ORIGINAL ARTICLE

Functional Neuroanatomical Substrates of Altered Reward Processing in Major Depressive Disorder Revealed by a Dopaminergic Probe

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Context: The pathophysiology of major depressive disorder (MDD) includes disturbances in several neuroanatomical substrates and neurotransmitter systems. The challenge is to elucidate the brain mechanisms of MDD behavioral symptoms, chiefly those of anhedonia.

Objectives: To visualize the neuroanatomical substrates implicated in altered reward processing in MDD, using functional magnetic resonance imaging in combination with a dopaminergic probe (a 30-mg dose of oral dextroamphetamine sulfate) to stimulate the brain reward system; and to test the hypothesis that a hypersensitive response to dextroamphetamine in MDD involves the prefrontal cortex and the striatum.

Design and Interventions: Among subjects with MDD and healthy control subjects, functional magnetic resonance imaging data were collected before and after single-blind administration of dextroamphetamine.

Setting: Subjects were recruited through local newspaper advertisements and by word of mouth.

Participants: Twelve depressed subjects (mean age, 34.83 years; male-female ratio, 6:6) met criteria for MDD according to the *DSM-IV*, were not taking antidepressants, and had no comorbid Axis I disorders. Twelve control subjects (mean age, 29.33 years; male-female ratio, 5:7) were healthy volunteers without a history of Axis I disorders.

Main Outcome Measures: Functional magnetic resonance imaging blood oxygen level–dependent activation was measured during a controlled task, and dextroamphetamine-induced subjective effects were assessed using the Addiction Research Center Inventory.

Results: Subjects with MDD had a hypersensitive response to the rewarding effects of dextroamphetamine (2-fold increase; $t_{21}=2.74$, $P=.01$), with altered brain activation in the ventrolateral prefrontal cortex and the orbitofrontal cortex and the caudate and putamen ($F_{1,44}=11.93$, $P=.001$).

Conclusion: Dopamine-related neuroanatomical substrates are involved in altered reward processing in MDD, shedding light on the neurobiology of the anhedonic symptoms in MDD and suggesting these substrates as future therapeutic targets.

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DEPRESSED MOOD AND markedly diminished interest in previously enjoyed activities (ie, anhedonia) are key characteristics of major depressive disorder (MDD). Accompanying symptoms required for the diagnosis, including guilt, anxiety, sleep disturbances, and appetite changes, and suicidal ideation render it challenging to elucidate the central neurobiological disturbances in this costly and prevalent mood disorder.[1,2] Previous studies[3-9] focused on characterizing brain mechanisms of the disorder and found that MDD is associated with altered brain activity in a wide network of regions, including the prefrontal cortex, limbic regions, and basal ganglia, and with abnormalities in several neurotransmitter and neuroendocrine systems, including serotonin, dopamine, norepinephrine, and the hypothalamic-pituitary-adrenal axis. The relationship between these neurobiological disturbances and the specific behavioral symptoms of depression remains unclear.

The brain reward system (BRS) can be defined as a neurobiological system that consists of extensive neural pathways that mediate reward behaviors such as pleasure and motivation.[10-12] Rewards serve to elicit approach and consummatory behaviors, increase the frequency and intensity of the behaviors, maintain the behaviors, prevent extinction, and induce subjective feelings of pleasure or positive emo-

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tional states.[13,14] In light of our previous findings,[15] we proposed that the BRS may represent a key neuroanatomical substrate of anhedonia, a core symptom of depression. The BRS of patients diagnosed as having MDD was examined in that study by measuring the behavioral response to dextroamphetamine sulfate. As cocaine, this psychostimulant induces dopamine release in the mesocorticolimbic dopamine system, a major pathway of the BRS,[16-18] and elicits well-detected and measurable rewarding effects (eg, stimulation and euphoria).[19] Depressed patients with severe symptoms reported significantly enhanced dextroamphetamine-induced rewarding effects, indicating altered reward processing in MDD.[15]

Scientists have recently begun to visualize the human neuroanatomical substrates associated with positive subjective experiences from reinforcing drugs such as nicotine and dextroamphetamine, as well as from financial and food rewards, using techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography.[14,20-27] The importance of mesocorticolimbic dopamine in the BRS has been observed in multiple studies with human subjects.[28-31] The primary objective of the present study was to use dextroamphetamine as a dopaminergic BRS probe in association with fMRI to isolate the neuroanatomical substrates of the altered BRS response in MDD. We chose this pharmacological fMRI[32] approach because of its superior temporal and spatial resolution for visualizing brain activity and because of its avoidance of use of radioactive tracers. We also tested the hypothesis that altered BRS activity is associated with a disruption in a spatially distributed network of dopamine-rich brain regions such as the striatum and the limbic and prefrontal cortical regions.

METHODS

PARTICIPANTS

The inclusion criteria for the MDD and control groups were age between 18 and 65 years, willingness to participate, and ability to provide signed informed consent. The protocol was approved by the research ethics board of the Sunnybrook and Women's College Health Sciences Centre. Subjects were excluded if they had a current or past cardiovascular disorder, had a medical condition requiring immediate investigation or treatment, were pregnant or lactating, were taking a medication known to interact with the study drug (confirmed by urinalysis), had a neurological disorder (eg, Parkinson disease), or had conditions for which an MRI would be contraindicated (eg, metallic implants).

Depressed subjects were recruited through local newspaper advertisements. After obtaining informed consent, a trained researcher (L.K.T. or U.E.B.) assessed potential subjects with the Structured Clinical Interview for Axis I *DSM-IV* Disorders (SCID-IV).[33] This was followed by a medical consultation with a staff psychiatrist (N.H.). A urine sample was collected for drug toxicologic screening. Subjects were excluded if they were taking antidepressant medication, had a Hamilton Depression Rating Scale[34] (HDRS) score of less than 24 (subjects with moderate MDD were excluded because these patients responded similarly to control subjects in a previous study[15]), had suicidal ideation posing an immediate threat to life, or had a concurrent Axis I disorder such as anxiety disorders and schizophrenia. Of 265 advertisement responders, 49 were scheduled for the SCID-IV, 168 were ineligible (mostly because of current antidepressant use) or refused to participate, and 48 could not be contacted. Of the 49 scheduled for the SCID-IV, 12 completed the present study, 14 completed another study, and 23 were ineligible or dropped out.

Healthy control subjects were recruited by electronic mail advertising locally in the hospital surroundings and by word of mouth. After providing informed consent, they were screened using the SCID-IV and the HDRS. A urine sample was collected for drug toxicologic screening. The exclusion criteria for the control subjects were a HDRS score of greater than 6, a history of mood disorders, or any other *DSM-IV*, Axis I mental illness.

PROCEDURE

Potential subjects were screened by telephone using a standard screening form based on the criteria described in the previous subsection, the HDRS, and an MRI clinical screening form. They were then invited for an assessment session that included informed consent, the SCID-IV, a medical consultation, and urine sampling. Eligible subjects were recruited for a study session day.

At the beginning of the study session day, a battery of symptom assessment scales was administered, including the Beck Depression Inventory,[35] the Snaith-Hamilton Pleasure Scale,[36] and a modified version of the Sunnybrook Psychomotor Agitation and Retardation Questionnaire,[37] to evaluate depression, anhedonia, and psychomotor symptom severity, respectively. The severity of the depressive episodes experienced by subjects during the 2 to 3 weeks before the study session day was evaluated using the HDRS.[34] The Apathy Evaluation Scale[38] was used to better characterize anhedonic symptoms. The syndrome of apathy is defined as a lack of motivation without evidence of diminished level of consciousness, emotional distress, or cognitive deficits. This syndrome can occur in association with stroke, dementia, and depression. Items in this scale include negative symptoms experienced in depression such as diminished work or interest, psychomotor retardation, anergy, and lack of insight.[39] In a depressed patient, the HDRS–Apathy Evaluation Scale ratio must be greater than 3.5 to diagnose apathy.

Thirty-milligram oral dextroamphetamine doses, prepared in identical 10-mg capsules filled with drug or dextrose powder, were obtained from the hospital pharmacy and administered in a single-blind fashion to all subjects. The Addiction Research Center Inventory (ARCI),[40-42] a drug effect measurement tool, was administered at baseline and was repeated 40, 80, and 140 minutes after drug administration. The ARCI, the main outcome measure of the rewarding effects of dextroamphetamine in this study, is a well-validated questionnaire designed to measure positive effects of drugs that are reinforcing (ie, can promote drug self-administration) and negative effects (ie, increased anxiety and agitation). Specific sets of these questions (eg, "I feel now as I have felt after a very exciting experience; I feel so good I know people can tell it") comprise empirically derived scale classes (eg, Amphetamine and Stimulation Euphoria) validated to measure characteristic effects of drugs or drug.

Blood pressure and heart rate were measured at baseline and 140 minutes after drug administration for physiological assessment of the effects of dextroamphetamine and for safety monitoring. A blood sample was drawn 140 minutes after drug administration, and concentrations were determined using gas chromatography–mass spectrometry.[43]

Functional magnetic resonance imaging was performed using a research-dedicated whole-body MRI scanner operating at 1.5 T (software version LX 8.4; General Electric Medical Systems, Milwaukee, Wis). Sagittal multisection "scout" images to localize brain anatomy (256×192-pixel matrix, 1-cm thick) and axial, high spatial resolution, 3-dimensional images (1.2-mm thick) were acquired using fast spoiled-gradient echo imaging. Functional magnetic resonance images were obtained using T2-weighted single-shot spiral k-space readout and offline reconstruction[44] (echo time, 40 milliseconds; repetition time, 2000 milliseconds; 80° angle; 20-cm field of view; and 90×90-pixel matrix), a technique that is less sensitive to patient head motion than the more commonly used echo planar imaging.[45]

A set of fMRI experiments was performed twice for all subjects, before drug administration and then at peak drug effect (90 minutes after drug administration). In each set, fMRI was performed with the International Affective Picture System (IAPS)[46], in a block design. The IAPS task (described in the next paragraph) was used for 3 reasons. First, the IAPS task engages several brain regions[47] that are hypothesized to be involved in the BRS dysfunction in MDD. Second, the IAPS task provides a set of validated stimuli[46] that help evoke well-characterized and controlled behaviors in healthy adults, while minimizing unwanted interindividual effects (eg, somnolence and restlessness) that might occur in a resting state (without a task). Third, the IAPS task acts as a probe of relevant behaviors, making it possible to observe the action of drugs during a much longer period than has been possible in past pharmacological fMRI experiments.[21,23] Among patients with present or past drug addiction, these studies measured fluctuations in blood oxygen level–dependent (BOLD) signals corresponding immediately to intravenous drug administration (pharmacokinetic approach). In the present study, using an intravenous psychostimulant in "inexperienced" subjects would have compromised subject safety and recruitment.

The IAPS task consisted of rating a set of validated pictures containing neutral, positive, and negative images of humans, animals, and objects. The IAPS task was programmed using specialized software (E-Prime, version 1, beta 4; Psychology Software Tools, Inc, Pittsburgh, Pa) to ensure precise timing of stimulus presentation and to measure accuracy, picture ratings, and reaction times. An fMRI-compatible visual stimulus presentation system was used, which included a set of goggles connected to an LCD projector (Silent Vision, model SV022; Avotec, Inc, Jensen Beach, Fla). The goggles contained adjustments for visual acuity. Subject responses were recorded using fiberoptic-coupled keypads containing 2 buttons for each hand (Lumitouch; Light Wave Technology Inc, Surrey, British Columbia), providing measurements of accuracy and reaction times. Subjects were instructed to interpret or capture the images, presented in blocks of neutral, positive, and negative emotional content (4.5 seconds per picture and 4 pictures per block), and to rate the level of pleasantness for each picture by pressing 1 of the 4 available buttons (unpleasant, somewhat unpleasant, somewhat pleasant, or pleasant). Each picture block (3 neutral, 3 positive, and 3 negative) alternated with blocks of control stimuli. Control stimuli consisted of fixation crosses instead of pictures. The total duration of the task was approximately 8 minutes. The selected pictures and the order of block presentation had been shown to activate brain regions important to the study, including subregions of the prefrontal cortex (eg, dorsolateral), cingulate, amygdala, and nucleus accumbens.[47] The order of block presentation (neutral, positive, and negative) was used to allow time for subjects to process the emotions and to minimize overlap. The IAPS stimuli have been validated in terms of the affect and the degree of arousal elicited in healthy control subjects.[48] Pictures used in the task before drug administration were different from those used in the task at peak drug effect. However, each set of pictures contained similar themes (eg, 2 different pictures of children). Pictures were not repeated within tasks for the same subject.

In addition, 2 simple control tasks were administered at baseline and at peak drug effect to investigate potential drug effects on simple visual sensory and motor output. Finger tapping was performed to visualize the primary sensorimotor cortex and supplementary motor area, and a mondrianlike colored pattern was flickered at a rate of 8 Hz to visualize the primary visual cortex and other visual association areas. Both tasks were implemented in a block design (15-second "on condition," 15-second "off condition," and 8 repetitions), with approximately 4 minutes for each task. The off condition consisted of a blank screen. Because the brain regions activated with these tasks were not expected to be sensitive to dextroamphetamine administration, any observed changes would provide insight regarding whether dextroamphetamine significantly affected the neurovascular coupling that underlies BOLD signals.

DATA ANALYSIS

Statistical analysis of the behavioral data was conducted using a standard software package (SPSS for Windows, version 10.0.0; SPSS Inc, Chicago, Ill). For the dextroamphetamine behavioral effects, the main dependent outcome variable consisted of a composite of change scores from previously described subscales of the ARCI that measure positive reinforcing effects, namely, abuse-potential, amphetamine, benzedrine, morphine-benzedrine, and stimulation euphoria.[15] The peak dextroamphetamine effect was defined as the highest scale score among the 80- and 140-minute recordings. The corresponding baseline score was subtracted from this value to measure the change. Because of the different score ranges within the various scales, baseline and peak scores were converted to a score on a 100% scale before being added to the composite score. These ARCI data were analyzed using an independent *t* test contrasting the MDD subjects with the control subjects. Similarly to the ARCI scores, the baseline (predrug) picture ratings and reaction times were subtracted from the corresponding postdrug scores, which were then assessed in an independent *t* test contrasting the MDD subjects with the control subjects. Pearson product moment correlation was used for bivariate tests. Finally, independent *t* tests were performed to compare demographic and baseline measurements, including age and symptom scale scores, between the MDD subjects and the controls.

The imaging data were assessed with the Analysis of Functional Neuroimages statistical program.[49] Data sets were corrected for motion, detrended to eliminate slow global changes in the fMRI signal, transformed into Talairach coordinates, and spatially filtered (using a gaussian filter with a full width at half maximum of 6 mm). Brain activation maps were generated for each data set (at baseline and at peak drug effect for the MDD subjects and the controls) using the conventional block design correlation method, which involves contrasting blocks of task performance (on condition vs off condition).[50] For the IAPS task, all picture blocks (on condition) were contrasted with the blocks of fixation crosses (off condition). Therefore, signal intensity values represented the percentage change in BOLD signal between the on and off conditions. The brain activation maps were submitted to a 2-way analysis of variance in the Analysis of Functional Neuroimages program to assess the effects of mood (contrasting the MDD subjects vs the controls) and drug (contrasting before administration vs after administration), as well as the interaction between these 2 independent factors. We report the results at an uncorrected threshold of $P=.001$ in table format but use $P=.01$ for illustration purposes. In each region of interaction, there were the following 3 possible scenarios:

(1) There was no predrug difference between the MDD subjects and the controls, whereas there was a statistically significant postdrug difference. (2) Predrug and postdrug differences occurred, but the magnitude of the difference was statistically different between the MDD subjects and the controls. (3) There was a statistically significant predrug difference between the MDD subjects and the controls but no postdrug difference. Therefore, to best answer the question concerning the direction of change in the regions of interaction, post hoc *t* tests comparing the MDD group with the control group before drug administration and after drug administration were performed with the Analysis of Functional Neuroimages program (at an uncorrected threshold of $P=.001$ and illustrated at $P=.01$).

RESULTS

Twelve subjects with severe MDD and 12 healthy control subjects completed the study. **Table 1** gives the characteristics of the study population. Between-group *t* tests showed that the differences between the groups were statistically significant ($P<.05$) for all symptom assessment measures. In the MDD group, the duration of episodes reported during the SCID-IV interviews ranged from 2 to 24 months (mean, 13.75 months). Seven of 12 patients were experiencing their first MDD episode, and 2 of the 12 had been prescribed an antidepressant (2 days previously in one subject and 1 month previously in the other subject). No MDD subjects had been hospitalized for mental illness, and most reported good physical health except for migraine headaches (n=2) and stomach ulcer (n=1).

Independent *t* tests comparing the ARCI composite scores of the MDD subjects vs the controls revealed that the MDD subjects had a hypersensitive response to the rewarding effects of dextroamphetamine (2-fold increase; $t_{22}=1.92$, $P=.07$), replicating previous findings.[19] The difference became statistically significant ($t_{21}=2.74$, $P=.01$) with the removal of an outlier in the MDD group, who reported dextroamphetamine effects at least 2 SDs below the mean. The mean ARCI composite scores of the MDD group and the control group in the present study were statistically equivalent to previous findings.[15] Except for age (our study group was younger), no statistical differences between the studies were found in predrug or postdrug measurements. Pearson product moment correlation tests revealed positive correlations between ARCI scores and measures of anhedonia, including the Snaith-Hamilton Pleasure Scale (n=23; $r=0.58$, $P=.005$) and the Apathy Evaluation Scale (n=23; $r=0.43$, $P=.049$). Therefore, the degree of dextroamphetamine reward was associated with the severity of anhedonia.

Table 2 gives the IAPS task results and the physiological measures. The *t* tests comparing baseline picture ratings and reaction times (postdrug scores minus predrug scores) in the MDD subjects vs the controls showed no differences during the IAPS task. The ratings of the pleasantness of the IAPS pictures were equivalent between the MDD subjects and the controls before and after drug administration. Therefore, neither mood nor drug influenced these behavioral measures. Heart rate and blood pressure were increased by dextroamphetamine ($F=9.35$, $P=.006$), but no differences were found between the MDD subjects and the controls.

Table 1. Characteristics of the Study Groups*

Characteristic	MDD Group	Control Group
Demographics		
Age, y	34.83 ± 13.96	29.33 ± 9.31
Male/female ratio	6:6	5:7
Educational level, y†	3.83 ± 1.80	5.00 ± 1.04
Symptom assessment measures		
Hamilton Rating Scale for Depression score‡	27.75 ± 3.05	0.46 ± 0.93
Beck Depression Inventory score§	26.33 ± 8.67	0.33 ± 0.78
Snaith-Hamilton Pleasure Scale score‖	6.00 ± 4.52	0.08 ± 0.30
Sunnybrook psychomotor agitation subscore¶	31.18 ± 14.49	4.42 ± 4.60
Sunnybrook psychomotor retardation subscore#	11.55 ± 9.96	1.67 ± 1.88
Apathy Evaluation Scale score**	50.80 ± 10.28	30.33 ± 2.57

Abbreviation: MDD, major depressive disorder.
*Data are given as mean ± SD unless otherwise indicated. Two MDD subjects and 2 control subjects had a history of substance use disorder as determined by the Structured Clinical Interview for Axis I *DSM-IV* Disorders.
†High school education equals 1 year.
‡Measure of severity of the depressive episode experienced during the 2 weeks before the study session day.
§Self-assessment scale of the severity of the current depressive episode.
‖Self-assessment scale of the degree to which a person is able to experience pleasure or the anticipation of a pleasurable experience, with a score of 2 indicating anhedonia.
¶Self-assessment of psychomotor agitation symptoms that occurred in the past week.
#Self-assessment of psychomotor retardation symptoms that occurred in the past week.
**Measure of anhedonic symptoms experienced during the past month.

To compare differences in brain activation between the MDD subjects and the controls, we examined the interaction between mood and drug (using the 2-way analysis of variance model described in the last paragraph of the "Methods" section). The resulting regions of interaction with corresponding Talairach coordinates (x, y, and z) are given in **Table 3**. The patterns of change in these regions of interaction were explored by means of post hoc *t* tests, revealing no differences between the MDD subjects and the controls before drug administration, except for the right posterior cingulate, but revealing significant differences after drug administration. Therefore, the interaction corresponded to the first of the 3 possible scenarios described at the end of the "Methods" section. The last column of Table 3 gives the decreases in brain activation in the MDD subjects vs the controls, which were seen in all regions of interaction except those near Brodmann area (BA) 38, which showed increases compared with the controls. The decreases were caused by mean deactivations (negative BOLD signals) in the MDD subjects vs mean activations (positive BOLD signals) in the controls, whereas the increases were caused by the opposite, that is, activations in the MDD subjects and deactivations in the controls.

Results of the Pearson product moment correlation tests in the regions of interaction showed statistically significant correlations between brain activity (peak BOLD signal changes minus baseline values) and degree of dextroamphetamine reward (peak ARCI scores minus baseline values) in the ventrolateral prefrontal cortex (BA 10)

Table 2. International Affective Picture System (IAPS) Task Responses and Physiological Measures*

Variable	MDD Group		Control Group	
	Predrug	Postdrug	Predrug	Postdrug
IAPS task responses				
Neutral				
Picture rating	2.45 ± 0.49	2.60 ± 0.48	2.59 ± 0.30	2.64 ± 0.29
Reaction time	1764.50 ± 528.64	1854.71 ± 416.40	2046.09 ± 235.27	1886.76 ± 396.93
Positive				
Picture rating	3.40 ± 0.35	3.14 ± 0.73	3.59 ± 0.31	3.58 ± 0.19
Reaction time	1582.36 ± 423.63	1596.07 ± 478.37	1715.72 ± 313.56	1471.28 ± 346.66
Negative				
Picture rating	1.75 ± 0.54	1.76 ± 0.77	1.55 ± 0.28	1.46 ± 0.26
Reaction time	1448.37 ± 413.40	1559.90 ± 451.54	1845.88 ± 495.01	1711.74 ± 532.53
All pictures				
Picture rating	2.53 ± 0.36	2.50 ± 0.28	2.55 ± 0.27	2.56 ± 0.19
Reaction time	1598.41 ± 410.52	1670.23 ± 423.63	1857.41 ± 304.37	1689.93 ± 392.42
Physiological measures				
Heart rate, beats/min	67.17 ± 12.52	79.08 ± 15.41	66.82 ± 10.96	73.09 ± 15.62
Blood pressure, mm Hg	107.33/69.00 ± 7.06/9.06	122.83/83.92 ± 6.93/7.51	108.55/71.91 ± 12.48/7.46	119.27/79.18 ± 17.71/7.51

Abbreviation: MDD, major depressive disorder.
*Data are given as mean ± SD.

Table 3. Brain Interaction Findings

Region of Interaction*	Talairach Coordinates, x, y, z	MDD Group vs Control Group at Peak Drug, %†
BA 10 (right ventrolateral prefrontal cortex)	42, 50, 9	−0.34 (↓ 3.6-fold)
Left and right caudate and putamen	−13, 13, −1	−0.21 (↓ 1.3-fold)
	12, 12, −1	−0.26 (↓ 1.6-fold)
	16, 12, −4	−0.34 (↓ 3.6-fold)
BA 38 (left and right temporal pole)	−50, 13, −19	0.24 (↑ 3.4-fold)
	35, 4, −17	0.55 (↑ 2.7-fold)
Right posterior cingulate	15, −46, 23	Not significant
BA 11 (left orbitofrontal cortex)‡	−22, 40, −11	−0.33 (↓ 2.2-fold)
BA 25 (right medial frontal gyrus)‡	14, 11, −17	Not significant
BA 6 (supplementary motor cortex and premotor cortex)‡	4, −25, 64	−0.26 (↓ 3.7-fold)

Abbreviations: BA, Brodmann area; MDD, major depressive disorder.
*$F_{1,44}$ = 11.93, uncorrected P = .001. Interactions were demonstrated using post hoc t tests (t = 3.50, P = .001).
†Mean percentage blood oxygen level–dependent (BOLD) signal of the MDD group minus the mean percentage BOLD signal of the control group, with the direction (↑ vs ↓) and effect size of the difference. There were no significant differences between the MDD group and the control group before drug administration, except for the right posterior cingulate (0.18% [↑ 3.9-fold]).
‡Significant at P = .01.

(n = 23; r = −0.62, P = .002) and the premotor cortex (BA 6) (n = 23; r = −0.43, P = .04). In addition, a trend was observed in the caudate and putamen (n = 23; r = 0.36, P = .09). The effects of the mood and drug independent factors are given in **Table 4**. Neither of the simple control tasks (finger tapping or visual stimuli) showed statistically significant mood, drug, or interaction effects.

COMMENT

The MDD group demonstrated enhanced dextroamphetamine-induced rewarding effects compared with the control group, reproducing previous findings.[15] This hypersensitive response correlated with the severity of anhedonic symptoms, providing further support for the involvement of the BRS in the pathophysiology of MDD. Combining the dopaminergic probe (dextroamphetamine) with fMRI enabled us to determine the neuroanatomical substrates of altered reward processing in the MDD subjects vs the controls. The link between dextroamphetamine-induced dopamine release and rewarding effects in humans is well established.[16,17,51,52] Therefore, results of this study provide support for the involvement of dopaminergic mechanisms in the altered reward processing in MDD.

The neuroanatomical substrates shown in the **Figure**, particularly the caudate and putamen and the prefrontal region (BA 10), are regions that mediate reward and contain mesocorticolimbic dopaminergic neurons.[53-58] In our study reward scores (eg, euphoria and increased energy) of depressed patients correlated with underlying changes in brain activity in certain dopamine-rich regions, including BAs 10 and 6 and the caudate and putamen. The present study showed that this hypersensitive dextroamphetamine response was associated with negative BOLD signals rather than increased brain activation in most of the regions of interaction compared with the controls (Table 3, last column). The physiological mechanisms of negative BOLD signals are thought to be induced by reduced blood flow (ie, active neuronal inhibition and decreased cortical excitability).[59-61] The relative decrease in brain activity among depressed subjects could reflect exaggerated deactivation of glutamate–mediated transmission by amphetamine. According to Paladini et al,[62] amphetamine selectively inhibits metabotropic glutamate receptor–mediated inhibitory postsynaptic potentials in dopamine neurons, which subsequently induces burst firing of dopamine neurons. Therefore, depressed subjects in our study may have experienced enhanced behavioral effects due to abnormal disinhibition of dopaminergic neurons. Evidence of abnormal glutamate transmission in MDD has been reported,[63] and disturbances in glutamate-mono-

Table 4. Main Effects of the Mood and Drug Factors*

Mood (MDD Group vs Control Group)†		Drug (Predrug vs Postdrug)‡	
Brain Region	Talairach Coordinates, x, y, z	Brain Region	Talairach Coordinates, x, y, z
Frontal Cortex			
MDD group < control group		Postdrug < predrug	
BA 10 (L medial frontal gyrus)	–9, 66, 12	BA 6 (L superior frontal gyrus)	–10, 13, 50
BA 32 (L anterior cingulate)	–3, 38, 24		
R inferior frontal gyrus	27, 34, –9	Postdrug > predrug	
BA 47 (R inferior frontal gyrus)	25, 32, –8	None	. . .
BA 6 (L precentral gyrus)	–33, –13, 47		
MDD group > control group			
BA 8 (right superior frontal gyrus)	30, 42, 41		
BA 45 (right inferior frontal gyrus)	53, 27, 8		
Cingulate			
MDD group < control group		Postdrug < predrug	
None	. . .	L cingulate gyrus	–17, –18, 33
MDD group > control group		Postdrug > predrug	
R cingulate gyrus	6, –34, 36	L anterior cingulate	–11, 23, –4
		R anterior cingulate	11, 16, –7
Striatum and Basal Ganglia			
MDD group < control group		Postdrug < predrug	
R lentiform nucleus and putamen	19, 16, –4	None	. . .
L putamen	–29, 7, 1		
L caudate	–6, 4, 2	Postdrug > predrug	
R lateral globus pallidus	14, 3, –5	R nucleus accumbens	13, 13, –8
		R caudate and head	8, 19, 3
MDD group > control group		R putamen	18, 16, –6
None	. . .		
Other Regions			
MDD group < control group		Postdrug < predrug	
L insula	–32, 13, –5	None	. . .
Uncus	16, 3, –21		
R hypothalamus	3, –3, –6	Postdrug > predrug	
BA 18 (L lingual gyrus)	–6, –82, –10	None	. . .
MDD group > control group			
L precuneus	12, –49, 56		

Abbreviations: BA, Brodmann area; MDD, major depressive disorder.
*$F_{1,44}$ = 11.93, uncorrected P = .001. The > and < symbols indicate the direction of change revealed by the post hoc t tests (t = 3.50, P = .001).
†Regions where the MDD group showed greater or lesser activation than the control group.
‡Regions where dextroamphetamine sulfate elicited greater or lesser activation compared with baseline values.

amine interactions have been proposed as pathophysiological mechanisms in mental illnesses such as schizophrenia and depression.[64,65] Furthermore, *N*-methyl-D-aspartate receptor antagonists (metatropic glutamate receptor subtypes 1 and 5) have antidepressant properties that may be exploited for future pharmacotherapeutic strategies.[66] As previously proposed,[15] an alternative to the glutamatergic inhibition concept is that the hypersensitive dextroamphetamine behavioral response in depressed patients is mediated by stimulation of a higher density of D_2 dopamine receptors[67-69] or by stimulation in synapses containing a lower density of dopamine transporters,[70,71] which are thought to be neurobiological responses secondary to a chronic hypodopaminergic state in depression. Negative BOLD signals in the prefrontal regions and striatum may be due to increased D_2 receptor–mediated inhibition.[64] However, the notion of a dopamine storage deficit was refuted by findings that experimental depletion of dopamine in unmedicated MDD patients does not produce exacerbation of mood symptoms.[72] Furthermore, Parsey et al[73] found that depressed patients at baseline showed striatal D_2 dopamine receptor availability that was similar to that in controls and that amphetamine-induced displacement of the D_2 ligand (indicating dopamine release) was not different in the striatum between patients and controls.

Unlike the previously discussed regions of interaction such as the caudate and putamen, a different pattern occurred in the remaining regions of interaction, that is, increased brain activity with dextroamphetamine in the MDD subjects compared with the controls in the temporal pole (BA 38) and increased activity before dextroamphetamine administration followed by normalization (ie, a response equal to that of controls) with dextroamphetamine in the posterior cingulate. One report indicates that cortical gray matter volumes in temporal lobes correlate with degrees of cocaine euphoria.[74] D_2/D_3 dopamine receptor densities in the temporal cortex represent a source of extrastriatal dopamine and are an important therapeutic mechanism of atypical antipsychotic medications.[75,76]

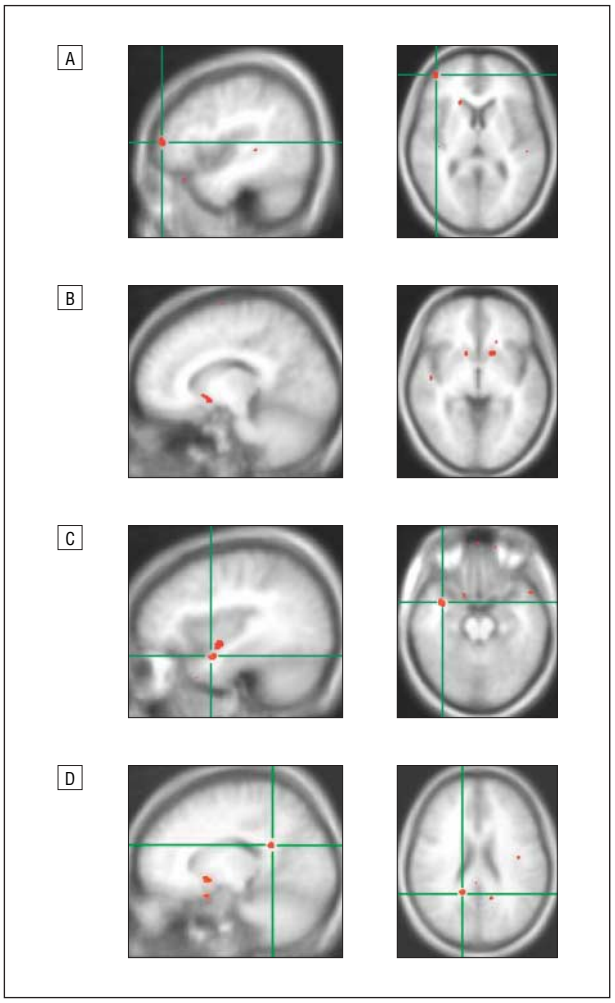

Figure. Four regions of brain interaction (for which the corresponding Talairach coordinates are given in Table 3) representing statistical differences ($F_{1,44}$ = 11.93, uncorrected P = .001), are displayed using P = .01 to view the extent of activation, with red color in the sagittal and axial views and green cross-lines for labeling. A, Brodmann area 10 (right ventrolateral prefrontal cortex). B, Left and right caudate and putamen. C, Brodmann area 38 (left and right temporal pole). D, Right posterior cingulate.

Decreased availability of these extrastriatal dopamine receptors has been linked to negative symptoms of schizophrenia such as anhedonia.[77] Antipsychotic medications are also used to augment the efficacy of antidepressants[78] and have in a few cases possibly induced manic or hypomanic symptoms.[79] A few reports link the posterior cingulate to reward mediation[26] via dopaminergic mechanisms.[80,81] Similar to the pattern in this study, normalization of activity has been induced with antidepressant treatment,[82] whereas tryptophan depletion (ie, induction of depressive symptoms) has been linked to increased posterior cingulate activation.[83]

The overall differences in brain activation found between the MDD subjects and the controls (Table 4) were consistent with previous neuroimaging findings in depressed patients at rest (ie, without pharmacological probing), including the prefrontal cortex (BAs 10, 8, 6, 47, and 45), cingulate gyrus (BA 24), basal ganglia (caudate, putamen, and globus pallidus), and subcortical structures such as the hypothalamus.[4,9,84] Furthermore, the overall effect of dextroamphetamine involved regions that have been linked to short-term rewarding effects of psychostimulants, including the striatum (caudate and putamen and nucleus accumbens), cingulate, and frontal cortex.[16,85,86] Therefore, the main effects given in Table 4 demonstrate that our pharmacological fMRI protocol provided consistent neuroimaging data and reliable interaction findings. The results of the control tasks involving finger tapping and visual stimuli also support the interpretation of the data. The associated activation maps, which primarily depicted primary sensory and motor cortices, showed no effect of dextroamphetamine on these tasks, as anticipated. This lends additional credence to the observation and interpretation of activity within regions associated with the BRS that are specific to dextroamphetamine administration. Compliance was excellent in the MDD and control groups, with the groups performing the tasks with similar picture ratings and reaction times (Table 2).

Elucidating the neuroanatomical substrates of altered reward processing in MDD provides potential targets for the development of more effective antidepressants. Disturbances in dopaminergic and other BRS pathways (eg, opioids) have been found in animal models of depression (eg, chronic mild stress).[87] Findings in animal models also suggest that the mesocorticolimbic dopamine pathway may be a potential target for more rapid onset of action,[88] a significant problem in current antidepressant treatment. However, interpretations involving single neurotransmitters are not ideal, in light of the ability of dextroamphetamine to modulate the release of neurotransmitters other than dopamine, as well as the involvement of multiple neurotransmitter systems in the neurobiology of the BRS and MDD.[19] Instead of the continued use of single or multiple neurotransmitter system targeting, perhaps a more promising treatment approach would be to consider the BRS, specifically the regions identified in this study, as a target for future "plasticity-enhancing" drugs such as *N*-methyl-D-aspartate receptor antagonists. This approach may be more in line with the complex pathophysiology of MDD.[66,89] Findings in animal models suggest that antidepressants in general produce neurotrophic and neuroplastic effects (eg, increases in brain-derived neurotrophic factor), including neurogenesis, which could explain the 6 to 8 weeks required for a therapeutic response and the alleviation of depressive symptoms.[90] The dopaminergic system and the BRS components (eg, the nucleus accumbens and the caudate and putamen) exhibit important plastic properties, as seen after repeated drug administration,[91] with environmental changes,[92] and during postnatal development.[93] Therefore, the brain reward system may be an excellent target for novel treatment approaches in drug development research.

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