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ORIGINAL INVESTIGATION

Increase in thalamic cerebral blood flow is associated with antidepressant effects of ketamine in major depressive disorder

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ABSTRACT

Ketamine is a promising treatment option for patients with Major Depressive Disorder (MDD) and has become an important research tool to investigate antidepressant mechanisms of action. However, imaging studies attempting to characterise ketamine's mechanism of action using blood oxygen level-dependent signal (BOLD) imaging have yielded inconsistent results- at least partly due to intrinsic properties of the BOLD contrast, which measures a complex signal related to neural activity. To circumvent the limitations associated with the BOLD signal, we used arterial spin labelling (ASL) as an unambiguous marker of neuronal activity-related changes in cerebral blood flow (CBF). We measured CBF in 21 MDD patients at baseline and 24 h after receiving a single intravenous infusion of subanesthetic ketamine and examined relationships with clinical outcomes. Our findings demonstrate that increase in thalamus perfusion 24 h after ketamine administration is associated with greater improvement of depressive symptoms. Furthermore, lower thalamus perfusion at baseline is associated both with larger increases in perfusion 24 h after ketamine administration and with stronger reduction of depressive symptoms. These findings indicate that ASL is not only a useful tool to broaden our understanding of ketamine's mechanism of action but might also have the potential to inform treatment decisions based on CBF-defined regional disruptions.

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Introduction

The NMDA receptor antagonist ketamine is not only a promising treatment option for patients with Major Depressive Disorder (MDD), but due to its rapid antidepressant properties, it has also become an important research tool to investigate antidepressant mechanisms of action *per se* (Coyle and Laws 2015). While it is well-known that ketamine exerts its antidepressant efficacy *via* glutamatergic modelling, the underlying response mechanisms are still not fully understood (Shin and Kim 2020). Several imaging studies attempting to characterise ketamine's mechanism of action using blood oxygen level-dependent (BOLD) imaging during resting state conditions or during emotional and cognitive tasks have yielded inconsistent results regarding implicated brain regions and direction of effects (Ionescu et al. 2018). Discrepancies regarding ketamine's effects on the brain may at least in part be due to intrinsic properties of the BOLD contrast, which measures a complex signal, which is indirectly related to neural activity (Ogawa et al. 1993; Detre and Wang 2002). In contrast, regional cerebral blood flow (rCBF) as measured with positron emission tomography (PET) or arterial spin labelling (ASL) MRI, is a single physiological marker reflecting metabolic activity which is more directly related to neuronal activity within a given region (Stewart et al. 2014). ASL exhibits a temporally stable and relatively straightforward signal to interpret and might thus be ideally suited to study the effects of ketamine (Wang et al. 2003; Borogovac and Asllani 2012). ASL (Detre and Alsop 1999) magnetically labels arterial blood water as an endogenous perfusion tracer allowing CBF to be determined without the use of contrast media.

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ASL uses RF pulses to magnetically invert arterial blood water (Alsop et al. 2015) proximal to the imaging slices which then travels into and subsequent exchanges with the tissue magnetisation. After subtraction with a control image without inverting inflowing blood water, cerebral blood flow values can be quantified. While ASL-derived perfusion has mainly been used to investigate cerebrovascular diseases, dementia, and neuro-oncological disorders, it is gaining traction in psychiatry and other fields of neuroscience as a widely used research tool (Cooper et al. 2019). Among the various MRI modalities, ASL actually has ideal prospects of being translated into a tool for clinical diagnostics and informing treatment decisions. The relatively short scan-time, capacity for automated processing, and direct, quantifiable physiological measure are all desired qualities of a biomarker. In combination with clinical symptom profiles, CBF-defined regional disruptions could thereby inform tailored antidepressant or therapy decisions. Accordingly, ASL has been demonstrated as sensitive for detecting relevant drug effects (Wang et al. 2011; Khalili-Mahani et al. 2015), and may thereby not only offer novel insights into ketamine's mechanism of action but also identify patients most likely to benefit from this treatment.

Earlier studies using ASL in MDD reported significantly lower CBF in frontal-, limbic-, and paralimbic areas, while CBF was increased in the subcallosal cingulate area, putamen, and fusiform gyrus (Ho et al. 2013; Ota et al. 2014) compared to healthy controls. Lui et al. (2009) and Järnum et al. (2011) reported differences between responders and non-responders to pharmacological treatment; with responders showing hypoperfusion mainly in limbic-striatal areas while non-responders manifested hypoperfusion in the left occipital lobe, bilateral frontal and bilateral thalamic regions, frontal lobes, and anterior cingulate cortex.

Previous studies investigating effects of ketamine on CBF in healthy volunteers consistently reported increases in prefrontal, orbitofrontal, and cingulate cortices (Holcomb et al. 2001, 2005) as well as subcortical regions including the thalamus, caudate, and putamen (Holcomb et al. 2005; Pollak et al. 2015; Shcherbinin et al. 2015; Bojesen et al. 2018; Bryant et al. 2019), but a decrease in CBF in the hippocampus (Pollak et al. 2015) and cerebellum (Holcomb et al. 2001). Perfusion increases measured with ASL following administration of ketamine are consistent with the reported increases in fluorodeoxyglucose uptake in similar areas, which suggests that changes in CBF reflect proximate effects of ketamine-induced changes in neuronal activity and thus in glucose and oxygen metabolism. This is supported by studies that indicate that ketamine does not disrupt neurovascular coupling (Långsjö et al. 2003, 2004).

To the best of our knowledge, so far only one study used ASL to investigate perfusion changes after ketamine treatment in MDD and reported increases in the posterior and mid cingulate, precuneus, cuneus, and visual association areas. Baseline perfusion in the fusiform cortex was related to symptom improvement after ketamine treatment (Sahib et al. 2020).

Using ASL imaging, in this study we measured CBF in MDD patients at baseline and 24 h after receiving a single infusion of subanesthetic ketamine and examined relationships with clinical outcomes.

Methods

Participants

In total 21 patients (12 females, age: $M = 43.62$, $SD = 12.17$) diagnosed with MDD were recruited at the Department of Psychiatry and Psychotherapy, Charité–Universitätsmedizin Berlin (CHAR), and at the Department of Psychiatry, Psychotherapy, and Psychosomatics, Psychiatric Hospital, University of Zurich (UZH). There were no restrictions regarding antidepressant medication at the time of enrolment, however, medication intake was documented. Exclusion criteria comprised lifetime antidepressant treatment with ketamine, lifetime recreational use of ketamine, cardiovascular diseases, such as hypertension, cardiac insufficiency or myocardial infarct in the past six months, insufficiently treated anaemia, hyper- or hypothyroidism, lifetime increased intracranial pressure or glaucoma, chronic physical diseases, in particular hepatorenal dysfunction, recent heart or head surgery, current pregnancy, as well as any relevant psychiatric or neurological comorbidity, in particular dementia, epileptic seizures, schizophrenia, psychosis, or post-traumatic stress disorder, substance abuse disorders, acute suicidality. Additional exclusion criteria regarding the scanning procedure were metallic body implants and claustrophobia. The study was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the Institutional Review Board of Charité–Universitätsmedizin Berlin and the Ethics Committee Zurich. All patients gave written informed consent before participation.

Study design

All participants underwent a baseline MRI scan before the ketamine infusion (2–24 h). After the baseline scan participants received an intravenous ketamine infusion (45 min) of either 0.5 mg/kg racemic ketamine (R/S, enantiomer ratio of 1:1, received at CHAR) or S-ketamine (0.25 mg/kg, Ketanest-S, received at UZH). The S(+)-isomer of ketamine is characterised by a 3–4 times higher affinity or potency at specific receptors so that a dose reduction of 50% compared to racemic ketamine is recommended (Sinner and Graf 2008). Although more studies applied racemic ketamine in previous studies, similar effect sizes have been reported for S-ketamine (Singh et al. 2016), and differences with respect to antidepressant mechanisms of action are unknown. At UZH, S-ketamine is used to treat depressed patients and racemic ketamine is used at CHAR. For this study, we decided not to change the clinical routine, and to investigate potential differences between substances as an exploratory endpoint. Since the antidepressant effect of ketamine is most prominent after one day (Zarate et al. 2006), the follow-up fMRI scans were scheduled 24 h after the ketamine infusion to assess the related effects on perfusion that might contribute to the understanding of its antidepressant efficacy.

Psychological assessment

Depression severity was assessed at baseline and 24 h after the ketamine infusion, using the Montgomery-Åsberg Depression Rating Scale (Montgomery and Åsberg 1979), and the Hamilton Rating Scale for Depression (Hamilton 1980). To achieve comparability between the two different rating scales, symptom improvement was calculated as percent-change from baseline for both scales: symptom improvement $=$ 100% $\times$ (baseline $-$ follow-up)/baseline.

Data acquisition and analyses

ASL data were acquired on a Siemens Trio 3 T with a 12-channel head coil (CHAR), and a Philips Achieva TX 3-T scanner (UZH). A high resolution 3-dimensional T1-weighted anatomical scan was obtained for structural reference at both scanning sites. The following parameters were used: TR $=$ 1.9 s, TE $=$ 2.52 ms, flip angle $=$ 9°, FOV 256 $\times$ 256 $\times$ 176 mm, voxel size $=$ 1 mm isotropic.

The first ASL dataset (CHAR) was acquired with the product PASL sequence (Siemens) which employed QUIPPS II (quantitative imaging of perfusion using a single subtraction, version 2), by using a thin slice TI_1, periodic saturation (Q2TIPS), and proximal inversion with control for off-resonance effects (PICORE) labelling scheme. The adiabatic inversion pulse used for labelling was planned as a 100 mm slab spaced 22.1 mm below the imaging volume, followed by inversion time delays TI1 700 ms (time between the inversion pulse and the beginning of periodic saturation pulses), TI1s 1600 ms (time between the inversion pulse and the end of periodic saturation pulses), TI2 1800 ms (time between the inversion pulse and acquisition of the first of 16 slices), 2 D multi-slice single-shot gradient-echo EPI readout with TR/TE 3000/13 ms, flip angle 90°, voxel size $3 \times 3 \times 5\,mm^3$, GRAPPA acceleration factor 2, 50 control-label pairs, and scan duration 05:14 min.

The second ASL dataset (UZH) was acquired with a custom pCASL sequence (Philips) which consisted of a pre-saturation pulse, pseudo-continuous inversion applied for a duration of 1650 ms, a post-label delay of 1525 ms in which 2 background suppression inversion pulses were applied at 1710 and 2860 ms, and a 2 D multi-slice single-shot gradient-echo EPI readout with a TR/TE 4120/14 ms, flip angle 90°, voxel size $3 \times 3 \times 6\,mm^3$, SENSE acceleration factor 2.5, 35 control-label pairs, and scan duration 04:56 min.

After a visual check of data quality for each individual scan, cerebral blood flow (CBF) was quantified (in units of ml/100 g/min) from pCASL as previously described (van Osch et al. 2009; Alsop et al. 2015). For PASL, CBF was quantified using the one-compartment model (Wang et al. 2003; Alsop et al. 2015):

$$CBF = 6000 \cdot \lambda \cdot \Delta M \cdot \exp(TI_2/T_{1a})/(2\alpha \cdot M_0 \cdot TI_1)$$

Where λ is the blood/tissue water partition coefficient, ΔM is the average difference in magnetisation between label and control images, α is the inversion efficiency, M_0 is the voxelwise equilibrium magnetisation value, obtained for each subject and each session TI_1 is 700 m, TI_2 is 1800 ms and increases incrementally by 35 ms per slice, and T_{1a} is 1650 ms. CBF was calculated in native space using an in-house written pipeline (LUMC) and FSL version 6.0.4 (FMRIB Software Library, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl) and included the following preprocessing steps: motion correction using McFlirt as implemented in FSL, brain extraction using BET, registration to the MNI152 template and smoothing using a Gaussian kernel of 6 mm FWHM.

Statistical analysis

Preprocessed images were analysed using MATLAB 2015b (The Mathworks Inc., Natick, MA, USA) and SPM12 (Statistical parametric mapping software, SPM;

Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). For each subject, the pre– and post-treatment images were used to calculate a contrast image (post–pre). These contrast images were used in a multiple regression model that included symptom improvement, calculated as percent change from baseline, as the main predictor of interest. Additionally, scanning site and whole-brain grey matter CBF were included as covariates in the model. Statistical thresholds were set to $p < 0.001$ (uncorrected) at the single voxel level and to $p < 0.05$ (FDR corrected) at the cluster level. However, because of the small sample size, uncorrected results are reported and marked as exploratory findings. For *post-hoc* testing and investigation of single-subject effects, ROI masks were calculated from the significant clusters in the whole brain regression analysis.

Results

Clinical results

In total, 91% of the patients (19/21) showed a reduction of depressive symptoms 24 h after the ketamine infusion. The mean symptom improvement was 29.81% (SD 19.77%). At CHAR, the mean symptom improvement was 27.52% (SD 18.88%), and at UZH the mean symptom improvement was 32.62% (SD 21.36%). The average symptom improvement did not differ between sites ($p = 0.54$). Eighty-one percent of the patients (17/21) took antidepressant medication. Demographic and clinical data including comparisons between study sites are shown in Table 1.

CBF results

The whole-brain multiple regression analysis revealed a significant relationship between symptom improvement and rCBF in the left thalamus ($p = 0.02$, FDR corrected, $k = 211$, MNI coord. = −12 − 32 12, see Figure 1(A)), i.e. increased thalamus perfusion 24 h after ketamine administration was associated with a greater reduction in symptom severity. Explorative correlation analyses for separate study sites revealed strong positive relationships for both sites (CHAR: $r = 0.76$, $p = 0.0067$; UZH: $r = 0.87$, $p = 0.0009$; see Figure 1(B)).

Table 1. Demographic and clinical data.

	Study site		
	CHAR ($N = 11$)	UZH ($N = 10$)	Group statistics
Age (*M*, *SD*)	45.0 ± 11.82	42.1 ± 12.99	$t(19) = 1.04$, $p = 0.54$
Sex (m/f)	6/5	6/4	$c^2(1, N = 21) = 0.06$, $p = 0.8$
Symptom improvement (%)	27.25 ± 18.88	33.66 ± 21.15	$t(19) = -0.73$, $p = 0.47$
Medication status* (med. free/on med.)	3/8	1/9	$c^2(1, N = 21) = 1.01$, $p = 0.31$

CHAR: Charité–Universitätsmedizin Berlin; UZH: University of Zürich

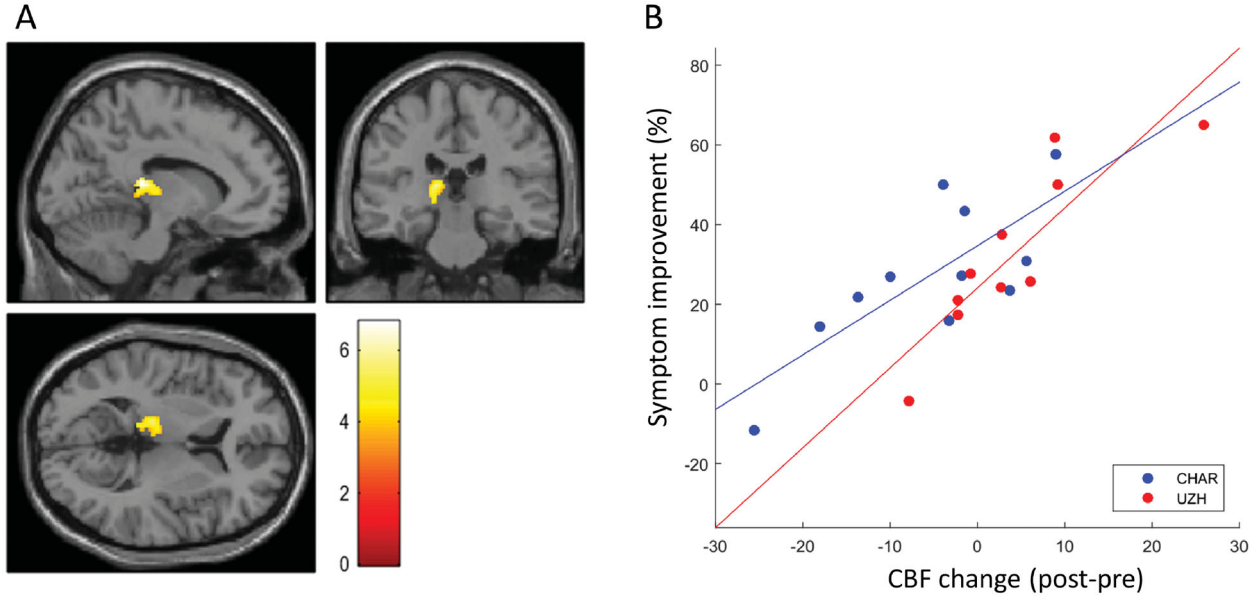

Figure 1. Perfusion changes linked to symptom improvement after ketamine. (A) Whole-brain multiple regression analysis revealed a single significant cluster in the left thalamus. (B) Single subject cerebral blood flow (CBF) changes (Δ-ml/min/100 g) in the observed left thalamus cluster and respective symptom improvement expressed as a percentage change relative to baseline. Subjects from the two study sites are marked in different colour.

Table 2. Brain regions showing perfusion changes after ketamine related to symptom reduction.

Region	Direction	Coordinates	Cluster size	*P* FDR	*P* uncorr.
Left thalamus	+	−12 −32 12	193	0.026	<0.001
Left PCC	+	−10 −50 10	57	ns.	0.031
Left insula	+	−44 −10 −10	54	ns.	0.035
Left precuneus	+	−8 −62 20	53	ns.	0.036
Right precuneus	+	16 −56 24	50	ns.	0.041
Right thalamus	+	8 −30 10	44	ns.	0.053

PCC: posterior cingulate cortex; + sign: positive relationship; ns.: not significant.

Additional brain regions that showed a significant ($p \leq 0.05$, uncorrected) relationship between symptom improvement and perfusion changes after ketamine were found in the left insula, right thalamus, and precuneus (see Table 2). Additional control analyses showed that the main finding in the left thalamus remained robust even when other covariates, such as age, sex, and medication were added (see Supplementary Table 1).

Post-hoc correlation analysis showed a significant negative relationship between perfusion in the left thalamus at baseline and perfusion changes after ketamine ($r = -0.55$; $p = 0.011$), with patients with lower baseline thalamus perfusion showing subsequent larger increases in perfusion. Furthermore, a significant negative relationship between perfusion in the left thalamus at baseline and reduction of depressive symptoms was observed ($r = -0.52$; $p = 0.016$). Patients with lower thalamus perfusion at baseline showed a stronger reduction of depressive symptoms.

Discussion

We used ASL to investigate CBF in MDD patients before and 24 h after receiving a single infusion of subanesthetic ketamine and examined relationships with clinical outcomes. Our findings demonstrate that increased thalamus perfusion 24 h after ketamine administration is associated with greater improvement of depressive symptoms. Furthermore, lower thalamus perfusion at baseline was associated both with larger increases in perfusion 24 h after ketamine administration and stronger reduction of depressive symptoms. At a more lenient statistical threshold, we also found relationships between symptom improvement and perfusion changes after ketamine in the insula and precuneus.

Currently, only a few neuroimaging studies have addressed how ketamine modulates brain function in relation to antidepressant response (Abdallah et al. 2017; Evans et al. 2018; Reed et al. 2018). Most of these studies have explored treatment effects using functional magnetic resonance imaging (fMRI) which is based on the BOLD signal. Though results suggest both discrete and network-related changes in brain activity, relationships with symptom improvement remain unclear, which may partly be due to the complex relationship between neural activity and BOLD signals (Ogawa et al. 1993; Detre and Wang 2002). As such, perfusion MRI demonstrated as sensitive for detecting effects of clinically effective drug doses (Wang et al. 2011; Khalili-Mahani et al. 2015), may broaden our understanding of brain systems-level antidepressant effects of ketamine. Furthermore, the quantifiable physiological measure, short scan-time, and capacity for automated processing might make ASL a useful tool for both clinical diagnostics and informing treatment decisions. Findings in healthy subjects reported increases in prefrontal, orbitofrontal, and cingulate cortices (Holcomb et al. 2001, 2005) as well as subcortical regions including the thalamus, caudate, and putamen (Holcomb et al. 2005; Pollak et al. 2015; Shcherbinin et al. 2015; Bojesen et al. 2018; Bryant et al. 2019), but a decrease in CBF in the hippocampus (Pollak et al. 2015) and cerebellum (Holcomb et al. 2001). To our knowledge, there is currently only one ASL-based study (Sahib et al. 2020) examining the effects of ketamine treatment in MDD, which reported a significant increase of CBF in the posterior cingulate, precuneus, cuneus, and visual association areas after ketamine infusion.

It has been shown that administration of ketamine results in a surge of glutamate (Milak et al. 2016; Chowdhury et al. 2017) as well as in immediate effects on CBF, which diminish and then remain relatively static in the hours after ketamine infusion (Khalili-Mahani et al. 2015). CBF presents a quantitative index of brain hemodynamics and is related to oxygen and glucose metabolism and therefore neurofunction (Stewart et al. 2014). Our results show that changes in CBF are observable 24 h after treatment and thereby demonstrate that metabolic changes occur beyond the immediate effects of ketamine on glutamate signalling.

Our main finding concerns the association between increased thalamus perfusion and symptom improvement 24 h after ketamine administration. Along that line, lower thalamus perfusion at baseline was associated both with larger increases in perfusion 24 h after ketamine administration and stronger reduction of depressive symptoms. The thalamus is involved in the regulation of synchronous cortical activity and in relaying sensory information by interacting with subcortical

and cortical areas (Guillery 1995; Saalmann and Kastner 2011). It has been proposed that symptoms of MDD are associated with dysfunction of cortico-striatal-pallidal-thalamic brain circuits (Pizzagalli 2011). These circuits connect regions of the prefrontal cortex and the anterior cingulate cortex with the basal ganglia and thalamus in a highly organised and integrated manner to support diverse motor, cognitive and emotional processes (Haber and Calzavara 2009). Preclinical animal models of depression consequently linked a defective thalamocortical circuit to depression (Li et al. 2013; Delevich et al. 2015). Along that line, Nugent et al. (2019) reported that tracts connecting corticolimbic areas with the thalamus are dysfunctional and show reduced fractional anisotropy in MDD patients. Both decreased perfusion and functional abnormalities of the thalamus have previously been demonstrated in MDD and linked to biased valence processing of emotional stimuli (Diener et al. 2012; Cooper et al. 2020). Accordingly, successful antidepressant therapy was shown to increase perfusion and metabolism as well as response to positive emotions in the thalamus (Fregni et al. 2006; Delaveau et al. 2011; Ma 2015). Also, responders to antidepressant therapy undergo extensive enhancement of connectivity in the thalamus (Riva-Posse et al. 2014; Evans et al. 2018). In rodents, NMDA receptor (NMDA-R) blockade in the thalamus affects thalamocortical communication (Bygrave et al. 2019) and data from animal models indicate that ketamine reduces GABA levels by acting on NMDA-R interneurons (Grasshoff et al. 2005). GABA release reduction might then lead to the increased firing rate of thalamic relay neurons and activation of thalamo-cortical circuits, which could trigger a widespread shift in excitability levels (Ferrarelli and Tononi 2011). This evidence is consistent with preclinical findings of thalamic-driven changes of connectivity patterns following acute ketamine administration (Kim et al. 2012; Dawson et al. 2013). Also, studies in healthy volunteers reported enhanced thalamic activity as well as increased connectivity of cortico-thalamic pathways originating from the somatosensory cortex (De Simoni et al. 2013; Höflich et al. 2015, 2017; Joules et al. 2015; Downey et al. 2016; Maltbie et al. 2016). As the thalamus is an integral part of perceptual networks in both visual and somatosensory modalities, the CBF changes observed in our study might be related to perceptual distortions induced by ketamine. Both preclinical data and EEG studies in healthy volunteers indicate that ketamine can elicit a 'hyper-attentional' state, during which the thalamus becomes hyperactive and excessive network gamma noise would interfere with incoming sensory information (Pinault 2008; Rivolta et al. 2015; Anderson et al. 2017; Furth et al. 2017). It has been hypothesised that the increase in thalamo-cortical activity might be associated with the rapid psychotomimetic action of ketamine. Subsequently, these acute effects might then trigger a cascade of events involving increased synaptogenesis and could ultimately lead to the persistent antidepressant effects of ketamine (Amat-Foraster et al. 2019; Tarrés-Gatius et al. 2020; but see also Miller et al. 2016). The increased perfusion values observed here in the thalamus are consistent with increased relative cerebral blood volume and glucose metabolism observed in animal models following acute ketamine challenge (Duncan et al. 1999; Gozzi et al. 2008). Also, corresponding to our finding of an association between lower thalamus perfusion at baseline with stronger reduction of depressive symptoms, Lui et al. (2009) reported that MDD patients who did not respond to pharmacological treatment with SSRIs showed hypoperfusion in thalamic regions.

At a more lenient statistical threshold, our data also demonstrate relationships between symptom improvement and perfusion increases after ketamine in the insula and precuneus, corresponding to prior studies reporting decreased CBF in these regions in acute MDD (Lui et al. 2009; Cooper et al. 2020; Sahib et al. 2020). The insula plays an important role in MDD pathophysiology (McGrath et al. 2013) and is involved in interoceptive error detection, such as signalling a discrepancy between actual and desired somatic states and triggering an increase in anxious affect, worrisome thoughts, and other avoidance behaviours (Paulus and Stein 2006). In MDD, patients show increased insula reactivity to negative stimuli and a previous resting-state fMRI study implicates the insula in switching between states of the relative dominance of the default mode network (DMN) and cognitive control network (TPN) (Hamilton et al. 2011). Furthermore, the insula plays a central role in attention to interoceptive states (Critchley et al. 2004; Menon and Uddin 2010), and increased interoceptive awareness might be considered a facet of increased self-focus in MDD and reflect the patients' inability to shift the focus of perception/awareness from the own body to the environment (Wiebking et al. 2011). In healthy volunteers, ketamine increases neural activation in the insula, while in MDD patients increased global connectivity in the insula was associated with ketamine's antidepressant effects (Höflich et al. 2015, 2017; Abdallah et al. 2017). Further, prior research suggests that insula activity predicts response to standard antidepressant treatments (Dunlop et al. 2015).

The precuneus and the posterior cingulate cortex (PCC) are key nodes of the default-mode network (DMN) and frequently show altered functional connectivity in depression (Cheng et al. 2018). Specific symptoms of depression, such as maladaptive self-focus, rumination, and impaired cognitive control have been linked to DMN dysregulation (Sheline et al. 2010). Changes in perfusion in DMN nodes may thus also contribute to the acute therapeutic effects of ketamine. Even though resting-state fMRI measures different aspects of functional plasticity, their findings are compatible with our results. Specifically, a single dose of ketamine has been associated with a normalisation of functional connectivity between the DMN and insula (Evans et al. 2018).

There are several limitations to this study.

Compared to other functional imaging approaches ASL is relatively new in the field of psychiatry (Wang et al. 2011), therefore, there is hardly any clinically relevant data with which to compare our data. Our study sample was rather small, and results will benefit from further replication in larger studies. Furthermore, considering the ongoing debate on antidepressant placebo outcomes (Holper 2020), the lack of a placebo group in our study might imply that the reported perfusion changes predicted spontaneous improvement and are not directly linked to the effects of ketamine. However, as our primary aim was to link an imaging biomarker to symptom improvement after ketamine treatment, we argue that conclusions can be drawn from our analyses without a placebo condition. Due to the rapid improvement of depressive symptoms 24 h after ketamine in severely depressed patients, it can be reasonably assumed that corresponding brain changes can be linked to the effects of ketamine. It should be taken into account that the reported data comes from two study sites and that the procedures at both sites were slightly different, with patients at UZH receiving S-ketamine and imaged with pCASL and at CHAR racemic ketamine and imaged with PASL. Racemic ketamine is the mixture of the enantiomers R-ketamine and S-ketamine. From a clinical point of view, the S isomer causes more psychotomimetic reactions than the R isomer, which is more strongly associated with feelings of relaxation (Vollenweider et al. 1997; Zanos et al. 2018). However, consistent with our results, racemic ketamine and esketamine were shown to have similar antidepressant efficacy (Correia-Melo et al. 2020). However, S- and R-ketamine are associated with different patterns of metabolic activity in humans and animals (Vollenweider et al. 1997; Masaki et al. 2019) and even though we included site as a covariate in our analyses, further studies are needed to investigate if S- and R-ketamine enantiomers perturb distinct neural circuits and thereby affect diverse functional dimensions of relevance to depression. Although PASL and pCASL are known to result in different CBF-values and patterns (Gevers et al. 2011), the main aim of this study focussed on *changes* in CBF upon ketamine administration and how these relate to changes in symptoms, i.e. an inter-subject measurement for which differences in acquisition protocol can be expected to be less important. The main difference will most probably be a difference in sensitivity to detect local changes with pCASL known to have higher SNR than PASL (Alsop et al. 2015). This might have impacted our overall statistical power. Considering the above-mentioned limitations, our investigation might be considered a pilot study on the utility of ASL for investigating the mode of action of ketamine.

To conclude, the current study shows that increased thalamus perfusion 24 h after ketamine administration is associated with greater improvement of depressive symptoms. Since changes in CBF are present 24 h after treatment, our findings indicate that these effects are a consequence of neurofunctional plasticity. Our results thereby demonstrate that ASL is not only a useful tool to broaden our understanding of ketamine's mechanism of action but might also have the potential to inform treatment decisions based on CBF-defined regional disruptions.

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Statement of interest

The authors declare no conflict of interest.

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