Effects of Intravenous Ketamine on Explicit and Implicit Measures of Suicidality in Treatment-Resistant Depression

Abstract word count: 200
Article word count: 1500
Tables: 4
Figures: 2
References: 20
Supplementary Material: 2

Running Head: EFFECTS OF KETAMINE ON EXPLICIT AND IMPLICIT SUICIDALITY

Effects of Intravenous Ketamine on Explicit and Implicit Measures of Suicidality in Treatment-Resistant Depression

Rebecca B. Price[1,2], Matthew K. Nock[3], Dennis S. Charney[1,4,5], Sanjay J. Mathew[1]

Brief report for submission to: *Biological Psychiatry*

Departments of Psychiatry[1], Neuroscience[4], and Pharmacology & Systems Therapeutics[5], Mount Sinai School of Medicine, New York, NY; [2]Department of Psychology, Rutgers, the State University of New Jersey, Piscataway, NJ; [3]Department of Psychology, Harvard University, Cambridge, MA

Key Words: ketamine; suicide; implicit association test

Corresponding Author:
Rebecca B. Price
One Gustave L. Levy Place, Box 1230
New York NY 10029
Phone: 347-200-4234
rprice@eden.rutgers.edu

ABSTRACT

Background: Intravenous ketamine has shown rapid antidepressant effects in early trials, making it a potentially attractive candidate for depressed patients at imminent risk of suicide. The Implicit Association Test (IAT), a performance-based measure of association between two concepts, may have utility in suicide assessment. **Methods:** Twenty-six patients with treatment-resistant depression were assessed for suicidality 2 hours prior to, and 24 hours following, a single subanesthetic dose of intravenous ketamine using the suicidality item of the Montgomery-Asberg Depression Rating Scale (MADRS-SI). Ten patients also completed IATs assessing implicit suicidal associations at comparable time points. In a second study, 9 patients received thrice-weekly ketamine infusions over a 12-day period. **Results:** 24-hours after a single infusion, MADRS-SI scores were reduced by an average of 2.08 points on a 0-6 scale ($p<.001$; $d=1.37$), and 81% of patients received a rating of 0 or 1 post-infusion. Implicit associations between self- and escape-related words were also reduced following ketamine ($p=.003$; $d=1.36$), with reductions correlated across implicit and explicit measures. MADRS-SI reductions were sustained for 12 days by repeated-dose ketamine (2.9-point mean reduction; $p<.001$; $d=2.42$). **Conclusions:** These preliminary findings support the premise that ketamine has rapid beneficial effects on suicidal cognition and warrants further study.

[Registered at ClinicalTrials.gov as trial numbers NCT00419003, "Research Study for Major Depressive Disorder: Investigation of Glutamate Medications" and NCT00548964, "Continuation Intravenous Ketamine in Major Depressive Disorder"]

INTRODUCTION

Current treatment options for severe mood disorders are limited by the slow time course of change in suicidal thoughts. For instance, in major depressive disorder (MDD) patients receiving thrice-weekly electroconvulsive therapy, suicidal thoughts persisted in 62% of patients after 1 week of treatment and 39% after 2 weeks (1). Conventional antidepressant treatment produced slower and less robust response in elderly MDD patients with moderate-to-high suicide risk than in non-suicidal patients (2).

Treatment of acute suicidality is further constrained by inaccuracies in patients' explicit reports of suicidal thoughts (3, 4). The Implicit Association Test (IAT)(5) may be useful as a behavioral measure of suicidal cognition, as the task is reliable (6) and resistant to attempts to intentionally control its outcome (7). Furthermore, when socially "taboo" cognitions are assessed (e.g., prejudicial attitudes), the IAT is a superior predictor of future behavior relative to explicit measures (8). IAT variants assessing suicide- and self-injury-related cognition have shown promise in discriminating between self-injurious and non-injurious adolescents (9), suicidal and non-suicidal adolescents (3), and adult suicide attempters and non-attempters presenting to a psychiatric emergency department (10).

Early evidence suggests that a single subanesthetic dose of intravenous (IV) ketamine, a glutamate-modulating agent, acutely reduces depressive symptoms in approximately 70% of MDD patients 24 hours after infusion (11-13). We tested ketamine's impact on suicidal cognition in a sample of adults with treatment-resistant depression (TRD). We hypothesized that ketamine would yield rapid, correlated reductions in explicit and implicit suicidal indices. Furthermore, we expected that rapid initial reductions in explicit suicidality would be sustained through repeated ketamine infusions.

MATERIALS AND METHODS

Twenty-six TRD patients were recruited via media advertisement or clinician referral. Treatment-resistance was defined as two or more failed, adequate antidepressant trials in the current episode, as determined by the Antidepressant Treatment History Form (14). DSM-IV-TR diagnoses of MDD were established by SCID-I/P interview. Eligible participants had moderate-to-severe depression (Inventory of Depressive Symptomatology score ≥32)(15); were psychotropic medication-free for ≥2 weeks prior to infusion (4 weeks for fluoxetine); free of substance abuse/dependence for ≥6 months; denied lifetime use of ketamine and PCP; had no lifetime history of psychotic disorder, mania or hypomania; and had no clinically unstable medical or neurological conditions. Patients whom research team psychiatrists deemed unsafe for study participation due to highly active suicidality were excluded.

Patients were admitted to a private hospital room for a 28-hour period for racemic ketamine hydrochloride infusion (0.5 mg/kg diluted in saline, administered over 40 minutes by IV pump(12)) and cardiorespiratory monitoring. Patients were assessed for depressive symptoms 150 minutes prior to, and 24-hours following, infusion using the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-administered measure that includes a single suicidality item (**Table 1**)(16). MADRS raters held graduate degrees and achieved high inter-rater reliability both during training and when co-rating a random sample of videotaped study interviews (ICC's≥0.96). The timeframe for post-infusion MADRS was modified to reflect the period since last assessment. Ketamine's antidepressant effects in this sample (not including suicidality analysis) have been reported previously (13).

A subset of patients (n=12)[1] completed the IAT and the 21-item self-report Beck Scale for Suicidal Ideation (BSI)(17) at baseline. Ten patients repeated these measures 24-hours post-infusion[2] (**Supplement A**).

A distinct subset of single-dose ketamine responders (n=10)[3] enrolled in a subsequent study of repeated-dose IV ketamine. Detailed methods, tolerability, and antidepressant effects will be reported separately (18). Following a Day 1 infusion identical to that described above, patients were assessed for 24-hour antidepressant response (MADRS≤50% of baseline score). Responders (9/10 participants) then received up to 5 additional infusions (Days 3,5,8,10,12) identical to the first, except that patients were assessed and discharged 4-hours post-infusion.

Table 2 presents clinical and demographic characteristics of the three samples. All participants signed informed consent. The Mount Sinai School of Medicine Institutional Review Board approved procedures.

Implicit Association Test (IAT)

Two recently developed variants of the IAT (IAT-Death, assessing the strength of association between words related to "Death" and "Me"; IAT-Escape, assessing associations between "Escape" and "Me") were selected based on the hypothesis that individuals contemplating suicide would be characterized by greater self-identification with death (relative to life) and escape (relative to stay). Preliminary evidence suggests these associations are stronger in suicide attempters than non-attempters (10). IATs were administered and scored in accordance with recommended procedures (19) and followed a design described previously (9)(**Supplement B**). "Escape=Me" and "Death=Me" D-scores were calculated for each

[1] IAT and BSI data were collected from patients enrolled during the latter half of the enrollment period only
[2] Time constraints prevented post-infusion data collection in 2 patients
[3] 3 participants in the repeated-dose study were also participants in the IAT subsample

participant, where D=[(mean RT during Escape=Me [or Death=Me] block) – (mean RT during Stay=Me [or Life=Me] block) ÷ (SD of RT across all trials)].

Statistical Analysis

A composite suicidality index ($SI_{composite}$) was calculated by summing z-scores on the BSI and MADRS suicidality item (MADRS-SI). Change scores for all measures were calculated as 24-hour value – baseline value. Baseline and post-ketamine scores were compared by paired t-tests, with effect sizes calculated as Cohen's *d* (20), and by repeated-measures analysis of covariance (ANCOVA). Due to violation of Small's test for multivariate normality in several baseline measures, baseline correlations were calculated nonparametrically with Spearman's *rho*. Correlations for change scores were calculated using Pearson's *r*. Two-tailed alpha level was set at .05, unadjusted.

RESULTS

A single infusion of ketamine reduced scores on the MADRS-SI by an average of 2.08 points on a 0-6 scale (t_{25}=6.42, p<.001; d=1.37), with 81% of patients achieving a rating of 0 or 1 24-hours post-infusion (**Table 3; Figure 1**). Of the 13 patients with clinically significant suicidal ideation at baseline (MADRS-SI scores ≥4), 8 (62%) received a rating of 0 or 1 24-hours post-infusion, 3 (23%) endorsed fleeting suicidal thoughts (ratings of 2 or 3), while 2 (15%) remained at or above a rating of 4. With change scores in non-suicide-related MADRS items ($MADRS\text{-}total_{nonSI}$) entered as a covariate, repeated-measures ANCOVA of baseline and 24-hour MADRS-SI scores was not significant ($F_{1,24}$=.38, p=.54), suggesting ketamine's anti-suicidal effects are mediated by depression reduction.

In the TRD subsample completing baseline IATs (n=12), stronger "Escape=Me" implicit associations were associated with greater MADRS-SI scores (*rho*=.60; p=.04), and marginally

with $SI_{composite}$ scores (*rho*=.57; *p*=.052), but not with non-suicide-related depression severity (MADRS-$total_{nonSI}$: *rho*=.24; *p*=.46). Baseline "Death=Me" associations were unrelated to other measures (*p*s >.34). In patients who repeated the measures 24-hours post-infusion (*n*=10), there was a reduction in "Escape=Me" associations (t_9=3.76; *p*=.006; *d*=1.37)(**Figure 2**) and in BSI (t_9=3.15; *p*=.012) and MADRS-SI (t_9=5.24; *p*<.001). "Death=Me" associations were not significantly changed (t_9=.658; *p*=.52). "Escape=Me" reductions were correlated with reductions in BSI (*r*=.65; *p*=.042), $SI_{composite}$ (*r*=.64; *p*=.048), and MADRS-SI at the trend level (*r*=.57; *p*=.09), but not with MADRS-$total_{nonSI}$ changes (*r*=-.03; *p*=.94). "Death=Me" changes showed a trend-level association with BSI changes only (*r*=.60; *p*=.06). Most zero-order correlations were maintained or increased after controlling for change in MADRS-$total_{nonSI}$ and baseline $SI_{composite}$ (**Table 4**).

In patients who subsequently enrolled in the repeated-dose ketamine study (n=10), the first infusion again significantly reduced MADRS-SI scores (2.8-point mean decrease; t_9=5.47, *p*<.001; *d*=2.17), with 90% of patients receiving a 24-hour rating of 0 (**Table 3; Figure 1**). Acute reductions were maintained throughout the 12-day treatment period by the 9 patients receiving repeated infusions (baseline-to-day-12 mean decrease=2.89; t_8=5.12, *p*=.001; *d*=2.42), with no patient scoring >2 at any post-baseline assessment (before and after each infusion).

DISCUSSION

These preliminary findings support the premise that a single subanesthestic dose of IV ketamine has rapid effects on suicidal cognition in TRD, and that acute improvements in suicidality can be sustained through repeated ketamine infusions. Confidence intervals for MADRS-SI suggested moderate to very large effects, despite small sample sizes.

An IAT assessing the association between 'Me' and 'Escape' was related to explicit suicidal ideation at baseline and showed sensitivity to therapeutic change, an important criterion if the IAT is to have utility as a clinical assessment tool. Associations between 'Me' and 'Death' did not change as predicted, suggesting that the implicit representation of suicide in TRD might more closely relate to the concept of escape than to death itself. "Death=Me" associations were low at baseline, possibly limiting room for improvement. Prospective studies in high-risk samples should test whether the IAT can improve prediction of suicide risk in clinical settings, where motivation to conceal suicidal thoughts may exist (4). The IAT might also be useful in revealing psychological mechanisms of change. For instance, mediational analysis in larger samples could test the hypothesis that ketamine reduces depressed mood in suicidal patients, thereby decreasing implicit desire to escape from an unbearable emotional state, leading to downstream reductions in explicit suicidal thoughts.

The rapid onset and maintenance of improvement we observed suggests that IV ketamine, administered in the hospital setting with appropriate safety monitoring, may offer an attractive therapy for acutely suicidal depressed patients. Whether high-risk patients with markedly active suicidality will respond similarly remains an open question. Controlled studies are needed to establish whether ketamine is efficacious in such samples and whether decreased suicidality, once achieved, can be maintained through alternative pharmacological or psychosocial interventions. Given that all three datasets analyzed here were obtained from a single group of patients, these findings require independent replication.

ACKNOWLEDGEMENTS

This work was supported by National Institutes of Health grants K23-MH-069656 and

MO1-RR-00071 (SJM) and NARSAD (SJM, DSC). We thank Marije aan het Rot, Kate Collins, Kimberly Hunter, Michele Gonen, James Murrough, M.D., Andrew Perez, M.D., David Reich, M.D., all additional members of the Mood & Anxiety Disorders Program, and the staff of the Mount Sinai General Clinical Center for their assistance with the study.

FINANCIAL DISCLOSURES

Ms. Price and Dr. Nock report no biomedical financial interests or potential conflicts of interest. Dr. Mathew has received lecture or consulting fees from AstraZeneca and Jazz Pharmaceuticals, and has received research support from Alexza Pharmaceuticals, GlaxoSmithKline Pharmaceuticals, and Novartis Pharmaceuticals. Dr. Charney discloses consultant activities with Unilever UK Central Resources Limited in the past two years. Drs. Charney and Mathew have been named as an inventor on a use-patent of ketamine for the treatment of depression. If ketamine were shown to be effective in the treatment of depression and received approval from the Food and Drug Administration for this indication, Dr. Charney and the Mount Sinai School of Medicine could benefit financially. Dr. Mathew has relinquished his claim to any royalties and will not benefit financially if ketamine is approved for this use.

REFERENCES

1. Kellner CH, Fink M, Knapp R, Petrides G, Husain M, Rummans T, et al. (2005): Relief of expressed suicidal intent by ECT: a consortium for research in ECT study. *Am J Psychiatry*. 162:977-982.
2. Szanto K, Mulsant BH, Houck P, Dew MA, Reynolds CF, 3rd (2003): Occurrence and course of suicidality during short-term treatment of late-life depression. *Arch Gen Psychiatry*. 60:610-617.
3. Nock MK, Banaji MR (2007): Prediction of suicide ideation and attempts among adolescents using a brief performance-based test. *J Consult Clin Psychol*. 75:707-715.
4. Busch KA, Fawcett J, Jacobs DG (2003): Clinical correlates of inpatient suicide. *Journal of Clinical Psychiatry*. 64:14-19.
5. Greenwald AG, McGhee DE, Schwartz JL (1998): Measuring individual differences in implicit cognition: the implicit association test. *J Pers Soc Psychol*. 74:1464-1480.
6. Cunningham WA, Preacher KJ, Banaji MR (2001): Implicit attitude measures: consistency, stability, and convergent validity. *Psychol Sci*. 12:163-170.
7. Banse R, Seise J, Zerbes N (2001): Implicit attitudes towards homosexuality: reliability, validity, and controllability of the IAT. *J Exp Psychol*. 48:145-160.
8. Greenwald AG, Poehlman TA, Uhlmann EL, Banaji MR (in press): Understanding and using the Implicit Association Test: III. Meta-analysis of predictive validity. *J Pers Soc Psychol*.
9. Nock MK, Banaji MR (2007): Assessment of self-injurious thoughts using a behavioral test. *Am J Psychiatry*. 164:820-823.
10. Nock MK, Deliberto TL, Dour HJ, Finn CT, Park JL, Banaji MR (submitted): Identification of a behavioral marker that predicts suicide attempts.
11. Zarate CA, Jr., Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. (2006): A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 63:856-864.
12. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. (2000): Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 47:351-354.
13. Mathew SJ, Murrough JW, Aan Het Rot M, Collins KA, Reich DL, Charney DS (2009): Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. *Int J Neuropsychopharmacol*. 17:1-12.
14. Sackeim HA (2001): The definition and meaning of treatment-resistant depression. *J Clin Psychiatry*. 62 Suppl 16:10-17.
15. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH (1996): The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 26:477-486.
16. Montgomery SA, Asberg M (1979): A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 134:382-389.
17. Beck AT, Steer RA (1991): Manual for the Beck Scale for Suicide Ideation. San Antonio, TX: Psychological Corporation.
18. aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, et al. (submitted): Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression.
19. Nosek BA, Greenwald AG, Banaji MR (2005): Understanding and using the Implicit Association Test: II. Method variables and construct validity. *Pers Soc Psychol Bull*. 31:166-180.

20. Cohen J (1988): Statistical power analysis for the behavioral sciences. Hillsdale, NJ: Lawrence Erlbaum Associates.

Table 1. Montgomery-Asberg Depression Rating Scale scoring guidelines for item 10: "Suicidal Thoughts"

Score	Description
0	"Enjoys life or takes it as it comes."
1	[none provided]
2	"Weary of life. Only fleeting suicidal thoughts."
3	[none provided]
4	"Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention."
5	[none provided]
6	"Explicit plans for suicide when there is an opportunity. Active preparation for suicide."

Table 2. Baseline descriptive and clinical characteristics of full sample treated with single infusion intravenous ketamine; subsample who subsequently completed the repeated infusions study; and IAT subsample who completed additional implicit and explicit measures of suicidality at baseline

	Single Infusion Sample (n=26)[†]	**IAT Subsample (n=12)**	**Repeated Infusions Subsample (n=10)**
Age, mean (SD), y	48.2 (11.8)	50.1 (10.3)	51.4 (14.6)
Female, No. (%)	10 (39%)	5 (42%)	5 (50%)
Non-Hispanic Caucasian, No. (%)	18 (69%)	8 (67%)	7 (70%)
IQ, mean (SD)	115.0 (10.3)	118.7 (10.2)	115.7 (11.8)
Median household annual income	$15,000-24,999	$10,000-14,999	$15,000-24,999
Time Since Illness Onset, mean (SD), y	29.3 (13.3)	29.7 (10.5)	29.6 (13.0)
Age-of-Onset, mean (SD), y	18.5 (12.2)	20.4 (11.2)	20.9 (15.4)
Number of Episodes, mean (SD)	1.9 (1.7)	2.3 (2.1)	2.1 (1.7)
Duration of Current Episode >= 2y, No. (%)	26 (100%)	12 (100%)	10 (100%)
Number of Failed Antidepressant Trials in Current Episode, mean (SD)	6.0 (4.1)	6.8 (3.9)	7.1 (4.2)
History of Suicide Attempts, No. (%)	5 (19%)	3 (25%)	1 (10%)

Clinically Significant Suicidal Ideation (MADRS-SI score >=4), No. (%)	13 (50%)	6 (50%)	6 (60%)
MADRS-SI=4	10 (38.5%)	5 (41.7%)	5 (50%)
MADRS-SI=5	3 (11.5%)	1 (8.3%)	1 (10%)
MADRS-SI=6	0	0	0

Note: MADRS-SI = Montgomery-Asberg Depression Rating Scale (16) suicidality item; IAT = Implicit Association Test (5)

Table 3. Ketamine effects on explicit and implicit suicidality

	Single Infusion Study (n=26)		*IAT Subsample (n=10)*		*Repeated Infusions Study (n=10)*	
Measure	**Mean (SD)**	**Effect Size: Cohen's *d* [95% CI]**	**Mean (SD)**	**Effect Size: Cohen's *d* [95% CI]**	**Mean (SD)**	**Effect Size: Cohen's *d* [95% CI]**
MADRS total						
Baseline	36.92 (5.41)		37.80 (5.8)		32.70 (6.43)	
Day 2: 24-hours after infusion 1	14.85 (13.14)***	*d*=2.11 [1.25-2.97]	9.40 (8.9)***	*d*=3.79 [1.21-6.37]	8.10 (4.63)***	*d*=4.43 [0.89-7.97]
Day 12: 4-hours after infusion 6	--	--	--	--	5.11 (3.66)*** †	*d*=5.98 [1.52-10.44]
MADRS-SI						
Baseline	2.85 (1.6)		2.90 (1.7)		3.00 (1.63)	
Day 2: 24-hours after infusion 1	0.77 (1.4)***	*d*=1.37 [0.79-1.95]	0.40 (.97)***	*d*=1.67 [0.70-2.64]	0.20 (0.63)***	*d*=2.17 [0.75-3.59]
Day 12: 4-hours after infusion 6	--	--	--	--	0.00 (0.00)*** †	*d*=2.42 [1.20-3.63]
BSI						
Baseline	--	--	8.00 (9.3)		--	--
Day 2: 24-hours after infusion 1	--	--	3.3 (7.8)*	*d*=0.53 [0.18-0.87]	--	--
IAT: Escape=Me						
Baseline	--	--	-.04 (.31)		--	--
Day 2: 24-hours after infusion 1	--	--	-.53 (.40)**	*d*=1.36 [0.38-2.34]	--	--
IAT: Death=Me						
Baseline	--	--	-.48 (.63)		--	--
Day 2: 24-hours after infusion 1	--	--	-.28 (.43) (*ns)*	*d*=-0.38 [-1.56-0.79]	--	--

Note: TRD = treatment-resistant depression; MADRS = Montgomery-Asberg Depression Rating Scale (16); MADRS-SI = MADRS Suicidality Item; BSI = Beck Scale for Suicidal Ideation (17); IAT = Implicit Association Test (5)

*** p<.001; ** p < .01; * p < .05; *ns* = not significant; baseline and post-infusion scores compared by paired t-tests; baseline-to-post infusion effect size (*d*) calculated from means, SDs, and pre-post correlation coefficients (20)

†n=9 for Day 12 assessments

Table 4. Partial correlations between change scores (24-hours – baseline) in implicit and explicit suicidality measures, controlling for change in other depressive symptoms (MADRS, excluding suicidality item)

	MADRS-SI	BSI	$SI_{composite}$
IAT: Escape=Me	**.74 (p=.022)**	**.72 (p=.028)**	**.78 (p=.014)**
IAT: Escape=Me, *adding baseline $SI_{composite}$ as an additional covariate*	*.64 (p=.086)*	.60 (p=.118)	**.71 (p=.048)**
IAT: Death=Me	.34 (p=.366)	**.69 (p=.038)**	.55 (p=.122)
IAT: Death=Me, *adding baseline $SI_{composite}$ as an additional covariate*	.31 (p=.460)	**.80 (p=.016)**	*.65 (.078)*

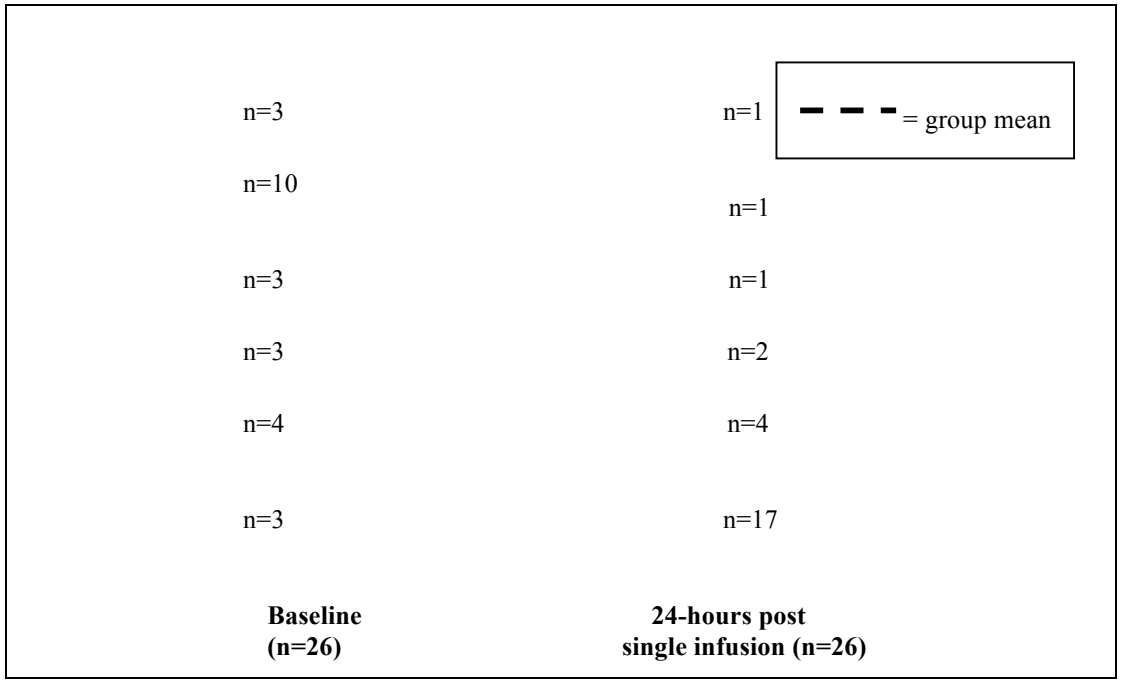
Note: MADRS = Montgomery-Asberg Depression Rating Scale (16); MADRS-SI = MADRS Suicidality Item; BSI = Beck Scale for Suicidal Ideation (17); $SI_{composite}$ = composite suicidality index: sum of z-scores on BSI and MADRS-SI; IAT = Implicit Association Test (5)

FIGURE LEGENDS

FIGURE 1. Individual patient scores on the Montgomery-Asberg Rating Scale—Suicide item at baseline (Day 1; 150 minutes prior to infusion), 24-hours following a single subanesthetic infusion of ketamine (Day 2), and 4-hours following the final repeated infusion (Day 12 of study; Panel 2 only).

FIGURE 2. Mean IAT-Escape D-scores (± SEM) representing the strength of association between words related to "Me" and words related to "Escape" at baseline and 24-hours following a single subanesthetic infusion of ketamine. D-scores calculated as D = [(mean response latency during Escape/Me block – mean response latency during Escape/Not Me block) ÷ SD of response latency across all trials]. More positive D-score indicates stronger implicit self-identification with words related to "Escape," in comparison to words related to "Stay."

Figure 1.


Single-infusion study
n=3
n=10
n=3
n=3
n=4
n=3
n=1
n=1
n=1
n=2
n=4
n=17
= group mean
Baseline
(n=26)
24-hours post
single infusion (n=26)

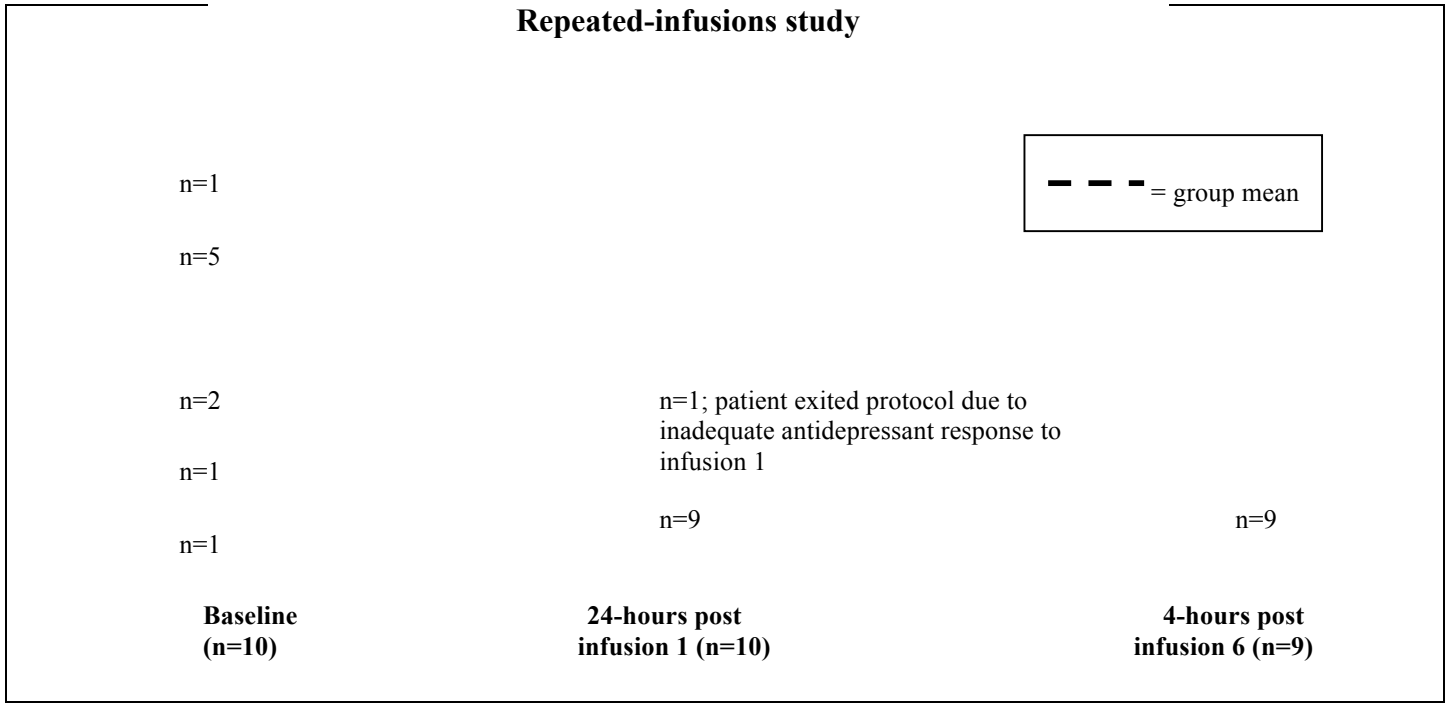
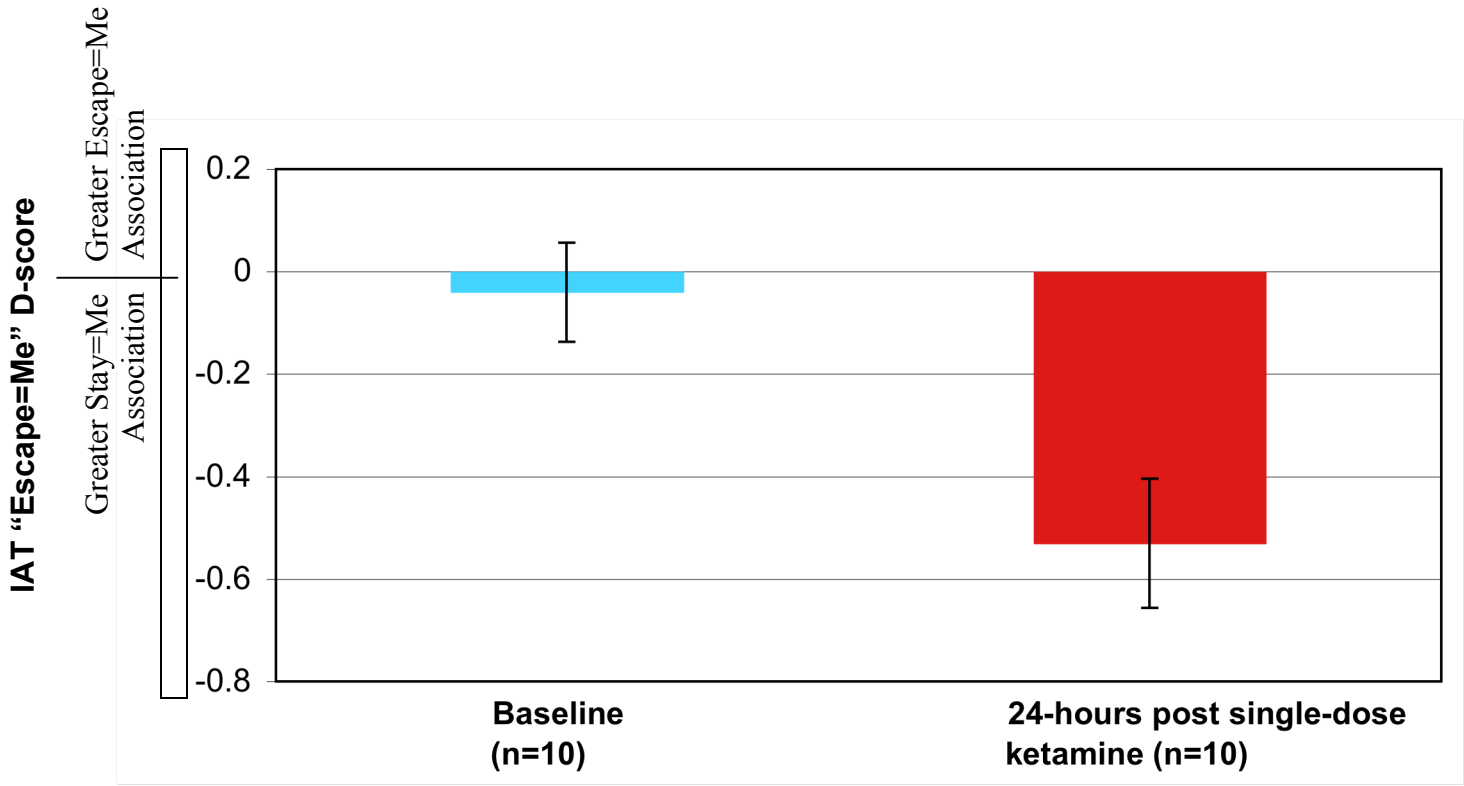
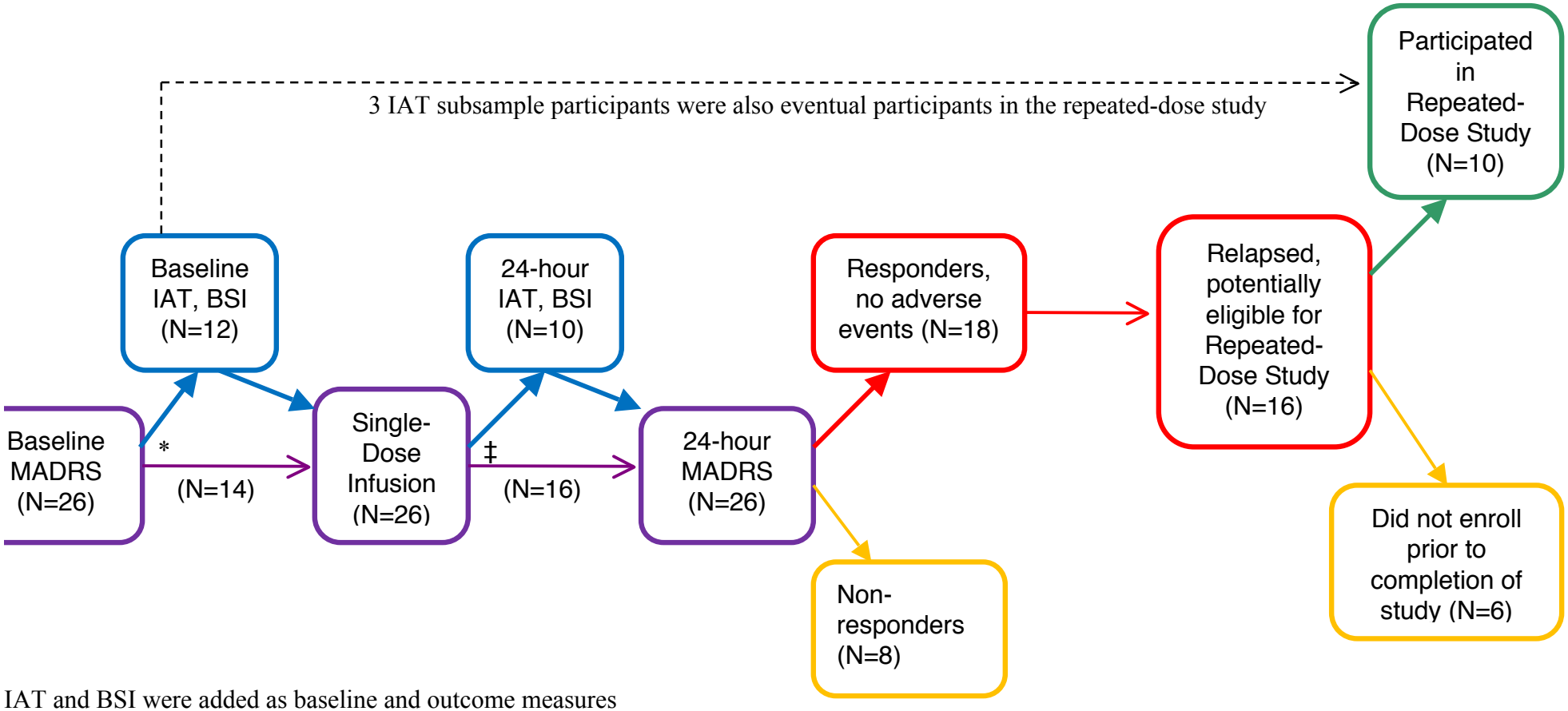

Repeated-infusions study
= group mean
n=1
n=5
n=2
n=1
n=1
n=1; patient exited protocol due to inadequate antidepressant response to infusion 1
n=9
n=9
Baseline (n=10)
24-hours post infusion 1 (n=10)
4-hours post infusion 6 (n=9)

Figure 2.


IAT "Escape=Me" D-score
Greater Escape=Me Association
Greater Stay=Me Association
0.2
0
-0.2
-0.4
-0.6
-0.8
Baseline (n=10)
24-hours post single-dose ketamine (n=10)

Supplement 1

Supplemental Figure 1. Flow chart of events in single-dose and repeated-dose studies



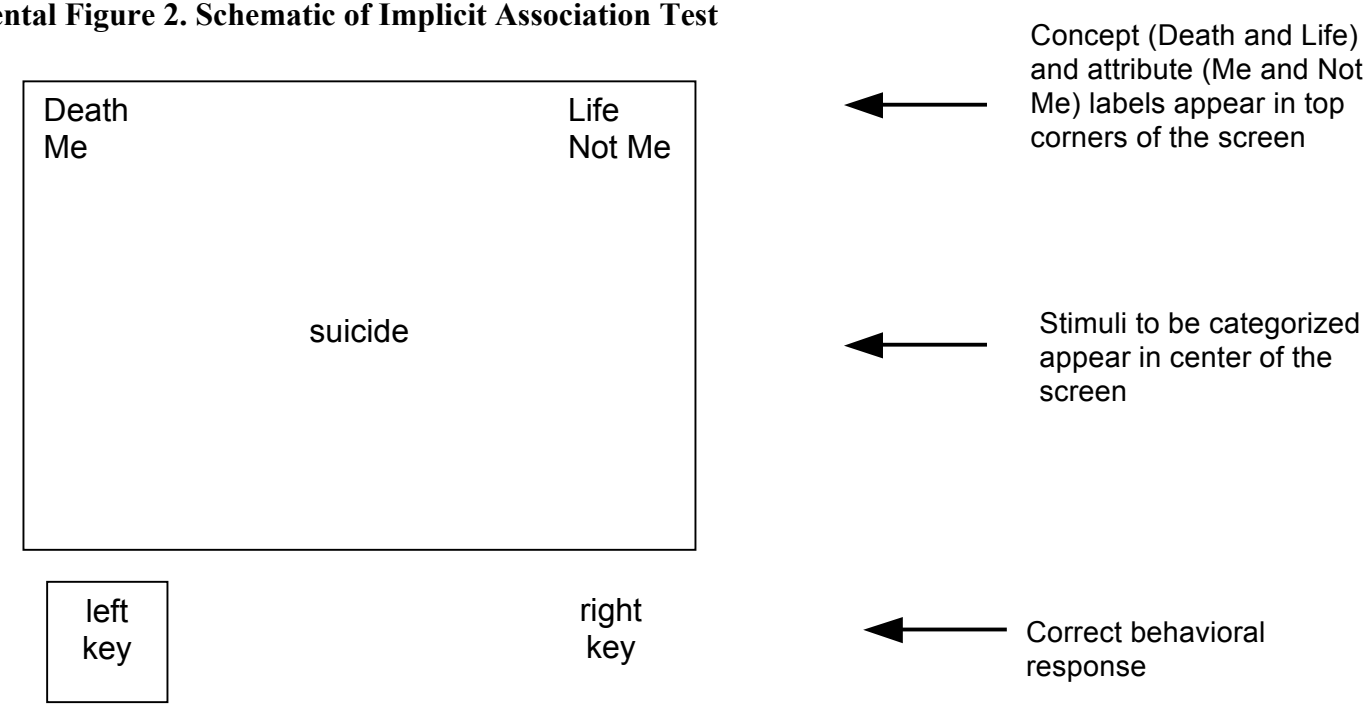
IAT and BSI were added as baseline and outcome measures
ıring latter half of study enrollment period.

Time constraints prevented post-infusion IAT
ıd BSI data collection in 2 of the 12 patients who
›mpleted all measures at baseline.

Supplement 2

The Implicit Association Test (IAT) rests on the assumption that it is easier to map two concepts onto a single behavioral response (e.g., left key press) when they are closely associated than when they are loosely associated. The two IATs (IAT-Death; IAT-Escape) were completed in counterbalanced order on a Dell laptop computer running Inquisit (Millisecond Software, Seattle, WA). Participants were instructed to classify stimuli appearing at the center of the screen by pressing the "e" key for words belonging to categories on the left of the screen and the "i" key for words belonging to categories on the right. In the IAT-Death, a series of words related to death (suicide, die, dead, deceased, lifeless) or life (alive, live, survive, thrive, breathing) were presented in random order, intermixed with a series of self-relevant (I, Myself, My, Mine, Self) or other-relevant (They, Them, Their, Other, Theirs) words. Category labels ("Death," "Life," "Me," "Not Me") remained in the upper left and right corners of the screen throughout the task (**Supplemental Figure 2**).

Supplemental Figure 2. Schematic of Implicit Association Test



Stimuli remained onscreen until the correct response was made. Incorrect classifications resulted in the presentation of a red "X" below the stimulus. In the first critical block (presented in randomized order) the category labels "Death" and "Me" appeared on the same side of the screen and thus required the same key response, while "Life" and "Not Me" appeared on the opposite side. In the second critical block, the category pairings were reversed—"Death" and "Not Me" required the same key press, as did "Life" and "Me." The relative strength of association between self and death was inferred from the speed of responses during these two blocks. A D score was calculated for each participant, where D=[(mean response latency during Death/Me block – mean response latency during Death/Not Me block) ÷ SD of response latency across all trials]. The IAT-Escape followed an identical design with words related to escape (exit, quit, end, leave, depart) and stay (continue, remain, hold on, persist, endure), as well as self-referential and other-referential words (as before), classified under the headings "Escape," "Stay," "Me," and "Not Me."