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Amygdala response to explicit sad face stimuli at baseline predicts antidepressant treatment response to scopolamine in major depressive disorder

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ABSTRACT

The muscarinic antagonist scopolamine produces rapid antidepressant effects in individuals with major depressive disorder (MDD). In healthy subjects, manipulation of acetyl-cholinergic transmission modulates attention in a stimulus-dependent manner. This study tested the hypothesis that baseline amygdalar activity in response to emotional stimuli correlates with antidepressant treatment response to scopolamine and could thus potentially predict treatment outcome. MDD patients and healthy controls performed an attention shifting task involving emotional faces while undergoing functional magnetic resonance imaging (fMRI). We found that blood oxygenation level dependent (BOLD) signal in the amygdala acquired while MDD patients processed sad face stimuli correlated positively with antidepressant response to scopolamine. Amygdalar response to sad faces in MDD patients who did not respond to scopolamine did not differ from that of healthy controls. This suggests that the pre-treatment task elicited amygdalar activity that may constitute a biomarker of antidepressant treatment response to scopolamine. Furthermore, in MDD patients who responded to scopolamine, we observed a post-scopolamine stimulus processing shift towards a pattern demonstrated by healthy controls, indicating a change in stimulus-dependent neural response potentially driven by attenuated cholinergic activity in the amygdala.

1. Introduction

Major depressive disorder (MDD) affects approximately 4.7% of the global population at any given time (Ferrari et al., 2013) and is one of the leading causes of disability in the United States (Kessler, 2012). Although many therapeutic options exist for patients diagnosed with MDD, the rate of treatment response is variable and remains difficult to predict. Thus, identifying biomarkers of treatment response could both minimize participation in trials not likely to succeed and significantly reduce time to relief from depressive symptoms and the restoration of social and occupational functioning for those patients who do respond (Insel, 2009; Luyten et al., 2006; Machado-Vieira et al., 2009; Simon and Perlis, 2010). Given their enormous public health implications, biomarkers of treatment response are being widely pursued, and several have been tentatively identified in multiple domains (Breitenstein et al., 2014; Schmidt et al., 2011; Siegle et al., 2006). However, it remains unclear whether the biomarkers are specific to a particular intervention, or whether they identify subjects more likely to respond to treatment in general. Nevertheless, improving our ability to predict treatment response for specific patient profiles, as well as identifying rapid-acting medications, is key to improving clinical outcomes (Zarate et al., 2013).

Clinical trials found that the muscarinic cholinergic antagonist scopolamine exerts significant antidepressant effects within three days of treatment administration in depressed patients with either MDD or bipolar disorder (Drevets and Furey, 2010; Furey and Drevets, 2006). Specifically, approximately half of patients treated with scopolamine experienced remission, and 65% achieved clinical response after a relatively short treatment period (three infusions over approximately two weeks). Several potential predictors of antidepressant response to scopolamine have been identified; these include baseline mood-state measures (Furey

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et al., 2012), antidepressant treatment history (Ellis et al., 2014), and blood oxygenation level dependent (BOLD) activity in the anterior cingulate and middle occipital cortex while processing emotional stimuli (Furey et al., 2015).

The cholinergic neurotransmitter system, which is known to be disrupted in mood disorders (Janowsky et al., 1972), is widely distributed in the brain. It is a crucial regulator of many CNS functions including arousal, attention, memory, and stimulus processing (Bentley et al., 2003; Himmelheber et al., 2001). Studies found that cholinergic upregulation or downregulation influenced performance in a stimulus-dependent manner in healthy volunteers (Bentley et al., 2003; Furey, 2011; Furey et al., 2008a). Evidence also suggests that the cholinergic system is upregulated in MDD compared to healthy subjects (Dilsaver, 1986; Janowsky et al., 1972, 1974). Specifically, attention and stimulus processing in individuals with depression is biased toward negatively valenced stimuli (Erickson et al., 2005; Fales et al., 2008; Surguladze et al., 2004), and this effect is potentially related to increased cholinergic activity in mood disorders (Overstreet et al., 1988). Furthermore, changes in stimulus processing have been observed following conventional antidepressant treatment (Siegle et al., 2006), and change in neural correlates of the task post-treatment were also observed (Gotlib et al., 2004; Victor et al., 2012).

Given the evidence of cholinergic dysfunction in MDD, the known antidepressant properties of scopolamine, and the role of the cholinergic system in stimulus processing, pre-treatment imaging measures acquired during attentional processing with emotional stimuli may conceivably reflect cholinergic dysfunction. They may therefore also reflect the putative association between cholinergic modulation and potential treatment response.

Human studies have shown that the amygdala, a richly connected limbic structure, is involved in processing emotional stimuli and forming emotional memories (for a review, see Phelps (2006)). Because it is linked to both cortical and subcortical networks, the amygdala rapidly evaluates the salience of environmental cues, particularly those signaling the presence of danger or threat, as well as emotional stimuli with both positive and negative valence (Canli et al., 2005; Pessoa and Adolphs, 2010; Whalen et al., 2002). The amygdala bi-directionally interacts with the nucleus basalis of Meynert, a major source of cholinergic projections to the forebrain (Mesulam, 2013; Mesulam and Geula, 1988). Notably, cholinergic signaling modulates the functional connectivity of the amygdala in response to salient stimuli (Gorka et al., 2015). Interestingly, amygdalar structure and function are altered in MDD, and the amygdala is especially sensitive to functional modulation by antidepressant treatment; in this context, tasks involving emotional probes may be used to evaluate biomarkers of response to standard antidepressant treatment (Drevets et al., 2002; Fu et al., 2004; Sheline et al., 2001; Victor et al., 2010; Williams et al., 2015).

The main objective of this study was to determine whether baseline neural activity in the amygdala during emotional processing is associated with antidepressant response to scopolamine in individuals with MDD. As a secondary aim, we also investigated post-treatment changes in BOLD activity in responders versus non-responders to scopolamine. Given previous evidence that individuals with MDD exhibit a negative bias in stimulus processing —including emotional face processing (Elliott et al., 2002; Harmer et al., 2009; Surguladze et al., 2004; Victor et al., 2010)—we hypothesized that the level of amygdalar activity during processing of negative emotional faces would differentiate treatment responders from non-responders. We also expected to observe baseline differences in amygdalar activity and task performance (as assessed by both accuracy and reaction time measures) between healthy controls and MDD patients. We also hypothesized that post-treatment amygdalar activity in patient responders would be similar to that of healthy subjects at baseline, as the attenuation of the putatively elevated muscarinic cholinergic function was expected to normalize neural response.

2. Methods

2.1. Subjects

All participants were evaluated at the National Institute of Mental Health (NIMH) outpatient clinic for participation in protocol 03-M-0108, approved by the Combined Neuroscience Institutional Review Board (IRB) of the National Institutes of Health (NIH). Entrance criteria were as previously described (Furey and Drevets, 2006). Briefly, healthy volunteers had no current or past psychiatric illness, as established by the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) (First et al., 1997), and no known history of first-degree relatives with an Axis I diagnosis. MDD patients were diagnosed using the SCID and an unstructured interview conducted by a psychiatrist. In addition, MDD subjects were required to have a score of at least 20 on the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Exclusion criteria for patients included other Axis I disorders except anxiety disorders, exposure to psychotropic or other medications likely to affect central nervous system or cholinergic function within three weeks (eight weeks for fluoxetine), suicidal ideation suggesting high suicide risk, current or past history of substance use disorders, and current delusions or hallucinations. All subjects were right handed, non-smokers, medically healthy, and provided written informed consent before entering the study.

The subjects in this study comprised a subset from a larger study investigating the antidepressant effects of scopolamine (Furey and Drevets, 2006). All patients who completed the baseline functional magnetic resonance imaging (fMRI) scan without excessive motion artifacts, performed the task with at least 60% accuracy, completed the treatment protocol, and were evaluated for treatment response at the conclusion of the study were included. Control subjects who completed the baseline scan without excessive motion artifacts and performed the task with at least 60% accuracy were selected to match the age and gender of the patients.

The final subject pool included 14 MDD patients (11F/3M, average age $=32.53 \pm 6.89$) and 15 healthy controls (9F/6M, average age $=31.14 \pm 9.77$). In previously published data (Furey et al., 2015), the healthy control sample was identical, and the MDD sample overlapped by 13 participants. Of the 14 MDD patients included in the study, seven had been diagnosed with co-morbid anxiety disorder. Of the seven patients who responded to scopolamine, three had comorbid anxiety disorder and four did not. Of the 14 MDD patients, 11 were included in the post-scopolamine analysis; one subject was excluded due to scanner failure and two subjects were excluded due to low ($<60\%$ accuracy) performance.

2.2. Study design

The subjects participated in a double-blind, placebo-controlled, cross-over study that consisted of seven 15-min infusion sessions of either a placebo saline solution, or 4.0 μg/kg of scopolamine. Following a single-blind, placebo lead-in session, individuals were subsequently randomized into either a placebo-scopolamine or scopolamine-placebo double-blind, placebo-controlled, cross-over design; the placebo arm included a series of three placebo infusions and the scopolamine arm comprised a series of three scopolamine infusions. Sessions were scheduled three to five days apart. The MADRS was used to assess the severity of depressive