

## Online Supplemental Material

### Methods

#### *Subjects*

A diagnosis of MDD was verified via the Mini International Neuropsychiatric Interview [S1]. Subjects were required to demonstrate resistance to at least one adequate trial of antidepressants in the current episode and had a baseline score  $\geq 21$  on the Hamilton Rating Scale for Depression-17-item [S2]. Exclusion criteria were: any axis I or II disorders, which at screening were clinically predominant to their depressive episode; schizophrenia or schizoaffective disorder; active suicidal thoughts with a plan; current or recent (within 6 months) substance use disorder; dementia, delirium, or any other neurological or mental disease that might affect cognition or the ability to meaningfully participate in CBT. All patients underwent a physical examination, routine hematologic and chemistry tests, and an electrocardiogram prior to receiving ketamine to assure good general physical health.

#### *Ketamine Infusions*

During ketamine infusions, pulse oximetry, heart rate, and 3-lead EKG were monitored continuously throughout the infusion, with blood pressure measurements every 5 minutes. Immediate effects of ketamine on perception were measured using the Clinician-Administered Dissociative States Scale (CADSS), administered at baseline, 40, and 80 minutes following infusion [S3]. As part of discharge readiness criteria, post-ketamine CADSS assessments returned to baseline prior discharge.

#### *Cognitive Assessments*

Tests were administered via computer 4 times per week during the first 2 weeks of the protocol (Figure S1). On ketamine treatment days, assessments were always given prior to infusions. These cognitive tests have been used in other psychopharmacology trials, have multiple parallel versions, have minimal practice effects, and have demonstrated acceptable test-retest reliability [S4-S6]. Specific domains tested were attention, working and visual memory, processing speed, and verbal memory. Further description of these tasks can be found elsewhere [S7, S8].

#### *Data Analytic Methods*

The data analytic method followed strategies of similar protocols [S9]. Changes between two time-points for depression severity were calculated using paired t-tests. Time-to-relapse among responders was calculated using the Kaplan-Meier method. Survival analyses were performed for all patients who received at least one CBT session. Our approach to missing data due to subject withdrawal in the survival analyses consisted of last observation carried forward (LOCF); given that those who withdrew did so after relapse, we considered this a conservative approach in this design.

The general linear mixed model approach to the repeated cognitive assessments allowed for the inclusion of some subjects who did not complete all cognitive assessments. As this aim was exploratory in nature, it was not powered to detect changes in cognition, but rather, to provide preliminary data to estimate the presence of a signal and to provide figures for approximate power calculations for future studies.

All statistical analyses were performed in Stata/SE (StataCorp LP, version 14.2; College Station, Texas).

## **Results**

### *Subject Retention*

Sixteen subjects initiated the combined ketamine and CBT protocol, with 14 subjects who completed all 4 infusions. One subject withdrew after 2 ketamine infusions (due to clinical worsening) and 1 withdrew after 3 infusions (due to lack of efficacy). Five additional subjects withdrew during the CBT phase of the protocol, either due to lack of clinical efficacy (in the case of 3 ketamine non-responders) or relapse (in the case of 2 ketamine responders, Figure S2).

### *Concomitant Medications*

Concomitant medications were not controlled in this study. Most responders (6/8, 75%) had no changes to their medications throughout the study (Table S1); one responder stopped an antidepressant (MAOI) as ketamine infusions began and subsequently relapsed within 1 week of the last infusion. The other responder started a new antidepressant during the study and remained well through study end. Half (4/8) of non-responders had medication changes (see Table S1).

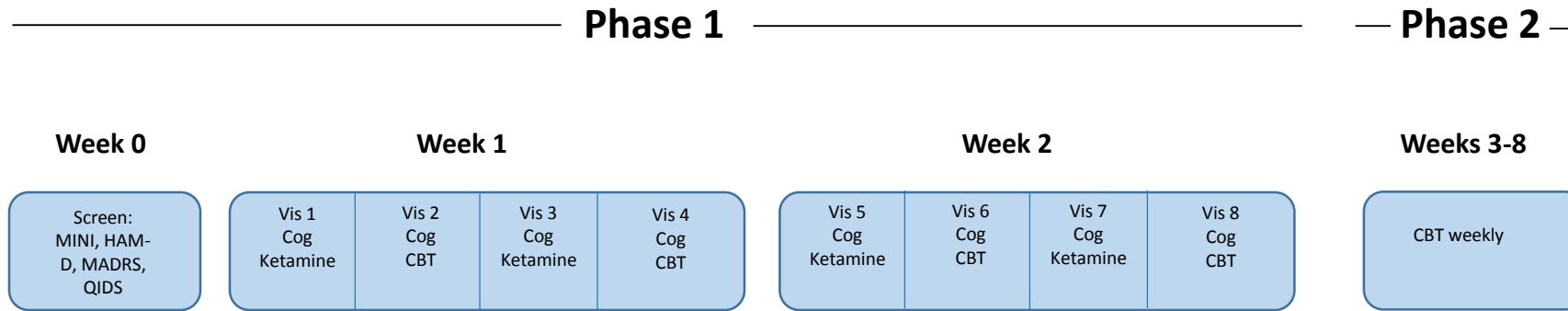
### *Dissociative Effects, General Side Effects, and Hemodynamic Changes*

Though the ketamine was provided as part of the patient's clinical treatment, outside the research protocol, we include dissociative and general side effects for completeness. Dissociative and general side effects were measured for all subjects who received at least one ketamine infusion. Pre-infusion mean (SD) CADSS scores were 0.40 (0.84). Mean (SD) scores at 40-minutes post-infusion were 5.77 (7.92) and at 80-minutes post-infusion were 0.05 (SD 0.22). General side effects that were not captured in the CADSS measure were elicited at each study visit. The most common general side effects were nausea (25%), headache (25%), and fatigue (12.5%) (Table S2). Notably, one ketamine non-responder developed overvalued ideas to a near delusional level (insight was preserved) related to her fears of contracting a rare tropical infectious disease. Upon further investigation and discussions with the patient's previous long term care provider, it became evident that the subject had experienced several similar episodes previously. These symptoms eventually resolved and returned to pre-ketamine baseline levels (which had waxed and waned over the previous years). One subject developed elevated blood pressure during the first infusion (181/72) that necessitated stopping the infusion 10 min early. This subject received low-dose PO labetalol as pre-treatment prior to subsequent infusions with good effect (max blood pressures of 161/79, 141/61, and 152/69 for the 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> infusions, respectively).

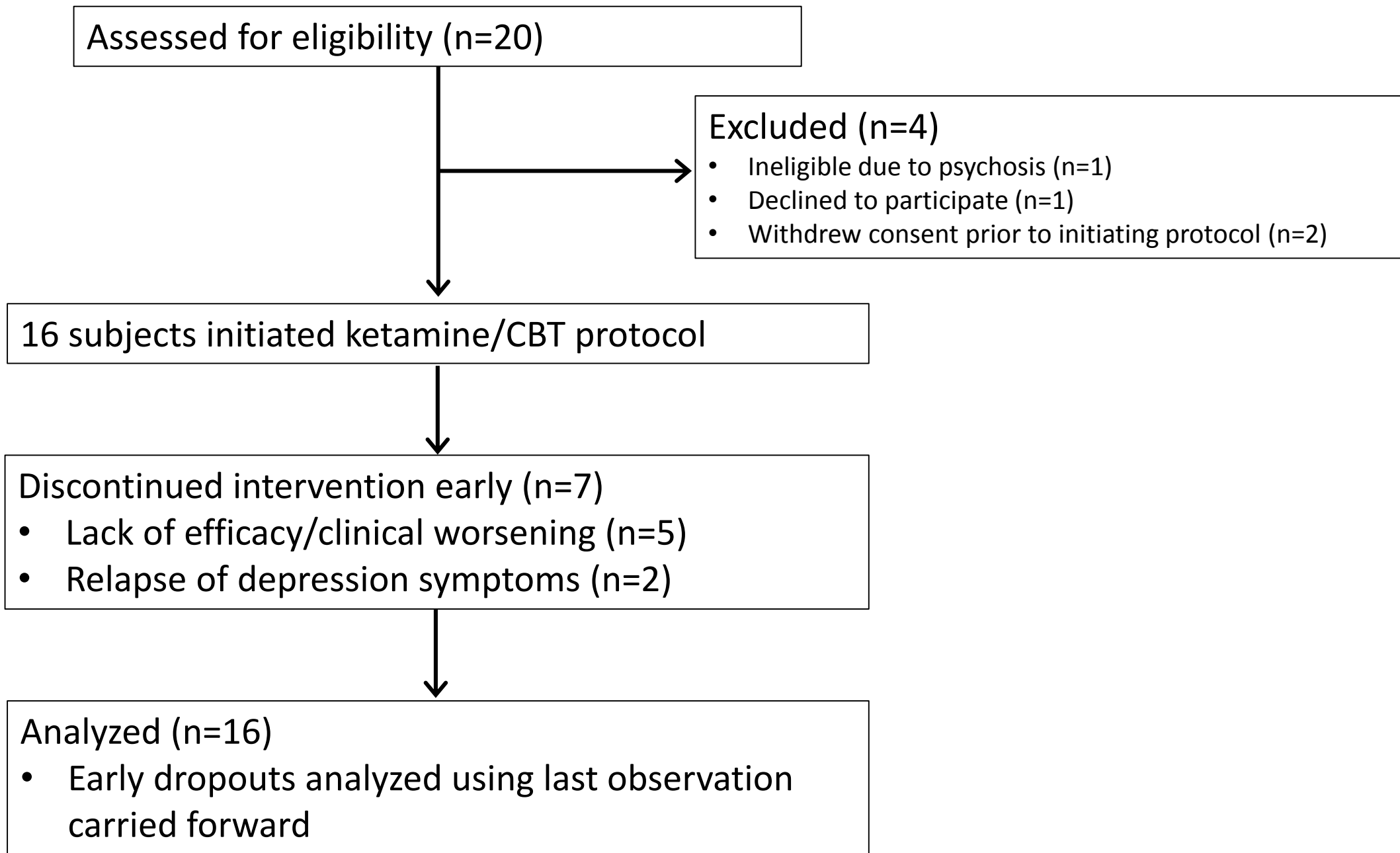
## **Supplementary References**

- S1 Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC: The mini-international neuropsychiatric interview (m.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for dsm-iv and icd-10. *J Clin Psychiatry* 1998;59 Suppl 20:22-33;quiz 34-57.
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- S4 Snyder PJ, Werth J, Giordani B, Caveney AF, Feltner D, Maruff P: A method for determining the magnitude of change across different cognitive functions in clinical trials: The effects of acute administration of two different doses alprazolam. *Hum Psychopharmacol* 2005;20:263-273.
- S5 Falletti MG, Maruff P, Collie A, Darby DG: Practice effects associated with the repeated assessment of cognitive function using the cogstate battery at 10-minute, one week and one month test-retest intervals. *J Clin Exp Neuropsychol* 2006;28:1095-1112.
- S6 Collie A, Maruff P, Darby DG, McStephen M: The effects of practice on the cognitive test performance of neurologically normal individuals assessed at brief test-retest intervals. *J Int Neuropsychol Soc* 2003;9:419-428.
- S7 Maruff P, Thomas E, Cysique L, Brew B, Collie A, Snyder P, Pietrzak RH: Validity of the cogstate brief battery: Relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and aids dementia complex. *Arch Clin Neuropsychol* 2009;24:165-178.
- S8 Fredrickson J, Maruff P, Woodward M, Moore L, Fredrickson A, Sach J, Darby D: Evaluation of the usability of a brief computerized cognitive screening test in older people for epidemiological studies. *Neuroepidemiology* 2010;34:65-75.
- S9 Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV: Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry* 2013;74:250-256.



**Figure S1.** Study design. Cog – Cognitive Testing (CogState); CBT – cognitive behavioral therapy; HAM-D Hamilton Depression Rating Scale; MADRS – Montgomery-Åsberg Depression Rating Scale; MINI – Mini International Neuropsychiatric Interview; QIDS – Quick Inventory of Depressive Symptomatology



**Figure S2. Patient flow diagram**

### Depression severity following 4 ketamine infusions plus cognitive behavior therapy

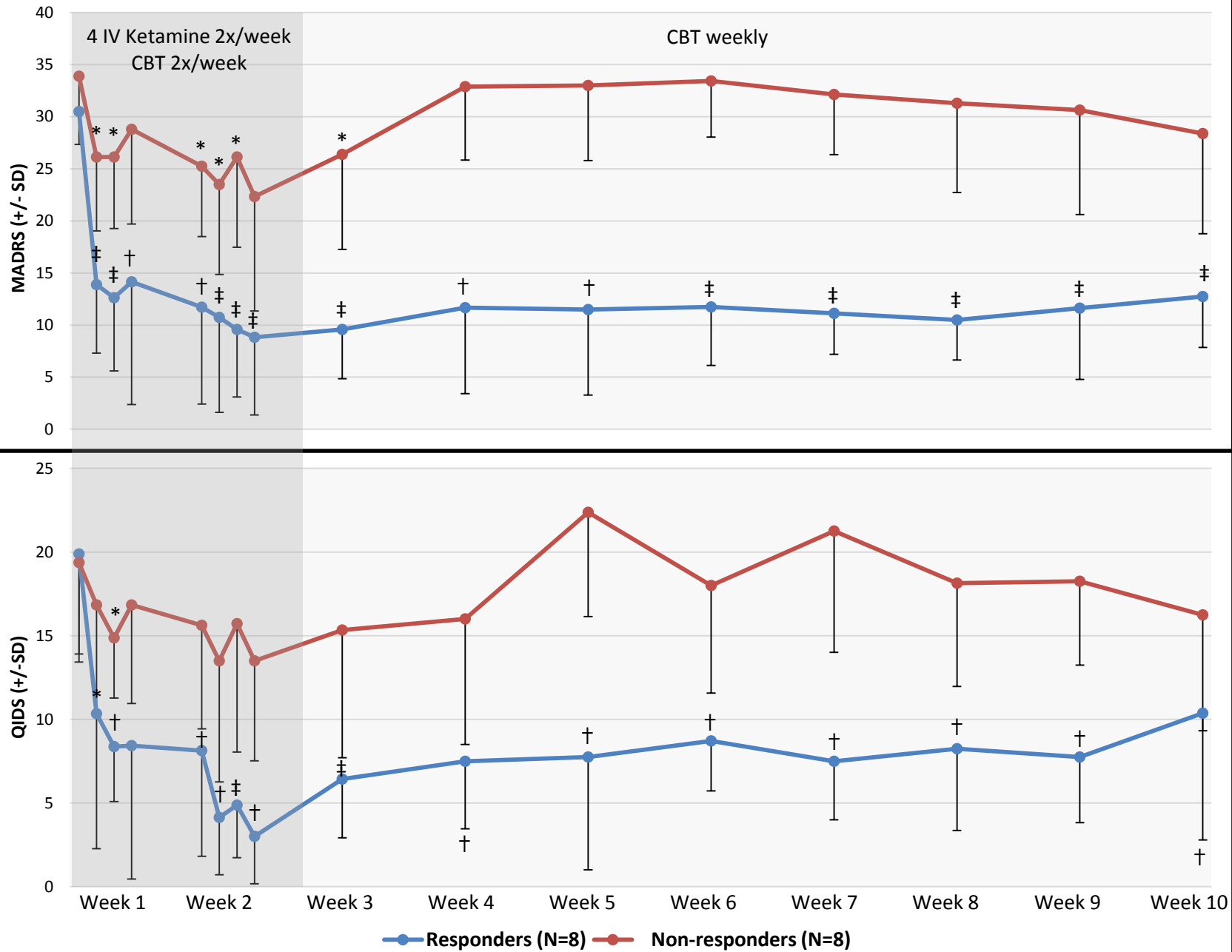
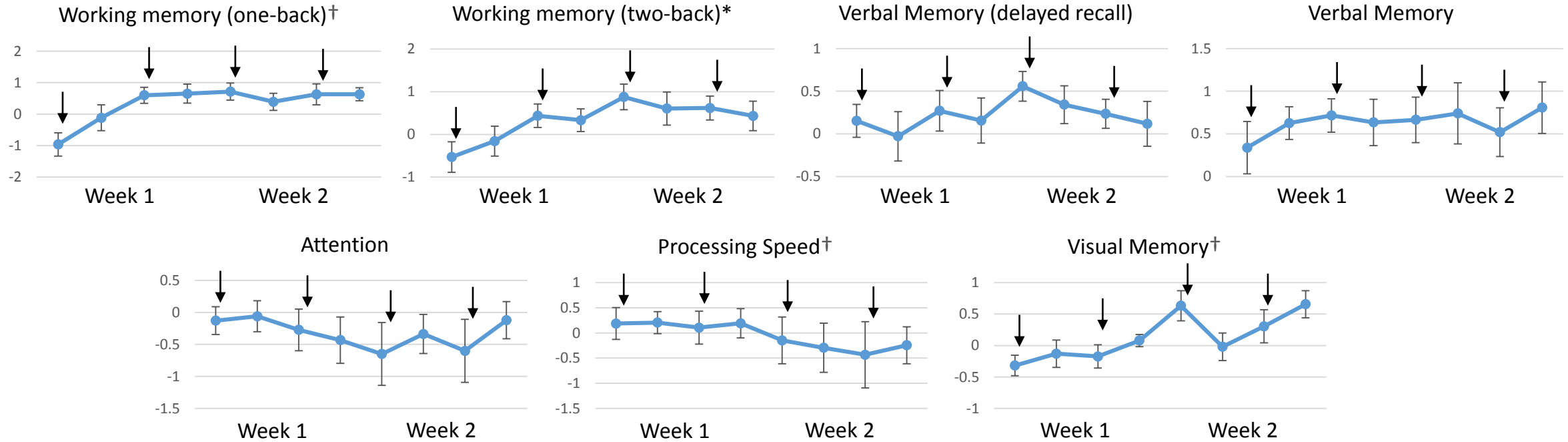


Figure S3. Depression severity over time in responders and non-responders. Last observation carried forward.

## Cognitive Measures During Ketamine Treatment Phase

Z Score



**Figure S4.** Cognitive assessments done repeatedly over 2 weeks with IV ketamine given twice weekly (n=16). Scores are z-scores, based on age-adjusted population means. Arrows indicate ketamine infusions. Improvements were seen over time in working and visual memory, while a decline was seen in processing speed, \*p<0.05; †p<0.01 for overall trend, general linear mixed-model, co-varying for changes in depression severity.

**Table S1. Concomitant Medications**

<b>Subject Number</b>	<b>Responder?</b>	<b>Psychotropic Medications at Study Start</b>	<b>Psychotropic Medications at Study End</b>	<b>Other Medications</b>
1	N	lisdexamphetamine, amphetamine salts, lamotrigine, vortioxetine, quetiapine, clonazepam	lisdexamphetamine, amphetamine salts, lamotrigine, vortioxetine, quetiapine, clonazepam	
2	N	lorazepam	hydroxyzine	aspirin
3	N	amitriptyline, aripiprazole, amphetamine salts, chlorazepate	amitriptyline, aripiprazole, amphetamine salts, chlorazepate	
4	Y	tranylcypromine	none	
5	N	lorazepam, neurontin, ziprasidone	lorazepam, neurontin, ziprasidone	
6	Y	lamotrigine, liothyronine, oxcarbazepine, quetiapine	lamotrigine, liothyronine, oxcarbazepine, quetiapine	testosterone, levothyroxine
7	Y	alprazolam, liothyronine, phenelzine	alprazolam, liothyronine, phenelzine	loratidine
8	N	bupropion, desvenlafaxine, oxycodone	phenelzine, oxycodone	
9	N	venlafaxine, quetiapine, clonazepam	risperidone, clonazepam, benztropine, fluoxetine	
10	Y	venlafaxine, bupropion, zolpidem	venlafaxine, bupropion, lorazepam	levothyroxine, aspirin, insulin, ramipril, atorvastatin
11	Y	desvenlafaxine, aripiprazole, amphetamine salts, modafinil, clonazepam	desvenlafaxine, aripiprazole, amphetamine salts, modafinil, clonazepam	topical testosterone gel
12	Y	duloxetine, bupropion, lorazepam, neurontin	duloxetine, bupropion, lorazepam, neurontin	
13	N	venlafaxine, trazodone, alprazolam	venlafaxine, trazodone, alprazolam, aripiprazole, modafinil	
14	Y	lamotrigine, alprazolam	lamotrigine, alprazolam, nefazodone	
15	Y	none	none	celecoxib prn
16	N	valproic acid, risperidone, clonazepam	fluoxetine, aripiprazole, clonazepam	



**Table S2. General side effects associated with 4 repeated intravenous ketamine infusions in treatment-resistant depression**

<b>Item</b>	<b>Number (%)</b>
Nausea	4 (25%)
Headache	4 (25%)
Weakness or fatigue	2 (12.5%)
Dizziness or faintness	1 (6.3%)
Appetite decreased	1 (6.3%)
Difficulty swallowing	1 (6.3%)
ringing in ears	1 (6.3%)
Poor coordination	1 (6.3%)
Development of overvalued ideas	1 (6.3%)