

Ayahuasca-inspired DMT/HAR formulation reduces brain differentiation between self and other faces

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ABSTRACT

Background: Psychedelics are known to profoundly alter perception and self-referential processing, yet their specific effects on face recognition—particularly with regard to the recognition of face familiarity—remain underexplored.

Objective: This study investigates the effects of an ayahuasca-inspired novel DMT/HAR (N,N-dimethyltryptamine/Harmine) formulation and Harmine alone on face recognition and self-referential processing, as measured by event-related potentials (ERPs) and subjective behavioral measures.

Methods: In a within-subject, double-blind, placebo-controlled design, 30 healthy male participants underwent EEG recording during a visual oddball task involving Self, Familiar, and Unknown Faces. The study compared the effects of a DMT/HAR formulation, Harmine alone, and Placebo on key visual ERP components: P1, N170, and P300.

Results: DMT/HAR increased the P1 and decreased the N170 amplitudes across all face categories, indicating enhanced early visual responsiveness and disrupted face structural encoding. Crucially, DMT/HAR reduced the neural differentiation between self and other faces occurring within the P300 wave compared to Harmine alone, and Placebo. Familiar face processing remained stable across conditions, suggesting that socially meaningful representations were preserved despite psychedelic-induced perceptions shifts.

Conclusion: While broadly disrupting early visual processing across face categories, the DMT/HAR formulation selectively attenuated the neural distinction between self and other faces, revealing a potential neural correlate of diminished self-referential processing. This effect underscores the serotonergic modulation of face recognition and suggests a reorganization of self-related neural dynamics under psychedelics. By reducing self-other differentiation, psychedelics may promote cognitive and emotional flexibility. These mechanisms could support

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therapeutic effects in conditions marked by rigid self-focus, such as depression and social anxiety, offering new perspectives on their clinical application.

1. Introduction

Psychedelics (serotonergic hallucinogens) temporarily alter perception and profoundly impact self-referential processing, notably influencing visual sensory experiences and the subjective perception of oneself. One of the most striking characteristics of the psychedelic experience is the alteration of sensory processing, particularly visual perception (Komater and Vollenweider, 2016). These alterations are not only central to the psychedelic experience but also serve as a crucial window into understanding how psychedelics modulate the brain's visual processing systems. Psychedelics such as psilocybin, lysergic acid diethylamide (LSD), and N, N-dimethyltryptamine (DMT) exert their hallucinogenic effects primarily through agonism of serotonin (5-HT) receptors, which are densely distributed in cortical pyramidal neurons and key visual processing areas (López-Giménez and González-Maeso, 2018). The intricate role of serotonin receptors in visual perception is further underscored by findings showing that the visual distortions induced by psychedelics involve not only 5-HT_{2A} receptor agonism but also interactions with the 5-HT_{1A} receptor (Quednow et al., 2012; Pokorny et al., 2016). The impact of psychedelics on visual perception is complex and involves alterations across multiple stages of sensory and cognitive processing. Neuroimaging studies have demonstrated that psychedelics influence visual perception by enhancing functional connectivity between primary visual areas and other cortical regions (Carhart-Harris et al., 2016), increasing resting-state neural activity in visual cortices (de Araujo et al., 2012; Roseman et al., 2016), facilitating bottom-up traveling waves (Alamia et al., 2020), and modulating neural oscillatory activity (Komater et al., 2013; Muthukumaraswamy et al., 2013; Timmermann et al., 2019).

In parallel with broader functional changes, psychedelics also influence visual event-related potentials (ERPs), the P1 and N170 components of visual ERPs, revealing distinct effects on sensory and cognitive processing. The P1 component, occurring 50–100 milliseconds post-stimulus, exhibits increased amplitude under the influence of psychedelics, indicating enhanced early sensory processing potentially contributing to the vivid and intensified visual experiences reported by users (Komater et al., 2011, 2013). Conversely, the N170 component, which is critical for the processing of complex visual stimuli like faces and objects, is disrupted by psychedelics (Schmidt et al., 2012; Komater et al., 2011). This disruption, evident in altered N170 amplitude and latency, correlates with the visual distortions and hallucinations experienced during a psychedelic experience, reflecting how these substances interfere with the brain's ability to integrate and interpret visual information (Komater et al., 2011).

In addition to their effects on visual perception, psychedelics induce transient and dose-dependent reductions in one's subjective experience of self, also known as ego dissolution (Letheby and Gerrans, 2017; Stoiliker et al., 2022). During ego dissolution, the boundaries between subjective and objective realities blur, leading to a profound sense of oneness. This experience may offer therapeutic benefits, including improved mood, enhanced prosocial behavior, increased altruism, and overall well-being (Griffiths et al., 2008; Komater et al., 2015). Research has consistently demonstrated that psychedelics such as psilocybin, LSD, and DMT disrupt the default mode network (DMN)—a network of brain regions, including the posterior cingulate cortex, medial prefrontal cortex (mPFC), and inferior parietal lobule, crucial for self-referential processing (Qin and Northoff, 2011). However, studies investigating the relationship between 5-HT_{2A} receptor activation and ego dissolution have yielded mixed findings. While some studies suggest a correlation between ego dissolution and reduced DMN integrity (Carhart-Harris et al., 2016), others report no clear association (Müller

et al., 2018) or instead highlight involvement of alternative networks, such as the salience network (Lebedev et al., 2015). Complementing these findings, electrophysiological studies have shown that alterations in the P300 ERP component—associated with cognitive resource allocation and self-referential processing—correlate with enhanced feelings of connectedness and altered perceptions of meaning during psychedelic experiences (Bravermanová et al., 2018; Smigielski et al., 2020).

Building on previous research demonstrating psychedelic-induced alterations in visual and self-referential processing, as well as earlier studies examining emotional face processing (Rocha et al., 2019), this study investigates a previously unexplored domain: how psychedelics affect the neural processing of face familiarity. To address this gap, the present study was designed to explore the effects of an ayahuasca-inspired formulation combining DMT and harmine on face recognition. Ayahuasca is a traditional South American plant brew known for its potent psychoactive properties. This brew typically contains two key ingredients: beta-carboline alkaloids such as harmine or harmaline derived from the *Banisteriopsis caapi* vine and the hallucinogenic compound DMT sourced from the *Psychotria viridis* plant (McKenna et al., 1984). When ingested orally, DMT alone is rendered inactive due to rapid first-pass metabolism by monoamine oxidase A (MAO-A) in the body. To counteract this, ayahuasca includes beta-carbolines that inhibit MAO-A, thereby preventing the breakdown of DMT and allowing it to produce its psychoactive effects (McKenna, 2004). In this study, we employed a novel formulation that combines buccally administered harmine with intranasally administered DMT (Dornbierer et al., 2023) to evaluate its impact on face recognition using a within-subject, double-blind, placebo-controlled design with three randomized conditions. During each session, participants' electrophysiological activity (EEG) was recorded while they performed a visual oddball task with stimuli categorized as Self, Familiar, and Unknown Faces. We investigated the effects of the DMT/HAR formulation and harmine alone compared to placebo on key visual event-related potentials, including P1, N170, and P300. Additionally, we explored the relationship between these electrophysiological measures and critical features of the psychedelic experience, such as elementary and complex imagery scores. We hypothesized that DMT/HAR, but not harmine, would significantly blur the neural boundaries between self and other faces, potentially providing new insights into the neural underpinnings of face recognition under psychedelic influence.

2. Methods

2.1. Experimental design

This study employed a within-subject, double-blind, placebo-controlled design with three sessions of counterbalanced drug administrations: DMT/HAR, harmine alone (HAR), placebo (PLA), each separated by a two-week washout period. This experiment is part of a larger series of studies, detailed in Aicher and Mueller et al. (2024) and was conducted at the peak drug effect, 60 min post initial DMT (or placebo) administration. The experimental task lasted for 30 min, while the entire duration of study was 360 min. Blinding was maintained until EEG preprocessing was complete and initial statistical models were finalized, preventing bias in data processing and analysis.

2.2. Participants

Thirty-six right-handed healthy male volunteers (20–40y, BMI 18.5–30) were recruited for this study. Inclusion criteria comprised: (a) no current or previous history of neurological disorders or psychotic or

bipolar disorders, and no family history of psychotic or bipolar disorders (b) fluent German language (c) normal or corrected-to-normal vision (d) normal hearing (e) little to no experience with hallucinogenic drugs (max. 15 lifetime). All participants underwent medical and psychological screening upon completing the initial telephone screening. On-site screenings were conducted in the same room as the experiments, ensuring familiarity with the surroundings, which was found conducive to the psychedelic experience (Hartogsohn, 2017). During the screenings, participants completed a training session to familiarize themselves with the tasks. The study enrolled 36 participants, Five participants voluntarily withdrew from the study, and one was excluded due to technical difficulties during data collection. Consequently, the final sample analyzed for this article comprised 30 participants. The study was conducted according to the World Medical Association Declaration of Helsinki. The study was approved by the Cantonal Ethics Committee of the Canton of Zurich (Basec-Nr. 2018-01385) and Swiss Federal Office of Public Health (BAG-Nr. (AB)-8/5-BetmG-2019/008014), and it was registered on clinicaltrials.gov (ID: NCT04716335). Participants gave written informed consent and were reimbursed commensurate with the time invested for participation (320.- CHF total, or 60.- per completed intervention day).

2.3. Drug and dosing

A counterbalanced order of (i) DMT/HAR, (ii) harmine alone (HAR), and (iii) placebo (PLA) were administered on three separate test days with identical procedure with a minimum 2 weeks of interval to prevent carry-over effects. (i) For the DMT/HAR condition, we used a nasal spray for standardized administration of DMT (isolated from *Mimosa tenuiflora*) and a buccal orodispersible tablet containing the monoamine oxidase inhibitor harmine (purchased from Sigma-Aldrich / Merck KGaA) (Dornbierer et al., 2023). Thirty minutes after buccal administration of 100 mg harmine, the DMT nasal spray was administered at intervals of 15 min. Each administration contained 10 mg of DMT, and the EEG experiment started 60 min after the first DMT administration when participants reached a total dose of 50 mg. This repeated-intermittent dosing regimen demonstrated that participants exhibited good self-control and coped well with the drug experience in an experimental setting (Aicher and Mueller et al., 2024). (ii) For the harmine condition (HAR), participants were administered 100 mg harmine buccally, along with a placebo nasal spray which was indistinguishable from drug with respect to taste, smell, and appearance. (iii) In the placebo condition (PLA), both orodispersible tablet and nasal spray were without active molecules and mimicked the natural drugs' appearance and taste.

2.4. Procedure

2.4.1. Measures of acute subjective effects

Participants' subjective experiences were evaluated using the 11-Dimensional Altered States of Consciousness questionnaire (11D-ASC) (Studerus et al., 2010), a comprehensive self-report measure derived from the 5D-ASC (Dittrich, 1998). Administered retrospectively at $T = 360$ min via a digital display and button-press format, this questionnaire captures a broad spectrum of altered state experiences, including Oceanic Boundlessness, Impaired Control and Cognition, Changed Meaning of Percepts, Experience of Unity, Insightfulness, Disembodiment, and both Elementary and Complex Imagery scores.

2.4.2. Stimuli

In the EEG experiment, the set of face stimuli consisted of 396 images pertaining to four different categories: (i) self faces, (ii) familiar faces, (iii) unknown faces ($n = 120$ in each condition), and (iiii) target ($n = 36$). (i) For self-face images, participants were photographed during on-site medical screening (Sony DSLR-A350). (ii) Unknown-face images were selected from the Chicago Face Database (Ma et al., 2015). (iii) For

the familiar-face images, we chose to use celebrity pictures instead of participants' own family or friends to avoid additional biases that can arise in self-referential information processing from ingroup membership (Platek and Kemp, 2009). A total of 262 male celebrity pictures were collected over the internet, including the faces of politicians, musicians, athletes, and actors. During the on-site medical screening, participants went through a pre-experiment familiarity test, where they rated each celebrity face as (a) I do not recognize, (b) I recognize somehow, (c) I recognize, and (d) I can name the person. Based on the ratings, 120 celebrity pictures were selected from the (c) and (d) categories to create participant-specific familiar-face stimuli. (iiii) Finally, scrambled images of participants' self-faces were used as a target (all image pixels were randomly oriented and placed).

All face stimuli were presented in a frontal view with a neutral expression and converted to greyscale. An ellipse mask (562×762 pixels resolution, 600 DPI) was applied to each face, cropping the exterior features such as hairline and ears, leaving only the inner facial features against a black background. This was achieved using the GNU Image Manipulation Program (GIMP) (GNU Image Manipulation Program, 1995). To maintain consistency, the contrast and luminance histograms of the images were standardized using the default function provided in the SHINE toolbox (Willenbockel et al., 2010), which was implemented within the MATLAB R2020a environment (The MathWorks Inc., 2022). The spatial frequencies of the images across different face categories—namely, Self ($M = 0.179$, $SD = 0.079$), Familiar ($M = 0.169$, $SD = 0.042$), and Unknown ($M = 0.175$, $SD = 0.044$)—were analyzed. Statistical analysis using ANOVA revealed no significant differences in spatial frequencies between these face categories (ANOVA: $t(2419) = 1.245$, $p = 0.289$). Stimuli were electronically presented using E-Prime 3.0 software (Psychology Software Tools, Inc., 2016) at a fixed viewing distance of 90 cm on a 25-inch screen. This setup provided a visual angle of $11^\circ \times 15^\circ$ (horizontal \times vertical). Responses were collected via the E-Prime Chronos Device.

2.4.3. Experiment procedure

Subjects were instructed to keep their gaze on the fixation cross placed at the center of the screen for the entire block duration and were asked to press a button with their right index finger when the scrambled face (target) appeared. Targets could occur with a probability between 8 and 12 %. This procedure ensured that participants attended each visual image and prevented eliciting motor responses for the relevant face categories (self-faces, familiar faces, unknown faces). The stimulus duration was 100 ms, and the interstimulus interval varied randomly between 1 and 1.4 s. The experiment was divided into three blocks, interleaved by a 3-minute break, and the overall duration was 30 min. To prevent habituation, stimuli were presented pseudo-randomly so that no more than three faces of the same category could consecutively occur. On average, participants performed target detection with 98 % accuracy. All conditions were presented in each experimental session (drug condition): DMT/HAR, HAR, and PLA. From this point forward, we will use the following abbreviations: SELF for Self, FAM for Familiar, and UNK for Unknown. Therefore, the condition labels are as follows: DMT/HAR_{SELF}, HAR_{SELF}, PLA_{SELF}, DMT/HAR_{FAM}, HAR_{FAM}, PLA_{FAM}, DMT/HAR_{UNK}, HAR_{UNK}, PLA_{UNK}.

2.4.4. EEG recordings

Continuous EEG was recorded with the BioSemi Active 2 system with 64 Ag-AgCl pin-type active electrodes mounted on an elastic cap, according to the international 10–20 system. Eight additional flat-type active electrodes were used for body surface measurements. For horizontal and vertical electrooculography (EOG), electrodes were placed on each eye's outer canthus and the left eye's supraorbital and infraorbital. For electrocardiography (ECG), electrodes were placed on the end of the left collarbone and the lower left rib. Additional electrodes were placed on the right and left mastoid bones. Data were referenced to the Common Mode Sense (CMS) and the Driven Right Leg (DRL) electrodes,

while the average voltage was kept in the range of ± 40 mV signal using Biosemi's electrodes offset tool. Signals were recorded with a 0.1 Hz high-pass filter and a 100 Hz low-pass filter, with a sampling rate of 2048 Hz. Triggers were sent to the BioSemi software and recorded using a parallel port along with the EEG data.

2.4.5. EEG preprocessing

The preprocessing was performed offline using EEGLAB (Delorme and Makeig, 2004) within the MATLAB environment (The MathWorks Inc., 2022). Data were preprocessed with a semi-automatic pipeline implemented in MATLAB (Stropahl et al., 2018). Data were re-referenced to the Fz electrode after they were imported. Stereotypical artifacts (eye blinks, lateral eye movements, and heartbeats) were detected using an infomax independent component analysis (ICA) (Bell and Sejnowski, 1995). To improve ICA decomposition, data were low-pass filtered (windowed sinc FIR filter, cut-off frequency 40 Hz, filter order 256), resampled to 256 Hz and high-pass filtered (windowed sinc FIR filter, cut-off frequency 1 Hz, filter order 512) and finally, segmented into consecutive dummy epochs of 1 s. The epochs with joint probabilities greater than 4 standard deviations were rejected (Bottari et al., 2020). ICA weights were then attributed to the unfiltered raw data (Stropahl et al., 2015). Topographies of each component were plotted and visually inspected for artifacts (eye blinks, saccades, and heartbeat). Across all datasets, components representing the best stereotypical artifacts were used as a template for a semi-automated CORRMAP algorithm to identify ICA components with similar topography across all datasets (Viola et al., 2009). A correlation of the ICA inverse weights was computed, and the components with a correlation coefficient higher or equal to 0.8 were removed (from the raw data). Artifact-free data were low-pass filtered (windowed sinc FIR filter, cut-off frequency 40 Hz, filter order 256), resampled to 256 Hz and high-pass filtered (windowed sinc FIR filter, cut-off frequency 0.1 Hz, filter order 5120). Bad channels were interpolated with the spheric spline. The proportion of interpolated electrodes was kept at $<10\%$ for each participant. Data were re-referenced to the average. Data were segmented as a function of stimulus category (SELF, FAM, UNK) and conditions (DMT/HAR, HAR, PLA), into epochs containing 200 ms pre-stimulus and 800 ms post-stimulus. Within the same stimulus category/condition, epochs that had a higher joint probability of 4 standard deviations were excluded from further analysis, to remove epochs contaminated by non-stereotypical artifacts. Finally, epochs exceeding $\pm 100 \mu\text{V}$ were also excluded. The number of removed epochs did not differ across conditions/stimulus categories (repeated-measures ANOVA ($F(4, 116) = 0.35, p = 0.843, \eta^2 = 0.013$); the mean and the \pm SD of removed epochs for each conditions across stimulus categories were as follows: $5.9\% \pm 2.6$ for DMT/HAR_{SELF}, $5.8\% \pm 2.3$ for DMT/HAR_{FAM}, $5.7\% \pm 2.7$ for DMT/HAR_{UNK}; $5.4\% \pm 1.7$ for HAR_{SELF}, $5.4\% \pm 1.5$ for HAR_{FAM}, $5.5\% \pm 1.6$ for HAR_{UNK}; $5.8\% \pm 1.7$ for PLA_{SELF}, $5.6\% \pm 1.3$ for PLA_{FAM}, $5.4\% \pm 1.3$ for PLA_{UNK}). Finally, epochs were baseline-corrected from -200 to 0 ms.

2.5. Statistical approach

2.5.1. Measures of acute subjective effects

Scores from 11D-ASC were analyzed using repeated measures analyses of variance (rmANOVAs; JASP) with the within-participant conditions as factors (DMT/HAR, HAR, PLA). The assumption of sphericity was tested using Mauchly's test. If epsilon (ϵ) values were <0.75 , Greenhouse-Geisser correction were used, and if they were >0.75 , Huynh-Feldt correction was applied. When the F-statistics were significant, post-hoc paired t -tests were performed using a Bonferroni correction (adjusted $\alpha=0.017$, to account for three tests).

2.5.2. EEG experiment

First, we assessed the main effects of the drug conditions (DMT/HAR, HAR, PLA) on each face category (Self, Familiar, Unknown). We

employed cluster-based nonparametric permutation F-statistics (MANOVA, Monte Carlo sampling method, 1000 iterations, cluster alpha $p < 0.05$, maxsum criterion, cluster-based method for multiple comparison correction, minimum spatial extent 2 adjacent channels (Maris and Oostenveld, 2007) to determine whether the response to each face category differed across conditions. In case of significant effects in the MANOVA, we then employed cluster-based nonparametric permutation t -statistics (Monte Carlo sampling method, 1,000 iterations, two-tailed, cluster alpha $p < 0.025$ (corresponding to a critical alpha level of 0.05 for two-tailed testing, accounting for both positive and negative clusters), maxsum criterion, minimum spatial extent 2 adjacent channels) between pairs of conditions. For both F- and t -statistics, analyses were run across all electrodes and within the whole-time window (0–600 ms). This data-driven approach allowed for identifying the significant difference between conditions without bias from a priori assumptions of a specific region of interest (ROIs) or time intervals while solving multiple comparison problems (Maris and Oostenveld, 2007). If the cluster-based p -value was <0.025 , we rejected the null hypothesis that there was no difference between conditions.

Secondly, we examined the specific hypothesis that the modulation induced by DMT/HAR was greater for the self-face compared to both familiar and unknown faces. To this end, the interaction effect of drug conditions (DMT/HAR, HAR, PLA) and face stimuli (Self, Familiar, Unknown) was investigated by running a series of nonparametric cluster-based permutation t -statistics (Monte Carlo sampling method, 1,000 iterations, one-tailed for negative clusters, cluster alpha $p < 0.05$, maxsum criterion, minimum spatial extent 2 adjacent channels) of the differential waves calculated by subtractions across face categories (e.g. DMT/HAR_{SELF-FAM} vs. PLA_{SELF-FAM} or DMT/HAR_{SELF-UNK} vs. PLA_{SELF-UNK}), within the whole time-window (0–600 ms) across all electrodes.

2.5.3. Correlations between EEG and behavioral data

To examine the relationship between EEG activity and self-rated 11D-ASC scales, Spearman's rank-order correlation was used to assess associations between event-related potentials (P1, N170, P300) and 11D-ASC scores. To account for individual baseline differences, we calculated DMT-PLA difference scores for both EEG and behavioral measures. This approach ensured that correlations reflected DMT-induced effects rather than individual variability. EEG activity was analyzed at occipital (P1: OZ, O1, O2; 90–150 ms), posterior (N170: P8, PO8; 160–190 ms), and central-posterior (P300: Pz, CPz; 350–450 ms) electrodes at their respective latency windows.

3. Results

3.1. Measures of acute subjective effects

We examined how different drug conditions (DMT/HAR, HAR, PLA) influenced subjective experiences as measured by the 11D-ASC scale. The analysis revealed a statistically significant main effect of drug condition across all 15 behavioral measures (all $p < 0.001$), including Anxiety, Anxious Ego Dissolution, Audio-Visual Synesthesia, Blissful State, Changed Meaning of Percepts, Complex Imagery, Disembodiment, Elementary Imagery, Experience of Unity, Impaired Cognition and Control, Insightfulness, Oceanic Boundlessness, Spiritual Experience, Vigilance Reduction, and Visionary Restructuralization. Post-hoc tests indicated that the DMT/HAR condition significantly increased all measures compared to PLA and HAR (all $p < 0.05$), whereas there were no significant differences between the PLA and HAR conditions (all $p > 0.05$). Refer to Figure S1 in the *Supplementary Materials* for a detailed visualization.

3.2. Face processing EEG experiment

3.2.1. Self face

First, we investigated the neural response to self-faces. A

nonparametric cluster-based permutation analysis was run to investigate the effect of drug conditions (DMT/HAR, HAR, and PLA) on the ERPs in response to self-face category (refer to Table S1 in *Supplementary Materials* for all statistical results). Cluster-based analysis (MANOVA, comparing the three drug conditions) revealed 2 positive clusters at 140–199 ms and between 207 and 600 ms (all $p < 0.001$), suggesting a statistical difference between the responses to self-faces across drug conditions. The direct comparison revealed that the DMT/HAR condition increased the neural response to self-face within the time window of 140–200 ms at posterior-occipital electrodes compared to both PLA and HAR conditions (DMT/HAR vs. PLA, $p = 0.022$; DMT/HAR vs. HAR, $p < 0.001$; Fig. 1A, B). The same analysis revealed a reduction of N170-P300 waves in the DMT/HAR condition compared to the other two drug conditions (Fig. 1B). In addition, DMT/HAR increased neural responses within the time window of 200–600 ms at the frontal electrodes compared to the other drug conditions (DMT/HAR vs. PLA, all clusters $p < 0.025$; DMT/HAR vs. HAR, $p < 0.001$; see Fig. 1A). There was no significant difference between HAR and PLA.

3.2.2. Familiar face

The same analytical approach was performed on the familiar face category. Cluster-based analysis (MANOVA) revealed 2 positive clusters between 80 and 400 ms and 400–580 ms ($p < 0.001$ and $p = 0.017$), suggesting a statistical difference between the response to familiar face images as a function of drug condition. The direct comparison revealed that DMT/HAR increased the neural response to familiar faces within the time window of 90–200 ms at the posterior-occipital electrodes compared to the other drug conditions (DMT/HAR vs. PLA, $p = 0.013$; DMT/HAR vs. HAR, $p = 0.018$) (Fig. 2A). The effect revealed altered P1-N170 waves in the DMT/HAR condition compared to both PLA and HAR conditions (Fig. 2B). In addition, DMT/HAR increased neural responses within the time window of 200–600 ms at frontal electrodes compared to HAR (all clusters $p < 0.025$) but not when compared to PLA ($p > 0.025$) (Fig. 2A). Interestingly, HAR increased the neural response to familiar faces within the time window of 265–480 ms compared to PLA

($p = 0.01$) at right central-parietal-temporal electrodes (see Figure S2 in *Supplementary Materials*).

3.2.3. Unknown face

The same analytical approach was performed on the unknown face category. Cluster-based analysis (MANOVA) revealed 2 positive clusters at 125–205 ms and between 215 and 600 ms (all $p < 0.001$), suggesting a statistical difference in drug conditions on an unknown face. The direct comparison revealed that DMT/HAR increased the neural response to an unknown face within the time window of 130–205 ms at the posterior-occipital electrodes compared to the PLA condition ($p = 0.02$) but not when compared to HAR ($p > 0.025$) (Fig. 3A). The effect revealed altered N1-P300 waves in the DMT/HAR condition compared to the PLA condition (Fig. 3B). In addition, DMT/HAR decreases neural responses within the time window of 300–600 ms at the right central-posterior-temporal electrodes compared to both PLA ($p < 0.001$) and HAR ($p = 0.004$).

3.2.4. Interim summary of early ERP modulations in face perception

In summary, our investigation revealed a consistent impact of DMT/HAR on ERP components within the first 200 milliseconds across all face categories (self, familiar, and unknown). During this period, we observed a selective DMT/HAR-induced increase in neural responses at parieto-occipital electrode sites, compared to both placebo (PLA) and harmine (HAR). In the next section, we investigate whether psychedelics distinctly modify the processing of one's own face in comparison to familiar and unknown faces.

3.2.5. "Does DMT/HAR modulate self-referential face processing by reducing neural differentiation?"

We hypothesized that DMT/HAR would attenuate the processing of self-relevant facial stimuli relative to other facial categories, thereby reducing the neural differentiation between self and other faces. However, our initial analysis revealed a different pattern: at later stages (300–600 ms), DMT/HAR increased neural responses to self-faces at

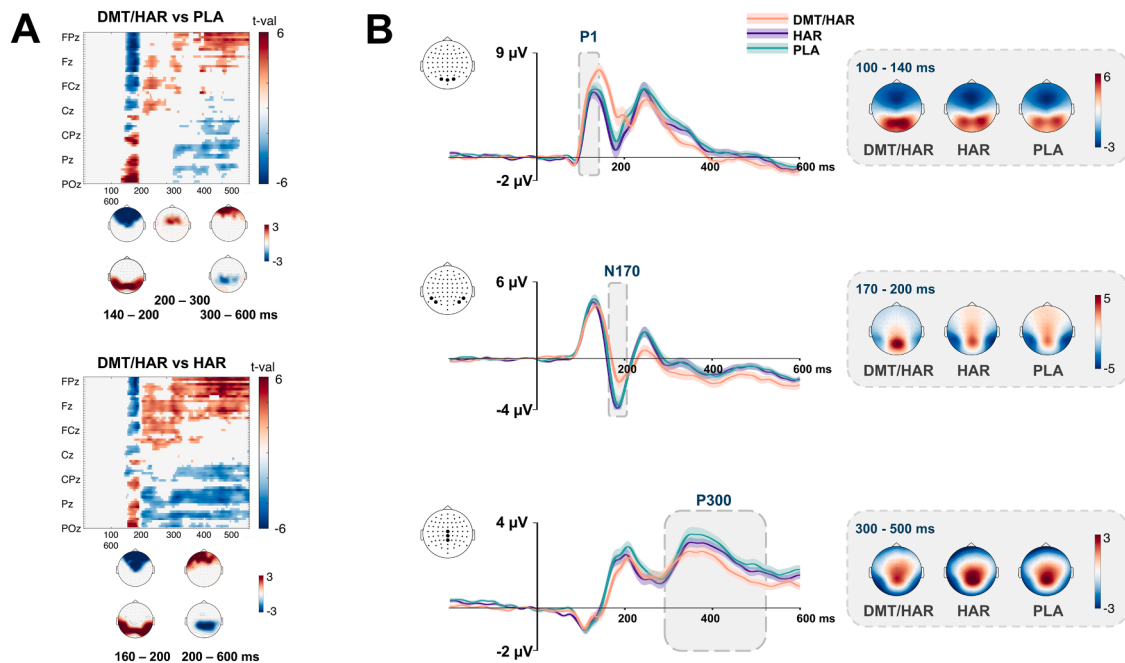


Fig. 1. The effect of DMT/HAR on self-face.

(A) Spatiotemporal matrices display the results of the cluster-based permutation test, comparing the responses across conditions (DMT/HAR vs. PLA and DMT/HAR vs. HAR) to self-face stimuli. Significant clusters are shown as topographic distributions at the bottom. (B) Grand averaged ERPs (mean and SE) computed across all participants, averaged over O1, O2, Oz for P1 (upper), PO8, P8, PO7, P7 for N170 (middle) and Pz, CPz, Cz for P300 (lower) and scalp topography of each drug condition averaged within relevant time-windows on the right side. Electrodes were chosen based on the results of the cluster-based permutation test. DMT/HAR decreased N170 and P300 compared to both HAR and PLA. No significant differences emerged between HAR and PLA.

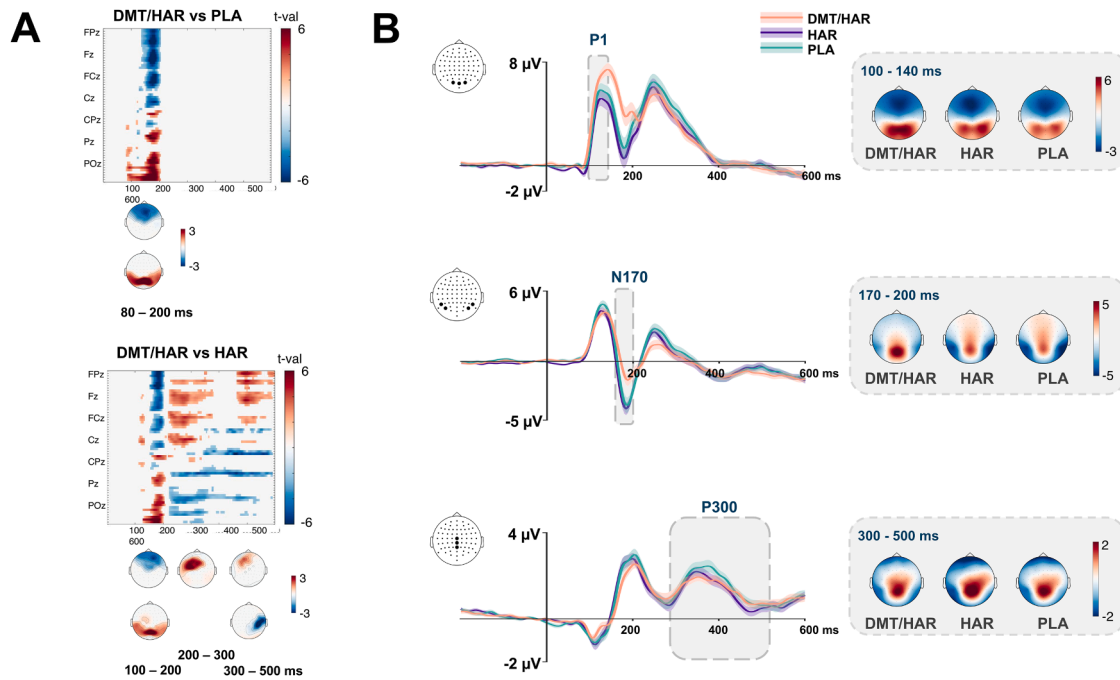


Fig. 2. The effect of DMT/HAR on familiar faces. (A) Spatiotemporal matrices display the results of the cluster-based permutation test, comparing the response to familiar face stimuli across drug conditions (DMT/HAR vs. PLA and DMT/HAR vs. HAR). Significant clusters are shown as topographic distributions at the bottom of the graphs. (B) Grand averaged ERPs (mean and SE) computed across all participants, averaged over O1, O2, Oz for P1 (upper), PO8, P8, PO7, P7 for N170 (middle) and Pz, CPz, Cz for P300 (lower) and scalp topography of each drug condition at relevant time windows on the right side. Electrodes were chosen based on the results of the cluster-based permutation test. DMT/HAR elicited increased P1 and decreased N170 compared to both HAR and PLA. DMT/HAR did not affect P300.

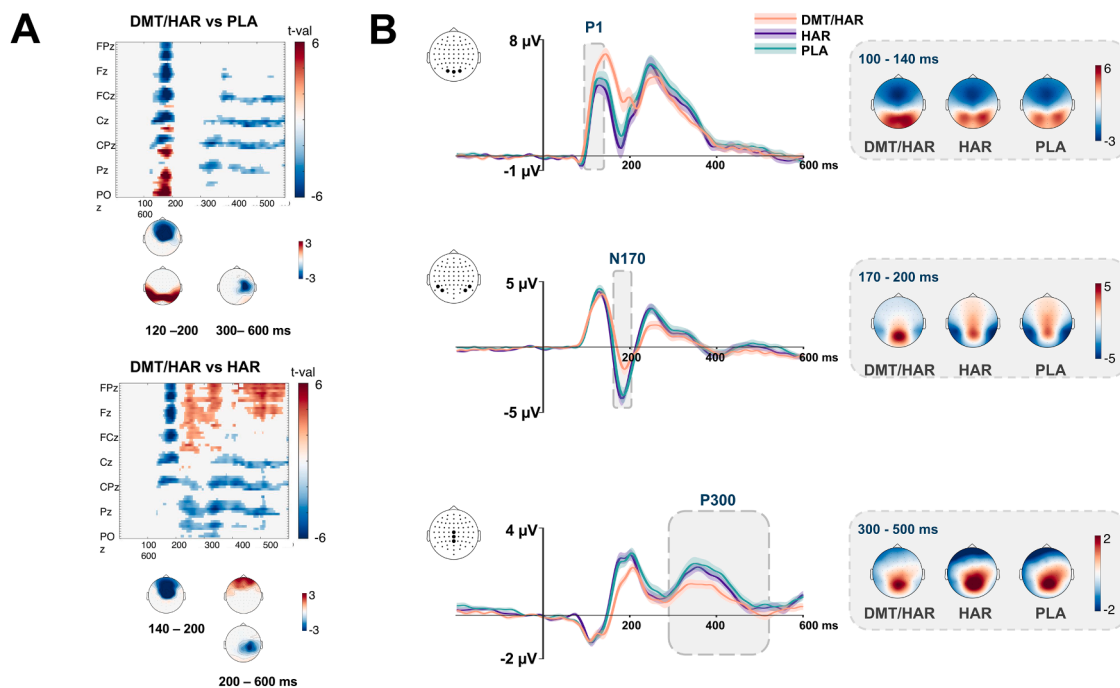


Fig. 3. The effect of DMT/HAR on unknown faces. (A) Spatiotemporal matrices display the results of the cluster-based permutation test, comparing the conditions (DMT/HAR vs. PLA and DMT/HAR vs. HAR) response to unknown face stimuli. Significant clusters are shown as topographic distributions at the bottom of the graphs. (B) Grand averaged ERPs (mean and SE) computed across all participants, averaged over O1, O2, Oz for P1 (upper), PO8, P8, PO7, P7 for N170 (middle) and Pz, CPz, Cz for P300 (lower) and scalp topography of each drug condition at relevant time windows on the right side. Electrodes were chosen based on the results of the cluster-based permutation test. DMT/HAR elicited decreased N170 and P300 compared to PLA and decreased P300 compared to HAR. There were no significant differences between PLA and HAR drug conditions.

frontal electrodes while decreasing responses to unknown faces at right central-parietal electrodes, suggesting a reorganization of self-referential salience. To further investigate whether psychedelics modulate the distinction between self and other face categories, we conducted a nonparametric cluster-based permutation analysis examining the interaction effect between drug conditions and differential ERP waveforms, calculated by subtracting the neural responses across face categories (e.g., $DMT/HAR_{Self-Unknown}$ vs. $PLA_{Self-Unknown}$; $DMT/HAR_{Self-Unknown}$ vs. $HAR_{Self-Unknown}$; etc.) (refer to Table S2 in *Supplementary Materials* for all the detailed statistical results).

The results confirmed the hypothesis, showing that the differential EEG responses to self-minus-unknown and self-minus-familiar faces were significantly reduced in DMT/HAR compared to both PLA and HAR. This corresponded to a negative cluster approximately between 320 and 550 ms (Self-Unknown: DMT/HAR vs. PLA, $p = 0.024$; Self-Familiar: DMT/HAR vs. PLA, $p = 0.004$; DMT/HAR vs. HAR, $p = 0.002$) comprising several central-posterior electrodes (Fig. 4A). These results suggest that the neural response measured at centro-posterior electrodes when processing self-faces was more similar to familiar and unknown faces under the effect of DMT/HAR. A post-hoc cluster-based analysis was run to compare amplitudes of responses to self, familiar and unknown faces within a 300–500 ms time window (comprising the P300) at the central posterior electrodes (CPz, POz, Pz). Results revealed that the neural response to self-faces was greater in PLA and HAR compared to unknown and familiar faces. This increase in neural response for self faces was substantially reduced in DMT/HAR (Fig. 4C).

3.2.6. Correlations between EEG and psychometric data

Correlation analyses revealed that DMT/HAR-induced decreases in N170 amplitude were positively correlated with increases in Spiritual Experience ($r = 0.370$, $p = 0.044$), Impaired Cognition and Control ($r = 0.394$, $p = 0.031$), global ASC ($r = 0.384$, $p = 0.036$), Anxious Ego Dissolution ($r = 0.422$, $p = 0.020$), and Complex Imagery scores ($r = 0.370$, $p = 0.044$). Similarly, DMT/HAR-induced reductions in P300 amplitude positively correlated with increased Anxious Ego Dissolution

($r = 0.384$, $p = 0.037$) and Elementary Imagery scores ($r = 0.405$, $p = 0.027$) (Fig. 5). No significant correlations emerged for the P1 component or other subjective measures (all $p > 0.05$). Refer to *Supplementary Materials*, Figure S3 for detailed statistical results across all measures of 11D-ASC.

4. Discussion

The results of this placebo-controlled, double-blind, within-subject randomized design study provided novel insights into psychedelics' effects on the neurophysiological signatures of face recognition. Our findings demonstrate significant alterations in early visual processing during the psychedelic experience induced by novel ayahuasca-inspired DMT/HAR formulation. Most importantly, we observed specific modulation of the self-face perception compared to familiar and unknown faces, emphasizing the effect of psychedelics on self-referential information processing.

4.1. General effects of psychedelics on early visual processing

Our study's primary finding is that DMT/HAR administration enhances neural activity in the parieto-occipital cortex during the early stages of visual perception (<200 ms) for all face categories (Self, Familiar, Unknown). This time frame includes both the early P1 and N170 waves of event-related potentials (ERPs). Specifically, DMT/HAR increases the P1 amplitude at medial occipital electrodes while decreasing the N170 amplitude at lateral occipital-temporal electrodes. These changes in early visual ERP components – marked by an increased P1 and a reduced N170 – indicate that DMT/HAR influences face processing differently depending on the stage of visual analysis.

This finding shows that the effect of psychedelics can be dissected within the chronology of face perception, ultimately expanding our understanding of the differential effects of serotonergic modulation during visual processing. 5-HT_{2A} receptors are highly expressed in the visual cortex (Dyck and Cynader, 1993; Gerstl et al., 2008; Watakabe

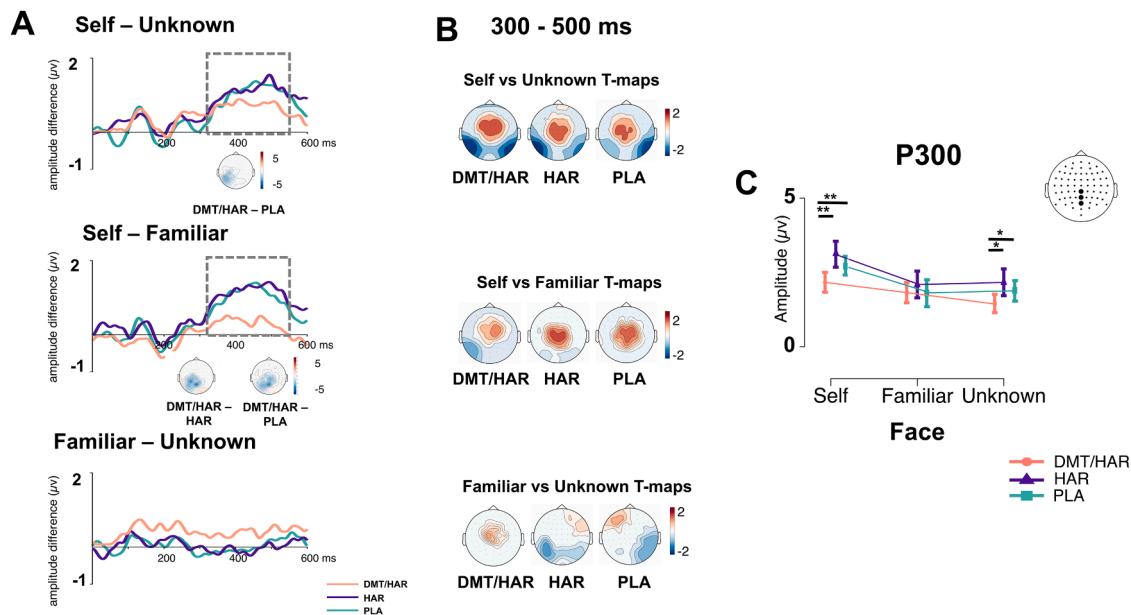


Fig. 4. Interaction effect.

Plots showing the significant differential ERPs of Self-Unknown (upper) and Self-Familiar (middle), and Familiar-Unknown (lower) at the posterior electrodes (POz, Pz, CPz) within 300–550 ms. Topographies of significant interaction effects of drug conditions are shown below the differential ERP plots. (B) Topographies of the difference responses for Self - Unknown, Self - Familiar and Familiar - Unknown for each drug condition (DMT/HAR, HAR, PLA). (C) Interaction plots show decreased responses to self and unknown faces in DMT/HAR condition compared to HAR and PLA conditions during the P300 time window over central-posterior electrodes (POz, Pz, CPz). Results revealed that the DMT/HAR condition attenuated the neural response to self-faces, and in turn, the differences between neural responses to self-faces and the other face categories were reduced.

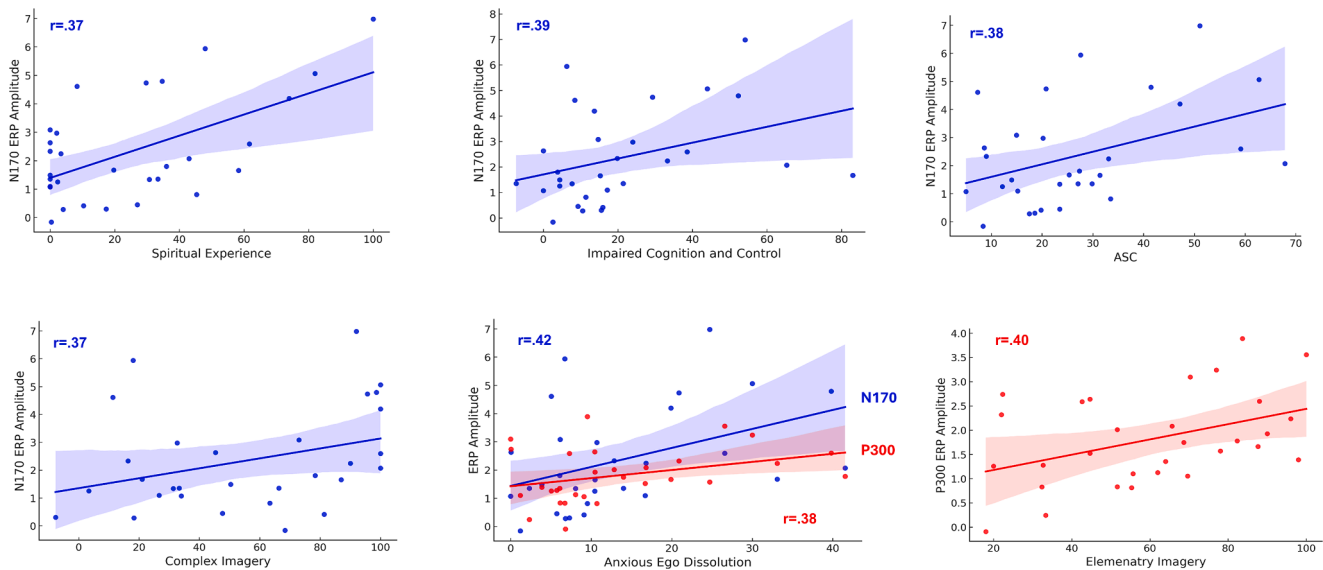


Fig. 5. Correlations between event-related potential (ERP) components and 11D-ASC scores.

Scatterplots illustrate the relationships between N170 ERP (blue) and P300 ERP (red) amplitudes and self-rated subjective experience scores. N170 ERP amplitudes are positively correlated with Spiritual Experience, Impaired Cognition and Control, Global ASC Score, and Complex Imagery. Both N170 and P300 ERP amplitudes are positively correlated with Anxious Ego Dissolution. P300 ERP amplitudes are positively correlated with Elementarity Imagery. Trend lines represent linear regression models with 95 % confidence intervals, and Spearman's correlation coefficients (r -values) are displayed in each plot.

et al., 2009). Within the ventral occipitotemporal face processing network, faces are processed across different selective regions. The information process initiates in the inferior occipital region ("occipital face area", OFA), which is sensitive to the low-level features of the visual input (e.g., size, luminance, contrast, spatial frequency spectrum). The activity of this region has been associated with the P1 ERP component. Subsequently, the information reaches the lateral middle fusiform gyrus (commonly referred to as the fusiform face area, FFA) and the posterior superior temporal sulcus (pSTS), which are responsible for high-level structural encoding of faces and linked to the N170 component of the ERPs (Duchaine and Yovel, 2015; Haxby et al., 2000; Rossion and Jacques, 2011; Sadeh et al., 2010; Tsao and Livingstone, 2008). Our results indicate that DMT/HAR alters the core system of face processing by increasing the P1 component, resulting in an enhanced visual gain while impairing the structural encoding of faces as captured by the attenuated N170 component. Similar findings from previous studies (Komater et al., 2011, 2013) using non-face stimuli suggest that the altered responses observed as increased or decreased early visual ERP components might not be exclusive to face processing. Instead, these changes could reflect a broader effect of psychedelics on early visual processing. For example, Komater et al. (2011) demonstrated that psilocybin dose-dependently increased the medial P1 and decreased the N170 during an object completion task. Furthermore, research utilizing a forced-choice direction of motion discrimination task revealed that psilocybin specifically impairs coherence sensitivity for random dot patterns, likely affecting high-level global motion detectors. In contrast, there was no notable impact on contrast sensitivity for drifting gratings, which are typically governed by low-level detectors (Carter et al., 2004).

Integrating these EEG findings – where psychedelics increase the P1 component and decrease the N170 – suggests that psychedelics may differentially influence low-level and high-level visual processing. Specifically, they seem to enhance the perception of basic visual features (e.g., brightness, contrast, local motion detection) while disrupting higher-level integration processes (e.g., structural encoding of faces, object recognition, global motion detection). Consistent with previous research (Komater et al., 2011, 2013), we found that reductions in N170 amplitude, a marker of high-level visual processing, correlated positively with subjective increases in Complex Imagery scores. This suggests that disruptions in face and object encoding may contribute to the generation of

elaborate visual imagery under psychedelics.

4.2. Specific effects of psychedelics on self-referential information processing

Psychedelics profoundly alter self-experience, often inducing ego dissolution, which is frequently linked to heightened empathy and compassion. This suggests that psychedelics modulate the neural representations of self and others (Blatchford et al., 2020; Letheby and Gerrans, 2017; Tagliazucchi et al., 2022). Given that prosocial traits, such as empathy, rely on shared self-other representations (Preston and Hofelich, 2012), we hypothesized that DMT/HAR would reduce neural differentiation between self and other faces, leading to smaller ERP differences between these categories. Consistently, spatiotemporal analysis of EEG signals across the 0–600 ms window revealed a significant drug-by-face interaction, indicating that DMT/HAR alters self-referential face processing. Specifically, during the P300 time frame (300–500 ms), neural response differences between self and other faces were significantly reduced at posterior midline electrodes (Fig. 4). This effect, observed in comparison to both harmine and placebo conditions, suggests a weakening of perceptual boundaries between self and external social stimuli, a hallmark of ego dissolution experiences.

The P300 component is a well-established marker of attentional resource allocation (Polich, 2007, 2012) and has been closely linked to default mode network (DMN) activity, which underlies self-referential cognition (Knyazev, 2013). Under typical conditions, self-relevant stimuli elicit heightened P300 amplitudes, as they receive prioritized attentional processing due to their social and adaptive significance (Gray et al., 2004). Electrophysiological studies consistently report heightened P300 amplitudes for self-referential stimuli, such as one's own face compared to famous or unknown faces (Scott et al., 2005; Sui et al., 2006; Tacikowski and Nowicka, 2010), a pattern also reflected in our data (Fig. 4C). Similar effects have been observed for one's own name (Tacikowski et al., 2014), which continues to elicit an enhanced response even during sleep (Perrin et al., 1999) and even unconscious perception (Doradzinska et al., 2020). The observed reduction in P300 amplitude under the DMT/HAR condition for self-faces, and to a lesser extent for unknown faces, relative to both harmine and placebo, suggests a significant decrease in attentional focus on self-relevant

information during the psychedelic experience. Notably, the P300 amplitude for familiar faces remained stable across all drug conditions (Fig. 4C), the processing of socially familiar faces remained intact. This reduction in self-referential prioritization likely contributed to the blurring of boundaries between self, familiar, and unknown faces.

Interestingly, our results revealed a distinct dissociation between posterior and frontal effects during the P300 time frame: DMT/HAR increased neural responses to self-faces (Fig. 1A) at the frontal electrodes, decreased responses to unknown faces (Fig. 3A) at the right central-parietal electrodes, and left familiar face processing unchanged (Fig. 2A). This pattern suggests that while posterior regions exhibit a weakening of self-other differentiation, frontal areas selectively preserve self-salience, reflecting a reorganization rather than a uniform attenuation of self-referential processing. The blurring of perceptual boundaries at posterior sites aligns with reports of ego dissolution under psychedelics, indicating a loosening of rigid self-other distinctions at lower-level sensory processing stages. However, the heightened frontal response to self-faces may suggest that higher-order cognitive mechanisms continue to prioritize self-relevant stimuli, potentially acting as a compensatory process to stabilize self-representation despite underlying perceptual instability. Meanwhile, the reduction in neural responses to unknown faces was localized at right central-parietal electrodes rather than frontal sites, suggesting a diminished engagement in mid-to-late stage processing of unfamiliar social stimuli.

This finding is consistent with hierarchical predictive coding models, where psychedelics disrupt lower-level perceptual priors, requiring higher-order cognitive areas to re-weight social and self-referential information (Carhart-Harris et al., 2014). By reducing the salience of unknown faces, psychedelics may lead to a weakened drive to categorize unfamiliar individuals as socially distinct, potentially contributing to increased social openness and reduced interpersonal vigilance (Preller and Vollenweider, 2018). Alternatively, this attenuation may reflect a shift in cognitive resources away from external social evaluation, redirecting attention toward introspective or personally meaningful experiences.

At the same time, the stability of familiar face processing at frontal sites suggests that socially meaningful representations remain intact, even as psychedelics alter self-referential processing. This resilience may stem from familiar faces being deeply embedded in semantic and social memory networks (Gobbini and Haxby, 2007), making them less susceptible to fluctuations in attentional salience or psychedelic-induced reweighting of self-referential cues. Unlike self-faces, which require continuous updating within a dynamic self-representation framework, familiar faces are anchored in long-term social memory, allowing their processing to persist even as self-other boundaries become more fluid. This selective preservation of familiar identities highlights their potential role as cognitive anchors during altered states of consciousness, reinforcing the importance of trusted therapists, familiar settings, or relational grounding techniques in psychedelic-assisted therapy.

Taken together, these findings suggest that psychedelics do not simply dissolve self-boundaries but instead dynamically reshape self-referential cognition, potentially in a dose-dependent manner. While posterior regions show a weakening of perceptual self-other distinctions, frontal areas may compensate by preserving self-salience in a reorganized manner. This restructuring likely reflects a delicate dose-sensitive balance between ego dissolution and interoceptive awareness, where the loosening of rigid self-other boundaries at sensory processing levels is counteracted by higher-order mechanisms that sustain a coherent sense of self.

While the blurring of self-other distinctions is often framed as a mechanism for increased feeling of connectedness, it is important to recognize that ego dissolution is not universally experienced as positive. Previous research has shown that reductions in P300 self-other differentiation under psilocybin correlated with experiences of unity and altered perception (Smigielski et al., 2020). However, our data indicate that reductions in P300 amplitude under DMT/HAR correlated more

strongly with anxious rather than blissful ego dissolution (oceanic boundlessness, $p > 0.05$). Thus, the valence of ego dissolution may depend on how these neural changes interact with individual traits such as anxiety levels, personality structure, and prior psychedelic experience. While some individuals may interpret a loss of self-boundaries as liberating, others may experience it as disorienting or distressing, suggesting that self-processing alterations under psychedelics are not universally adaptive.

Interestingly, we found that reductions in N170 amplitude also correlated with Anxious Ego Dissolution, as well as Spiritual Experience, Impaired Cognition and Control, and global ASC scores. Given that self-other face differentiation only emerged at P300 (~300–500 ms), this suggests that early-stage perceptual instability (as indexed by N170 attenuation) may contribute to later self-boundary distortions. Rather than P300 reductions directly driving ego dissolution, it is possible that a weakened perceptual distinctiveness of face stimuli disrupts late-stage perceptual integration at P300, making self-referential differentiation more susceptible to interference. A similar pattern was observed in the relationship between P300 reductions and Elementary Imagery scores, where increased sensory vividness was linked to P300 attenuation, despite no significant relationship with earlier-stage visual components (P1/N170). Together, these findings suggest that psychedelic-induced alterations in self-processing and imagery intensification may stem from shifts in attentional dynamics and the hierarchical structuring of perceptual processing.

Ultimately, this study provides neurophysiological evidence that psychedelics do not merely dissolve the self but rather reconfigure self-referential processing, balancing perceptual disruptions with adaptive cognitive adjustments. This restructuring may be a key mechanism underlying their therapeutic potential, particularly in conditions marked by rigid self-perception and impaired social cognition (Dinulescu et al., 2021; Reiff et al., 2020). By altering how self-related information is processed, psychedelics may induce a shift in cognitive dynamics that modifies self-boundary perception and social salience, potentially explaining their efficacy in reducing symptoms of depression and anxiety in clinical settings (Griffiths et al., 2016).

4.3. Limitations and future directions

While our study provides novel insights into how psychedelics influence face perception and self-referential processing, several limitations must be considered. First, the observed effects may be specific to the DMT/HAR formulation and dosage used, raising questions about their generalizability to other psychedelics (e.g., LSD, psilocybin) and different dosing regimens. Future research should investigate whether similar ERP modulations occur across different compounds, doses, and administration methods to determine the broader applicability of these findings. Second, while EEG offers high temporal resolution, it lacks the spatial precision needed to localize the specific neural networks driving these effects. Future studies integrating fMRI or MEG could provide a clearer picture of how psychedelics influence self-referential and face-processing networks at both functional and structural levels. Third, it remains unclear whether the reductions in P300 and N170 represent temporary state-dependent effects or contribute to long-term shifts in self-processing. Longitudinal EEG studies could help determine whether these changes persist beyond the psychedelic state and whether they play a role in lasting cognitive or emotional flexibility. Additionally, while psychedelics have therapeutic potential, alterations in self-processing are not inherently beneficial. Some individuals might report distressing ego-dissolution experiences, suggesting that the effects of psychedelics on self-referential processing may not be universally adaptive. Future studies should explore individual differences in susceptibility to these effects, particularly in populations with pre-existing dissociative traits or anxiety disorders. Finally, in this study, celebrity faces were used as familiar stimuli. Given the expanding nature of the self (Aron and Aron, 2006; Aron and Fraley, 1999; Mattan et al.,

2016), it has been proposed that personally familiar faces (e.g., a partner's face, family member) may be processed not only as familiar faces but also as self-related stimuli, as if they were part of the self (Taylor et al., 2009). Exploring the potential overlap between personally familiar faces and self-related stimuli during psychedelic experiences could provide deeper insights into the intricate relationship between psychedelics, face recognition, and self-referential processing.

5. Conclusion

Our findings reveal that DMT/HAR profoundly alters self-referential face processing by dynamically modulating both early and late-stage neural responses. Enhanced P1 amplitudes indicate heightened sensory processing, while reduced N170 amplitudes suggest disrupted structural encoding of faces, pointing to an imbalance between sensory input and perceptual integration. Crucially, the attenuation of P300 responses for self-faces at posterior sites reflects a blurring of self-other boundaries, aligning with experiences of ego dissolution. However, this effect was not uniform—frontal regions exhibited increased neural responses to self-faces and decreased responses to unknown faces, suggesting a reorganization rather than a complete loss of self-referential salience. The preservation of familiar face processing at frontal sites further highlights the selective nature of these alterations, indicating that socially meaningful representations remain intact despite shifts in self-processing. Taken together, these findings suggest that psychedelics restructure the way self-relevant information is processed, offering mechanistic insights into their potential therapeutic applications for conditions characterized by rigid self-referential cognition, such as depression and social anxiety disorders.

Research ethics and patient consent

The study was conducted in full compliance with the ethical principles outlined in the World Medical Association's Declaration of Helsinki. Informed written consent was obtained from each participant prior to their inclusion in the study.

Clinical trial registry name and URL incl. registration number

Neurodynamics of Prosocial Emotional Processing Following Serotonergic Stimulation With N,N-Dimethyltryptamine (DMT) and Harmine in Healthy Subjects. <https://clinicaltrials.gov/ct2/show/NC04716335>

CRediT authorship contribution statement

Dila Suay: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Helena D. Aicher:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Data curation, Conceptualization. **Micheal Kometer:** Writing – review & editing, Conceptualization. **Michael J. Mueller:** Writing – review & editing. **Luzia Cafilisch:** Writing – review & editing, Investigation. **Alexandra Hempe:** Writing – review & editing, Investigation. **Camilla P. Steinhart:** Writing – review & editing, Investigation. **Claudius Elsner:** Writing – review & editing, Investigation. **Ilhui A. Wicki:** Writing – review & editing, Investigation. **Jovin Müller:** Writing – review & editing, Investigation. **Daniel Meling:** Writing – review & editing, Investigation. **Dario A. Dornbierer:** Writing – review & editing. **Milan Scheidegger:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Davide Bottari:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

MS, MK and DAD co-founded Reconnect Labs, an academic spin-off at the University of Zurich. MJM is a shareholder of Reconnect Labs. All other co-authors have no conflict of interest to declare related to this work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.neuroimage.2025.121247](https://doi.org/10.1016/j.neuroimage.2025.121247).

Data availability

Data will be made available on request.

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