Association of Ketamine-Induced Psychosis With Focal Activation of the Prefrontal Cortex in Healthy Volunteers

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Objective: *Agents that antagonize the* N-*methyl-*D*-aspartic acid (NMDA) receptor, such as phencyclidine and ketamine, produce an acute psychotic state in normal individuals that resembles some symptoms of schizophrenia. The aim of this study was to determine which brain regions are involved in NMDA receptor-mediated psychosis.* *Method:* *Positron emission tomography with [18F]fluorodeoxyglucose was used to determine cerebral metabolic activity in 17 healthy volunteers while an acute psychotic state was induced simultaneously by the administration of subanesthetic doses of ketamine.* *Results:* *Ketamine produced focal increases in metabolic activity in the prefrontal cortex and an acute psychotic state. A change in one psychotic symptom, conceptual disorganization, was significantly related to prefrontal activation.* *Conclusions:* *These data suggest that the prefrontal cortex may be involved in mediating NMDA receptor-induced psychosis.*

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Phencyclidine (PCP) antagonizes the *N*-methyl-D-aspartic acid (NMDA) receptor (1, 2), a major site of excitatory neurotransmission in the brain, and produces a broad range of cognitive and behavioral disturbances that include psychosis (3, 4). As early as the 1950s, it was noted that in healthy volunteers, PCP and its analogues produced an acute psychotic state that resembled some of the symptoms of schizophrenia, particularly thought disorder, delusions, perceptual alterations, and negative symptoms (5–8). This led to speculation that PCP might be a useful pharmacologic tool for studying pathophysiologic processes of this illness. Subsequently, it was learned that PCP had long-lasting behavioral effects in some individuals and that PCP and other potent NMDA antagonists caused neuropathologic damage in the rat brain (9). Ketamine, on the other hand, is a lower-potency NMDA antagonist and a widely used "dissociative" anesthetic agent (10). It has a short half-life, and in subanesthetic doses it does not appear to have long-term behavioral effects in healthy volunteers (11). Subanesthetic doses of ketamine produce a range of cognitive and behavioral effects similar to those of PCP, including psychotic symptoms (11, 12). Thus, ketamine has been proposed as a pharmacologic probe of NMDA function for clinical studies and provides a means of studying NMDA-mediated psychosis in human subjects (11, 12).

Brain regions responsible for NMDA-mediated psychosis have not been established. NMDA receptors are located throughout the mammalian brain, with highest densities in the cerebral cortex, limbic system, and striatum (13). Autoradiographic studies of PCP and ketamine administration in rodents demonstrate activation in limbic and some cortical regions (14–17). Low doses tend to focally activate the neocortex and limbic structures, while higher doses cause more homogeneous activation throughout these areas. Deactivation in somatosensory and auditory systems has been reported (14–17), and in the case of PCP there is some evidence that acute activation predominates, with deactivation occurring 24 hours later (18). In a $[^{15}O]H_2O$ positron emission tomography (PET) study of five patients with schizophrenia (19), ketamine caused an increase in blood flow in the anterior cingulate and a decrease in blood flow in the hippocampus and primary visual cortex.

The aim of the present study was to identify brain regions involved in NMDA-induced psychosis in healthy human subjects. We examined cerebral metabolic activity in 17 healthy volunteers, using [18F]fluorodeoxyglucose (FDG) and PET, while simultaneously inducing an acute psychotic state with subanesthetic doses of ketamine. Healthy volunteers, as opposed to patients with neuropsychiatric illnesses, were considered desirable for this study because they are free of the

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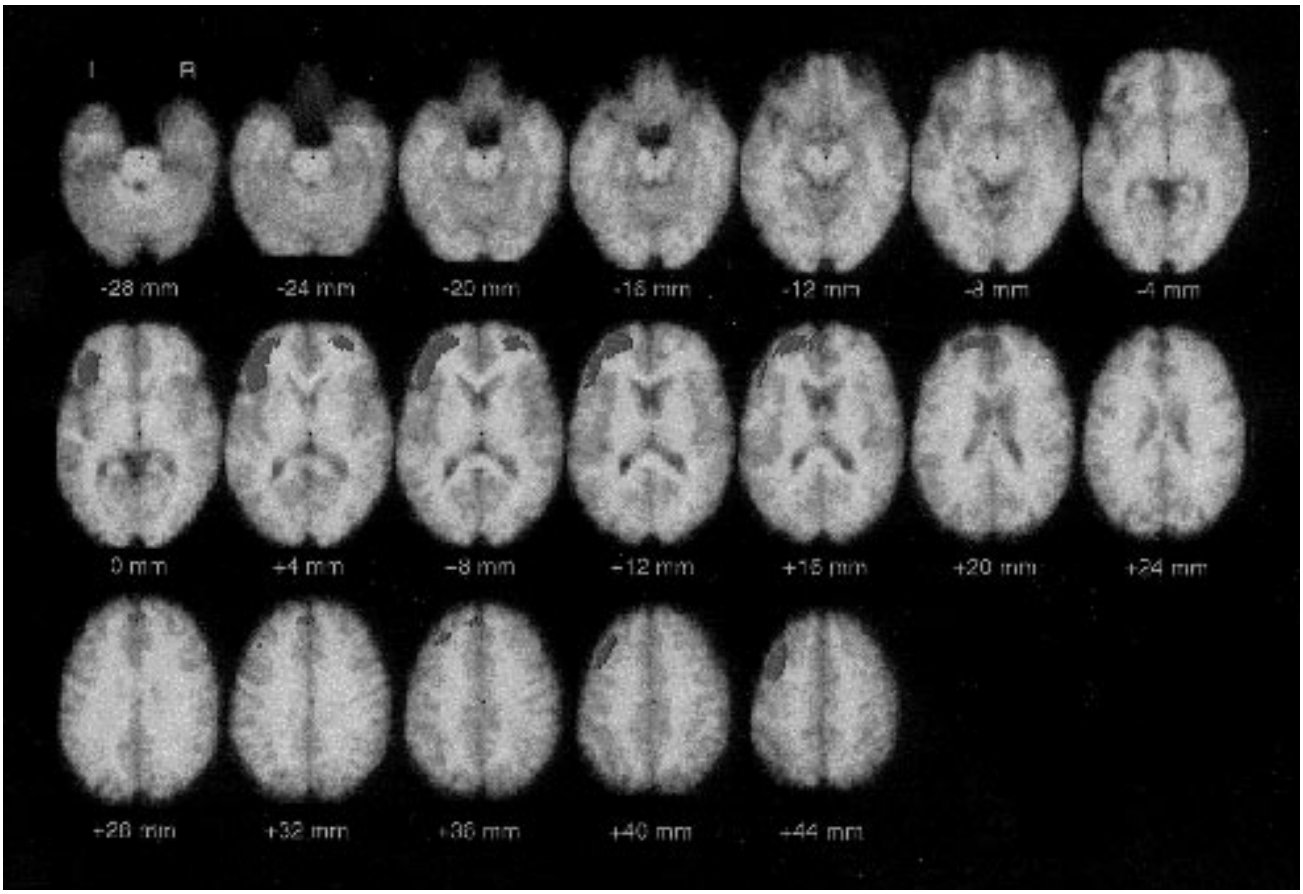
FIGURE 1. Adjusted Mean Cerebral Metabolic Activity During Ketamine Infusion After Subtraction of Metabolic Data Obtained During Placebo Infusion in 17 Healthy Volunteers in a PET Study[a]



[a]The data are displayed as statistical maps overlaid on a single subject's magnetic resonance imaging scan, with each individual transverse slice cut parallel to the anterior-posterior commissural plane according to the brain atlas of Talairach and Tournoux (22). Negative and positive slice numbers are millimeters below and above the anterior-posterior commissural plane.

effects of prior drug treatment and long-standing pathophysiologic processes. The ketamine dose we used is severalfold lower than the anesthetic dose (10) and was determined on the basis of earlier studies of ketamine's cognitive effects at subanesthetic doses in healthy subjects (11, 12) and our own dose-finding studies. We chose the lowest dose that consistently produced psychosis, in order to reduce the likelihood of metabolic effects in regions not involved in this phenomenon.

METHOD

Seventeen healthy volunteers (15 male and two female; mean age=30.4 years, SD=6.8) were recruited through the National Institutes of Health normal volunteer program and participated in the study after giving written informed consent to the protocol, which was approved by the institutional review board. Three subjects had completed high school, eight had a partial college education, five were college graduates, and one had completed graduate school. The group's racial/ethnic composition was 14 white, two black, and one Hispanic. The subjects were in good physical health, as determined by physical examination, ECG, and screening blood work, and had no past or current psychiatric illnesses, including polysubstance abuse and alcohol dependence, as determined from a structured diagnostic interview (20).

The subjects participated in two FDG PET studies conducted on separate days (mean number of days between studies=7.8, SD=6.5). On one day, ketamine (a 0.12-mg/kg bolus, followed by a 0.65-mg/kg constant infusion for 1 hour) was administered, and on the other day, placebo (saline) was administered for 1 hour. Ketamine and placebo administration was double-blind and in random order.

PET Studies

The PET studies were conducted with a Scanditronix (Uppsala, Sweden) PC 1024-7B tomograph. Four blocks of seven axial images were obtained sequentially as interleaved data sets with 3.5-mm spacing between each of the blocks. In-plane resolution was 5.2 mm, and axial resolution was 10 mm. A thermoplastic mask was fitted for each subject and fixed in place to minimize head movement. Eye patches were fixed to the mask, and lights were dimmed throughout the procedure. Following a transmission scan, the ketamine and placebo infusions commenced. Ten minutes after the initiation of infusions, a single injection of 5 mCi of FDG in 9 cc of normal saline was administered. Serial sampling of warmed, "arterialized" venous blood was conducted throughout the postinjection and scanning periods. Thirty-five minutes after FDG injection, scanning began. Regional cerebral metabolic rates of glucose utilization were determined on the basis of the Sokoloff model (21). In an attempt to "standardize" mental activity across subjects and conditions, we asked subjects to per-

form a simple auditory continuous performance task during FDG uptake; this involved indicating discrimination of a low-volume tone by pressing a hand-held button.

Scans were rescaled and resliced to produce stereotactically normalized images corresponding to those of the atlas of Talairach and Tournoux (22). Individual images were registered according to the method of Woods et al. (23). Images were then "smoothed" with Gaussian filters of 20 mm, 20 mm, and 12 mm for the x, y, and z axes, respectively. Differences between the ketamine and placebo conditions were evaluated with the use of the statistical parametric mapping developed by Friston et al. (24–26). A pixel-based analysis of covariance produced two metabolic maps (placebo infusion and ketamine infusion) for each subject, normalized to mean global metabolic activity; changes in metabolic activity from placebo data were determined by calculating F ratios for planned comparisons and using a pooled estimate of error variance. The F values were converted to z scores. Clusters of contiguous voxels that exceeded a threshold z score of 3.09 were identified and assessed for significance ($p<0.05$) by means of the particle analysis method of Friston et al. (27). This method determines the probability that an activation or deactivation of a given spatial extent (i.e., cluster) could occur by chance anywhere in the brain volume under investigation. Each significant cluster is listed with its volume (in centimeters cubed) and probability level. The probability level is determined from the following equation:

$$p(n_{max} \geq k) = 1 - \exp(-E\{m\} \cdot e^{-\beta k^{2/D}}),$$

where n_{max} refers to the maximum number of voxels in any of the clusters found, k is the parameter in the equation, exp and e are the base of the natural logarithm, E is the expected value, m represents the number of clusters, β is a parameter that depends on the number of significant clusters and the number of voxels throughout the brain for which the associated z value exceeded the threshold, and D is the dimensionality of the data set (three in this case) (27). Estimated spatial smoothness (full width at half maximum) was 10.99 mm in x, 10.65 mm in y, and 12.74 mm in z (Friston's W=2.72). Local maxima within each cluster were identified as voxels that had a higher z score than any voxel in a 1.8×1.8×2-cm space (9×9×5 voxels) centered on that voxel. The locations of local maxima are expressed as Talairach and Tournoux coordinates and corresponding Brodmann areas.

For correlative analyses with behavioral data, regions of interest were placed on individual unprocessed images before their deformation and registration for pixel-by-pixel analyses. This was done post hoc (i.e., regions of interest were placed on areas corresponding to regions of significant activation that were identified in the pixel-by-pixel analyses). The regions of interest were spherical in shape and placed blind to drug administration condition (i.e., ketamine versus placebo), and data were normalized for global activity (region of interest divided by global activity, mg glucose/100 g tissue per minute).

Behavioral Assessments

Behavioral ratings were made from a clinical interview conducted by a research psychiatrist (A.K.M.) blind to ketamine versus placebo administration, using the Brief Psychiatric Rating Scale (BPRS) (28). Ratings were obtained before ketamine and placebo administration (baseline), 10 minutes after commencement of ketamine and placebo administration (during drug exposure), and 30 minutes after the cessation of the infusion (end of the study). Each BPRS item is rated from 1 (not present) to 7 (severe), and scores were based on the content and form of verbal products of the subject. Four symptoms (conceptual disorganization, hallucinatory behavior, unusual thought content, and suspiciousness) were summed as a psychosis cluster, and both the cluster and individual symptoms were examined. The anxiety-depression cluster, composed of three items, was also examined. Although we (11) and others (12) have reported that ketamine induces negative symptoms, these were not included in this study because of the limitations in assessing these symptoms while a subject is actively undergoing a PET scan. The thermoplastic mask and positioning in the scanner prevented adequate visual inspection for appropriately assessing blunted affect and social withdrawal.

An analysis of variance with drug condition (ketamine versus placebo) and time as factors was conducted. Drug-by-time interactions are reflected by F and p values. Post hoc Newman-Keuls tests were used to determine significant differences between the drug conditions at the individual time points, and Pearson's correlation coefficients were used to relate the ratings made during drug exposure on the ketamine infusion test day to the regions of interest from the ketamine infusion test day. The data are presented as means and standard deviations, and the comparisons are two-tailed.

TABLE 1. Local Maxima for Each Area Demonstrating Significantly Increased Metabolic Activity During Ketamine Infusion as Compared to Placebo Infusion in 17 Healthy Volunteers in a PET Study

Area of Significantly Increased Activity[a]	Talairach Coordinate			z Score[b]
	x	y	z	
Left inferior, middle, and medial frontal cortex (16.7 cm^3, $p<0.00001$)				
Inferior (area 45)	–42	+28	+4	4.39
Middle (area 10)	–30	+50	+12	4.19
Medial (area 10)	–4	+54	+20	3.73
Left middle frontal cortex (area 9) (3.0 cm^3, p=0.0009)	–42	+8	+44	3.98
Right middle frontal cortex (area 10) (1.7 cm^3, p=0.02)	+26	+52	+4	4.12

[a]Brodmann's area for each local maximum is indicated in parentheses.
[b]Conversion of F value for planned comparison of effect of ketamine versus placebo on metabolic activity.

RESULTS

Ketamine produced bilateral increases in metabolic activity in the prefrontal cortex but no significant activation in other areas (figure 1, table 1). Probability levels for each cluster were determined according to the method of Friston et al. (27), as mentioned in the Method section. Two significant clusters of increased activity were found on the left: one large cluster (16.7 cm^3) including the inferior, middle, and medial frontal gyrus, and another that was more superiorly located (3.0 cm^3) in the middle frontal gyrus (table 1). There was one significant cluster of increased activity on the right (1.7 cm^3) in the middle frontal gyrus. There was a very small area of deactivation (1.3 cm^3) (p=0.04, N= 17) in the right cerebellum (Brodmann's area 37; Talairach and Tournoux coordinates +14, –61, –16). There were no significant differences in global mean metabolic activity for placebo (11.37 mg glucose/100 g tissue per minute, SD=1.93) and ketamine (11.65 mg glucose/100 g tissue per minute, SD=1.93) (t=0.52, df=16, p=0.61).

Similar to our previously reported findings (11), ketamine produced significant increases in psychosis, beginning moments after the bolus injection and persisting throughout the hour-long infusion period (table 2). The individual psychotic symptoms that were significantly affected were conceptual disorganization, unusual thought content, and hallucinatory behavior; suspiciousness was not significantly affected, and there were no significant effects on the anxiety-depression factor (table 2).

Regions of interest were placed on the left and right

TABLE 2. Effects of Ketamine and Placebo on BPRS Scores of 17 Healthy Volunteers in a PET Study

Symptoms and Drug Condition	Score: Baseline Mean	Baseline SD	During Drug Infusion Mean	During Drug Infusion SD	End of Study Mean	End of Study SD	Analysis[a]: F (df=2, 32)	p
Psychosis cluster[b]							39.3	<0.0001
Placebo	4.0	0.0	4.4	1.0	4.0	0.0		
Ketamine	4.2	0.5	9.2[c]	3.2	4.7	0.8		
Conceptual disorganization							26.8	<0.0001
Placebo	1.0	0.0	1.1	0.5	1.0	0.0		
Ketamine	1.1	0.3	2.7[c]	1.1	1.2	0.4		
Unusual thought content							16.4	<0.0001
Placebo	1.0	0.0	1.1	0.5	1.0	0.0		
Ketamine	1.0	0.0	2.7[c]	1.4	1.3	1.0		
Hallucinatory behavior							3.7	0.03
Placebo	1.0	0.0	1.1	0.2	1.0	0.0		
Ketamine	1.0	0.0	1.5	0.9	1.0	0.0		
Suspiciousness							1.7	0.20
Placebo	1.0	0.0	1.0	0.0	1.0	0.0		
Ketamine	1.0	0.0	1.2	0.8	1.0	0.0		
Anxiety-depression cluster							0.5	0.50
Placebo	3.2	0.4	3.2	0.4	3.0	0.0		
Ketamine	3.2	0.6	3.4	1.1	3.1	0.3		

[a]Repeated measures analysis of variance, drug-by-time interaction.
[b]Consists of conceptual disorganization, unusual thought content, hallucinatory behavior, and suspiciousness.
[c]Significantly different from placebo condition (Newman-Keuls post hoc test, df=32, p<0.001).

middle frontal gyri that appear on three consecutive slices beginning at the anterior-posterior commissural line and extending superiorly approximately 12 mm, which corresponded to bilateral areas of significant activation identified by the statistical parametric mapping. There was a significant relationship between ketamine-induced changes in conceptual disorganization and right and left prefrontal metabolic activity (figure 2). The three other psychotic symptoms, the psychosis cluster, and the anxiety-depression cluster were not related to frontal metabolic activity (range of correlations: r=–0.32, p=0.21, to r=0.20, p=0.43; df=16). Age was not significantly related to either left prefrontal metabolic activity (r=–0.04, df=16, p=0.90) or right prefrontal metabolic activity (r=–0.12, df=16, p=0.60).

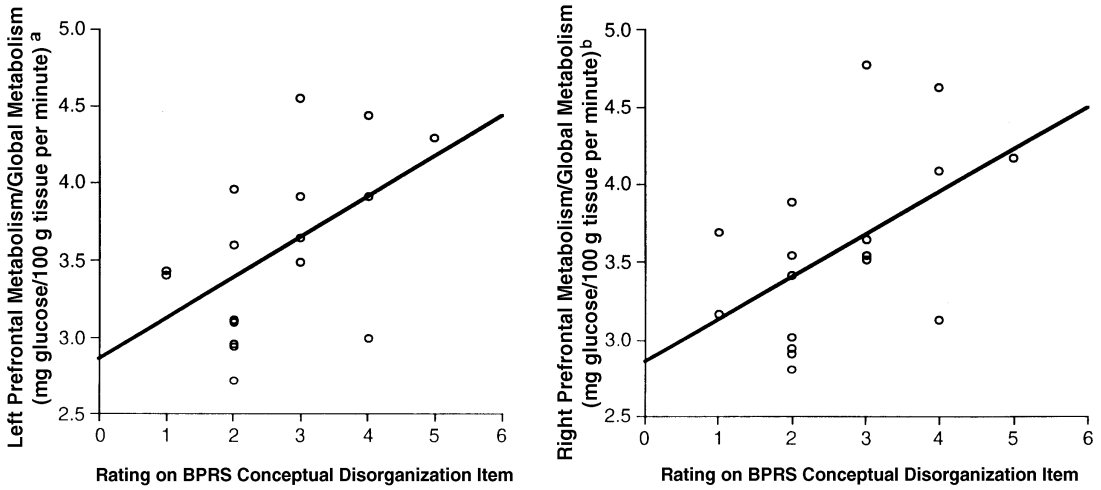
DISCUSSION

The results of this study indicate that the prefrontal cortex is focally activated during ketamine-induced psychosis in healthy individuals. Ketamine produced bilateral prefrontal activation, with greater effects on the left side, and an acute psychosis that was characterized by conceptual disorganization, perceptual alterations, and unusual thought content. Conceptual disorganization was found to be specifically correlated with prefrontal metabolic effects, providing support for the hypothesis that the prefrontal cortex may be involved in the mediation of ketamine-induced thought disorder.

Although ketamine has effects at other sites, including the σ receptor, μ opiate receptor, acetylcholinesterase, and monoamine transporter sites, several lines of evidence indicate that ketamine-induced psychosis is mediated through the PCP site. Ketamine's affinity for the PCP site is severalfold greater than for other sites (29, 30), and drug discrimination studies indicate that low doses of NMDA antagonists enhance PCP site selectivity (31). Thus, our low-dose infusion paradigm would favor mediation of effects through the PCP site. Selective agents for σ, opiate, cholinergic, and monoamine transporters do not block ketamine-induced cognitive effects (32). Moreover, selective agents for these systems produce behavioral states unlike that induced by ketamine, while the ketamine-induced behavioral state is similar to the clinical picture produced by other agents with even higher selectivity for the PCP site than ketamine (such as PCP itself) (5–8, 11, 12).

A striking finding in this study was the focalization of ketamine-related metabolic effects, in that activation was restricted to the prefrontal cortex. Other neocortical and limbic areas are rich in NMDA receptors (13), and studies in rodents have demonstrated ketamine-induced increased glucose utilization in limbic areas (14). The reason for activation of the prefrontal cortex without metabolic effects in other brain regions rich in NMDA receptors may have been the ketamine dose we used; it was sufficient to produce a psychotic state consistently but low enough to minimize activation in brain regions not involved in psychosis. Studies in laboratory animals have demonstrated dose-dependent effects of ketamine and other NMDA antagonists on glucose utilization in the neocortex in which low doses produced a laminar pattern of increased metabolic activity and higher doses produced more homogeneous effects (14, 17, 33). Weissman and colleagues (33) found that low doses of PCP increased glucose utilization in the superficial layers of the frontal cortex, whereas high

FIGURE 2. Relationships Between Ketamine-Induced Effects on Left and Right Prefrontal Metabolism and Ratings of Conceptual Disorganization in 17 Healthy Volunteers in a PET Study



[a]r=0.53, df=16, p=0.03. [b]r=0.52, df=16, p=0.03.

doses reduced glucose utilization in this region. Studies in rodents have shown that NMDA antagonists produce increased glucose utilization in the limbic cortex, with more marked increases when higher doses were used (14, 17, 33). In addition, the rodent prefrontal cortex is comparatively underdeveloped (34), so there may be poor homology between humans and rats for specific prefrontal cognitive processes. Last, it is also possible that additional regions may have been affected by ketamine but were below the statistical threshold of detection used in this study.

In a recently reported study of five neuroleptic-treated patients with schizophrenia (19), ketamine caused blood flow increases in the cingulate cortex and decreases in the visual cortex and hippocampus. Several differences between this study and ours make direct comparisons difficult. The differences include subjects (patients versus healthy volunteers), neuroleptic treatment, study group size, ketamine dose and administration (single bolus versus bolus/constant infusion), use of $[^{15}O]H_2O$ versus FDG, and study design (preketamine versus postketamine comparisons as opposed to a randomized, placebo-controlled design). Nevertheless, the activation of the anterior cingulate (recently reported) and of the prefrontal cortex (reported here)—two regions in close neuroanatomical proximity and functionally interrelated (34)—provides support for anterior corticolimbic involvement in ketamine-induced psychosis. We are now examining the effects of ketamine on cerebral metabolic activity in neuroleptic-free and neuroleptic-treated patients with schizophrenia, which will add to the growing body of data relevant to this issue.

The prefrontal cortex is of particular interest as a possible site of NMDA-associated psychosis. In addition to having a high density of NMDA receptors (13), it integrates cortical and subcortical information for the execution of complex cognitive programs (34). Glutamate is a major neurotransmitter in cortical-subcortical and cortical connections (35). Perturbation of normal prefrontal glutamatergic neurotransmission would be expected to disrupt these association functions. In nonhuman primates prefrontal cortical lesions that include association areas cause distractibility, poor concentration, and impaired performance on cognitive tasks that reflect thought integration and processing (36, 37). It is reasonable to hypothesize that disruption in prefrontal association functions could be involved in the pathophysiology of psychosis. In schizophrenic patients, thought disorder has been positively correlated with right frontal blood flow (38), and activation of auditory hallucinations has been associated with increases in left prefrontal blood flow (39)—both in regions corresponding to areas activated in this study (i.e., Brodmann's areas 10 and 45, respectively).

Several caveats should be considered before interpreting the relevance of these data for the pathophysiology of schizophrenia. First, caution must be used in extrapolating from the effects of an acute pharmacologic challenge to a chronic neuropsychiatric illness. Although the drug administration was double-blind, it was generally apparent when ketamine was given because of its psychotogenic effects. In addition, the behavioral state produced by subanesthetic doses of ketamine bears resemblance to some, but not all, features of schizophrenia (11, 12). Conceptual disorganization, perceptual alterations, and unusual thought content are observed in both conditions, whereas gross temporal and spatial distortions are commonly observed with NMDA antagonists but are relatively rare in schizophrenia. Conceptual disorganization is particularly important, because it is a hallmark psychotic symptom of schizophrenia. Although ketamine-induced conceptual disorganization resembles the thought dis-

order observed in schizophrenia, the magnitude of ketamine's effects is relatively modest, and a single BPRS item does not adequately reflect this complex behavioral state.

In several brain imaging studies of subjects with schizophrenia, the prefrontal cortex has not been activated during certain cognitive tasks (40–42), a phenomenon called "hypofrontality." This literature has been summarized by Andreasen and associates (40). Our data suggest, however, that prefrontal *activation* may be related to some positive-type symptoms of this illness. Perhaps the acute onset of these symptoms is an energy-demanding state reflected in activation in brain imaging studies, whereas chronic symptoms relate to relative decrements in blood flow and glucose utilization. Support for this hypothesis comes from investigations in schizophrenic patients which have demonstrated that prefrontal activation is associated with the acute onset of specific psychotic symptoms (39, 43) and from studies indicating that chronic symptoms, such as negative symptoms, are related to prefrontal hypofunction (40, 44, 45).

In conclusion, our data suggest that subanesthetic doses of ketamine produce focal prefrontal activation and an acute psychotic state in healthy subjects. A component of the psychosis, conceptual disorganization, was related to prefrontal activation. These findings contribute to a growing body of data implicating NMDA/glutamate systems and the prefrontal cortex in the genesis of some forms of psychotic symptoms.

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