Psychiatry Research: Neuroimaging 254 (2016) 56–66

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Preliminary differences in resting state MEG functional connectivity pre- and post-ketamine in major depressive disorder

Allison C. Nugent [a,*], Stephen E. Robinson [b], Richard Coppola [b], Carlos A. Zarate Jr.[a]

[a] Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA
[b] NIMH Magnetoencephalography Core Facility, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

ARTICLE INFO

Article history:
Received 29 January 2016
Received in revised form
13 June 2016
Accepted 14 June 2016
Available online 23 June 2016

Keywords:
Magnetoencephalography (MEG)
Depression
Ketamine
Resting state
Connectivity
Independent components analysis (ICA)

ABSTRACT

Functional neuroimaging techniques including magnetoencephalography (MEG) have demonstrated that the brain is organized into networks displaying correlated activity. Group connectivity differences between healthy controls and participants with major depressive disorder (MDD) can be detected using temporal independent components analysis (ICA) on beta-bandpass filtered Hilbert envelope MEG data. However, the response of these networks to treatment is unknown. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, exerts rapid antidepressant effects. We obtained MEG recordings before and after open-label infusion of 0.5 mg/kg ketamine in MDD subjects (N=13) and examined networks previously shown to differ between healthy individuals and those with MDD. Connectivity between the amygdala and an insulo-temporal component decreased post-ketamine in MDD subjects towards that observed in control subjects at baseline. Decreased baseline connectivity of the subgenual anterior cingulate cortex (sgACC) with a bilateral precentral network had previously been observed in MDD compared to healthy controls, and the change in connectivity post-ketamine was proportional to the change in sgACC glucose metabolism in a subset (N=8) of subjects receiving [11F]FDG-PET imaging. Ketamine appeared to reduce connectivity, regardless of whether connectivity was abnormally high or low compared to controls at baseline. These preliminary findings suggest that sgACC connectivity may be directly related to glutamate levels.

Published by Elsevier Ireland Ltd.

1. Introduction

Major depressive disorder (MDD) is a highly prevalent and frequently debilitating disease. Current FDA-approved treatments for MDD are frequently inadequate and require weeks of administration before maximal antidepressant effects appear. In contrast, the N-methyl-D-aspartate (NMDA) antagonist ketamine exerts rapid antidepressant effects that appear within 240 min post-IV infusion, even in treatment-resistant subjects (Zarate et al., 2006). However, little is known of ketamine's mechanism of action at the molecular level (for a review, see Abdallah et al. (2015)), and even less is known of ketamine's effects on brain activity in individuals with MDD.

The mechanisms of action of various antidepressant treatments have been studied by investigating their effects on brain connectivity, particularly using resting state functional magnetic resonance imaging (rs-fMRI). Results of these studies do not converge to a common finding (Dichter et al., 2014). Nevertheless, reports of increased frontal-limbic connectivity following treatment are common (reviewed in Gudayol-Ferre et al. (2015)); these are hypothesized to represent increased cognitive control over enhanced limbic threat reactivity. In addition, decreased connectivity within the Default Mode Network (DMN)—towards levels seen in healthy controls—has also been reported following treatment with conventional antidepressants (Li et al., 2013; Posner et al., 2013). Resting state fMRI studies of acute ketamine administration in healthy controls generally report widespread enhanced connectivity (Driesen et al., 2013; Khalili-Mahani et al., 2014), although both increased and decreased connectivity with sensory/somatosensory networks have been reported (Niesters et al., 2012). While a substantial literature has investigated the neural correlates of the acute psychotomimetic effects of ketamine administration, relatively few studies have examined brain responses at later time points, such as those associated with antidepressant response after dissociative effects have dissipated. One rs-fMRI study investigated connectivity 24 h post-infusion in healthy control subjects and reported significantly reduced

* Correspondence to: Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health, National Institutes of Health, 9000 Rockville Pike, MSC 1030, Bethesda, MD 20892, USA.
E-mail address: nugenta@mail.nih.gov (A.C. Nugent).

http://dx.doi.org/10.1016/j.pscychresns.2016.06.006
0925-4927/Published by Elsevier Ireland Ltd.

connectivity between the DMN and the dorsomedial prefrontal cortex (DMPFC)/pregenual anterior cingulate (pgACC), as well as reduced connectivity between the subgenual anterior cingulate cortex (sgACC) and the DMPFC (Scheidegger et al., 2012). The etiology of these alterations in connectivity is unknown; however, it has been hypothesized that glutamate levels may be involved given that prior work found an association between glutamate levels and/or glutamate plus glutamine (Glx) levels and connectivity (Duncan et al., 2013; Horn et al., 2010).

Because of the uptake of glucose into glial cells in response to neuronal glutamate release, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) may serve as a useful proxy measure of glutamate levels in the brain (Magistretti and Pellerin, 1996). We previously reported alterations in regional glucose metabolism approximately two hours following ketamine infusion in a sample that overlaps those reported here (Carlson et al., 2013). That study found significantly decreased glucose metabolism in the right habenula and right insula post-ketamine compared to post-placebo. Significant increases were also observed in the right amygdala and bilateral parieto-occipital cortex. In more targeted analyses, we also found correlations between reduced suicidal ideation post-ketamine and reduced glucose metabolism in the infralimbic cortex (Ballard et al., 2015), as well as correlations between changes in anhedonia post-ketamine and changes in dorsal cingulate and orbitofrontal cortex glucose metabolism (Lally et al., 2015). To the best of our knowledge, no other groups have reported the effects of ketamine on glucose metabolism at time periods removed from its acute drug effects, so these results await replication.

Although network connectivity during the resting state—that is, in the absence of any imposed task—has been primarily investigated via fMRI, interest has recently grown in using magnetoencephalography (MEG), which is capable of assessing brain function on a time scale that better reflects neural activity (Scholvinck et al., 2013). Recently, a MEG study of acute ketamine administration demonstrated increased gamma power in both motor and visual cortices, a finding that animal studies have linked to disinhibition of pyramidal cells (Shaw et al., 2015). A subsequent study using source localization showed increases in anterior theta and gamma power, reduced posterior theta, delta, and alpha power, and decreased NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-mediated connectivity between frontal and parietal cortices (Muthukumaraswamy et al., 2015). The alterations in NMDA- and AMPA-mediated connectivity may reflect the phenomenon whereby ketamine binds to NMDA receptors in inhibitory gamma-aminobutyric acid (GABA)-ergic interneurons, disinhibiting cortical pyramidal cells and increasing AMPA throughput (Duman, 2014). Despite these important results in acute electrophysiological responses to ketamine infusion, as with fMRI, little is known regarding brain responses on a time scale corresponding to antidepressant response.

A significant recent development in resting state MRI research is the work by Brookes and colleagues (Brookes et al., 2011), who demonstrated an ICA-based model-free method for identifying resting state networks in MEG data. We previously found that this method can be extended to group analyses (Nugent et al., 2015b). Comparing healthy subjects to subjects with MDD at baseline, we found reduced connectivity between the sgACC and a bilateral precentral independent component (IC), as well as increased amygdalar connectivity with insulo-temporal ICs in individuals with MDD (Nugent et al., 2015b).

Building on this work, in the present study we applied the same ICA methodology to a group of 13 subjects with MDD who received a single open-label dose of ketamine; 11 had been examined at baseline in our prior study (Nugent et al., 2015b). While there are advantages and disadvantages to ICA methods for resting state data analysis, we chose the ICA method to maximize the interpretability of the current paper in the context of our prior publication. MEG scans were acquired both at baseline and six to seven hours following ketamine administration. Recordings from healthy control subjects who did not receive ketamine were also included. The primary aim of this preliminary study was to assess the overall effects of ketamine on connectivity in MDD subjects, as our sample size was too limited to assess responders versus non-responders. Although we already reported the baseline effects of ketamine in a larger cohort that overlapped with this one (Nugent et al., 2015b), we felt that the additional scans acquired post-ketamine infusion justified further analysis, albeit preliminary and hypothesis-generating in nature. The formulation of hypotheses in this area is difficult given the dearth of research using resting state MEG to study MDD, as well as the lack of literature investigating the effects of ketamine on connectivity in subjects with MDD at a time point corresponding to its antidepressant effects. Notably, this analysis is the first to evaluate ketamine induced changes in resting state connectivity in MDD at a time point corresponding to antidepressant response in a depressed cohort. Based upon studies showing that successful antidepressant treatment normalizes sgACC and amygdala function, we hypothesized that ketamine would normalize connectivity to that seen in healthy control subjects. In addition, because the extant literature suggests that connectivity is reduced 24 h after ketamine, we were particularly confident that the elevated insulo-temporal-amygdala connectivity seen at baseline would be reduced after ketamine. In addition, we present *post-hoc* correlations between connectivity and glucose metabolism in order to further explore the relationship between connectivity and the glutamatergic system.

2. Methods

2.1. Study participants

Thirteen medically healthy subjects with MDD participated in the study, 11 of whom had participated in a prior baseline analysis (Nugent et al., 2015b). Although it could be argued that re-use of subjects is somewhat problematic, this study is the first to analyze post-ketamine MEG recordings, and use of baseline scans was necessary to provide a reference. For all subjects, diagnosis was confirmed using the Structured Clinical Interview for DSM-IV-TR (SCID) and an unstructured interview with a psychiatrist. In addition, all subjects were required to not have responded to two prior adequate antidepressant trials. Co-morbidities were common, with nine of the 13 subjects presenting with a comorbid anxiety and/or eating disorder. In addition, four subjects had a prior history of substance abuse or dependence, although none in the last three months. These subjects were recruited as part of a much larger cohort (Ibrahim et al., 2012), but of the recruited subjects, many were either not eligible for MEG or had artifacts or movement rendering scans at one or both time points unusable.

Eighteen control subjects with no personal or family history of mood disorders were included as a control group; 17 of these overlapped with the primary analysis from our previously published study (Nugent et al., 2015b). In this present, preliminary study, healthy control subjects did not receive ketamine. Because these healthy subjects were not independent from the prior analysis, we should emphasize that we include them not to demonstrate between-group differences but instead to provide a normative reference. In addition, because the unpaired comparison between the MDD and healthy control groups is underpowered, we did not expect that all results would be replicated between groups; our primary aim was to demonstrate differences in the MDD subjects pre- and post-ketamine.