

# Comparative and Interactive Human Psychopharmacologic Effects of Ketamine and Amphetamine

## *Implications for Glutamatergic and Dopaminergic Model Psychoses and Cognitive Function*

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**Background:** In healthy individuals, ketamine hydrochloride and amphetamine sulfate produce cognitive, behavioral, and subjective effects resembling endogenous psychoses. Studying the comparative and interactive effects of these agents may provide insights into the roles of the glutamate and monoamine systems in psychosis and cognition.

**Objectives:** To directly compare the effects of ketamine and amphetamine and to explore their interactive effects within individuals.

**Design:** Placebo-controlled, randomized, double-blind psychopharmacologic trial.

**Setting and Participants:** Forty-one healthy individuals recruited from the community who completed up to 4 test days.

**Main Outcome Measures:** On each test day, participants received amphetamine (a 1-minute infusion of amphetamine sulfate, 0.25 mg/kg, or saline) and ketamine (a 1-minute intravenous infusion of ketamine, 0.23 mg/kg, followed by a 1-hour infusion of 0.5 mg/kg or an identical saline bolus and infusion). The order of amphetamine and ketamine infusions was randomized.

**Results:** At the doses studied, ketamine and amphetamine produced positive symptoms and euphoria. However, perceptual changes were produced only by ketamine, and hostility, grandiosity, and somatic concern were stimulated only by amphetamine. Amphetamine and ketamine produced conceptual disorganization, but only ketamine produced concrete ideation and unusual mannerisms. Ketamine produced negative symptoms and disrupted delayed recall. Ketamine and amphetamine showed 3 types of interactive effects: (1) amphetamine attenuated the impairment of working memory produced by ketamine; (2) amphetamine and ketamine had additive effects on thought disorder, arousal, and euphoria; and (3) amphetamine and ketamine had less-than-additive effects on psychosis.

**Conclusions:** These findings implicate *N*-methyl-D-aspartate glutamate receptors and dopamine systems in psychosis. However, glutamate and dopamine may differentially contribute to psychosis, thought disorder, and euphoria. Regarding medication development for cognitive dysfunction, the pattern of the interactive effects of ketamine and amphetamine is consistent with the hypothesis that facilitation of prefrontal cortical dopamine levels would attenuate some cognitive impairments associated with deficits in *N*-methyl-D-aspartate receptor function.

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**D**YSFUNCTION IN THE GLUTAMATERGIC and dopaminergic systems contributes to the pathogenesis and treatment of psychotic and addictive disorders.<sup>1-11</sup> However, in vivo human data that describe the interplay of agents acting on the glutamate and dopamine systems are limited.<sup>12,13</sup> Also, differences between the psychotic states produced by psychostimulants and *N*-methyl-D-aspartate (NMDA) receptor antagonists have been discussed in the

absence of direct comparisons of these states.<sup>14</sup> Amphetamine sulfate produces a transient psychotic state in healthy individuals dominated by positive symptoms and thought disorder.<sup>15-20</sup> In contrast, phencyclidine hydrochloride and ketamine hydrochloride evoke positive, disorganized, negative, and cognitive symptoms that resemble schizophrenia.<sup>21-26</sup> Findings from a retrospective study<sup>27</sup> that compared the clinical presentations of cocaine abusers, phencyclidine abusers, and patients diagnosed as having schizophrenia

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**Table. Ordering of Procedures Associated With the “Amphetamine First” and “Ketamine First” Test Days**

Time, min	Procedure	
	Amphetamine First	Ketamine First
-60	Intravenous and ECG leads placed for continuous monitoring, PANSS, VAS	Intravenous and ECG leads placed for continuous monitoring, PANSS, VAS
-30	VS	VS
-10	Amphetamine sulfate, 0.25 mg/kg, infused over 1 min, VS*	VS*
0	Ketamine hydrochloride bolus plus infusion	Ketamine bolus plus infusion
10	PANSS, VAS, HVLTL (fixed order)	Amphetamine infusion, PANSS, VAS, HVLTL (fixed order)
30	CPT (distractibility)	CPT (distractibility)
60	Ketamine infusion terminated, PANSS, VAS	Ketamine infusion terminated, PANSS, VAS
120	PANSS, VAS, ECG (12-lead)	PANSS, VAS, ECG (12-lead)

Abbreviations: CPT, continuous performance test; ECG, electrocardiography; HVLTL, Hopkins Verbal Learning Test; PANSS, Positive and Negative Syndrome Scale; VAS, visual analog scale; VS, vital signs.

\*Blood pressure and pulse were assessed every 2 minutes between -10 and 20 minutes, every 5 minutes between 20 and 40 minutes, every 10 minutes between 40 and 60 minutes, and every 30 minutes between 60 and 120 minutes.

support the hypothesis that amphetamine abuse is associated with paranoia and phencyclidine abuse is associated with bizarre delusions and altered sensory experiences.

This study directly compares the effects of ketamine and amphetamine within healthy individuals. In addition, it evaluates the interactive effects of these drugs. This study used a relatively high dose of amphetamine, in the range that worsened psychosis in patients diagnosed as having schizophrenia.<sup>28,29</sup> As a result, a relatively low sub-anesthetic dose of ketamine was used to minimize the cardiovascular risk to the research participants. In addition, this study randomized the order of ketamine and amphetamine infusion to explore the possibility that amphetamine-stimulated glutamate release<sup>30,31</sup> or ketamine effects on dopaminergic activity<sup>32</sup> might affect study outcome measures in a manner that might depend on the order in which these drugs were administered.

## METHODS

### RESEARCH PARTICIPANTS

This study was approved by the human subjects subcommittee of the VA Connecticut Healthcare System and by the Yale Human Investigations Committee (New Haven). Participants were recruited via public advertisements, and they were paid for their participation. Individuals were healthy by physical examination, history, electrocardiography, and laboratory testing. They had no personal history of or first-degree relative with a history of psychiatric illness or substance abuse disorder, no history of psychotherapy, no history of extended (>6 months)

unemployment, and no major family or occupational disruption in the month before screening. Screening procedures included the *Structured Clinical Interview for DSM-IV, Non-patient Edition*<sup>33</sup> and tests of latent psychosis.<sup>34-36</sup> An outside informant was interviewed to confirm information provided by the individual. Participants were instructed to abstain from psychoactive substances for 4 weeks before the study. Urine toxicology tests were performed at screening and on each test day.

Written informed consent was obtained from 67 individuals before enrollment. Twenty-six individuals who signed consent forms were excluded or withdrew before testing. Forty-one individuals completed at least 1 test day (5 individuals were recruited to complete a single test day in a pilot phase of the study). Of the 41 individuals, 37 (90%) were nonsmokers and 3 (7%) smoked 1 to 2 cigarettes per week; smoking data were not available for 1 participant (2%). Also, 20 participants (49%) had never ingested an illicit drug of abuse. Eighteen participants (44%) had ingested marijuana in the past, 1 (2%) had ingested marijuana and cocaine, and 1 (2%) had tried marijuana and D-lysergic acid diethylamide; data were not available for 1 participant (2%). There were no significant effects of previous drug exposure on reported outcome measures.

Nine of the 36 participants scheduled for 4 test days did not complete testing. Twenty-seven participants (16 men [mean (SD) age, 33 (8.9) years] and 11 women [mean (SD) age, 28 (5.2) years]; 18 whites, 4 African Americans, 2 Asians, and 3 other races) completed 4 test days separated by a minimum of 3 days in approximately 4 weeks. The reasons for discontinuation were unpleasant perceptual effects of ketamine (n=1); nausea and insomnia after taking the ketamine-amphetamine combination (n=1); hypertension or premature atrial or ventricular contractions after the administration of ketamine and amphetamine (n=2); anxiety, diaphoresis, or dizziness during amphetamine infusion (n=3); and scheduling difficulties (n=2). Follow-up revealed that all adverse effects from testing resolved spontaneously without late-appearing clinical complications, as in other ketamine studies.<sup>37</sup> Each study discontinuation was reported to the Veterans Affairs human subjects subcommittee.

### TEST DAYS

This study is a placebo-controlled, randomized, double-blind, psychopharmacologic trial. On each test day, each participant received amphetamine (a 1-minute infusion of amphetamine sulfate, 0.25 mg/kg, followed by a slow saline infusion or a saline bolus and infusion) and ketamine (a 1-minute intravenous infusion that contained ketamine, 0.23 mg/kg, followed by a 1-hour infusion of 0.5 mg/kg or an identical saline bolus and infusion). The order of amphetamine and ketamine infusion was randomized across participants. The group randomized to receive amphetamine first (14 study completers) underwent the following test days: amphetamine followed by ketamine, placebo amphetamine (saline) followed by ketamine, amphetamine followed by placebo ketamine, and placebo amphetamine followed by placebo ketamine. The group randomized to receive ketamine first (13 study completers) was exposed to the following test days: ketamine followed by amphetamine, placebo ketamine (saline) followed by amphetamine, ketamine followed by placebo amphetamine, and placebo ketamine followed by placebo amphetamine. Except as noted in the “Results” section, the order of ketamine and amphetamine infusion did not affect the results.

Behavioral ratings were obtained at baseline and periodically after the administration of amphetamine and ketamine for both test day orders as outlined in the **Table**. Schizophrenia symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS).<sup>38</sup> This study analyzed PANSS data according to an empirically derived PANSS factor structure<sup>39</sup> rather

than the subscales proposed on an a priori basis by the developers of this scale. Drowsiness and euphoria were assessed using 100-mm visual analog scales (VASs).<sup>23</sup>

Cognitive functions were also evaluated in this study. A continuous performance test was administered within 5 minutes of completion of the intravenous infusions to assess distractibility.<sup>40</sup> Immediate and delayed recall were assessed using the Hopkins Verbal Learning Test (HVLT), a memory test with 6 equivalent versions.<sup>41</sup> Amphetamine and ketamine levels were measured 30 and 60 minutes after the start of the ketamine infusion.

## ANALYSIS OF AMPHETAMINE AND KETAMINE PLASMA LEVELS

Amphetamine and methamphetamine were quantitated as their *N*-heptafluorobutyl derivatives via gas chromatography–mass spectrometry using a capillary column with the mass spectrometer, with simultaneous ion monitoring in the negative chemical ionization mode and reactant gas methane/ammonia (95:5). The method was essentially the same as that described previously,<sup>42</sup> with the following modifications. A 30-m DB-17 capillary column was substituted to improve separation and peak symmetry. Trideuterated amphetamine was used as the internal standard. Standard curves for both compounds were uniformly linear ( $r=0.999+$ ) across the range tested (0.1–500 ng/mL), with negligible intercepts. Sensitivity was less than 0.1 ng/mL for each when 1 mL of plasma was extracted. Interassay relative standard deviation was 5.2% at 5 ng/mL.

Plasma ketamine and norketamine were assayed using a validated liquid chromatography procedure with UV detection. After the addition of 500 ng of internal standard (2-phenylmorpholinol, BW306U), ketamine and the metabolite norketamine were extracted from 1 mL of plasma and were made alkaline using 0.5M sodium hydroxide, with 5.0 mL of 1.5% isoamyl alcohol in *n*-heptane. The organic extract was back-extracted using 0.25 mL of 0.01M hydrochloride and was transferred to inserts for injection on liquid chromatography. Chromatography was carried out using a trimethylsilyl bonded silica column (LC-1; Supelco, Sigma-Aldrich Co, Bellefonte, Pa) with a mobile phase consisting of 85% phosphate buffer and 15% acetonitrile, adjusted to pH 2.4 using phosphoric acid, triethylamine, and heptane sulfonate. At a flow rate of 2.0 mL/min, ketamine, norketamine, and the internal standard were separated and detected at a UV wavelength of 210 nm in less than 12 minutes. The within-day coefficient of variation of ketamine and norketamine did not exceed 10.6% (range, 25–2000 ng/mL; 12 samples studied at each of 7 ketamine/norketamine concentrations). Day-to-day variation of ketamine and norketamine quality controls at 1250, 250, and 50 ng/mL did not exceed 5.6% and 5.8%, respectively ( $n=20$  days). The minimum quantifiable limits were set at 10 ng/mL for ketamine and norketamine.

## DATA ANALYSIS

Data were checked for normality before analysis. The PANSS total score, the 5 PANSS subscale scores (positive, negative, cognitive, emotional, and hostility), the delayed recall score on the HVLT, and the VAS data (euphoria and drowsiness) exhibited floor effects and positive skewness. These outcome measures were analyzed using a nonparametric approach for repeated-measures data.<sup>43</sup> For the PANSS and the VAS, the overall analysis model included the between-participant factor of order of ketamine and amphetamine administration (ketamine first vs amphetamine first) and the within-participant factors of (1) ketamine (active and placebo), (2) amphetamine (active and placebo), and (3) time (baseline and 1 minute, 60 minutes, and

120 minutes after infusion). Participant was used as the clustering factor. The analysis was performed by rank-transforming the data, then fitting a mixed-effects model with an unstructured variance-covariance matrix using PROC MIXED in SAS (SAS Institute Inc, Cary, NC), and finally adjusting the *P* values for the analysis of variance–type statistics (ATS) as outlined by Brunner et al.<sup>43</sup> For all outcome measures, the order main effect and all its interactions with other factors in the model were not significant and hence were dropped from the models. If the 3-way interaction among ketamine, amphetamine, and time was significant, contrasts for testing interactions between ketamine and amphetamine were performed at each point. For the points where significant interactions were observed, the simple effects of ketamine and amphetamine were tested to determine the nature of the interaction. Bonferroni corrections were applied for multiple analyses within but not across domains. Throughout this article, we report Bonferroni-adjusted *P* values. *A'* measures were defined for the distractibility task. Owing to the skewness of the data, they were also analyzed using the nonparametric approach described previously herein, with order as the between-participant factor and ketamine and amphetamine as within-participant factors. On the HVLT, delayed recall scores were analyzed using a nonparametric approach, with and without the last immediate recall measure as a covariate. Immediate recall scores on the HVLT and vital signs data were approximately normally distributed and hence were analyzed using linear mixed models, with ketamine and amphetamine as within-participant factors and a nested variance structure.<sup>44</sup> Simple effects were tested to illustrate significant interactions.

## RESULTS

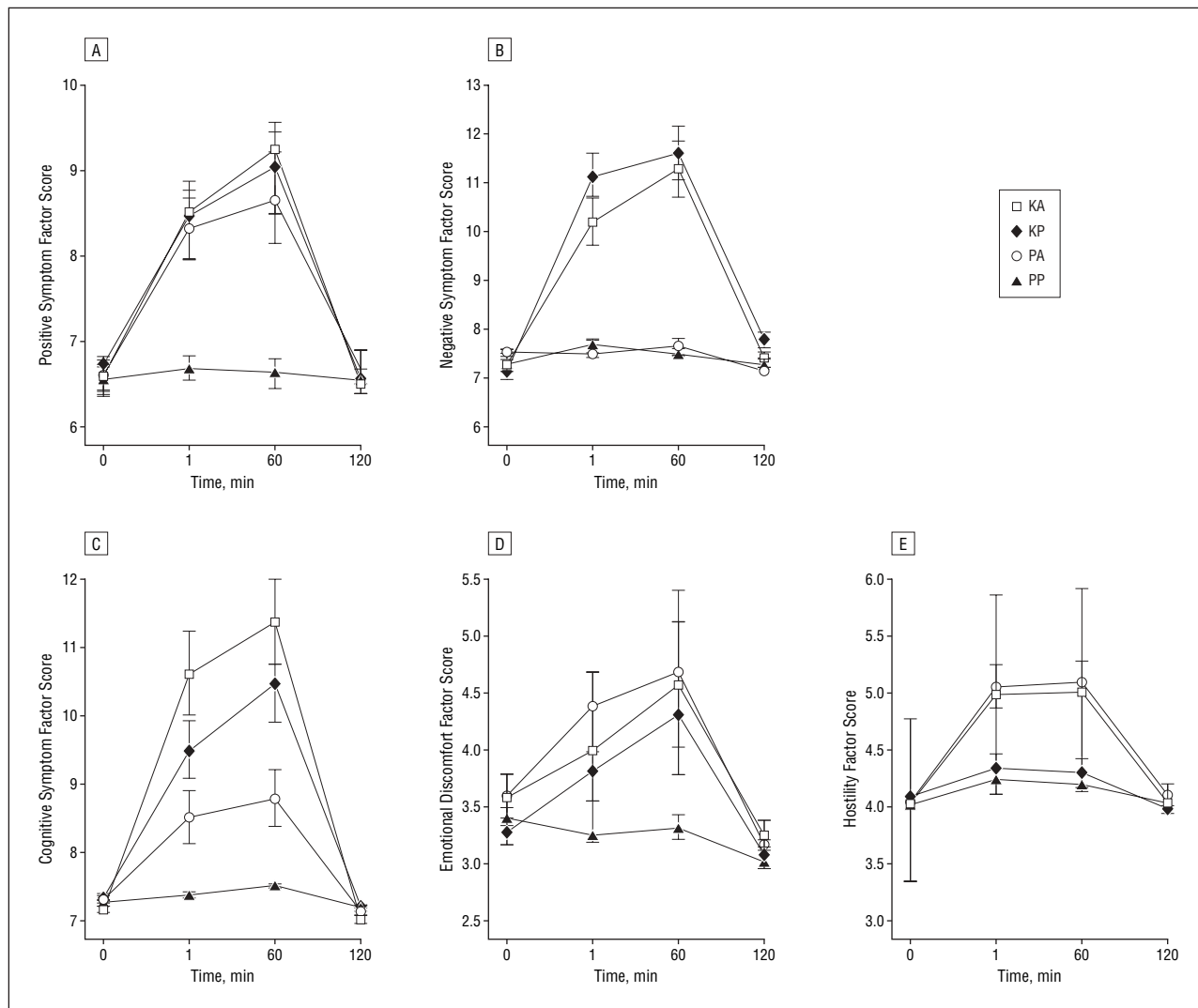
### PANSS TOTAL SCORE

The magnitude of the combined effects of ketamine and amphetamine was significantly less than that of the effects of each drug administered separately. The 3-way interaction among ketamine, amphetamine, and time was significant ( $ATS_{2,41}=9.54$ ;  $P<.001$ ). Post hoc testing found that the interaction between amphetamine and ketamine was significant at 1 minute ( $ATS_1=22.77$ ) and at 60 minutes ( $ATS_1=15.18$ ) ( $P<.001$  for both).

Post hoc testing revealed that ketamine significantly increased PANSS total scores regardless of whether it was administered with placebo (1 minute:  $ATS_1=67.59$  and 60 minutes:  $ATS_1=80.23$ ;  $P<.001$  for both) or amphetamine (1 minute:  $ATS_1=8.31$ ;  $P=.03$  and 60 minutes:  $ATS_1=12.69$ ;  $P<.001$ ). However, amphetamine increased PANSS total scores significantly relative to placebo when administered with placebo (1 minute:  $ATS_1=35.7$  and 60 minutes:  $ATS_1=30.04$ ;  $P<.001$  for both), but amphetamine did not increase PANSS total score when administered with ketamine relative to the effects of ketamine at the 1-minute ( $P>.99$ ) and 60-minute ( $P=.40$ ) time points.

### PANSS PSYCHOSIS/POSITIVE SYMPTOM FACTOR

The results for the psychosis factor were similar to those for the total PANSS in that amphetamine and ketamine produced psychotic symptoms, but the combination of both drugs produced interactive effects that were signifi-



**Figure 1.** Interactive effects of amphetamine sulfate and ketamine hydrochloride on the mean scores of the 5 empirically derived factors of the Positive and Negative Syndrome Scale (described in the “Methods” section): the positive symptom factor (A), the negative symptom factor (B), the cognitive symptom factor (C), the emotional discomfort factor (D), and the hostility factor (E). The time of 0 minutes in each graph reflects the timing of the initiation of the ketamine bolus. KA indicates ketamine-amphetamine; KP, ketamine-placebo; PA, placebo-amphetamine; and PP, placebo-placebo. Error bars represent SEM.

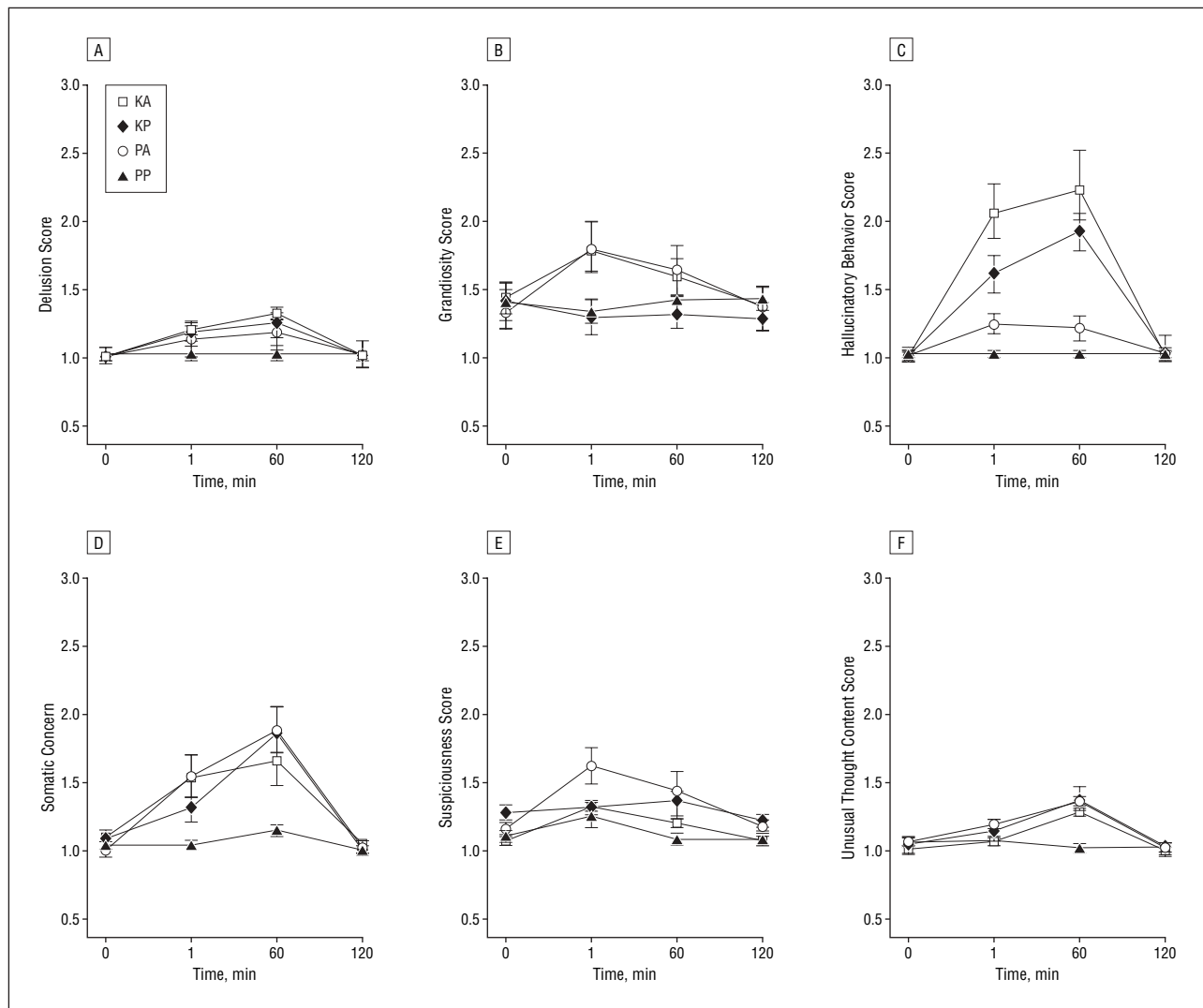
cantly less than additive. There was a significant ketamine  $\times$  amphetamine  $\times$  time interaction ( $ATS_{2,32}=6.96$ ; Bonferroni-corrected  $P=.002$ ). At 1 minute and at 60 minutes, the interaction between ketamine and amphetamine was significant ( $ATS_1=9.94$ ;  $P=.03$  and  $ATS_1=15.21$ ;  $P<.002$ , respectively) (**Figure 1A**). Ketamine significantly increased positive symptoms over the placebo-placebo combination (1 minute:  $ATS_1=27.44$  and 60 minutes:  $ATS_1=40.72$ ;  $P<.002$  for both), but the combination of ketamine and amphetamine was not significantly different from amphetamine (corrected  $P>.99$ ). Similarly, at both points amphetamine significantly increased positive symptoms (1 minute:  $ATS_1=25.64$  and 60 minutes:  $ATS_1=29.13$ ;  $P<.002$  for both), but the combination of amphetamine and ketamine was not significantly different from ketamine alone (corrected  $P>.99$ ).

Amphetamine and ketamine produced different profiles of psychotic symptoms (**Figure 2**). Individual items were explored separately, using corrections for multiple comparisons. Amphetamine, but not ketamine, signifi-

cantly increased grandiosity (amphetamine  $\times$  time interaction:  $ATS_{2,25}=7.58$ ;  $P=.002$ ). In contrast, ketamine, but not amphetamine, produced delusions (ketamine  $\times$  time interaction:  $ATS_{1,72}=5.25$ ;  $P=.047$ ). Somatic concern was produced by ketamine and amphetamine in a less-than-additive manner (ketamine  $\times$  amphetamine  $\times$  time interaction:  $ATS_{2,31}=4.82$ ;  $P=.03$ ). In contrast, hallucinatory behavior was produced by ketamine and amphetamine in an additive manner (ketamine  $\times$  time interaction:  $ATS_{1,84}=32.61$ ;  $P<.001$  and amphetamine  $\times$  time interaction:  $ATS_{1,94}=5.35$ ;  $P=.03$ ).

#### PANSS NEGATIVE SYMPTOM FACTOR

Ketamine substantially increased negative symptom factor scores, whereas amphetamine did not produce significant main or interactive effects (Figure 1B). The ketamine  $\times$  time interaction was significant ( $ATS_{2,20}=51.19$ ;  $P<.001$ ). The post hoc test results for blunted affect, emotional withdrawal, and motor retardation mirrored the



**Figure 2.** Interactive effects of amphetamine sulfate and ketamine hydrochloride on mean scores of 6 positive symptom items from the Positive and Negative Syndrome Scale (as described in the "Methods" section): delusions (A), grandiosity (B), hallucinatory behavior (C), somatic concern (D), suspiciousness (E), and unusual thought content (F). The time of 0 minutes in each graph reflects the timing of the initiation of the ketamine bolus. KA indicates ketamine-amphetamine; KP, ketamine-placebo; PA, placebo-amphetamine; and PP, placebo-placebo. Error bars represent SEM.

overall negative symptom factor analysis findings, with significant time-related ketamine ( $P < .001$ ) but not amphetamine effects. Ketamine ( $ATS_{2,43} = 29.81$ ;  $P < .001$ ) and amphetamine ( $ATS_{2,34} = 5.33$ ;  $P = .003$ ) increased lack of spontaneity.

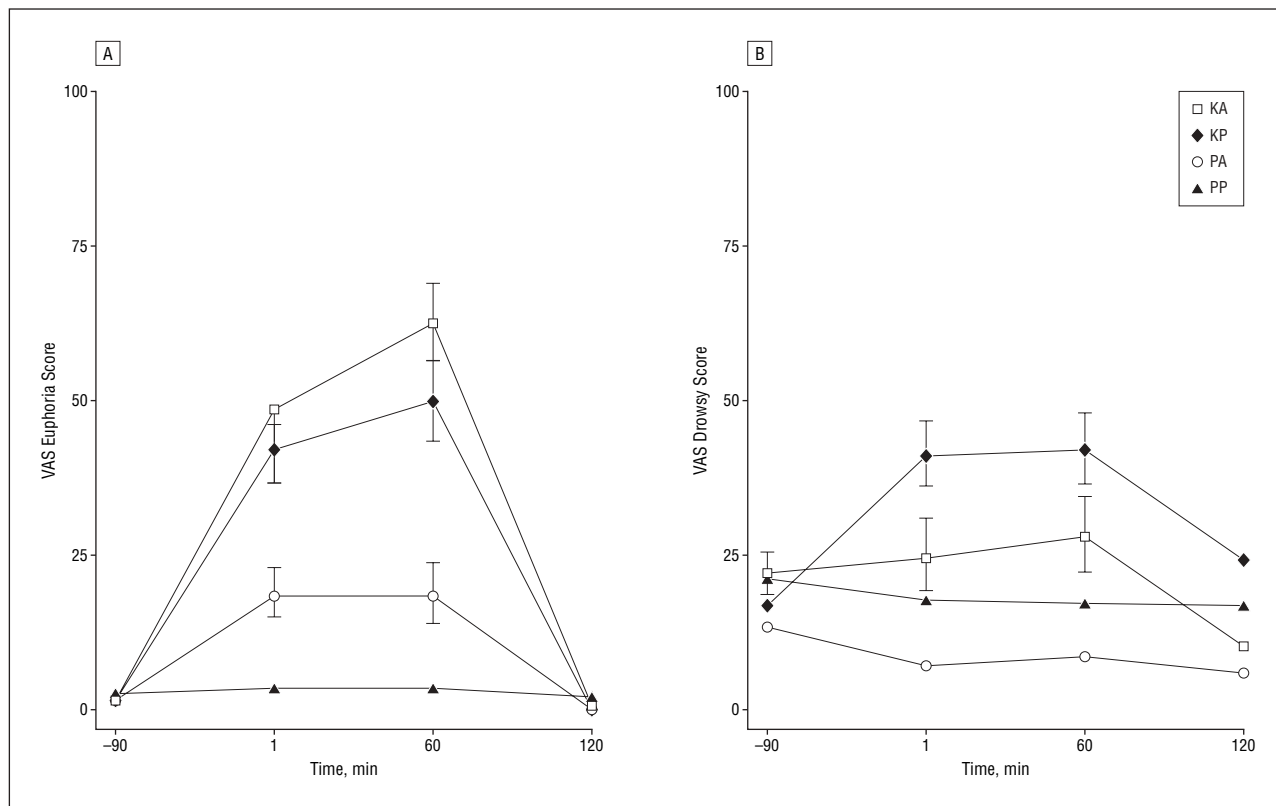
#### PANSS COGNITIVE SYMPTOM FACTOR

Ketamine and amphetamine seemed to have additive effects on this factor in that each drug had significant effects, but there was no significant interaction between these drugs (Figure 1C). There was a significant ketamine  $\times$  time interaction ( $ATS_{2,25} = 34.76$ ;  $P < .001$ ) and a significant amphetamine  $\times$  time interaction ( $ATS_{1,54} = 8.72$ ;  $P = .003$ ) but not a significant ketamine  $\times$  amphetamine  $\times$  time interaction. Ketamine at 1 minute ( $ATS_1 = 36.87$ ;  $P < .002$ ) and at 60 minutes ( $ATS_1 = 74.92$ ;  $P < .002$ ) and amphetamine at 60 minutes ( $ATS_1 = 10.79$ ;  $P = .02$ ) increased cognitive symptom factor scores, although there was no significant interaction between the effects of these drugs.

Post hoc analyses revealed that ketamine had effects on several dimensions of thought disorder, whereas amphetamine produced only conceptual disorganization. Significant ketamine  $\times$  time interaction effects were found for conceptual disorganization ( $ATS_{1,73} = 38.00$ ;  $P < .001$ ), difficulties in abstract thinking ( $ATS_{2,12} = 14.50$ ;  $P < .001$ ), mannerisms ( $ATS_{1,82} = 20.74$ ;  $P < .001$ ), and poor attention ( $ATS_{1,85} = 6.37$ ;  $P = .01$ ). Significant amphetamine  $\times$  time interactions were observed for conceptual disorganization ( $ATS_{1,64} = 9.93$ ;  $P = .007$ ). No significant drug-related effects were observed for the stereotyped thinking, lack of judgment, or tension items.

#### PANSS EMOTIONAL SYMPTOM FACTOR

Ketamine and amphetamine showed significantly less-than-additive interactive effects (ketamine  $\times$  amphetamine  $\times$  time interaction:  $ATS_{2,67} = 9.09$ ;  $P < .001$ ) (Figure 1D). Ketamine and amphetamine interacted significantly at 1 minute ( $ATS_1 = 21.47$ ;  $P < .002$ ) but not at



**Figure 3.** Interactive effects of amphetamine sulfate and ketamine hydrochloride on mean visual analog scale (VAS) euphoria (A) and drowsiness (B) scores. KA indicates ketamine-amphetamine; KP, ketamine-placebo; PA, placebo-amphetamine; and PP, placebo-placebo. Error bars represent SEM.

60 minutes ( $ATS_1=8.95$ ;  $P=.06$ ). Ketamine significantly increased dysphoria relative to placebo at 1 minute and at 60 minutes ( $ATS_1=26.74$  and  $ATS_1=17.24$ , respectively;  $P<.004$  for both), but ketamine in combination with amphetamine was not different from amphetamine ( $P=.50$ ). Similarly, amphetamine significantly increased emotional symptoms at 1 minute and at 60 minutes ( $ATS_1=13.09$ ;  $P=.01$  and  $ATS_1=20.59$ ;  $P=.004$ , respectively), but the ketamine-amphetamine combination was not different from ketamine alone ( $P>.99$ ). Anxiety was the only symptom of this factor that was increased by amphetamine ( $ATS_{2,36}=4.42$ ;  $P=.01$ ).

#### PANSS HOSTILITY FACTOR

Amphetamine (amphetamine  $\times$  time interaction:  $ATS_{1,86}=23.64$ ;  $P<.005$ ), but not ketamine, elevated hostility factor scores (Figure 1E). However, this finding reflected a significant amphetamine effect on the excitement item ( $ATS_{2,02}=19.50$ ;  $P<.001$ ) but no significant effects on hostility, impulse control, or uncooperativeness.

#### VAS OF EUPHORIA AND DROWSINESS

There was a significant ketamine  $\times$  amphetamine  $\times$  time interaction for euphoria ( $ATS_{2,16}=7.12$ ;  $P=.002$ ) (Figure 3A). Whereas amphetamine significantly increased self-rated euphoria relative to placebo (1 minute:  $ATS_1=31.94$  and 60 minutes:  $ATS_1=21.33$ ;  $P<.003$  for both), the combination of ketamine and amphetamine was not significantly greater than ketamine. In contrast,

ketamine increased euphoria relative to placebo (1 minute:  $ATS_1=40.98$  and 60 minutes:  $ATS_1=17.26$ ;  $P<.003$  for both) and amphetamine (1 minute:  $ATS_1=13.39$ ;  $P=.01$  and 60 minutes:  $ATS_1=48.17$ ;  $P<.003$ ).

The stimulant effects of amphetamine seemed to reduce the sedative effects of ketamine in an additive manner. The amphetamine  $\times$  time ( $ATS_{2,74}=7.92$ ;  $P<.001$ ) and the ketamine  $\times$  time ( $ATS_{2,27}=6.91$ ;  $P=.002$ ) interactions were significant, although there was no significant interaction between the effects of these drugs (Figure 3B).

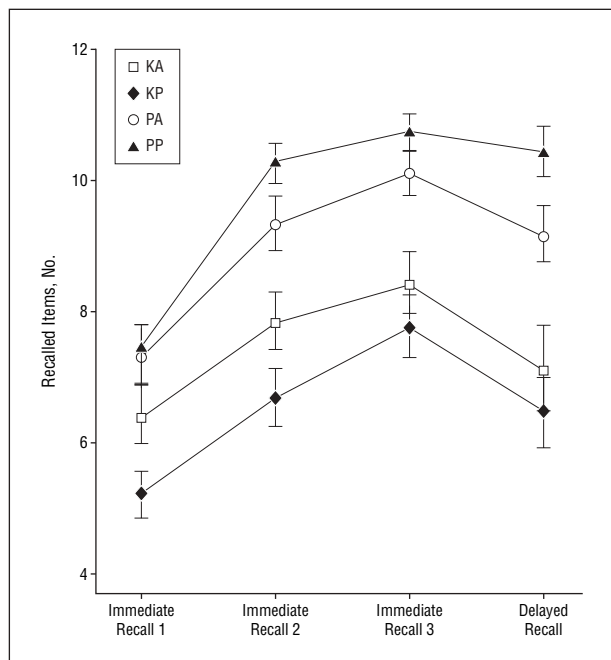
#### COGNITIVE MEASURES

##### Distractibility

The analysis of  $A'$  score revealed a significant ketamine effect ( $ATS_1=12.0$ ;  $P<.001$ ) but not a significant amphetamine effect or a significant interaction of ketamine and amphetamine.

##### HVLT Immediate and Delayed Recall

Analysis of the immediate recall data indicated that amphetamine attenuated immediate recall relative to placebo administration but that the combination of ketamine and amphetamine improved performance relative to ketamine (Figure 4). The effects of ketamine ( $F_{1,81.9}=57.6$ ;  $P<.001$ ), the number of list repetitions ( $F_{2,224}=196.0$ ;  $P<.001$ ), and the interaction of ketamine and repetition effects ( $F_{2,224}=7.2$ ;  $P=.002$ ) were signifi-



**Figure 4.** Interactive effects of ketamine hydrochloride and amphetamine sulfate on mean performance on the Hopkins Verbal Learning Test. KA indicates ketamine-amphetamine; KP, ketamine-placebo; PA, placebo-amphetamine; and PP, placebo-placebo. Error bars represent SEM.

cant. Whereas the main effect of amphetamine was not significant, the interactive effects of amphetamine and ketamine achieved significance ( $F_{1,80.8}=5.71$ ;  $P=.04$ ).

Ketamine and amphetamine seemed to impair delayed recall. There was a highly significant interaction of ketamine and amphetamine effects on delayed recall scores ( $ATS_1=15.73$ ;  $P<.001$ ) (Figure 4). Post hoc test results indicated that the combination of ketamine and amphetamine impaired delayed recall relative to amphetamine ( $t_{21.6}=-4.09$ ;  $P=.004$ ) but not ketamine ( $t_{20.4}=0.51$ ;  $P=.62$ ). Ketamine ( $t_{23.0}=-6.89$ ;  $P<.001$ ) and amphetamine ( $t_{23.4}=-3.15$ ;  $P=.03$ ) impaired delayed recall relative to saline.

Ketamine had effects on immediate and delayed recall. However, secondary analyses suggested that the amphetamine effect on delayed recall was accounted for by its disruptive effect on immediate recall. Covarying for the level of encoding into working memory, that is, the third repetition of immediate recall (the recall score for the third immediate recall trial), ketamine ( $ATS_1=32.11$ ;  $P<.001$ ), but not amphetamine ( $ATS_1=0.29$ ;  $P=.59$ ), reduced delayed recall scores. There were no significant interactions between these medications on this outcome measure (Figure 4). The results of this analysis suggested that ketamine had an effect on delayed recall independent of its effect on immediate recall. However, the apparent impact of amphetamine on delayed recall reflected an artifact of its disruption of immediate recall.

## VITAL SIGNS

### Systolic Blood Pressure

The 2 sequences were analyzed separately owing to the differing points with respect to drug infusion between

these orders (Figure 5). When amphetamine was administered first, only the amphetamine  $\times$  time interaction was significant ( $F_{17,773}=10.0$ ;  $P<.001$ ). However, when ketamine was administered first, the ketamine  $\times$  time interaction ( $F_{16,817}=2.4$ ;  $P=.006$ ), the amphetamine  $\times$  time interaction ( $F_{16,817}=18.1$ ;  $P<.001$ ), and the ketamine  $\times$  amphetamine  $\times$  time interaction ( $F_{16,817}=2.1$ ;  $P=.02$ ) were significant.

### Diastolic Blood Pressure

Amphetamine was administered as a bolus, and ketamine was administered as a bolus followed by a constitution. Consistent with this pattern, amphetamine produced blood pressure increases that were more pronounced, but briefer, than ketamine. There was no significant interaction of the pressor effects of these drugs. The 2 sequences were analyzed separately owing to the differing points with respect to drug infusion between these orders. The ketamine  $\times$  time and amphetamine  $\times$  time interactions were significant for both orders of drug infusion ( $P<.03$ ).

### Pulse Rate

There were no significant drug effects on pulse rate.

## KETAMINE PLASMA LEVELS

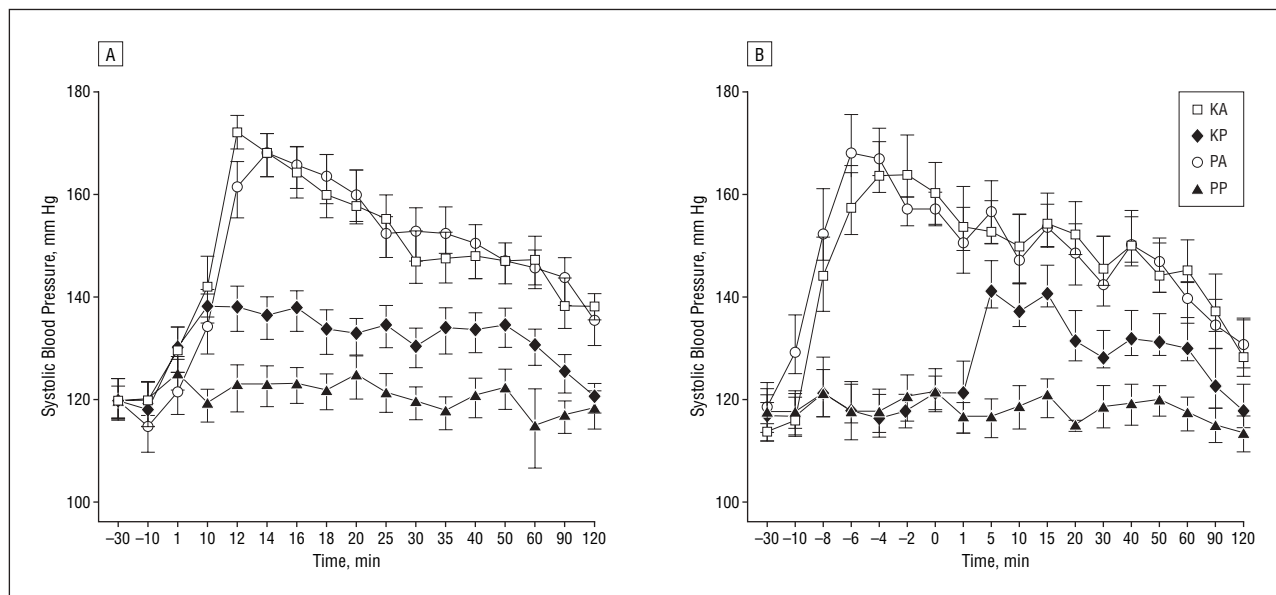
There was no main effect of amphetamine infusion on ketamine plasma levels ( $F_{1,14.9}=0.44$ ;  $P=.5$ ) or interaction between amphetamine and infusion order effects ( $F_{1,14.9}=0.31$ ;  $P=.6$ ) (Figure 6). However, there was a significant interaction among amphetamine, order, and time effects ( $F_{1,32.2}=5.24$ ;  $P=.03$ ). In addition to the time effect ( $F_{1,32.2}=41.91$ ;  $P<.001$ ), post hoc test results indicated that this 3-way interaction reflected a nonsignificant trend toward lower plasma ketamine levels at 60 minutes in the group that received amphetamine before ketamine ( $F_{1,7.71}=5.72$ ;  $P=.08$ ) relative to the group that received ketamine before amphetamine.

## AMPHETAMINE PLASMA LEVELS

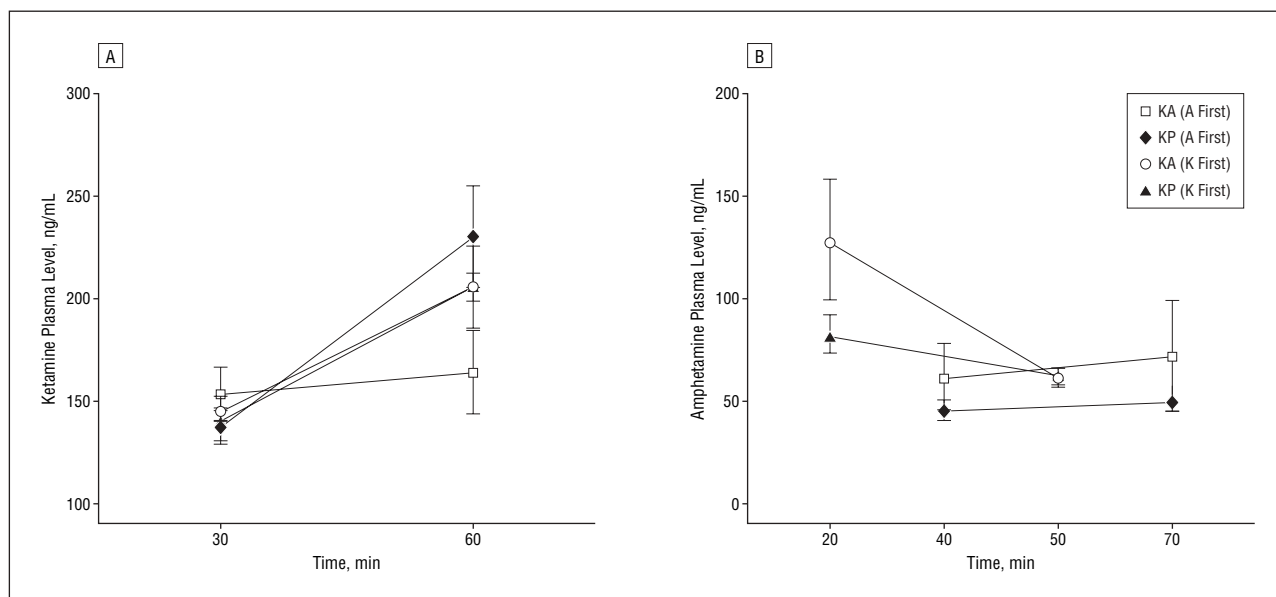
Ketamine infusion did not significantly alter amphetamine plasma levels. There were significant effects of time ( $F_{1,41.2}=9.38$ ;  $P=.004$ ), order of drug infusion ( $F_{1,25.9}=9.22$ ;  $P=.005$ ), and the interaction of order and time ( $F_{1,41.2}=16.33$ ;  $P<.001$ ). This analysis is consistent with the bolus infusion of amphetamine and the different intervals between bolus infusion and plasma sampling when amphetamine was administered before or after ketamine (Figure 5).

## COMMENT

The present study sheds new light on the comparative and interactive effects of ketamine and amphetamine and, by implication, on the functions and interactions of NMDA glutamate receptor and monoaminergic systems in the human brain. Ketamine and amphetamine produced tran-



**Figure 5.** Interactive effects of ketamine and amphetamine on mean systolic blood pressure when ketamine hydrochloride was administered before amphetamine sulfate (A) and when amphetamine was given before ketamine (B). KA indicates ketamine-amphetamine; KP, ketamine-placebo; PA, placebo-amphetamine; and PP, placebo-placebo. Error bars represent SEM.



**Figure 6.** Interactive effects of ketamine hydrochloride and amphetamine sulfate on the mean plasma levels of each drug. A, Ketamine plasma levels. Because timing in this study was synchronized to the initiation of ketamine administration, both orders of drug infusion begin at 0 minutes. B, Amphetamine plasma levels. In this case, plasma amphetamine level sampling in the 2 infusion orders do not overlap and can be seen separately in this figure. KA indicates ketamine-amphetamine; and KP, ketamine-placebo. Error bars represent SEM.

sient psychotic symptoms in healthy individuals. However, the positive symptoms produced by each drug could be distinguished within individuals. Also, the combination of ketamine and amphetamine produced positive symptoms that were, overall, less severe than the sum of the effects of each drug administered individually. In contrast, ketamine and amphetamine produced additive effects on euphoria and thought disorder. In addition, amphetamine attenuated the disruption of working memory produced by ketamine, as reflected by immediate recall scores on the HVLT. Also, the order of ketamine and amphetamine infusion did not alter their interactive effects.

#### DIFFERENTIAL EFFECTS OF KETAMINE AND AMPHETAMINE

The symptom profiles produced by ketamine and amphetamine within participants were consistent with the symptom profiles in studies<sup>15-20,22,23,25,26,45</sup> in which each drug was assessed individually. Ketamine produced perceptual changes and delusions, negative symptoms, several aspects of thought disorder, and impairments in the executive control of attention, working memory, and declarative memory. In contrast, amphetamine stimulated positive symptoms related to thought content (somatic

concerns, grandiosity, and suspiciousness), thought disorder, and psychomotor activation. However, it did not produce perceptual changes, negative symptoms, or prominent cognitive impairments.

Amphetamine and ketamine produced euphoria and emotional distress, predominantly tension or anxiety. However, the amphetamine euphoria was associated with psychomotor activation and hostility, whereas that of ketamine was associated with sedation. This distinction may be relevant to the behavioral effects of alcohol, where dopamine may contribute to the stimulant-related "high" associated with the ascending blood alcohol levels, and blockade of NMDA receptors may contribute to the sedative effects associated with high levels of alcohol consumption and descending blood alcohol levels.<sup>46,47</sup> In summary, the present data suggest that despite some overlap, ketamine and amphetamine produce distinct profiles of cognitive and behavioral effects.

## INTERACTIVE EFFECTS OF KETAMINE AND AMPHETAMINE

### Working Memory

Amphetamine reduced the disruption in working memory produced by ketamine. Dopamine, via dopamine D<sub>1</sub> receptors, and glutamate, via NMDA receptors, contribute to the sustained prefrontal cortical activity underlying working memory.<sup>48-52</sup> Working memory performance may be enhanced by optimizing the level of D<sub>1</sub> receptor stimulation and may be impaired by deficient or excessive stimulation of this receptor.<sup>48,49,53-55</sup> This "inverted U" curve relating the level of monoaminergic activation to working memory performance also seems to apply to amphetamine effects on working memory.<sup>56</sup> In the present study, amphetamine impaired delayed recall owing to a disruptive effect on immediate recall, suggestive of a supraoptimal stimulation of cortical dopamine receptors. Amphetamine effects on working memory may also reflect modulation of other monoamine systems.<sup>57-59</sup> Also, the present data may support the hypothesis that D<sub>1</sub> receptor agonists might treat working memory impairments in patients with disorders associated with deficits in NMDA receptor function or cortical dopamine-related abnormalities, as is the case for schizophrenia.<sup>2,3,60</sup>

### Psychosis

Consistent with a previous study,<sup>61</sup> there was no evidence that the combination of NMDA receptor blockade and dopamine release resulted in supra-additive or even fully additive psychotic effects. Thus, this study did not suggest that endogenous psychoses are better modeled by the combination of ketamine and amphetamine than by either drug alone. Instead, the combined effects of these drugs were substantially less than their separate effects added together, that is, ketamine substantially increased positive symptom levels when administered in combination with saline but not with amphetamine. Amphetamine increased positive symptom levels when administered with saline but not with ketamine.

It is not yet clear why ketamine and amphetamine had less-than-additive interactive effects. It might be explained by a common psychotogenic mechanism, perhaps convergent effects on dopamine release,<sup>62</sup> dopamine D<sub>2</sub> receptors,<sup>63</sup> or signal transduction pathways,<sup>64</sup> resulting in a ceiling effect when the drugs were administered together. However, a common mechanism might lead one to predict that ketamine and amphetamine would produce a common profile of psychotic symptoms, and this did not seem to be the case in the present study. Also, a ceiling effect on psychosis seems unlikely because previous studies<sup>65-67</sup> that administered higher ketamine doses produced higher levels of positive symptoms than were found herein. Also, a common dopaminergic mechanism might be inconsistent with the lack of effects of dopamine D<sub>2</sub> receptor antagonists on the ketamine psychosis.<sup>28,66,68</sup> Alternatively, it is possible that amphetamine and ketamine antagonized some effects of the other drug.<sup>69,70</sup> However, mutual antagonism was not evident in the analyses of individual items. Further research is needed to clarify this pattern of interaction.

### Thought Disorder, Euphoria, Arousal, and Negative Symptoms

For the PANSS cognitive factor score, the VAS drowsy score, and, to some extent, the VAS euphoria score (where the combination of ketamine and amphetamine produced greater effects than amphetamine but not ketamine), the combination of ketamine and amphetamine produced effects that did not differ significantly from the effects of each drug added together. For the PANSS cognitive factor score, the additive effects may have reflected the broader profile of thought disorder produced by ketamine than by amphetamine. Outcome measures where ketamine and amphetamine produce additive effects may be related to the regulation of striatal dopaminergic stimulation, where ketamine has been shown to increase the impact of amphetamine on dopamine release in humans, although ketamine may not stimulate striatal dopamine release by itself.<sup>61,71</sup> If the thought-disordering and euphoric effects of ketamine are mediated by striatal dopamine systems, then it is likely that non-D<sub>2</sub> dopamine receptors mediate these effects because, with the possible exception of concrete ideation, they do not seem to be blocked by the dopamine D<sub>2</sub> receptor antagonist haloperidol.<sup>66</sup> Similarly, dizocilpine (MK-801) self-administration into the nucleus accumbens in animals was not blocked by sulpiride microinjections into this brain region at doses that blocked the self-administration of dopamine transporter antagonists.<sup>72</sup>

There were several outcome measures where one of the medications did not produce an effect by itself and did not modify the effect of the other agent. The present study further dissociated the sedative effects of ketamine and its effects on negative symptoms. For example, amphetamine reduced the sedative effects but not the negative symptoms produced by ketamine. The absence of an amphetamine modulation of the negative symptoms produced by ketamine is consistent with the absence of haloperidol pretreatment effects on this outcome measure.<sup>66</sup> Alternatively, ketamine did not pro-

duce hostility and did not modify the amphetamine effect on hostility.

## STUDY LIMITATIONS

Methodological limitations in the present study may have affected the findings. First, the demanding nature of the study design on research participants necessitated a restriction of this study to a single dose of ketamine and amphetamine. The findings of this study may not fully generalize to the interactions of other doses of ketamine and amphetamine. Second, to mirror previous studies of amphetamine effects on dopamine release,<sup>28,29</sup> amphetamine was administered as a bolus. Thus, amphetamine plasma levels changed across time during the study. Although statistical analysis steps were taken to try to address its impact, some variance in amphetamine levels was introduced in comparing the 2 drug infusion orders.

In conclusion, this study contributes to the effort to better understand the interplay of the glutamate and dopamine systems. The diverse pattern of interactions observed may have implications for psychiatric and addictive disorders. The partial overlap of the psychotogenic effects of ketamine and amphetamine, their additive effects on thought disorder, and their lack of interactive effects on negative symptoms are consistent with the hypothesis that the neurobiologic features of each symptom cluster associated with schizophrenia are complex and distinct and may require novel pharmacotherapeutic approaches. This study also supports the evaluation of D<sub>1</sub>-agonists for treating working memory impairments associated with schizophrenia.

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