# Ketamine reduces the neural distinction between self- and other-produced affective touch - a randomized double-blind placebo-controlled study

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**Abstract**

A coherent sense of self is crucial for social functioning and mental health. The N-methyl-D-aspartate antagonist ketamine induces short-term dissociative experiences and has therefore been used to model an altered state of self-perception. This randomized double-blind placebo-controlled within-subject study investigated the mechanisms for ketamine's effects on the bodily sense of self in the context of affective touch. Participants received intravenous ketamine while performing self-touch and receiving touch by someone else during functional MRI – a previously established neural measure of tactile self-other-differentiation. Afterwards, tactile detection thresholds during self- and other-touch were assessed, as well as dissociative states, interoceptive awareness, and social touch attitudes. Compared to placebo, ketamine administration elicited dissociation and reduced neural activity associated with self-other-differentiation in the right temporoparietal cortex. This reduction correlated with ketamine-induced reductions in interoceptive awareness. The temporoparietal cortex showed higher connectivity to somatosensory cortex and insula during other- compared to self-touch. This difference was augmented by ketamine, and correlated with dissociation strength for somatosensory cortex. These results demonstrate that disrupting the self-experience through ketamine administration affects neural activity associated with self-other-differentiation in a region involved in touch perception and social cognition. This process may be driven by ketamine-induced effects on top-down signaling, rendering the processing of predictable self-generated and unpredictable other-generated touch more similar. These findings provide further evidence for the intricate relationship of the bodily self with the tactile sense.

## Introduction

Our sense of self is crucial for our wellbeing and social interactions. Self-related disturbances can be found in several psychiatric conditions, including schizophrenia (Gallagher, 2000). Ketamine offers a pharmacological model for an altered state of self-perception as it induces short-term dissociative experiences. Here, we investigated the effects of ketamine on self-other-distinction and its neural underpinnings in the context of affective touch, using functional MRI and psychophysical measures.

The profound and multifaceted experience of selfhood is widely considered to be anchored in bodily self-awareness (Blanke, 2012). A coherent bodily self relies on the multimodal integration of sensory information, including interoceptive and proprioceptive signals from within our body (Craig, 2009; Seth & Tsakiris, 2018). The sense of touch plays a crucial role in forming and maintaining this bodily self (Serino & Haggard, 2010). From early life on, touch enables us to experience bodily self-boundaries (Ciaunica et al., 2021). These experiences are often social in nature and involve affective touch, for example when a baby perceives caressing touch from a parent (Tuulari et al., 2019). Affective touch, which is typically slow in speed and perceived as pleasant, typically involves C-tactile (CT) afferents peripherally (Löken et al., 2009) and affect-related cortical areas such as the insula centrally (Morrison et al., 2010). Interestingly, the insula is known to be involved in processing interoceptive signals, i.e. sensations from within our own body (Craig, 2002). Following these observations, the CT-system has been suggested to be concerned with the establishment and maintenance of the bodily self (McGlone et al., 2014). Cortical processing of CT-mediated signals seems to differentiate between self- and non-self- generated sensations, further supporting the notion of a critical role for the social other in maintaining a functional bodily self: Activation across a broad range of regions involved in somatosensation and socio-affective processing is attenuated during self-produced touch compared to affective touch from others (Boehme et al., 2019). This raises the question: does the somatosensory system play a role in self-related dysfunctions?

Disturbances related to the sense of self can be found across several psychiatric disorders, e.g. in schizophrenia, dissociative disorders, and anorexia (Northoff & Heinzel, 2003), and "Perceptions and understanding of self" has been included as a transdiagnostic Research Domain Criteria dimension (Insel, 2014; Sui & Gu, 2017). Such disturbances severely impact well-being and mental health: self-disorders correlate with impaired social functioning and suicidality (Henriksen et al., 2021). Self-related dysfunctions are rarely addressed in currently available therapies, and they often persist even when other symptoms improve. This might be in part due to the complexity of self-related dysfunction and its co-occurrence with other symptoms.

The N-methyl-D-aspartate (NMDA) receptor antagonist ketamine is a dissociative anesthetic drug, clinically used in anesthesia and in lower doses in the treatment of depression (Popova et al., 2019; Zarate et al., 2006) and chronic pain (Niesters et al., 2014; Rogachov et al., 2019). It has been suggested as a pharmacological model of self-related functional alterations, since it produces a state that resembles aspects of endogenous psychoses (Corlett et al., 2007, 2016; Krystal et al., 1994). For example, ketamine administration in healthy individuals is associated with an aberrant experience of agency (Moore et al., 2011) and increased illusory body ownership (Morgan et al., 2010). If a coherent sense of self and bodily self-other-distinction are intertwined, a reduced self-other-distinction is expected in the dissociated state elicited by ketamine. However, it remains unknown if ketamine administration alters tactile self-other-distinction, and if so, through which neural mechanisms.

In this randomized double-blind placebo-controlled within-subject study, participants received intravenous ketamine during functional MRI, while experiencing self- or other-produced affective touch on the forearm (Figure 1). Affective touch is operationalized as slow and gentle touch which is generally perceived as pleasant (Croy et al., 2021). Moreover, dissociative states were assessed, and a psychophysical task was employed to determine tactile detection thresholds during self- and other-touch. Our preregistered hypotheses were that

ketamine reduces the distinction of self- and non-self-generated touch. Specifically, we hypothesized that differences in neural signatures of self-touch and other-touch (Boehme et al., 2019) are smaller under ketamine than under placebo, as we have previously shown that regions involved in somatosensation and socio-affective processing differentiate between other-touch and self-touch (Boehme et al., 2019). We now predicted that these regions would differentiate less during the ketamine session when participants are expected to have dissociative experiences. Moreover, we predicted that tactile detection thresholds during self-touch are lower under ketamine, in line with notions of reduced attenuation of self-produced sensations in self-disorders (Blakemore et al., 2000; Lemaitre et al., 2016). We further expected these changes to relate to measures of interoception and of attitudes towards social touch.

## Materials and Methods

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Swedish Ethical Review Authority (2020-06515) and the Swedish medical products agency. The study protocol is registered in clinical trials database EudraCT (2020-004487-25). The analysis plan was preregistered on the Open Science Framework before unblinding (https://osf.io/grud4).

### Participants

After a pre-screening during the initial phone contact, 34 potential participants were screened, of whom 31 were included. One participant dropped out during the second MRI session (visit 4), due to nausea. A total of 30 participants (15 females, 15 males, mean age: 24.8 years, age range 19-39) completed the study. This sample size is preregistered and based on a power calculation for a two-phase cross-over comparison with 80% power to detect an effect size of Cohen's $D \geq 0.6$ at alpha$=0.05$, i.e., a medium - large effect size. Exclusion criteria included: any clinically significant medical condition, any current clinically significant psychiatric problems including a diagnosis of substance dependence, history of psychotic experiences, familial history (first and second degree relatives) of psychosis or alcohol use disorder, known hypersensitivity to ketamine, use of central nervous system active medications, inability to provide a negative drug screen test, pregnancy or breastfeeding and contraindications for MRI. Participants received 1500 Swedish kronor (approximately $150) as reimbursement. All participants provided written consent before study participation.

### Procedure

The study has a within-subject, cross-over, double-blind, randomized placebo-controlled design. The study consisted of four sessions: (1) a screening visit; (2) a baseline visit including informed consent, questionnaires (social touch questionnaire (STQ) (Wilhelm et al., 2001),

autism spectrum quotient (AQ) (Baron-cohen et al., 2001), multidimensional assessment of interoceptive awareness (MAIA) (Mehling et al., 2012)), and a heartbeat detection task; and two (3 & 4) ketamine/placebo administration sessions including functional MRI (self-other-touch task), interview of dissociative experiences (Clinician-Administered Dissociative States Scale (CADSS), psychophysics (tactile threshold task) and the aforementioned questionnaires. Participants were randomized 1:1 to either of two groups which received ketamine (Ketamin Abcur 10 mg/ml, dosage 0.5 mg/kg body weight during a 40 min i.v. infusion without bolus) on either the first or second MRI session. During the other MRI session, participants received placebo (standard saline infusion). Randomization was stratified by sex. To optimize blinding, participants were informed that they may receive placebo or ketamine in any or both sessions, and that the dosage may differ between sessions. They also received basic information about the potential side-effects of ketamine, including dissociative symptoms. See supplement for a detailed description of each session and the analysis of questionnaire data.

**Experimental tasks**

*Self-other-touch paradigm*

Participants performed the previously established self-other-touch paradigm (Figure 1) (Boehme et al., 2019; Frost-Karlsson et al., 2022). The task has a randomized block design and consists of three different conditions: stroking of the own left forearm (self-touch), being stroked by the experimenter (other-touch) or stroking a pillow (object-touch). To allow for stroking movements within the scanner, the left forearm was placed on the participant's belly. For the object-touch condition, a small, sand-filled, rectangular pillow with a soft, skin-like surface was placed right above the left forearm. Participants were instructed to stroke gently, as they would touch someone they like, with their right hand. They received textual instructions regarding the upcoming block on a screen viewed through MR-compatible goggles (VisuaStim Digital; Resonance Technologies). The instructions were presented in Swedish for 3 s: "Active,

please stroke your arm"; "Active, please stroke the object"; "Passive, your arm will be stroked by the experimenter." When the text turned from white to green, the participant was stimulated or had to perform the stimulation for as long as the text was on the screen (12 s). The female experimenter performing the strokes stood next to the scanner bore and received auditory cues on the timing of the other-touch condition via headphones. During this condition the experimenter mimicked the motion and touched area of the participants as closely as possible. Each of the three conditions occurred 10 times and consisted of stimulation for 12 s followed by 12 s rest, resulting in a total duration of 13.5 min (Figure 1).

*Touch threshold task*

A previously described procedure for the touch threshold task was followed (Boehme et al., 2019), using von-Frey monofilaments (Bioseb) of increasing thickness and the same three different touch conditions as during the MRI session. See supplement for a full description of the procedure and the analysis.

**Functional MRI Analysis**

See supplement for a detailed description of the MRI acquisition protocol and preprocessing steps. Statistical analyses were performed using the general linear model approach (SPM12). At the first-level (single-subject level), regressors of interest were the blocks of stimulation (self-touch, other-touch, and object-touch). Regressors of no interest were added for the cue phase (separately for each block) and arm movements after each active block (self-touch and object-touch; duration: 1 sec), when subjects put their arm back into a resting position. To account for movement associated variance, realignment parameters and their first temporal derivates were included as regressors of no interest, as well as a regressor censoring scans with more than 1 mm scan-to-scan movement. Contrast maps were generated for the other-touch vs. self-touch condition, as well as the self-touch vs. object-touch condition.

Movement-corrected contrast maps were generated by contrasting other-touch vs. [self-touch minus object-touch].

At the second-level, a paired samples t-test was used to quantify ketamine vs. placebo effects on other-touch vs. (movement-controlled) self-touch contrast maps. For whole-brain analyses. results were corrected for multiple comparisons using the family-wise error (FWE) correction based on Gaussian random field theory at the voxel-level (as implemented in SPM and shown to be valid (Eklund et al., 2016)). In addition, within four a-priori (and preregistered) regions of interest (anatomically defined), a small volume correction (SVC) was used: right posterior superior temporal gyrus, right insula, right anterior cingulate cortex, and right postcentral cortex (functionally known as primary somatosensory cortex).

Initial analyses of a treatment (ketamine vs. placebo) effect on activation differences for self vs. other touch revealed significant voxels showing reduced activation in the cerebellum (See supplementary data). Control analyses showed the same effect of ketamine on activation differences for object-touch vs. other-touch, indicating that the cerebellar activation differences related to the arm movements (inherent to the self-touch and object-touch conditions), rather than touch sensations. We anticipated this issue in our preregistered analysis plan, so we used a movement-controlled analysis in the remainder of our analysis, in line with previous work (Frost-Karlsson et al., 2022). For this analysis, object-touch contrast maps were subtracted from the self-touch contrast maps. Crucially, control analyses showed that ketamine did not modulate differences between self- and object-touch ((1) paired-sample t-test on self-object contrast maps for ketamine vs. placebo; (2) paired-sample t-test on object-self contrast maps for ketamine vs. placebo; no significant voxels on the whole-brain FWE-corrected level). See supplement for a description of the follow-up generalized psycho-physiological interaction (gPPI) analysis (McLaren et al., 2012).

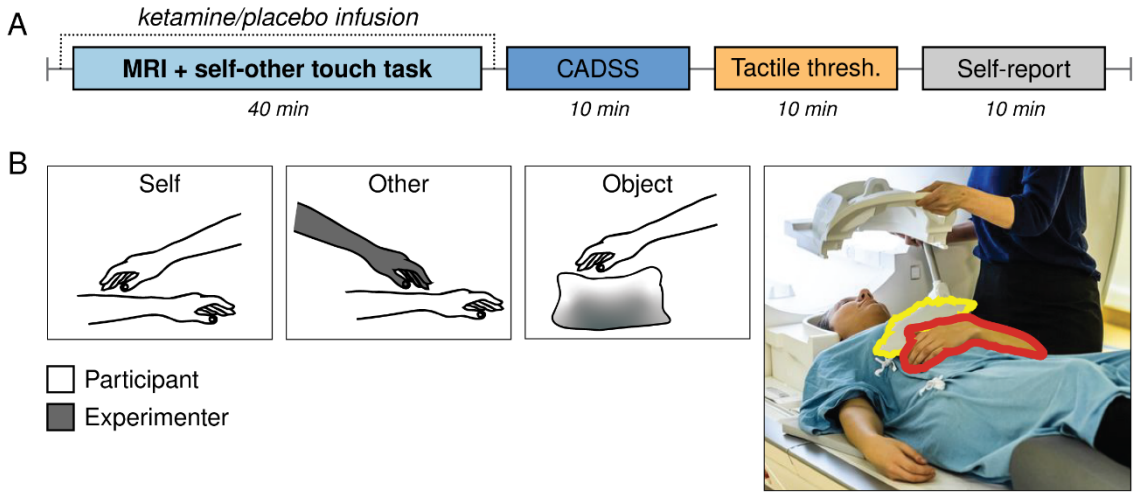


**Figure 1. Experiment overview. A.** Timeline of the drug administration sessions. CADSS = clinician administered dissociative state scale. **B.** Self-other-touch paradigm(Boehme et al., 2019). The position of the touched arm (red) and object (yellow) during the MRI session.

## Results

### Ketamine induces a dissociative state

Participants indicated a significantly higher dissociative state after receiving ketamine compared to placebo (range increase 1-39 points, $t(29)=9.81$, $p<.001$, Cohen's $d=1.79$, Figure 2). See figure S2 for difference scores on individual items and distribution across participants.

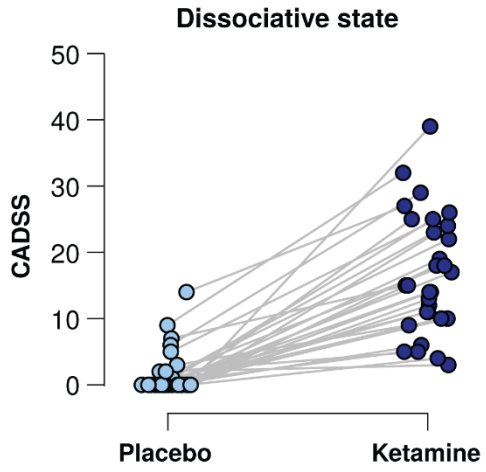


**Figure 2. Ketamine administration induces a dissociative state.** Dissociative states determined by a clinical interview (clinician administered dissociative state scale, CADSS) were higher for all participants during the ketamine session compared to the placebo session

### Ketamine is associated with reduced neural distinction of self- versus other-generated touch sensations

Stronger activation for other-touch compared to self-touch during the placebo session was found in right postcentral gyrus (S1) and bilateral posterior superior temporal gyrus (pSTG)/parietal operculum, among other regions, replicating previous findings (Boehme et al., 2019). See figure 2A and table S1. During the ketamine session, a similar pattern was found, i.e. higher S1 and bilateral pSTG activation for other- vs. self-touch (Figure2B and table S2).

Comparing ketamine and placebo directly revealed that the difference in right temporo-parietal cortex (rTPC) activation for other- vs. self-produced affective touch was reduced when

participants received ketamine (interaction between treatment (placebo vs. ketamine) and condition (other-touch vs. self-touch): $p_{FWE(whole\ brain)}$=.012, $MNI_{xyz}$=58,-32,22; Figure 2C; see figure 2C for an illustration of the nature of the interaction). The peak of this interaction effect was located on the border between the parietal operculum (or S2), pSTG, and supramarginal gyrus (SMG), and the expanded dorsally towards the anterior temporoparietal junction and ventromedially towards the posterior insula. This interaction effect overlapped with two preregistered volumes of interest (Figure 2E): the STG (SVC $p_{FWE}$<.001, $MNI_{xyz}$=58,-32,22) and the border of S1 (SVC $p_{FWE}$=.032, $MNI_{xyz}$=62,-16,22). No suprathreshold voxels were found in the right ACC and right insula. See supplement for an exploratory task-based functional connectivity analysis using the rTPC as a seed region.

In sum, during ketamine administration, the neural distinction between self- and other-produced affective touch was preserved but attenuated in the right temporoparietal cortex, rendering the neural signal during other-touch more similar to the neural signal during self-touch (Figure 2CD). Hereafter, this interaction effect is referred to as “reduction in temporoparietal distinction”.

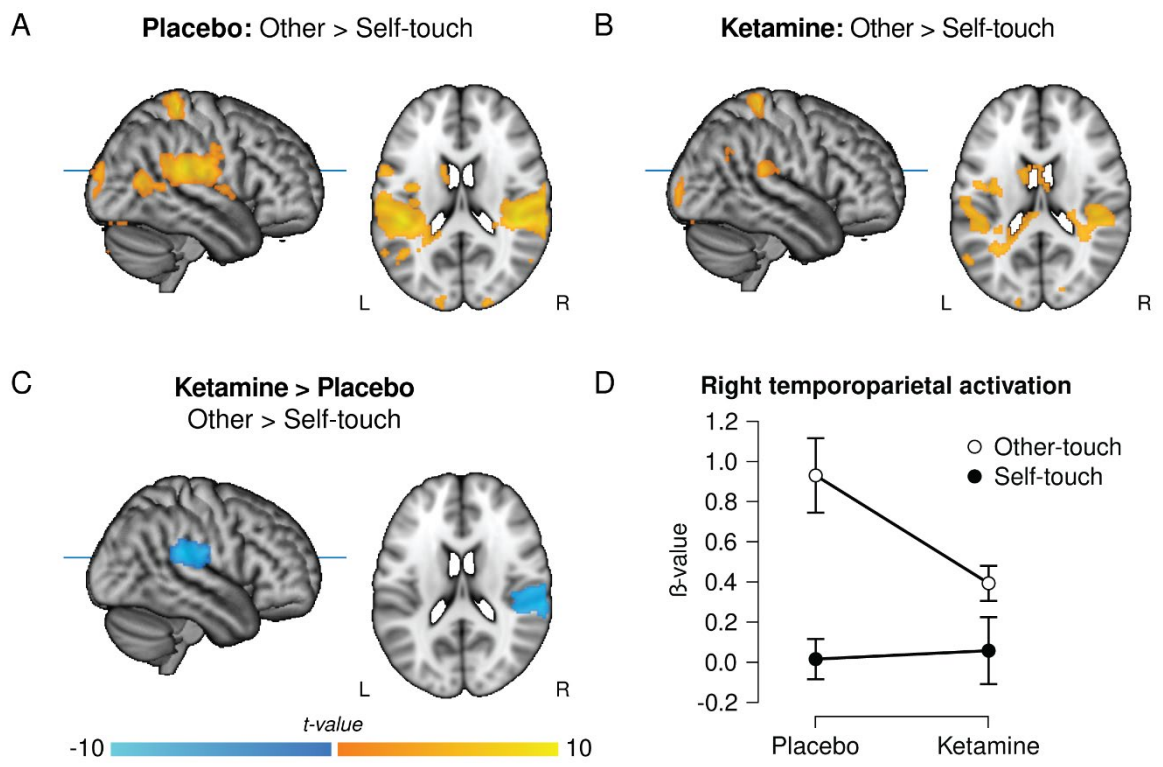


**Figure 3. Ketamine administration is associated with a reduced distinction of self- versus other-generated touch sensations at the neural level. A-B** Activation differences for other- vs. self-touch under placebo (A) and ketamine (B). **C** Ketamine reduces self-other-differentiation in the right temporoparietal cortex. **D** Mean beta-values for the different treatment and touch conditions, extracted from the cluster of voxels for display purpose showing the significant interaction depicted in panel C. All statistical maps displayed according to the neurological convention, thresholded at $p < .001$ uncorrected for display purpose. Axial cut-through slices are at level Z = 18 according to the MNI system.

## Ketamine does not affect tactile detection thresholds during self- and other-generated touch

Participants showed increased touch thresholds for stimulation with von Frey filaments administered simultaneously with both the self- and other-touch condition compared to baseline in the placebo condition (Figure S4). No evidence was found for the hypothesized reduction in tactile detection thresholds during self-touch under ketamine ($t(28)=0.97$, $p=.34$), indicating that a sub-anesthetic dose of ketamine does not significantly affect basic sensing of tactile stimuli. See supplement for further analyses.

**Ketamine is associated with alterations in social touch attitudes and interoceptive awareness**

Social touch (STQ) scores were lower after ketamine compared to placebo, indicating a relative increase in social touch seeking (or decrease in social touch avoidance) during the ketamine session ($t(29)=-2.14$, $p=.041$, Cohen's d=0.39). Total interoceptive awareness (MAIA) scores did not differ between ketamine and placebo sessions ($t(29)=-0.087$, $p=.93$). See supplement of an analysis of MAIA-subscales. Session differences for total MAIA-scores (Δ-MAIA) and STQ-scores (Δ-STQ) were inversely correlated ($r=-.41$, $p=.024$), indicating that increases in interoceptive awareness accompanied increases in social touch seeking.

**Ketamine-induced changes in reported experiences relate to changes in neural markers of self-other-distinction**

An exploratory analysis assessed the relationships between ketamine-related changes in reported experiences and ketamine-related reductions in temporoparietal distinction. Reductions in temporoparietal distinction correlated with reductions in interoceptive awareness (Δ-MAIA; $r=.54$, $p=.002$, Figure 4A). Δ-MAIA was also associated with reductions in self-other-distinction in rInsula, rSTG, and rACC (see table S5). In accordance with the negative relationship between Δ-MAIA and Δ-STQ described above, reduced temporoparietal distinction correlated negatively with increased social touch seeking tendencies (Δ-STQ) ($r=-.39$, $p=.034$). However, mediation analyses showed that this was an indirect relationship mediated by Δ-MAIA (indirect relationship: $B=-.15$, bootstrapped CI [-.35, -.0033], $p<.05$, see Figure 4B).

In an additional exploratory connectivity analysis, change in dissociation symptoms (Δ-CADSS) was included as a regressor. Δ-CADSS correlated with the increase in ketamine-induced rTPC-rS1 connectivity during other- vs. self-touch (SVC $p_{FWE}=.034$, $MNI_{xyz}=26,-32,56$, Figure

4CD), but not with rTPC-rIns and rTPC-rACC connectivity. See supplement for a similar analysis assessing the relationship between functional connectivity and Δ-MAIA.

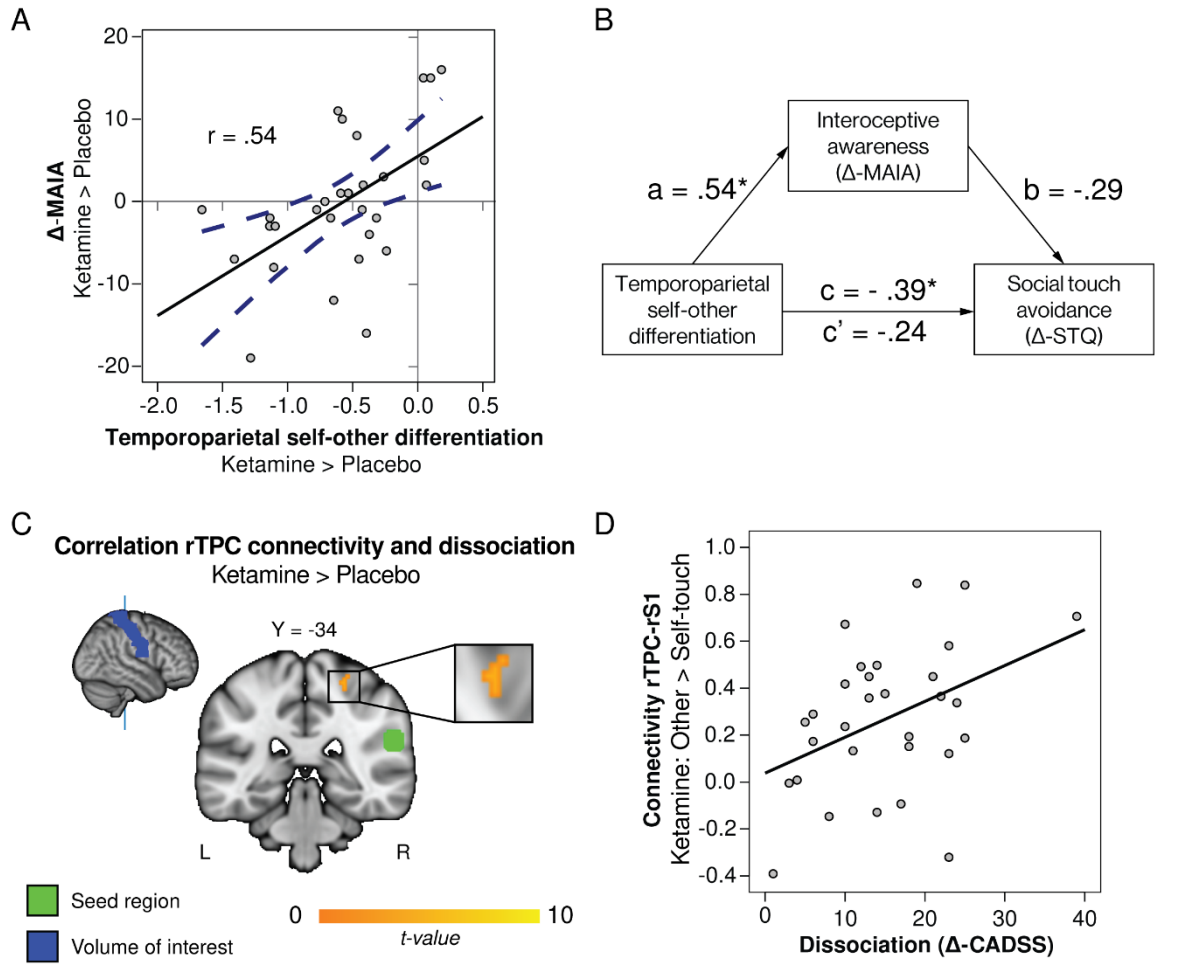


**Figure 4. Ketamine-induced changes in experiences relate to ketamine-induced changes in neural self-other-distinction. A.** Reductions in self-other-distinction correlated with reductions in interoceptive awareness (Δ-MAIA) **B.** The relationship between ketamine-induced changes in temporoparietal self-other-distinction and social touch seeking (the inverse of touch-avoidance; Δ-STQ) was mediated by ketamine-induced changes in interoceptive awareness. *$p$<.05. **C.** Ketamine-induced connectivity differences (other>self-touch) between the right temporoparietal cortex and right S1 correlated with ketamine-induced dissociative states. Y-value refers to MNI-coordinate of cut-through slice. Maps are thresholded at p < .001 uncorrected for display purpose. **D.** Visualization of the relationship between dissociation and connectivity between the temporoparietal cortex and S1, for the ketamine session. Mean beta-values for the different touch conditions are extracted from the voxels depicted in panel C.

## Discussion

This study investigated the effects of ketamine on self-other-distinction in the context of affective touch. Since the bodily self is established and maintained through tactile inputs (among others), we hypothesized that changing the experience of the bodily self using ketamine would be accompanied with a change in touch processing. Using an established task that shows strong neural self-other-distinction of touch under normal conditions (Boehme et al., 2019), we found that this distinction was reduced in the right temporoparietal cortex (rTPC) when people experienced a dissociative state. Activity in this region related to changes in interoceptive awareness and its connectivity with the right S1 correlated with dissociation.

The effects of ketamine on the bodily self are of special interest as ketamine has been 1) suggested as a model for certain aspects of schizophrenia (Corlett et al., 2016; Krystal et al., 1994), and 2) shown efficacy in treating depression (Krystal et al., 2019; Popova et al., 2019; Zarate et al., 2006) and types of chronic pain (Niesters et al., 2014; Rogachov et al., 2019). Similar to other psychedelic drugs, ketamine induces an altered state of consciousness, but its effect on disembodiment is more pronounced compared to, for example, psilocybin (Vollenweider & Kometer, 2010). Ketamine is a non-competitive NMDA receptor antagonist, and its pharmacological effects include disruptions of glutamatergic and dopaminergic systems (Corlett et al., 2007). Proposedly, these psychomimetic effects of ketamine are comparable to the mechanism suggested to lead to the formation of delusions in psychosis: altered predictive coding, resulting in aberrant associative learning and, in the long term, the formation of delusions (Corlett et al., 2007, 2016). More specifically, glutamatergic signaling occurs mainly via NMDA receptors at descending (top-down) connections (Self et al., 2012). NMDA receptor blockade leads to a reduction of top-down signaling, i.e. reduces constraints on inferences about the causes of sensory inputs (Weber et al., 2020) (Note however, that evidence is mixed, as NMDA receptor blockade by substances other than ketamine has been shown to increase top-down signaling (Ranson et al., 2019), and top-down effects of blockade may depend on the

subunit specificity of the antagonist (Self et al., 2012)). Reduced (or aberrant) top-down inference will render the processing of predictable and unpredictable stimuli more similar (Weber et al., 2020). This process was illustrated by a recent study showing that ketamine reduced activation during surprising tactile stimuli in the mouse S1 and S2 (English et al., 2023) – note that this S2 region in the mouse is homologous to our locus of decreased activation after ketamine. Similarly to the reduction of top-down inference on sensory input by ketamine, predictive coding accounts of psychosis assign a central role to decreased precision of prior expectations (Adams et al., 2013; Sterzer et al., 2018), potentially due to increased volatility estimates , i.e. the expectation that the outside world is unstable and changing at a high rate (Deserno et al., 2020).

Naturally, predictive coding plays a crucial role in the distinction of self- vs. other-generated sensation, including touch. Touch perceived from others is intrinsically more unpredictable than self-generated touch (Blakemore et al., 1998; Von Helmholtz, 1867). Consequently, the processing of self-produced sensations is attenuated and perceived as less intense than other-generated sensations. An illustration of this phenomenon is that we do not perceive self-touch as ticklish (Blakemore et al., 1998; Kilteni & Ehrsson, 2020; Weiskrantz et al., 1971). In the placebo condition of the current study, the stark difference in predictability of other- vs. self-generated touch is reflected in stronger activation during other-touch. In accordance with the proposed working mechanism of ketamine described here, this difference in activation was reduced during the ketamine session, rendering the neural signal closer to that of self-generated touch. This suggests that the difference in predictability of other- and self-touch was reduced because of decreased top-down signaling and less constrained inferences about the causes of sensory input under ketamine.

Our results provide new information regarding two open issues in predictive coding accounts of NMDA receptor functioning in psychosis: 1) the model is opaque about the exact processing level on which the predictive coding deficits occur and 2) it is unclear if the

predictive processing deficits vary between sensory domains (Sterzer et al., 2018). As we will discuss in more detail below, we showed that 1) ketamine affects an intermediate processing area and 2) at least two sensory domains, social touch and interoception, which have relevance for both self-experience and social interactions – functions that are severely impacted in psychotic experiences.

The reduction in self-other-distinction under ketamine was specific for a region in the right temporo-parietal cortex, on the border of the parietal operculum, posterior superior temporal gyrus (STG), and supramarginal gyrus (SMG). The parietal operculum is the anatomical site of the secondary somatosensory cortex (S2) (Eickhoff et al., 2006) and is consistently involved in tactile self-other-distinction (Blakemore et al., 1998; Boehme et al., 2019; Kilteni & Ehrsson, 2020). The S2 is one of the main output regions of the primary sensory cortex (S1), and is involved in a broad range of somatosensory functions, such as haptic object recognition, action-related somatosensory processing, body ownership, and (affective) body perception (Haan & Dijkerman, 2020). Tactile stimulation is not crucial for S2 activation: both anticipation of touch (Carlsson et al., 2014) and the mere vision of touch (Keysers et al., 2004) activate this region. Patients with impaired touch perception (but intact S1) show S2 and insula damage, suggesting that these regions are responsible for the conscious perception of touch (Preusser et al., 2015). Interestingly, the functional profile of S2 neurons is intermediate between S1 and the frontal lobe, showing a mixture of invariant sensory responses and context-dependent categorical responses (Rossi-Pool et al., 2021). Both the posterior STG and SMG are consistently involved in cognitive (e.g. theory of mind) as well as affective aspects (e.g., empathy) of social cognition (Schurz et al., 2021). This appears to be in line with their location, in between a unimodal processing area, S1, and a transmodal/abstract area, the temporo-parietal junction (TPJ) (Margulies et al., 2016; Schurz et al., 2021). The TPJ is considered to play a crucial role in self-other-distinction in the cognitive domain, which is an important prerequisite for our ability to understand others. However, self-other-distinction in the affective

domain is suggested to specifically involve the SMG (bordering the TPJ) (Lamm et al., 2016), which is in keeping with our current and previous results (Boehme et al., 2019). Taken together, ketamine affected tactile processing in an intermediate processing area located between the S1, responsible for processing the primary tactile input, and higher-order processing areas, including 1) the insula, which plays an important role in the conscious perception of touch and its integration with interoceptive information from the body (Craig, 2002), and 2) the TPJ, involved in social cognition (Schurz et al., 2021).

Underlining this central role in touch processing, rTPC showed increased task-based connectivity to the right S1 and right insula during other-touch, amongst other regions. rTPC-rS1 connectivity strength was positively correlated to dissociation symptoms under ketamine. These findings complement a previous report on ketamine-induced hyperconnectivity, which related to ketamine-induced schizophrenia-like symptoms (Driesen et al., 2013). Although schizophrenia is predominantly linked to hypo- rather than hyperconnectivity (Dong et al., 2018; Friston et al., 2016), it has recently been argued that psychedelic-induced hyper-connectivity and schizophrenia-related dysconnectivity show a similar relationship to psychotic symptoms because they both lead to disruptions in the integration of information and increased entropy (Sapienza et al., 2023).

The effect of ketamine on neural self-other-distinction paralleled a shift in interoceptive awareness, which was in turn associated with social touch seeking. Understanding others involves the engagement of brain and bodily functions primarily used to assess our own state (Lamm et al., 2016). However, for this mechanism to work adequately, it is important that we are able to distinguish ourselves from others (Lamm et al., 2016). Here, we show that blunted interoception is associated with blunted neural self-other-distinction, in line with the notion that our internal model of ourselves is highly dependent on interoceptive processing (Seth & Tsakiris, 2018). This relationship is also in line with the suggestion that the C-tactile-system is concerned with the establishment and maintenance of the bodily self (McGlone et al., 2014)

and the consistently reported involvement of the insula in both social touch perception and interoception (Craig, 2002; Morrison et al., 2010). Increased touch seeking might be interpreted as a direct reaction to perceiving the own body and its boundaries less clearly under ketamine, in line with the proposed role of social touch in strengthening (and re-establishing) these bodily self-boundaries.

In contrast to the effects of ketamine on the neural level, we did not find any significant differences between tactile detection thresholds for self- and other-touch during the ketamine and placebo sessions. This could indicate that ketamine does not affect basic tactile discrimination in general, which fits with the fact that the neural effects did not occur in the primary somatosensory area. However, the results should be interpreted with caution, as we did not replicate earlier findings on differential thresholds during self-touch and other-touch in the placebo condition, suggesting that our manipulation was not completely successful. Moreover, the tactile detection thresholds were assessed approximately 15 min after administration ended, so the ketamine effects may already have been wearing off.

Participants in the current study had an accurate intuition about whether they had received ketamine during a session or not – a common challenge in placebo-controlled psychedelic studies. Although there is no obvious mechanism by which this awareness may have influenced our main result, it would be valuable to compare our results with other psychoactive drugs. Another limitation of the current study is that it did not evaluate the phenomenology of the actual touch, for example by evaluating differences in subjective experiences like perceived intensity of pleasantness. While definitely of interest, such a measure was not implemented due to methodological concerns, i.e. the risk of drawing or altering the attention to the touch, inducing expectations about the task's purpose, and altering touching behavior during the task.

## Conclusion

This study demonstrated that pharmacologically manipulating the experience of the bodily self is accompanied by a change in neural processing of affective touch. During ketamine administration, self-other-distinction was reduced in a region associated with touch perception and social cognition. This process may be driven by a ketamine-induced reduction in top-down signaling, rendering the processing of predictable self-generated and unpredictable other-generated touch more similar. Our findings provide further evidence for the intricate relationship of the bodily self with social touch.

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## Author contributions

Conceptualization, R.B.; Formal Analysis, R.K., R.B., and P.C.S.; Investigation, A.E., P.C.S., R.K., L.Ö., M.P., A.J.C., H.K., A.L., E.G., M.S., and S.G.; Writing – Original Draft, R.K., R.B. P.C.S., and A.E.; Writing – Review & Editing, R.B., H.O., M.H. A.J.C., and R.K.; Visualization, R.K.; Supervision, R.B.

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**Competing interests**

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