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Increased association over time between regional frontal lobe BOLD change magnitude and cardiac vagal control with sertraline treatment for major depression

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ABSTRACT

Regions of the medial visceromotor network (MVN) participate in concurrently regulating shifts in both affective state and cardiac vagal control in the attentional background, and this regulatory ability may be impaired in depression. We examined whether the relationship between changes in BOLD within MVN regions and changes in cardiac vagal control (VC) during affective state shifting changed with depression treatment. Ten depressed and ten control subjects performed an emotional counting Stroop task designed to trigger affective change in the attentional background while undergoing functional magnetic resonance imaging and concurrent electrocardiography (ECG) on four occasions: week 0 (pre-treatment) and weeks 2, 6 and 12 of treatment on sertraline. We measured the absolute value of change between adjacent emotional and neutral conditions in both VC and the BOLD signal in specific regions of the MVN. Over time consistent increases were observed in BOLD–VC magnitude correlations in depressed subjects in subgenual ACC and left DLPFC, which strongly correlated with depressive symptom improvement. Symptom improvement over time was also associated with decreases in the magnitude of both BOLD shifts and VC shifts within-subjects. This suggests that as depressive symptoms improve on sertraline, subgenual ACC and DLPFC may more efficiently regulate visceral states during affective state shifting.

1. Introduction

Recent research has demonstrated that major depressive disorder (MDD) is associated with increased mortality rates in several medical conditions, including stroke, breast cancer, diabetes, and coronary artery disease (Frasure-Smith and Lesperance, 2005; Katon et al., 2005; Onitilo et al., 2006; Lane, 2008). Decreased heart rate variability (HRV) has also been observed in depressed relative to healthy subjects (Kemp et al., 2010), and low HRV has also been associated with adverse health outcomes in relation to stress (Thayer et al., 2012). However, brain–body medicine is currently lacking, and would greatly benefit from, an increased understanding of the physiological mechanisms that contribute to such adverse health outcomes in depression. Further, it is not currently understood whether antidepressant treatment alters disease risk. A better understanding of the mechanisms by which treatment for depression reduces somatic health risks could lead to more informed deployment of existing treatments and could facilitate development of novel treatments.

Combining neuroimaging techniques with peripheral physiological measures has provided a novel means of addressing these questions. A network of brain structures has been implicated in both emotional processing and the monitoring and/or control of HRV and other visceral bodily states by means of connections with the autonomic nervous system (Craig, 2009; Thayer and Lane, 2009; Roy et al., 2012; Thayer et al., 2012). Many key regions that are a part of, or linked to, this medial visceromotor network (MVN) have also been found to be functionally or structurally abnormal in depression, including the insula (Sprengelmeyer et al., 2011), anterior cingulate (ACC)/medial prefrontal cortex (MPFC) (Mayberg et al., 1999; Kennedy et al., 2007; Lozano et al., 2008; Pizzagalli, 2011), dorsolateral prefrontal cortex (DLPFC) (Fales et al., 2009; Koenigs and Grafman, 2009; Smith et al., 2013), and amygdala (Sheline et al., 2001; Frodl et al., 2002). These structures therefore provide an attractive starting point in the search for mechanisms that link depression and systemic medical disorders.

One key structure to emerge from this research is the subgenual ACC, also known as Brodmann area 25 (BA25). BA25 is hyperactive in

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depression and this hyperactivity has been shown to normalize with successful treatment including antidepressant medication, electroconvulsive therapy (ECT), or deep brain stimulation (Mayberg et al., 1999, 2005; Kennedy et al., 2007; McCormick et al., 2007, 2009; Lozano et al., 2008). BA25 participates in the generation of the context-dependent affective meaning of stimuli (Roy et al., 2012), as well as the regulation of autonomic, neuroendocrine, and immune function through its influence on the hypothalamus and periaqueductal grey (Frysztak and Neafsey, 1994; Ongur and Price, 2000; Drevets et al., 2008; Phillips et al., 2008; Thayer and Sternberg, 2010; Critchley et al., 2011). Inspired by these findings, we recently investigated the strength of the correlation between the magnitude of change in vagal control (VC) of heart rate (as measured by respiratory sinus arrhythmia or RSA) and the magnitude of change in the blood oxygen level dependent (BOLD) signal in multiple anterior brain regions when subjects shifted between different emotional states during an emotional counting stroop task. This task was selected in order to keep emotion in the attentional background to specifically target the role of subgenual ACC (and surrounding ventral MPFC) in the automatic (unconscious) regulation of emotional and concomitant visceral states (Bechara et al., 1997; Fellows and Farah, 2003; Williams et al., 2006; Schiller and Delgado, 2010; Roy et al., 2012). We observed that the subgenual ACC bilaterally, the left anterior insula, and left BA47 each had significant correlations with VC in healthy subjects (Lane et al., 2013). Moreover, the correlations in subgenual ACC during state shifts from a depression-specific to neutral condition were significantly smaller in depressed than in control subjects. These findings are consistent with the known autonomic dysregulation in depression and suggest that this paradigm for assessing affective state shifting may provide a novel measure of dysregulated brain–autonomic coupling. The results further supported other work suggesting that a key deficit in depression may be the inability to shift out of a depressed mood (Holtzheimer and Mayberg, 2011) and that ventromedial frontal regions, including BA25, play a critical role in this form of automatic emotion regulation (Fellows and Farah, 2003; Phillips et al., 2008). As multiple anterior regions, including subgenual ACC, and insular cortex, have been shown to be dysfunctional in depression (Mayberg et al., 1999, 2005; Kennedy et al., 2007; Sprengelmeyer et al., 2011), as well as to participate in visceral regulation (Thayer and Lane, 2009; Thayer et al., 2012), our findings appeared to converge with previous literature regarding the neural basis of depression.

Based on these preliminary findings, and the key role of subgenual ACC in MDD and visceral regulation, we used this same paradigm to examine the relationship between BOLD signal change magnitude and VC change magnitude during affective state shifting among depressed participants during the course of 12 weeks of antidepressant treatment. In addition to depressed participants, control subjects were also assessed repeatedly, with the primary interest being the correlations between BOLD signal magnitude and vagal control magnitude over the 12-week antidepressant treatment course. Based on our previous findings (Lane et al., 2013) we performed the present study with the specific hypothesis that, in depressed subjects, changes over time in the correlations between reactivity in vagal control and reactivity in subgenual ACC during affective state shifting would predict response to treatment, and that changes in this reactivity would mirror symptomatic improvement. Specifically, we hypothesized that BOLD–VC correlations in subgenual ACC would increase as depressive symptoms decreased over a 12-week sertraline treatment course. Moreover, based on previous findings suggesting a role for dorsal prefrontal structures in emotional disorders as well as in emotion regulation (Ochsner and Gross, 2005; Phillips et al., 2008), we further hypothesized that the functional BOLD–VC relationship during affective state shifting would also increase in the DLPFC as a function of sertraline treatment. We also chose to examine these measures in the other MVN and emotion regulation-related regions, as in our previous study (Lane et al., 2013).

2. Methods

2.1. Participants

The study protocol was approved by University of Arizona's Human Subjects Protection Program. After being given a full description of the study, the subjects gave written informed consent. Ten patients with MDD (mean age, 36.8±9.3 years, one male and nine females) were recruited from the Depression Clinic in the Department of Psychiatry, as well as through Tucson newspaper and radio advertising. An MDD diagnosis was established by a clinician trained in using the Hamilton Depression Inventory (HAM-D; minimum required score=16) and the MINI International Neuropsychiatric Interview (MINI) at intake. This diagnosis was subsequently confirmed in a clinical interview with a study psychiatrist. Ten healthy controls (mean age, 35.6±12.3 years, one male and nine females) without a history of psychiatric illness were recruited via advertising on University of Arizona campuses (main campus and the health sciences complex).

2.2. Procedure

At study onset no subjects had been on antidepressant medication. Patients were required to not have taken any SSRI for the past month, and if patients were using any other centrally acting medications they were required to have discontinued their use at least five half-lives prior to study onset and remained off of them throughout the study. After week 0 assessment and imaging, depressed patients began treatment with sertraline. Sertraline was started at 50 mg and prescribed on a schedule that escalated as needed based on weekly Montgomery–Asberg Depression Rating Scale (MADRS) ratings up to a maximum of 200 mg. Patients treated with sertraline were seen weekly by a study psychiatrist. Due to the vicissitudes of clinical research, however, not all depression scores were available for each subject at every time point in the study.

2.3. Measures

2.3.1. Hamilton Depression Scale (HAM-D)

The 24-item HAM-D was administered at baseline (Week 0) only to assess depressive symptoms over the past 7 days.

2.3.2. Montgomery–Asberg Depression Rating Scale (MADRS)

The MADRS served as the dependent measure of depression severity during the course of treatment. The MADRS has 10 items and each is rated from 0 to 6 (maximum score 60). At Week 0 and each week during the testing period the MADRS was administered by a research clinician blind to the patient's diagnostic and treatment status. These ratings were obtained prior to the treatment session and shared with the treating clinician. We accomplished rater blinding by using different clinicians for weekly ratings and intake assessments.

2.3.3. Beck Depression Inventory (BDI)

This 21-item self-report measure of depressive symptoms was obtained at Week 0, 2, 6 and 12 in conjunction with the clinical ratings performed on those weeks.

We chose to separate depression rating scales for entry (HAM-D) and for outcome (MADRS and Beck Depression Inventory (BDI)) in order to diminish the phenomenon of "rating inflation," in which investigators may give patients higher scores to maximize recruitment into the study. In the face of such "inflation," there is a greater likelihood of regression to the mean, which in turn obtunds the ability of a study to detect a true treatment effect. The HAM-D, the MADRS, and the BDI are well established in depression treatment trials.

2.4. Imaging parameters

All participants were scanned at each of the four time points on the same 3.0 T GE Signa VH/I system with an eight-channel head coil. Scan parameters for the gradient echo spiral in–out pulse sequence are as follows: TR=3000 ms, TE=30 ms, flip angle=90°, FOV=22 cm, 64×64 matrix, with 3-mm-thick slices acquired in the coronal plane.

2.5. Vagal Control assessments

To obtain electrocardiographic (ECG) data in the electrically-hostile fMRI environment, an In Vivo 3150M Magnitude MRI Patient Monitor was routed to Biopac-based MP100WSW system and acquired with Acqknowledge software, collecting ECG (from a lead II configuration) and also respiration. The subsequent