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Brief Report

BRIEF REPORT

Neural Correlates of Suicidal Ideation and Its Reduction in Depression

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Abstract

Background: The neural correlates of suicidal ideation and its reduction after treatment are unknown. We hypothesized that increased regional cerebral glucose metabolism in the infralimbic cortex (Brodmann area 25), amygdala, and subgenual anterior cingulate cortex would be associated with suicidal ideation and its reduction after ketamine infusion.
Methods: Medication-free patients (n = 19) with treatment-resistant major depressive disorder underwent positron emission tomography imaging at baseline and 230 minutes after an open-label ketamine infusion (0.5 mg/kg for 40 minutes).
Results: Baseline suicidal ideation and regional cerebral glucose metabolism in the infralimbic cortex were significantly correlated ($r = .59$, $P = .007$); but not overall mood scores ($r = -.07$, $P = .79$). Reductions in suicidal ideation after ketamine infusion were correlated with decreased regional cerebral glucose metabolism in the infralimbic cortex ($r = .54$, $P = .02$). Metabolism in other areas of interest was not significantly correlated with suicidal ideation or depression.
Conclusion: The infralimbic cortex may be implicated in suicidal ideation.

Keywords: suicidal ideation, PET imaging, ketamine, depression

Introduction

Suicide is the 10th leading cause of death nationally (Centers for Disease Control and Prevention, 2013). An estimated 8 million American adults consider suicide each year (Crosby et al., 2011). Although the FDA has approved clozapine for the treatment of suicidal behavior in patients with schizophrenia, there is a dearth of available treatments that specifically target suicidal thoughts, a widespread symptom across psychiatric diagnoses. Effective and rapid-acting pharmacologic treatments for suicidal thoughts are critically needed.

Thoughts of suicide (ie, suicidal ideation) are related to, but distinct from, acting on those thoughts (ie, suicide attempts or behavior) (Klonsky and May, 2014). Although suicidal thoughts are predictive of future suicide attempts and death, not all individuals who think about suicide make the decision to attempt (ten Have et al., 2009). The suicide neuroimaging literature has predominately focused on individuals who have made prior suicide attempts but who may or may not have current suicidal ideation (Oquendo et al., 2003). Although this research is valuable to understand individuals who engage in suicidal behavior, the investigation of the neural correlates of active suicidal thoughts is also needed to understand biological pathways for the development of targeted treatments. Perhaps due to logistic

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and ethical obstacles, neuroimaging research in individuals with current suicidal ideation remains relatively rare.

Ketamine, an N-methyl-D-aspartate receptor antagonist, has demonstrated efficacy in rapidly decreasing both depression and suicidal thoughts within hours after intravenous infusion (DiazGranados et al., 2010; Price et al., 2014). Whereas the neural correlates of reductions in depressive symptoms post-ketamine infusion have been investigated (Carlson et al., 2013), potential correlates of reductions in suicidal ideation after ketamine infusion have yet to be reported.

The aim of this posthoc investigation was to identify the neural correlates of suicidal ideation and its reduction using [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (FDG-PET) scanning in a sample of unmedicated patients with treatment-resistant major depressive disorder (MDD) administered ketamine. FDG-PET provides an indirect quantitative measure of cerebral glutamate metabolism throughout the entire brain, as almost all glucose entering the central nervous system is transformed into glutamate via glial cells (Shen et al., 1999). Specifically, we hypothesized that 3 brain regions of interest (ROIs) would be associated with suicidal thoughts: the amygdala, subgenual anterior cingulate cortex (sgACC; Brodmann area [BA] 24), and infralimbic cortex (BA 25). These ROIs were chosen due to their relationship to suicide (Hercher et al., 2010; Steiner et al., 2011; Maheu et al., 2013) as well their role in regulating emotional responses to the environment and stress (Drevets et al., 1997; Roozendaal et al., 2009), as negative events often precede suicidal thoughts and behaviors (Cooper et al., 2002). The sgACC and infralimbic cortex were analyzed separately because of evidence implicating the former and latter in clinical and preclinical manifestations of major depression, respectively (Drevets et al., 2008). Importantly, the infralimbic cortex is homologous in human, monkey, and rodent models (Drevets et al., 2008).

We hypothesized that increased glucose metabolism in these ROIs would be associated with increased suicidal thoughts at baseline and that reductions in ideation would be associated with changes in glucose metabolism after ketamine infusion. Because of the relationship between suicidal thoughts and depression as well as ketamine's impact on depression, we also evaluated the relationship between depressive symptoms and glucose metabolism. Additionally, complimentary whole-brain voxelwise analyses were used to investigate the association of baseline suicidal ideation levels and their change following ketamine with rMRGlu.

Methods

Participants

Twenty patients with treatment-resistant MDD participated in the original study of neural correlates of antidepressant response to ketamine (Carlson et al., 2013). Diagnoses were confirmed via Structured Clinical Interview for DSM-IV, and patients were required to score above or equal to 22 on the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) at the time of the baseline scan and ketamine infusion for inclusion into the study. Treatment resistance was defined as 2 or more failed attempts of adequate antidepressant trails. Participants were inpatients at the National Institute of Mental Health at the time of infusion and scanning and had been medication free for at least 2 weeks before ketamine infusion (4 weeks for fluoxetine). All participants provided written informed consent as approved by the Combined Neuroscience Institutional Review Board and Radiation Safety Committee at the National Institutes of Health.

Pharmacologic Intervention

All participants received an open-label infusion of intravenous ketamine hydrochloride (0.5 mg/kg) for 40 minutes.

Assessment of Suicidal Ideation and Depression

Suicidal ideation and depression were rated at baseline (60 minutes prior to ketamine infusion) and 230 minutes post-ketamine infusion. Suicidal ideation was measured using the suicide item from the Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960), measured on a scale of 0 to 4. Individuals receiving a score of 0 were considered to have "no suicidal ideation." Depressive symptoms were measured via the remaining items on the HAMD. To confirm any significant suicidal ideation correlations, the relationship to the MADRS suicide item and first 5 items from the Scale for Suicide Ideation (SSI) (Beck et al., 1979) were evaluated. Because baseline suicide assessment did not occur on the date of baseline PET imaging, the suicide item from the HAMD obtained 1 to 10 days before ketamine infusion, together with the baseline rating, was used to assess stability of ideation prior to infusion.

Image Acquisition and Analysis

Baseline PET scanning occurred 1 to 3 days before ketamine infusion. The post-ketamine PET scan was initiated around 120 minutes after the infusion and lasted approximately 1.5 hours. The explicit details of the scanning procedure, images acquired, and image modeling can be found elsewhere (Carlson et al., 2013). Images were acquired on a GE Advance PET scanner (GE Medical Systems, Waukesha, WI) in 3-dimensional mode (35 contiguous slices, 4.25-mm plane separations) following an infusion of 4.5 mCi [^{18}F]-FDG for 2 minutes. According to the method used by Brooks and colleagues (Brooks et al., 1982), quantitative regional metabolic rate of glucose (rMRGlu) images were calculated using a cardiac input function derived from a dynamic left ventricular scan collected at baseline prior to both the brain emission scan and venous sampling, which occurred every 5 minutes beginning 15 minutes after the FDG infusion. The reconstructed resolution was 6 mm full-width at half-maximum in all planes.

For accurate anatomical localization of the PET results, all patients underwent magnetic resonance imaging (MRI) on a 3.0 T scanner (Signa, GE Medical Systems) using a 3-dimensional magnetization prepared rapid acquisition gradient-echo sequence (echo time = 2.982 milliseconds, repetition time = 7.5 milliseconds, inversion time = 725 milliseconds, voxel size = 0.9×0.9×1.2 mm). Non-brain tissue was removed from brain images via the Analysis of Functional NeuroImages (Bethesda, MD) function 3dSkullStrip. These brain images were then segmented into grey and white matter and cerebrospinal fluid components using the FSL (Oxford, UK) automated segmentation tool. Separate binary mask images were created for each component. The ROIs were drawn based on the BAs distinguished in the Talairach Atlas.

To test our a priori hypotheses, metabolism was assessed in the infralimbic cortex and in the left and right amygdala and sgACC using the MRI images for anatomic localization. A sagittal image of a template brain overlaid with ROI locations for the infralimbic cortex and sgACC is presented in Figure 1. ROIs were defined on a standard template and transferred to registered

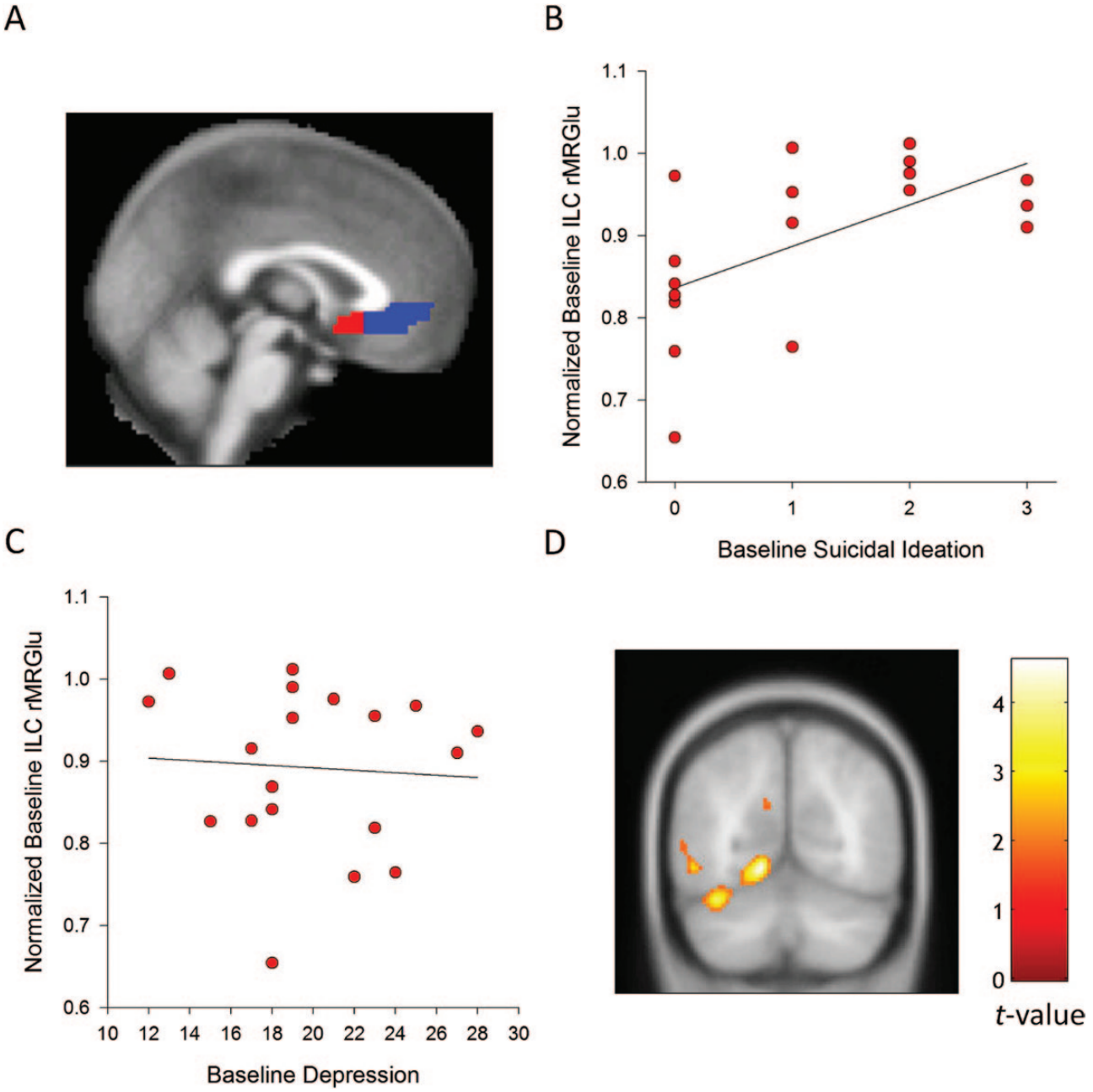

Figure 1. (A) Regional placement of the infralimbic cortex (in red) and subgenual cingulate cortex (in blue) overlaid on template. (B) Scatterplot depicting the relationship between baseline suicidal ideation (suicide item from Hamilton Depression Rating Scale [HAMD]) and normalized rate of metabolic change (rMRGlu) in infralimbic cortex. (C) Scatterplot depicting the relationship between baseline depression (all other items from HAMD) and rMRGlu in infralimbic cortex. (D) Statistical parametric map illustrating the voxelwise correlation between change in metabolism and change in suicidal ideation 230 minutes following ketamine infusion, relative to baseline. The color bar depicts the corresponding voxel *t* statistic value. Only the cluster surviving family wise error cluster correction is presented.

individual patient structural MRIs and adjusted to account for inter-individual anatomical variation. These ROIs were then transferred back to native MRI space and masked such that only grey matter was included in the region. Normalized rMRGlu values, relative to mean grey matter metabolism, were then calculated within each ROI.

Whole-brain voxelwise analyses were performed using Statistical Parametric Mapping software 5 (SPM5, Wellcome Trust Centre for Neuroimaging, London, UK) within MATLAB (MathWorks Inc, Natick, MA). PET rMRGlu images were co-registered to the MRI scans and then spatially normalized to the Montreal Neurological Institute brain template. A 6-mm Gaussian smoothing kernel was applied to PET images to account for variability in anatomy and alignment.

Statistical Analysis

A priori hypotheses were tested using Pearson correlations of suicidal ideation and depressive symptoms in relation to glucose metabolism in the 3 ROIs. Change in suicidal ideation and depression was calculated using raw scores of the HAMD suicide item and the remaining HAMD items, respectively. Significant findings were confirmed by the MADRS suicide item and the SSI-5. Change was measured at 230 minutes, as this is the time

point associated with antidepressant and antisuicide responses to ketamine (DiazGranados et al., 2010) and the proximity of this time to PET scanning. The stability of the baseline suicide assessment with a prebaseline rating was assessed using an intra-class correlation coefficient statistic. Because of the preliminary nature of this approach and small sample size, adjustment for multiple comparisons was not conducted. Significance levels are reported at $P<.05$ (2-tailed).

Two whole-brain voxelwise analyses were conducted using all available subjects. First, baseline correlates of suicidal ideation were calculated by regressing suicide levels, as measured by the HAMD suicidal item, onto the baseline rMRGlu image. Second, to examine the neural correlates of change in suicidal ideation, we regressed the difference in the suicidal item of the HAMD between baseline and post-ketamine ratings onto the weighted (baseline-ketamine) difference image. A binary explicit brain mask based on the Montreal Neurological Institute template was applied to both analyses to remove extracerebral voxels. The uncorrected threshold for these whole-brain regression analyses was set at $P<.05$ (1-tailed); however, only clusters surviving family-wise error correction for multiple corrections using Gaussian random field theory ($P_{corr}<.05$) are reported.

Results

Behavioral Response to Ketamine

Twenty patients with a mean age of 48 years (SD=12) and a length of illness of 26 years (SD=13) underwent ketamine infusion (6 females). Twelve patients reported some suicidal ideation at baseline. The intra-class correlation coefficient between the baseline suicide assessment and prebaseline rating was .900 ($P<.01$, 95% CI [.75-.96]). For the 12 patients with any suicidal ideation at baseline, there was a significant reduction in ideation at 230 minutes after ketamine ($t_{(11)}=3.19$, $P=.009$) (7/12 showed a reduction).

PET: ROI Analyses

Because of problems with venous sampling, quantitative modeling of the raw PET images was not possible in 1 subject; ROI rMRGlu was successfully modelled in 19 of the 20 patients. At baseline, suicidal ideation was associated with increased metabolism in the infralimbic cortex (r = .59, P = .007) (Table 1; Figure 1). Findings were confirmed by the MADRS suicide item (r = .55, P = .02) and showed a trend on the SSI-5 (r = .41, P = .08). None of the ROIs were significantly correlated with depressive symptoms (Table 1; Figure 1). Reductions in suicidal ideation after ketamine infusion were associated with reductions in rMRGlu in the infralimbic cortex (r = .54, P = .02), with subjects showing the largest decrease in suicidal ideation also demonstrating the largest reduction in rMRGlu (Table 1). When this correlation was limited to only the 12 patients with suicidal ideation at baseline, the correlation was comparable but no longer significant (r = .51, P = .11). These findings were not confirmed by the MADRS suicide item (r=.38, P = .11) or the SSI-5 (r=–.17, P = .48). Change in depression scores following ketamine infusion was not associated with change in metabolism in any of the ROIs.

PET: Whole-Brain Analyses

Our whole-brain analyses did not identify any regions relating rMRGlu metabolism and levels of suicidal ideation at baseline. However, we identified a large posterior cluster, which extended

Table 1. Pearson Correlations between Baseline and Change in Globally Normalized rMRGlu with Suicidal Ideation and Depression in Areas of Interest

		Baseline				Change at 230 minutes			
		Suicidal ideation as measured by HAMD		Total HAMD score, with suicide item removed		Suicidal ideation as measured by HAMD		Total HAMD score, with suicide item removed	
Region		r	P	r	P	r	P	r	P
Infralimbic cortex		.59	.007	–.07	.79	.54	.02	.10	.69
Amygdala	Left	.01	.98	<.01	.99	.08	.76	.39	.10
	Right	.16	.52	–.15	.53	.14	.57	<.01	.99
Subgenual anterior cingulate cortex	Left	.39	.10	.02	.92	.08	.74	.30	.21
	Right	.26	.28	–.20	.42	–.01	.96	–.10	.70

Abbreviations: HAMD, Hamilton Depression Rating Scale; rMRGlu, metabolic rate of glucose metabolism.

from the left lingual gyrus (V4; [x = −14, y = −64, z = −6], $t_{(19)} = 4.60$) to the left middle occipital gyrus ([x = −46, y = −74, z = 6], $t_{(19)} = 4.59$) and also the left superior cerebellum ([x = −26, y = −78, z = −20], $t_{(19)} = 4.53$), which was negatively related to change in suicidal ideation ($P_{corr} = .026$). Patients showing the strongest decrease in suicidal ideation had the largest increases in rMRGlu in these regions (Figure 1).

Discussion

In this posthoc analysis of patients with treatment-resistant MDD, glucose metabolism in the infralimbic cortex was associated with both suicidal ideation at baseline and reductions in ideation after ketamine infusion. Significant correlations were not found for the amygdala and the sgACC. Depressive symptoms were not significantly associated with any ROI at baseline. These findings implicate the infralimbic cortex in suicidal thoughts and provide initial suggestions that ketamine may reduce suicidal thoughts through impact on this brain region. Our whole-brain investigation revealed an association between increased metabolism in occipital and cerebellar structures and reductions in suicidal ideation following treatment with ketamine.

Interest in the infralimbic cortex has arisen out of deep-brain stimulation depression treatment research in BA 25 (Mayberg et al., 2005) as well as evidence that activity in this region is associated with antidepressant treatment response (Keedwell et al., 2010). This area has predominately been studied using rat models, such as those bred to demonstrate learned helplessness behavior, which have shown decreased postsynaptic density in the infralimbic cortex (Seese et al., 2013). Additionally, transient inactivation of the infralimbic cortex has demonstrated an antidepressant effect on rats in a forced swim test (Slattery et al., 2011). Furthermore, transient optogenetic inhibition of infralimbic cortex neurons during maze navigation resulted in a decrease in habitual behavior (Smith et al., 2012), which may indicate that the infralimbic cortex is involved in behavioral flexibility. As suicidal thoughts are associated with cognitive rigidity, particularly when low mood is induced (Williams, 2008), decreased rMRGlu in this region after ketamine infusion may reflect a rapid enhancement in behavioral and cognitive flexibility which then leads to decreased suicidal thoughts.

Our whole-brain investigation revealed a large posterior cluster spanning the occipital lobe, particularly the anterior left lingual gyrus and the cerebellum, which correlated negatively with alterations in suicidal ideation. Increased metabolism in these regions was found in patients who exhibited the greatest reduction in suicidal ideation in response to ketamine. Previous analyses of depressed bipolar patients have also found reduced rMRGlu in this region after ketamine infusion (Nugent et al., 2014). This finding relates to research demonstrating structural and/or functional differences between patients with and without suicide attempts in visual (Jollant et al., 2010) and cerebellar (Hwang et al., 2010) regions. In contrast to low lethal suicide attempters, reductions in left lingual gyrus grey matter have been linked to highly lethal suicide methods in the context of both psychosis (Giakoumatos et al., 2013) and borderline personality disorder (Soloff et al., 2012). Since our finding was specific to suicidal ideation, not behavior, further examination of the role of these regions in the continuum of suicide risk is needed.

Limitations of this study underscore the need for further replication. Participants in this ketamine trial were selected for depression diagnosis, not suicidal thoughts, and patients at acute suicide risk were not consented into study. Replication of this result in patients selected for suicidal thoughts across psychiatric diagnoses is required. Reductions in suicidal ideation and corresponding changes in brain metabolism may be confounded by the open-label study design, as the study lacked a placebo control. Additionally, ideation change results were not confirmed by other suicide measures. The small sample size precluded comparisons between depression and suicidal thoughts to examine if findings for suicidal ideation were independent of depression symptoms. Lastly, the baseline suicide assessment and PET scan did not occur on the same day; although suicidal ideation appeared relatively stable, a more proximate assessment to scanning time would strengthen the findings. Nonetheless, this study represents a preliminary step towards a neurobiological explanation for suicidal ideation.

Identifying the neural correlates of suicidal thoughts and their reduction are essential in understanding the neurobiology of suicidal thoughts and the development of appropriate treatments for suicidal patients. There is likely an overlap in neural circuitry involved in suicidal thoughts and behavior, although the extent of this overlap has yet to be defined. Two regions previously associated with suicidal behavior, the amygdala and the sgACC, were not significantly associated with current suicidal thoughts in this analysis. Although these findings require replication, this is the first known study to connect metabolism in a brain region to suicidal thoughts. Further examination of the infralimbic cortex in relation to suicidal thoughts and behaviors is warranted.

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Interest Statement:

M. Furey is listed as a co-inventor on a patent application for the use of scopolamine in major depression and C. A. Zarate Jr is listed as a co-inventor on a patent application for the use of ketamine and its metabolites in major depression. Drs. Furey and Zarate have assigned their rights in the patent to the U.S. Government but will share a percentage of any royalties that may be received by the Government. The remaining authors have no conflicts of interest to disclose, financial or otherwise.

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