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Ketamine increases fronto-posterior functional connectivity during meta-perceptual confidence ratings☆

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ABSTRACT

Recent advances in the neuropsychopharmacology of metacognition indicate a constituent role of glutamate for the integrity of metamnestic processes. However, the extent to which previous results can be generalized across functional domains to characterize the relationship between glutamate and metacognition remains unclear. Here, in a randomized, double-blind, placebo-controlled, preregistered fMRI study, we tested the effects of a psychotomimetic dose (target plasma concentration 100 ng/mL) of the *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine on metacognition in a perceptual decision-making framework. We collected trial-by-trial metacognitive reports as participants performed a two-alternative forced-choice perceptual task during functional magnetic resonance imaging (fMRI). Results indicated ketamine-induced deterioration in metacognitive performance, whereas no significant effects were observed for perceptual performance, response times and – unexpectedly – metacognitive bias. Whilst there were no detectable ketamine effects on mean BOLD activation, exploratory psychophysiological interaction (PPI) analysis revealed alterations in functional connectivity during metacognitive confidence ratings under ketamine. Specifically, there was increased task-specific connectivity for ketamine compared to placebo between right anterior dorsolateral prefrontal cortex and left middle temporal, supramarginal and precentral gyrus, as well as between right insula/inferior frontal gyrus and left lingual gyrus, possibly indicating re-representations of object-level features supplied for metacognitive evaluations. Overall, these findings contribute towards the emerging picture of the substructures underlying metacognitive operations at the neurotransmitter level and may shed light on a neural pattern characteristic of pharmacologically challenged metacognition.

1. Introduction

The term *metacognition*, albeit a notoriously heterogeneous concept, is most commonly described as "thinking about thinking" and refers to the human ability to reflect about one's own cognition and the use of these reflections to regulate cognitive processes [1,2]. The concept was first introduced into the psychological literature by Flavell [3,4] and involves two major functions: monitoring and control of cognition [5,6]. Metacognition serves behavioral optimization, as it guides adaptive decisions e.g. in conditions when external feedback is absent or ambiguous [7]. Furthermore, it is useful in that it can provide a representation of the absence of knowledge [8]. The modification of metacognitive processes is a focus in various psychological therapies, e.g. in the treatment of depression, generalized anxiety disorder, or

☆ This study was preregistered; a link to preregistration, analysis scripts and other relevant materials can be found in the Section 2.

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schizophrenia [9–11].

The measurement of metacognition typically requires participants to report their subjective confidence following a cognitive or perceptual judgment; this confidence rating is then evaluated in relation to objective task performance. Therefore, a second-order, metacognitive judgment is adjusted to a first-order judgment, based on a trial-by-trial introspection of the underlying process [12]. Traditionally, two aspects are of major interest: metacognitive *bias*, which expresses an individual's tendency to be generally under- or overconfident, and metacognitive *sensitivity*, which expresses the individual's ability to appropriately discriminate between own correct and incorrect judgments by means of confidence ratings.

Moreover, it is relevant to consider some confounding factors affecting the accuracy of conventional approaches to quantify metacognitive ability. Apart from first-order type 1 (task-related) and second-order type 2 (metacognitive) response tendencies, this primarily concerns the influence of type 1 sensitivity on metacognition [13]. Type 1 task performance may therefore be fixed at a predetermined level using a staircase procedure [14–16], which can be implemented before and/or during collection of metacognitive judgments and which accounts for important sources of bias in the estimation of metacognitive performance [17]. However, staircase procedures may introduce another problem, as they were recently shown to lead to inflated estimates of metacognitive ability due to the mixing of low and high contrast stimuli, which – among other potential solutions – makes it advisable to control for stimulus variability [18]. Finally, the meta-d′ framework [19,20] allows to correct for confounding factors: In addition to "absolute" metacognitive sensitivity (meta-d′), an index of performance-corrected "relative" metacognitive sensitivity or *efficiency* (meta-d′/d′) can be obtained. Metacognition studies employing staircase procedures have therefore used both absolute and relative indices of metacognitive sensitivity to obtain a reliable estimate of an individual's metacognitive ability [18].

Despite a strong increase in efforts and insights over recent years, such as identifying the importance of specific subregions of the prefrontal cortex (PFC) for different metacognitive requirements [21], there are still various remaining questions regarding the functional and biological architecture of metacognition. In particular, there is only a handful of pharmacological challenge studies of metacognition, including a demonstration of increased metacognitive performance after noradrenaline blockade [22] as well as observations of selectively impaired metacognitive efficiency after hydrocortisone administration [23] or, following dopaminergic modulation, for 'New' decisions in a memory paradigm [24].

In a previous functional magnetic resonance imaging (fMRI) study of our group [25], the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine led to a deterioration of metacognitive sensitivity (meta-d′) and larger overall confidence in an episodic memory paradigm. This effect was accompanied by unspecific activation increases in posterior brain areas linked with the "posterior hot zone" of the neural correlates of consciousness, a postulate proposed by Koch et al. [26] and recently substantiated by use of dynamic causal modeling [27]. Likewise, activations of visual areas were observed prominently both in ketamine-associated and metacognition-related BOLD contrasts in our previous study. This is unsurprising given the importance of the visual system for cortical organization and, ultimately, various aspects of consciousness [28], but could further be argued to represent increased processing of visual input in relation to hallucination-like percepts [25]. Moreover, there is evidence for increased functional connectivity between a core area of confidence formation anchored in right rostrolateral PFC and visual cortex (i.e., lingual gyrus) during metacognitive reports about visual percepts [29].

Given the results of our previous study [25], ketamine represents a promising candidate for pharmacological modulations of metacognition. The primary pharmacological mechanism of ketamine, which for many years has been used clinically for its anesthetic effects [30], appears to be its role as an uncompetitive antagonist at the NMDA receptor, an ionotropic glutamate receptor type [31–33]. Recently, a growing body of studies has focused on the glutamatergic system as a viable target for the treatment of mood disorders, as ketamine evokes rapid and sustained antidepressant effects in patients with treatment-resistant depression [34–36]. Modulations of the glutamatergic system also offer promising insights into mechanisms and treatments of schizophrenia [37,38]. Notably, at subanesthetic levels, ketamine possesses psychotomimetic properties [39], which include dissociative bodily experiences with spatiotemporal distortions [40] and a general "broadening" of the scope of conscious contents, enhancing the vividness of imagination and modulating the flexibility of cognition [41–43].

The observation that subanesthetic doses of ketamine reliably induce the so-called *psychedelic state* [39,44] is of particular interest to consciousness research, as it allows to modulate different aspects of consciousness in fundamentally different ways [45], e.g. by eliciting a state of *ego dissolution* [46]. Within the framework of Integrated Information Theory (IIT) [47,48], regarded as one of the preeminent contemporary theories of consciousness (although Hanson and Walker [49] recently outlined deficiencies in its falsifiability), the psychedelic state is attributed with various alterations in awareness: Potentially increased cognitive flexibility, creativity, and imagination, which, however, comes at functional costs, such as a degradation of the brain's ability to organize, categorize, and differentiate the constituents of conscious experiences, as well as an inflation of possible cause-effect mechanisms [50]. In the psychedelic state, the brain is thus characterized by a higher state of entropy, experientially richer and more flexible, but less informative than normal waking consciousness [42,50]. Focusing specifically on subanesthetic doses of ketamine, this state of elevated entropy is associated with reduced resting-state connectivity between anterior and posterior parts of the brain's default-mode network (DMN) [51].

Furthermore, ketamine was shown to lead to a reduction of brain activity in regions involved in self-monitoring while increasing activity in regions associated with reward processing and emotional blunting [52]. Specifically, pregenual and subgenual aspects of anterior cingulate cortex (ACC) have been subject to closer scrutiny in previous studies; for the former, a ketamine-associated, region-specific increase in BOLD response was argued to implicate a role of ketamine in attenuating an inordinate self-focus during negative experiences [53]. Interestingly, these regions are functionally associated with posterior medial frontal cortex (pMFC), which was identified as a central hub of metacognition-related activations in our previous study as well as a meta-analysis of MRI studies on metacognitive judgments [54]. Whereas much research focused on BOLD activation or resting-state connectivity, it is in some contexts more informative to consider context-dependent connectivity of brain areas in relation to specific task conditions [55]; here, ketamine was shown to increase coupling between medial prefrontal and parahippocampal areas in an emotional memory task [56].

The identification of the neural correlates and neurotransmitter systems underlying metacognition is meanwhile complicated by the fact that distinct metacognitive subsystems may exist for different tasks and requirements. Multiple studies [14,57,58] failed to obtain significant correlations regarding the accuracy of metacognitive judgments across experimental domains, which was substantiated in a meta-analysis [59]. At the neural level, Baird et al. [15] reported evidence for spatial specialization within the anterior PFC for different types of metacognitive processes, namely in relation to perceptual decision-making ("meta-perception") and mnemonic retrieval ("meta-memory"). Consequently, meta-perception and meta-memory may represent distinct processes with distinct neural correlates, and findings obtained about metacognition with respect to one specific domain are thus not necessarily applicable to other functional domains.

However, recent studies demonstrated that domain-general contributions to the structure of metacognition can be revealed under optimized methodological conditions and with sufficient statistical power

[60,61], and beyond functional specializations, there is also some unity in the neural profiles of different metacognitive processes [54]. Although little is known about the domain-generality or domain-specificity of the effects of pharmacological challenges on metacognition, one might reasonably assume a shared reliance of metacognitive processes on specific neuronal mechanisms. Detecting congruent effects of the same pharmacological intervention across tasks would suggest a domain-general neurophysiological substrate at the level of (partially) shared neuronal mechanisms that could subserve the computation of metacognitive processes, which would contribute towards a fundamental account of the biological substructures that constitute the functional architecture of metacognition.

Building upon our previous study [25], which suggested ketamine impacts meta-memory, we conducted a double-blind, placebo-controlled, preregistered fMRI study to investigate the effects of a psychotomimetic dose of ketamine on meta-perception and associated brain activity. As participants' primary task performance was maintained at a constant level by use of a staircase procedure, they provided confidence ratings on their trial-by-trial decisions on a two-alternative forced-choice (2AFC) perceptual magnitude comparison task with static visual stimuli. Induction of a psychedelic state was assessed using a self-report questionnaire. In accordance with preregistration, we hypothesized that we would find evidence for ketamine-induced alterations in metacognitive performance as well as neural activity during metacognitive reports. Thereby, we aimed to contribute to the emergent understanding of metacognition under pharmacological challenges.

2. Materials and methods

2.1. Participants

Seventy young adult volunteers were recruited via mailing lists and online advertisements. They provided written, informed consent and received financial reimbursement for their participation. Volunteering individuals were excluded if they met any of the following criteria: Serious physical illness; history of neurological or psychiatric illness; hyperthyroidism; hypo- or hypertension; under- or overweight; prior experience with ketamine; history of alcohol or drug abuse within the last twelve months or complications during anesthesia; concurrent medication, MRI incompatibility (metalliferous implants, claustrophobia), positive urine drug test, and positive urine pregnancy test. An extensive screening procedure was carried out, as detailed in a previous publication employing a different study sample, but the same equipment and infusion protocol [25]. Participants arrived at the testing facility after a minimum of 2 h fasting clear fluids, 6 h fasting solid food and 24 h fasting alcohol. On the assessment day, an on-site physical examination was performed by medical professionals prior to MRI testing. Consistent with ethical and anesthesiological standards, participants received pre-experimental information about the possibility of ketamine application and potential side effects of the drug. All participants were treated with equal care, and the double-blind protocol was maintained at all times. Two participants failed to complete the full course of the study (dropouts), and twenty-three participants were excluded due to a technical error, which led to a large deviation of their responses from the targeted percentage of correct responses. Data of forty-five healthy, right-handed, non-smoking participants (21 female, 24 male; aged 19–34 years; M=23.96, SD=4.06) with normal or corrected-to-normal vision were included in data analysis.

In accordance with the study's Research Ethics Committee approval (Department of Psychology, University of Bonn; approval number: 19–03–29), behavioral data are provided as supplementary materials and MRI data will be made available upon request; analysis scripts, preregistration and other relevant materials can be accessed via OSF (https://osf.io/gucm2/).

2.2. Experimental design and infusion protocol

This study employed a randomized, double-blind, placebo-controlled between-subjects design. As in previous studies of our group [25,62,63], drug administration was carried out via an intravenous access in the non-dominant arm. Of the included participants, a subset of 19 individuals (8 female) received a placebo infusion (0.9% sodium chloride saline solution, Ratiopharm©, Ulm, Germany), while the other 26 participants (13 female) were administered a subanesthetic dose of racemic ketamine (Ketamin-Ratiopharm 500 injection solution, Ratiopharm©, Ulm, Germany) as a 2 mg/mL solution with a constant target plasma level of 100 ng/mL by a bolus and continuous intravenous infusion through a computer-controlled infusion pump (Graseby 3500, Smith Medical Int. Ltd, Luton, UK). Upon termination of the infusion, participants were asked to report their internal states and subjective experiences during drug administration on the Altered States of Consciousness (5D-ASC) rating scale [64,65], a 94-item inventory assessing five dimensions by which altered states of consciousness can be characterized via ratings on a visual-analogue scale (VAS). These encompass three oblique primary dimensions, "Oceanic Boundlessness", "Dread of Ego Dissolution" and "Visionary Restructuralization", which can be summed to form a global measure of altered consciousness, and two ancillary dimensions, "Vigilance Reduction" and "Auditory Alterations".

2.3. Stimuli

Meta-perception was investigated in a 2AFC magnitude comparison task (MC-T). Presentation of the experiment and recording of behavioral responses were performed using *Presentation*® software (Version 17.2, Neurobehavioral Systems). Stimuli were presented on a 32-inch NordicNeuroLab LCD monitor (1920 ×1080 pixels, 120 Hz refresh rate) and viewed via a head coil-mounted mirror; eye gaze was not monitored. Participants gave predefined button-presses on ResponseGrip hardware (NordicNeuroLab, Bergen, Norway), using fingers of both hands.

The MC-T (Fig. 1) was modified from Fleming et al. [66,67] and implemented in a block design. A 2:1 staircase procedure was applied to maintain individual task performance at a constant level, so that all relevant between-group differences could reliably be attributed to group differences in metacognition [18,68]. The following event sequence was reiterated during the task: For 1000 ms, participants were initially presented with two white circles (diameter: 3.96° of visual angle) on dark background with white central crosshairs (global x-shift from center of the screen: ± 2.64°). Subsequently, the crosshairs were removed and randomly distributed white dots (diameter: 0.11°) were

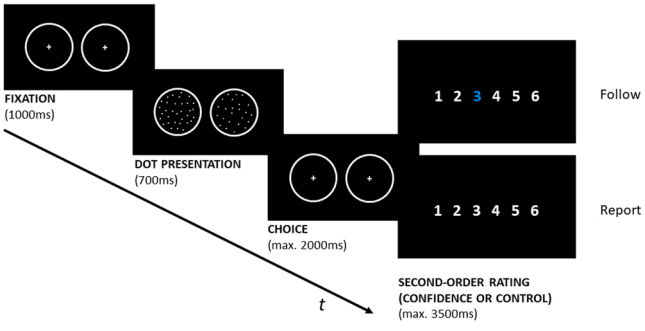

Fig. 1. Schematic trial representation for the 2AFC magnitude comparison task (MC-T). After a fixation period and presentation of dots, participants were required to make binary judgments about which circle (left/right) contained the higher number of dots. On each trial during the experimental phase, they subsequently stated either their confidence in their decision ("Report") or moved the cursor to a color-coded position on the scale ("Follow"). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

presented inside both circles for 700 ms before being replaced by identical crosshairs as before. Within 2000 ms after dot offset, participants were asked to indicate which circle (left/right) had contained the higher number of dots. On each trial during the experimental phase, they were then required to provide a second-order rating.

Corresponding to the experimental design of our previous study [25], there were two second-order (type 2) rating conditions, one requiring the employment of genuine metacognitive processes ("Report", 100 trials) and one serving as a matched control condition with identical motor, but different cognitive demands ("Follow", 50 trials). Each block of 10 "Report" trials was followed by 5 "Follow" trials, which were then succeeded by a new "Report" block. On "Report" trials, participants were required to state their subjective confidence in having rendered a correct perceptual judgment within 3500 ms on a 6-point-Likert-scale with discrete levels of confidence (1 = "no confidence at all", 6 = "very high confidence"). Participants moved a cursor along the scale by index finger button-presses, starting from a randomly determined initial cursor position, until they arrived at the position on the scale most consistent with their subjective feeling of confidence, which they were asked to confirm via thumb button-presses. In the "Follow" condition, participants were required to navigate towards and confirm a randomly determined color-coded number on the scale and withhold from reporting their subjective confidence.

Before initiation of the experimental phase, participants performed 100 training trials without second-order ratings, which were used to calibrate task difficulty for the experimental phase. In line with Fleming et al. [66], one randomly assigned circle on each trial (left/right) contained a variable number of dots ("variable circle") depending on the participant's performance, whereas the other circle always contained exactly 50 dots ("fixed circle"). At the beginning of staircase calibration, a dot number between 35 and 49 or between 51 and 65 was randomly determined for the variable circle, so either circle type could represent the target circle (i.e., the one with the greater number of dots). Equating the difficulty of the MC-T was achieved by titrating the difference in dot number (Δd) between the two circles; the Δd value in the final trial of the training phase was entered as the starting point for the staircase during the experimental phase. After two consecutive correct responses in the training or experimental phase, Δd was decreased by one dot; after one incorrect response, however, Δd was increased by one dot [66]. The variable circle was not allowed to contain exactly 50 dots (Δd=0), so in the case of two consecutive correct responses at Δd= 1, Δd was not decreased.

2.4. Imaging protocol

Imaging data were collected using a 3-Tesla field strength MAGNETOM Tim-Trio MRI system (Siemens, Erlangen, Germany) equipped with a standard 12-channel head coil for signal transmission and reception. Participants' heads were fitted with foam pads to minimize motion-related artifacts. Functional MRI time-series with blood-oxygenation-level-dependent (BOLD) contrast of the whole brain were acquired using a T_2*-weighted gradient-echo planar image (EPI) sequence (repetition time=2500 ms; echo time=30 ms, matrix size=96×96, slice thickness=3.0 mm, field of view=192 mm, flip angle=90°, voxel size=2×2×3 mm, 37 transversal slices). A T_1-weighted gradient-echo sequence with inversion recovery (repetition time=1660 ms, echo time=2.54, inversion time=850 ms, matrix size=320×320, slice thickness=0.8 mm, field of view=256 mm, flip angle=9°, voxel size=0.8 × 0.8 × 0.8 mm, 208 sagittal slices) was used to acquire whole-brain high-resolution anatomical images for normalizing functional imaging data and detecting participants with apparent brain pathologies.

2.5. fMRI analyses

fMRI data were preprocessed and analyzed using *SPM8* and *SPM12* (Statistical Parametric Mapping; Wellcome Centre for Neuroimaging, London, UK) implemented in *Matlab R2014a* and *MatlabR2020b* (The MathWorks Inc., Natick, USA), respectively. Preprocessing was carried out using standardized protocols [69]. First, origins were set manually to anterior commissure to facilitate co-registration [70,71]. Anatomical images were segmented into grey matter, white matter, and cerebral spinal fluid using mutual information and a priori tissue probability maps [72]. After discarding the first five volumes of each functional time-series to ensure steady-state magnetization, functional images were motion-corrected during realignment using a least-squares approach and a six-parameter rigid body transformation; the segmented structural image was co-registered to the mean individual T_2*-weighted image. Furthermore, functional images were spatially normalized into standard stereotaxic Montreal Neurological Institute (MNI) space [73] via non-linear transformations, resampled at 2×2×2 mm resolution, and spatially smoothed using an isotropic full-width-at-half-maximum Gaussian kernel of 8 mm.

On the 1st (participant-wise) level, fMRI time-series were regressed onto the general linear model (GLM) in *SPM12*. Individual trials were modeled as events, as previously implemented by Fleming et al. [29], containing stick functions representing type 1 stimulus onsets and boxcar functions spanning the time from scale onset until confirmation of the second-order (i.e., report/follow) rating; low-frequency fluctuations in BOLD signal were excluded with a 128-s high-pass filter. Consequently, there were five regressors (Perception, CorrectReport, IncorrectReport, CorrectFollow, IncorrectFollow), the latter four "second-order regressors" parametrically modulated by the selected confidence rating in each trial, enabling discrimination between correct and incorrect responses, levels of confidence and perceptual (type 1) and metacognitive (type 2) judgments. Motion-correction parameters were added to the GLM as covariates of no interest; regressors were convolved with a canonical hemodynamic response function (HRF).

As a first exploratory step on the 2nd (group-wise) level, separate random-effects analyses (one-sample *t*-tests) were carried out on 1st level contrast images for perceptual judgments and combined second-order regressors against zero to identify overall patterns of activation, irrespective of Drug or Rating Type (see below). As preregistered, corresponding contrast images of second-order regressors were subsequently entered into a full factorial analysis using the between-subjects factor "Drug" (ketamine/placebo) and within-subject factors "Rating Type" (report/follow) and "Perceptual Performance" (correct/incorrect). Analyses were conducted on the whole-brain level, not masking for any region of interest (ROI). Anatomical labels were inferred by the SPM anatomy toolbox atlas [74]; all reported activations survived $p < .05$, family-wise-error (FWE) corrected at the cluster-level, with a voxel-level threshold of $p < .001$ (uncorrected). Imaging data of one participant were excluded due to missing parts of the PFC in the anatomical image.

As preregistered full factorial analyses of BOLD activation yielded inconclusive results (see below), exploratory psychophysiological interaction (PPI) analyses were applied to assess ketamine effects on task-specific connectivity, i.e. regional changes in the relationship between activity in different areas of the brain as a function of the experimental manipulation [75]. PPI analyses are a powerful tool to explore task-specific functional connectivity, as they do not rely on a priori definitions of possible models [55]. Importantly, PPI measures explain the regional activity of different brain areas in terms of the interaction between a psychological (the task) and a deconvolved physiological factor (e.g., neural responses in a given seed region). Following Fleming et al. [29], we constructed a separate block-level 1st level design matrix for PPI analyses containing boxcar functions spanning the time from onset of one second-order rating block until onset of the succeeding block; consequently, events were defined as an entire block of Report (10) or Follow (5) trials. PPI analyses thus revealed regions exhibiting significant co-activations with the seed regions during Report compared to Follow trials. The time course vector of the

psychophysiological interaction was entered in a fixed-effect GLM along the Report and Follow vectors, the time course of the seed regions and motion-correction parameters as covariates of no interest, yielding a map of co-activations that systematically increased with genuine metacognition [29,76]. The automated generalized PPI toolbox (gPPI) [77] in *SPM8* was used to carry out PPI analysis based on the deconvolved first eigenvariate of the seed region time series [78], which among other advantages has proven to be particularly suited for analyzing fMRI data in block designs [79,80].

Seed regions were determined as a 6 mm sphere centered around the peak coordinate of clusters identified in the meta-analysis by Vaccaro and Fleming [54], which contained five clusters specifically related to metacognition in perceptual decision-making (coordinates are in MNI space): right anterior dorsolateral PFC [x = 26, y= 48, z = 28], right insula [x= 32, y= 20, z = -12], right insula/inferior frontal gyrus (IFG) [44, 14, 0], as well as two global maxima in bilateral pMFC [6, 38, 42; 2, 20, 38]. In 2nd level analyses for each of the seed voxels, drug-related differences in functional connectivity were assessed using random-effects analyses (two-sample *t*-tests) to investigate the differential co-activation maps in a metacognition network during ketamine vs. placebo. Again, we applied a whole-brain cluster-level FWE-correction ($p < .05$) with a peak-level threshold of .001 (uncorrected).

2.6. Behavioral analyses

Both type 1 (task) and type 2 (metacognitive) performance were assessed in a signal detection theory (SDT) framework [81,82]. As reported previously [25], only confidence ratings given on "Report" trials following a completed perceptual judgment contributed to analysis. Since perceptual performance was equated by use of a staircase procedure, there is substantial interpretative value of absolute metacognitive sensitivity (meta-d′) in and by itself [13]. However, as staircase-related stimulus variability could lead to differential effects on ability estimates [18], we considered measures of both absolute metacognitive sensitivity (meta-d′) and type 1 performance-corrected metacognitive sensitivity or *efficiency* (meta-d′/d′), computed in Matlab using the HMeta-d toolbox, which implements a hierarchical Bayesian framework [83]. Among other advantages, this approach yields a more accurate estimation of subject-level parameters by constraining subject-level fits to the group-level estimate and avoiding the need for edge correction, which may otherwise lead to biased subject-level estimates especially with smaller trial counts. In addition, regularization of efficiency estimates by use of the hierarchical approach consistently improves their test-retest reliability [84]. Analysis of the difference between the group posterior densities of independently fitted models for ketamine and placebo groups can be found in the supplementary materials. The HMeta-d toolbox uses Markov-Chain-Monte-Carlo sampling from the posterior distributions [83]; three chains were run for estimation and parameter convergence was assessed by inspection of scale-reduction statistics [85].

Although the variability-based inflation of metacognitive performance estimates may be negligible for studies (a) employing very small step sizes ($\Delta d \pm 1$) and (b) which achieve staircase calibration prior to actual data collection [18], two conditions satisfied in the present study, we monitored stimulus variability in our staircase by testing for group differences in variability (normalized *SD*) and conducting an analysis of covariance (ANCOVA) for drug effects on metacognition measures, controlling for variability (see supplementary materials). In addition, we considered the absolute perceptual threshold, i.e., the stimulus value (Δd) at the end of staircase calibration and its mean value during the experiment, as systematic stimulus differences between groups would suggest perceptual impacts by ketamine despite equating performance. Following a reviewer's comment, this was also investigated in a Bayesian model comparison framework (see supplementary materials) beyond the analyses reported here, using the BayesFactor package [86] in *R* (Version 4.0.1, The R Foundation).

As in our previous publication [25], we extended our preregistered analysis plan to metacognitive bias (quantified as average confidence rating minus average performance) to test for group differences in level of confidence which cannot be explained by group differences in performance, and conducted Pearson's correlations between ability estimates and metacognitive bias with the individual 5D-ASC scores, while correcting for multiple comparisons (Bonferroni-corrected $\alpha = 0.05$, divided by number of correlations). Due to the potential ambiguity of interpretations regarding the lower end of the confidence scale in a 2AFC task [60], we also report group differences in average confidence level, not corrected for performance. Finally, mean beta-values for peak-voxels of significant clusters obtained in the two-sample *t*-tests on PPI contrasts were extracted using the *MarsBar* toolbox in Matlab [87] by transforming clusters into binary mask images. We consequently explored the relationship of behavioral outcomes with regions significantly co-activated with core areas of metacognition during ketamine compared to placebo via separate Pearson's correlations for ketamine and placebo groups.

All analyses of behavioral data were carried out in *SPSS* 22 (IBM Corp., Armonk, USA). As preregistered, data points outside three interquartile ranges of a boxplot were considered to be extreme outliers and not included in data analysis. To ensure that all requirements for statistical analyses were met, data were screened for normality of distribution using histograms, skewness scores and Kolmogorov-Smirnov tests ($\alpha = 0.05$); Levene's statistics were inspected to ensure homoscedasticity. Two-sample *t*-tests were employed to test for drug effects on 5D-ASC scales, stimulus value and variability, metacognitive bias, type 1 (d′) and type 2 (meta-d′; meta-d′/d′) performance as well as perceptual and second-order response times, the latter separately for Report and Follow; Cohen's *d* [88] was calculated for effect sizes. Raincloud plots [89] were created in *R* to visualize data distributions.

3. Results

3.1. Behavioral results

Descriptive statistics of dependent variables per group are in Table 1.

Table 1
Descriptive statistics of 5D-ASC measures, behavioral outcome measures, and response times, per group.

Measure	Ketamine ($n = 26$)		Placebo ($n = 19$)	
	M	*SD*	*M*	*SD*
5D-ASC				
[Global Index of Altered State]*	10.29	9.67	0.68	1.14
Oceanic Boundlessness*	13.89	15.53	0.49	1.22
Dread of Ego Dissolution*	8.53	9.55	0.86	1.36
Visionary Restructuralization*	6.94	7.83	0.74	1.34
Auditory Alterations*	5.85	6.64	1.27	2.24
Vigilance Reduction*	28.67	19.25	5.76	6.41
Stimulus properties				
Initial stimulus value	3.85	3.08	4.42	2.46
Mean stimulus value	4.13	1.04	3.98	1.08
Stimulus variability	2.07	0.46	1.96	0.58
Behavioral outcome measures				
Type 1 sensitivity (d′)	0.87	0.23	0.99	0.25
Type 2 sensitivity (meta-d′)*	0.33	0.39	0.61	0.52
Type 2 efficiency (meta-d′/d′)	0.39	0.45	0.63	0.50
Average confidence level	3.74	0.95	4.02	0.48
Metacognitive bias	-0.10	0.20	-0.05	0.10
Response times (RT, in ms)				
Type 1 RT	671	150	625	168
Report RT	1637	285	1643	281
Follow RT	1494	236	1450	225

Note: Scale values are in percent. M, mean; ms, milliseconds; RT, response time; SD, standard deviation. *significant effect of Drug ($P < .05$).

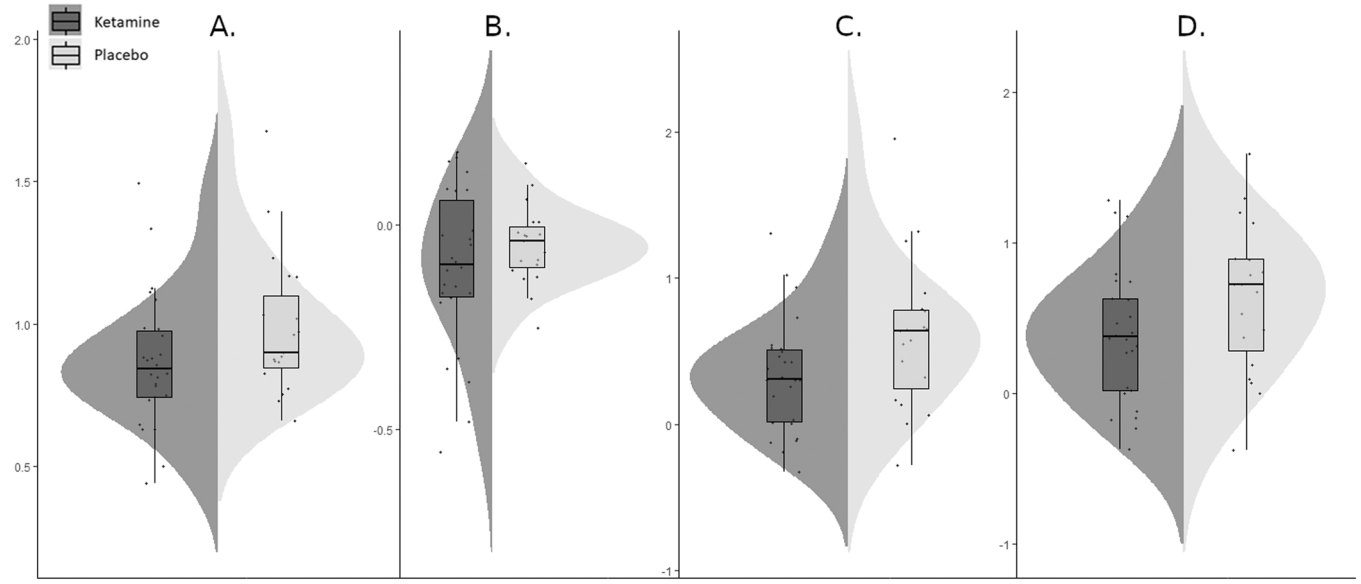

Fig. 2. Raincloud plots for behavioral outcome measures, per group (ketamine, dark grey; placebo, light grey). **A.** Type 1 sensitivity (d′), **B.** performance-corrected metacognitive bias, **C.** Type 2 sensitivity (meta-d′), and **D.** Type 2 efficiency (meta-d′/d′).

Raincloud plots for key outcome measures per group are in Fig. 2; additional raincloud plots for average confidence ratings, response times and stimulus properties can be found in the supplementary materials.

5D-ASC: Highly significant group differences emerged on all scales, with the ketamine group exhibiting higher values on "Oceanic Boundlessness" ($t(25.42) = 4.38$, $p < .001$, $d = 1.22$); "Dread of Ego Dissolution" ($t(26.37) = 4.04$, $p < .001$, $d = 1.12$); "Visionary Restructuralization" ($t(26.94) = 3.91$, $p = .001$, $d = 1.09$); "Auditory Alterations" ($t(32.32) = 3.26$, $p = .003$, $d = 0.92$) and "Vigilance Reduction" ($t(32.14) = 5.66$, $p < .001$, $d = 1.6$) as well as on the composite score of altered consciousness ($t(25.94) = 4.3$, $p < .001$, $d = 1.4$).

However, the 5D-ASC scores did not correlate significantly with type 1 and type 2 outcome measures (all $P > .001$), not even when applying a less conservative correction threshold (all $P > .05$).

Behavioral outcome measures: No significant group difference was observed in stimulus variability ($t(43) = 0.71$, $p = .482$, $d = 0.21$); therefore, a confounding influence of this factor on behavioral outcome variables was not assumed. There were also no significant between-group differences for d′ as the measure of task performance ($t(43) = 1.64$, $p = .109$, $d = 0.49$), or for the initial ($t(43) = 0.70$, $p = .506$, $d = 0.21$) and mean ($t(43) = 0.45$, $p = .65$, $d = 0.14$) stimulus value during experimental blocks. These results were validated by ANCOVA and Bayesian model comparisons (see supplementary materials).

At the type 2 level, meta-d′ or absolute metacognitive sensitivity ($t(43) = 2.04$, $p = .047$, $d = 0.6$) significantly deteriorated under ketamine, whilst the group difference on meta-d′/d′, the measure of relative metacognitive sensitivity/efficiency, was only marginally significant ($t(43) = 1.7$, $p = .096$, $d = 0.51$). There was no significant difference between groups in average confidence level ($t(38.89) = 1.29$, $p = .206$, $d = 0.37$) or performance-corrected metacognitive bias ($t(38.19) = 1.23$, $p = .225$, $d = 0.35$). See supplementary materials for further hierarchical Bayesian analyses on group-level values of metacognitive efficiency.

Response times: Neither type 1 ($t(43) = 0.96$, $p = .343$, $d = 0.29$), nor report ($t(43) = 0.07$, $p = .947$, $d = 0.02$), nor follow response times ($t(43) = 0.62$, $p = .538$, $d = 0.19$) significantly differed between groups.

3.2. BOLD results

One-sample *t*-tests: Random-effects analyses revealed increased activation across groups during perceptual judgments compared to baseline in bilateral pMFC and superior frontal gyrus. One-sample *t*-tests furthermore revealed increased activation during second-order reports (Report and Follow) compared to baseline in left fusiform gyrus; bilateral occipital cortex; superior, inferior and middle temporal gyrus; and motor cortex; decreases in activation were mainly observed in bilateral angular gyrus. For detailed information on clusters and peak-voxels in one-sample *t*-tests, see supplementary tables 1–3.

Full factorial analysis: Our preregistered full factorial analysis with factors "Drug", "Rating Type" and "Perceptual Performance" failed to reveal significant differences in BOLD activation between ketamine and placebo. In contrast to results of our previous study, we were also unable to observe clusters significantly more activated during Report than Follow trials. However, we found increased BOLD signal for the reverse contrast (Follow > Report) in two clusters centered around peak-voxels in bilateral cuneus and precuneus, the latter representing a core structure of the DMN [90]; details are given in Table 2. There were no significant effects in either direction of the factor "Perceptual Performance" (correct/incorrect) and no significant interactions (all $P > .05$).

Functional connectivity analyses: Two-sample *t*-tests revealed significantly higher task-specific connectivity under ketamine compared to placebo (Fig. 3) between the seed voxel in right anterior dorsolateral PFC and two left-hemispheric clusters (Table 3) during Report compared to Follow ratings: one centered in middle temporal gyrus, with additional local maxima in supramarginal, superior temporal and angular gyrus, the other cluster centered in precentral gyrus with an additional local maximum in mid cingulum.

There was also significantly higher functional connectivity under

Table 2
Summary of significant clusters for the Follow > Report contrast.

Anatomical label	Laterality	Cluster size [*k*]	*T*-Value	Peak-voxel MNI coordinates		
Cuneus	L/R	398	3.94	0	-82	36
Cuneus	R		3.80	6	-82	36
Precuneus	R		3.56	16	-78	46
Cuneus	L		3.55	-6	-88	24
Precuneus	L	174	4.43	-4	-46	74
Precuneus	R		4.14	6	-46	74

Note: Combined sample. Only unique anatomical labels are reported for each cluster at one laterality. Whole-brain cluster-level FWE-corrected ($P < .05$). FWE, familywise error; L, left; MNI, Montreal Neurological Institute; R, right.

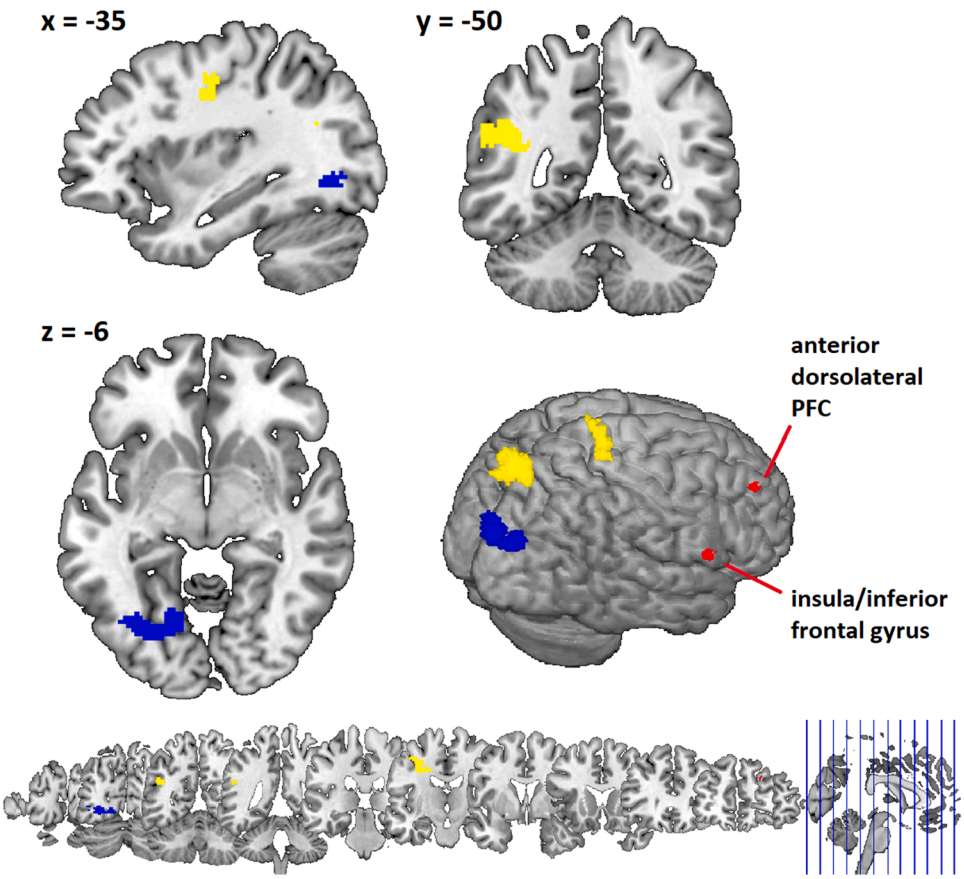

Fig. 3. Increases in functional connectivity during metacognition under ketamine, significant at $P < .05$ (FWE-corrected). Blue and yellow colors indicate areas with significantly higher task-specific connectivity under ketamine compared to placebo with the seed voxel in anterior dorsolateral PFC (yellow) and with the seed voxel in right insula/IFG (blue) during Report trials. Positions of seed voxels are highlighted in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Summary of areas displaying significantly higher task-specific connectivity with the seed voxel in right anterior dorsolateral PFC under ketamine compared to placebo.

Anatomical label	Laterality	Cluster size [*k*]	*T*-Value	Peak-voxel MNI coordinates		
Middle temporal gyrus	L	396	4.82	-46	-48	22
Supramarginal gyrus	L		4.49	-54	-50	24
Superior temporal gyrus	L		4.41	-44	-46	18
Angular gyrus	L		3.99	-42	-64	26
Precentral gyrus	L	150	4.65	-32	-10	38
Mid cingulum	L		3.95	-20	-14	36

Note: Only unique anatomical labels are reported for each cluster at one laterality. Whole-brain cluster-level FWE-corrected ($P < .05$). FWE, familywise error; L, left; MNI, Montreal Neurological Institute.

Table 4
Summary of areas displaying significantly higher task-specific connectivity with the seed voxel in right insula/IFG under ketamine compared to placebo.

Anatomical label	Laterality	Cluster size [*k*]	*T*-Value	Peak-voxel MNI coordinates		
Lingual gyrus	L	299	4.74	-16	-66	-4
Occipital fusiform gyrus	L		4.36	-30	-72	-6
Middle occipital gyrus	L		4.08	-40	-68	-2

Note: Only unique anatomical labels are reported for each cluster at one laterality. Whole-brain cluster-level FWE-corrected ($P < .05$). FWE, familywise error; L, left; MNI, Montreal Neurological Institute.

ketamine compared to placebo between the seed voxel in right insula/IFG and one left-hemispheric cluster in lingual gyrus, with local maxima in occipital fusiform gyrus and middle occipital gyrus (Fig. 3, Table 4).

Correlations with behavioral outcomes: There were no significant correlations between behavioral outcome measures and mean beta-values extracted for peak-voxels of significant clusters in the two-sample *t*-tests on PPI maps (all $P > .001$).

4. Discussion

This study aimed to improve our understanding of the role of the glutamatergic system in metacognition by means of a ketamine challenge, as participants provided trial-by-trial confidence ratings on a perceptual decision-making task during functional brain imaging. Our data indicate that the NMDA-glutamate-receptor antagonist ketamine impacted on the accuracy of meta-perceptual judgments, as it led to significantly lower absolute metacognitive sensitivity. Together with our previous study [25], we conclude that the precision of metacognitive evaluations is attenuated during the ketamine-induced psychedelic state. Since there was no clear evidence of ketamine-induced alterations in other task-related components in either study, neither at the behavioral nor at the neural level, there also appears to be some specificity in the effects of glutamatergic modulation of metacognition, although several factors warrant caution about such conclusions, as outlined below. We were surprised to find that metacognitive bias was unaffected by the drug and that the neural correlates of the ketamine effect on metacognitive performance remained obscure in the preregistered full factorial analysis; however, exploratory PPI analysis revealed ketamine-induced increases in fronto-posterior functional connectivity, thereby providing firm evidence for specific ketamine-induced alterations in metacognitive processes at the neural level. Finally, the induction of substantial alterations of consciousness was confirmed by

significant ketamine effects on all scales of the 5D-ASC questionnaire, although these were somewhat smaller overall than previously observed [25]. As can be inferred from Table 1, effects on sleepiness (vigilance reduction) as well as joyful aspects of subjective experience (oceanic boundlessness) were most prominent, whereas visual or auditory perceptual alterations were reported to a lesser extent.

Whereas our previous study demonstrated stable overconfidence with ketamine, independent of whether or not the drug was currently administered at the time of metacognitive reports, the present analysis was unable to reveal significant group differences in metacognitive bias, with average bias even descriptively lower for ketamine than placebo (Table 1). As discussed previously [25], it cannot be ruled out that baseline differences between groups may have caused the effect reported there; after all, experimental control of such factors is inevitably limited in a between-subjects design. Nevertheless, an interesting notion arises with regard to the noticeably wider spread of bias values in the ketamine group compared to placebo, as evident from Fig. 2B, suggesting that ketamine may in fact be associated with both under- and overconfidence. Such response-heterogeneity might reflect individual differences potentially amplified by ketamine application: Since metacognitive bias has been demonstrated to possess domain-general properties [91,92] that can partially be tapped by self-report measures [61], it may well represent a trait-like quality which could be differentially affected by pharmacological stimulation. Even so, the present finding is not readily placed within the context of the clinical metacognition literature, which e.g. focuses on ketamine as a model system of schizophrenia [93], since overconfidence in incorrect responses has repeatedly been demonstrated in patients with schizophrenia [94,95]. It should be noted, however, that metacognitive phenomena such as jumping-to-conclusions in perceptual decision-making have been argued to depend on the type of schizophrenic symptomatology [96] and that a recent meta-analysis attributed the reported global metacognitive deficit in schizophrenia to methodological shortcomings of multiple studies, such as failures to account for the influence of task performance on metacognitive performance estimates [97].

Although the link between fluctuations in conscious awareness and metacognitive bias is not straightforward, the present finding may also provide clues on whether alterations in conscious experiences and/or a reduction of the sensory reliability of the input to the metacognitive process give rise to the ketamine-associated deterioration of metacognitive accuracy, as outlined previously [25]. Indeed, it could be suggested that the neural correlates reported there may qualify more as a neural correlate of subjective awareness [13] and thus reflect alterations in conscious experience (such as hallucinations etc.), which would be consistent with the association of involved brain areas with the posterior hot zone of conscious functions [26]. Ultimately, the unspecific nature of our previous finding (as the activation reported there was observed in a contrast aggregating over both second-order rating conditions, [25]) restrains confidence in such considerations.

To interpret ketamine effects on metacognitive evaluations and their underlying neuronal mechanisms as thoroughly as possible, it is important to ensure that these are not biased by potential effects on perceptual processes. Given the absence of statistically significant group differences in perceptual performance and response times, this could reasonably be assumed. However, not only descriptively lower average accuracy and slower type 1 response times in the ketamine group warrant a cautionary note regarding our interpretations for the behavioral and neural effects; most importantly, the group difference in relative metacognitive sensitivity or efficiency was slightly above the required significance level. Although it appears ultimately likely that this comes a result of insufficient statistical power following the extensive data exclusion due to a technical error, the possibility must be acknowledged that this non-significance may reflect the influence of relevant group-heterogeneity in perceptual performance. Importantly, however, neither staircase variability nor the initial or mean stimulus value were significantly different between the groups, which augments the relative informativeness of the ketamine effect on absolute metacognitive sensitivity.

At the neural level, the preregistered full factorial analysis yielded neither a significant main effect of Drug nor significant interactions with other factors. Likewise, we were unable to replicate the previously observed activation pattern in the Report > Follow contrast [25]. Instead, the functional connectivity patterns observed in our exploratory PPI analysis may offer a complementary explanation to the fluctuations in conscious awareness for the involvement of posterior brain areas during the ketamine challenge. Using two-sample *t*-tests, we observed increased task-specific connectivity with ketamine compared to placebo between frontal and posterior regions, namely between anterior dorsolateral PFC and temporal and posterior frontal structures, as well as between insula/IFG and a left-hemispheric occipital cluster centered in lingual gyrus.

The latter finding offers an intriguing association with Fleming et al. [29], who demonstrated increased task-specific connectivity in Report > Follow between right rostrolateral PFC and left lingual gyrus. Benedek et al. [98] also found increased connectivity between right anterior inferior parietal lobe and bilateral lingual gyrus, which they associated with internally directed attention and a potential perceptual decoupling process that shields ongoing internal processes from distracting sensory stimulation. Although no connectivity analyses were performed in our previous study, lingual gyrus was bilaterally activated more strongly under ketamine than placebo across both second-order ratings, and also displayed higher right-hemispheric activations during Report than Follow, independent of drug.

Notably, connectivity effects reported here were contralateral in both cases (see Tables 3–4), i.e. with the seed voxel located in the right and the significantly co-activated clusters in the left hemisphere. Based on this convergent evidence, one might suggest this ketamine-induced increase in task-specific connectivity to be the clearest neural correlate of impacted metacognition under ketamine obtained so far, as it could reveal a potential pattern within the neurocircuitry underlying operations of a pharmacologically challenged metacognitive system. Reframing previous arguments about a perceptual decoupling process [98], said connectivity could also be regarded as the manifestation of a compensatory mechanism to counteract the ketamine-induced loss of cause-effect information associated with each concept [50], as the brain explores an expanded repertoire of dynamical states in an unconstrained and hyper-associative fashion [99]. As it could be argued that metacognitive reports in standard experimental paradigms essentially tap such concepts or (meta-)representations, the diminished behavioral performance observed here could be indicative of this loss of information. Such an interpretation would be consistent with brain networks being less anti-correlated in the psychedelic state, according to resting-state connectivity analyses [100], perhaps accompanied by a shift from cortically centered to subcortically centered patterns of connections [101]. A more recent study suggested ketamine-associated increases in resting-state connectivity within the executive network, but decreases in salience network connectivity [102]; see Cavanna et al. [103] for a thorough account of how altered states of consciousness affect meta-stability in brain dynamics. It is worth noting, however, that results obtained in resting-state analyses of functional connectivity should be regarded as complementary to task-specific connectivity patterns as illustrated in the present study due to the limited comparability of both methods, because changes in connectivity during the resting state can indicate either alterations in connectivity between the nodes of the network or changes in activity within the network [55].

Interestingly, Fleming et al. [29] suggested their finding of increased connectivity between rostrolateral PFC and lingual gyrus to be indicative of "neural representations of object-level task uncertainty that may be then re-represented for use in metacognitive report" (p. 6123). The precision of perceptual decisions is determined by a flow of information processing from early posterior (in particular, occipital) sources, signaling a representation of accumulated decision evidence, to anterior

regions, which track internal evidence for metacognitive confidence throughout perceptual decision-making [104]. Accordingly, one could argue with respect to IIT that such re-representation is increasingly invoked under the ketamine challenge, as core areas of confidence formation rely more on information provided e.g. by the lingual gyrus, a structure known to be involved in the encoding and recollection of complex visual memories [105]. This could encompass neural representations of words in our previous study or of quantitative sets in the present study. Such an explanatory approach could also accommodate increased functional connectivity under ketamine compared to placebo between right anterior dorsolateral PFC and left middle temporal, supramarginal and precentral gyrus, as areas dedicated to higher-order metacognitive monitoring may feed off an evidence accumulation process integrating information on inter-sensory conflict during action-feedback monitoring [106] or other relevant somatosensory information, e.g. on space and limbs location [107].

4.1. Limitations

Several shortcomings of the present study have to be acknowledged. First, the neuroanatomical specificity of glutamatergic modulations is inevitably limited, as glutamate is the primary excitatory neurotransmitter of the central nervous system [108]. Another limitation concerns the study's sample size. Whilst each group was within the range or exceeded sample sizes of previous studies employing within-subject designs [109,110], the sample size may yet have been too small to detect ketamine effects beyond those reported here. This can be attributed to the extensive exclusion of participants with unsuccessful staircase calibration, and may account not only for the failure to reproduce the main effects on BOLD in the Ketamine > Placebo and Report > Follow contrasts as reported previously, but in particular to ketamine effects on relative metacognitive sensitivity or efficiency, for which we only observed a marginally significant difference between the groups. Finally, it should be noted that comparability with previous findings is limited by factors unrelated to genuine metacognition. In particular, this concerns differences in task requirements, which may generally obscure a latent domain-general factor [111]. In our previous study [25], a meta-memory task was conducted using a Yes-No response format for the first-order task, whereas the MC-T employed a 2AFC response format. Although we were nonetheless able to provide evidence that glutamatergic modulations may tap an at least partially shared neurophysiological substrate at the neurotransmitter level of both metacognitive subsystems, confidence in conclusions about variations in result patterns is limited due to this heterogeneity. In the future, direct comparisons should be carried out by applying both tasks in a single session within the same sample, and should eliminate differences in task requirements, timing of task application during infusion, and other relevant factors.

5. Conclusions

Our findings suggest that the accuracy of metacognitive evaluations in a perceptual decision-making framework is impacted as a consequence of acute ketamine administration. Building on these findings as well as previous evidence, we suggest that the integrity of the glutamatergic system at least represents a precondition for preserved metacognition. Nevertheless, given the moderate effect sizes of the reported findings, contributions from other neurotransmitter systems seem eminently plausible. The observed increases in fronto-posterior task-specific connectivity under ketamine might be indicative of re-representations of object-level features for use in metacognitive report. The generalizability of such conclusions should be elucidated by future research to help compose a fundamental account of the biological substructures that constitute the functional architecture of metacognition.

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CRediT authorship contribution statement

Mirko Lehmann: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Claudia Neumann:** Investigation, Resources, Writing – review & editing. **Sven Wasserthal:** Investigation, Writing – review & editing. **Achilles Delis:** Investigation, Resources, Writing – review & editing. **Johannes Schultz:** Supervision, Writing – review & editing. **René Hurlemann:** Resources, Writing – review & editing. **Ulrich Ettinger:** Conceptualization, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Declarations of interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbr.2022.113925.

References

[1] B. Timmermans, L. Schilbach, A. Pasquali, A. Cleeremans, Higher order thoughts in action: consciousness as an unconscious re-description process, Philos. Trans. R. Soc. B Biol. Sci. 367 (2012) 1412–1423, https://doi.org/10.1098/rstb.2011.0421.
[2] J.E. Szczepanik, H. Brycz, P. Kleka, A. Fanslau, C.A. Zarate, A.C. Nugent, Metacognition and emotion – how accurate perception of own biases relates to positive feelings and hedonic capacity, Conscious. Cogn. 82 (2020), 102936, https://doi.org/10.1016/j.concog.2020.102936.
[3] J.H. Flavell, Metacognitive aspects of problem solving, in: L. Resnick (Ed.), Nat. Intell., Lawrence Erlbaum Associates, Hillsdale, NJ, 1976, pp. 231–235.
[4] J.H. Flavell, Metacognition and cognitive monitoring: a new area of cognitive–developmental inquiry, Am. Psychol. 34 (1979) 906.
[5] T.O. Nelson, L. Narens, Why investigate metacognition, in: J. Metcalfe, A. P. Shimamura (Eds.), Metacognition: Knowing about Knowing, The MIT Press, Cambridge, MA, US, 1994, pp. 1–25, https://doi.org/10.7551/mitpress/4561.001.0001.
[6] T.O. Nelson, Consciousness and metacognition, Am. Psychol. 51 (1996) 102–116, https://doi.org/10.1037//0003-066x.51.2.102.
[7] M. Allen, D. Frank, D.S. Schwarzkopf, F. Fardo, J.S. Winston, T.U. Hauser, G. Rees, Unexpected arousal modulates the influence of sensory noise on confidence, Elife 5 (2016) 1–17, https://doi.org/10.7554/eLife.18103.
[8] B. Bahrami, K. Olsen, D. Bang, A. Roepstorff, G. Rees, C. Frith, What failure in collective decision-making tells us about metacognition, Philos. Trans. R. Soc. B Biol. Sci. 367 (2012) 1350–1365, https://doi.org/10.1098/rstb.2011.0420.
[9] C. Eichner, F. Berna, Acceptance and efficacy of metacognitive training (MCT) on positive symptoms and delusions in patients with schizophrenia: a meta-analysis taking into account important moderators, Schizophr. Bull. 42 (2016) 952–962, https://doi.org/10.1093/schbul/sbv225.
[10] S. Moritz, C. Andreou, B.C. Schneider, C.E. Wittekind, M. Menon, R.P. Balzan, T. S. Woodward, Sowing the seeds of doubt: a narrative review on metacognitive training in schizophrenia, Clin. Psychol. Rev. 34 (2014) 358–366, https://doi.org/10.1016/j.cpr.2014.04.004.
[11] A. Wells, P. Fisher, S. Myers, J. Wheatley, T. Patel, C.R. Brewin, Metacognitive therapy in recurrent and persistent depression: a multiple-baseline study of a new treatment, Cogn. Ther. Res. 33 (2009) 291–300, https://doi.org/10.1007/s10608-007-9178-2.
[12] P. Grimaldi, H. Lau, M.A. Basso, There are things that we know that we know, and there are things that we do not know we do not know: confidence in decision-making, Neurosci. Biobehav. Rev. 55 (2015) 88–97, https://doi.org/10.1016/j.neubiorev.2015.04.006.

[13] S.M. Fleming, H.C. Lau, How to measure metacognition, Front. Hum. Neurosci. 8 (2014) 1–9, https://doi.org/10.3389/fnhum.2014.00443.

[14] L.M. Fitzgerald, M. Arvaneh, P.M. Dockree, Domain-specific and domain-general processes underlying metacognitive judgments, Conscious. Cogn. 49 (2017) 264–277, https://doi.org/10.1016/j.concog.2017.01.011.

[15] B. Baird, J. Smallwood, K.J. Gorgolewski, D.S. Margulies, Medial and lateral networks in anterior prefrontal cortex support metacognitive ability for memory and perception, J. Neurosci. 33 (2013) 16657–16665, https://doi.org/10.1523/jneurosci.0786-13.2013.

[16] S.M. Fleming, R.S. Weil, Z. Nagy, R.J. Dolan, G. Rees, Relating introspective accuracy to individual differences in brain structure, Science (80-) 329 (2010) 1541–1543, https://doi.org/10.1126/science.1191883.

[17] S.J. Galvin, J.V. Podd, V. Drga, J. Whitmore, Type 2 tasks in the theory of signal detectability: discrimination between correct and incorrect decisions, Psychon. Bull. Rev. 10 (2003) 843–876, https://doi.org/10.3758/BF03196546.

[18] D. Rahnev, S.M. Fleming, How experimental procedures influence estimates of metacognitive ability, Neurosci. Conscious (2019) (2019), https://doi.org/10.1093/nc/niz009.

[19] B. Maniscalco, H. Lau, A signal detection theoretic approach for estimating metacognitive sensitivity from confidence ratings, Conscious. Cogn. 21 (2012) 422–430, https://doi.org/10.1016/j.concog.2011.09.021.

[20] B. Maniscalco, H. Lau, Signal detection theory analysis of type 1 and type 2 data: meta-d′, response-specific meta-d′, and the unequal variance SDT model, in: Cogn. Neurosci. Metacognition, Springer, 2014: pp. 25–66. ⟨https://doi.org/10.1007/978-3-642-45190-4_3⟩.

[21] S.M. Fleming, R.J. Dolan, The neural basis of metacognitive ability, Philos. Trans. R. Soc. B Biol. Sci. 367 (2012) 1338–1349, https://doi.org/10.1098/rstb.2011.0417.

[22] T.U. Hauser, M. Allen, N. Purg, M. Moutoussis, G. Rees, R.J. Dolan, Noradrenaline blockade specifically enhances metacognitive performance, Elife 6 (2017) 1–13, https://doi.org/10.7554/eLife.24901.

[23] G. Reyes, A. Vivanco-Carlevari, F. Medina, C. Manosalva, V. de Gardelle, J. Sackur, J.R. Silva, Hydrocortisone decreases metacognitive efficiency independent of perceived stress, Sci. Rep. 10 (2020) 14100, https://doi.org/10.1038/s41598-020-71061-3.

[24] M. Clos, N. Bunzeck, T. Sommer, Dopamine is a double-edged sword: dopaminergic modulation enhances memory retrieval performance but impairs metacognition, Neuropsychopharmacology 44 (2019) 555–563, https://doi.org/10.1038/s41386-018-0246-y.

[25] M. Lehmann, C. Neumann, S. Wasserthal, J. Schultz, A. Delis, P. Trautner, R. Hurlemann, U. Ettinger, Effects of ketamine on brain function during metacognition of episodic memory, Neurosci. Conscious 2021 (2021), https://doi.org/10.1093/nc/niaa028.

[26] C. Koch, M. Massimini, M. Boly, G. Tononi, Neural correlates of consciousness: Progress and problems, Nat. Rev. Neurosci. 17 (2016) 307–321, https://doi.org/10.1038/nrn.2016.22.

[27] R. Ihalainen, O. Gosseries, F. Van de Steen, F. Raimondo, R. Panda, V. Bonhomme, D. Marinazzo, H. Bowman, S. Laureys, S. Chennu, How hot is the hot zone? Computational modelling clarifies the role of parietal and frontoparietal connectivity during anaesthetic-induced loss of consciousness, Neuroimage 231 (2021), 117841, https://doi.org/10.1016/j.neuroimage.2021.117841.

[28] R. Kupers, P. Pietrini, E. Ricciardi, M. Ptito, The nature of consciousness in the visually deprived brain, Front. Psychol. 2 (2011) 19, https://doi.org/10.3389/fpsyg.2011.00019.

[29] S.M. Fleming, J. Huijgen, R.J. Dolan, Prefrontal contributions to metacognition in perceptual decision making, J. Neurosci. 32 (2012) 6117–6125, https://doi.org/10.1523/JNEUROSCI.6489-11.2012.

[30] M.W. Tyler, H.B. Yourish, D.F. Ionescu, S.J. Haggarty, Classics in chemical neuroscience: ketamine, ACS Chem. Neurosci. 8 (2017) 1122–1134, https://doi.org/10.1021/acschemneuro.7b00074.

[31] J.H. Krystal, G. Sanacora, R.S. Duman, Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond, Biol. Psychiatry 73 (2013) 1133–1141, https://doi.org/10.1016/j.biopsych.2013.03.026.

[32] L. Barnett, S.D. Muthukumaraswamy, R.L. Carhart-Harris, A.K. Seth, Decreased directed functional connectivity in the psychedelic state, Neuroimage 209 (2020), 116462, https://doi.org/10.1016/j.neuroimage.2019.116462.

[33] J. Sleigh, M. Harvey, L. Voss, B. Denny, Ketamine – more mechanisms of action than just NMDA blockade, Trends Anaesth. Crit. Care 4 (2014) 76–81, https://doi.org/10.1016/j.tacc.2014.03.002.

[34] C.G. Abdallah, L.A. Averill, K.A. Collins, P. Geha, J. Schwartz, C. Averill, K. E. DeWilde, E. Wong, A. Anticevic, C.Y. Tang, D.V. Iosifescu, D.S. Charney, J. W. Murrough, Ketamine treatment and global brain connectivity in major depression, Neuropsychopharmacology 42 (2017) 1210–1219, https://doi.org/10.1038/npp.2016.186.

[35] T.M. Hillhouse, C.R. Merritt, J.H. Porter, Effects of the noncompetitive N-methyl-D-aspartate receptor antagonist ketamine on visual signal detection performance in rats, Behav. Pharmacol. 26 (2015) 495–499, https://doi.org/10.1097/FBP.0000000000000160.

[36] I.A. Paul, P. Skolnick, Glutamate and depression: clinical and preclinical studies, Ann. N.Y. Acad. Sci. 1003 (2003) 250–272, https://doi.org/10.1196/annals.1300.016.

[37] J.W. Olney, N.B. Farber, Glutamate receptor dysfunction and schizophrenia, Arch. Gen. Psychiatry 52 (1995) 998–1007, https://doi.org/10.1001/archpsyc.1995.03950240016004.

[38] T. Schwartz, S. Sachdeva, S. Stahl, Glutamate neurocircuitry: theoretical underpinnings in schizophrenia, Front. Pharmacol. 3 (2012) 195, https://doi.org/10.3389/fphar.2012.00195.

[39] A.T. Bowdle, A.D. Radant, D.S. Cowley, E.D. Kharasch, R.J. Strassman, P.P. Roy-Byrne, Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations, Anesthesiology 88 (1998) 82–88, https://doi.org/10.1097/00000542-199801000-00015.

[40] F.X. Vollenweider, M. Kometer, The neurobiology of psychedelic drugs: implications for the treatment of mood disorders, Nat. Rev. Neurosci. 11 (2010) 642–651, https://doi.org/10.1038/nrn2884.

[41] M.M. Schartner, R.L. Carhart-Harris, A.B. Barrett, A.K. Seth, S. D. Muthukumaraswamy, Increased spontaneous MEG signal diversity for psychoactive doses of ketamine, LSD and psilocybin, Sci. Rep. 7 (2017) 46421, https://doi.org/10.1038/srep46421.

[42] R.L. Carhart-Harris, R. Leech, P.J. Hellyer, M. Shanahan, A. Feilding, E. Tagliazucchi, D.R. Chialvo, D. Nutt, The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs, Front. Hum. Neurosci. 8 (2014) 1–22, https://doi.org/10.3389/fnhum.2014.00020.

[43] S.D. Muthukumaraswamy, A.D. Shaw, L.E. Jackson, J. Hall, R. Moran, N. Saxena, Evidence that subanesthetic doses of ketamine cause sustained disruptions of NMDA and AMPA-mediated frontoparietal connectivity in humans, J. Neurosci. 35 (2015) 11706, https://doi.org/10.1523/JNEUROSCI.0903-15.2015 (11694 LP –).

[44] N. Farnes, B.E. Juel, A.S. Nilsen, L.G. Romundstad, J.F. Storm, Increased signal diversity/complexity of spontaneous EEG, but not evoked EEG responses, in ketamine-induced psychedelic state in humans, PLoS One 15 (2020), e0242056, https://doi.org/10.1371/journal.pone.0242056.

[45] T. Bayne, O. Carter, Dimensions of consciousness and the psychedelic state, Neurosci. Conscious 2018 (2018), https://doi.org/10.1093/nc/niy008 (niy008).

[46] C. Letheby, P. Gerrans, Self unbound: ego dissolution in psychedelic experience, Neurosci. Conscious (2017) (2017), https://doi.org/10.1093/nc/nix016.

[47] G. Tononi, Consciousness as integrated information: a provisional manifesto, Biol. Bull. 215 (2008) 216–242, https://doi.org/10.2307/25470707.

[48] G. Tononi, M. Boly, M. Massimini, C. Koch, Integrated information theory: from consciousness to its physical substrate, Nat. Rev. Neurosci. 17 (2016) 450–461, https://doi.org/10.1038/nrn.2016.44.

[49] J.R. Hanson, S.I. Walker, Formalizing falsification for theories of consciousness across computational hierarchies, Neurosci. Conscious 2021 (2021), https://doi.org/10.1093/nc/niab014.

[50] A.R. Gallimore, Restructuring consciousness –the psychedelic state in light of integrated information theory, Front. Hum. Neurosci. 9 (2015) 346, https://doi.org/10.3389/fnhum.2015.00346.

[51] M. Scheidegger, M. Walter, M. Lehmann, C. Metzger, S. Grimm, H. Boeker, P. Boesiger, A. Henning, E. Seifritz, Ketamine decreases resting state functional network connectivity in healthy subjects: implications for antidepressant drug action, PLoS One 7 (2012), e44799, https://doi.org/10.1371/journal.pone.0044799.

[52] D.F. Ionescu, J.M. Felicione, A. Gosai, C. Cusin, P. Shin, B.G. Shapero, T. Deckersbach, Ketamine-associated brain changes: a review of the neuroimaging literature, Harv. Rev. Psychiatry 26 (2018) 320–339, https://doi.org/10.1097/HRP.0000000000000179.

[53] M. Lehmann, E. Seifritz, A. Henning, M. Walter, H. Böker, M. Scheidegger, S. Grimm, Differential effects of rumination and distraction on ketamine induced modulation of resting state functional connectivity and reactivity of regions within the default-mode network, Soc. Cogn. Affect. Neurosci. 11 (2016) 1227–1235, https://doi.org/10.1093/scan/nsw034.

[54] A.G. Vaccaro, S.M. Fleming, Thinking about thinking: A coordinate-based meta-analysis of neuroimaging studies of metacognitive judgements, Brain Neurosci. Adv. 2, 2018. 239821281881059. ⟨https://doi.org/10.1177/2398212818810591⟩.

[55] J.X. O'Reilly, M.W. Woolrich, T.E.J. Behrens, S.M. Smith, H. Johansen-Berg, Tools of the trade: psychophysiological interactions and functional connectivity, Soc. Cogn. Affect. Neurosci. 7 (2012) 604–609, https://doi.org/10.1093/scan/nss055.

[56] B. Becker, M. Steffens, Z. Zhao, K.M. Kendrick, C. Neumann, B. Weber, J. Schultz, M.A. Mehta, U. Ettinger, R. Hurlemann, General and emotion-specific neural effects of ketamine during emotional memory formation, Neuroimage 150 (2017) 308–317, https://doi.org/10.1016/j.neuroimage.2017.02.049.

[57] J. Morales, H. Lau, S.M. Fleming, Domain-general and domain-specific patterns of activity supporting metacognition in human prefrontal cortex, J. Neurosci. 38 (2018) 3534–3546, https://doi.org/10.1523/JNEUROSCI.2360-17.2018.

[58] B. Baird, M. Cieslak, J. Smallwood, S.T. Grafton, J.W. Schooler, Regional white matter variation associated with domain-specific metacognitive accuracy, J. Cogn. Neurosci. 27 (2015) 440–452, https://doi.org/10.1162/jocn_a_00741.

[59] M. Rouault, A. McWilliams, M.G. Allen, S.M. Fleming, Human metacognition across domains: insights from individual differences and neuroimaging, Personal. Neurosci. 1 (2018), https://doi.org/10.1017/pen.2018.16.

[60] A. Mazancieux, S. Fleming, C. Souchay, C. Moulin, Is there a G factor for metacognition? Correlations in retrospective metacognitive sensitivity across tasks, J. Exp. Psychol. Gen. 149 (2020), https://doi.org/10.1037/xge0000746.

[61] M. Lehmann, J. Hagen, U. Ettinger, Unity and diversity of metacognition, J. Exp. Psychol. Gen. (2022), https://doi.org/10.1037/xge0001197.

[62] M. Steffens, B. Becker, C. Neumann, A.M. Kasparbauer, I. Meyhöfer, B. Weber, M. A. Mehta, R. Hurlemann, U. Ettinger, Effects of ketamine on brain function during smooth pursuit eye movements, Hum. Brain Mapp. 37 (2016) 4047–4060, https://doi.org/10.1002/hbm.23294.

[63] M. Steffens, C. Neumann, A.M. Kasparbauer, B. Becker, B. Weber, M.A. Mehta, R. Hurlemann, U. Ettinger, Effects of ketamine on brain function during response inhibition, Psychopharmacology 235 (2018) 3559–3571, https://doi.org/10.1007/s00213-018-5081-7.
[64] A. Dittrich, The standardized psychometric assessment of altered states of consciousness (ASCs) in humans, Pharmacopsychiatry 31 (1998) 80–84, https://doi.org/10.1055/s-2007-979351.
[65] A. Dittrich, S. von Arx, S. Staub, International study on altered states of consciousness (ISASC): Summary of results., Ger. J. Psychol., 1985.
[66] S.M. Fleming, J. Ryu, J.G. Golfinos, K.E. Blackmon, Domain-specific impairment in metacognitive accuracy following anterior prefrontal lesions, Brain 137 (2014) 2811–2822, https://doi.org/10.1093/brain/awu221.
[67] S.M. Fleming, S. Massoni, T. Gajdos, J.-C. Vergnaud, Metacognition about the past and future: quantifying common and distinct influences on prospective and retrospective judgments of self-performance, Neurosci. Conscious. 2016 (2016), https://doi.org/10.1093/nc/niw018 (niw018).
[68] M. Allen, J.C. Glen, D. Müllensiefen, D.S. Schwarzkopf, F. Fardo, D. Frank, M. F. Callaghan, G. Rees, Metacognitive ability correlates with hippocampal and prefrontal microstructure, Neuroimage 149 (2017) 415–423, https://doi.org/10.1016/j.neuroimage.2017.02.008.
[69] A.M. Kasparbauer, N. Petrovsky, P.M. Schmidt, P. Trautner, B. Weber, B. Sträter, U. Ettinger, Effects of nicotine and atomoxetine on brain function during response inhibition, Eur. Neuropsychopharmacol. 29 (2019) 235–246, https://doi.org/10.1016/j.euroneuro.2018.12.004.
[70] A.C. Evans, S. Marrett, P. Neelin, L. Collins, K. Worsley, W. Dai, S. Milot, E. Meyer, D. Bub, Anatomical mapping of functional activation in stereotactic coordinate space, Neuroimage 1 (1992) 43–53, https://doi.org/10.1016/1053-8119(92)90006-9.
[71] P.T. Fox, J.S. Perlmutter, M.E. Raichle, A stereotactic method of anatomical localization for positron emission tomography, J. Comput. Assist. Tomogr. 9 (1985) 141–153.
[72] J. Ashburner, K.J. Friston, Unified segmentation, Neuroimage 26 (2005) 839–851, https://doi.org/10.1016/j.neuroimage.2005.02.018.
[73] K.J. Friston, J. Ashburner, C.D. Frith, J. Poline, J.D. Heather, R.S.J. Frackowiak, Spatial registration and normalization of images, Hum. Brain Mapp. 3 (1995) 165–189, https://doi.org/10.1002/hbm.460030303.
[74] S.B. Eickhoff, K.E. Stephan, H. Mohlberg, C. Grefkes, G.R. Fink, K. Amunts, K. Zilles, A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data, Neuroimage 25 (2005) 1325–1335, https://doi.org/10.1016/j.neuroimage.2004.12.034.
[75] K.J. Friston, C. Buechel, G.R. Fink, J. Morris, E. Rolls, R.J. Dolan, Psychophysiological and modulatory interactions in neuroimaging, Neuroimage 6 (1997) 218–229, https://doi.org/10.1006/nimg.1997.0291.
[76] R. Schröder, A.-M. Kasparbauer, I. Meyhöfer, M. Steffens, P. Trautner, U. Ettinger, Functional connectivity during smooth pursuit eye movements, J. Neurophysiol. 124 (2020) 1839–1856, https://doi.org/10.1152/jn.00317.2020.
[77] D.G. McLaren, M.L. Ries, G. Xu, S.C. Johnson, A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches, Neuroimage 61 (2012) 1277–1286, https://doi.org/10.1016/j.neuroimage.2012.03.068.
[78] K. Weidacker, S.-G. Kim, C.L. Nord, C. Rua, C.T. Rodgers, V. Voon, Avoiding monetary loss: a human habenula functional MRI ultra-high field study, Cortex 142 (2021) 62–73, https://doi.org/10.1016/j.cortex.2021.05.013.
[79] J.M. Cisler, K. Bush, J.S. Steele, A comparison of statistical methods for detecting context-modulated functional connectivity in fMRI, Neuroimage 84 (2014) 1042–1052, https://doi.org/10.1016/j.neuroimage.2013.09.018.
[80] J. Kim, B. Horwitz, Investigating the neural basis for fMRI-based functional connectivity in a blocked design: application to interregional correlations and psycho-physiological interactions, Magn. Reson. Imaging 26 (2008) 583–593, https://doi.org/10.1016/j.mri.2007.10.011.
[81] D.G. Green, J.A. Swets, Signal Detection Theory and Psychophysics, 1966, https://doi.org/10.1901/jeab.1969.12-475.
[82] A.B. Barrett, Z. Dienes, A.K. Seth, Measures of metacognition on signal-detection theoretic models, Psychol. Methods 18 (2013) 535, https://doi.org/10.1037/a0033268.
[83] S.M. Fleming, HMeta-d: hierarchical Bayesian estimation of metacognitive efficiency from confidence ratings, Neurosci. Conscious 2017 (2017) 1–14, https://doi.org/10.1093/nc/nix007.
[84] M. Guggenmos, Measuring metacognitive performance: type 1 performance dependence and test-retest reliability, Neurosci. Conscious (2021) (2021), https://doi.org/10.1093/nc/niab040.
[85] A. Gelman, D.B. Rubin, Inference from iterative simulation using multiple sequences, Stat. Sci. 7 (1992) 457–472, https://doi.org/10.1214/ss/1177011136.
[86] R.D. Morey, J.N. Rouder, BayesFactor: Computation of Bayes Factors for Common Designs. R package version 0.9.12–4.3., 2021. ⟨https://cran.r-project.org/package=BayesFactor⟩ (Accessed 12 February 2022).
[87] M. Brett, J.-L. Anton, R. Valabregue, J.-B. Poline, Region of interest analysis using an SPM toolbox, in: 8th Int. Conf. Funct. Mapp. Hum. Brain, Sendai, Japan, 2002: p. 497.
[88] J. Cohen, A. Maydeu-Olivares, A. Power Primer, Psychol. Bull. (1992), https://doi.org/10.1038/141613a0.
[89] M. Allen, D. Poggiali, K. Whitaker, T.R. Marshall, R.A. Kievit, Raincloud plots: a multi-platform tool for robust data visualization, Wellcome Open Res. 4 (2019) 63, https://doi.org/10.12688/wellcomeopenres.15191.1.
[90] A.V. Utevsky, D.V. Smith, S.A. Huettel, Precuneus is a functional core of the default-mode network, J. Neurosci. 34 (2014) 932–940, https://doi.org/10.1523/JNEUROSCI.4227-13.2014.
[91] J. Ais, A. Zylberberg, P. Barttfeld, M. Sigman, Individual consistency in the accuracy and distribution of confidence judgments, Cognition 146 (2016) 377–386, https://doi.org/10.1016/j.cognition.2015.10.006.
[92] R.F. West, K.E. Stanovich, The domain specificity and generality of overconfidence: individual differences in performance estimation bias, Psychon. Bull. Rev. 4 (1997) 387–392, https://doi.org/10.3758/BF03210798.
[93] J. Frohlich, J.D.Van Horn, Reviewing the ketamine model for schizophrenia, J. Psychopharmacol. 28 (2014) 287–302, https://doi.org/10.1177/0269881113512909.
[94] J.S. Mayer, M. Stäblein, V. Oertel-Knöchel, C.J. Fiebach, Functional dissociation of confident and not-confident errors in the spatial delayed response task demonstrates impairments in working memory encoding and maintenance in schizophrenia, Front. Psychiatry 9 (2018) 202, https://doi.org/10.3389/fpsyt.2018.00202.
[95] S. Moritz, A.S. Göritz, J. Gallinat, M. Schafschetzy, N. Van Quaquebeke, M.J. V. Peters, C. Andreou, Subjective competence breeds overconfidence in errors in psychosis. A hubris account of paranoia, J. Behav. Ther. Exp. Psychiatry 48 (2015) 118–124, https://doi.org/10.1016/j.jbtep.2015.02.011.
[96] E. Bristow, P. Tabraham, N. Smedley, T. Ward, E. Peters, Jumping to perceptions and to conclusions: specificity to hallucinations and delusions, Schizophr. Res. 154 (2014) 68–72, https://doi.org/10.1016/j.schres.2014.02.004.
[97] M. Rouy, P. Saliou, L. Nalborczyk, M. Pereira, P. Roux, N. Faivre, Systematic review and meta-analysis of metacognitive abilities in individuals with schizophrenia spectrum disorders, Neurosci. Biobehav. Rev. 126 (2021) 329–337, https://doi.org/10.1016/j.neubiorev.2021.03.017.
[98] M. Benedek, E. Jauk, R.E. Beaty, A. Fink, K. Koschutnig, A.C. Neubauer, Brain mechanisms associated with internally directed attention and self-generated thought, Sci. Rep. 6 (2016) 22959, https://doi.org/10.1038/srep22959.
[99] E. Tagliazucchi, R. Carhart-Harris, R. Leech, D. Nutt, D. Chialvo, Enhanced repertoire of brain dynamical states during the psychedelic experience, Hum. Brain Mapp. 35 (2014), https://doi.org/10.1002/hbm.22562.
[100] L. Roseman, R. Leech, A. Feilding, D.J. Nutt, R.L. Carhart-Harris, The effects of psilocybin and MDMA on between-network resting state functional connectivity in healthy volunteers, Front. Hum. Neurosci. 8 (2014) 204, https://doi.org/10.3389/fnhum.2014.00204.
[101] R. Joules, O.M. Doyle, A.J. Schwarz, O.G. O'Daly, M. Brammer, S.C. Williams, M. A. Mehta, Ketamine induces a robust whole-brain connectivity pattern that can be differentially modulated by drugs of different mechanism and clinical profile, Psychopharmacology 232 (2015) 4205–4218, https://doi.org/10.1007/s00213-015-3951-9.
[102] F. Mueller, F. Musso, M. London, P. de Boer, N. Zacharias, G. Winterer, Pharmacological fMRI: Effects of subanesthetic ketamine on resting-state functional connectivity in the default mode network, salience network, dorsal attention network and executive control network, NeuroImage Clin. 19 (2018) 745–757, https://doi.org/10.1016/j.nicl.2018.05.037.
[103] F. Cavanna, M.G. Vilas, M. Palmucci, E. Tagliazucchi, Dynamic functional connectivity and brain metastability during altered states of consciousness, Neuroimage 180 (2018) 383–395, https://doi.org/10.1016/j.neuroimage.2017.09.065.
[104] T. Balsdon, P. Mamassian, V. Wyart, Separable neural signatures of confidence during perceptual decisions, Elife 10 (2021), e68491, https://doi.org/10.7554/eLife.68491.
[105] W.C. Machielsen, S.A. Rombouts, F. Barkhof, P. Scheltens, M.P. Witter, FMRI of visual encoding: reproducibility of activation, Hum. Brain Mapp. 9 (2000) 156–164, https://doi.org/10.1002/(sici)1097-0193(200003)9:3<156::aid-hbm4>3.0.co;2-q.
[106] B.M. van Kemenade, B.E. Arikan, K. Podranski, O. Steinsträter, T. Kircher, B. Straube, Distinct roles for the cerebellum, angular gyrus, and middle temporal gyrus in action–feedback monitoring, Cereb. Cortex 29 (2019) 1520–1531, https://doi.org/10.1093/cercor/bhy048.
[107] C.L. Reed, R.J. Caselli, The nature of tactile agnosia: a case study, Neuropsychologia 32 (1994) 527–539, https://doi.org/10.1016/0028-3932(94)90142-2.
[108] B. Moghaddam, D. Javitt, From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment, Neuropsychopharmacology 37 (2012) 4–15, https://doi.org/10.1038/npp.2011.181.
[109] A.M. Van Loon, J.J. Fahrenfort, B. Van Der Velde, P.B. Lirk, N.C.C. Vulink, M. W. Hollmann, H. Steven Scholte, V.A.F. Lamme, NMDA receptor antagonist ketamine distorts object recognition by reducing feedback to early visual cortex, Cereb. Cortex 26 (2016) 1986–1996, https://doi.org/10.1093/cercor/bhv018.
[110] M. Scheidegger, A. Henning, M. Walter, H. Boeker, A. Weigand, E. Seifritz, S. Grimm, Effects of ketamine on cognition-emotion interaction in the brain, Neuroimage 124 (2016) 8–15, https://doi.org/10.1016/j.neuroimage.2015.08.070.
[111] E. Ruby, N. Giles, H. Lau, Finding domain-general metacognitive mechanisms requires using appropriate tasks, BioRxiv (2017), 211805, https://doi.org/10.1101/211805.