ORIGINAL ARTICLE

Glutamate and the Neural Basis of the Subjective Effects of Ketamine

A Pharmaco–Magnetic Resonance Imaging Study

J. F. William Deakin, PhD, FRCPsych, FmedSci; Jane Lees, BSc, MSc; Shane McKie, MEng, MSc, PhD; Jaime E. C. Hallak, MD, PhD; Steve R. Williams, BA, MA, DPhil; Serdar M. Dursun, MD, PhD, FRCPC

Context: Ketamine evokes psychosislike symptoms, and its primary action is to impair *N*-methyl-D-aspartate glutamate receptor neurotransmission, but it also induces secondary increases in glutamate release.

Objectives: To identify the sites of action of ketamine in inducing symptoms and to determine the role of increased glutamate release using the glutamate release inhibitor lamotrigine.

Design: Two experiments with different participants were performed using a double-blind, placebo-controlled, randomized, crossover, counterbalanced-order design. In the first experiment, the effect of intravenous ketamine hydrochloride on regional blood oxygenation level–dependent (BOLD) signal and correlated symptoms was compared with intravenous saline placebo. In the second experiment, pretreatment with lamotrigine was compared with placebo to identify which effects of ketamine are mediated by increased glutamate release.

Setting: Wellcome Trust Clinical Research Facility, Manchester, England.

Participants: Thirty-three healthy, right-handed men were recruited by advertisements.

Interventions: In experiment 1, participants were given intravenous ketamine (1-minute bolus of 0.26 mg/kg, followed by a maintenance infusion of 0.25 mg/kg/h for the remainder of the session) or placebo (0.9% saline solution). In experiment 2, participants were pretreated with 300 mg of lamotrigine or placebo and then were given the same doses of ketamine as in experiment 1.

Main Outcome Measures: Regional BOLD signal changes during ketamine or placebo infusion and Brief Psychiatric Rating Scale and Clinician-Administered Dissociative States Scale scores.

Results: Ketamine induced a rapid, focal, and unexpected decrease in ventromedial frontal cortex, including orbitofrontal cortex and subgenual cingulate, which strongly predicted its dissociative effects and increased activity in mid-posterior cingulate, thalamus, and temporal cortical regions (r=0.90). Activations correlated with Brief Psychiatric Rating Scale psychosis scores. Lamotrigine pretreatment prevented many of the BOLD signal changes and the symptoms.

Conclusions: These 2 changes may underpin 2 fundamental processes of psychosis: abnormal perceptual experiences and impaired cognitive-emotional evaluation of their significance. The results are compatible with the theory that the neural and subjective effects of ketamine involve increased glutamate release.

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Author Affiliations: Neuroscience and Psychiatry Unit (Drs Deakin, McKie, Hallak, and Dursun and Ms Lees) and Imaging Science and Biomedical Engineering (Dr Williams), The University of Manchester, Manchester, England; and Neurology, Psychiatry, and Psychological Medicine Department, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil (Dr Hallak).

Impaired signaling through *N*-methyl-D-aspartate (NMDA) glutamate receptors has been implicated in the pathogenesis of schizophrenia. The main evidence is the ability of the NMDA channel blockers phencyclidine and ketamine to induce symptoms that resemble schizophrenia in healthy volunteers and to exacerbate them in patients. Although it is now clear that short-term experimental administration of ketamine does not elicit the full range of psychotic symptoms, nevertheless, it is of considerable interest to understand the neurobiologic mechanisms involved.[1-7]

In their seminal contribution, Olney and Farber[8] suggested that NMDA antagonists block excitation of γ-aminobutyric acid (GABA) interneurons, resulting in removal of GABA restraint of cholinergic, serotonergic, and glutamatergic afferents to posterior cingulate cortex. This, they suggested, caused a triple excitotoxic effect on posterior cingulate pyramidal cells, accounting for the focal neurodegeneration they had observed after phencyclidine administration.[8] Subsequent studies using in vivo microdialysis have confirmed that the administration of NMDA channel blockers causes increased glutamate release in frontal cortex. This was also suspected

from the remarkable observation that AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) glutamate antagonists could antagonize hyperactivity induced by NMDA blockade (phencyclidine) in rats.[9] More recently, mGluR2 (metabotropic glutamate 2/3 receptor) agonists, which act presynaptically to decrease the release of glutamate, have been reported to reverse the behavioral effects of phencyclidine.[10]

To test the theory that ketamine acts through increased glutamate release to produce its subjective effects in humans, Anand et al[11] pretreated volunteers with the anticonvulsant lamotrigine, a use-dependent sodium channel blocker that decreases glutamate release.[12] They found that lamotrigine attenuated the increase in Brief Psychiatric Rating Scale (BPRS) psychosis scores after intravenous ketamine administration. However, they also observed that the mood-elevating effects of ketamine were briefly enhanced by lamotrigine.[11] This suggests that some effects of ketamine are mediated by enhanced glutamate release onto non-NMDA receptors, whereas others may be directly mediated by reduced NMDA function and thus potentiated by lamotrigine.

Three research groups[13-15] have used positron emission tomography (PET) to image the effect of ketamine on regional cerebral blood flow (oxygen-15 PET) or metabolism (^{18}fluorodeoxyglucose [FDG] PET). All 3 groups report frontal activation, and 2 report anterior cingulate activation, but Breier et al[13] did not. Anterior cingulate activation occurred only in studies in which participants received a familiarization dose of ketamine, and it may reflect an anticipatory neural response. No PET studies have reported activation in the posterior cingulate, retrosplenial cortex, or hippocampus, as described in immediate early gene studies in rodents. This may be because the human doses are equivalent to doses in the rat that are too low to affect posterior cingulate function. The FDG-PET studies measured FDG uptake during 25 minutes of continuing ketamine infusion beginning 10 minutes after an initial bolus. This reflects the steady state of the brain associated with steady symptoms of dissociation well after the intense immediate action of ketamine. The oxygen-13 studies were single blind (no placebo), relying instead on before-and-after comparisons, with the first postinfusion scan at 6 minutes showing the greatest changes. We chose to follow the immediate neural effects of ketamine hydrochloride as symptoms developed using continuous functional magnetic resonance imaging (fMRI) during the initial period of the infusion with placebo control in drug-naive healthy volunteers.

Pharmaco-MRI (phMRI) has been used to investigate the direct effects of drugs (eg, cocaine and nicotine) on the blood oxygenation level–dependent (BOLD) signal[16,17] and the modulation of BOLD signal changes during conventional fMRI studies involving tasks or sensory stimulation.[18] We have previously used direct and indirect phMRI approaches to probe the functioning of the serotonin system in man.[19-21]

A variety of studies have used ketamine to investigate the effect of NMDA antagonism on brain regions engaged by various cognitive fMRI paradigms, including face emotion processing,[22] working memory,[23] memory recall,[24] verbal fluency,[25] and learning.[26] Typically, ketamine has not affected performance but has altered brain networks that subserve the cognitive process under investigation. However, the origins of ketamine's subjective effects were not the chief concern of these studies.

We used direct phMRI to follow the effect of short-term ketamine administration on regional blood oxygenation with a minute-to-minute time course and determined which regional brain responses correlated with ratings of ketamine's subjective effects. We then investigated the effects of lamotrigine pretreatment to identify the regional components of ketamine's effects that are mediated by enhanced glutamate release.

METHODS

PARTICIPANTS

This study was approved by the Committee on the Ethics of Research on Human Beings of the University of Manchester and was conducted in the Wellcome Trust Clinical Research Facility in Manchester to audited standards of good clinical practice. Male participants were recruited via public advertisements, and they were paid for their participation. Individuals were healthy according to physical examination, history, electrocardiography, and laboratory findings. They had no personal history, and no first-degree relative with a history, of psychiatric illness or substance abuse disorder and no major family or occupational disruption in the month before screening. Screening procedures included the Mini International Neuropsychiatric Interview. Volunteers with a pacemaker or other metallic objects (eg, surgical clips and metal implants) were excluded. Participants were asked about their use of psychoactive substances and were included in the study provided that they had not used them in the 12 weeks preceding the study. Urine drug tests were performed at screening. Written informed consent was obtained from 33 individuals before enrollment.

EXPERIMENTAL DESIGN

Two separate experiments were performed with a double-blind, placebo-controlled, randomized, within-subjects design. In both studies, participants attended 2 sessions with a 1-week interval between sessions. The first experiment aimed to establish that BOLD imaging could detect ketamine effects compared with placebo, and the second experiment aimed to test the prediction that lamotrigine would attenuate ketamine effects.

In the first experiment, participants received either intravenous ketamine or saline placebo at the first visit and the other infusion at the second visit. In the second study, all the participants received intravenous ketamine but were pretreated with 300 mg of lamotrigine on one occasion and matching placebo on the other occasion 2 hours before the ketamine infusion. In both experiments, imaging began 8 minutes before infusion and continued for a further 8 minutes while the infusion continued. Participants were allowed to leave 1 hour after the end of the infusion following a debriefing with the experimenter.

PROCEDURES

Ketamine-Placebo Experiment

Twelve healthy right-handed men participated in the study (mean [SD] age, 22.2 [3.85] years). Each session consisted of a placebo (0.9% saline solution) or racemic ketamine hydro-

chloride (Ketalar; Parke Davis, Morris Plains, NJ) infusion, which was administered as a 1-minute bolus of 0.26 mg/kg, followed by a maintenance infusion of 0.25 mg/kg/h for the remainder of the session.

Ketamine-Lamotrigine Experiment

Twenty-one healthy men were recruited. One individual dropped out after becoming anxious during MRI, and 1 participant's data could not be used because the MRI was stopped halfway through and then restarted. Nineteen individuals completed the experiment (mean [SD] age, 21.95 [3.20] years). The 2 experimental sessions were 1 week apart. Each session began with the oral administration of 300 mg of lamotrigine (GlaxoSmithKline, Ware, England) or matching placebo 2 hours before MRI. Participants were cannulated and connected to an infusion pump through which ketamine was infused as described in the previous paragraph.

IMAGE ACQUISITION

T2-weighted images were acquired using a 1.5-T scanner (Intera; Philips Medical Systems, Eindhoven, the Netherlands) and a single-shot, multislice, echoplanar imaging sequence. Each volume comprised 40 contiguous axial slices (repetition time/echo time = 5000/40 milliseconds, 3.5-mm thickness with an in-plane resolution of 3.5 × 3.5 mm). A T1-weighted structural image was also acquired for each participant to exclude any structural abnormalities. No abnormalities were reported for any of the 31 participants.

CLINICAL INTERVIEW

Each participant was interviewed before and after the phMRI period and was evaluated using the BPRS and the Clinician-Administered Dissociative States Scale (CADSS).[27] The BPRS total and 6 subscale (anxiety-depression, activation, withdrawal, thought disorder, hallucinations, and hostility-suspicion) scores and the CADSS total, subjective, and objective subscale (amnesia, depersonalization, and derealization) scores were used. In the lamotrigine-ketamine experiment, additional BPRS and CADSS ratings were performed before administration of oral lamotrigine or placebo to provide a baseline for the pre-MRI rating and the detection of changes due to lamotrigine pretreatment.

STATISTICAL ANALYSIS

Behavioral data were analyzed using a statistical software program (SPSS 11.5; SPSS Inc, Chicago, Illinois). Treatment effects on BPRS total and 6 subscale scores as well as the CADSS total and 4 subscale scores were analyzed individually using repeated-measures analysis of variance with factors for treatment (placebo-ketamine vs lamotrigine-ketamine) and stage (after lamotrigine vs after ketamine). For simplicity, *t* tests are presented for the postinfusion–preinfusion differences.

The phMRI data were analyzed using Statistical Parametric Mapping (SPM2; The Wellcome Department of Cognitive Neurology, London, England). Images were realigned to correct for motion artifacts using the first image as a reference and were normalized into the Talairach and Tournoux stereotactic space[28] using Montreal Neurological Institute templates. Images were smoothed using a 10-mm gaussian kernel to facilitate interindividual averaging.

The time series analysis was performed using the pseudoblock analysis method described previously[19] and used for analyzing human[19] and animal[29] phMRI data. The method is a modification of the standard block analysis approach used in SPM, and the data acquisition and preprocessing are exactly as they would be for a conventional task fMRI experiment. Thus, temporal and spatial resolution, spatial filtering, and normalization follow the standard techniques. However, in phMRI, drugs are administered once only, so there are no well-defined "on" and "off" periods and no averaging of the task across a number of cycles. We make an informed guess as to the likely time constant of drug-related changes and use this as the length of the block. We chose 1 minute, which is long compared with the hemodynamic response but still short enough to capture all but the most transient responses to the drug. We treat the preinfusion minute as a baseline block (or "epoch" in SPM terminology) and each subsequent minute as an independent test block ("task epochs"). These are then entered into an SPM design matrix as separate columns and the conventional regression analysis is performed, comparing each time block after infusion to the preinfusion period. For each time block, an effect size map is generated (average signal change in a voxel compared with before infusion) for each participant. Just as for a regular SPM analysis, these images become the input data into statistical analysis of the effects of drug vs placebo, the effect of time after drug or placebo administration, and the effect of lamotrigine or placebo pretreatment.

To determine the overall differences between paired drug treatment conditions irrespective of time (the main effect of treatment condition) across the group, the 8 epochs (time blocks) in the repeated-measures, random-effects, 1-way analysis of variance were averaged together and contrasted to zero. The overall effect of ketamine infusion was identified in the first experiment using a familywise error–corrected statistical threshold of $P < .05$. To determine the effects of lamotrigine pretreatment in areas in which ketamine was shown to have an effect on the BOLD signal, we applied a small-volume correction to the second experiment data using a sphere with a 20-mm radius centered on the peak voxel from the first experiment.

Correlation analysis was used to determine which effects of ketamine might mediate its subjective effects. A single image of the paired drug treatment condition irrespective of time (the main effect of treatment) was created for each participant by subtracting the average of the 8 time blocks for the placebo condition from the average of the 8 time blocks for the drug condition (ketamine). These images were correlated with the differential (ketamine-placebo) behavioral measures for total BPRS and total CADSS scores. To highlight areas that showed significant changes in the BOLD signal after ketamine infusion and that also correlated with the behavioral measures, the results of the correlations were masked by the main effect of treatment (detailed in the "Statistical Analysis" subsection of the "Methods" section).

RESULTS

BEHAVIORAL

Ketamine-Placebo Experiment

Ketamine evoked increases in all the BPRS subscale scores and in the CADSS score. The 2 were not highly correlated ($r = 0.33$), suggesting that they assess partially different aspects of the subjective effects of ketamine. In pilot studies, outside the scanner we confirmed the very rapid onset and rapid partial tolerance to the subjective effects of ketamine. Typically, there was behavioral arrest and mutism for the first 2 to 4 minutes, after which participants were able, with effort, to complete the tasks and report their

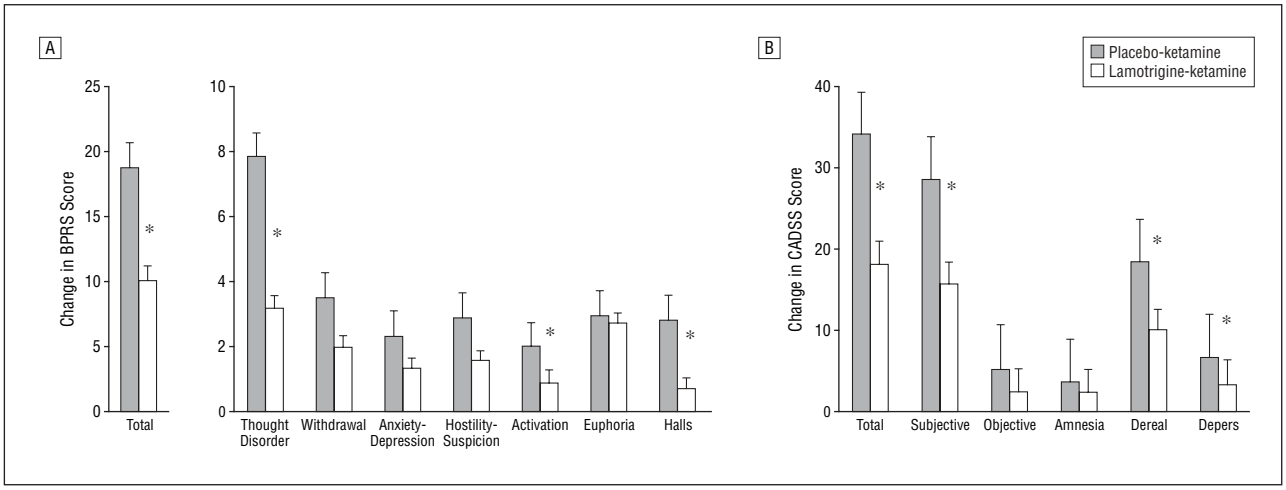

Figure 1. Lamotrigine reduces ketamine experiences assessed by postinfusion–preinfusion differences in Brief Psychiatric Rating Scale (BPRS) (A) and Clinician-Administered Dissociative States Scale (CADSS) (B) scores. Participants were instructed to rate the peak of their experiences. Halls indicates hallucinations; dereal, derealization; and depers, depersonalization. *$P<.05$ by *t* test. Error bars represent SD.

experiences. Frank psychosis did not occur at the doses used, but anecdotally noises were misperceived and actions were misinterpreted as being suspicious. Total BPRS and CADSS scores showed statistically significant increases after ketamine infusion compared with placebo infusion, as did the various subscale scores and the BPRS ratings for euphoria and hallucinations (**Figure 1**).

Lamotrigine-Ketamine Experiment

There were no statistically significant subjective effects of lamotrigine compared with placebo before ketamine infusion. After ketamine infusion, total BPRS scores and most BPRS subscale scores were lower after lamotrigine pretreatment than after placebo pretreatment, and this was statistically significant for BPRS total, thought disorder, activation, and hallucinations scores but not for withdrawal, anxiety-depression, or hostility-suspicion scores (Figure 1). Mean scores for euphoria were almost identical and were unaffected by pretreatment. Similarly, CADSS scores were lower after lamotrigine therapy, and this was significant for CADSS total, derealization, and depersonalization scores (Figure 1).

PHARMACO-MRI

Ketamine-Placebo Experiment

The overall effects of ketamine compared with placebo are summarized in **Table 1** and **Table 2** and are shown in **Figure 2**. The histograms in Figure 2 show that most regions also had time-dependent effects, typically reaching maxima or minima 4 to 5 minutes after infusion and returning toward baseline thereafter. The time of peak response is further documented in Table 1. Ketamine evoked increases in BOLD signal in the precuneus (Brodmann area 7 [BA7]), mid-posterior cingulate gyrus (BA24), motor cortex (BA6), superior frontal gyrus (BA8), inferior temporal gyrus (BA20), hippocampus, and superior temporal gyrus (BA22) bilaterally. Decreases in BOLD signal after ketamine infusion were seen bilaterally in medial orbitofrontal cortex (OFC) (BA11) and temporal pole (BA38).

The time course of ketamine-evoked BOLD signal responses is illustrated in **Figure 3**. The colors indicate regions where the BOLD signal response was significantly greater (red-yellow) or less (blue) after ketamine infusion compared with placebo infusion during successive minutes. Within 2 minutes of the intravenous ketamine bolus, BOLD signal had decreased significantly in medial OFC (Figure 3) and temporal pole (BA38) (not shown). Deactivation spread to the subgenual cingulate and BA10 and remained significantly depressed for 7 minutes, which was 2 minutes longer than other changes (Figure 3). In the third minute, there was significant extensive activation of the anterior thalamus and mid-posterior cingulate cortex (BA23/30/31) extending to the posterior parahippocampal gyrus.

The 2 areas of deactivation after ketamine infusion in the OFC/subgenual cingulate and temporal pole (BA38) correlated with increases in the CADSS score ($r=0.90$) (**Figure 4**), but only deactivation of OFC correlated with the increase in psychosis (BPRS) ratings. Of the ketamine-placebo activations, the frontal pole (left BA10) correlated most strongly with psychosis ratings ($r=0.70$), with weaker correlations in the parahippocampal gyrus and posterior cingulate ($r=0.60$). Only the latter activation correlated with dissociative symptoms ($r=0.60$). Changes in the thalamus did not correlate with symptom ratings.

Ketamine-Lamotrigine Experiment

Figure 5 compares the placebo-ketamine–lamotrigine-ketamine effects (bottom row) with the ketamine-placebo effects from experiment 1 (top row). The similarity of the maps indicates regions where lamotrigine pretreatment diminished the effect of ketamine toward saline placebo. It can also be seen in Table 1 that several areas showing BOLD signal responses to ketamine in the

Table 1. Areas With Significant Increases in the BOLD Signal After Intravenous Ketamine Infusion in the K-P and PK-LK Experiments

			K-P Experiment					PK-LK Experiment				
			MNI Coordinates			Peak % Signal Change	Peak at Tn	MNI Coordinates			Peak % Signal Change	Peak at Tn
Region	BA	Side	x	y	z			x	y	z		
Superior frontal gyrus	6	R	3	−9	72	3.62	5	9	−15	75	1.61	4
	8	R	3	33	63	3.63	5	−6	30	63	1.38	4
	10	R	27	60	−9	1.64	5	33	45	−12	0.61	4
		L	−12	63	−6	2.19	3	−24	57	−6	0.58[a]	6
Medial frontal gyrus	6		0	−9	45	2.12	4	−3	−3	45	1.09	7
	8	R	6	42	45	1.42	5	9	51	42	0.69[a]	4
	11	L	−3	60	−12	4.46	3	9	60	−3	1.33	4
Middle frontal gyrus	10	R	42	45	18	1.05	4	33	48	21	1.08	4
		L	−33	48	18	1.22	4	−18	51	24	0.91	5
Inferior frontal gyrus	44	R	57	12	30	1.06	3	48	6	30	1.10	4
		L	−45	3	30	1.36	4	−39	3	18	0.68	5
	46	R	51	27	15	1.16	4	60	27	15	0.77	4
		L	−48	30	12	1.21	3	−51	30	12	0.77	3
Midcingulate gyrus	24	R	3	3	42	2.06	3	6	−3	39	0.84	5
Posterior cingulate gyrus	30	L	−3	−57	18	2.37	3	3	−66	3	1.55	4
Superior temporal gyrus	38	R	57	15	−9	3.94	4	57	18	−12	0.89	6
		L	−54	3	−6	3.01	4	−60	9	−6	1.30	5
	42	R	60	−18	9	1.77	4	60	−27	18	1.04	4
		L	−57	−27	12	1.59	5	−57	−27	12	1.35	5
Middle temporal gyrus	21	R	60	−57	3	1.48	3	54	−60	−3	0.71	4
		L	−63	−54	0	1.28	5	−57	−57	3	0.74	4
		R	63	−42	−18	0.93	5	51	−54	−18	1.10	4
		L	−63	−42	−18	1.68	5	−63	−45	−15	1.68	5
Inferior temporal gyrus	20	R	63	−36	−21	1.42	5	54	−27	−21	0.98	5
		L	−63	−33	−21	1.78	5	−57	−33	−21	0.96	5
	37	R	51	−72	−9	1.65	3	54	−60	−3	0.79	4
		L	−54	−72	−9	1.59	4	−51	−72	−12	0.82	4
Precentral gyrus	4	R	30	−39	69	1.77	3	21	−27	72	1.00	5
		L	−27	−30	66	1.13	5	−21	−27	75	0.77[a]	4
Paracentral lobule	5	L	−6	−18	45	1.66	5	−15	−18	45	0.73	4
Superior parietal lobule	7	R	3	−54	63	3.41	4	9	−48	69	1.34	4
		L	−21	−54	63	1.62	5	−21	−45	57	0.95	4
Inferior occipital gyrus	19	R	39	−90	−9	1.02	5	36	−75	−9	0.67	4
		L	−36	−90	−18	1.69	6	−36	−78	−21	1.11[a]	4
Precuneus	7	R	15	−84	45	2.10	5	24	−78	42	0.54[a]	4
		L	−18	−78	51	1.51	4	−18	−75	39	0.47[a]	4
Parahippocampal gyrus	28	R	27	−30	−21	0.89	5	21	−36	−15	0.93	5
		L	−18	−21	−18	1.57	5	−21	−30	−15	0.70	5
Thalamus			0	−9	9	2.10	4	3	−9	6	0.59	6
Corpus pineale		L	−3	−30	0	2.14	4	3	−24	−6	0.66	6
Cerebellum		R	42	−75	−36	0.83	5	27	−66	−30	0.83	5
		L	−42	−81	−36	1.94	5	−33	−84	−30	0.71[a]	4

Abbreviations: BA, Brodmann area; BOLD, blood oxygenation level–dependent; K-P, ketamine-placebo; MNI, Montreal Neurological Institute; IPK-LK, placebo-ketamine–lamotrigine-ketamine; Tn, minute time block into infusion.

[a] Not significant at $P < .05$, familywise error corrected, after small-volume correction using a sphere with a radius of 20 mm from the ketamine-placebo coordinate.

ketamine-placebo experiment also showed significantly greater responses to ketamine after placebo infusion than after lamotrigine infusion. In other words, most of ketamine's effects were antagonized by lamotrigine. Positive BOLD signal effects common to both experiments included the mid-posterior cingulate gyrus (BA23), superior temporal gyrus (BA22), middle temporal gyrus (BA21/39), inferior temporal gyrus (B20), supramarginal gyrus (BA40), hippocampus, and parahippocampal gyrus. In addition, deactivations after ketamine infusion in experiment 1 were closely reproduced in experiment 2 in the OFC (BA11)/subgenual cingulate and temporal pole (BA38). These results are summarized in Tables 1 and 2.

COMMENT

PHARMACO-MRI

This study describes the novel use of fMRI to detect directly the effects of ketamine on the regional BOLD signal rather than the modulatory effects of ketamine on a task. Most previous "direct" studies of the central ner-

Table 2. Areas With Significant Attenuation of the BOLD Signal After Intravenous Ketamine Infusion in the K-P and PK-LK Experiments

			K-P Experiment					PK-LK Experiment				
			MNI Coordinates			Peak % Signal Change	Peak at Tn	MNI Coordinates			Peak % Signal Change	Peak at Tn
Region	BA	Side	x	y	z			x	y	z		
Middle frontal gyrus	6	R	36	9	48	−2.31	8	33	12	51	−0.47[a]	3
Medial orbitofrontal gyrus	11	R	3	39	−21	−5.99	3	6	39	−15	−3.30	5
Superior temporal gyrus	38	R	30	3	−51	−3.08	4	30	3	−45	−2.66	7
		L	−27	3	−39	−2.15	5	−36	9	−45	−2.21	7
Lingual gyrus	17	R	6	−93	−12	−1.82	4	3	−87	−12	−1.59	8
	18	R	18	−87	−3	−0.81	8	18	−99	0	−0.73	8
		L	−18	−81	−6	−0.78	6	−9	−90	−12	−0.89	8
	19	R	33	−60	−9	−0.84	8	24	−75	−3	−0.40	7
		L	−24	−66	−9	−0.98	8	−24	−60	−15	−0.74	7
Caudate		L	−6	9	18	−1.17	4	−12	3	24	−0.35	3
Brainstem			0	−18	−39	−1.51	6	−3	−15	−33	−1.30	7
Cerebellum		R	6	−66	−30	−1.13	8	12	−60	−15	−0.57[a]	8
		L	−6	−57	−30	−0.85	7	−21	−57	−42	−0.38[a]	7
		R	48	−48	−42	−1.31	5	45	−51	−45	−1.17	5
		L	−48	−48	−39	−1.65	6	−45	−57	−45	−0.91[a]	7

Abbreviations: BA, Brodmann area; BOLD, blood oxygenation level–dependent; K-P, ketamine-placebo; MNI, Montreal Neurological Institute; PK-LK, placebo-ketamine–lamotrigine-ketamine; Tn, minute time block into infusion.

[a] Not significant at $P < .05$, familywise error corrected, after small-volume correction using a sphere with a radius of 20 mm from the ketamine-placebo coordinate.

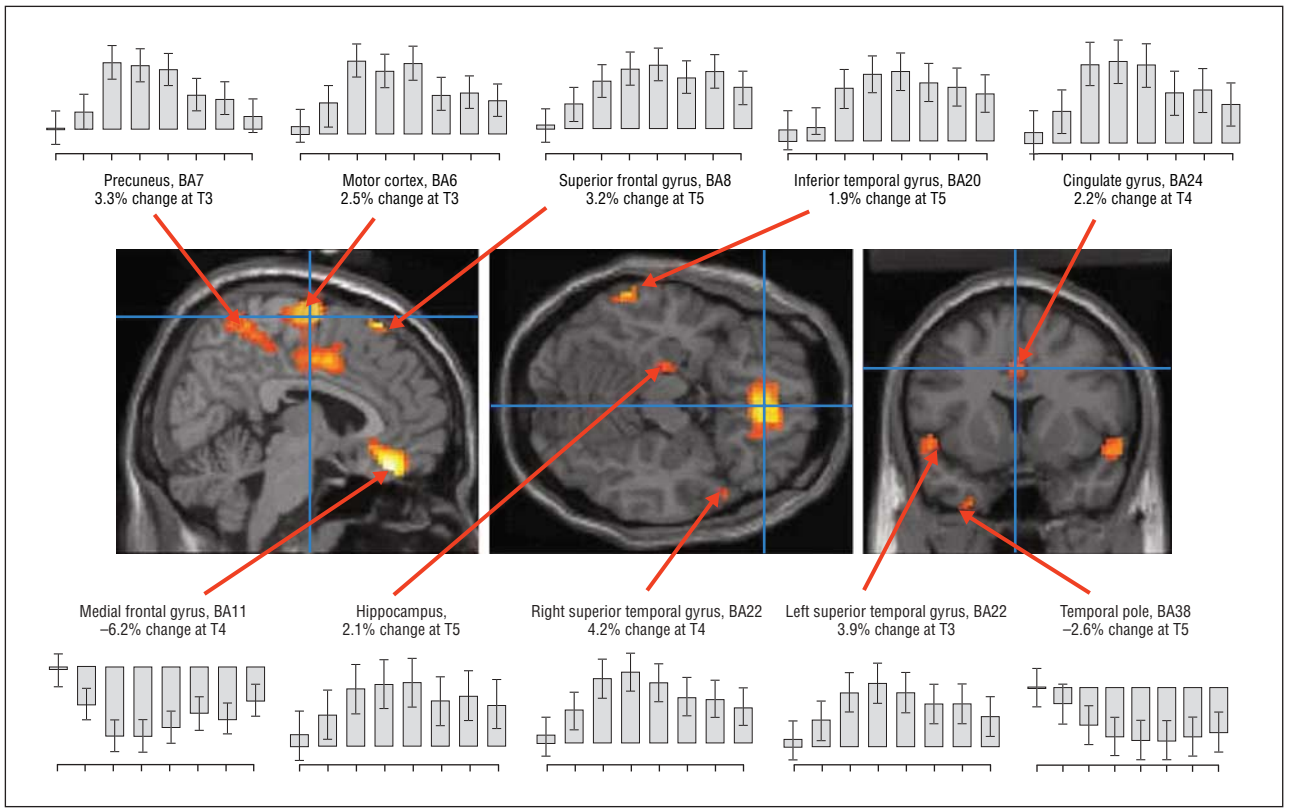

Figure 2. Regions showing significant effects of ketamine vs placebo on the blood oxygenation level–dependent signal during the 8-minute infusion. The *F*-ratio maps have a threshold of $P = .05$, familywise error corrected. The histograms show extracted time series of ketamine-placebo from areas showing significant main effects of the drug. Error bars represent 90% confidence intervals. BA indicates Brodmann area; T3, T4, and T5, the third-, fourth-, and fifth-minute time block after infusion, respectively.

vous system action of drugs have used an independent physiological/psychological or pharmacokinetic regressor to detect significant drug effects.[30] This approach may miss some regional brain activity induced by the drug if the time course does not match that of the regressor, which may be specific for particular responses or, in the case

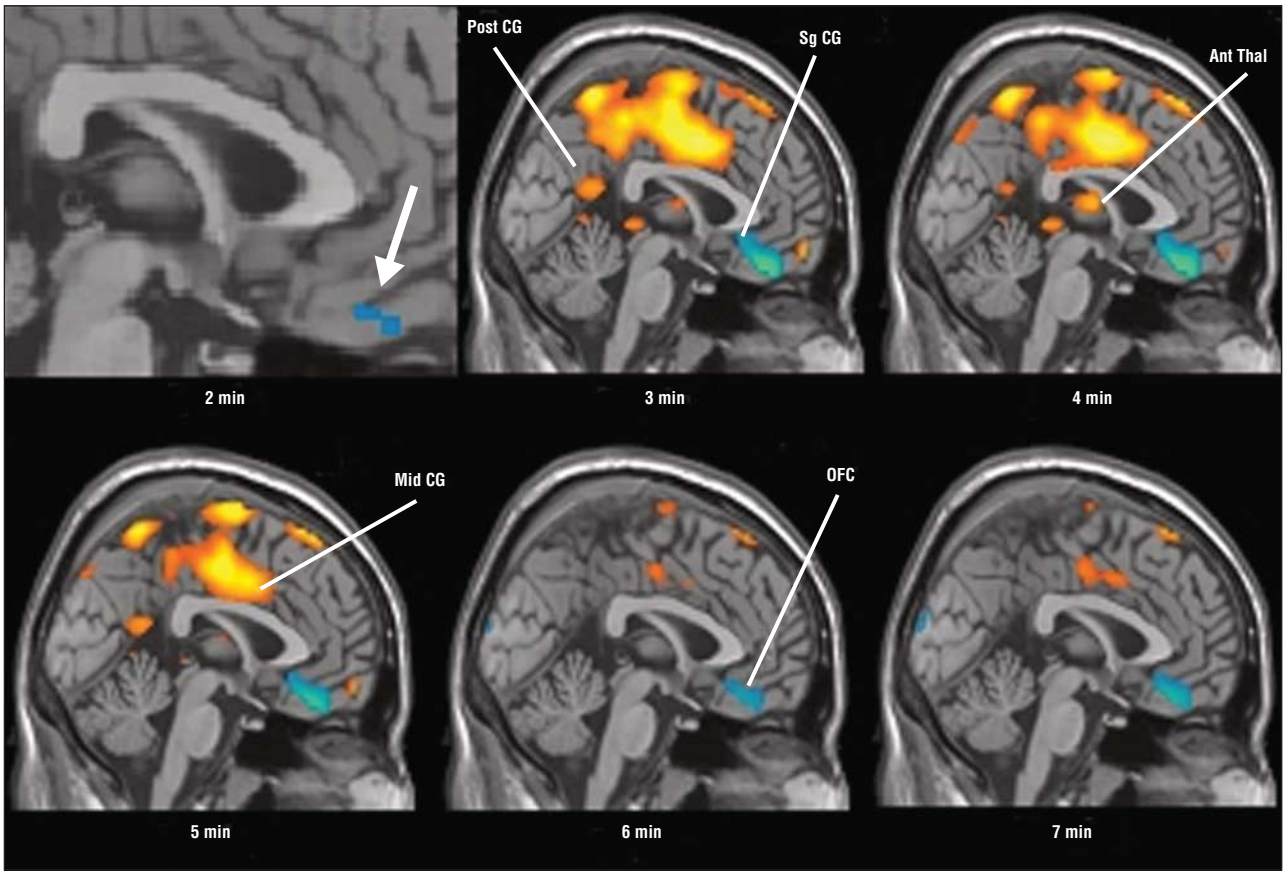

Figure 3. Time-dependent effects of ketamine-placebo. The *t*-maps show significant differences between ketamine and saline placebo infusion (baseline corrected) at successive minutes after infusion. Color scale: warm = blood oxygenation level–dependent (BOLD) signal increase; cold = BOLD signal decrease. Threshold $P < .05$, familywise error corrected, for each postinfusion time block. Ant Thal indicates anterior thalamus; Mid CG, by midcingulate gyrus; OFC, orbitofrontal cortex; Post CG, posterior cingulate; and Sg CG, subgenual cingulate. Arrow indicates that first response to ketamine is OFC deactivation.

of a pharmacokinetic regressor, a systemic average measure. Note that the pseudoblock analysis reveals different time courses in different brain regions, strengthening the case for this type of data-driven analysis method. The choice of 1-minute time blocks will militate against detecting very rapid effects (reversed in <1 minute) or very slow effects that are small in magnitude, but the compromise seems appropriate for ketamine.

ROLE OF GLUTAMATE

The BPRS and CADSS total and subscale scores were significantly increased after ketamine infusion during experiment 1. In experiment 2, lamotrigine pretreatment attenuated these scores, in most cases achieving statistical significance. The exception was the euphoria rating, which was unaffected by lamotrigine pretreatment. These results suggest that the subjective effects of ketamine are mediated by enhanced glutamate release. To the extent that the symptoms model psychosis, the findings are compatible with the theory that increased non-NMDA glutamate neurotransmission may underlie aspects of the symptoms of schizophrenia even if the primary event is impaired NMDA receptor function.[8,31-33] The reported efficacy of an mGluR2 agonist in schizophrenia is in keeping with this idea.[34,35] However, studies in postmortem brain point to impaired synaptic connectivity and glutamate release.[33,35] As suggested by some magnetic resonance spectroscopy studies, it may be that the control of glutamate release is dysfunctional in psychosis, perhaps increased in acute episodes but impaired in chronic.[34] In contrast, the mood-elevating effects of ketamine may directly involve blockade of NMDA function, as originally suggested by Anand et al,[11] who reported that lamotrigine augmented euphoria evoked by ketamine.

There is a good case that the BOLD signal response is principally mediated through the metabolic costs of glutamate synaptic neurotransmission,[36] but this may not constitute a final common pathway, and a role for other intercellular signaling pathways (eg, nitric oxide, adrenaline, and potassium), either independently or concertedly with glutamate, cannot be ruled out. Nevertheless, the important aspect of our work is that we are challenging the glutamate system relatively specifically with ketamine and isolating it with lamotrigine. However, neurovascular coupling is ultimately mediated; it is the upstream effects of glutamate on neural activity that are important in the context of this study. Furthermore, the effects of ketamine and lamotrigine are not due to some general effect on the hemodynamic response because the drugs did not show any general tendency to modify cognitive activations, as will be reported in a subsequent publication.

The pattern of BOLD signal responses to ketamine shows 3 main features of interest in relation to psychosis that

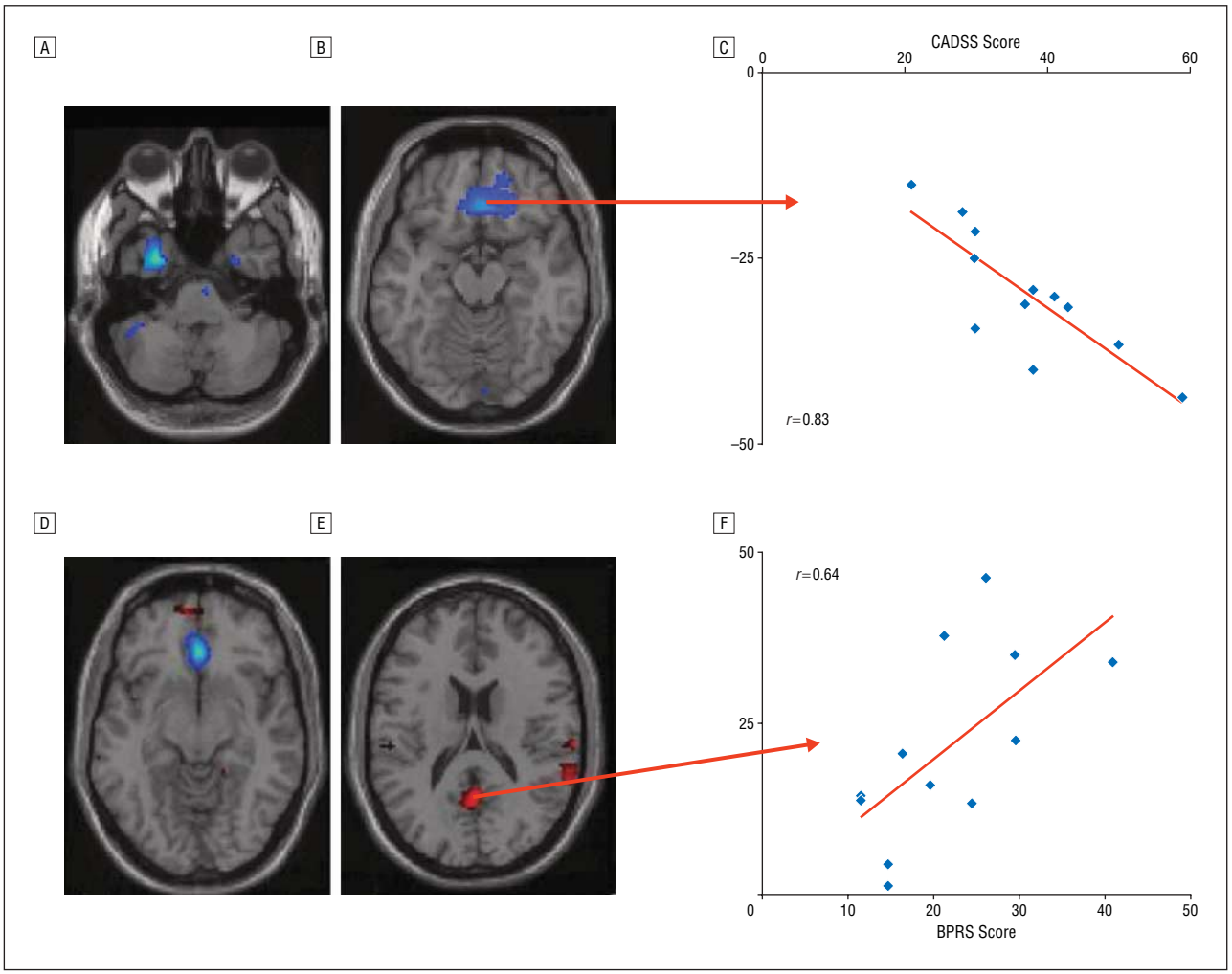

Figure 4. Regions activated by ketamine that correlate with dissociative (A-C) and psychotic (D-F) symptoms. The ketamine-placebo overall images show areas where normalized percentage signal change correlated with Clinician-Administered Dissociative States Scale (CADSS) (A and B) and Brief Psychiatric Rating Scale (BPRS) (D and E) scores. A, Temporal pole. B, Medial orbito-frontal cortex (arrow). Blue in A and B indicates areas of ketamine-evoked deactivation that correlate with symptoms. C, CADSS correlation with temporal pole (arrow). D, Subgenual cingulate deactivation (blue). E, Posterior cingulate activation (arrow). Red in D and E indicates areas of ketamine-evoked activation that correlate with symptoms. F, BPRS correlation with cingulate (arrow).

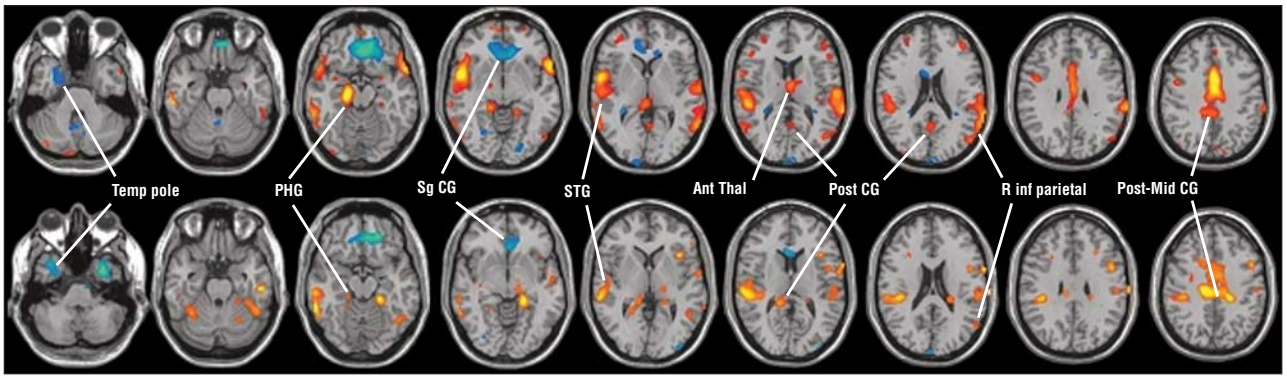

Figure 5. Overall effect of ketamine compared with placebo (top row) and with ketamine after lamotrigine pretreatment (placebo-ketamine–lamotrigine-ketamine; bottom row). Axial Statistical Parametric Mapping *t*-maps, every 9 mm starting at $z=-33$, have a threshold $P<.05$, familywise error corrected. Color scale: warm = blood oxygenation level–dependent (BOLD) signal increase; cold = BOLD signal decrease. Ant Thal indicates anterior thalamus; PHG, parahippocampal gyrus; Post CG, posterior cingulate gyrus; Post-Mid CG, posterior to midcingulate gyrus; R inf, right inferior; Sg CG, subgenual cingulate gyrus; STG, superior temporal gyrus; and Temp pole, temporal pole.

correspond to major neuroanatomical systems: (1) deactivations in ventral anterior limbic cortex, (2) activation in mid-posterior cingulate, and (3) activations in temporal lobe–hippocampus/parahippocampal cortex and superior, middle, and inferior temporal cortices. Similar to the symptoms evoked by ketamine, most of the BOLD sig-

nal responses were attenuated by lamotrigine pretreatment. This is demonstrated by most of the areas listed in the ketamine-placebo experiment in Table 1 being significantly attenuated in experiment 2 and by the remarkable similarity between the placebo-ketamine–lamotrigine-ketamine maps and the ketamine-placebo maps (Figure 5). This indicates that a single dose of lamotrigine partially antagonizes most of the BOLD signal responses to ketamine so that the lamotrigine-ketamine condition approximates the intravenous saline placebo condition of experiment 1. The results suggest that the symptoms and the BOLD signal responses evoked by ketamine involve increased glutamate release.

The correlational evidence suggests that some of the glutamatergic neural responses to ketamine produce the psychological effects. The subgenual cingulate deactivation and the mid-posterior cingulate activation may have a pivotal mediating role because BOLD signal responses in these areas correlated with dissociative and psychosis ratings. Furthermore, OFC deactivation preceded and outlasted all other BOLD signal changes. It is also of note that left frontal pole (BA10) activation correlated with BPRS scores because in the very different circumstances of FDG-PET, Breier et al[13] found correlations with the BPRS cognitive disorganization subscale score.

VENTRAL FRONTAL AND INFERIOR TEMPORAL CORTICAL DEACTIVATION

Ketamine caused decreased BOLD signal in medial OFC (BA10 and 11), subgenual cingulate (BA24 and part of 25), and bilateral temporal pole (BA38), and this implies a decrease in local glutamate release. However, the changes were convincingly reversed by lamotrigine. This suggests that ketamine-induced glutamate release remote from OFC activated a direct or indirect inhibitory input.

One neurochemical characteristic of the ventral cingulate cortex is its high concentration of serotonin uptake sites and serotonin 1A receptors.[37] It is known that NMDA antagonists evoke serotonin release and that serotonin receptors modify the behavioral effects of NMDA antagonists.[38,39] This suggests the speculative possibility that ketamine-evoked increases in serotonin 1A receptor activation caused hyperpolarization of pyramidal cells, resulting in the local decrease in BOLD signal in ventromedial prefrontal and temporal cortices. According to this view, lamotrigine partially reversed the ketamine-induced decrease in BOLD signal because the increase in serotonin release is likely to be triggered by ketamine-evoked glutamate release.

Several studies[40] suggest that the medial OFC is activated by rewards and has an important role in the online evaluation of motivational significance of cues in guiding choices. This function includes the organization of autonomic responses appropriate to the motivational significance of environmental cues. Suppression of these functions by ketamine-induced deactivation of ventromedial prefrontal cortex is a plausible substrate for the dissociative state of emotional detachment it produces.

Mayberg et al[41] has shown that the subgenual cingulate is overactive in depression whereas the dorsal frontal regions and posterior cingulate are underactive and that successful treatment normalizes the pattern. The effect of ketamine resembles the pattern of normalization: a decreased OFC/subgenual cingulate BOLD signal and increases in the dorsolateral prefrontal cortex (BA8) and posterior cingulate. The results of recent studies suggest that a single dose of intravenous ketamine exerts a delayed antidepressant effect[42,43]; however, a study with memantine showed negative results.[44] That an increased subgenual cingulate may be the organizing region is suggested by the apparent efficacy of deep brain stimulation of this structure in treatment-resistant depression.

MID-POSTERIOR CINGULATE

The medial OFC, subgenual cingulate, and temporal pole (BA38) project specifically to the dorsal midcingulate (BA23/24), which was strongly activated, along with the overlying dorsomedial motor and parietal cortices after ketamine infusion. It has been suggested that limbic modulation of motor behavior and facial expression is mediated by the afferents from the OFC and polar temporal cortex to the midcingulate motor cortex.[45] These inputs were deactivated by ketamine. This would account for the lack of affective expression seen in this study and the vacant lack of expression described in users (see also discussion of catatonia by Northoff and colleagues[46,47]). The findings suggest that one mechanism of affective blunting in psychosis is impaired function in the basolateral limbic cortex or its connection with the midcingulate motor system.

Midcingulate activation extended into the posterior cingulate (BA23/30/31) and precuneus (BA7), and this correlated with the dissociative and psychosis ratings. The posterior cingulate and cuneus have been implicated in memory recall and visual imagery, possibly with a special role in self-awareness.[48,49] It is striking that neural activity in posterior cingulate and ventromedial prefrontal cortex changed in opposite directions after ketamine; their activity is normally strongly correlated in the resting, self-reflective, or default mode of processing.[50]

Experiments in rodents indicate that the posterior cingulate and retrosplenial cortex are a focus of the effects of systemically applied NMDA channel blockers. For example, they induce neuronal vacuolization and expression of heat shock protein and immediate early gene expression in this region. Tomitaka et al[51] and Sharp et al[52] showed that injection of MK801 into the thalamus could induce neuronal changes in the posterior cingulate and that thalamic injection of GABA agonists could prevent the neuronal effects of systemic MK801 in the posterior cingulate. Although the findings suggest that loss of GABA tone in the thalamus disinhibits glutamatergic projections to the cortex, they do not explain why the posterior cingulate is selectively affected and other cortical areas that receive inputs from the nonspecific thalamic system are not. Focal activation of the anterior thalamus was seen after ketamine infusion in the present study, and the widespread projections of this nucleus may have contributed to the activation seen in several cortical regions.

Two studies in humans have reported focal effects of ketamine in the posterior cingulate. Northoff et al[24] reported that ketamine lessened activation of the poste-

rior cingulate during retrieval of previously exposed words. Activation in the ketamine group correlated with some aspects of the symptom profile. The direct effect of ketamine on this region might have increased neuronal processing of retrieval in the study by Northoff et al,[24] thus accounting for the correlation with symptom profile. Aalto et al[53] reported that intravenous ketamine evoked release of dopamine in this region, as detected by displacement of [^{11}C]fallypride binding specifically in BA23/31. To determine whether dopamine release in this region mediated the BOLD signal response we observed, it would be necessary to determine whether dopamine antagonists block the BOLD signal response. The posterior cingulate and cuneus have been implicated in autobiographical memory and self-reflection, and aberrant activation could be related to an impaired sense of self after ketamine infusion and in psychosis. The differential effect of ketamine in decreasing ventral anterior cingulate and increasing mid-posterior cingulate BOLD signal strongly resembles the pattern of aberrant cingulate metabolism in untreated patients with schizophrenia described by Haznedar et al.[54]

TEMPORAL CORTEX AND HIPPOCAMPAL REGION

The mid-posterior cingulate cortex is the focus of extensive reciprocal connections with the hippocampus and parahippocampal regions and superior, middle, and inferior temporal cortices.[55,56] Each of these regions showed increased BOLD signals after ketamine infusion, and each has been implicated in the pathogenesis of the positive symptoms of schizophrenia, for example, in fMRI studies in hallucinating patients.[57,58] Participants in the present study did not experience frank hallucinations, but the results suggest that their altered perceptual experiences after ketamine infusion may have been due to aberrant processing of auditory information in superior temporal cortex, of motor plans in midcingulate cortex, and of self and memory in posterior cingulate and parahippocampal gyrus caused by enhanced glutamate release.[59,60]

In conclusion, ketamine evokes abnormal perceptual experiences and dissociation by increasing glutamate release. The latter results in (1) aberrant perceptual processing in a network of auditory and visual association cortices centered on mid-posterior cingulate and (2) focal suppression of the OFC/subgenual cingulate and temporal pole (BA38), which prevents integration of aberrant percepts with visceromotor function and the sense of self. These mechanisms suggest a neural basis for the splitting of mental functions or schizophrenia that Bleuler[61] proposed gave rise to the "fundamental symptoms" of the disorder. These findings also suggest that ketamine-induced suppression of OFC/subgenual cingulate function may mediate antidepressant effects by disconnecting the excessive effect of an aversive visceromotor state on cognition and the self in depression. It would seem an important research priority to determine how ketamine suppresses ventromedial frontal neuronal function.

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Correspondence: J. F. William Deakin, PhD, FRCPsych, FmedSci, Neuroscience and Psychiatry Unit, The University of Manchester, G.907 Stopford Building, Oxford Rd, Manchester M13 9PT, England (bill.deakin@manchester.ac.uk).

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