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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 acetylcholinergic 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

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Author Contributions

JS: completed and interpreted the statistical analysis, drafted the manuscript, revised the manuscript, approved the final version of the manuscript.

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AK: conducted the laboratory assays, revised the manuscript, approved the final version of the manuscript.

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a pattern demonstrated by healthy controls, indicating a change in stimulus-dependent neural response potentially driven by attenuated cholinergic activity in the amygdala.

Keywords

Major depressive disorder; amygdala; rapid-acting antidepressants; scopolamine; stimulus processing; functional magnetic resonance imaging (fMRI)

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 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., 1974; Janowsky et al., 1972). 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±6.89) and 15 healthy controls (9F/6M, average age=31.14±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 comorbid 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 comprised seven 15-minute 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 symptoms at the beginning of each study session. Follow-up interviews were obtained three to five days after the last infusion to provide final clinical assessment and establish treatment response.

2.3 Treatment response

Treatment response—defined as a decrease in MADRS score by more than 50%—was calculated as percent change from the pre-infusion lead-in session to the rating obtained at the follow-up appointment one day after the final infusion. Placebo response was calculated as percent change in MADRS score from the pre-infusion lead-in session to the post-placebo session.

2.4 Imaging

BOLD signal was measured using fMRI at three time points during the course of the study: during Session 1 (following the single-blind placebo lead-in), during Session 2 (following either placebo or scopolamine infusion), and during Session 5 (the cross-over condition). Data were acquired once after scopolamine infusion and once after placebo infusion—always after the first infusion in the series—in order to examine the acute effects of the drug and to avoid the carry-over effects of the drug. Hence, the post-scopolamine scan could have been obtained during either session 2 or session 5. Scanning began 45 minutes post-infusion, and the actual task-based BOLD data were obtained between 45 and 90 minutes post-infusion; this allowed the peak cognitive effects of scopolamine to develop and the peak side effects (e.g. drowsiness) to diminish (Furey et al., 2015; Safer and Allen, 1971). A 3 Tesla General Electric scanner (GE Signa, Milwaukee, WI) and an eight-channel phased-array head coil and echo-planar imaging (EPI) sequence were used to measure BOLD signal (TE=24; TR= 2500; sagittal slices= 35; voxel dimensions= 3.75 * 3.75 * 3.5mm; 238 time-points per run). A spoiled gradient echo sequence was used to acquire anatomical data (matrix = 224 * 224, number of sagittal slices = 128 to 140 (to obtain full brain coverage), slice thickness = 1.2mm). Four images were discarded from the beginning of each EPI acquisition to allow for steady-state tissue magnetization.

2.5 Task design

A more detailed description of the task was previously published (Furey et al., 2015; Furey et al., 2008a). Briefly, during the scans, subjects performed a selective attention task. Two superimposed images of faces and houses were presented side by side. Subjects were cued to attend to one stimulus component (face versus house) and were instructed to perform a matching task. Every four to seven trials the subjects were cued to shift their attention from one stimulus component to the other. The faces expressed either happy or sad emotion and were processed either explicitly (during the ‘attention to faces’ portion of the task) or implicitly (during the ‘attention to houses’ portion of the task), thus creating four task conditions: attention to happy faces (AFh), attention to sad faces (AFs), attention to houses when faces were happy (AHh), and attention to houses when faces were sad (AHs). In the control conditions, the unattended stimulus component was phase scrambled—that is, the pictures retained properties such as saturation and light, but the pixels were scrambled so no object could be identified. This created three control conditions: happy faces on scrambled

house pictures, sad faces on scrambled house pictures, and houses on scrambled face pictures. Stimuli were presented for 2.5 seconds followed by a 1.5 second inter-trial interval. Reaction time and accuracy were recorded.

2.6 Behavioral data analysis

Reaction time data and accuracy data for MDD patients and healthy controls were determined for each task condition and compared using ANOVA. Patients' pre- and post-treatment performance was also assessed with ANOVA. Post-hoc *t*-tests were performed for significant interactions.

2.7 Imaging data analysis

BOLD data were pre-processed and analyzed using AFNI (Cox, 1996). Echo-planar images were aligned, slice timing corrected, smoothed, and normalized to the mean. Results of the statistical analyses were spatially normalized to the stereotaxic atlas of Talairach and Tournoux (Talairach and Tournoux, 1988). Regressors were created for each task component (AFh, AFs, AHh, AHs) as well as for the three control conditions. The multiple regression analyses (3dDeconvolve) of the BOLD signal were designed to exclude non-response trials. A standard atlas-based anatomical mask (see Figure 1) (Desikan et al., 2006) was used for the region of interest (ROI) analysis of the left and right amygdala. Mean BOLD activity estimate (Beta value) was extracted for each of the seven task conditions and averaged across ROIs: AFh, AFs, AHh, AHs, and the three control conditions, attention to faces (happy or sad) on phase-scrambled house or attention to houses on phase-scrambled faces. The mean BOLD signal for left and right amygdala was correlated with the magnitude of treatment response (percent change in score). Separate correlations were also performed with placebo response, and these were calculated in the same manner. Positive values represent percent improvement (drop in MADRS score) and negative values indicate worsening of depressive symptoms (increase in MADRS score) from baseline to post-scopolamine or post-placebo. Significance was defined as $p<0.007$ to account for multiple comparisons of the seven task conditions (0.05/7). BOLD signal estimate for healthy control subjects was calculated for conditions that correlated with treatment response in patients.

The magnitude of the BOLD signal in the task conditions that correlated with treatment outcome was then compared using one-way ANOVA between healthy control subjects, patients who subsequently responded to scopolamine (that is, who experienced a percent change on the MADRS > 50%), and patients who did not respond to scopolamine (those whose depressive symptoms were not reduced by at least 50% on the MADRS).

In addition, the post-scopolamine BOLD signal in the amygdala was measured for MDD patients (N=11). The BOLD signal values for conditions that might predict treatment response were compared between MDD patients after scopolamine treatment with baseline values from the healthy control subjects.

3. Results

3.1 Sample size and treatment outcome

The sample comprised 15 healthy control subjects (age 32.5±6.9, 9F/6M) and 14 MDD outpatients (age 31.1±9.8, 11F/3M). One healthy control subject was included in the imaging analysis but not in the behavioral analysis because of technical issues recording the responses; the partial data indicated acceptable performance accuracy.

Seven MDD patients responded to scopolamine by the end of the study and seven patients failed to reach this criterion and were considered non-responders. Responders and non-responders to scopolamine did not differ with regard to length of illness (responders: 12.86 yrs; SD=10.02 and non-responders: 14 yrs; SD=6.5; $p = 0.68$).

One patient responded to both placebo and scopolamine, and one patient who did not respond to scopolamine did not complete the placebo arm of the study.

3.2 Behavioral results

Subjects were included in the analysis if they completed a pre-treatment baseline scan with the acceptable level of performance accuracy set at 60% correct responses. Two ANOVA analyses were conducted to examine performance accuracy and reaction time (group * emotion (happy/sad) * condition (faces/houses)). The healthy control and MDD groups did not differ on task performance accuracy or reaction time ($F(1, 26) = 0.103$, $p > 0.05$). With regard to accuracy, significant main effects for attention ($F(1, 26) = 9.54$, $p < 0.01$) and for attention by emotion interaction ($F(1, 26) = 5.98$, $p = 0.02$) were observed across groups. Similarly, for reaction time, significant main effects for attention ($F(1, 26) = 23.46$, $p < 0.01$) and for attention by emotion interaction were observed ($F(1, 26) = 12.68$, $p < 0.01$). Both accuracy and reaction time effects were driven by more accurate and faster responses when matching faces rather than houses ($p < 0.01$). A significant three-way interaction between emotion, drug, and antidepressant response to scopolamine was observed in the MDD group for reaction time ($F(1,23) = 6.66$, $p = 0.03$). None of the post-hoc comparisons reached significance ($p > 0.05$). The full behavioral results are available in Supplemental Tables 1 and 2.

3.3 Imaging

All subjects who completed the tasks with the acceptable level of accuracy and who completed scanning without excessive motion (exceeding 1.5 mm) were included. The BOLD response recorded during the placebo lead-in scan during the attention to sad faces condition (AFs) correlated negatively with treatment response to scopolamine in the left amygdala ($r = -.72$, $p = 0.004$), and a trend was observed in the right amygdala ($r = -.55$, $p = 0.042$; Figure 2). In contrast, the BOLD signal in the amygdala recorded during attention to houses (AHh, AHs) or during the attention to happy faces condition (AFh) did not correlate with treatment outcome ($p > 0.1$).

Notably, for the MDD patients, no correlation was found between BOLD signal in the amygdala during any task condition and percent change in MADRS score from baseline to post-placebo infusion ($p>0.32$).

All subsequent analyses focused on the AFs condition because of the observed correlations with treatment response to scopolamine. The amygdala BOLD response at baseline showed a significant main effect for group (healthy controls, treatment responders, and treatment non-responders, one-way ANOVA, $F(2,26)=6.11$, $p=0.007$ and $F=4.24$, $p=0.025$ for left and right amygdala, respectively; see Figure 3). In post-hoc *t*-tests, BOLD activity differed between healthy controls and those MDD patients who responded to scopolamine in both the left ($t=2.38$, $p=0.03$) and right amygdala ($t=2.65$, $p=0.02$). In addition, the comparison between treatment responders and non-responders was significant in both the left ($t=-4.21$, $p=0.001$) and right amygdala ($t=-2.79$, $p=0.02$). Both the healthy control subjects and the treatment non-responders had higher levels of activation than the treatment non-responders. No significant difference was observed between non-responders and healthy controls ($p>0.15$). Lastly, baseline measures for the healthy control subjects were compared to the patients' post-scopolamine BOLD activity; no differences were observed between healthy controls, MDD responders, and MDD non-responders to scopolamine, (one-way ANOVA, $F(2,23)=0.09$, $p=0.91$ for the left amygdala, and $F(2,23)=1.15$, $p=0.33$ for the right amygdala).

4. Discussion

This study demonstrated that, prior to treatment, neural activity in the amygdala during the explicit processing of sad faces correlated with magnitude of antidepressant response to the muscarinic antagonist scopolamine in MDD patients. The observed effect was uniquely associated with attentional focus on faces (specifically, under the AFs condition); when the same sad face stimuli were processed implicitly—that is, they were present but attention was directed towards the house component (AHs)—BOLD signal did not correlate with treatment outcome. Furthermore, processing of sad faces without competing meaningful stimuli (as in the control condition—the phase scrambled house component) was not related to treatment outcome with scopolamine. This suggests that the link between processing of sad emotion and the antidepressant effects of scopolamine was only present during a cognitively demanding condition requiring the disambiguation of a double exposed image with the focus on face.

Interestingly, previous studies that used conventional antidepressant drugs observed post-treatment changes in the amygdala specifically related to the processing of sad faces (Arnone et al., 2012; Fu et al., 2004; Victor et al., 2010), although at least one study observed that amygdalar response was associated with treatment outcome regardless of whether faces were happy, sad, or fearful (Canli et al., 2005). That study investigated no specific treatment, but instead controlled for medication status; thus, the observed greater responsiveness of the amygdala to emotional facial stimuli during a task of gender determination may have been a marker of better overall prognosis. The task demands were relatively low—unobscured faces appeared one at a time, and the emotion type was sustained over time (blocked). In contrast, we used a cognitively demanding task that

required the disambiguation of a complex stimulus that included emotional expression; the goal of the task was to identify a biomarker that might be specific to antidepressant response to scopolamine. The task had previously been shown to be modulated by the manipulation of cholinergic transmission (Furey et al., 2008a). We observed that abnormally low amygdalar activity during selective attention to face stimuli displaying sad emotion was related to effective antidepressant response to scopolamine (Figure 3).

BOLD activity during the explicit processing of the sad faces condition (AFs) also differentiated treatment responders from both treatment non-responders and healthy subjects. Because the selective attention process is cholinergically mediated (Bentley et al., 2003; Furey et al., 2008b), and because an intact cholinergic system is required to increase neural responsivity to task-relevant stimuli, attenuating a cholinergic deficit could potentially normalize neural activity in relevant neural structures. Our results may thus indicate that the treatment responders had some degree of cholinergic impairment at baseline that was corrected by scopolamine; our non-responders may have had no such deficit.

It should be noted that hypoactivity—rather than hyperactivity—in the amygdalar response to sad faces was the processing deficit in our study, and that this deficit was no longer discernable in treatment responders post-treatment. This finding and its relevance to treatment response may be interpreted in the context of cognitive demands and neural efficiency. Our processing task required disambiguating facial stimuli from the competing house stimuli and evaluating the faces for similarity. When faces were sad, the depressed patients with the cholinergic deficit may have identified these more efficiently than treatment non-responders and control subjects. This selectivity—which occurred solely during the processing of sad stimuli— would be consistent with enhanced cholinergic activity and a mood congruent processing advantage. To the best of our knowledge this is the first study relating hypoactivity to sad faces with greater antidepressant treatment response. However, Williams and colleagues (2015) reported pre-treatment hypoactivity to subliminally processed happy and threatening (fearful, angry) faces as a general biomarker of response to selective serotonin reuptake inhibitors (SSRIs) as well as serotonin norepinephrine reuptake inhibitors (SNRIs), as well as modification of that response post-treatment (Williams et al., 2015).

In addition to there being no difference between responders and non-responders post-scopolamine treatment, both patient groups did not differ from the baseline values of healthy controls, potentially suggesting that scopolamine selectively enhanced neural responsivity in the amygdala of treatment responders. Larger sample sizes are needed to explore putative differences between healthy controls and MDD patients who responded to scopolamine, as the lack of significance may be due to high variance (Supplemental Figure 1).

Our study has several limitations. First, the sample size was small, particularly with regard to our ability to compare patients post-scopolamine; nevertheless, such sample sizes are common in pharmacoimaging studies. Second, our primary findings were associated with pre-treatment baseline measures and assume good reproducibility of the BOLD signal; however, some investigators have raised concerns regarding the reliability of the BOLD signal (Boubela et al., 2015). Nevertheless, studies have found that emotional stimuli evoke

a consistent pattern of responsivity over repeated sessions (Johnstone et al., 2005). Third, we limited the between-group analysis to the conditions found to significantly correlate with treatment response and, hence, do not address possible differences between healthy control subjects and MDD patients in stimulus processing, including happy emotions. Finally, because our post-hoc, between-group analyses were not corrected for multiple comparisons, they are by their nature exploratory.

Despite these limitations, the present study identified a pre-treatment neurobiological difference between MDD responders and non-responders to scopolamine consistent with previous research that similarly found distinct patterns of amygdalar responsivity to sad face processing in MDD samples. In our study, baseline responsivity to sad facial stimuli observed under a cognitively demanding task—specifically, engagement in active selective attention when two meaningful stimuli competed and when one of these stimuli also contained negative valence—may potentially represent a measure indicating cholinergic dysfunction. The neural correlates of stimulus processing in patients with depression may indicate an underlying neurochemical dysfunction, and the pattern of that dysfunction may provide insight into who will most likely respond to treatment. Cholinergic hyperactivity has been identified as a feature of mood disorders (Janowsky et al., 1974; Janowsky et al., 1972). The hypothesized overactivity of cholinergic transmission might be reflected by automatic processing bias to emotion in nonattended stimuli (Furey et al., 2015), where higher neural activity in the middle occipital cortex in response to sad relative to happy faces was associated with better clinical response. Conversely, higher neural activity in the subgenual anterior cingulate cortex in response to happy vs sad faces was associated with greater symptom improvement. The condition of explicit processing of faces with sad emotion attenuated amygdala response at baseline only in treatment responders, suggesting that focal attention in this condition did not engage the amygdala in emotion processing, possibly because of the ease of the mood congruent, task-driven processing. Such a complex cognitive probe may engage the amygdala in seemingly counterintuitive fashion—signal to noise ratio would be enhanced (with a focus on emotion as a normative response)—but also decreased, making it more efficient and possibly easier to detect in those with overactive cholinergic transmission.

Critically, the extant literature broadly reflects highly variable findings with regard to the concept of illness or response markers (Miller and O'Callaghan, 2013). This variability is likely related to true biological differences within the population under study. The search for biomarkers of response centers around the expectation that different biological features likely separate population subtypes, where different biological subtypes will respond differently to antidepressant treatment options (Zarate et al., 2013). Here, we suggest that those patients with a more muted response to sad faces are also more likely to have an antidepressant response to scopolamine. Moreover, looking selectively at treatment non-responders, we observed that this subset of patients may reflect the more typical or expected pattern of increased amygdala response to sad faces. Thus, our findings may suggest that amygdalar response to sad faces identifies a subpopulation of MDD patients who will preferentially respond to scopolamine.

In the study by Furey and colleagues (2015), a processing bias was estimated from BOLD responses to happy and sad faces, and this processing bias correlated with treatment outcome (Furey et al., 2015). As these earlier findings implicated both occipital and prefrontal cortical areas, the authors proposed that emotion processing biases were reflected in networks, and that network dysfunction might reflect subsequent treatment response. The amygdala is part of the network of regions responding to emotional facial stimuli, and amygdalar activity is a component of the full network response. In this capacity, the finding that the magnitude of response to sad faces is related to treatment outcome is wholly consistent with the results obtained by Furey and colleagues. As networks modulate across regions in positive and negative directions, the absolute direction of correlation is less important than the presence of the correlation. However, additional research is needed to validate the biomarker identified in this study.

The results further suggest that individuals with MDD who display impaired amygdalar response to sad face stimuli under selective attention conditions may be good candidates for treatment with scopolamine. Again, replication of this result in an independent and larger subject sample is needed to definitively show the utility of this measure as a biomarker of treatment response.

Finally, it should be noted that this biomarker may be uniquely sensitive to cholinergic function and specific to treatment with scopolamine; thus, future studies should investigate post-scopolamine change in neural activity. Such studies should also expand the search for biomarkers of functional deficits related to specific neurotransmitter systems and examine neural changes following successful treatment with a modulatory agent targeting the affected pathway. Ultimately, the identification of specific biomarkers will help clinicians narrow treatment choices to those most likely to attenuate disease symptoms in biologically defined subgroups of MDD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest and Role of Funding Source

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Highlights

- Identifying biomarkers of antidepressant response may improve patient outcomes
- Rapid-acting scopolamine may work by attenuating an overactive cholinergic system
- Amygdalar activity correlates with post-scopolamine antidepressant response

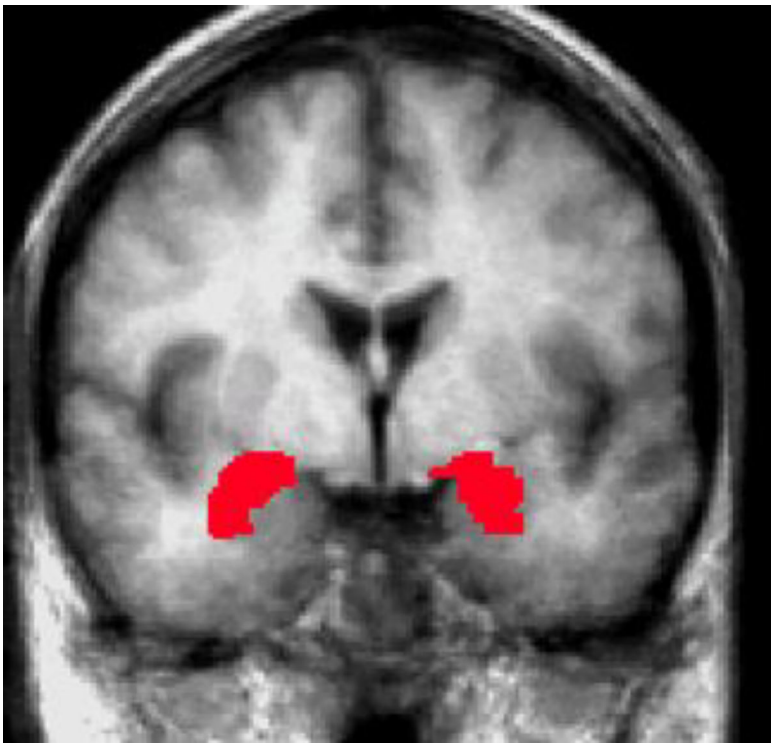

Figure 1.
Anatomically defined left and right amygdala region of interest (ROI) placement.

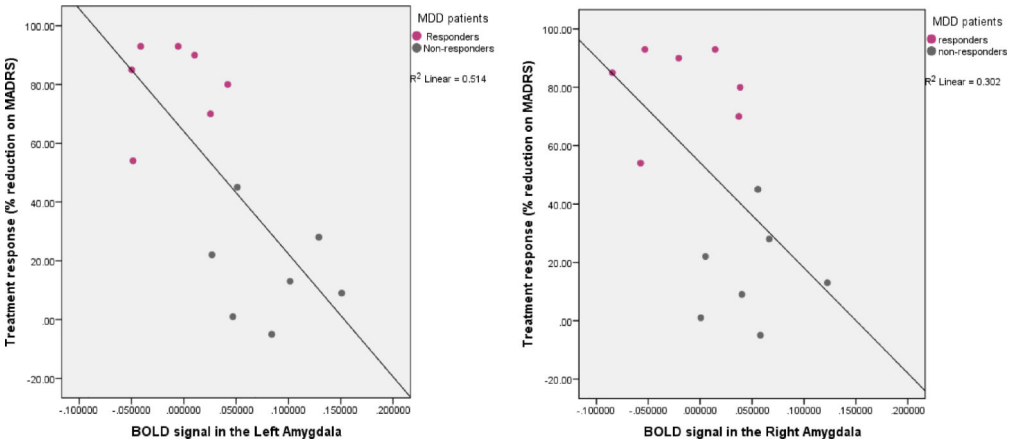

Figure 2.

Amygdalar activity and treatment response to scopolamine. Pre-treatment activity during explicit processing of sad faces (AFs) correlated negatively with antidepressant response (percent reduction of symptoms relative to baseline, represented by positive numbers) to scopolamine, $r = -.72$, $p = 0.004$ in the left amygdala (a) and $r = -.55$, $p = 0.04$ in the right amygdala (b).

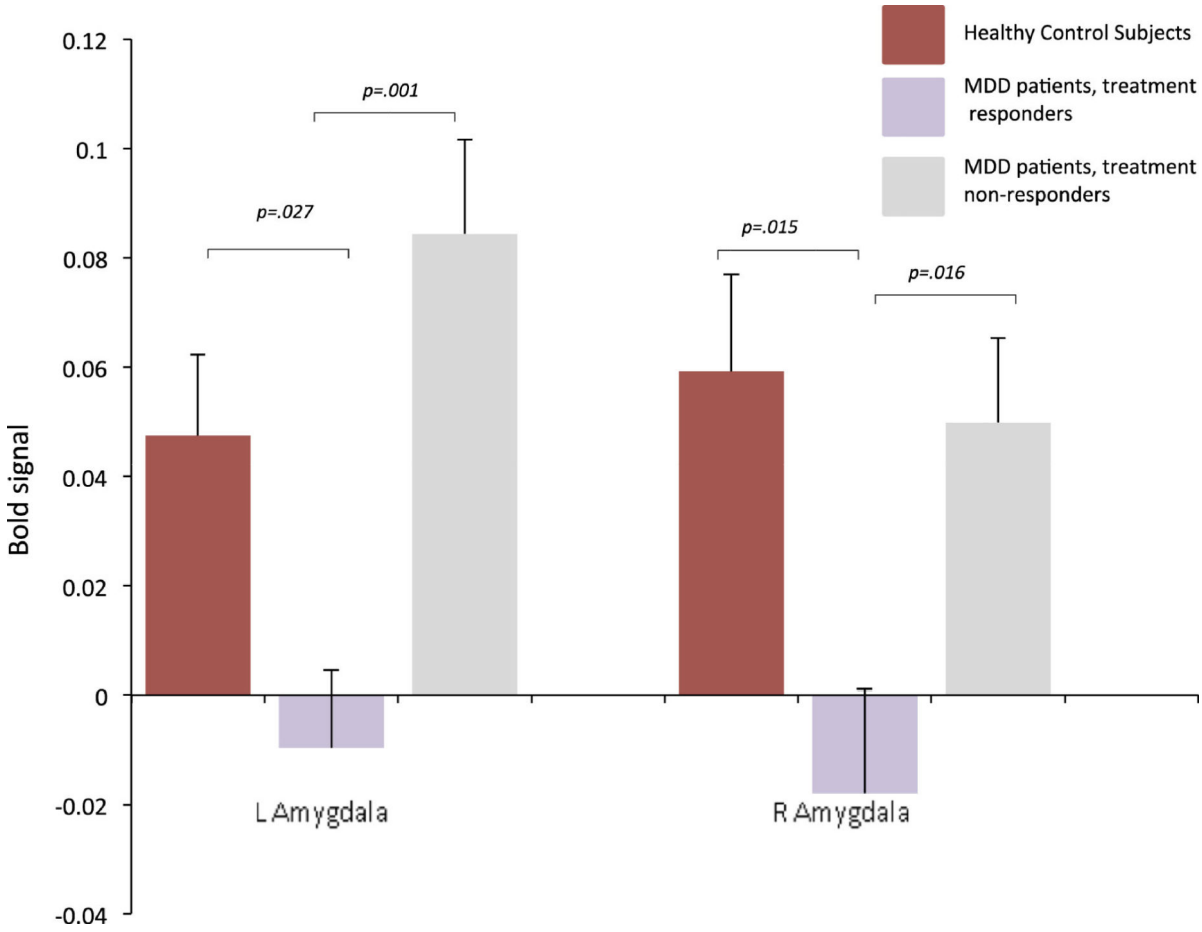

Figure 3.

Baseline amygdalar activity in healthy control subjects (N=14), subjects with major depressive disorder (MDD) who responded to subsequent scopolamine treatment (N=7), and MDD subjects who did not respond to scopolamine treatment (N=7). Treatment responders differed significantly from healthy subjects and treatment non-responders in both the left (p<0.03) and right (p<0.02) amygdala.