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Acute effects of intranasal esketamine application on thalamic structures in healthy individuals

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Abstract

Background: The N-methyl-D-aspartate receptor antagonist ketamine has found broad application in the field of psychiatry. Due to its rapid antidepressant and anti-suicidal properties, it is used as a treatment for major depressive disorder. Furthermore, ketamine evokes dissociative and psychotropic states, which allows the modeling of schizophrenic symptoms. The thalamus, a main target for ketamine's actions, consists of different nuclei responsible for sensory gating, attention, and consciousness. Thus, we here examine the effects of intranasally applied ketamine on thalamic structures in healthy individuals in a cross-over placebo-controlled study.

Methods: Twenty-six subjects (14 female, mean age ± SD = 24.3 ± 3 years) underwent two magnetic resonance imaging scans on a 3T system immediately after receiving a subanesthetic dose of 56 mg esketamine (2x Spravato 28mg nasal sprays) or placebo in a cross-over study design. FreeSurfer was used for morphological analysis of the thalamus and its distinct nuclei based on derived T1-weighted MPRAGE images. Repeated measure analyses of covariance across the whole group, regardless of measurement order, and the subgroup, receiving placebo in the first scan, were performed for the thalamus and all its nuclei, for each hemisphere, separately. Post hoc tests on thalamic nuclei were done in an exploratory manner.

Results: We found a significant volume increase in the right thalamus ($p_{corr.}$ = .048), the pulvinar anterior nucleus (p = .048), and the right mediodorsal lateral parvocellular (p = .034) after esketamine in the subsample receiving placebo application in the first scan.

Conclusion: Our results suggest rapid structural adaptations in right thalamic structures which serve as relay stations for the visual cortex. This emphasizes the thalamus' role in visual perception after esketamine and its importance as a target to model schizophrenic symptoms.

Keywords: ketamine; thalamus; intranasal; structural; MDD; schizophrenia.

Significance Statement

Ketamine is a rapid working antidepressant. However, its use is often accompanied by dissociative states and altered visual perception. Therefore, ketamine is often used to mimic schizophrenic symptoms. The thalamus plays a crucial role for sensory gating and represents a main target for ketamine. Here we investigated the effects of intranasal application of esketamine on morphological features of the thalamus compared to placebo treatment in healthy volunteers. Especially thalamic nuclei involved in sensory gating showed significant volumetric changes after esketamine. Thus, this work sheds light on the importance of the thalamus in altered sensory states after esketamine use and its implications in modeling schizophrenic symptoms.

INTRODUCTION

Ketamine is widely used as a treatment option for major depressive disorder (MDD) due to its rapid antidepressant and anti-suicidal effects. For a better understanding of its clinical effects, it is crucial to investigate ketamine's manifold neurobiological impacts. This glutamatergic receptor antagonist is thought to act via N-methyl-D-aspartate receptor activation on GABAergic cells,[1] resulting in glutamatergic disinhibition. In addition, direct α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) activation was reported.[2] Furthermore, neuroplastic processes likely play a key role in the antidepressant properties of ketamine. Neuroplastic effects are facilitated via indirect and direct

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effects on the tropomyosin receptor kinase B (TrkB) receptor, activating the mammalian target of rapamycin pathway.[3] The TrkB-receptor is the main target for brain-derived neurotrophic factor (BDNF) in the brain, inducing neuroplastic effects via synaptogenesis and rewiring mechanisms.[4] Finally, a variety of neurotransmitter systems, including serotonin, gamma-aminobutyric acid (GABA), glutamate, and catecholamines, show alterations after ketamine administration.[5-9] Nevertheless, it is unclear which of these mechanisms are directly associated with ketamine's antidepressant properties.

Although ketamine was shown to effectively reduce depressive and suicidal symptoms within hours of actions, its side effects, including dissociative and psychotropic states, limit its use.[10] On the other hand, due to its side effects mimicking dissociative states, ketamine has been used to model schizophrenic symptoms.[11]

In particular, the thalamus, a key region for sensory gating, is thought to be a main target for the effects of ketamine.[12] The thalamus is involved in sensory processing, consciousness, and attention by acting as a relay center for sensory and motor signals.[13,14] Studies suggested that by the inhibition of thalamic relay neurons, ketamine can block sensory signals from reaching the cortex, which in turn are thought to contribute to sensations of detachment from the environment (ie, derealization and depersonalization).[15] Disruptions in thalamocortical connectivity were shown to impair sensory processing and cognitive integrations. Functional magnetic resonance imaging studies showed modulations in thalamocortical functional connectivity after ketamine infusion. Hoflich et al. reported an increase in cortico-thalamic connectivity of the somatosensory and temporal cortex.[16] Furthermore, Tu et al. investigated the link between changes in the thalamocortical network and antidepressant effects.[17] On the neurotransmitter level, increased cortical glutamate release by the inhibition of GABAergic interneurons in the thalamus after ketamine administration has been suggested.[18] Thus, the short-lasting increase in thalamocortical activity after ketamine treatment among other adaptions in the thalamus highlights this region as a potential biomarker for the antidepressant effects of ketamine.[16,19]

The thalamus comprises a complex region, consisting of different nuclei with distinct functions. Segmentation tools enable the structural differentiation of thalamic nuclei in order to narrow down effects on substructures.[20] Thus, we aimed to investigate the acute morphological effects of intranasal ketamine administration on thalamic substructures in healthy volunteers.

METHODS

Study Design

To this end, 30 healthy subjects underwent 2 magnetic resonance imaging (MRI) scanning sessions, at least 7 days apart from each other, on a 3T Magnetom Prisma system. All MRI measurements were performed immediately after esketamine or placebo administration. Subjects received an intranasal dose of 56 mg esketamine or placebo application, respectively, directly before each measurement in a cross-over, double-blind study setup (see Figure 1). To reduce the effects of seasonal variations on the brain,[21,22] 4 subjects were excluded from the analyses since the time between measurements exceeded more than 4 weeks. Thus, a total of 26 subjects (14 female, mean age ± SD = 24.3 ± 3 years) was included in the analyses. This study was approved by the ethics committee of the Medical University of Vienna (EK 2014/2021) and was performed in accordance with the Declaration of Helsinki (1964).

All subjects were right-handed and had no history of psychiatric or neurological disease, brain injuries, or drug abuse. Exclusion criteria included pregnancy or current breastfeeding, diagnosis of an Axis-1 psychotic disorder in first-degree relatives, pulmonary insufficiency, known aneurysmal vascular disease, history of intracerebral hemorrhage or cardiovascular events, or any contraindications to MR scanning.

MRI Scanning and Morphological Analysis

Magnetic resonance imaging scans were conducted on a 3T Magnetom Prisma system (Siemens Medical) installed at the High-field MR Center, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, using a 64-channel head coil. We used a T1-weighted MPRAGE sequence with a repetition time of 2500 ms, echo time of 2.82 ms, and 1 mm isotropic voxel size (192 sagittal slices, 256 × 256 matrix size) utilizing GRAPPA acceleration with a factor of 2.

For the structural segmentation of the brain, FreeSurfer (Version 7.1—freesurfer-linux-centos6_x86_64-7.1.0-20200511-813297b) was utilized.[23] Subsegmentation of the thalamus and its nuclei was performed as described in Iglesias et al.[20]

Esketamine Administration

Participants received an intranasal subanesthetic dose of 56 mg esketamine or placebo (0.9% saline solution) prior to each measurement in a double-blind, cross-over design. Therefore, 2x Spravato 28 mg nasal sprays were utilized. Study medication was administered immediately before study subjects entered the MRI scanning room. For placebo administration, identical original nasal applicators were filled with 0.9% saline solution. All applicators used were free from any labels, ensuring double-blind administration.

Esketamine and Metabolite Plasma Levels

For the detection of plasma levels of esketamine and norketamine, venous blood samples were drawn directly after each MRI scanning session. Samples were frozen at ≤ –80 °C until further analysis after centrifugation and plasma separation of plasma. Plasma levels of esketamine and norketamine (in ng/mL) were determined using gas chromatography-mass spectrometry at the Clinical Department of Laboratory Medicine, Medical University of Vienna, Austria. The applied method was validated according

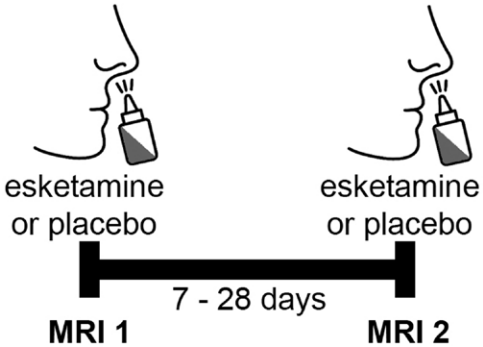

Figure 1. Study design. Healthy study subjects underwent two magnetic resonance imaging (MRI) sessions which were conducted between 7 and 28 days apart from each other. In each scanning session, subjects received an intranasal dose of 56 mg esketamine or placebo respectively in a double-blind, cross-over study design.

to the European Medicines Agency guideline on bioanalytical method validation.

Statistical Analyses

Statistical analyses were conducted using SPSS Statistics (v24.0, 2010, SPSS, Inc., an IBM Company). Repeated measure analyses of covariance (rmANCOVA) were used to determine potential morphological changes in the thalamus and its nuclei after esketamine administration compared to placebo. Therefore, a factor substance was used. Treatment order (placebo or esketamine first), time between measurements, and plasma levels of esketamine and norketamine (ng/mL) were used as covariates. Repeated measure analyses of covariance were conducted for the left and right thalamus independently. In the case of significant changes, post hoc tests in the respective thalamic nuclei were done in an exploratory manner. Analyses on whole thalamic structures were corrected for multiple comparisons using the Bonferroni correction method.

To differentiate acute from long-lasting effects of esketamine application, we conducted independent rmANCOVA models in the subgroup of participants receiving placebo treatment before the first and esketamine treatment before the second MRI scan. Twelve subjects (7 female, mean age ± SD = 23.2 ± 2 years) were included in these subanalyses.

RESULTS

Repeated measure analyses of covariance across the whole group, including all subjects, regardless of measurement order, revealed no significant effects of esketamine administration compared to placebo. However, analyses in the subgroup, receiving placebo application in the first scan, revealed a significant effect of esketamine administration on the right thalamus ($p_{corr.}$ = .048, F = 7.279) compared to volumetric data after placebo administration (see Figure 2).

Analyses of structural changes of the nuclei of the right thalamus were conducted on an exploratory basis. Figure S1. A significant increase in the right pulvinar anterior nucleus (PuA) (P = .048, F = 5.409) and the right mediodorsal lateral parvocellular (MDI) nucleus (P = .034, F = 6.527) was revealed (see Figure 3). All residuals of rmANCOVAs were normally distributed based on visual inspection and the Kolmogorov-Smirnov test. Venous blood samples were drawn on average 115 ± 8 minutes after application. Plasma levels of esketamine and norketamine are depicted in Figure S1.

Based on significant morphological adaptions in the thalamic nuclei, serving as relay stations for visual input, we performed a post hoc analysis on structural adaptions in the visual cortex (the left and right lateral occipital cortex, based on FreeSurfer segmentations) on an exploratory basis. However, no significant morphological changes were found within these structures.

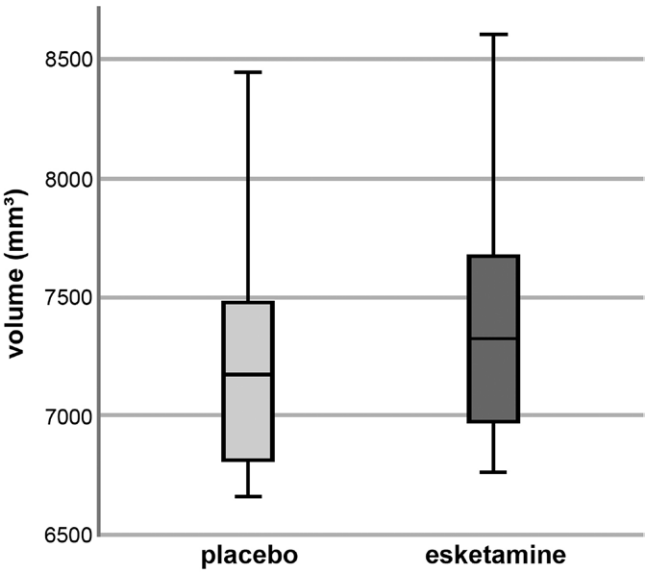

Figure 2. Mean volumes of the right thalamus. Boxplots showing mean volumes of the whole right thalamus after placebo administration in the first scan (light gray) and esketamine administration in the second scan (dark gray).

DISCUSSION

Here we describe the acute morphological effects of intranasal esketamine administration on the right thalamus and 2 distinct nuclei (the pulvinar anterior and the right MDI) in healthy individuals. These volume increases after esketamine application in the right thalamic structures were prominent in the subgroup, starting with placebo administration in the first scan (which can be considered as baseline measures). However, there was no significant effect in the whole study sample. Thus, volume increases after esketamine application in right thalamic structures were prominent in the subgroup starting with placebo administration in the first scan, which can be considered as baseline measures. Hence, our results are suggestive of rapid volumetric effects of esketamine on the thalamus.

The thalamus serves a variety of different roles. Thus, it is of utter importance to allocate changes to its distinct nuclei. The thalamus is responsible for sensory relay and processing, motor control, or cognitive functions.[13,14] Here we found adaptions in the anterior pulvinar nucleus (PuA) and the MDI nucleus, both serving as a relay station for the visual cortex and thereby contributing to visual processing and reflexive orientation.[24]

So far, different structural adaptions have been shown after ketamine. A study reported increased thalamus volume after 6-week oral administration.[25] Moreover, several studies reported that repeated ketamine treatment in patients with MDD led to increased volumes of the amygdala and the hippocampus.[26,27] In addition, it was shown that hippocampal subfield volumes can potentially predict treatment response[27] and correlate with anxiety-related experiences during ketamine infusion.[28] Furthermore, a study reported increased amygdalar volumes in patients suffering from treatment-resistant depression 10 days after ketamine infusion, which highlights the importance of the timing of measurements, revealing different adaptions in the brain in temporal orders.[29] Hence, it can be assumed that neurobiological adaptions follow certain sequential processes evoking short and long-term adaptions in the human brain. On the other hand, it was shown that ketamine does not only increase certain brain volumes, but chronic ketamine (mis-)use may lead to lower gray matter volumes.[30]

Underlying neurobiological reasons for increased brain volumes can be manifold. Besides actual increases in gray or white matter, swelling due to increased blood volume could lead to (rapid) structural adaptions.[31] In addition, neuroplastic adaptions, including rewiring mechanisms are potential explanations for morphological changes. Ketamine has been shown to increase BDNF levels, a marker for neuroplastic events, which are thought to lead to sustained antidepressant effects of ketamine.[32] Our results suggest fast structural adaptions within the thalamus,

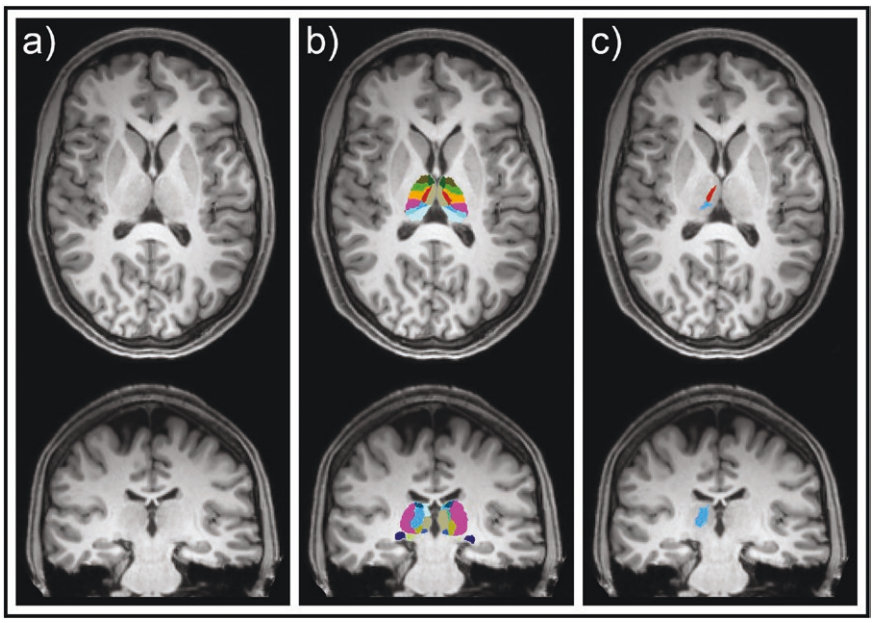

Figure 3. Visual representation of thalamic nuclei segmentation. Segmentation of the whole thalamus based on structural magnetic resonance imaging (MRI) data (a,b). Thalamic nuclei showing significant morphological adaptions after esketamine administration (c): right pulvinar anterior nucleus (blue) and right mediodorsal lateral parvocellular nucleus (red).

which would explain significant differences in the subgroup receiving placebo first, that were not shown in the whole group. Thus, these morphological changes are potentially arising from swelling or the beginning of neuroplastic changes within this region.

Besides structural changes in the thalamus, so far, mainly alterations in thalamic activity were shown. The thalamus is part of the cortico-limbic network implicated in mood disorders. Changes in thalamic activity may contribute to ketamine's rapid antidepressant effects. Functional adaptions in thalamocortical networks following ketamine administration have been reported[16] along with enhanced synaptic transmission in rodent models.[33] Furthermore, ketamine increases glucose uptake in several thalamic nuclei, including the lateral posterior, lateral dorsal, medial dorsal, gelatinosus, antero-ventral, and antero-medial nuclei. However, it decreases metabolic activity in the ventro-basal complex.[34] By disrupting thalamocortical connectivity and altering glutamatergic signaling, ketamine modifies sensory processing, consciousness, and mood. These interactions highlight the thalamus as a critical node in understanding ketamine's therapeutic and psychotropic effects.

Structural and functional alterations among different brain regions can potentially be associated with different effects and side-effects of ketamine. While the described structural alterations in the hippocampus in combination with functional adaptions in the thalamocortical network may underline antidepressant properties of ketamine,[27] changes in the amygdala may be associated with fear-related experiences during ketamine use.[28] Here, we found rapid alterations in thalamic nuclei, that are mainly involved in sensory processing. The thalamus's altered function under ketamine mimics certain features of schizophrenia. Similar to schizophrenic patients, ketamine users often experience a breakdown in the thalamus's ability to filter sensory stimuli. Thus, especially psychotropic (side-) effects, that are often used to model schizophrenic characteristics, may be linked to acute structural adaptions in the PuA and MDI nucleus. The MDI was previously associated with disruptions in cognitive function in schizophrenia.[35] Since these nuclei mainly act as relay stations for sensory inputs, ketamine-induced disruptions in their function are likely reflected in fast morphological adaptions.

Our study is not without limitations. Subjects received an intranasal application of esketamine directly before MRI scans. Due to the scanning protocol, no continuous control of esketamine plasma levels could be performed while scanning. Hence, a single measure of plasma levels of esketamine and norketamine was used as covariates in the analyses. Moreover, statistical analyses of thalamic nuclei were done on an exploratory basis if higher-order structures revealed significant morphological changes.

CONCLUSION

The thalamus represents a critical node in understanding ketamine's therapeutic and psychotropic effects. Fast morphological adaptions in thalamic nuclei, acting as sensory relay stations, may represent neurobiological underpinnings for altered visual perception and dissociative symptoms following esketamine application. Thus, structural changes reported in this work highlight the importance of thalamic function during ketamine application as a model for schizophrenia. Further research is needed to clarify the role of the thalamus and its nuclei in the antidepressant and anti-suicidal properties of ketamine.

Supplementary material

Supplementary material are available at *International Journal of Neuropsychopharmacology* (IJNPPY) online.

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Author contributions

Benjamin Spurny-Dworak (Data curation [equal], Formal analysis [lead], Investigation [equal], Resources [equal], Software [equal], Validation [lead], Visualization [lead], Writing—original draft [lead]), Thomas Liebe (Conceptualization [equal], Data curation [equal], Funding acquisition [lead], Methodology [equal], Project administration [equal], Writing—review & editing [equal]), Samantha Graf (Investigation [equal], Writing—review & editing [equal]), Gregor Dörl (Investigation [equal], Writing—review & editing [equal]), Peter Stöhrmann (Investigation [equal], Writing—review & editing [equal]), Elisa Briem (Investigation [equal], Writing—review & editing [equal]), Manfred Klöbl (Conceptualization [equal], Methodology [equal], Supervision [supporting], Writing—review & editing [equal]), Clemens Schmidt (Investigation [equal], Writing—review & editing [equal]), Marie Spies (Conceptualization [equal], Project administration [equal], Supervision [supporting], Writing—review & editing [equal]), and Rupert Lanzenberger (Conceptualization [equal], Methodology [equal], Project administration [lead], Supervision [lead], Validation [equal], Writing—review & editing [equal])

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Conflicts of interest

R.L. received investigator-initiated research funding from Siemens Healthcare regarding clinical research using PET/MR and travel grants and/or conference speaker honoraria from Janssen-Cilag Pharma GmbH in 2023, and Bruker BioSpin, Shire, AstraZeneca, Lundbeck A/S, Dr. Willmar Schwabe GmbH, Orphan Pharmaceuticals AG, Janssen-Cilag Pharma GmbH, Heel and Roche Austria GmbH., and Janssen-Cilag Pharma GmbH in the years before 2020. He is a shareholder of the start-up company BM Health GmbH, Austria since 2019. M.S. received speaker honoraria from Janssen and Austroplant as well as travel grants and/or workshop participation from Janssen, Austroplant, AOP Orphan Pharmaceuticals, and Eli Lilly. C.S. received a travel grant by Eli Lilly to attend a scientific exchange meeting.

Data availability

Due to data protection laws, processed data are available from the authors upon reasonable request. Please contact rupert.lanzenberger@meduniwien.ac.at with any questions or requests.

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