

## RESEARCH ARTICLE

# Ketamine-Induced Modulation of the Thalamo-Cortical Network in Healthy Volunteers As a Model for Schizophrenia

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## Abstract

**Background:** Schizophrenia has been associated with disturbances of thalamic functioning. In light of recent evidence suggesting a significant impact of the glutamatergic system on key symptoms of schizophrenia, we assessed whether modulation of the glutamatergic system via blockage of the N-methyl-D-aspartate (NMDA)-receptor might lead to changes of thalamic functional connectivity.

**Methods:** Based on the ketamine model of psychosis, we investigated changes in cortico-thalamic functional connectivity by intravenous ketamine challenge during a 55-minute resting-state scan. Thirty healthy volunteers were measured with pharmacological functional magnetic resonance imaging using a double-blind, randomized, placebo-controlled, crossover design.

**Results:** Functional connectivity analysis revealed significant ketamine-specific changes within the thalamus hub network, more precisely, an increase of cortico-thalamic connectivity of the somatosensory and temporal cortex.

**Conclusions:** Our results indicate that changes of thalamic functioning as described for schizophrenia can be partly mimicked by NMDA-receptor blockage. This adds substantial knowledge about the neurobiological mechanisms underlying the profound changes of perception and behavior during the application of NMDA-receptor antagonists.

**Keywords:** ketamine, functional MRI, thalamus, glutamate, schizophrenia

## Introduction

In the last years, compelling evidence has been raised that the glutamatergic system plays a major role in the neurobiology of schizophrenia. This has been supported by the observation that

dissociative anesthetics, which block the N-methyl-D-aspartate (NMDA) receptor, such as phencyclidine and ketamine, can elicit transient effects in healthy volunteers, which mimic positive,

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negative, and cognitive symptoms seen in patients with schizophrenia. Furthermore, previous studies using ketamine in healthy volunteers have reported a significant impact of NMDA blockage on neuronal activation and functional connectivity (Anticevic et al., 2012; Driesen et al., 2013). Ketamine-induced changes of neuronal activation have been shown during a number of MRI tasks with major relevance in the context of schizophrenia, such as self-monitoring, attentional functions, and affective processing (Abel et al., 2003; Daumann et al., 2010; Stone et al., 2011) as well as during resting state (Scheidegger et al., 2012; Driesen et al., 2013). Furthermore, a recent multimodal imaging study using simultaneous acquisition of functional MRI (fMRI) and EEG during a visual oddball task could show a significant impact of a subanesthetic dose of ketamine both on the blood oxygenation level dependent (BOLD) signal and the P300 amplitude. These effects were evident in regions involved in sensory processing and selective attention (Musso et al., 2011). The implication of glutamatergic dysfunction in schizophrenia has been further substantiated by studies in patients with schizophrenia showing abnormalities of glutamatergic pathways compared with healthy volunteers. Postmortem studies in patients with schizophrenia showed significant alterations of glutamate metabolism, with abnormalities of phosphate-activated glutaminase and glutamic acid decarboxylase activities and NMDA receptor binding (Kornhuber et al., 1989; Gluck et al., 2002). More recently, a number of functional neuroimaging studies showed changes of glutamine levels or the glutamine/glutamate ratio in the anterior cingulate cortex and the thalamus in patients with schizophrenia in vivo as measured with magnetic resonance spectroscopy (MRS) (Theberge et al., 2002; Bustillo et al., 2010; Kegeles et al., 2012), indicating higher turnover rates of glutamate. It was also shown that clinical response to antipsychotic treatment is associated with the degree of glutamatergic dysfunction as assessed with MRS (Szulc et al., 2013; Egerton et al., 2012).

Clinical symptoms seen in patients with schizophrenia may partly arise from dysfunction in sensory processing. Therefore, the thalamus as a major modulator of integration of sensory, cognitive, and emotional information has gained particular attention. In this context, several studies have investigated the involvement of the glutamatergic system in thalamic dysfunction in schizophrenia (Meador-Woodruff et al., 2003; Watis et al., 2008). It was thus shown that glutamatergic transmission of the thalamus is disturbed in patients with schizophrenia, with histological, structural, and functional findings supporting this concept (Clinton and Meador-Woodruff, 2004; Smith et al., 2011).

A number of task-independent functional networks, so-called resting-state networks, have been defined and investigated in healthy individuals, patients suffering from neuropsychiatric disorders, and during pharmacological interventions (Whitfield-Gabrieli and Ford, 2012). Subsequently, these networks were shown to be associated with a number of functions, which are highly relevant in the context of schizophrenia. Tomasi and Volkow (2011) were able to detect the thalamus hub network involving the thalamus, motor, premotor, visual, auditory, and limbic regions and the cerebellum in a large cohort of healthy volunteers. This network was shown to represent a functional correlate of the sensory gating function of the thalamus based on the extensive functional connections to primary sensory cortical areas and limbic regions such as the cingulate gyrus. A number of neuroimaging studies in animals and humans have shown differential involvement of thalamic nuclei and their functional projections in distinct behavioral processes as recently reviewed by Metzger et al. (2013).

Several fMRI investigations in patients with schizophrenia have demonstrated significant disruption of thalamo-cortical

connectivity compared with healthy volunteers. Using various analysis techniques for fMRI data, these studies showed connectivity dysfunctions, in particular dysfunction of thalamo-prefrontal connections (Szulc et al., 2013; Meador-Woodruff et al., 2003; Watis et al., 2008). Importantly, alterations of cortico-thalamic connectivity with reduced prefrontal-thalamic connectivity and increased motor/somatosensory-thalamic connectivity in patients with schizophrenia were recently reported (Zhang et al., 2010; Woodward et al., 2012).

Based on this vast scientific evidence relating the glutamatergic system in general and the NMDA receptor more specifically to the neurobiology of schizophrenia, the aim of the present study was to further investigate the involvement of NMDA blockage on thalamic functioning. Using the ketamine model of psychosis, we assessed time-dependent changes of functional connectivity before, during, and after intravenous application of a subanaesthetic dose of ketamine in healthy volunteers using long-term resting-state fMRI lasting for 55 minutes. Two functional systems were analyzed using 2 independent seed-voxel correlation analyses. First, we analyzed the thalamus hub network described by Tomasi and Volkow (2011) for assessment of overall thalamic functional connectivity. Second, we analyzed cortico-thalamic functional connections using the analysis approach recently published by Woodward et al. (2012) to assign network changes more specifically to different connections of thalamic nuclei. Based on the already existing literature, the goal of this study was thus to further explore the involvement of specific functional connections of the thalamus in the schizophrenia-like state seen in healthy volunteers caused by the administration of ketamine.

## Methods

### Participants

Thirty-five healthy volunteers (mean age  $\pm$  SD: 25  $\pm$  4.58, 18 males) without any history of psychiatric, neurological, or somatic disorders were included in the study. Recruitment was performed by advertisement on dedicated message boards of the General Hospital of Vienna. Prior to inclusion, potential participants underwent a medical examination and a psychiatric interview performed by experienced psychiatrists. To ensure psychiatric health, the Structured Clinical Interview for DSM-IV was performed as well as routine medical check-up, including physical examination, electrocardiogram, and blood and urine analyses. Exclusion criteria were the history of any psychiatric, neurological, or relevant somatic illness; current or former substance abuse; current use of any prescribed or nonprescribed medication; treatment with psychotropic agents within the last 6 months; lifetime use of antipsychotic drugs; the existence of first-degree relatives with a history of psychiatric illness or substance abuse; pregnancy; or any contraindication for the performance of MRI. All procedures were approved by the Ethics committee of the Medical University of Vienna, and the study was registered at the European Union Drug Regulating Authorities Clinical Trials (EudraCT Nr. 2010-022772-31) and approved by the Austrian Federal Office for Safety in Health Care. The study was further registered on clinicaltrials.gov (NCT01394757).

### Study Design and Medication

Thirty of 35 participants (25  $\pm$  4.58 years, 18 males) included in the study completed 2 fMRI sessions in a double-blind, placebo-controlled, randomized, crossover study design. Patients were

randomly assigned to 1 of 2 experimental arms, one receiving ketamine at first measurement and placebo at the second measurement, the other vice versa (for a graphical depiction of the study design, see [Figure 3](#)).

The study drug was provided in standard syringes of 55-mL volume containing either 5 mL S-ketamine (Ketanest S 5 mg/mL ampoules, Actavis Italy S.P.A./Pfizer) diluted in 50 mL 0.90% NaCl or placebo (55 mL of 0.90% NaCl). The administration of the study drug was performed using an MR-compatible fully-automated infusion system (65/115 Injector System, MEDRAD) in the MRI scanner. The MR-compatible infusion system consisted of 2 separate syringes, one of which was filled with the study drug and the other with a standard volume of 100 mL of 0.90% NaCl. The ketamine dosage was applied using a 1-minute bolus of 0.11 mg/kg body weight followed by a maintenance infusion of 0.12 mg/kg for 19 minutes. The dosage was based on previous studies using the S(+)-enantiomer of ketamine, which was shown to have a 3 to 4 times higher affinity or potency at specific receptors than the R(-)-enantiomer, usually leading to a 50% reduction of the dosage compared with studies using the racemate of ketamine ([Sinner and Graf, 2008](#)). Furthermore, the dosage was chosen to lie within a range that provokes reliable psychoactive effects and shows tolerability of an application in the MRI scanner and the following MRI measurement of about 1 hour, which was validated in a pilot study prior to the main investigation ( $n=10$ ). Equal dosage per kilogram body weight as well as constant bolus and maintenance times across subjects were ensured by adjusting the flow rate of the infusion. The infusion protocol was timed to begin 5 minutes after the start of the resting state scan. First, a standardized infusion of 0.90% NaCl for 5 minutes with increasing injection speed was applied to ensure that subjects did not know from the injection itself when ketamine was administered. On few occasions, long fMRI scanning times caused technical problems and/or subjects to preemptively terminate the scan towards the end of the measurement. Thus, data for the time period between 22.5 and 55 minutes after the start of the resting-state scan refer to 25 participants, whereas results for the preceding time periods refer to all 30 participants. After the MRI measurement, participants were observed in the clinical setting for a minimum of 2 hours to ensure the lack of side effects. This period further comprised a debriefing done with the experimenter and collection of blood samples for the analysis of plasma ketamine levels (see below). Furthermore, participants were asked if they fell asleep during the resting-state scan; this information was recorded in addition to neurophysiological data, which gave indirect information about the status of the participants during the scan.

## Psychometric Measures

Psychoactive effects of ketamine were assessed using the German versions of Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS) and the Altered State of Consciousness Scale (5D-ASC) ([Dittrich, 1998](#)). PANSS and BPRS were tested both before and after the MRI measurement to have a baseline value for every participant.

## Resting-State fMRI Acquisition and Analysis

During the resting-state scan, subjects were instructed to relax with eyes open, let their mind wander, and not think of anything specific, as previously described ([Weissenbacher et al., 2009](#);

[Hahn et al., 2011](#)). Resting-state measurements were performed at 3 Tesla (Siemens Trio, Erlangen, Germany) using single-shot gradient-recalled echo planar imaging (EPI) with repetition time/echo time (TR/TE)=1800/38ms, a matrix size of 128×128 voxel, and a field-of-view of 190×190 mm. Hence, voxel size was 1.48×1.48×3.0 mm with 23 axial slices (slice gap = 1.8 mm).

## Functional Connectivity Analysis

Preprocessing was performed as previously described ([Hahn et al., 2013](#)) using SPM8 ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)) with default parameters unless specified. Preprocessing included correction for slice-timing differences (reference=middle slice) and head motion (reference=mean image), normalization to Montreal Neurological Institute space using a scanner-specific EPI template, spatial smoothing with an isotropic Gaussian kernel of 9 mm FWHM. In addition to standard preprocessing, resting-state data were corrected as proposed in a previous study ([Weissenbacher et al., 2009](#)) and successfully used in other studies of our research laboratory (eg, [Hahn et al., 2011](#)). In short, linear regression was used to correct for changes in movement-related, ventricular, white matter, and global signals as well as physiological confounds (heart rate; blood pressure). Data were band-pass filtered with a 12-term finite impulse response filter ( $0.007 < f < 0.08$  Hz). Head motion was quantified from realignment parameters as framewise displacement ([Power et al., 2012](#)). Functional connectivity analysis was carried out by applying a seed-based approach ([Biswal et al., 1995](#)).

### Analysis 1: Functional Connectivity of the Thalamus Hub Network

To investigate overall connectivity changes of the thalamus during ketamine infusion, the thalamus hub network as defined by [Tomasi and Volkow \(2011\)](#) was used as seed region. To avoid seed selection bias ([Cole et al., 2010](#)) for the thalamus hub network, we used the averaged time courses of 4 seeds, namely the thalamus bilaterally ( $x/y/z=10,-10/-18/8$  mm MNI space), the cingulate cortex ( $x/y/z=0/12/38$  mm), and the lingual gyrus ( $x/y/z=0/-80/-1$  mm).

To evaluate the time course of the effect of ketamine on functional connectivity, the total time-period of ketamine infusion (20 minutes) plus the following 35 minutes were split in periods of 2.5 minutes, as previously proposed in pharmacofMRI ([McKie et al., 2005](#)). Spontaneous fluctuations in BOLD signal within these periods in the respective seed region were correlated voxel-wise with the entire brain. Here, the average time course across all 4 seeds (cubes of 3×3×3 voxel at each coordinate) was correlated with the entire brain. Correlation maps were converted to z-values using Fisher's r-to-z transformation to enable statistic comparisons across subjects.

### Analysis 2: Cortico-Thalamic Functional Connectivity

For the calculation of thalamo-cortical connectivity, the cortex was divided in nonoverlapping regions of interest, as previously proposed ([Behrens et al., 2003](#); [Zhou et al., 2007](#); [Woodward et al., 2012](#)). The prefrontal cortex, motor cortex/supplementary motor area, somatosensory cortex, temporal lobe, posterior parietal cortex, and occipital lobe were defined with the automated anatomical labeling atlas ([Tzourio-Mazoyer et al., 2002](#)) included in the MRICro software package (<http://www.sph.sc.edu/comd/rorden/mricro.html>). Similar to the assessment of the thalamus hub network, BOLD signal fluctuations of 2.5-minute blocks were correlated between respective seeds and the entire brain.

Correlation maps were converted to z-values, whereas statistical evaluation was focused on the thalamus.

### Statistical Analysis

Using repeated-measures ANOVA in SPM8, the interaction effect of time (ie, 2.5-minute periods of infusion vs baseline) and drug (ie, ketamine vs placebo) was evaluated for both the cortico-thalamic connectivity and the thalamus hub network analysis. Following an overall F-test, posthoc t tests were computed. Hence, for each 2.5-minute time period, the change from baseline during the ketamine condition was compared with the corresponding change from baseline in the placebo condition. Again, the baseline in each condition was given by a 5-minute resting-state period before the infusion. Statistical inference was drawn at  $P < .05$  corrected using the family wise error rate (FWE) at voxel level. Since for the cortico-thalamic connectivity we were only interested in subregions of the thalamus, small volume correction was applied using the thalamus of the anatomical labeling atlas as a mask ( $P < .05$  FWE-corrected voxel level).

### Blood Samples

As the collection of blood samples during MRI measurements may disturb participants as well as introduce changes in the magnetic field and thus signal fluctuations, ketamine levels were measured via HPLC and triple-quadrupole mass spectrometry on blood samples taken after the resting-state MRI scan, that is, 60, 75, 90, and 120 minutes after the end of the drug application on the descending part of the pharmacokinetic curve.

### Results

Descriptive data are summarized in Table 1. The mean dosage of intravenous ketamine was  $15.46 \pm 3.13$  mg, with mean ketamine plasma level of  $17.77 \pm 4.49$  ng/mL (10–27 ng/mL) 60 minutes after the end of the administration of ketamine. Compared with placebo, the infusion of ketamine led to a significant increase on the positive and negative syndrome scale (PANSS) and the Altered State of Consciousness Scale. There was no significant difference between the ketamine and placebo condition regarding movement during the MRI scan (ketamine mean  $\pm$  SD =  $0.12 \pm 0.06$  mm; placebo mean  $\pm$  SD =  $0.13 \pm 0.06$  mm;  $P = .57$  paired t test).

**Table 1.** Clinical Effects of Ketamine on Neuropsychological Parameters

Test	Placebo Scan	Ketamine Scan	P
<b>PANSS</b>			
Positive scale	7.2 $\pm$ 0.4	14.5 $\pm$ 4.7	<.001
Negative scale	7.3 $\pm$ 1.0	9.2 $\pm$ 2.9	.002
General scale	16.6 $\pm$ 1.5	30.4 $\pm$ 8.9	<.001
Overall score	31.1 $\pm$ 2.4	54.1 $\pm$ 14.6	<.001
<b>5D-ASC</b>			
Oceanic boundlessness	1.45 $\pm$ 3.3	84.26 $\pm$ 57.9	<.001
Anxious ego-dissolution	3.08 $\pm$ 5.6	40 $\pm$ 34.83	<.001
Visual reconstruction	0.6 $\pm$ 2.5	44.9 $\pm$ 33.9	<.001
Auditory alterations	1.63 $\pm$ 4.3	21.72 $\pm$ 18.8	<.001
Vigilance reduction	8.75 $\pm$ 12.8	40.33 $\pm$ 25.15	<.001

Abbreviations: 5D-ASC, Altered State of Consciousness Scale, PANSS, Positive and Negative Syndrome Scale.

P-values derived from a paired t test; mean values are indicated  $\pm$  SD; n = 30.

### Analysis 1: Ketamine Effects on the Thalamus Hub Network

The investigation of the thalamus hub network showed significantly higher functional connectivity within the network in the ketamine condition compared with placebo. The overall F-test of the interaction (levels: drug + placebo; 22 time points of 2.5 minutes) showed significant results with a maximum  $P_{[41,984]} = .001$  (FWE-corrected, voxel-level) for bilateral temporo-parietal areas. Posthoc t tests of the interaction drug\*time revealed a significant increase of connectivity 2.5 minutes after the start of the ketamine infusion in a bilateral cluster extending from the superior parietal lobule toward the temporal cortex, including the post- and precentral gyri. This cluster proved to be largely stable over the total time period of ketamine infusion as shown in Figure 1 and Table 2 (peak  $t = 6.51$ ). After the infusion, significant differences in temporal regions (peak  $t = 5.48$ ,  $P < .001$ , FWE-corrected) remained evident until 17.5 minutes after the end of the ketamine application with no significant results thereafter.

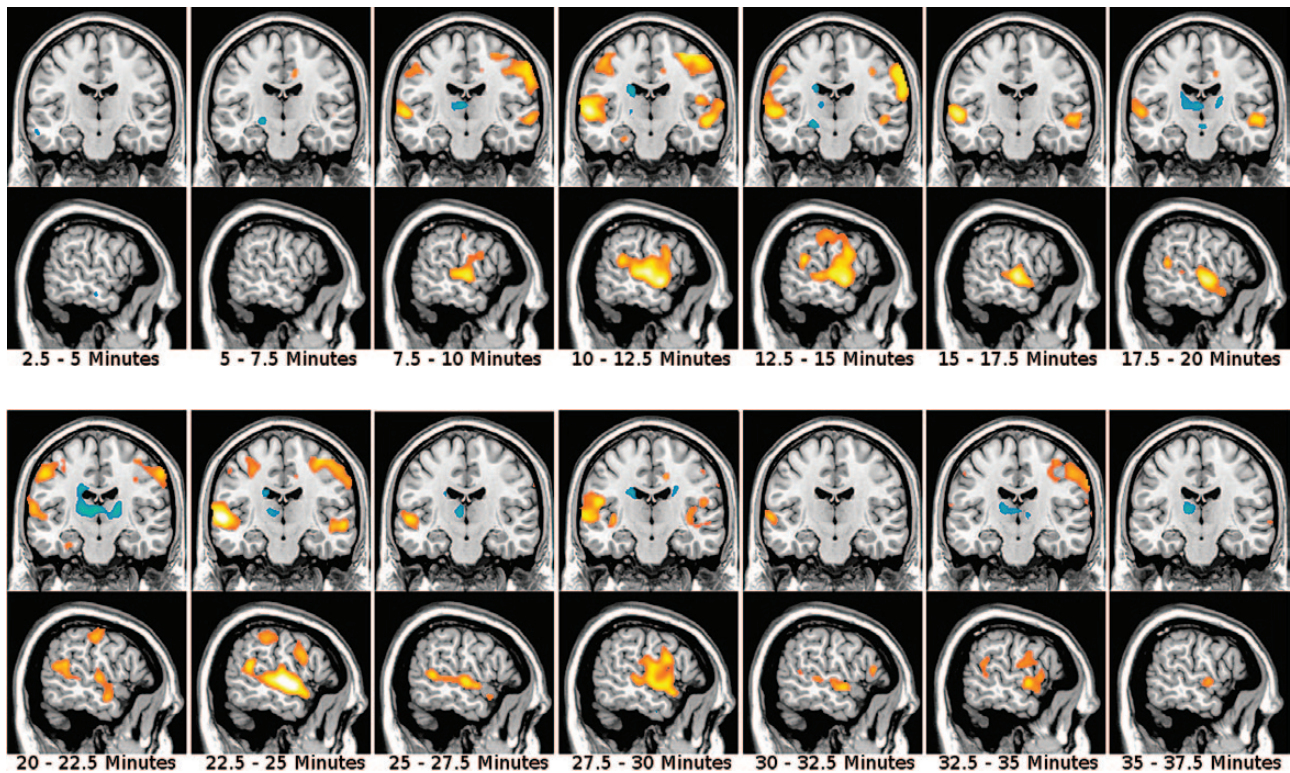
### Analysis 2: Ketamine Effects on Cortico-Thalamic Connectivity

Using the method recently published by Zhang et al. (2010) and Woodward et al. (2012), the dynamics of cortico-thalamic connectivity during and after ketamine infusion were investigated. First, baseline resting-state data before the application of ketamine were used to identify specific subregions of the thalamus; the results of our analysis turned out to largely overlap with findings reported previously using the same methodology (Zhang et al., 2008, 2010; Woodward et al., 2012). Functional connections of the somatosensory and motor seed regions were found to ventral-lateral and ventral posterior-lateral thalamic regions; the prefrontal cortex was functionally connected to anterior and dorsomedial regions of the thalamus. The temporal lobe and occipital cortex seed region were connected to anterolateral and dorsal medial thalamic subregions. The posterior parietal cortex was found to be connected to the lateral posterior nucleus and the pulvinar.

Comparing ketamine with placebo infusion showed significant differences in cortico-thalamic connectivity for 2 seed regions: the somatosensory and temporal cortices. A detailed description of the results is presented in Table 3 and Figure 2. No significant effect of ketamine compared with placebo was observed in the connectivity of the prefrontal, motor, posterior parietal, and occipital cortex.

For the somatosensory cortex, a significant increase in functional connectivity of the postcentral gyrus with the ventrolateral region of the thalamus was observed. The overall F-test showed significant results with a maximum  $P_{[41,984]} = <.001$  (FWE-corrected, voxel-level) for the thalamus. Posthoc t-values ranged between 3.50 and 4.69, all  $P < .05$ , FWE-corrected for the volume of the thalamus. According to the Oxford thalamic connectivity atlas, the increase was allocated mainly in the ventral anterior nucleus and ventral lateral nucleus.

The temporo-thalamic functional connectivity revealed a maximum  $P_{[41,984]} = <.001$  (FWE-corrected, voxel-level) for the thalamus. The posthoc analysis showed a ketamine-associated increase of the temporal seed region with the medial dorsal nucleus, ventral lateral, and ventral anterior nucleus. Again, differences between the ketamine and placebo scan were present shortly after start of the infusion, with t-values ranging from 3.45 to 4.58, all  $P < .05$ , FWE-corrected for the volume of the thalamus.



**Figure 1.** Ketamine effects on functional connectivity of the thalamus hub network (analysis 1). Each period of 2.5 minutes is depicted. Interaction effects drug\*time of posthoc t tests are displayed and data overlaid on a standard-MNI brain. Warm colors stand for increase of connectivity and cold colors for decreased connectivity, while color intensity refers to t-values (range  $t=3.09\dots 6$ ). A significant increase is shown in temporo-parietal regions throughout the ketamine application.  $x=-58\text{mm}$ ,  $y=-16\text{mm}$ .

## Discussion

Here, we show that the application of ketamine has a substantial impact on thalamic functioning in healthy volunteers, with 2 main findings. First, we demonstrate that the administration of a subanesthetic dose of ketamine leads to a significantly higher functional connectivity in the thalamus hub network consisting of motor, premotor, visual, auditory, and limbic regions and the cerebellum compared with placebo (analysis 1). Second, the investigation of specific cortico-thalamic connections revealed significant increases of the connectivity of the somatosensory cortex to ventrolateral and ventral anterior thalamic areas and the temporal cortex to mediodorsal and antero-ventral and -lateral thalamic areas (analysis 2).

The results of this study fit well into the context of theoretical concepts that propagate a significant impact of the glutamatergic system on key symptoms of schizophrenia, such as perturbation of perception. Accordingly, our study provides a more comprehensive understanding of the connection between the glutamatergic system and thalamic functioning. More specifically, we could show that the blockage of the NMDA receptor can cause functional alterations of thalamic connectivity in healthy volunteers similar to those reported for patients with schizophrenia.

A number of previous studies have investigated thalamic alterations in schizophrenia. These include differences in morphology such as significant changes of thalamic volume as well as disruption of functioning using neuroimaging techniques such as PET and fMRI (for review, see Sim et al. 2006). Importantly, nucleus-specific volume reductions, particularly in the mediodorsal and anterior nucleus and the pulvinar, have

been described, pointing toward a differential involvement of specific thalamic nuclei in schizophrenia. In accordance with these results, we found a specific strengthening of functional cortico-thalamic connectivity for the somatosensory and temporal seed regions but not for prefrontal, occipital, and parietal regions.

Significant effects of NMDA antagonist on thalamic nuclei and thalamo-cortical networks have also been reported in animal studies. Importantly, phencyclidine and acute ketamine administration were shown to provoke a significant alteration of the discharge rate of the centromedial and mediodorsal thalamic nucleus, which project to the medial prefrontal cortex and within the nucleus reuniens of the thalamus, respectively (Santana et al., 2011; Zhang et al., 2012) (for review, see Celada et al. 2013). Furthermore, another recently published animal study could show that phencyclidine leads to a significant reduction of the discharge rate of GABAergic interneurons in the reticular nucleus of the thalamus, leading to a disinhibition of thalamo-cortical activity (Troyano-Rodriguez et al., 2014). In accordance with the results of the present study, an [ $^{18}\text{F}$ ] FDG-PET investigation in unmedicated patients with schizophrenia revealed metabolic disconnectivity of the mediodorsal nucleus of the thalamus and medial temporal areas compared with healthy controls (Adolphs, 2003).

Recently, a general hyperconnectivity was described after intravenous application of ketamine in a group of healthy volunteers, which persisted for more than 45 minutes (Driesen et al., 2013). In line with the findings of this study, our study indicates that ketamine induces hyperconnectivity rather than reduction of connectivity both on a larger network level and on thalamus-specific connectivity.

**Table 2.** Differences of Functional Connectivity of the Thalamus Hub Network (Analysis 1) during and after Ketamine Infusion

Time	Anatomical Region (Anatomical Labeling Atlas)	MNI Coordinates			Statistic
		x	y	z	T-value
2.5–5 min	Calcarine L	-16	-80	4	-5.19
5–7.5 min	Anterior cingulate cortex L	-12	30	26	-5.16
	Gyrus postcentralis L	-48	-24	44	4.61
	Gyrus postcentralis R	64	-14	30	5.04
	Middle temporal gyrus L	-58	-14	0	5.36
7.5–10 min	Inferior occipital gyrus R	40	-86	-8	4.74
	Gyrus precentralis R	36	-14	60	5.09
	Superior temporal gyrus L	-58	-4	-6	5.55
10–12.5 min	Gyrus precentralis R	62	8	32	4.91
	Supramarginal gyrus R	64	-18	34	4.82
	Rolandic operculum R	48	4	14	4.74
	Superior temporal gyrus L	-58	-4	-4	5.71
12.5–15 min	Middle Temporal Gyrus L	-58	-14	0	4.87
	Middle Temporal Gyrus L	-56	-8	-8	5.79
15–17.5 min	Superior Temporal Pole L	-54	8	-18	4.68
	Superior Temporal Gyrus R	56	-8	0	4.75
17.5–20 min	Thalamus R	18	-16	8	-4.60
	Middle temporal pole R	56	14	-22	4.85
	Gyrus precentralis R	62	4	32	4.64
20–22.5 min	Superior temporal gyrus L	-58	-6	6	6.51
	Middle temporal pole R	54	10	-18	4.74
22.5–25 min	Middle temporal gyrus L	-56	-14	-2	4.61
	Superior temporal pole R	52	8	-12	5.19
25–27.5 min	Superior temporal gyrus L	-62	-2	-6	5.00
	Middle temporal gyrus L	-64	-28	4	4.96
	Rolandic operculum R	52	6	12	4.91
	Insula L	-40	-2	2	4.87
	Insula R	38	2	6	4.85
	Rolandic operculum L	-52	-16	16	4.74
27.5–30 min	Medial temporal pole R	58	10	-20	4.76
	Middle temporal gyrus R	46	-40	4	5.11
30–32.5 min	Supplementary motor area L	-8	0	56	4.92
	Middle temporal gyrus L	-58	-6	-6	5.48
35–37.5 min	Thalamus L	-10	-20	8	-4.84

Time points refer to the start of the ketamine application. All values are family wise error rate (FWE)-corrected at  $P < .05$  voxel-level.

Recently, [Woodward et al. \(2012\)](#) described differences of cortico-thalamic connectivity between patients with schizophrenia and healthy volunteers using resting-state fMRI. In this study, a significant increase of motor/somatosensory-thalamic connectivity along with a reduction of prefrontal-thalamic connectivity was shown ([Woodward et al., 2012](#)). Similarly, [Klingner et al. \(2013\)](#) reported a significant increase in thalamo-cortical connectivity in patients with schizophrenia compared with healthy controls, which was caused both by increased connectivity of the thalamus to prefrontal and superior temporal correlations and a relative lack of negative correlation of the thalamus to secondary sensory areas, somatosensory, visual, and auditory cortices.

Notably, results found with the ketamine model of psychosis in healthy volunteers seem to only partly overlap with results found in patients with schizophrenia. The finding of increased somatosensory-thalamic connectivity was evident both in studies in schizophrenia and under ketamine application. This result is also compatible with findings in patients with schizophrenia showing deficits in sensory and higher-order processing regions as measured with EEG ([Leitman et al., 2010](#)). In contrast, we could not replicate the finding of decreased prefrontal-thalamic connectivity. As this finding may be a highly relevant one, given

the vast number of evidence reporting deficits of top-down functional control of prefrontal areas in schizophrenia, this issue might be worth highlighting ([Lesh et al., 2011](#); [Tu et al., 2013](#)). The discrepancy might be based on the fact that disruption of functional connections in patients with schizophrenia is influenced by a number of endogenous disease-specific and treatment-associated molecular changes, whereas the present study included solely the modulation of the glutamatergic system. This difference could be further based on the smaller sample size of our study, as in the investigation by [Woodward et al. \(2012\)](#). Eighty patients were included, showing effect sizes of prefrontal-thalamic connectivity, which were clearly lower than for somatosensory regions.

The changes of connectivity within the thalamus network are also complementary to findings in patients with schizophrenia. In accordance with our results of a significant increase of connectivity to temporo-parietal regions, changes of the functional connectivity of the temporal lobe during resting state have been shown for patients suffering from a first episode of psychosis ([Alonso-Solís et al., 2012](#)) and patients with schizophrenia with chronic auditory verbal hallucinations ([Sommer et al., 2012](#)). Moreover, structural deviations of the superior, middle, and inferior temporal gyrus have been found in patients

**Table 3.** Ketamine-Induced Difference of Cortico-Thalamic Connections (Analysis 2)

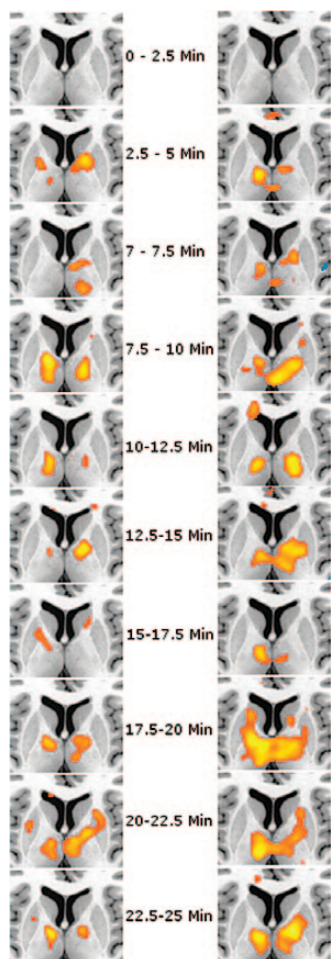
Cortico-Thalamic Connectivity					
Time, min	Anatomical Region (Oxford thalamic connectivity atlas)	MNI coordinates			Statistics
		x	y	z	T
<b>Somatosensory cortex seed</b>					
2.5–5	Ventral lateral nucleus	-10	-12	4	4.00
5–7.5	Ventral anterior nucleus	10	-4	4	4.11
	Pulvinar	18	-24	12	4.06
7.5–10	Medial dorsal nucleus	4	-16	10	3.58
	Ventral anterior nucleus	-12	-4	6	4.58
	Pulvinar	20	-26	14	4.21
10–12.5	Ventral lateral nucleus	16	-8	8	3.78
	Ventral lateral nucleus	-12	-8	10	3.99
12.5–15	Ventral anterior nucleus	12	-4	6	3.94
15–17.5	Ventral anterior nucleus	-12	-6	10	3.75
	Ventral lateral nucleus	14	-10	0	3.50
17.5–20	Ventral anterior nucleus	-14	-6	8	3.84
20–22.5	Ventral lateral nucleus	10	-6	2	3.66
22.5–25	Ventral anterior nucleus	-10	-6	8	4.57
	Ventral lateral nucleus	-16	-16	18	3.72
25–27.5	---	--	--	--	--
30–32.5	Medial dorsal nucleus	-10	-20	6	4.69
	Ventral anterior nucleus	-10	-6	6	4.04
	Ventral lateral nucleus	-14	-10	14	3.79
32.5–35	Pulvinar	-8	-30	4	3.61
35–37.5	Ventral anterior nucleus	-10	-6	10	3.89
	Medial dorsal nucleus	6	-14	10	3.52
37.5–40	Ventral anterior nucleus	-10	-6	8	3.95
	Medial dorsal nucleus	-10	-20	6	3.77
<b>Temporal gyrus seed</b>					
2.5–5	Medial dorsal nucleus	2	-18	8	3.64
	Ventral anterior nucleus	8	-8	12	4.37
	Ventral lateral nucleus	-14	-14	14	4.36
5–7.5	Ventral lateral nucleus	16	-14	14	4.16
7.5–10	Ventral anterior nucleus	-10	-6	8	3.86
	Medial dorsal nucleus	8	-18	4	3.75
10–12.5	Ventral lateral nucleus	-14	-14	6	4.20
12.5–15	Medial dorsal nucleus	10	-14	14	3.82
	Ventral anterior nucleus	10	-4	6	3.83
	Ventral lateral nucleus	8	-10	4	3.45
15–17.5	Medial dorsal nucleus	-8	-14	8	4.14
	Ventral lateral nucleus	12	-16	2	3.76
17.5–20	Medial dorsal nucleus	-8	-12	10	3.63
	Ventral lateral nucleus	20	-16	12	4.46
20–22.5	Medial dorsal nucleus	-10	-18	6	3.98
22.5–25	Medial dorsal nucleus	10	-18	6	3.72
	Ventral lateral nucleus	-10	-10	4	4.58
25–27.5	Ventral lateral nucleus	16	-8	8	3.90
27.5–30	Ventral lateral nucleus	-12	-8	6	4.16
30–32.5	Medial dorsal nucleus	6	-18	8	4.34

Only the 2 cortical seed regions (somatosensory and temporal) are shown. Time points refer to the start of ketamine infusion. All values are family wise error rate (FWE)-corrected at  $P < .05$  voxel-level after small volume correction for the thalamus.

with first-episode psychosis (Kasai et al., 2003). These alterations might partly account for psychosis-like symptoms, as the areas of significant changes found in our analysis cover both somatosensory cortex and temporal regions, including the primary and secondary auditory cortex. Furthermore, the superior temporal gyrus has been shown to be involved in perception of emotional facial stimuli and social cognition processes (Adolphs, 2003; Radua et al., 2010), and the middle and inferior temporal gyrus are thought to subserve functions such as language and

semantic memory processing, visual perception, and multi-modal sensory integration. Concerning the calcarine, which covers the primary visual cortex (V1), an absence of contextual modulation within V1 was detected in patients with schizophrenia. This disruption was hypothesized to affect local inhibitory mechanisms within V1 or feedback connections from higher areas as described by Seymour et al (2013).

The neurochemical mechanisms that link glutamatergic modulation via NMDA blockage and large-scale changes in

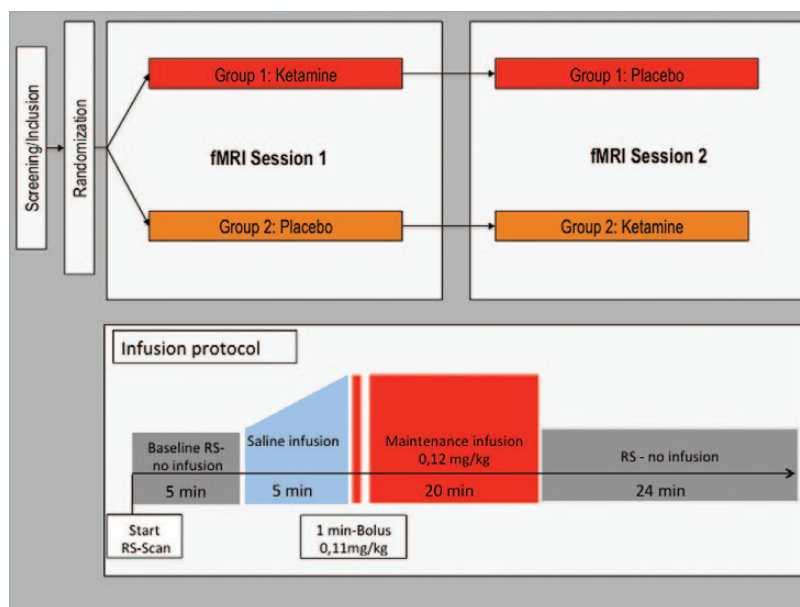


**Figure 2.** Ketamine-induced alterations of cortico-thalamic functional connectivity (analysis 2). Posthoc *t* tests of the interaction drug\*time show a significant increase of functional connectivity for the somatosensory (left row) and temporal cortex (right row). Other regions without significant results are not shown. Results of seed-to-voxel correlation analysis are overlaid onto a single-subject standard brain (range of *t*-values=3.09...6). Results are shown for each period of 2.5 minutes. *z*=7mm.

distinct cortico-thalamic networks are not fully understood. Our study reveals that the intravenous application of ketamine leads to an acute alteration of the thalamic network and cortico-thalamic connections within a few minutes, which is paralleled by profound clinical symptoms. Current models describing the modulation of the glutamatergic system propose that the blockage of NMDA receptors on GABAergic interneurons leads to a disinhibition of the activity of pyramidal cells, resulting in an increase of glutamate release within afferent and connected regions (Lorrain et al., 2003; Lopez-Gil et al., 2007). MRS studies directly investigating the impact of acute ketamine on glutamate in the brain have shown a significant increase of these glutamine and glutamate levels in the ACC (Rowland et al., 2005; Stone et al., 2012), although not all studies have shown positive results (Taylor et al., 2012). This increase of the glutamate level is thought to have a significant impact on the BOLD signal, as it is known that glutamate is decisively involved in neuronal activity in the cerebral cortex. In fact, modulation of the glutamatergic system, more specifically the NMDA and AMPA receptor, has been shown to have a significant impact on the BOLD signal in response to somatosensory modulation in an animal model (Gsell et al., 2006). However, imaging studies using MRS combined with fMRI paint a more complex picture of the connection between excitatory and inhibitory neurotransmitter systems with regard to the influence of the BOLD signal. It was thus hypothesized by Falkenberg et al. (2012) that glutamate might have a global effect on BOLD response, whereas GABA might have a more local impact (Falkenberg et al., 2012).

Aside from its role as a model for schizophrenia, ketamine has gained attention as a treatment for treatment-resistant depression. Although research in this scientific field has focused particularly on neuroplastic properties of ketamine (Li et al., 2010, 2011), the fact that depression significantly alters thalamic functioning as revealed by fMRI studies in depressed patients (Fu et al., 2004; Dichter et al., 2009; for review, see Hoflich et al., 2012) might point toward the relevance of the results gained in this study also in the context of depression.

A limitation of this study is the lack of direct comparison of results in patients with schizophrenia and changes seen in



**Figure 3.** Graphical representation of study design, resting-state fMRI protocol, and the application of the study drug.



healthy volunteers under ketamine infusion. Therefore, differences in scanning protocols and analysis techniques, which might influence the retrieved results, cannot be excluded and the comparison must rely on indirect information with regard to patients with schizophrenia. Further studies might overcome this limitation by using data gained within the same research infrastructure or by including both groups within one study.

Furthermore, it should be mentioned that ketamine has a relevant impact on a number of physiological parameters such as heart rate, respiratory rate, and blood pressure. As parameters such as heart rate variability were shown to have a significant effect on resting state functional connectivity (Chang et al., 2013), this data might have had an influence on the results retrieved in our analysis, although we tried to account for this fact by applying state-of-the-art preprocessing steps, as described earlier (see Methods).

Another issue is the fact that fMRI does not allow for a very accurate discrimination of thalamic nuclei. To relate the peak coordinates gained in the analysis with specific nuclei, MNI coordinates derived from a standardized atlas implemented in SPM were used. However, this approach does not account for potential individual differences in the thalamic area. To overcome this issue, future studies might additionally employ DTI to gain information about individual connections that can be included in the analysis.

In summary, the present study shows that findings of thalamic dysfunction can be partly mimicked by blockage of the NMDA receptor in healthy volunteers. These findings provide additional information on how the modulation of the glutamatergic system can lead to profound changes of perception and behavior, creating a psychosis-like state in healthy volunteers. According to its gating function for the integration of sensory, cognitive, and emotional information, the finding that thalamic functioning is disrupted gives an intuitive explanation for the loss of sensory filtering observed in these individuals.

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## Statement of Interest

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