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The antidepressant efficacy of subanesthetic-dose ketamine does not correlate with baseline subcortical volumes in a replication sample with major depressive disorder

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Abstract

Background—This study sought to reproduce, in a larger sample, previous findings of a correlation between smaller raw 3-Tesla (3T) hippocampal volumes and improved antidepressant efficacy of ketamine in individuals with major depressive disorder (MDD). A secondary analysis stratified subjects according to functional BDNF rs6265 (val66met) genotype.

Methods—Unmedicated subjects with treatment-resistant MDD ($n=55$) underwent baseline structural 3T MRI. Data processing was conducted with FSL/FIRST and Freesurfer software. The amygdala, hippocampus, and thalamus were selected a priori for analysis. All subjects received a single 0.5mg/kg $\times$ 40-minute ketamine infusion. Pearson correlations were performed with subcortical volumes and percent change in MADRS score (from baseline to 230 minutes, 1 day, and 1 week post-infusion).

Results—Raw and corrected subcortical volumes did not correlate with antidepressant response at any timepoint. In val/val subjects ($n=23$), corrected left and right thalamic volume positively correlated with antidepressant response to ketamine at 230 minutes post-infusion but did not reach

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Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Zarate is listed as a co-inventor on a patent for the use of ketamine and its metabolites in major depression and suicidal ideation. Dr Zarate is listed as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (5*S*)-dehydronorketamine, and other stereoisomeric dehydro and hydroxylated metabolites of (2*R*,6*R*)-ketamine metabolites in the treatment of depression and neuropathic pain. Dr Zarate is listed as co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorders; he has assigned his patent rights to the US government but will share a percentage of any royalties that may be received by the government. All other authors have no conflict of interest to disclose, financial or otherwise.

statistical significance. In met carriers ($n=14$), corrected left and right thalamic volume negatively correlated with antidepressant response to ketamine.

Conclusion—Baseline subcortical volumes implicated in MDD did not correlate with ketamine's antidepressant efficacy. Baseline thalamic volume and BDNF genotype may be a combinatorial rapid antidepressant response biomarker.

Keywords

Major depressive disorder; ketamine; thalamus; brain-derived neurotrophic factor (BDNF); val66met

Introduction

The glutamatergic modulator ketamine, a U.S. Food and Drug Administration (FDA)-approved dissociative anesthetic, has demonstrated rapid-acting antidepressant efficacy in several randomized, double-blind, placebo-controlled (Berman et al., 2000; Diazgranados et al., 2010; Murrough et al., 2013a; Valentine et al., 2011; Zarate et al., 2006, 2012) and open-label (Ibrahim et al., 2012; Murrough et al., 2013b) studies. Unlike monoaminergic antidepressants, which often require weeks to months to achieve maximal efficacy, a single subanesthetic dose of ketamine produces a rapid (within hours) and potent antidepressant response (Coyle and Laws, 2015; Kishimoto et al., 2016; Newport et al., 2015). Antidepressant response to a single ketamine infusion is typically transient (lasting several days to 1 week), though a small percentage of subjects may experience an extended antidepressant effect (Niciu et al., 2014b; Pennybaker et al., 2017).

Several potential neuroimaging biomarkers of antidepressant efficacy have been identified for ketamine across multiple imaging modalities—magnetic resonance imaging (MRI, structural and functional), magnetoencephalography (MEG), and positron emission tomography (PET) (Abdallah et al., 2015b; Niciu et al., 2014c; Zarate et al., 2013)—but most of these findings have not been replicated. Abdallah and colleagues found a correlation between uncorrected left hippocampal volumes and ketamine's antidepressant efficacy 24 hours post-infusion in 13 subjects with major depressive disorder (MDD) (Abdallah et al., 2015a). However, statistical significance was lost after controlling for several demographic and clinical variables. In addition, baseline right hippocampal volume did not correlate with antidepressant response in this small sample.

The met allele of the brain-derived neurotrophic factor (BDNF) rs6265 single nucleotide polymorphism (SNP) has been associated with impaired processing of proBDNF and decreased activity-dependent secretion of the mature polypeptide (Egan et al., 2003). The BDNF rs6265 SNP has also been associated with hippocampal volume alterations in MDD subjects, with the val/val genotype typically correlating with larger hippocampi and met carriers having smaller hippocampi (Frodl et al., 2007; Gonul et al., 2011; Kanellopoulos et al., 2011; Molendijk et al., 2012). Both this polymorphism (Laje et al., 2012) as well as peripheral BDNF levels (Haile et al., 2014) were preliminarily shown to correlate with same-day (~4 hours post-infusion) anti-depressant response to ketamine; that is, met carriers

had a poorer antidepressant response to ketamine, and ketamine responders had increased post-infusion plasma BDNF levels.

This study sought, first, to replicate the findings of Abdallah and colleagues (Abdallah et al., 2015a) using an existing ketamine dataset. Our hypothesis was that smaller baseline hippocampal volumes would predict greater antidepressant response to ketamine. We also examined other subcortical brain volumes affected in MDD, specifically the thalamus (Nugent et al., 2013a) and amygdala (Hamilton et al., 2008), with analogous hypotheses. A secondary post hoc analysis stratified subjects by BDNF rs6265 SNP genotype to determine whether the combination of this SNP and baseline subcortical volumes could better identify depressed subjects who were more or less likely to respond to ketamine, with the hypothesis that met carriers with smaller subcortical volumes would have greater antidepressant response to ketamine. As noted above, research suggests that met carriers with smaller baseline hippocampi may have impaired proBDNF processing, lower secretion of mature BDNF, and decreased dendritic complexity, that is, decreased arborization and more immature dendritic spines; therefore, we hypothesized that met carriers with smaller baseline hippocampi might have the greatest potential for dynamic dendritic and synaptic spine morphogenesis, both of which have been shown to be critical neurobiological substrates of antidepressant efficacy in preclinical studies (Autry et al., 2011; Li et al., 2010, 2011).

Methods

Subject selection

Participants were drawn from a larger pool of MDD subjects (18–65 years old) who were admitted to the National Institutes of Health (NIH) Clinical Research Center's inpatient mood disorders research unit in Bethesda, Maryland. The subjects were recruited to participate in NIH ketamine protocols, including a completed open-label ketamine-riluzole extension study (NCT#00088699, NIH Protocol #04-M-0222, substudy 3) (clinical results previously published in Ibrahim et al., 2012 and Niciu et al., 2014a, 2014b) and an ongoing double-blind, placebo (saline)-controlled ketamine mechanism of action/neuroimaging study (NCT#00088699, NIH Protocol #04-M-0222, substudy 4).

From this larger pool of treatment-resistant MDD subjects, 55 had baseline (pre-ketamine) 3T MRIs suitable for automated subcortical volume processing with FSL-FIRST (see below). Briefly, all 55 subjects were evaluated face-to-face by a licensed psychiatric practitioner and administered the Structured Clinical Interview for Axis I DSM-IV Disorders-Patient Version (SCID) (First et al., 2002). All subjects had a Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) score of ≥ 20 at screening and on the day of ketamine infusion. All subjects were also experiencing a major depressive episode lasting at least 4 weeks at the time of screening, and none had psychotic features. Treatment resistance was confirmed by prior failure to respond to ≥ 1 adequate antidepressant trial(s), as assessed using a modified version of the Antidepressant Treatment History Form (ATHF) (Sackeim, 2001). Selected demographic and clinical characteristics of the sample are presented in Supplemental Table 1.

All subjects were in stable physical health, as assessed by medical history, physical examination, standard laboratory measures, electrocardiogram, urinalysis, and urine toxicology. Participants could not meet criteria for an active substance use disorder (excluding nicotine or caffeine) for at least 3 months prior to enrollment. Comorbid axis I anxiety disorders were permitted if they were not the primary focus of treatment within 12 months prior to screening. Exclusion criteria also included any serious unstable medical conditions (e.g., uncontrolled asthma or hypertension) or concomitant treatment with psychotropic medications or electroconvulsive therapy (ECT) in the 2 weeks prior to infusion (at least 5 weeks for fluoxetine). Female subjects could not be pregnant or nursing and agreed to use approved methods of birth control or complete abstinence during the study. All females of reproductive potential had negative urine pregnancy tests at admission and within 24 hours of neuroimaging and ketamine infusion.

The NIH Combined Neuroscience Institutional Review Board approved the protocol. All subjects provided written informed consent for screening as well as a ketamine-specific protocol consent, and were assigned a clinical research advocate to independently monitor the consent process and ethical research participation.

Ketamine infusion and measures

Subjects were rated with a battery of neuropsychiatric measures at 60 minutes prior to infusion (baseline) as well as at 230 minutes (same-day/hyperacute), 24 hours (next-day/acute), and 1 week (sustained) post-infusion. The primary depression outcome measure was the MADRS. All assessments were administered by research nurses, licensed independent practitioners (including psychiatrists), and psychologists, who often evaluated the same patients concurrently to maximize reliability; for the MADRS, the interclass correlation coefficient (ICC) was 0.94. Whenever possible, the same blinded rater conducted all clinician-administered ratings for an individual participant. Percent change in MADRS was calculated from baseline to the three post-infusion timepoints.

Image acquisition and processing

Prior to infusion, all MRIs were acquired on 3T GE scanners. Images were T1 weighted, high-resolution ($0.9 \times 0.9 \times 1.2 \text{ mm}^3$ or $1 \times 1 \times 1 \text{ mm}^3$), gradient echo type sequences (MP-RAGE, IR-fSPGR, or GE proprietary BRAVO). The repetition time (TR) and echo time (TE) were both set as the minimum allowable for a full echo sequence; changes in the operating system may have caused small changes in these parameters that would not be anticipated to alter the results. Intra- and interscanner reliability on these scanners has previously been reported (Nugent et al., 2013b).

After image acquisition, intensity non-uniformity was corrected using the N3 algorithm (McConnell Brain Imaging Centre, Montreal Neurological Institute, Montreal, CA). To calculate total intracranial volume (TIV), non-brain material (e.g., skull) was removed using the Analysis of Functional NeuroImages (AFNI) (NIMH Scientific and Statistical Computing Core) tool “3dSkullStrip”. These images were then linearly registered to the 512 Montreal Neurological Institute (MNI) whole brain template (McConnell Brain Imaging Centre, Montreal Neurological Institute, Montreal, CA) using the FSL tool FLIRT

(Functional MRI of the Brain (FMRIB), University of Oxford, Oxford, UK) (Jenkinson et al., 2002). A secondary registration was also performed using a mask including only the subcortical structures to optimize registration of the areas of interest.

FIRST version 1.2 (FSL toolbox, FMRIB, Oxford, UK) was used to segment the bilateral hippocampi and bilateral thalami. Prior data from our laboratory suggested that amygdalar subcortical volumes segmented by FSL-FIRST are unreliable (Nugent et al., 2013b); therefore, this brain region was excluded from the FSL-FIRST segmentation analysis. FIRST uses an iterative process to generate surface mesh segmented structures derived from 317 basis functions in a set (Patenaude et al., 2011). A boundary correction is then performed to remove extraneous voxels on a mesh segmentation surface, and all segmentations are visually inspected for post-processing quality control/quality assurance to exclude and potentially correct gross failures of the algorithm.

Freesurfer automated brain segmentation was performed for the images acquired under the mechanism of action portion of this study. These images were acquired with an eight-channel coil and had superior signal-to-noise ratio (SNR); thus, they were also appropriate for Freesurfer processing using the “recon-all” pipeline in the image analysis package (<http://surfer.nmr.mgh.harvard.edu>). This automated processing includes the isolation and removal of non-brain tissue (i.e., “skullstripping”), subcortical segmentation, and whole brain and subcortical brain region volume estimation (Fischl and Dale, 2000). All segmented images were visually inspected for post-processing quality control/quality assurance. No data were discarded for poor quality, and no manual correction was required to salvage a poor segmentation. Freesurfer provides automated segmentation of many subcortical brain structures as part of the package; however, only whole brain volumes and three specific brain regions—amygdala, hippocampus, and thalamus—were used in this study.

BDNF rs6265 SNP genotyping

During screening, subjects gave specific consent for genetic blood draws (NIH protocol #s 01-M-0254, 04-M-0222). DNA was extracted from blood using the Qiagen-Gentra protocol (Qiagen Inc., Valencia, CA, USA). Approximately half of the samples were genotyped on Human OmniExpress BeadChip, and the remaining samples were genotyped on Infinium OmniExpressExome BeadChip from Illumina (Illumina Inc., San Diego, CA, USA). Both these beadchips include the BDNF rs6265 SNP (val66met). Genotypes were called using GenomeStudio software (Illumina Inc., San Diego, CA, USA), and the average call rate was 99.2%. In this subgroup analysis, subjects were functionally bifurcated into wild-type (val/val) and met carriers (val/met and met/met).

Statistics

After normality assessment, bivariate parametric (Pearson) correlations were performed with baseline subcortical volumes and MADRS percent change at the three post-infusion timepoints (230 minutes, 1 day, and 1 week). Both raw/uncorrected and normalized/corrected (TIV for FSL-FIRST and whole brain for Freesurfer) subcortical volumes were analyzed. For the BDNF rs6265 SNP exploratory analysis, we performed analogous Pearson correlations with subcortical volumes and percent change in MADRS in each group (val/val

vs. met carriers). All correlations were corrected by Bonferroni adjustment for multiple comparisons.

We then compared interactions between antidepressant response to ketamine and subcortical brain volumes based on genotype in a univariate analysis of covariance (ANCOVA) model (Olkin and Finn, 1995). Based on the covariates included in the study by Abdallah and colleagues (Abdallah et al., 2015a) and other potential correlates (Trivedi et al., 2006), the following covariates were individually regressed: age, gender, height, age of depression onset, length of depressive illness, and length of current major depressive episode. In this sample, all met carriers were Caucasian and right-handed, so race and handedness could not be included as regressors. Therefore, the analysis was repeated excluding val/val subjects who were non-Caucasian ($n=2$), left-handed ($n=4$), or ambidextrous ($n=1$).

All analyses used two-tailed significance criteria of $p .05$ and were performed with SPSS 21 (IBM SPSS, 2010, Chicago, IL, USA, www.spss.com).

Results

A total of 55 treatment-resistant MDD subjects had baseline (pre-ketamine) 3T MRIs suitable for automated subcortical volume processing with FSL-FIRST. The mechanism of action study sample had subcortical volumes automatically processed with Freesurfer ($n=27$). Same-subject subcortical brain volumes obtained by both image processing modalities were strongly correlated (all $p<.001$). Representative segmented FSL-FIRST and Freesurfer images in three planes are displayed in Figure 1.

No statistically significant correlations were observed between FSL-FIRST-processed raw and TIV-corrected hippocampal and thalamic volumes with percent change in antidepressant efficacy at 230 minutes, 1 day, or 1 week post-infusion (all p -values $>.05$) (Table 1). Similarly, no statistically significant correlations were found between Freesurfer-processed raw and whole brain-corrected hippocampal, thalamic, and amygdalar volumes and percent change in antidepressant response to ketamine at all three post-infusion timepoints (all p -values $>.05$) (Table 1).

We next performed a BDNF rs6265 SNP-stratified functional (val/val vs. met carrier) subgroup analysis in the FSL-FIRST-segmented sample (as there was an insufficient number of met carriers ($n=3$) in the Freesurfer-segmented sample for reliable statistics). There was no statistically significant difference in mean thalamic and hippocampal volumes across the BDNF rs6265 SNP (Supplemental Table 2A). In the val/val subjects ($n=23$), TIV-corrected left thalamic volume was not significantly correlated with antidepressant response to ketamine at 230 minutes post-infusion ($r=-.34$, $p=.12$; Figure 2, Supplemental Table 2B). In the met carriers ($n=14$), however, TIV-corrected left thalamic volume correlated with antidepressant response at 230 minutes post-infusion ($r=.72$, $p=.004$)—that is, smaller baseline thalamic volumes correlated with greater antidepressant response (Figure 2, Supplemental Table 2B). This association survived Bonferroni correction for multiple comparisons ($p_{\text{adjusted}}=.024$). Interestingly, at 230 minutes post-infusion, the sole met/met participant had a 19.4% increase in MADRS-rated depressive symptoms (Figure 2). No

additional statistically significant correlations were noted between TIV-corrected left thalamic volumes and anti-depressant response at the other two post-infusion timepoints (val/val: 1 day ($r=-.21$, $p=.33$, $n=23$) and 1 week ($r=-.17$, $p=.61$, $n=12$); met carriers: 1 day ($r=.28$, $p=.34$, $n=14$) and 1 week ($r=.01$, $p=.99$, $n=7$; Supplemental Table 2B). Similarly, in the val/val subjects, TIV-corrected right thalamic volume did not significantly correlate with antidepressant response to ketamine at 230 minutes post-infusion ($r=-.28$, $p=.19$; Supplemental Table 2B). In the met carriers, TIV-corrected right thalamic volume again correlated with greater antidepressant response to ketamine at 230 minutes post-infusion ($r=.77$, $p=.001$; Supplemental Table 2B), and this survived Bonferroni adjustment for multiple comparisons ($p_{\text{adjusted}}=.006$). Again, no additional statistically significant correlations were observed between TIV-corrected right thalamic volumes and antidepressant response at 1 day or 1 week post-infusion (val/val: 1 day ($r=-.14$, $p=.52$, $n=23$) and 1 week ($r=-.14$, $p=.66$, $n=12$); met carriers: 1 day ($r=-.18$, $p=.54$, $n=14$) and 1 week ($r=.12$, $p=.79$, $n=7$; Supplemental Table 2B).

Differences in correlations were compared in a genotype-by-antidepressant response interaction. The BDNF rs6265 SNP differentiated the association between TIV-corrected left thalamic volume and antidepressant response at 230 minutes post-infusion ($F=11.51$, $p=.002$). This association survived Bonferroni correction for multiple comparisons ($p_{\text{adjusted}}=.012$) and persisted after adjustment for the following variables: age, sex, race, height, handedness, age of onset, length of psychiatric illness, and length of current depressive episode. Similar results were obtained with TIV-corrected right thalamic volumes, BDNF rs6265 SNP, and antidepressant response to ketamine at 230 minutes post-infusion.

No statistically significant correlations were noted with FSL-FIRST-derived raw and TIV-corrected hippocampal volumes, BDNF rs6265 SNP, and antidepressant response to ketamine at all three post-infusion timepoints (Supplemental Table 2B).

Discussion

This study used two automated imaging analysis platforms (FSL-FIRST and Freesurfer) and a larger dataset in an attempt to replicate potential correlations between baseline hippocampal volume and antidepressant response to ketamine at three post-infusion timepoints (230 minutes, 1 day, and 1 week). Across both imaging analysis platforms and at all three time-points, no statistically significant correlations were observed between baseline volumes in the hippocampus, thalamus, or amygdala (two other subcortical brain areas implicated in MDD pathophysiology and/or treatment response) and antidepressant response to ketamine.

A secondary analysis explored the correlation between TIV-corrected thalamic volumes and antidepressant response to ketamine and found that the functional BDNF rs6265 SNP significantly affected results. In met carriers, TIV-corrected thalamic volumes were negatively correlated with antidepressant response to ketamine at 230 minutes post-infusion. This association remained significant following stringent (Bonferroni) correction for multiple comparisons and also persisted after controlling for several potential covariates. Nonetheless, this observation is preliminary and warrants attempted replication.

Abdallah and colleagues found that correlation between raw left hippocampal volume and antidepressant efficacy 1 day after ketamine administration survived correction for multiple comparisons, but the correlation did not persist after controlling for covariates, including overlapping covariates in our analysis: total brain volume, handedness, age, gender, height, and race (Abdallah et al., 2015a). Although our met allele association is in the same direction as that observed by Abdallah and colleagues (smaller subcortical volumes correlating with greater antidepressant response to ketamine), several critical discrepancies between the two studies deserve attention. Specifically, our study was considerably larger than the study by Abdallah and colleagues ($n=55$ vs. $n=13$), our participants were inpatients while theirs were outpatients, and there were several key differences in treatment-resistance criteria (failure to respond to 1 or 2 antidepressant trials vs. 3, although our subjects had a numerically greater average number of antidepressant trials (7.0 ± 3.8 vs. 5.5 ± 0.7)), antidepressant response rates (34% vs. 77%), and the primary neuroimaging analysis platforms used (FSL-FIRST vs. Freesurfer, although we did have a Freesurfer replication subset) (Abdallah et al., 2015a).

Altered subcortical brain volumes have been associated with antidepressant response at baseline (Hsieh et al., 2002; Joshi et al., 2016; MacQueen et al., 2008; Vakili et al., 2000; Wade et al., 2016) and longitudinally in response to both psychopharmacological and psychosomatic interventions (Arnone et al., 2013; Frodl et al., 2008; Joshi et al., 2016; Perini et al., 2017; Phillips et al., 2015; Schermuly et al., 2011; Wade et al., 2016). The BDNF rs6265 SNP has also been associated with response to successful interventions (Chi et al., 2010; Choi et al., 2006; Colle et al., 2015; Hwang et al., 2006; Laje et al., 2012). Overall, the preponderance of the evidence suggests that met carriers are more likely to have a poorer response to treatment; however, it should be noted that some studies have reported that met carriers have greater circulating levels of BDNF and respond better to traditional antidepressants (El-Hage et al., 2015; Kang et al., 2010; Lang et al., 2009). Nevertheless, to our knowledge, the combinatorial effect of subcortical brain volumes and this SNP has not previously been investigated with regard to antidepressant response, and we believe that treatment response biomarker research and development may benefit from such a combinatorial, multimodal approach.

The met allele of the BDNF rs6265 SNP has been associated with decreased subcortical brain volume; thus, dendritic complexity (arborization and spine morphology) may be reduced at baseline in met carriers due to impaired BDNF processing/secretion. Given that ketamine rapidly alters synaptic plasticity in preclinical models of despair—for instance, increased expression of postsynaptic density proteins and dendritic spine morphogenesis from immature filopodia to mature mushroom-shaped spines (Li et al., 2010, 2011)—met-carrying ketamine responders with smaller thalami may have more proverbial “room for improvement” in their neuropil than wild-type val/val subjects. This hypothesis, however, stands in contrast to the continued synaptic dysfunction and impaired antidepressant-like response on the forced swim test observed in BDNF rs6265 SNP val/met and met/met knock-in mice exposed to low-dose ketamine (Liu et al., 2012). While these abnormalities were much more pronounced in the met/met knock-in mice, the relevance of this finding to the current human sample is unclear, given that we had only one met/met subject in our sample. At 1 day and 1 week post-ketamine administration, the lack of correlation between

decreased baseline thalamic volume and anti-depressant response to ketamine in met carriers might be lost due to the emergence of other non-volumetric mechanisms responsible for *continued* response, that is, improved connectivity in frontothalamic circuits. Future studies can test these hypotheses in met carriers using *repeated* structural and functional neuroimaging analyses after ketamine administration.

In conclusion, in the largest ketamine neuroimaging dataset to date, we found no correlation between antidepressant response to ketamine and several subcortical brain volumes implicated in the pathophysiology and/or treatment response of MDD. Nevertheless, genetic stratification revealed subgroup-specific correlations, emphasizing the potential importance of a combinatorial biomarker approach to enhance treatment response prediction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Abdallah CG, Salas R, Jackowski A, et al. Hippocampal volume and the rapid antidepressant effect of ketamine. *J Psychopharmacol*. 2015a; 29:591–595. [PubMed: 25122038]
- Abdallah CG, Sanacora G, Duman RS, et al. Ketamine and rapid-acting antidepressants: A window into a new neurobiology for mood disorder therapeutics. *Annu Rev Med*. 2015b; 66:509–523. [PubMed: 25341010]
- Arnone D, McKie S, Elliott R, et al. State-dependent changes in hippocampal grey matter in depression. *Mol Psychiatry*. 2013; 18:1265–1272. [PubMed: 23128153]
- Autry AE, Adachi M, Nosyreva E, et al. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature*. 2011; 475:91–95. [PubMed: 21677641]
- Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000; 47:351–354. [PubMed: 10686270]
- Chi MH, Chang HH, Lee SY, et al. Brain derived neurotrophic factor gene polymorphism (val66met) and short-term antidepressant response in major depressive disorder. *J Affect Disord*. 2010; 126:430–435. [PubMed: 20674983]
- Choi MJ, Kang RH, Lim SW, et al. Brain-derived neurotrophic factor gene polymorphism (val66met) and citalopram response in major depressive disorder. *Brain Res*. 2006; 1118:176–182. [PubMed: 16979146]
- Colle R, Gressier F, Verstuyft C, et al. Brain-derived neurotrophic factor val66met polymorphism and 6-month antidepressant remission in depressed Caucasian patients. *J Affect Disord*. 2015; 175:233–240. [PubMed: 25658497]

- Coyle CM, Laws KR. The use of ketamine as an antidepressant: A systematic review and meta-analysis. *Hum Psychopharmacol*. 2015; 30:152–163. [PubMed: 25847818]
- Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry*. 2010; 67:793–802. [PubMed: 20679587]
- Egan MF, Kojima M, Callicott JH, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*. 2003; 112:257–269. [PubMed: 12553913]
- El-Hage W, Vourc'h P, Gaillard P, et al. The BDNF Val(66)Met polymorphism is associated with escitalopram response in depressed patients. *Psychopharmacology (Berl)*. 2015; 232:575–581. [PubMed: 25074447]
- First, MB., Spitzer, RL., Gibbon, M., et al. Structured Clinical Interview for DSM-IV-TR Axis I Disorders Research Version, Patient Edition with Psychotic Screen (SCID-I/P). New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002.
- Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000; 97:11050–11055. [PubMed: 10984517]
- Frodl T, Jager M, Smajstrlova I, et al. Effect of hippocampal and amygdala volumes on clinical outcomes in major depression: A 3-year prospective magnetic resonance imaging study. *J Psychiatry Neurosci*. 2008; 33:423–430. [PubMed: 18787661]
- Frodl T, Schule C, Schmitt G, et al. Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. *Arch Gen Psychiatry*. 2007; 64:410–416. [PubMed: 17404118]
- Gonul AS, Kitis O, Eker MC, et al. Association of the brain-derived neurotrophic factor Val66Met polymorphism with hippocampus volumes in drug-free depressed patients. *World J Biol Psychiatry*. 2011; 12:110–118. [PubMed: 20726825]
- Haile CN, Murrough JW, Iosifescu DV, et al. Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression. *Int J Neuropsychopharmacol*. 2014; 17:331–336. [PubMed: 24103211]
- Hamilton JP, Siemer M, Gotlib IH. Amygdala volume in major depressive disorder: A meta-analysis of magnetic resonance imaging studies. *Mol Psychiatry*. 2008; 13:993–1000. [PubMed: 18504424]
- Hsieh MH, McQuoid DR, Levy RM, et al. Hippocampal volume and antidepressant response in geriatric depression. *Int J Geriatr Psychiatry*. 2002; 17:519–525. [PubMed: 12112175]
- Hwang JP, Tsai SJ, Hong CJ, et al. The val66met polymorphism of the brain-derived neurotrophic factor gene is associated with geriatric depression. *Neurobiol Aging*. 2006; 27:1834–1837. [PubMed: 16343697]
- Ibrahim L, Diazgranados N, Franco-Chaves J, et al. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: Results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacology*. 2012; 37:1526–1533. [PubMed: 22298121]
- Jenkinson M, Bannister P, Brady M, et al. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002; 17:825–841. [PubMed: 12377157]
- Joshi SH, Espinoza RT, Pirnia T, et al. Structural plasticity of the hippocampus and amygdala induced by electroconvulsive therapy in major depression. *Biol Psychiatry*. 2016; 79:282–292. [PubMed: 25842202]
- Kanellopoulos D, Gunning FM, Morimoto SS, et al. Hippocampal volumes and the brain-derived neurotrophic factor val66met polymorphism in geriatric major depression. *Am J Geriatr Psychiatry*. 2011; 19:13–22. [PubMed: 21218562]
- Kang RH, Chang HS, Wong ML, et al. Brain-derived neurotrophic factor gene polymorphisms and mirtazapine responses in Koreans with major depression. *J Psychopharmacol*. 2010; 24:1755–1763. [PubMed: 19493959]
- Kishimoto T, Chawla JM, Hagi K, et al. Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: A meta-analysis of efficacy, safety and time trajectories. *Psychol Med*. 2016; 46:1459–1472. [PubMed: 26867988]

- Laje G, Lally N, Mathews D, et al. Brain-derived neurotrophic factor Val66Met polymorphism and antidepressant efficacy of ketamine in depressed patients. *Biol Psychiatry*. 2012; 72:e27–28. [PubMed: 22771240]
- Lang UE, Hellweg R, Sander T, et al. The Met allele of the BDNF Val66Met polymorphism is associated with increased BDNF serum concentrations. *Mol Psychiatry*. 2009; 14:120–122. [PubMed: 19156154]
- Li N, Lee B, Liu RJ, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010; 329:959–964. [PubMed: 20724638]
- Li N, Liu RJ, Dwyer JM, et al. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. *Biol Psychiatry*. 2011; 69:754–761. [PubMed: 21292242]
- Liu RJ, Lee FS, Li XY, et al. Brain-derived neurotrophic factor Val66Met allele impairs basal and ketamine-stimulated synaptogenesis in prefrontal cortex. *Biol Psychiatry*. 2012; 71:996–1005. [PubMed: 22036038]
- MacQueen GM, Yucel K, Taylor VH, et al. Posterior hippocampal volumes are associated with remission rates in patients with major depressive disorder. *Biol Psychiatry*. 2008; 64:880–883. [PubMed: 18722590]
- Molendijk ML, van Tol MJ, Penninx BW, et al. BDNF val66met affects hippocampal volume and emotion-related hippocampal memory activity. *Transl Psychiatry*. 2012; 2:e74. [PubMed: 22832736]
- Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979; 134:382–389. [PubMed: 444788]
- Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site randomized controlled trial. *Am J Psychiatry*. 2013a; 170:1134–1142. [PubMed: 23982301]
- Murrough JW, Perez AM, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry*. 2013b; 74:250–256. [PubMed: 22840761]
- Newport DJ, Carpenter LL, McDonald WM, et al. Ketamine and other NMDA antagonists: Early clinical trials and possible mechanisms in depression. *Am J Psychiatry*. 2015; 172:950–966. [PubMed: 26423481]
- Niciu MJ, Luckenbaugh DA, Ionescu DF, et al. Riluzole likely lacks antidepressant efficacy in ketamine non-responders. *J Psychiatr Res*. 2014a; 58:197–199. [PubMed: 25139008]
- Niciu MJ, Luckenbaugh DA, Ionescu DF, et al. Ketamine's anti-depressant efficacy is extended for at least four weeks in subjects with a family history of an alcohol use disorder. *Int J Neuropsychopharmacol*. 2014b; 18 pii: pyu039.
- Niciu MJ, Mathews DC, Nugent AC, et al. Developing biomarkers in mood disorders research through the use of rapid-acting anti-depressants. *Depress Anxiety*. 2014c; 31:297–307. [PubMed: 24353110]
- Nugent AC, Davis RM, Zarate CA Jr, et al. Reduced thalamic volumes in major depressive disorder. *Psychiatry Res*. 2013a; 213:179–185. [PubMed: 23850106]
- Nugent AC, Luckenbaugh DA, Wood SE, et al. Automated subcortical segmentation using FIRST: Test-retest reliability, interscanner reliability, and comparison to manual segmentation. *Hum Brain Mapp*. 2013b; 34:2313–2329. [PubMed: 22815187]
- Olkin I, Finn JD. Correlations redux. *Psychol Bull*. 1995; 118:155–164.
- Patenaude B, Smith SM, Kennedy DN, et al. A Bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage*. 2011; 56:907–922. [PubMed: 21352927]
- Pennybaker SJ, Niciu MJ, Luckenbaugh DA, et al. Symptomatology and predictors of antidepressant efficacy in extended responders to a single ketamine infusion. *J Affect Disord*. 2017; 208:560–566. [PubMed: 27839782]
- Perini GI, Toffanin T, Pigato G, et al. Hippocampal gray volumes increase in treatment-resistant depression responding to vagal nerve stimulation. *J ECT*. 2017; 33:160–166. [PubMed: 28658013]

- Phillips JL, Batten LA, Tremblay P, et al. A prospective, longitudinal study of the effect of remission on cortical thickness and hippocampal volume in patients with treatment-resistant depression. *Int J Neuropsychopharmacol*. 2015; 18 pii: pyv037.
- Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry*. 2001; 62(Suppl 16):10–17.
- Schermyly I, Wolf D, Lieb K, et al. State dependent posterior hippocampal volume increases in patients with major depressive disorder. *J Affect Disord*. 2011; 135:405–409. [PubMed: 21849213]
- Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *Am J Psychiatry*. 2006; 163:28–40. [PubMed: 16390886]
- Vakili K, Pillay SS, Lafer B, et al. Hippocampal volume in primary unipolar major depression: A magnetic resonance imaging study. *Biol Psychiatry*. 2000; 47:1087–1090. [PubMed: 10862809]
- Valentine GW, Mason GF, Gomez R, et al. The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [(1)H]-MRS. *Psychiatry Res*. 2011; 191:122–127. [PubMed: 21232924]
- Wade BS, Joshi SH, Njau S, et al. Effect of electroconvulsive therapy on striatal morphometry in major depressive disorder. *Neuropsychopharmacology*. 2016; 41:2481–2491. [PubMed: 27067127]
- Zarate CA Jr, Brutsche NE, Ibrahim L, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: A randomized controlled add-on trial. *Biol Psychiatry*. 2012; 71:939–946. [PubMed: 22297150]
- Zarate CA Jr, Mathews DC, Furey ML. Human biomarkers of rapid antidepressant effects. *Biol Psychiatry*. 2013; 73:1142–1155. [PubMed: 23374639]
- Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006; 63:856–864. [PubMed: 16894061]

Figure 1.

MRI-automated subcortical segmentation and regions of interest.

Subcortical brain regions were segmented with FSL-FIRST and Freesurfer automated software with manual quality assurance/quality control based on alignment to Talairach space. (a) FSL-FIRST-segmented sagittal brain view identifying the hippocampus and thalamus; (b) FSL-FIRST-segmented axial brain view identifying the bilateral thalami; (c) FSL-FIRST-segmented coronal brain view identifying the bilateral hippocampi and thalami; (d) Freesurfer-segmented sagittal brain view identifying the amygdala, hippocampus, and thalamus; (e) Freesurfer-segmented brain view identifying bilateral amygdala, hippocampi, and thalami; (f) Freesurfer-segmented brain view identifying the bilateral amygdala, hippocampi, and thalami. In the Freesurfer images, cortical grey matter is displayed in red-brown and cortical white matter is displayed in mint green.

Figure 2.

FSL-FIRST-segmented left thalamic volumes correlated with improved antidepressant response to ketamine at 230 minutes post-infusion in brain-derived neurotrophic factor (BDNF) rs6265 met carriers.

In BDNF rs6265 val/val subjects ($n=30$), antidepressant response to ketamine at 230 minutes did not correlate with total intracranial volume (TIV)-corrected left thalamic volumes.

However, in met carriers ($n=14$), antidepressant response to ketamine at 230 minutes correlated with smaller TIV-corrected left thalamic volumes. A statistically significant difference was also observed between these correlations in an ANCOVA-based genotype-by-antidepressant response interaction.

MADRS: Montgomery Åsberg Depression Rating Scale.

Table 1

Pearson r correlations between FSL-FIRST ($n=55$) and Freesurfer ($n=27$)-segmented subcortical brain volumes (thalamus, hippocampus, and/or amygdala) and antidepressant response to ketamine (MADRS percent change from baseline to 230 minutes, 1 day, and 1 week post-infusion).

FSL-FIRST	Uncorrected						TIV-Corrected											
	230 minutes			Day 1			Day 7			230 minutes			Day 1			Day 7		
	<i>r</i>	<i>p</i>		<i>r</i>	<i>p</i>		<i>r</i>	<i>p</i>		<i>r</i>	<i>p</i>		<i>r</i>	<i>p</i>		<i>r</i>	<i>p</i>	
Thalamus	L	.18	.21	.12	.40	-.14	.54	.12	.39	.14	.33	-.18	.42					
	R	.25	.08	.13	.37	-.07	.75	.18	.22	.15	.31	-.13	.57					
	L	.04	.79	-.05	.75	-.35	.10	.03	.86	<-.01	1.00	-.35	.10					
	R	.01	.97	.04	.78	-.15	.49	.02	.90	.08	.57	-.16	.46					
Freesurfer	Uncorrected						Whole Brain-Corrected											
	230 minutes			Day 1			230 minutes			Day 1								
	<i>r</i>	<i>p</i>		<i>r</i>	<i>p</i>		<i>r</i>	<i>p</i>		<i>r</i>	<i>p</i>							
Thalamus	L	.33	.13	.34	.11		.25	.25	.26	.23								
	R	.19	.38	.29	.18		.03	.89	.17	.45								
Hippocampus	L	.22	.31	.15	.50		.03	.91	-.12	.59								
	R	.16	.47	.07	.76		-.06	.79	-.22	.31								
Amygdala	L	.06	.78	-.03	.88		-.12	.59	-.27	.21								
	R	.03	.88	-.07	.76		-.13	.57	-.27	.21								

FSL-FIRST: FMRIB Software Library-FMRIB's Integrated Registration and Software Tool; MADRS: Montgomery-Åsberg Depression Rating Scale; TIV: total intracranial volume.