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Cortical thickness of the posterior cingulate cortex is associated with the ketamine-induced altered sense of self: An ultra-high field MRI study

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A B S T R A C T

Subanesthetic doses of ketamine induce an antidepressant effect within hours in individuals with treatment-resistant depression while it furthermore induces immediate but transient psychotomimetic effects. Among these psychotomimetic effects, an altered sense of self has specifically been associated with the antidepressant response to ketamine as well as psychedelics. However, there is plenty of variation in the extent of the drug-induced altered sense of self experience that might be explained by differences in basal morphological characteristics, such as cortical thickness. Regions that have been previously associated with a psychedelics-induced sense of self and with ketamine's mechanism of action, are the posterior cingulate cortex (PCC) and the pregenual anterior cingulate cortex (pgACC).

In this randomized, placebo-controlled, double-blind cross-over magnetic resonance imaging study, thirty-five healthy male participants (mean age ± standard deviation (SD) = 25.1 ± 4.2 years) were scanned at 7 T. We investigated whether the cortical thickness of two DMN regions, the PCC and the pgACC, are associated with *disembodiment* and *experience of unity* scores, which were used to index the ketamine-induced altered sense of self.

We observed a negative correlation between the PCC cortical thickness and the *disembodiment* scores ($R = -0.54$, $p < 0.001$). In contrast, no significant association was found between the pgACC cortical thickness and the ketamine-induced altered sense of self. In the context of the existing literature, our findings highlight the importance of the PCC as a structure involved in the mechanism of ketamine-induced altered sense of self that seems to be shared with different antidepressant agents with psychotomimetic effects operating on different classes of transmitter systems.

1. Introduction

Ketamine is an N-methyl-D-aspartate receptor (NMDA-R) antagonist, which was approved as an anesthetic by the US Food and Drug Administration (FDA) in 1970. While higher doses are used for anesthesia, at sub-anesthetic doses, ketamine demonstrates a rapid antidepressant effect within hours, which peaks 24 h after administration (Berman et al., 2000; Kryst et al., 2020). Ketamine is now increasingly used in psychiatry to treat depression and other psychiatric disorders in patients who do not respond adequately to conventional treatments (Newport et al., 2015; Walsh et al., 2022; Zarate et al., 2006). Besides, due to its immediate but transient subjective effects, ketamine administration has been used as a model for psychosis in rodents and humans.

Sub-anesthetic doses of ketamine induce a transient altered state of

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consciousness, namely dissociation, with a significant distortion in the perception of the body and its surrounding in time and space (Krystal et al., 1994; Pomarol-Clotet et al., 2006; van Schalkwyk et al., 2018). These dissociative effects of ketamine have gained considerable interest in the community following reports suggesting a positive association with its antidepressant properties (Bartoli et al., 2017; Luckenbaugh et al., 2014; Niciu et al., 2018; Sos et al., 2013; Sumner et al., 2021), while results are not entirely conclusive (Mathai et al., 2020; Valentine et al., 2011; Wilkinson et al., 2018). Of these dissociative effects, the experience of an altered sense of self has been the focus of attention. As an example, depersonalization (a close construct to disembodiment, describing feelings such as feeling disconnected from one's own body) has been the construct specifically associated with the antidepressant response to ketamine (Niciu et al., 2018), while another related construct, ego-dissolution, has been associated with the antidepressant mechanism of action of serotonergic psychedelics (Ko et al., 2022; Roseman et al., 2018). Ego-dissolution also denotes a dissociative state, specifically an altered sense of one's self and its boundaries (Millière, 2017).

A brain network likely to play a role in aspects of dissociation is the default mode network (DMN). This network is closely associated with self-related processes, such as "monitoring of the external environment, body, and emotional state" (Shulman et al., 1997). Two key nodes of the DMN, which have been repeatedly reported to be involved in ketamine's mechanism of action, are the posterior cingulate cortex (PCC) and the pregenual anterior cingulate cortex (pgACC) (Dandash et al., 2015; Danyeli et al., 2023; Li et al., 2020; Milak et al., 2020; Murrough et al., 2015; Rowland et al., 2005; Scheidegger et al., 2016; Stone et al., 2012). The PCC is an area associated with the sense of body ownership and the location of one's own body in space (Guterstam et al., 2015), while the pgACC is involved in emotional processing and the establishment of mood states (Etkin et al., 2011; Pizzagalli, 2011). However, the neural correlates of ketamine-induced dissociation have been scarcely examined. One study showed that ketamine-induced midcingulate activation extending to the PCC and parahippocampal cortex (PHC) and the deactivation in the ventromedial cortex were associated with ketamine's dissociative effects (Deakin et al., 2008). The role of the PCC and close neighboring areas in ketamine-induced dissociation has furthermore been supported by electroencephalography (EEG) and electrophysiological studies (de la Salle et al., 2016; Vesuna et al., 2020).

Beyond ketamine, there are plenty of neuroimaging findings related to psychedelics-induced ego-dissolution. DMN regions and specifically the PCC, have repeatedly been shown to be associated with psychedelics-induced ego-dissolution (Psilocybin: (Carhart-Harris et al., 2013; Muthukumaraswamy et al., 2013); lysergic acid diethylamide (LSD): (Carhart-Harris et al., 2016)). Relevant to the ego dissolution, resting-state functional connectivity (rsFC) analyses on psilocybin, e.g., observed a decreased coupling between the PCC and medial prefrontal cortex (mPFC)/pgACC (Carhart-Harris et al., 2012), whereas a magnetic encephalography (MEG) study reported desynchronization of ongoing oscillatory rhythms in the PCC (Muthukumaraswamy et al., 2013). In one recent psychedelic study, pgACC cortical thickness was associated with affect-related dissociation under psilocybin (Lewis et al., 2020). In summary, the brain areas associated with psychedelics-induced ego--dissolution are likely shared with ketamine-induced dissociation, especially with an altered sense of self.

While the significance of the drug-induced altered sense of self for an antidepressant effect has been put forward, it is of note that there is plenty of variation in the magnitude of dissociative effects reported by participants during ketamine administration, suggesting substantial inter-individual differences (Acevedo-Diaz et al., 2020; Derntl et al., 2019). Investigations of underlying biological mechanisms and factors that create this sensitivity to ketamine-induced dissociation remain scarce. Individual brain morphology measures have been used to predict pharmacological interventions and behavioral changes in different psychiatric disorders (Chaney et al., 2014; Cherkasova et al., 2017; Jaworska et al., 2017; Redlich et al., 2014; Schilling et al., 2013; Vogt, 2005). For ketamine interventions specifically, Herrera-Melendez et al. (2021) reported gray matter volume of the pgACC to be predictive of ketamine's antidepressant response. Also in disorders in which anomalous self-experiences are common, such as schizophrenia, dissociative identity disorder, or functional neurological disorder, altered cortical thickness in several brain regions was reported, which correlated with dissociative intensity (Perez et al., 2018; Reinders et al., 2018; Rimol et al., 2010; Schultz et al., 2010; van Haren et al., 2011). A study examining the individual differences in the rubber hand illusion reported a positive correlation between cortical thickness in parietal and somatosensory regions and the induced sense of body ownership (Matuz-Budai et al., 2022). Lewis et al. (2020) found that cortical thickness of the pgACC (but not the caudal and posterior-middle cingulate) predicted affect-related alterations in consciousness, including the *experience of unity*, under psilocybin. It, therefore, can be hypothesized that individual differences in brain morphological measures, such as cortical thickness, could be associated with a ketamine-induced altered sense of self.

In the present study, we analyzed the association of ketamine-induced alterations in the sense of self with the cortical thickness of two DMN regions, namely the PCC and the pgACC. Cortical thickness was chosen over other structural parameters due to its association with drug response in the previous literature (Chaney et al., 2014; Cherkasova et al., 2017; Jaworska et al., 2017). Furthermore, as ketamine's effect has previously been associated with layer-specific actions (Liu et al., 2015; Marek, 2018; Widman and McMahon, 2018; Yin et al., 2023), cortical thickness as a more direct imaging indicator of layer thickness compared to other structural imaging parameters has been employed. In addition, cortical thickness was used as the method of choice to take full advantage of the benefits of the present ultra-high field imaging data that enables increased precision in the estimation of cortical thickness and would not be of similar benefit for volumetric analysis. Highlighting the importance of the PCC in drug-induced dissociation and its role in body representation (Carhart-Harris et al., 2012; Guterstam et al., 2015; Muthukumaraswamy et al., 2013), we hypothesize that cortical thickness of the PCC is associated with the ketamine-induced *disembodiment*, which denotes an altered sense of bodily self-awareness. Furthermore, based on its reported involvement in the altered sense of self with the specific report of a link to a psilocybin-induced *experience of unity* (Lewis et al., 2020), we hypothesized that the cortical thickness of the pgACC is associated with the ketamine-induced *experience of unity,* which denotes an altered awareness of the distinction between one's self and its environment. By focusing our analysis on the altered sense of self related constructs, we aimed to shed light on shared mechanisms of action of ketamine and serotonergic psychedelics since the specific brain mechanisms underlying the psychedelics-induced ego-dissolution are relatively well studied compared to the mechanisms underlying the dissociative effects of ketamine.

2. Materials and methods

2.1. Study design and participants

A randomized, placebo-controlled, double-blind cross-over study was conducted to examine the association of cortical thickness with an altered sense of self induced by a single sub-anesthetic S-ketamine infusion in thirty-five healthy male participants (mean age ± standard deviation (SD) = 25.1 ± 4.2 years).

The exclusion criteria were as follows: a current or lifetime major psychiatric disorder, including substance or alcohol dependence or abuse, according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) as assessed by the Structured Clinical Interview for DSM-IV (SCID-I; (First and Gibbon, 2004)); a family history of psychiatric disorders as assessed by a demographic questionnaire or

neurological/physical constraints or severe illnesses as evaluated by the study physician during screening. Further exclusion criteria were left-handedness and the presence of any magnetic resonance imaging (MRI) contraindications. All participants gave informed written consent. The study was approved by the Institutional Review Board of the Otto-von-Guericke-University Magdeburg and was conducted following the recommendations of the Declaration of Helsinki and local legal requirements.

2.2. Experimental procedure

The present analysis is part of a bigger study. The full experimental procedure consisted of two consecutive days per treatment arm (ketamine and placebo treatment arm), including MR scanning directly before, during, and 24 h after each infusion. The interval between the two treatment arms was approximately three weeks to avoid carry-over effects. For the present research question, only the baseline measurements of the first day of each treatment arm are relevant.

Participants received a single intravenous (i.v.) infusion (*via* Injectomat® MC Agilia; Fresenius Kabi GmbH, Bad Homburg, Germany) of S-ketamine hydrochloride (0.33 mg/kg body weight; "Ketanest S Pfizer") or 0.9 % saline as the placebo control in a randomized order. The infusion consisted of a bolus (0.11 mg/kg body weight S-Ketamine or 0.9 % saline) followed by a maintenance dose (0.22 mg/kg body weight S-Ketamine or 0.9 % saline) administered over 40 min. To ensure medical safety, vital signs were monitored throughout the infusion (NONIN Pulse Oximeter 8600-FO), and participants were observed for a minimum of 4 h after infusion.

To quantify the extent of the dissociative effects, the validated 5-Dimensional Altered States of Consciousness questionnaire ((5D-ASC); (Dittrich, 1998)) was employed, which is the most widely used questionnaire to quantitatively index pharmacologically-induced altered states of consciousness (Prugger et al., 2022). Participants retrospectively completed the questionnaire approximately 2 h after the end of each infusion (items and mean item scores of the two subscales of interest are shown in Table S1; validated and frequently investigated subscales (Prugger et al., 2022) were obtained following (Studerus et al., 2010)). In line with the literature (Lewis et al., 2020; Mueller et al., 2018), participants' reports of both treatment arms were used to calculate delta scores (ketamine-placebo) that were utilized throughout the analysis since the relative sensory deprivation during MR scanning itself might induce a light dissociative state (Powers et al., 2015).

2.3. Magnetic resonance data acquisition

MR images were acquired on an ultra-high field 7 T scanner (Siemens Healthineers, Erlangen, Germany) with a 32–channel head array coil. Participants underwent structural MRI before (baseline) and 24 h after infusion. Furthermore, functional MRI and magnetic resonance spectroscopy (MRS) were acquired before, during, and 24 h after infusion unrelated to the present analysis. The imaging time point relevant to the present investigation is the baseline.

After automated shimming, a T1-weighted structural MR image was obtained using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence with the following parameters: echo time (TE) = 2.54 ms, repetition time (TR) = 1700 ms, inversion time (TI) = 1050 ms, flip angle = 5°, field of view (FoV) = 256 mm, 176 slices, grappa acceleration factor PE = 2, bandwidth = 160 Hz/pixel, isotropic voxel size = 1 mm^3.

2.4. Structural magnetic resonance imaging data preprocessing

Structural MR data preprocessing was performed employing fMRIPrep 20.1.1 (RRID:SCR_016216; (Esteban et al., 2019)), which is based on Nipype 1.5.0 (RRID:SCR_002502; (Gorgolewski et al., 2011)). Preprocessing steps are reported in detail in the Supplementary Information of Danyeli et al. (2023).

2.5. Estimation of cortical thickness

First, an individualized average T1w image was calculated from the two baseline T1-weighted (T1w) images using the module for longitudinal data analysis in the Computational Anatomy Toolbox (CAT12; v12.8 (r1977), http://www.neuro.uni-jena.de/cat/) as implemented in SPM12 (v7487, Statistical Parametric Mapping, Institute of Neurology, London, UK) running under MATLAB (v2018a, The MathWorks). Prior to further analysis, quality control with the derived images was performed by MRIQC (version 22.0.1; (Esteban et al., 2017)) and fMRIPrep. Based on the image quality metrics for structural images defined in MRIQC, as well as the tissue segmentation and the surface reconstruction in FreeSurfer reported in the fMRIPrep report, no subject was excluded due to abnormal data quality or cortical thickness reconstruction issues. Next, the cortical thickness was estimated within the fMRIPrep processing workflow for robust and reproducible preprocessing as employed in Danyeli et al. (2023). Considering fMRIPrep integrates the best-in-breed tools for each of the preprocessing tasks, a set of diverse readily available toolboxes was implemented in its workflow. The T1w image was corrected for intensity non-uniformity (INU) per participant with N4BiasFieldCorrection (Tustison et al., 2010), distributed with ANTs 2.3.3 (RRID:SCR_004757; (Avants et al., 2008)). The T1w-reference was then skull-stripped with a Nipype implementation of the antsBrainExtraction.sh workflow (from ANTs). Brain tissue segmentation of cerebrospinal fluid (CSF), white matter (WM), and gray matter (GM) was performed on the brain-extracted T1w using fast (FSL 6.0.5.1:57b01774, RRID:SCR_002823; (Zhang et al., 2001)). Within fMRIprep, brain surfaces were reconstructed using recon-all (FreeSurfer 7.2.0, RRID:SCR_001847; (Dale et al., 1999)), and the estimated brain mask was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical GM of Mindboggle (RRID:SCR_002438; (Klein et al., 2012)). According to the Desikan-Killiany-Tourville cortical labeling protocol in FreeSurfer, the cortical thickness of the following cortical regions was analyzed in the present study, "right isthmus cingulate", "right rostral anterior cingulate", "left isthmus cingulate", "left rostral anterior cingulate". For consistency between publications, the isthmus cingulate and the rostral anterior cingulate will hereafter be named PCC and pgACC, respectively. Regions used for extraction of cortical thickness are depicted in Fig. 1. For analysis, the mean of both hemispheres was calculated for each of the two regions of interest (ROIs).

2.6. Statistical analysis

All statistical analyses were performed in IBM SPSS Statistics (v26; Armonk, NY: IBM Corp) and the alpha value was set to 0.05. A

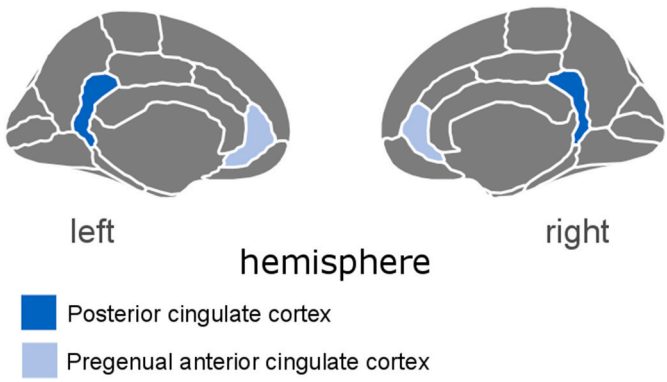

Fig. 1. Depiction of the regions of interest used for the cortical thickness estimation.

multivariate general linear model was used to test if the cortical thickness of the two ROIs (PCC and pgACC) is associated with the delta scores (ketamine-placebo) of the two subscales of interest, *disembodiment,* and *experience of unity*. The delta scores of *disembodiment* and *experience of unity* were included as dependent variables, and the cortical thickness of the PCC and pgACC, as well as age, were included as independent variables. Due to potential variations in the extent or quality of the subjective experience induced by ketamine depending on the order of treatment application (as observed in this dataset and reported in the previous literature (Lii et al., 2023; McIntyre et al., 2021)), treatment order and its interaction effect were added to the model (design: intercept + treatment order + PCC cortical thickness + pgACC cortical thickness + treatment order * PCC cortical thickness + treatment order * pgACC cortical thickness + age). Results were corrected for multiple comparisons of two dependent variables (adjusted $\alpha = 0.025$).

Pearson's correlation of the fitted values was employed for visualization of the results. Figures were generated using R (v4.0.3) with the package ggpubr (v0.4.0).

3. Results

3.1. Ketamine-induced experience of unity and disembodiment

A significant ketamine-induced increase in *experience of unity* (t(34) = -7.057, p < 0.001) and *disembodiment* (t(34) = -7.039, p < 0.001) subscales scores was observed when compared to the placebo condition (Fig. 2).

3.2. Multivariate general linear model of the ketamine-induced altered sense of self with the cortical thickness of pgACC and PCC

The model showed a significant association of the PCC cortical thickness with the altered sense of self scales (F(2,27) = 7.594, p = 0.002) (see Table 1). Parameter estimates of the model indicated a significant negative association of the cortical thickness of the PCC with ketamine-induced *disembodiment* ($\beta = -41.036$, SE = 13.663, p = 0.006), but not for pgACC cortical thickness (see Table S2). Fig. 3 shows the significant negative Pearson correlation ($R = -0.54$, p < 0.001) between the PCC cortical thickness and the *disembodiment* score, using the fitted values derived from the linear model. No significant association for the *experience of unity* was observed for either ROI.

4. Discussion

In the current study, we examined the association between the ketamine-induced altered sense of self, namely *disembodiment* and *experience of unity*, and the cortical thickness of two brain areas, which were shown to play a role in the psychedelics-induced altered sense of self, the PCC and pgACC. As hypothesized, our results showed a correlation between PCC cortical thickness and the *disembodiment*, which was negative. In contrast, no significant association between the cortical thickness of the pgACC and the *experience of unity* was found. Our findings point out the significance of the structural features of the PCC for ketamine-induced *disembodiment* and highlight the PCC as a structure involved in the mechanism of different antidepressant drugs operating on different classes of transmitter systems. An overview figure summarizing the study design, the study concept and the study result can be found in the supplementary material (Fig. S1).

The present findings add to the literature, reporting that the PCC plays a crucial role in ketamine-induced dissociation. Ketamine-induced reductions in alpha current density bilaterally in the PCC have been associated with increased depersonalization ratings (de la Salle et al., 2016). These observations overlap with the findings by Deakin et al. (2008), reporting midcingulate activation that extended into the PCC and precuneus, which was associated with dissociation and psychosis ratings. Besides ketamine, literature on psychedelics suggests a strong involvement of the PCC in an altered sense of self. Consistently overlapping spatial locations, namely high-level cortical regions such as the PCC, as well as the psychedelics-induced DMN rsFC decrease, have been replicated by investigations using ayahuasca (Palhano-Fontes et al., 2015), psilocybin (Carhart-Harris et al., 2012, 2013; Muthukumaraswamy et al., 2013) and LSD (Carhart-Harris et al., 2016). These findings point out a potentially shared mechanism underlying the altered sense of self experience induced by different agents, even though their main target neurotransmitter systems differ. Indeed, growing evidence suggests similar downstream mechanisms, with both psychedelics and ketamine being associated with the upregulation of the

Table 1
Multivariate general linear model results.

Effect	Wilks' lambda	F	p
Intercept	0.743	4.659	0.018
PCC cortical thickness	0.640	7.594	0.002
pgACC cortical thickness	0.926	1.081	0.353
Age	0.930	1.014	0.376
Treatment order	0.971	0.405	0.671
Treatment order * PCC cortical thickness	0.889	1.689	0.204
Treatment order * pgACC cortical thickness	0.962	0.536	0.591

Abbreviations: df = degrees of freedom, PCC = posterior cingulate cortex, pgACC = pregenual anterior cingulate cortex.

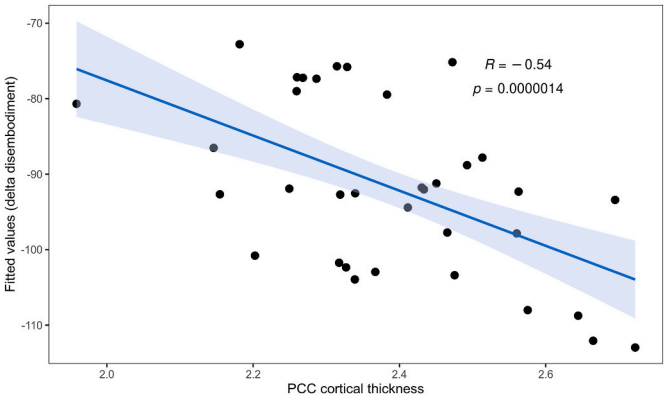

Fig. 3. Association between *disembodiment* and posterior cingulate cortex (PCC) cortical thickness. A significant negative association of the cortical thickness of the PCC with the delta scores (ketamine-placebo) of ketamine-induced *disembodiment* was observed. The shaded area represents the 95% confidence interval of the fit.

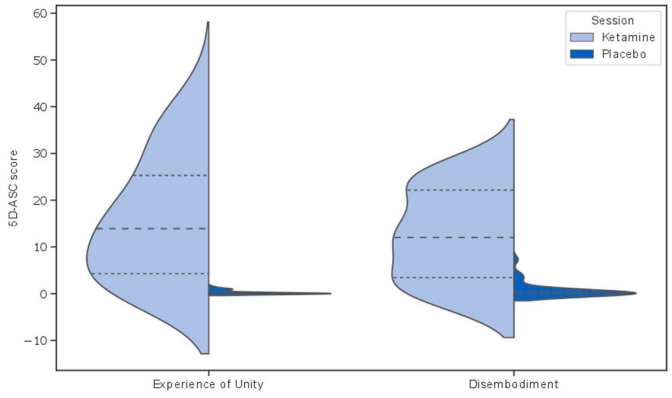

Fig. 2. Retrospective ratings of *experience of unity* and *disembodiment* under the ketamine and placebo infusion. A significant ketamine-induced increase in *experience of unity* and *disembodiment* was observed. Middle dashed lines depict the mean score and outer smaller-dashed lines depict the 25th percentiles.

glutamatergic α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor (AMPA-R) and consequent activation of the mammalian target of rapamycin (mTOR) pathway (Johnston et al., 2023).

In line with our findings that point towards an association between the cortical thickness of the PCC and ketamine-induced *disembodiment*, plenty of findings indicate the role of the PCC in the sense of body ownership and location of one's own body in space. A neuroimaging investigation of the PCC's involvement in bodily self-perception reported an engagement of the PCC in self-location in space measured through out-of-body illusions (Guterstam et al., 2015). This finding was supported by a recent case study of a tumor patient that observed dissociative "out-of-body experience" after PCC brain tumor development (Hiromitsu et al., 2020). Furthermore, there is convincing causal evidence that pinpoints the role of the PCC and the surrounding area in the constitution of bodily-self consciousness, using intracranial EEG and electrical stimulations (Lyu et al., 2023; Parvizi et al., 2021). In a clinical context, these findings are accompanied by structural and functional alterations in the PCC of individuals with schizophrenia (Franck et al., 2002; Haznedar et al., 1997; Holcomb et al., 2000; Miller et al., 2001), whereas rsFC between the PCC/isthmus cingulate and PHC positively correlated with anomalous self-experience in individuals with schizophrenia (Roig-Herrero et al., 2022).

In the light of the above-summarized role of the PCC in a drug-induced altered sense of self, we interpret our negative correlation between cortical thickness in the PCC and *disembodiment* in a way that less cortical thickness indicated an increased sensitivity to ketamine-induced *disembodiment*. This assumption is furthermore based on studies reporting an association of lower cortical thickness in several cortical areas with schizophrenia/high risk for psychosis (Benetti et al., 2013; Del Re et al., 2021; Jung et al., 2011; Tognin et al., 2014; Ziermans et al., 2012) or dissociative identity disorder (Reinders et al., 2018). Furthermore, our result and the emerging hypothesis are supported by a study reporting increased self-transcendence associated with cortical thinning of the PCC in regular ayahuasca users (Bouso et al., 2015). Confirming our hypothesis, we found an association between PCC cortical thickness with the item cluster *disembodiment* but not with the *experience of unity*. As summarized above, the role of the PCC in the concepts of body ownership and body location in space is evident. The perceived boundaries of the body or its location and their perceived alterations are better characterized by the items included in the measure of *disembodiment*. In contrast, the *experience of unity* rather addresses the more abstract feeling of losing the boundaries of the self and the other and the sense of time-wise separation of the past, present, and future (Studerus et al., 2010). In contrast to our hypothesis that an association between the pgACC cortical thickness and the *experience of unity* may exist, based on the findings under psilocybin of Lewis et al. (2020), we did not observe a significant association between the pgACC cortical thickness and the effect of ketamine on the *experience of unity* in our study population.

Since the ketamine-induced altered sense of self has been associated with its antidepressant effect, our findings might also be of clinical significance. Indeed, several findings in the literature point out the role of the PCC in the antidepressant mechanism of ketamine. RsFC studies reported an association between the delayed effect of ketamine and disturbed PCC connectivity patterns. A study investigating the PCC-centered effect of ketamine by comparing healthy participants and individuals with major depressive disorder reported normalization of rsFC between the PCC and insula two days after ketamine administration. This change in rsFC was positively associated with an improvement in depressive symptoms (Evans et al., 2018). The here-reported role of morphological features of the PCC in ketamine-induced disembodiment would complement the involvement of the PCC in ketamine's delayed antidepressant effect.

Of note, the participants were scanned by means of an ultra-high field 7 T MRI scanner, which resulted in more accurate cortical thickness measurements than acquisitions at lower field strengths (Lüsebrink et al., 2013). The cross-over design of the study should furthermore be highlighted as highly beneficial since there is a high interparticipant variation not only in the subjective effects of ketamine but also in the subjective effects of placebo. By calculating the difference between placebo- and ketamine-induced changes in subjective experiences, we were able to control the placebo-driven effect to some extent.

5. Limitations

Several limitations of this study must be acknowledged that should be addressed in future studies. First, the sample size is modest and only consists of healthy participants. While it is possible to make an association between cortical thickness and ketamine-induced dissociation for a deeper understanding of the mechanism of how ketamine evokes a dissociative state, it is not possible to draw a direct conclusion about the association of this relationship with its antidepressant effect. Second, we must consider that other regions besides the investigated regions might correlate with the behavioral effects investigated here due to some regions potentially sharing covariance with the PCC. Furthermore, while the investigated regions, PCC and pgACC, were strongly hypothesis- and literature-driven, we want to highlight that there are more regions potentially involved in the altered sense of self. Investigations in other regions, however, were beyond the scope of the present research question and methodology.

6. Conclusion

In the present study, we found an association between the cortical thickness of the PCC with *disembodiment* induced by ketamine. The negative correlation could indicate a higher susceptibility for a ketamine-induced altered sense of self, specifically, *disembodiment* with decreased cortical thickness in the PCC. Our study highlights the importance of the PCC as an effector region of drug-induced altered sense of self that was previously reported for drugs targeting the 5HT-2A system. Therefore, these PCC-centered drug-induced alterations seem to span different classes of neurotransmitter systems.

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CRediT authorship contribution statement

Lena Vera Danyeli: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Zümrüt Duygu Sen:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft. **Lejla Colic:** Writing – review & editing. **Nils Opel:** Writing – review & editing. **Alexander Refisch:** Writing – review & editing. **Nikolai Blekic:** Writing – review & editing. **Tamar Macharadze:** Writing – review & editing. **Moritz Kretzschmar:** Writing – review & editing. **MatthiasH.J. Munk:** Writing – review & editing. **Christian Gaser:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Oliver Speck:** Writing – review & editing. **Martin Walter:** Data curation, Investigation, Project administration, Supervision, Writing – review & editing. **Meng Li:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft.

Declaration of competing interest

MW is a member of the following advisory boards and has given

presentations to the following companies: Bayer AG, Germany; Boehringer Ingelheim, Germany; and Biologische Heilmittel Heel GmbH, Germany. MW has further conducted studies with institutional research support from HEEL and Janssen Pharmaceutical Research for a clinical trial (IIT) on ketamine in patients with MDD, unrelated to this investigation. MW did not receive any financial compensation from the companies mentioned above. All other authors report no biomedical financial interests or other potential conflicts of interest. We have made a preprint of our work available on the PsyArXiv preprint server for the psychological sciences. Furthermore, results independent of the present analysis but retrieved from the same data set have been published in Danyeli et al. (2023) (https://doi.org/10.1038/s41398-023-02346-0).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.02.019.

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