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Journal of Addiction Medicine and Therapy

Review Article

Ketamine and Pharmacological Imaging: Use of Functional Magnetic Resonance Imaging to Evaluate Mechanisms of Action

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Submitted: 15 March 2017

Accepted: 29 June 2017

Published: 30 June 2017

ISSN: 2333-665X

Keywords
- Ketamine infusion
- Pharmacological imaging
- Functional connectivity
- Dorsolateral prefrontal cortex

Abstract

Sub-anesthetic ketamine infusion is the primary pharmacological model used to study schizophrenia and similar administration protocols of the drug are under investigation as a treatment for depression and other psychiatric disorders. However, the mechanisms underlying both the psychotomimetic and therapeutic effects of ketamine remain poorly understood. This review provides an overview of what is known of the neural mechanisms underlying the effects of ketamine and details what functional magnetic resonance imaging studies have revealed at the systems-level. Multiple analysis techniques show that ketamine produces robust and consistent effects at the whole-brain level. These effects are highly conserved across primate species, validating the use of nonhuman primate models for further investigations with ketamine. Regional analysis of functional connectivity suggests that the therapeutic potential of ketamine may be derived from a strengthening of executive control circuitry, making it an intriguing candidate for the treatment of drug abuse. However, there are still many questions about ketamine that can be answered using current functional imaging techniques that have yet to be addressed.

ABBREVIATIONS

NMDA: N-methyl-D-aspartate; fMRI: Functional Magnetic Resonance Imaging; BOLD: Blood Oxygenation Level Dependent; GBC: Global Brain Connectivity; dlPFC: Dorsolateral Prefrontal Cortex; PET: Positron Emission Tomography

INTRODUCTION

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist with a fascinating profile of pharmacological effects that has made it a hot research target in several different fields of medicine and neuroscience. High doses of ketamine have long been used medically as a general anesthetic [1], and the recreational use of ketamine as a psychedelic drug of abuse has a lengthy history as well [2]. For the past twenty years, ketamine has been used as a pharmacological model for schizophrenia as sub-anesthetic infusions have been shown to produce temporary schizophrenia-like symptoms in healthy humans [3,4]. The strength of these models has helped lead to new hypotheses of glutamatergic system dysfunction in schizophrenia [5].

In addition to its utility for modeling schizophrenia, ketamine has emerged as a useful treatment for multiple psychiatric disorders. Sub-anesthetic doses of ketamine in the same range as those used for modeling schizophrenia have shown efficacy for treating postoperative pain [6], neuropathic pain [7], treatment resistant depression [8,9], and suicidal ideation [10]. Indeed, the rapid onset of improvement in suicidal ideation induced by ketamine, reported to emerge as quickly as 40 minutes post-infusion [11], provides a major advantage for treating this psychiatric emergency as other effective treatments are slower acting [12]. Additionally, recent studies have begun to investigate the potential use of ketamine as a treatment for drug addiction [13,14].

NEURAL MECHANISMS UNDERLYING THE EFFECTS OF KETAMINE

The discovery of these remarkable effects of sub-anesthetic ketamine has led to a great deal of research investigating the underlying neural mechanisms. High doses of ketamine result in general suppression of the central nervous system and produce general anesthesia. However, at the lower systemic doses that produce psychotomimetic and rapid antidepressant effects, ketamine administration actually produces enhancement of excitatory glutamatergic transmission [15,16]. There is growing evidence that at the microcircuit level these sub-anesthetic

doses of ketamine predominantly block the NMDA receptors on inhibitory interneurons [17,18], resulting in a disinhibition of excitatory projection neurons that is required for the antidepressant effects of ketamine [19]. The reason for ketamine to primarily inhibit interneurons remains unknown. It has been proposed that the tonic firing pattern displayed by many cortical interneurons is likely to persistently remove the magnesium block from NMDA receptors, allowing ketamine to block the channel. Meanwhile, burst firing pyramidal neurons may spend more time with the magnesium block in place, reducing the likelihood that ketamine will block the NMDA receptor channels on these excitatory neurons [20,21].

At the regional level, sub-anesthetic ketamine induces increased levels of both glutamatergic and dopaminergic transmission [15,22,23]. There is evidence suggesting that disinhibition of pyramidal projection neurons in the prefrontal cortex leads to downstream activation of dopaminergic neurons [24-26]. Thus, while sub-anesthetic ketamine induces excitation in many brain areas, its effects on prefrontal circuitry may be of particular importance for the induction of psychotomimetic and antidepressant effects [27-29]. The prominent role of prefrontal circuitry in the effects of sub-anesthetic ketamine may represent a critical limitation for the use of non-primate models [30], in such studies. The greater homology of the human prefrontal cortex to that of other primates [31], might add significant translational value to the use of nonhuman primate models for investigating the effects of ketamine. Indeed, even the micro-circuitry within the prefrontal cortex appears to be well conserved across primate species with NMDA receptors playing an important role in local processing that may not be present in rodents [32].

PHARMACOLOGICAL IMAGING METHODS AND KETAMINE

In order to further investigate the effects of ketamine infusion at the regional and whole-brain level, several different neuroimaging techniques have been used. Among these, functional magnetic resonance imaging (fMRI) has proven invaluable to the study of ketamine. Compared to positron emission tomography (PET), fMRI features higher spatial and temporal resolution [33], which is advantageous for studying ketamine given its relatively short half-life and regionally specific effects in many brain areas. This review will discuss the key findings that fMRI studies have contributed to the mechanistic understanding of the effects ketamine has on the brain and will focus primarily on studies featuring human and nonhuman primate subjects. Multiple fMRI methods have been used to examine the brain activation response to ketamine as well as ketamine-induced changes to functional connectivity.

BRAIN ACTIVATION

Blood oxygenation level dependent (BOLD) fMRI has been used to characterize the regional pattern of changes in neural activity induced by ketamine [34-36]. Importantly, strong evidence that BOLD fMRI reflects neural activity induced by ketamine is available from quantitative PET imaging [37,38]. Taken together, these studies show that cerebral blood flow and oxidative metabolism stay coupled during ketamine infusion (especially at sub-anesthetic doses), thus ensuring that BOLD response to ketamine provides an accurate and quantitative representation of underlying neural activity.

FUNCTIONAL CONNECTIVITY

The BOLD fMRI signal exhibits spontaneous fluctuations associated with temporal patterns of neural activity. Correlations in these spontaneous signal fluctuations between distant regions are termed functional connectivity and are thought to underlie communication within brain networks [39]. Functional connectivity has been used for many different clinical applications [40], including the study of ketamine infusion. The two types of functional connectivity analysis that have been most commonly used to study the effects of ketamine infusion are regional seed-based analysis and global brain connectivity (GBC).

Regional seed-based functional connectivity analysis utilizes a region-of-interest approach to calculate functional connectivity between specific regions. This technique compares the average time course of the BOLD signal within a specified seed region with the BOLD time course of every brain voxel outside of the seed region (or within a specified target region) usually by means of the cross-correlation coefficient (CC) between respective time courses [41]. This is the most common type of functional connectivity analysis used for determining regionally specific effects.

GBC is a measure of whole-brain functional connectivity [42], that calculates the average correlation between the BOLD time course in a given voxel and the BOLD time course of every other voxel in the brain. Alterations in GBC have been associated with schizophrenia [43]and thus ketamine-induced changes to GBC have been investigated in relation to the psychotomimetic effects of ketamine infusion.

Of note, independent component analysis [44,45] and graph network analysis [46,47] have also been used to investigate the effects of subanesthetic ketamine. However, with the exception of Joules, Doyle [47] (discussed below), these studies were designed to examine either the analgesic [44,45] or non-acute [46] effects of ketamine and employed considerably different scanning or ketamine infusion protocol, and thus are not discussed in detail in this review.

THE BRAIN ACTIVATION RESPONSE TO KETAMINE

Deakin, Lees [34], were the first group to examine the effects of ketamine infusion on BOLD activation. They found an extensive cortical BOLD signal response with peak signal changes occurring 3-5 minutes after the start of infusion in all regions. This timing corresponds very well with the peak ketamine concentration in the blood, and with the onset of behavioral effects. BOLD activation was quite extensive, with multiple frontal, parietal, temporal, and limbic regions showing increased signal. There were also prominent areas of deactivation in the subgenual cingulate and medial orbitofrontal cortex. These regions play an important role in cortico-limbic networks [48], responsible for affective processing and may be important for the antidepressant effects of ketamine [49]. Deakin et al. [34], further found several regions in which changes in BOLD were correlated with ratings of dissociative state or psychotic symptoms, thus establishing the

relevance of BOLD activation to the psychotomimetic effects of ketamine.

The test-retest reliability of ketamine-induced BOLD activation was later established by De Simoni et al., [35]. They found the BOLD response to ketamine to be a very robust effect, featuring a consistent magnitude and timecourse across different sessions, and both within and across subjects. Further, De Simoni et al. [35], investigated the dose dependence of ketamine-induced BOLD activation and found that a higher dose (75 ng/mL vs. 50 ng/mL) of ketamine corresponded to greater changes in BOLD signal and greater effect sizes. The full ketamine dose-response function has yet to be established with BOLD activation however, and future work should be focused in this area (as discussed in detail below).

Doyle, De Simoni [50], were the first to test the interaction of an antipsychotic drug with the ketamine-induced BOLD response. They tested the effect of pretreatment with risperidone on ketamine-induced brain activation. Clinically, risperidone is one of the most commonly prescribed antipsychotics, featuring similar efficacy and tolerability to other second-generation ("atypical") antipsychotics used for the treatment of schizophrenia [51]. Risperidone is an antagonist at both dopamine D2 and serotonin 5-HT2A receptors, but with no affinity for any glutamate receptor [52]. Doyle and De Simoni [50], showed that risperidone attenuated the BOLD response to ketamine globally, blunting signal changes in frontal, insular, striatal, and thalamic regions. However, ketamine still induced significant BOLD activation compared to saline in each of these areas following risperidone pretreatment. The magnitude of the activation was simply reduced. The antagonism of 5-HT2A receptors may play an important role in attenuating the effects of ketamine because the dopamine D2 antagonist haloperidol has been shown to be insufficient to prevent the psychotomimetic effects of ketamine [53]. Neurons expressing 5-HT2A in the prefrontal cortex project to the ventral tegmental area and local antagonism of these receptors blocks dopamine overflow in the prefrontal cortex [54].

Ketamine-induced BOLD activation also appears to be well conserved across species. Chin, Upadhyay [55], found extensive activation in the cortex and hippocampus of awake rats, and indeed, ketamine-induced BOLD activation has been shown in anesthetized rats as well [56]. However, a follow-up paper from the same group provides strong evidence that the isoflourane anesthesia used may confound the effects of sub-anesthetic ketamine [57]. Nonhuman primates provide a more translational model for studying the BOLD response to ketamine [30,32], and methods have been developed that enable rhesus monkeys to undergo MRI scanning without the use of anesthesia and with minimal restraint stress [58]. A recent study has shown that awake rhesus monkeys display ketamine-induced BOLD activation [36] that corresponds closely in both magnitude and extent to what appears in the human literature [34,35,50]. Pretreatment with risperidone attenuated the ketamine-induced changes in BOLD in rhesus monkeys [36], again to a similar extent as in humans [50]. This data suggests that the neurochemical effects of ketamine are well conserved across species and attests to the validity of using ketamine in nonhuman primates as an animal model for schizophrenia, and as a potential model for evaluating novel antipsychotics.

KETAMINE-INDUCED CHANGES TO GLOBAL BRAIN CONNECTIVITY

The first paper to use functional connectivity analysis to study ketamine infusion was published by Driesen, McCarthy [59]. They examined the effects of ketamine on global brain connectivity (GBC). Ketamine infusion was found to increase the GBC of voxels throughout the brain, illustrating a global increase in functional connectivity. This finding is consistent with coherent neural activity across the brain seen during psychosis [60,61]. Additionally, Driesen, McCarthy [59], found that increased GBC correlated with increases to positive schizophrenia symptom scores in a number of regions, implying that increased functional connectivity is associated with the psychotomimetic effects of ketamine.

Anticevic, Corlett [62], measured the effects of ketamine using a variant of GBC in which only voxels within the prefrontal cortex were considered. The restricted GBC was shown to increase after ketamine administration and this prefrontal specific GBC was also found to be significantly elevated in patients who were within one-year of the onset of schizophrenia symptoms. This finding may suggest that elevated functional connectivity in the prefrontal cortex could be a biomarker for schizophrenia and might indicate that the psychotomimetic effects of ketamine can be measured using functional connectivity. However, other than benefitting from decreased processing time, it is unclear why GBC should be restricted to prefrontal regions, because even if prefrontal regions are of primary interest these areas receive inputs from many other brain areas outside the prefrontal cortex and is part of highly integrative brain circuits [27,29]. Thus, it is likely more appropriate to consider changes to connectivity with a greater scope even when considering specific regions. Furthermore, Anticevic, Corlett [62], performed a global signal regression to remove the average brain signal from every voxel in the brain. Given that ketamine increases global signal as reported previously, the effects of this regression will be different for ketamine than for baseline or saline conditions and could confound any between-condition comparisons [63].

Recent work from our lab in awake rhesus monkeys has demonstrated that ketamine-induced changes in functional connectivity are also well conserved across primate species [64]. GBC analysis (Figure 1), shows that ketamine causes global hyperconnectivity in rhesus monkeys that is similar in both magnitude and regional pattern to what Driesen, McCarthy [59], observed in human subjects. Thus, there are data from multiple imaging modalities that nonhuman primates provide a highly translational model for the effects of ketamine.

Finally, Joules, Doyle [47], investigated the effects of ketamine infusion on whole-brain functional connectivity using a graph theory analysis. The measures of whole-brain connectedness they consider are similar to GBC, except instead of being calculated on every voxel they are calculated between anatomical regions within a whole-brain parcellation map. Joules, Doyle [47], found a shift in whole-brain functional connectivity with ketamine infusion that is consistent with the reported increase in GBC

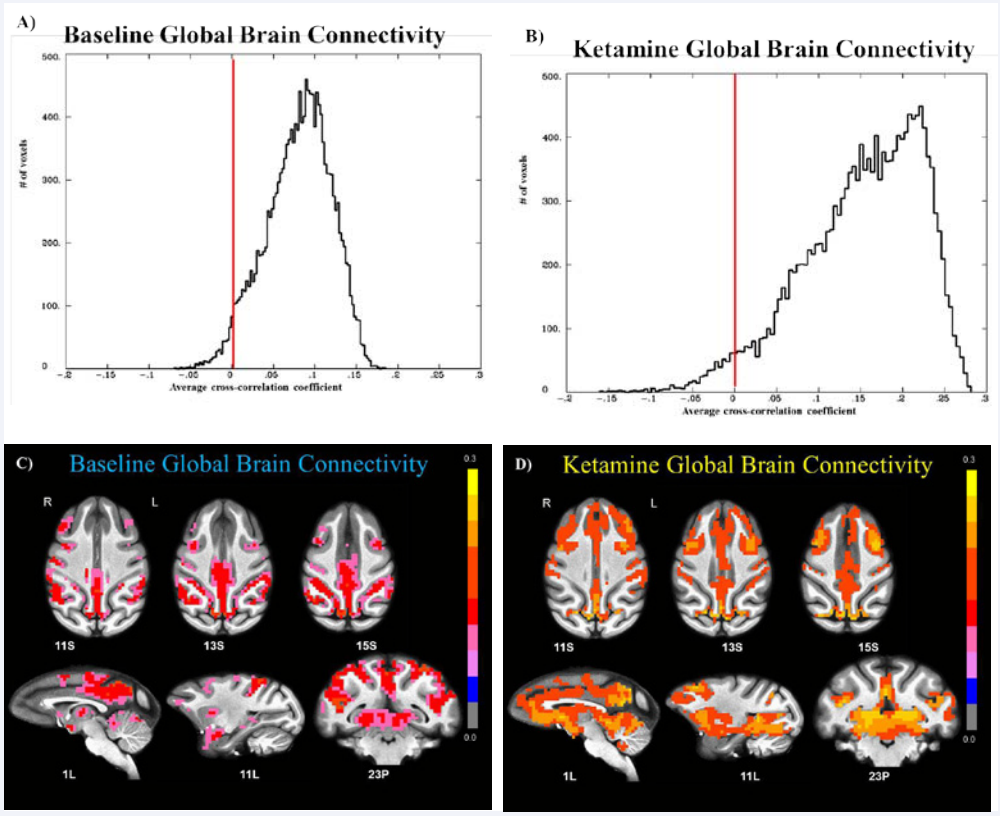

Figure 1 Sub-anesthetic ketamine increases global brain connectivity (GBC) in the awake rhesus brain (N=4). GBC for each voxel is expressed as the effective average cross-correlation (constructed by averaging z-transformed cross-correlations with all other voxel timecourses and expressing the result in the form of effective cross-correlation): A) Distribution of GBC in all gray matter voxels during baseline; B) Distribution of GBC in all gray matter voxels during ketamine infusion. The noticeable rightward shift in B compared to A indicates increased connectivity between brain regions during ketamine infusion; C) Voxel-wise GBC maps during baseline; D) Voxel-wise GBC maps during ketamine infusion. Ketamine-induced increases in GBC are noticeable throughout the brain. For comparison to human data see Driesen, McCarthy [59].

[59]. They further showed that a pattern recognition algorithm could be used to consistently classify the pattern of functional connectivity induced by ketamine infusion as different as placebo infusion. This finding demonstrates the robustness of the effects of ketamine infusion on whole-brain functional connectivity.

KETAMINE-INDUCED CHANGES TO REGIONAL SEED-BASED FUNCTIONAL CONNECTIVITY

In addition to their GBC study, Driesen, McCarthy [65], performed an investigation of the effects of ketamine on functional connectivity to a seed in the dorsolateral prefrontal cortex (dlPFC). The dlPFC is a region strongly implicated in schizophrenia because of its important role in working memory [17], and the group hypothesized that ketamine-induced changes in connectivity to the dlPFC would be associated with impaired performance on a working memory task. Unfortunately, for this study they used a global signal regression, which may have confounded their results for the reasons mentioned previously. Speculatively, while they found that ketamine reduced connectivity to the dlPFC seed, this could result from a greater impact of global signal regression under the ketamine condition than the saline condition.

Functional connectivity to the striatum was shown to be enhanced by Dandash, Harrison [66], who used a regional seed-based analysis with seeds placed in the dorsal and ventral putamen, dorsal caudate, and nucleus accumbens. While they did not find differences in connectivity to either of the seeds in the putamen, they found increased connectivity from the thalamus to the dorsal caudate and from the ventromedial prefrontal cortex to the nucleus accumbens. These results may have been limited by the high variability the group observed in ketamine plasma levels (68.6 ± 43.6 ng/ml) producing inconsistent drug effects. Still, their finding of increased connectivity between the medial prefrontal cortex and ventral striatum may inform the study of ketamine as a potential treatment for drug addiction (discussed in detail below); a condition in which fronto-striatal connectivity has been found to be impaired [67,68].

Our lab has recently performed a regional seed-based analysis of changes in functional connectivity induced by ketamine in awake rhesus monkeys [64]. Like Dandash, Harrison [66], we observed that ketamine increased connectivity to a seed in the nucleus accumbens, although the increases we observed were considerably more extensive. In addition to the accumbens seed, our analysis also featured seeds in the amygdala, posterior and sub-genual cingulate, orbitofrontal cortex, and dlPFC. Among these seed regions, the greatest ketamine-induced changes in functional connectivity were seen in dlPFC projections. This may be a key finding for explaining both the psychotomimetic and antidepressant effects of ketamine.

The dlPFC is a region strongly implicated in schizophrenia because of its important role in working memory [17]. The hyperconnectivity induced by ketamine could be related to aberrant processing leading to psychotic symptoms, as hypothesized by Driesen, McCarthy [65]. Further, the dlPFC plays an essential role in the executive control of emotion [69], which has been shown to be dysfunctional in major depression [70]. Direct activation of the dlPFC using repeated transcranial magnetic stimulation is an effective treatment for depression [71], presumably because of a resultant strengthening of network connections responsible for executive control of emotion [72,73]. Thus, the ketamine-induced increases in dlPFC connectivity may be a key indicator of psychotomimetic effects present during ketamine infusion as well as the neuroplastic changes thought to underlie the antidepressant effects that follow ketamine administration.

Another study [74], investigated ketamine-induced changes in functional connectivity specifically between the dlPFC and hippocampus. They found that acute ketamine administration increased dlPFC-hippocampus connectivity in both human subjects and in rats. The breadth of their results is limited because only a single connection was examined. However, this data does support the finding in rhesus monkeys [64], of robust ketamine-induced increases in dlPFC functional connectivity.

FUTURE DIRECTIONS FOR IMPROVING THE UNDERSTANDING OF KETAMINE

While ketamine-induced BOLD activation has been a useful first step for studying the whole-brain effects of ketamine, functional connectivity may prove to be more informative for understanding the mechanism of action of ketamine in the brain. It is important to note that when neural activity increases, metabolic activity (and therefore BOLD signal) is most enhanced at the synapses and not at the cell bodies [33]. Thus, in the case of localized disinhibition of pyramidal neurons, as presumed with ketamine, the downstream areas receiving projections from the disinhibited region(s) may show the greatest enhancement of BOLD signal. On the other hand, a region that becomes disinhibited may increase its functional coupling to downstream areas and hence may show increased functional connectivity even when it does not show as strong of an enhancement in BOLD signal [75]. This may explain why the dlPFC shows the most extensive increases in functional connectivity [64], but only moderately increased BOLD signal during ketamine infusion [35, 36].

Future studies could use fMRI to answer several other questions about ketamine. The dose-response relationship for ketamine remains poorly understood. This is true both for the efficacy of ketamine as an antidepressant and for the acute effects of ketamine on brain activity. De Simoni, Schwarz [35], reported that BOLD activation increased with increasing dose, however no peak dose has been established and no investigation of the dose dependence of changes to functional connectivity has been conducted. Further, investigation into the persistent effects of ketamine on brain activity is also warranted. Most fMRI studies to date have focused on examining the acute effects of ketamine, however the antidepressant effects do not typically begin until at least an hour post-infusion [8,28]. One study [46], investigating the sustained effects of ketamine, has reported significant changes to functional connectivity 24-hours post-infusion, however these results may be confounded by the effects of anesthesia [76], and should be replicated in awake subjects.

Another important question regarding the effects of ketamine is whether they are truly global or if a specific region (such as dlPFC) or subset of regions become disinhibited and drive the excitatory effects elsewhere in the brain. The use of a dynamic functional connectivity analysis [77,78] could potentially be used to determine whether there is a specific regional onset to the effects of ketamine. Currently, there are no published studies employing this type of analysis with any NMDA receptor antagonist.

The independent contributions of the individual pharmacological components of ketamine remain largely unknown. Ketamine is a chiral compound consisting of a pair of (R,S) enantiomers and there is some evidence suggesting that R-ketamine may have greater antidepressant efficacy [79] while also producing fewer psychotomimetic effects [80]. Further, there is one report that found a specific metabolite of ketamine to be sufficient for producing antidepressant effects [81]. Imaging these independent components of ketamine separately may lead to important new insights into how the effects of ketamine are mediated. Such experiments may also help to determine whether the psychotomimetic effects of ketamine can truly be segregated from the antidepressant effects.

FUTURE DIRECTIONS FOR INVESTIGATING THE THERAPEUTIC USE OF KETAMINE

Ketamine has already shown tremendous therapeutic value in the treatment of major depression, and the results from functional imaging experiments provide tantalizing evidence of further therapeutic uses for ketamine. The finding that ketamine enhances connectivity to the dlPFC [64], and potentially causes neuroplastic changes that strengthen executive control, has major implications for the potential use of ketamine in treating other psychiatric disorders. Impaired executive control has been associated with a number of disorders and is a particularly common finding in drug addiction [82-84]. Indeed, acute administration of cocaine has been shown to significantly reduce functional connectivity between dlPFC and nucleus accumbens in awake nonhuman primates, and the connectivity between these regions is negatively correlated with cocaine intake during self-administration [68]. There is already some evidence to indicate that sub-anesthetic ketamine infusion may be an effective treatment for cocaine abuse [13,14], and as there are currently no FDA approved medications for the treatment of psychostimulant abuse, further investigation is certainly warranted. Nonhuman primate self-administration represents the gold-standard for modeling addiction, andfMRI studies provide strong evidence that ketamine induces highly translational effects on BOLD signal and functional connectivity in nonhuman primates. An elegantly designed study could investigate the efficacy of ketamine for reducing drug self-administration, as well as the predictive value of dlPFC functional connectivity as a biomarker for drug addiction.

CONCLUSIONS

Acute administration of sub-anesthetic ketamine produces a robust, global increase in BOLD signal that is correlated with the psychotomimetic effects of ketamine. Functional connectivity also undergoes robust, global increases during acute ketamine administration that correlate with the psychotomimetic effects of ketamine. These effects are very well conserved across primate species and could be used to create a translational pharmacological model of schizophrenia in nonhuman primates. Ketamine shows exciting potential as a therapeutic and the results from fMRI experiments suggest it may bolster executive control circuits, making it a particularly good candidate for investigation in the treatment of drug abuse. Future fMRI studies should be able to elucidate many of the questions that still remain unanswered about the mechanisms mediating the effects of ketamine.

ACKNOWLEDGEMENTS

This research was supported by P51OD11132 (Yerkes National Primate Research Center), Sunovion Pharmaceuticals, Ltd (LLH) and DA031246 (LLH). Special thanks to the Yerkes Imaging Center, technicians Marisa Olsen and Juliet Brown, and to Christopher Muly, MD, PhD, Naoko Urushino, PhD, and Doty Kempf, DVM.

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Cite this article

Maltbie E, Kaundinya G, Howell L (2017) Ketamine and Pharmacological Imaging: Use of Functional Magnetic Resonance Imaging to Evaluate Mechanisms of Action. J Addict Med Ther 5(2): 1031.