ARCHIVAL REPORT

The Effects of Psychotherapy on Neural Responses to Rewards in Major Depression

Gabriel S. Dichter, Jennifer N. Felder, Christopher Petty, Joshua Bizzell, Monique Ernst, and Moria J. Smoski

Background: Unipolar major depressive disorder (MDD) is characterized by anomalous neurobiological responses to pleasant stimuli, a pattern that may be linked to symptoms of anhedonia. However, the potential for psychotherapy to normalize neurobiological responses to pleasant stimuli has not been evaluated.

Methods: Twelve adults with and 15 adults without MDD participated in two identical functional magnetic resonance imaging scans that used a Wheel of Fortune task. Between scans, MDD outpatients received Behavioral Activation Therapy for Depression, a psychotherapy modality designed to increase engagement with rewarding stimuli and reduce avoidance behaviors.

Results: Seventy-five percent of adults with MDD were treatment responders, achieving post-treatment Hamilton Rating Scale for Depression score of six or below. Relative to changes in brain function in the matched nondepressed group, psychotherapy resulted in functional changes in structures that mediate responses to rewards, including the paracingulate gyrus during reward selection, the right caudate nucleus (i.e., the dorsal striatum), during reward anticipation, and the paracingulate and orbital frontal gyri during reward feedback. There was no effect of diagnostic status or psychotherapy on in-scanner task-related behavioral responses.

Conclusions: Behavioral Activation Therapy for Depression, a psychotherapy modality designed to increase engagement with rewarding stimuli and reduce avoidance behaviors, results in improved functioning of unique reward structures during different temporal phases of responses to pleasurable stimuli, including the dorsal striatum during reward anticipation.

Key Words: Cingulate gyrus, depression, fMRI, orbital frontal cortex, reward, striatum

Neuroimaging research into the neurobiology of unipolar major depressive disorder (MDD) has established a model of the pathophysiology of MDD that implicates impaired corticolimbic functioning in the onset and maintenance of depressive symptoms (1–4). Most of this research has focused on either: 1) resting state data (5–7), or 2) the processing of unpleasant stimuli (8–11). However, far less research has focused on processing pleasant events, and thus the biological basis of anhedonia in MDD is less well-understood. Furthermore, the potential for change in regional neuroanatomical functioning in response to pleasant events after antidepressant treatment has not been evaluated.

Functional neuroimaging studies of responses to pleasant stimuli in MDD implicate the striatum (12–14) as well as a host of other reward structures, including the medial prefrontal cortex (15,16), the pregenual and subgenual anterior cingulate, and the medial frontal gyrus (17,18). However, these studies have assessed responses to the presentation of pleasant stimuli, whereas nonclinical neuroimaging studies have documented that certain reward structures and the striatum in particular respond preferentially to anticipation of pleasant stimuli (19–21).

To date, four studies of reward processing in MDD have investigated responses to different temporal phases of reward processing. Forbes *et al.* (22) reported that children with MDD demonstrated decreased orbitofrontal cortex, anterior cingulate, amygdala, and caudate activation during both reward anticipation and feedback but found little evidence of differential effects contingent on the temporal phase of the response. Additionally, MDD participants had a range of comorbid disorders. Forbes *et al.* (23) reported reduced striatal activation in depressed adolescents during reward anticipation and reward outcome that predicted positive affect in natural environments. Knutson *et al.* (24) employed a monetary incentive delay task and found no striatal activation differences between adult groups during reward anticipation but increased anterior cingulate activation during anticipation of monetary gains in MDD.

Finally, our own research group reported (25) anomalous neural responses during reward selection, anticipation, and feedback in adults with MDD with a Wheel of Fortune (WOF) task (19). The MDD group was characterized by reduced striatal activation during reward selection, anticipation, and feedback; by hyperresponsivity in orbitofrontal cortex during reward selection; and by decreased activation of the middle frontal gyrus and the anterior cingulate during reward selection and anticipation. This study demonstrated unique regions of functional deficits in MDD during different temporal phases of reward processing and, most critically, that striatal dysfunction in MDD was evident during the anticipatory phase.

There is a growing neuroimaging literature evaluating response to antidepressant interventions in MDD. Antidepressant medications increase glucose metabolism in the dorsolateral, ventrolateral, and medial aspects of the prefrontal cortex and the anterior cingulate cortex (26) as well as the striatum (27–30), the insular cortex (31), extrastriate cortex (32), and the caudate

From the Department of Psychiatry (GSD, JB); Neurodevelopmental Disorders Research Center (GSD, JNF, JB), University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina; Duke-UNC Brain Imaging and Analysis Center (GSD, JB); Department of Psychiatry and Behavioral Sciences (GSD, MJS), Duke University Medical Center; Mental Illness Research Education and Clinical Center (CP), Durham VA Medical Center, Durham, North Carolina; and the Mood and Anxiety Disorders Program (ME), National Institute of Mental Health/National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland.

Address correspondence to Gabriel S. Dichter, Ph.D., Department of Psychiatry, University of North Carolina School of Medicine, CB# 3366, 101 Manning Drive, Chapel Hill, NC 27599-3366; E-mail: dichter@med.unc.edu.

Received Jan 30, 2009; revised Jun 24, 2009; accepted Jun 24, 2009.

0006-3223/09/$36.00
doi:10.1016/j.biopsych.2009.06.021

nucleus and thalamus (33). Although less research has examined functional neural responses after psychotherapy, available data suggest that psychotherapy predicts metabolic changes in the cingulate and frontal cortices (8,34–37), basal ganglia (38), and hippocampus (39). Furthermore, a consistent pattern has emerged that antidepressant response is predicted by pretreatment functioning of the anterior cingulate, shown in studies of response to sleep deprivation (40–43), psychopharmacologic intervention (1,26,44–46), and cognitive behavioral therapy (34,35). However, no study has examined brain activation changes after antidepressant treatment (medication or psychotherapy) with tasks sensitive to the chronometry of reward responses. This omission is striking, given that reward anticipation may represent the most valid method to assay treatments that putatively improve anhedonia (47).

The present investigation evaluated the effects of Brief Behavioral Activation Treatment for Depression (BATD) (48) on brain activation with a WOF task that dissociates reward choice selection, anticipation, and feedback. Because of linkages between animal models of MDD, decreased reward-seeking behaviors, and functioning of the striatum (49–51), we had particular interest in psychotherapy-induced changes in striatal functioning during reward anticipation. We hypothesized that psychotherapy would cause decreased depressive symptoms accompanied by increased striatal functioning. We further hypothesized that psychotherapy would impact the activity of regions shown to have aberrant functioning pre-psychotherapy in a variety of studies, including the subgenual anterior cingulate cortex during reward decision-making, the striatum during reward anticipation, and the middle frontal gyrus and the orbitofrontal gyrus during reward feedback (24,25).

Methods and Materials

Participants

Inclusion/exclusion criteria and Time 1 functional magnetic resonance imaging (fMRI) results have been reported previously (25). After a complete description of the study to participants, written informed consent was obtained. Sixteen depressed (nine women) and 15 nondepressed (nine women) participants enrolled in the study. One depressed woman withdrew after her initial interview. Not included in the MRI analyses are the data from one depressed woman who had frank abnormalities in brain anatomy. Two depressed participants did not return for psychotherapy sessions after the first imaging session. Thus, the final sample was 12 depressed (six women, average age 39.0 years ± 10.4 years) and 15 nondepressed (nine women, average age 30.8 years ± 9.6 years) participants. Groups did not differ in age (MDD mean [± SD] = 34.8 [14.3] years, range = 23–53; nondepressed mean [± SD] = 30.8 [9.7] years, range = 21–43), estimated verbal IQ (52) (MDD = 112.8, nondepressed = 117.7), smoking status (all nondepressed participants were nonsmokers, all but two depressed participants were nonsmokers), the number of days between scans (MDD mean [± SD] = 102.2 [15.4] days; nondepressed mean [± SD] = 102.5 [10.1] days), p values $>$ .05, or gender distribution [$\chi^2(1) = .99$, $p > .32$] but differed in socioeconomic status (53) (MDD mean [± SD] = 36.8 [12.0]; nondepressed mean [± SD] = 45.8 [2.4].

BATD

The MDD outpatients received an average of 11.4 (SD = 2.0; range: 8–14) weekly sessions of BATD. Additional sessions (up to a total of 15 sessions; average of 1.4/participant) were subsequently offered to help participants consolidate therapeutic gains and transition to follow-up care, as necessary. Early responders were given the option to end therapy after eight sessions, and nonresponders received the maximum number of sessions before being referred for additional treatment.

BATD is a structured and validated psychotherapy method designed to increase engagement with functional, potentially rewarding behaviors and reduce avoidance behaviors (48). Patients are encouraged to expose themselves to reinforcing situations and to inhibit the behavioral withdrawal often characteristic of MDD (54). Behavioral activation interventions were recently shown to be as effective as Cognitive Behavioral Therapy or paroxetine in reducing depressive symptoms in a large-scale clinical trial (55).

fMRI Task

The WOF task is a computerized two-choice decision-making task involving probabilistic monetary outcomes (Figure 1). Participants were instructed that they would take home up to $45 of the money they won ($40 minimum) and that they should try to win as much money as possible. On each trial, participants first chose between two options, each with an assigned probability of winning a certain amount of money. If correct, the participant won the designated amount; if not, the participant won nothing.

Three conditions were used (56): selecting between: 1) a 10% chance of winning $7 and a 90% chance of winning $1; 2) a 30% chance of winning $2 and a 70% chance of winning $1; and 3) two 50% chances of winning $2. The task was originally designed so that all possible options would be selected by most participants. Each of the three monetary conditions was displayed as a two-slice WOF, with each slice representing a distinct option. The area of the slice matched the likelihood of winning (e.g., 10%) an explicit amount of money (e.g., $7). A control condition included all the sensory-motor attributes of the monetary conditions but lacked decision-making, anticipation of a gain, and response to gain. This control condition consisted of a WOF, but this wheel was of a single color (i.e., no slices).

During the "selection" phase, participants viewed one type of wheel and were asked to select either the blue or the magenta slice by pressing the button corresponding to where the color was located (i.e., right or left). During the "anticipation" phase, participants continued to view the wheel while a six-point rating scale appeared on the screen to prompt them to rate their level of confidence of winning (1 = unsure, 6 = sure). During the "feedback" phase, participants were shown the dollar amount won ($0 if not won), the cumulative dollar amount, and a six-point pictorial rating scale along which they rated how they felt (1 = neutral, 6 = very happy, if a win trial; 1 = very sad, 6 = neutral, if a loss trial). During the control condition, participants made button responses in a random fashion during all phases of the task. All responses were recorded on two four-key button-boxes, with three buttons/hand. This version of the task is identical to that described in Ernst *et al.* (19), except the anticipation and feedback phases included six instead of five behavioral response options.

Participants completed four runs of 46 trials that lasted approximately 12 min each. Each trial lasted between 10.5 sec and 14.5 sec and was composed of three phases: selection (3 sec), anticipation (jittered between 3.5 sec and 7.5 sec), and feedback (4 sec). Intertrial intervals were 1 sec–8 sec (i.e., the intertrial interval was jittered). Selection-phase responses were given with the right hand. Stimuli were presented with Eprime presentation software (Psychology Software Tools, Pittsburgh,

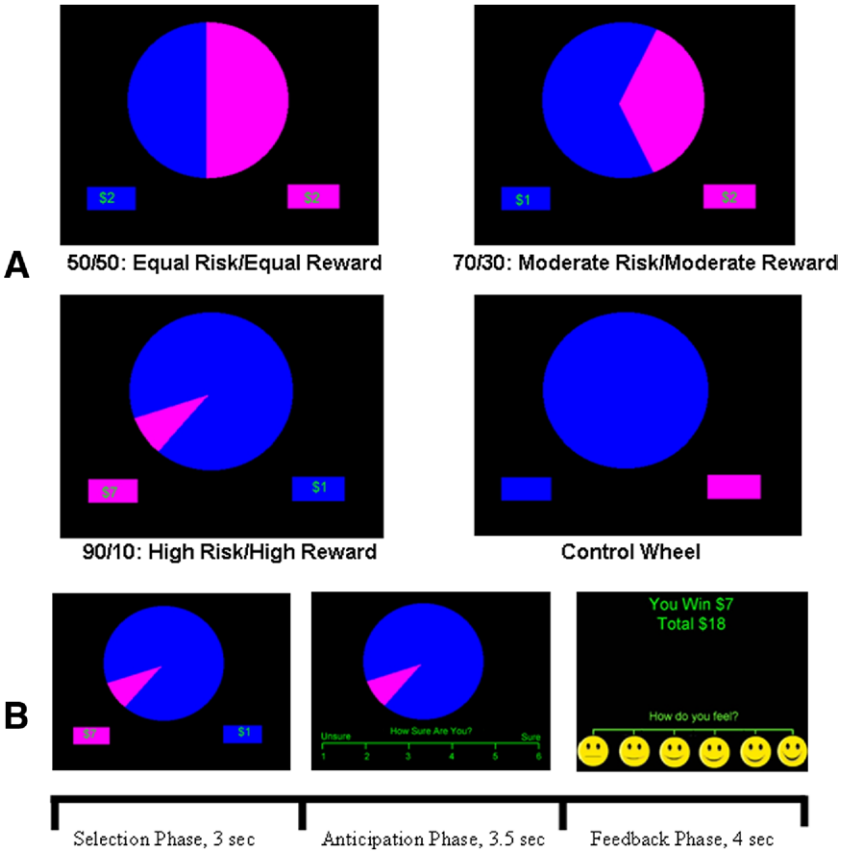

Figure 1. The wheel of fortune task; (**A**) the four different wheel types; (**B**) the timing of three task processes (i.e., reward selection, reward anticipation, and reward feedback).

Pennsylvania) and displayed through magnet-compatible goggles (Resonance Technology, Northridge, California).

Imaging Methods

Scanning was performed on a General Electric 4T LX NVi MRI scanner system equipped with 41 mT/m gradients (General Electric, Waukesha, Wisconsin). A quadrature birdcage radio frequency head coil was used to transmit and receive. A high-resolution T1-weighted image with 68 slices was acquired with a three-dimensional fast spoiled gradient recalled pulse sequence (repetition time = 500 msec; echo time = 20 msec; field of view = 24 cm; image matrix = 256 × 256; voxel size = 1.67 mm^3) and used for coregistration with the functional data. This structural image was aligned in a near axial plane defined by the anterior and posterior commissures. Whole brain functional images were acquired with an echo planar imaging pulse sequence sensitive to blood oxygenation level-dependent contrast (repetition time, 1500 msec; echo time, 31 msec; field of view, 24 cm; image matrix, 64 × 64; α = 62°; voxel size = 53.4375 mm^3; 34 axial slices). Functional images were aligned similarly to the T1-weighted structural image. A semiautomated high-order shimming program ensured global field homogeneity.

The primary neuroimaging analysis was to evaluate voxels that revealed significant 2 (Group: MDD, nondepressed) × 2 (Time: Time 1, Time 2) interactions on contrasts of interest. Activation values were uncorrected and combined with a cluster extent threshold of eight uninterpolated voxels (Supplement 1 provides a fuller description of these analyses). For the selection and anticipation phases, monetary and control trials were compared; for the feedback phase, win and loss feedback trials were compared separately to control feedback trials. Because voxels corresponding to significant interactions might reflect increased, decreased, or unchanged signal intensity in the MDD group relative to change in the nondepressed group, whole-brain analyses were followed by two-tailed within-groups *t* tests (α = .05) of changes in signal intensity in voxels identified by the interaction test described in the preceding text. In this manner, statistical tests of fMRI changes due to psychotherapy were restricted to voxels with significant interaction effects. This approach allows a reduction in the number of post hoc statistical tests performed. Activation localizations were based on Harvard-Oxford cortical and subcortical structural probabilistic atlases as implemented in FSLView v3.0. (http://www.fmrib.ox.ac.uk/fsl/fslview/index.html).

Results

Between-groups tests of Time 1 data have been reported previously (25). Here, we focus on the critical group × time interaction effects.

Symptom Profiles and Psychotherapy Outcomes

Table 1 illustrates symptom profiles of participants at both time points. Group × Time tests yielded significant interaction effects in depressive symptoms measured by both the Hamilton Rating Scale for Depression (HAM-D) (57) and the Beck Depression Inventory (58) (*p* values < .0001), reflecting significant declines in both measures in the MDD group (*p* values < .0001). Two measures of symptoms of anhedonia, the Jackson Appetitive Motivation Scale (59) and the Behavioral Activation/Behavioral Inhibition Scale (60), did not show significant interactions.

Within the MDD group, HAM-D scores changed from 23.8 (SD = 2.3) at Time 1 to 8.7 (SD = 9.4) at Time 2 (*p* < .003).

Table 1. Demographic Data and Symptom Profiles of Participants at Both Time Points

	MDD (n = 12)		Control (n = 15)		Time 1 Group p	Time 2 Group p	MDD Time p	Control Time p	Group × Time p
	Time 1	Time 2	Time 1	Time 2					
HAM-D	23.8 (2.3)	8.7 (9.4)	.2 (.6)	.5 (1.1)	<.0001	.0002	<.003	.217	<.0001
BDI	27.1 (5.1)	11.6 (8.6)	.7 (1.2)	1.0 (1.4)	<.0001	<.0001	<.0001	.265	<.0001
JAM[a]	10.8 (5.1)	12.9 (4.8)	14.7 (2.4)	14.9 (2.8)	.016	ns	ns	ns	ns
BAS Drive[a]	8.7 (2.1)	9.5 (1.8)	10.5 (2.2)	11.1 (1.8)	.048	ns	ns	ns	ns
BAS Fun-Seeking[a]	9.1 (3.8)	10.5 (3.4)	11.3 (2.1)	11.3 (2.1)	.072	ns	ns	ns	ns
BAS Reward Responsiveness[a]	15.5 (2.2)	16.3 (2.2)	16.5 (1.7)	16.7 (1.9)	ns	ns	ns	ns	ns
BIS[a]	23.5 (4.2)	23.3 (4.0)	18.1 (2.0)	19.1 (3.1)	<.0001	.006	ns	ns	ns

Means (SDs) of demographic data and symptom profiles of participants at both time points. Time (1) Day of Pretreatment Scan; Time (2) Day of Post-Treatment Scan.

MDD, major depressive disorder; HAM-D, Hamilton Rating Scale for Depression (57), 17-Item Version; BDI, Beck Depression Inventory (58); JAM, Jackson Appetitive Motivation Scale (59); BAS, Behavioral Activation Scale; BIS, Behavioral Inhibition Scale (60).

[a]Data are missing for one depressed male participant at Time 1.

Seventy-five percent (9 of 12) of participants were responders, defined as Time 2 HAM-D scores of six or below, and 83% (10 of 12) of participants were partial responders, defined as Time 2 HAM-D scores of 10 or below.

WOF Outcome

Figure 2 depicts in-scanner WOF behavioral outcomes. All Group × Trial Type × Time interactions were not significant, p values > .10 (Supplement 1 provides a fuller description of these analyses).

WOF Imaging Data

Selection Phase. The top of Figure 3 depicts voxels with significant 2 (Group: Depressed, Nondepressed) × 2 (Time: Time 1, Time 2) interaction effects on the money versus control contrast during reward selection. Table 2 denotes all clusters showing significant interactions as well as the results of paired t tests on signal intensity differences between time points in the MDD group in clusters with significant interaction effects. Areas that showed increased activation in the MDD group after psychotherapy included the paracingulate gyrus (marginally significant at p = .06), the left putamen, the right supramarginal gyrus, and the left posterior temporal fusiform cortex. Areas that showed decreased activation in the MDD group, relative to baseline MDD scans, included the left amygdala, the left superior frontal gyrus, the left superior lateral occipital cortex, the left occipital pole, the left postcentral gyrus, the left precentral gyrus, the right supramarginal gyrus, and the right inferior temporal gyrus.

Anticipation Phase. The bottom of Figure 3 depicts voxels with significant 2 (Group: Depressed, Nondepressed) × 2 (Time: Time 1, Time 2) interaction effects on money versus control contrasts during reward anticipation. Table 3 denotes clusters showing significant group × time interactions as well at the results of paired t tests on signal intensity differences between time points in the MDD group in clusters with significant interaction effects. Areas that showed increased activation in the MDD group after psychotherapy included the left caudate, the anterior cingulate gyrus, the left middle and superior frontal gyri, the left lingual gyrus, the left lateral and superior-lateral occipital cortex, the left posterior parahippocampal gyrus, the right insular

Figure 2. Top left: percentage of high-risk selections (i.e., smaller pie slices) for the 10/90 and 30/70 conditions for both diagnostic groups at both time points. Top right: average confidence ratings (range = 1 to 6) for both diagnostic groups at both time points. Note that the unequal wheels are subdivided on the basis of selections on a trial-by-trial basis (i.e., "risky" or "safe" selections). Bottom left: ratings of feedback valence for win trials for both diagnostic groups at both time points. On win trails, the range and direction of the ratings were 1 = neutral, 6 = very happy, whereas on no-win trials, the range and direction of the ratings were 1 = very sad, 6 = neutral. Bottom right: ratings of feedback valence for non-win trials for both diagnostic groups at both time points. On win trails, the range and direction of the ratings were 1 = neutral, 6 = very happy, whereas on no-win trials, the range and direction of the ratings were 1 = very sad, 6 = neutral.

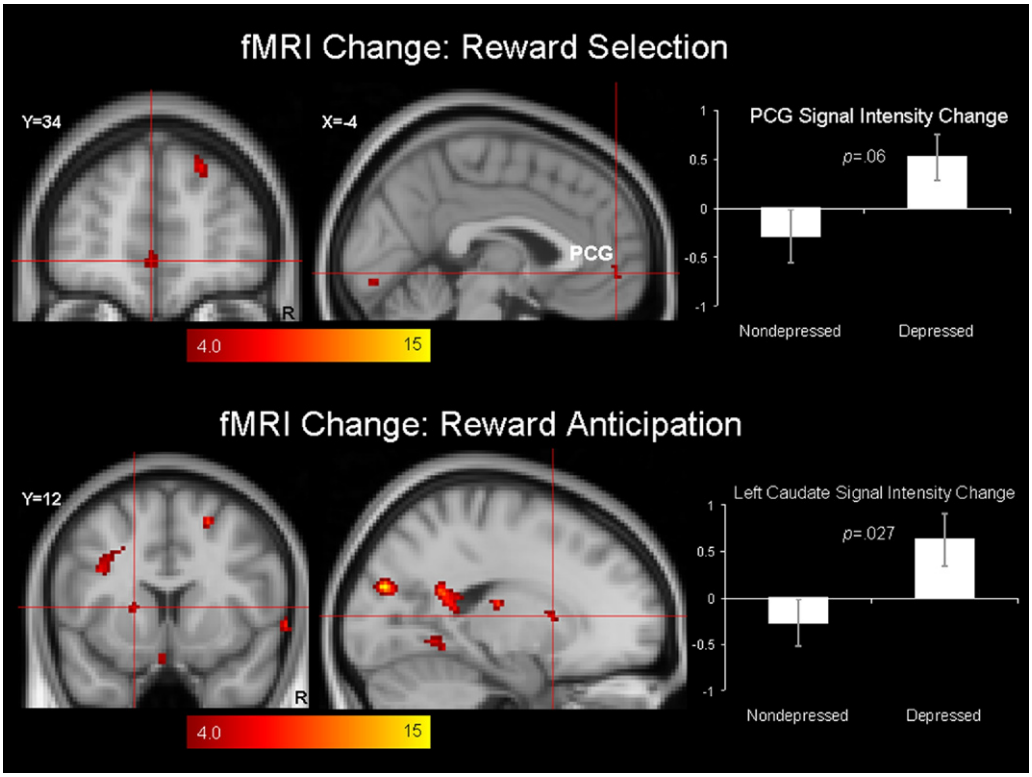

Figure 3. Reward selection (Top) and anticipation (Bottom) functional magnetic resonance imaging (fMRI) results (money vs. control). Activation images denote voxels with significant Group (depressed, nondepressed) × Time (Time 1, Time 2) interactions. Neurological convention (right on right) is used, and coordinates are in Montreal Neurological Institute space. Signal intensity is T statistic units. PCG, paracingulate gyrus.

cortex, right precuneus, right subcallosal cortex, right posterior temporal fusiform cortex, and bilateral precentral gyrus and temporal poles. Areas that showed decreased activation in the MDD group after psychotherapy included only the anterior inferior temporal gyrus.

Feedback Phase. Data from win and non-win trials were analyzed separately. Figure 4 depicts voxels with significant 2 (Group: Depressed, Nondepressed) × 2 (Time: Time 1, Time 2) interactions for win versus control (top) and non-win versus control (bottom) contrasts. Table 4 denotes clusters showing significant group × time interactions for these contrasts as well as the results of paired *t* tests on signal intensity differences between time points in the MDD group in clusters with significant interaction effects.

Areas that showed increased activation in the MDD group after psychotherapy during win feedback included the left planum temporale, right superior lateral occipital cortex, and right posterior temporal fusiform cortex. Areas that showed decreased activation after psychotherapy included the left posterior cingulate, left caudate, left postcentral gyrus, and left paracingulate gyrus. During non-win feedback, psychotherapy resulted in increased activation in left lingual gyrus, left angular gyrus, left anterior superior temporal gyrus, left orbital frontal cortex, left posterior superior temporal gyrus, right planum temporale, right posterior superior temporal gyrus, and right temporal pole. During non-win feedback, psychotherapy resulted in decreased activation in left putamen, left superior lateral occipital cortex, left precentral gyrus, and left anterior supramarginal gyrus in the MDD group.

Discussion

The goal of the present study was to elucidate BATD-related changes in brain function during reward processing in MDD. Given animal evidence indicating that a potential final common pathway of antidepressant treatments might be upregulation of mesolimbic systems (61) and because of linkages between mesolimbic functioning and reward anticipation (49,62), primary hypotheses concerned BATD-related changes in the striatum during reward anticipation.

Reward Selection

Analyses of selection data revealed a number of prefrontal regions with differential group responses over time, including the paracingulate gyrus, bilateral orbital cortex bilateral frontal pole, bilateral inferior frontal gyri, as well as limbic and occipital regions. Analyses of the effects of BATD in the MDD group revealed significant increases in functioning of the right paracingulate gyrus, the right posterior superior temporal gyrus, and portions of the left supramarginal gyrus. Increased activation in the right paracingulate gyrus, although only marginally significant, is particularly noteworthy, given that this region has been shown to predict treatment response in an array of functional and metabolic imaging paradigms (e.g., 2,63,64), although we note that this effect was a trend and should thus be interpreted with caution. Areas showing decreased activation after BATD included the right amygdala, a finding that was unexpected and bears replication. In a recent study using a modification of the WOF task, Smith *et al.*

Table 2. Clusters Showing Significant Group (Depressed, Nondepressed) × Time (Time One, Time Two) Interactions During Monetary Selections (Money vs. Control)

Region	Brodmann Area	Size (mm^3)	Z max	Coordinates			Effect of BATD: *t* (*p*)
				X	Y	*Z*	
Amygdala (Left)		208	9.1	−14	−8	−12	−3.64 (.001)
Caudate							
Left		160	6.63	−6	6	2	.47 (.64)
Right[a]		280	6.54	20	22	0	.66 (.52)
Right[a]		280	7.23	12	14	14	1.12 (.28)
Right[a]		336	8.02	10	10	2	1.30 (.21)
Frontal Gyrus (Inferior)							
Left	45	168	5.7	−46	30	8	.30 (.77)
Right	46	144	6.29	52	34	10	1.27 (.22)
Frontal Gyrus (Middle, Right)[a]	8	680	7.2	48	26	38	.79 (.087)
Frontal Gyrus (Superior)[a]							
Left	6	256	9.03	−12	30	58	−3.20 (.004)
Right	6	640	9.56	18	26	60	1.85 (.077)
Frontal Orbital Cortex							
Left[a]	47	384	8.01	−46	26	−8	1.03 (.31)
Right	47	176	7.96	36	28	−20	.51 (.62)
Frontal Pole[a]							
Left		160	6.86	−16	66	2	.33 (.74)
Left	9	664	14.46	−18	62	22	1.46 (.16)
Right	10	200	9.25	36	66	−4	.76 (.46)
Right	46	376	6.71	46	44	−2	1.08 (.29)
Right	9	1344	13.26	22	44	34	1.76 (.093)
Hippocampus (Right)	35	232	6.79	−30	−16	−24	1.74 (.096)
Intracalcarine Cortex (Right)	18	664	7.95	8	−82	2	−1.98 (.061)
Lateral Occipital Cortex (Superior, Left)	19	352	8.07	−16	−58	72	−2.12 (.046)
Lingual Gyrus							
Left	18	136	6.53	−2	−84	−8	1.10 (.28)
Right[a]	30	200	6.26	4	−62	6	−1.32 (.20)
Occipital Pole[a]							
Left	19	192	8.25	−16	−90	32	−2.51 (.02)
Left	17	200	8.16	−10	−90	12	−1.52 (.14)
Paracingulate Gyrus							
Left	32	256	5.72	−2	52	−2	1.98 (.06)
Left[a]	6	168	7.02	−10	14	50	1.18 (.25)
Parietal Lobule (Superior, Right)	7	152	8.31	12	−56	72	−1.49 (.15)
Postcentral Gyrus (Left)[a]	4	160	7.07	−56	−12	50	−3.12 (.005)
Precentral Gyrus							
Left[a]	6	120	8.06	−28	−8	50	1.14 (.27)
Left[a]	6	664	10.85	−12	−28	78	−3.00 (.007)
Right	6	352	8.57	26	−14	62	1.50 (.15)
Right	4	392	8.41	44	−10	44	1.13 (.27)
Precuneous (Left)[a]	23	504	7.87	−10	−64	18	−1.59 (.13)
Putamen (Left)		288	6.14	−32	−16	−8	2.56 (.018)
Supramarginal Gyrus							
Right	40	248	6.03	66	−28	34	2.21 (.038)
Left	40	288	7.32	−66	−38	38	−2.50 (.02)
Supramarginal Gyrus (Posterior, Right)[a]	13	480	5.98	50	−42	30	2.11 (.047)
Temporal (Posterior Inferior)							
Left	21	152	5.43	−60	−24	−6	2.03 (.054)
Right	20	208	7.42	46	−34	−18	1.21 (.24)
Left	20	488	7.64	−62	−18	−20	1.53 (.14)
Temporal Fusiform (Posterior, Left)[a]	36	448	6.75	−30	−34	−18	2.18 (.04)
Temporal Gyrus (Inferior)							
Right	20	168	6.38	50	−18	−34	1.63 (.12)
Right		920	8.73	42	−60	−2	−2.08 (.049)
Temporal Gyrus (Posterior Superior, Left)	42	152	6.77	−62	−28	6	2.05 (.052)

The last columns represent two-tailed paired *t* tests (i.e., Time 2—Time One) conducted on signal intensity *z* values from depressed participants on voxels identified as significant from the interaction tests. Positive *t* values denote a significant increase in the major depressive disorder (MDD) group after psychotherapy and that negative *t* values denote a significant decrease in the MDD group after psychotherapy.

BATD, Brief Behavioral Activation Treatment for Depression.

[a]Identifies overlap with regions that differentiated groups at baseline (25).

Table 3. Clusters Showing Significant Group (Depressed, Nondepressed) × Time (Time One, Time Two) Interactions During Monetary Anticipation (Money vs. Control)

Region	Brodmann Area	Size (mm^3)	Z max	Coordinates			Effect of BATD: *t* (*p*)
				X	Y	Z	
Caudate (Left)[a]		200	9.1	−18	−18	24	2.36 (.027)
Cingulate Gyrus (Left)		184	7.6	−10	0	40	2.13 (.045)
Frontal Gyrus (middle)[a]							
Left	9	200	7.3	−36	14	28	1.75 (.094)
Left	9	1,016	13	−28	26	28	3.48 (.002)
Left	6	184	7.1	−34	14	50	1.44 (.164)
Frontal Gyrus (Inferior, Left)	13	424	11	−44	24	4	.57 (.57)
Frontal Gyrus (Superior, Left)	6	544	10	−16	2	60	2.75 (.012)
Frontal Orbital Cortex							
Right	47	528	11	38	26	0	.92 (.37)
Left	47	136	7.5	−40	30	−10	.70 (.49)
Hippocampus (Left)[a]		408	10	−24	−24	−18	1.98 (.06)
Insular Cortex (Right)	13	368	11	36	−18	2	2.41 (.025)
Lingual Gyrus							
Right[a]	19	600	11	20	−56	−8	1.85 (.078)
Left	19	2104	11	−20	−56	−10	2.20 (.038)
Occipital Cortex (Lateral)							
Right	18	720	16	18	−82	24	2.01 (.057)
Left[a]	19	192	8.9	−34	−82	20	2.08 (.049)
Occipital Cortex (Superior, Lateral)							
Right	19	400	7.9	30	−74	44	1.88 (.073)
Left[a]	19	168	8	−30	−76	50	2.36 (.027)
Occipital Fusiform Gyrus (Left)[a]	18	168	7	−30	−70	−2	1.46 (.16)
Parahippocampal Gyrus (Posterior, Left)	35	168	8.2	−10	−40	−6	2.69 (.013)
Planum Polare (Right)	38	560	8	46	4	−12	2.00 (.058)
Postcentral Gyrus							
Right[a]	5	392	8.5	12	−40	58	1.45 (.16)
Left	5	1808	11	−8	−40	58	1.52 (.14)
Precentral Gyrus[a]							
Right		632	8.9	36	6	30	1.07 (.30)
Right	4	152	7.7	36	−12	44	2.75 (.012)
Left	4	208	12	−8	−30	74	1.69 (.10)
Left	6	152	6.5	−64	2	10	2.14 (.044)
Precuneous[a]							
Right	23	1448	11	18	−50	20	2.74 (.012)
Right	7	384	11	6	−52	68	−1.99 (.06)
Subcallosal Cortex (Right)	25	256	10	2	8	−18	2.22 (.037)
Supramarginal Gyrus (Anterior, Right)	40	168	8.5	60	−28	46	−1.92 (.068)
Supramarginal Gyrus (Posterior, Right)	41	256	7.6	42	−38	6	1.06 (.30)
Temporal Fusiform Cortex (Posterior)							
Right	20	888	11	40	−12	−24	3.59 (.002)
Right	36	200	8.2	26	−36	−18	1.03 (.31)
Temporal Gyrus (Anterior Inferior, Left)	20	192	7.4	−52	−10	−32	−2.87 (.009)
Temporal Gyrus (Anterior Middle, Right)	21	408	11	64	0	−16	−1.62 (.12)
Temporal Gyrus (Middle)							
Right	22	1392	10	60	−44	0	.38 (.71)
Left	21	128	7.9	−60	−18	−8	1.42 (.17)
Temporal Gyrus (Posterior Middle, Left)	20	136	7.3	54	−10	−20	.61 (.55)
Temporal Pole[a]							
Left	21	168	11	−58	6	−26	3.23 (.004)
Left	38	648	8.3	−44	4	−12	2.79 (.011)
Thalamus[a]		576	9.6	18	−20	14	1.82 (.082)

The last columns represent two-tailed paired *t* tests (i.e., Time 2—Time One) conducted on signal intensity *z* values from depressed participants on voxels identified as significant from the interaction tests. Positive *t* values denote a significant increase in the major depressive disorder (MDD) group after psychotherapy and that negative *t* values denote a significant decrease in the MDD group after psychotherapy.

BATD, Brief Behavioral Activation Treatment for Depression.

[a]Identifies overlap with regions that differentiated groups at baseline (25).

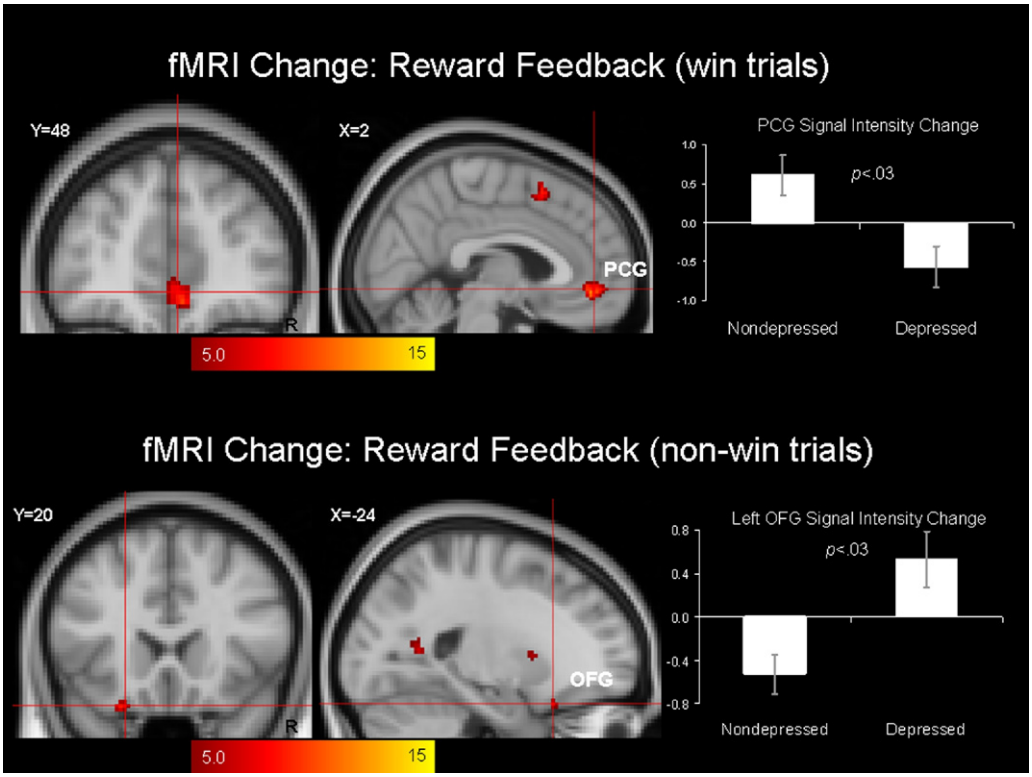

Figure 4. Reward feedback functional magnetic resonance imaging (fMRI) results for win (Top) and non-win (Bottom) trials, relative to control feedback. Activation images denote voxels with significant Group (depressed, nondepressed) × Time (Time 1, Time 2) interactions. Neurological convention (right on right) is used, and coordinates are in Montreal Neurological Institute space. Signal intensity is T statistic units. OFG, orbital frontal gyrus; PCG, paracingulate gyrus.

(65) reported that selection of relatively larger rewards activated the amygdala more strongly. Thus, in the present context, BATD treatment may have decreased perceived reward magnitudes. Alternatively, at baseline there may have been a mildly aversive quality to choosing a response for MDD participants due to the indecisiveness that defines the disorder (66), and BATD treatment may have diminished this aversive response. Other areas with decreased activation included the right superior frontal gyrus, right occipital cortex, right precentral gyrus, right precentral gyrus, left supramarginal gyrus, and left inferior temporal gyrus.

Reward Anticipation

Analyses of reward anticipation revealed differential group activation changes in the left caudate nucleus as well as a number of prefrontal regions, including the left cingulate gyrus, left frontal gyrus, and right insula. In line with predictions, analyses of change within the MDD group alone revealed that BATD produced significant increased activation in all these regions, including the left caudate nucleus (i.e., the dorsal striatum). These findings represent the first report of BATD-related increases in striatal activity during reward anticipation in MDD. A number of other areas demonstrated increased activity after BATD, including clusters in the left lingual gyrus, left occipital cortex, left parahippocampal gyrus, and right temporal cortex. No clusters showed decreased activation after BATD relative to changes in nondepressed group activations.

The BATD-related increased striatal activity during reward anticipation is consistent with preclinical and clinical models of MDD and anhedonia that implicate mesolimbic dysregulation in the pathophysiology of MDD (67–71) and is consistent with the conceptualization that the mechanisms of action of a range of antidepressant interventions is improved mesolimbic functioning (61,72–77).

Reward Feedback

A number of frontal and limbic regions showed decreased activation after BATD, including the right caudate nucleus and a large cluster in the left paracingulate gyrus. The decrease in right caudate activation after BATD treatment in the MDD group was surprising and bears replication. Caudate activation has been linked to learning cue-outcome contingencies (78,79), particularly when potential gains require a motor response (80,81). In the current study, although wins were probabilistically determined, they were not directly contingent on behavioral performance (e.g., reaction time or accuracy). Given that MDD is characterized by decreased estimation of contingencies between behaviors and outcomes (i.e., decreased positivity bias) (82), symptom remission might have normalized cue-outcome contingency estimations and thus caudate activation—this feature of the WOF might account for the apparent contradiction between the finding of decreased right caudate activation after BATD and other reports of reduced caudate activation in MDD (83,84), particularly given that groups did not differ at time 1 scans (23).

In contrast, analyses of non-win feedback revealed BATD-related increased activation in the right lateral orbitofrontal gyrus. We interpret this finding to reflect the role of the orbitofrontal cortex in modulating the affective evaluation of rewards, expectation, motivation, decision-making and goal-directed behavior (85–87), and more specifically to process violations of affective

Table 4. Clusters Showing Significant Group (Depressed, Nondepressed) × Time (Time One, Time Two) Interactions During Monetary Feedback

Region	Brodmann Area	Size (mm^3)	Z max	Coordinates			Effect of BATD: *t* (*p*)
				X	Y	Z	
Win Versus Control Trials							
Caudate (left)		1,128	11.41	−16	14	6	−2.16 (.042)
Cingulate gyrus (posterior, left)	30	120	7.11	−6	−52	18	−2.13 (.045)
Frontal gyrus (superior)							
Left	6	120	8.05	−12	20	66	−1.16 (.26)
Right	6	528	9.44	2	14	56	−1.3 (.21)
Insular cortex (left)	13	312	10.59	−34	8	−14	−1 (.33)
Intracalcarine cortex (left)	18	184	7.45	−8	−84	8	1.5 (.15)
Lingual gyrus (left)	18	248	10.05	−8	−70	0	1.95 (.064)
Occipital cortex (lateral superior, right)[a]	19	120	7.46	30	−72	34	2.64 (.015)
Paracingulate gyrus (right)	24	1968	11.51	4	44	−8	−2.32 (.03)
Parahippocampal gyrus (posterior, right)	37	536	10.34	18	−40	−16	1.65 (.11)
Planum temporale (left)	21	360	8.43	−40	−4	−18	2.55 (.018)
Postcentral gyrus (left)	2	160	7.64	−58	−18	42	−2.64 (.015)
Precentral gyrus (left)	6	376	12.85	−50	0	48	−1.29 (.21)
Supramarginal gyrus (posterior, left)	40	120	6.66	−64	−40	28	−1.45 (.16)
Temporal fusiform cortex (posterior, right)	20	544	12.83	40	−42	−26	2.24 (.036)
Temporal gyrus (middle posterior, left)	20	120	8.42	−64	−8	−24	−1.94 (.066)
Non-Win Versus Control Trials							
Angular gyrus (left)	13	1224	9.35	−48	−46	22	3.85 (.00087)
Frontal gyrus (inferior pars opercularis, right)	44	152	6.91	52	12	2	−.45 (.66)
Frontal gyrus (superior, right)	6	168	6.7	4	14	62	−1.66 (.11)
Frontal operculum cortex (right)	13	344	9.49	30	24	12	1.38 (.18)
Frontal orbital cortex							
Left	47	120	9.02	−24	20	−22	2.42 (.024)
Left	11	248	8.47	−26	42	−16	−1.71 (.1)
Lingual gyrus							
Left	18	208	7.14	−14	−72	0	2.83 (.0096)
Right[a]	19	160	8.15	10	−54	−8	1.55 (.14)
Occipital cortex (lateral superior)							
Left	18	424	10.72	−36	−68	22	1.82 (.082)
Left	19	344	9.7	−38	−78	34	−.18 (.86)
Left†	19	448	10.55	−36	−62	46	−2.46 (.022)
Occipital fusiform gyrus (Left)	19	168	9.85	−18	−80	−16	−1.09 (.29)
Parahippocampal gyrus (posterior, right)	36	288	8.28	18	−38	−16	1.03 (.32)
Parietal lobule (superior, left)	40	168	6.31	−36	−38	48	−1.88 (.073)
Planum polare (right)	13	960	9.65	44	−12	−6	3.6 (.0016)
Precentral gyrus							
Left	6	304	11.01	−50	2	48	−1.72 (.1)
Left	4	208	6.89	−38	−14	60	−2.1 (.048)
Right	4	200	8.75	8	−26	78	1.48 (.15)
Precuneous (left)	30	480	7.19	−22	−58	10	.62 (.54)
Putamen (left)[a]		176	7.27	−20	10	6	−2.03 (.055)
Subcallosal cortex (left)	25	152	8.56	−2	8	−6	.8 (.43)
Supramarginal gyrus (anterior, left)	40	208	10.06	−60	−32	44	−2.54 (.019)
Temporal gyrus (superior anterior)							
Left	21	184	6.72	−62	2	−12	2.33 (.029)
Left	21	1424	10.75	−56	−28	−2	2.61 (.016)
Left	42	208	9.25	−68	−20	6	1.5 (.15)
Right	21	200	7.69	56	−18	−8	1.89 (.072)
Right	22	688	10.79	54	−32	2	1.99 (.06)
Right	22	176	8.52	68	−36	12	2.46 (.022)
Temporal pole (right)[a]	38	1208	7.94	58	8	−18	3.12 (.005)

The last columns represent two-tailed paired *t* tests (i.e., Time 2—Time One) conducted on signal intensity *z* values from depressed participants on voxels identified as significant from the interaction tests. Positive *t* values denote a significant increase in the major depressive disorder (MDD) group after psychotherapy and that negative *t* values denote a significant decrease in the MDD group after psychotherapy.

BATD, Brief Behavioral Activation Treatment for Depression.

[a]Identifies overlap with regions that differentiated groups at baseline (25).

feedback expectancies (88). In other words, it might be the case that, at pretreatment, individuals with MDD expected not to win positive outcomes; however, BATD might have induced a change in this expectancy, such that not winning actually violated their expectancies to relatively a greater degree, prompting greater orbitofrontal cortex activation relative to their pretreatment scans.

Limitations and Conclusions

The finding of increased striatal activation during reward anticipation after BATD was localized to the dorsal striatum (i.e., caudate) rather than ventral striatum (i.e., nucleus accumbens). The nucleus accumbens is thought to mediate internal representations of predicted reward (79), whereas the caudate mediates linking rewards to behavior, reward-related decision-making, and encoding motivational feedback (89–92). The localization of activation to the caudate during reward anticipation may have been due to the WOF task: in contrast to other tasks used to assess reward anticipation (21,93), the WOF requires behavioral responses during all phases. This cognitive component might have prompted dorsal rather than ventral striatal responses (94).

The paracingulate cortex was reactive to BATD during two phases of reward responding (i.e., selection and win feedback). The localization of the paracingulate cortex across these three analyses (center of activations: +2, +52, −2; −4, 44, −8; and −2, 28, −10) overlaps the subgenual cingulate cortex (Brodmann area 25). Subgenual cingulate metabolism has been shown to predict response to a range of antidepressant interventions (both pharmacological and psychotherapy) (2,3,26,95), and subgenual cingulate reactivity to emotional stimuli has been implicated as a predictor of response to cognitive behavioral treatment in MDD with fMRI (37). This is in contrast to activation of medial aspects of the prefrontal cortex, which has been shown to predict response to sleep deprivation (43), and to activity of the rostral anterior cingulate cortex (approximately Brodmann areas 24 and 32), which has been shown to predict response to psychotropic medication in nonpsychotic depression with electromagnetic tomography (46,96). More broadly, the present study adds to the growing body of literature linking subregions of the anterior cingulate not only to the pathophysiology of MDD but to symptom remission in a variety of contexts.

We note that the present investigation did not include placebo or wait-list control groups, and thus it is unknown whether functional brain changes in the MDD group were due to the BATD intervention or to other variables, such as spontaneous improvement of symptoms over time. Additionally, many brain regions reactive to psychotherapy were clearly outside of reward structures. In this initial study, post hoc tests of the effects of BATD in the MDD group were not corrected for multiple comparisons, and thus findings regarding the effects of BATD warrant replication. We also note that the three types of reward trials (i.e., equal, moderate, and high-risk) were combined, and activation magnitudes of certain brain regions, such as the medial prefrontal cortex and the striatum, are known to vary parametrically with reward magnitudes (97,98). Finally, the relatively broader age range of the MDD group is an additional limitation of this study.

Although this preliminary investigation evaluated a relatively small number of patients, findings suggest that BATD results in recovery of function in brain regions related to processing rewards. By using a paradigm that allowed for an assessment of the different phases of responses to rewards, we were able to evaluate the effects of BATD on reward selection, reward anticipation, and reward feedback. Imaging data revealed that BATD normalized functioning in hypothesized areas, including the paracingulate cortex during reward selection, the striatum during reward anticipation, and the orbital frontal cortex during reward feedback. We conclude that functional changes within the reward network may be a valuable biomarker of the effects of antidepressant treatments in MDD.

We would like to thank Todd Harshbarger and Syam Gadde for assistance with image analysis; Prue Cuper, Shian-Ling Keng, and Justin Woodlief for assistance with data collection; and magnetic resonance imaging technologists Susan Music, Natalie Goutkin, and Talaignair Venkatraman for assistance with data acquisition. This research was supported by MH078145 to GSD. Assistance for this study was provided by the Neuroimaging Core of the University of North Carolina neurodevelopmental Disorders Research Center. The author MJS was supported by National Institute of Mental Health (NIMH) T32-MH070448, a National Alliance for Research on Schizophrenia and Depression (NARSAD) Young Investigator award, a career development award from Duke University Medical Center, National Institute of Child Health & Development (NICHD), K12 HD043446, and NIMH K23 MH087754. The author GSD was supported by Postdoctoral Research in Neurodevelopmental Disorders, NICHD T32-HD40127, NARSAD Young Investigator awards, a career development award from University of North Carolina-Chapel Hill, National Institutes of Health/National Center for Research Resources K12 RR023248, and NIMH K23 MH081285. The authors reported no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

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