's highest tolerable current or by the parameters of the multicenter dose-finding study. Parameter adjustments were allowed, where clinically indicated, during the study; however, little parameter variation occurred. At 3-month follow-up, mean current was 1.07 mA (SD = .36), mean signal frequency was 21.3 Hz (SD = 3.5), and mean pulse width was 300.7 μ s (SD = 131.0); all stimulation cycles were 30/5. Mean values at 12-month follow-up were 1.25mA (SD = .43), 21.3 Hz (SD = 3.5), 366.7 μ s (SD = 160.0), and 30/4.4 (SD = 0/1.1).

Depression severity was assessed with the HDRS at baseline and after 12 months of VNS. Treatment response was defined as $\geq 50\%$ decrease in HDRS from baseline; remission as HDRS < 10 at 12 months. Due to concerns over potential worsening of depression and/or emergence of suicidal intention, participants remained on their existing psychotropic medication regimens (unmodified) during the study (Supplemental Table 1S).

2.3. FDG PET

2.3.1. Imaging and scan acquisition—FDG PET was performed at Washington University Clinical Center for Imaging Research using a Siemens Biograph 40 TruePoint PET/CT scanner (Siemens, Berlin) in three-dimensional acquisition mode. Participants were intravenously injected with ~ 10 mCi of FDG and then reclined (awake, eyes open) in a quiet, dimly-lit, visually-neutral room for 40 minutes. They were instructed to avoid anxiety- or mood-related thoughts. Participants were then positioned supine in the scanner (awake, eyes open and fixed on a set point), with scanning planes oriented to the canthomeatal line, and a 20-minute emission PET scan was obtained. A computed tomography scan was obtained for attenuation correction. Participants also underwent a magnetic resonance imaging (MRI) scan using a 3 Tesla Siemens Sonata MRI scanner with the following parameters: 3-D fast gradient echo MR acquisition, magnetization prepared rapid gradient echo; TR = 10 ms, TE = 4 ms, inversion time = 300 ms, flip angle = 8, 1 slab = 160 mm, 3D partitions = 128, slice thickness = 1.25 mm, matrix = 256×256 .

2.3.2. Data processing and analysis—FDG PET images were reconstructed using DIFT algorithm (filtered back-projection in Fourier space) with Siemens (Berlin, Germany) software. Each scan was coregistered (within- and across-subject images) using an established protocol (Snyder, 1996). Scans were corrected for head motion by aligning the four 5-minute frames before summing. Images were then registered to the participant's MRI scan and aligned to the laboratory Talairach atlas (Talairach and Tournoux, 1988) using a 12-parameter linear affine transform. Scans were then transformed to the Talairach atlas coordinate system using the MRI transform (Rowland et al., 2005). Global normalization (within- and across-subject) was accomplished using atlas space pixels from all data sets, scaling the global average FDG uptake to 5000. Images were then smoothed with a Gaussian

filter to a final resolution of 10 mm full width half max. The resulting values represented CMRGlu and were scaled by dividing by 5000.

2.3.3. Demarcation of ROIs—Bilateral (combined left/right) AIC, OFC, ACC, and DLPFC were pre-selected as ROIs. Masks of each ROI were created by manual demarcation using a composite MRI of all 15 participants (Analyze® software, Rochester, MN, USA), with verification of anatomical demarcations by a neuroanatomist. These masks were then compared to each participant's MRI to verify anatomical alignment (with no corrections required). Standardized methodologies were used for each regional demarcation: AIC, traced in transverse and coronal planes per Naidich et al. (2004); OFC (Brodmann's area 10,11,47), traced in the coronal plane per Ballmaier et al. (2004); ACC, traced in the coronal plane per McCormick et al. (2006); DLPFC (Brodmann's area 9,46), traced per Rajkowska and Goldman-Rakic (1995a, 1995b).

2.4. Statistical analysis

Analyses of CMRGlu and HDRS data were performed using IBM SPSS Statistics Version 19 (IBM Corporation, Armonk, NY). Change in HDRS between baseline and 12 months was evaluated using a paired t test. Baseline CMRGlu differences between 12-month responders and nonresponders were evaluated using an independent samples t test. Univariate associations between CMRGlu and HDRS percentage change from baseline were estimated with Pearson product-moment correlations. Multivariate associations between CMRGlu and HDRS percentage change were evaluated using multiple linear regression (forward entry method). The *p*-value for significance was set at .0125 (.05/4 ROIs).

A whole brain, voxel-wise analysis was performed using Statistical Parametric Mapping software (SPM8, Wellcome Trust Center for Neuroimaging, $p_{\text{uncorrected}} = .002$ for peak voxel threshold). To be considered significant, a cluster must exceed the "minimum expected cluster size" (calculated by SPM8 based on Gaussian random field theory and the smoothness of image data and listed in the SPM output file; Friston et al., 1994). To definitively localize the cortical subregion positions, surface representations were created using a cortical mapping program (Caret, http://brainvis.wustl.edu/wiki/index.php/Main_Page).

3. Results

3.1. Sample description and VNS efficacy

There were 14 unipolar depression participants and 1 bipolar depression participant. Detailed sample characteristics are displayed in Table 1, for the total sample by VNS response status. There were 11 responders (73%, of which 6 were remitters) and 4 nonresponders at 12 months. Although there were no statistically significant differences between responders and nonresponders in disease/demographic variables, statistical power was low. Notable potential differences include more depression episodes and lifetime depression years in the responders, relative to the nonresponders. HDRS was significantly lower at 12 months (mean = 12.5, SD = 10.2) relative to baseline (mean = 28.1, SD = 3.4), $t(14) = 6.8$, $p < .001$. The mean percentage HDRS change from baseline to 12 months was -57% (SD = .32).

3.2. Baseline CMRGlu associations with antidepressant response

Table 2 indicates that baseline CMRGlu in the AIC was significantly lower in responders than nonresponders, $t(13) = 3.0$, $p = .01$. No other ROIs were associated with significant differences in CMRGlu as a function of response status. Also in Table 2, CMRGlu in the AIC was strongly correlated ($r = .64$, $p = .01$) with percentage change in HDRS from

baseline to 12 months. In the multiple regression analysis, a significant equation was obtained, $F(2,12) = 8.4$, $p = .005$, $R^2 = .58$. Baseline CMRGlu values for two ROIs entered the regression equation as significant predictors of HDRS change: AIC (standardized regression coefficient, $\beta = .66$, $p = .004$) and OFC ($\beta = -.41$, $p = .047$). Figure 1, **panel A** displays the association of observed HDRS change with change predicted by the regression equation. Figure 1, **panel B** compares the baseline PET images for VNS-responders and non-responders.

3.3. Whole brain, voxel-wise analysis

Regression of HDRS change against *increase* in baseline CMRGlu across the entire brain identified no significant clusters. Regression of HDRS change against *decrease* in CMRGlu identified clusters in the right putamen, right posterior cingulate (Brodmann's area 24), and right anterior insular/pre-insular cortex. The latter cluster (Talairach: 31, 30, 4) overlapped with the pre-selected AIC ROI, and correlated strongly with HDRS change ($r = .78$, $p = .001$). The exact cortical position of this cluster was determined to be the intersection of the anterior insular and pre-insular cortices (described by Ongür et al., 2003, as 47/12s intermediate agranular insular cortex).

4. Discussion

While preliminary, the current results are suggestive of a potential marker—pretreatment CMRGlu in the combined AIC and OFC regions—for antidepressant response in TRMD patients considering VNS therapy. The results are also instructive regarding brain regions that may be implicated in the mechanism of action of VNS in TRMD.

Using pretreatment brain activity as a marker for predicting antidepressant response has been previously proposed (Brannan et al., 2000; Goldapple et al., 2002; Kennedy et al., 2001; Little et al., 2005; Martinot et al., 2011; Mayberg, 1997b, 2003; Pizzagalli, 2011; Wu et al., 1992). In particular, Mayberg (1997b, 2003) has hypothesized that pretreatment regional brain activity differences between depressed patients and controls may represent “functional lesions” (ongoing self-correction attempts by the brain) in the depressed brain. In this model, antidepressant treatments are effective only if the compensatory capacity of the mood circuits remain intact. Hence, in progressively more resistant depression, the brain may have poor adaptive capacity, as represented in identifiable baseline neural activity patterns. The present results may represent such a pattern (higher AIC and lower OFC pretreatment activity in VNS-nonresponders).

With regard to the issue of mechanism of action, previous studies of non-TRMD major depressive disorder patients have generally reported *higher* insular activity at rest and with exposure to negatively-valenced stimuli, relative to controls (Anand et al., 2005; Drevets et al., 1992). In TRMD, however, resting state insular activity is relatively *lower* (Drevets et al., 2009; Kimbrell et al., 2002; Martinot et al., 2011; Mayberg et al., 2005). Further, in both epilepsy and TRMD studies, VNS acutely increases AIC activity (Conway et al., 2006; Henry et al., 1998; Kosel et al., 2011; Mu et al., 2004; Nahas et al., 2007). These studies provide indirect support for the current results, where lower pretreatment CMRGlu in the AIC was associated with VNS antidepressant response, both in the multivariate analysis and the whole brain regression. Thus, the AIC—critical to interoception and emotional awareness (Craig, 2002)—may play an important role in VNS efficacy.

Similarly, resting state OFC activity is *higher* in non-TRMD depressed patients, relative to controls (Drevets, 2007; Mayberg et al., 1997a). In TRMD, however, resting OFC activity is generally *lower* than or equivalent to that found in nondepressed controls (Drevets, 2007; Mayberg et al., 1994, 1997a), and both epilepsy and TRMD studies have noted OFC

activation in response to acute VNS (Bohning et al., 2001; Conway et al., 2006; Henry et al., 1998, 2004; Mu et al., 2004). In fact, recognition of increased VNS-induced prefrontal cortical activation in epilepsy was part of the rationale for the initial VNS trials in TRMD (George et al., 2000). In the current study, higher pretreatment OFC activity was associated with VNS response. Consistent with the hypothesis of Drevets (2007), it may be that depression-related elevations in OFC activity represent a compensatory effort to attenuate excessive limbic activity. TRMD patients with weaker pretreatment levels of this compensatory capacity—as evidenced by lower OFC activity—would therefore be at greater risk for nonresponse to VNS.

Why pretreatment AIC and OFC activity is associated with VNS response is unclear. One possible explanation is the existence of TRMD variants. Paulus and Stein (2010) proposed a model in which major depressive disorder patients are presumed to have a higher degree of afferent interoceptive noise-to-signal information entering the insula, such that a flood of noisy interoceptive amplification leads to top-down engagement of insula-associated brain regions (e.g., DLPFC and OFC) in a modulatory attempt to attenuate excessive interoceptive signals. This model may support TRMD variants (e.g., a strongly AIC activated nonresponsive type and a weakly AIC activated responsive type) distinguishable by resting state anterior insular-preinsular and lateral-orbitofrontal cortical activity. The concomitant lower OFC activity in VNS nonresponders would be consistent with the “strongly AIC activated” type; nonresponders may be demonstrating inadequate top-down engagement of the OFC (Drevets, 2007).

4.1. Limitations

The overall sample size was small, and the number of nonresponders was smaller, which limited statistical power. Also, participants remained on their psychotropic medication regimen during the study. This is important since whole brain metabolism can be reduced by benzodiazepines and antipsychotic drugs (Lesser et al., 1994; Silfverskiöld and Risberg, 1989). Generalizability must also be considered in light of our high response rate (73%). This is higher than rates of 27-53% seen in multicenter trials (Bajbouj et al., 2010; Marangell et al., 2002; Nahas et al., 2005; Rush et al., 2000, 2005). On the other hand, our response rate may be partly attributable to a rigorous exclusion protocol regarding confounding factors (e.g., personality disorder and substance abuse). Depression may also lead to structural changes in mood-related brain regions, including regions studied here (Kimbrell et al., 2002; Ongür et al., 1998; Rajkowska et al., 1999). These changes could cause misestimations of regional brain activity due to partial volume averaging (Mazziotta et al., 1981). This issue was addressed somewhat here by creating and verifying ROI masks based on a composite MRI.

4.2. Future directions

These preliminary results suggest the possibility of pre-surgical guidance regarding VNS response likelihood. Because VNS involves surgically implanting a semi-permanent system and is inefficacious in a significant subset of TRMD patients, determining variables which predict response is critical. Larger, controlled studies of the relationships between pretreatment brain activity and VNS response are warranted. Standardized and reproducible neuroimaging metrics are also needed. For example, it would be useful to develop a standardized CMRGlu ratio of identified “predictor” regions/regions unaffected by MDD, against which to compare an individual patient, to help guide decisions about potential VNS benefit. Functional connectivity analyses may help refine the network relationships among these predictive regions.

With regard to VNS as an efficacious and practical antidepressant therapy, several points are worth noting. First is the sustained antidepressant response. Of the 11 responders in this trial, we now have 18-month HDRS data on 10. Of this group, 8 were responding at 18 months (5/8 remitters); of the two that were not, 18-month HDRS change scores were -44% and -47%. Second, patients' self-reports of antidepressant efficacy (Inventory of Depressive Symptoms-Self Report, IDS-SR) mirrored those from the rater-administered HDRS. In the subset of 10, significant IDS-SR change from baseline (mean = 43.3, SD = 10.8) was noted at 12 months (mean = 24.7, SD = 13.0) and 18 months (mean = 23.6, SD = 13.1). VNS was also well-tolerated in this sample, with no significant adverse events. Lastly, optimal VNS parameter settings in TRMD have yet to be determined. A recent multicenter dose-finding trial may provide answers to this question (Aaronson et al., 2011, in submission); for now, our practice is to take patients to their maximally tolerated VNS dose.

A final VNS issue concerns cost and reimbursement. The Committee on Medicare and Medicaid Services (USA) decided not to reimburse for VNS for TRMD augmentation on the grounds that VNS is "experimental." This has led to decreased VNS availability for TRMD. Although VNS is initially expensive (~\$29,000; average Medicare VNS rate) and requires lifelong maintenance, it must be noted that unsuccessfully treated TRMD is more expensive (Cohen and Allen, 2008). A cost-benefit analysis concluded that the "break even" mark for successful VNS is about 38 months, assuming a one-year response rate of 44% (Cohen and Allen, 2008). A higher response rate would, of course, shorten the time to the "break even" point. Hence, identification of VNS response markers would contribute to a higher response rate. In the future, careful screening practices, perhaps in conjunction with neuroimaging methods, may contribute significantly to VNS cost-effectiveness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Panel A. Scatterplot of predicted Hamilton Depression Rating Scale (HDRS) percent change scores (as predicted from mean baseline relative cerebral metabolic rate for glucose, CMRGlucose, in a linear regression model including both the bilateral anterior insular and orbitofrontal cortices) with observed HDRS percent change scores (baseline to 12 months). Open circles are VNS responders; closed circles VNS non-responders. **Panel B.** Regional differences in baseline CMRGlucose between VNS nonresponders (left column; VNSnonResp) and VNS responders (rightmost column; VNSResp). Middle column depicts the MRI-localized region of interest. Images appear in radiological format (i.e., image left = subject right). Row 1: VNS-nonresponders demonstrate significantly greater baseline anterior insular mean CMRGlucose than VNS-responders ($p = .01$). Row 2: VNS responders had non-significantly greater baseline orbitofrontal cortex mean CMRGlucose than VNS nonresponders ($p = .15$). AIC = anterior insular cortex; OFC = orbitofrontal cortex.

Table 1
Participant demographic characteristics and depression history

	Total (N= 15)	Responders (n = 11)	Nonresponders (n = 4)	<i>p</i>-value
Age	45.7 (12.0)	46.3 (10.7)	44.0 (16.8)	.76
Female	80% (12)	73% (8)	100% (4)	.52
Caucasian race	93% (14)	91% (10)	100% (4)	1.0
Age of depression onset	17.8 (11.1)	17.1 (10.1)	19.8 (15.2)	.70
No. of depression episodes	2.9 (2.8)	3.4 (3.1)	1.8 (1.0)	.34
Years of current episode	13.3 (12.9)	13.3 (13.6)	13.4(12.4)	.99
Lifetime depression years	23.4 (13.8)	26.2 (13.6)	15.8 (12.7)	.21
No. of failed medication trials	7.4 (2.9)	7.3 (2.6)	7.7 (3.9)	.79
History of ECT (yes)	73% (11)	73% (8)	75% (3)	1.0
History of suicide attempt (yes)	33% (5)	27% (3)	50% (2)	.56
No. of lifetime hospitalizations	3.3 (5.3)	3.5 (5.6)	3.0 (4.8)	.89

For continuous variables, mean (SD), comparisons between responders and nonresponders were made using independent samples t test; comparisons for dichotomous variables, % (n), were made using Fisher's exact test.

Table 2
Comparisons between VNS responders and nonresponders on baseline (BL) CMRGlu; correlations between BL CMRGlu and percentage HDRS change from baseline to 12 months

BL ROI	CMRGlu (mean, SD)		Correlation (r): BL ROI CMRGlu, % HDRS change (BL-12 months)	
	Respon (n = 11)	Nonrespon (n = 4)	p-value	p-value
AIC	1.08 (.04)	1.14 (.01)	.01	.64
OFC	1.04 (.05)	1.00 (.04)	.15	-.39
ACC	1.02 (.08)	1.07 (.04)	.27	.43
DLPFC	1.12 (.02)	1.13 (.02)	.85	-.05

ACC = anterior cingulate cortex; AIC = anterior insular cortex; BL = baseline; CMRGlu = mean relative cerebral metabolic rate for glucose; DLPFC = dorsolateral prefrontal cortex; HDRS = Hamilton Depression Rating Scale -24 item; OFC = orbitofrontal cortex; SD = standard deviation.