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DMT, Madness, and Healing: Psychosis Model, Therapy Model, and Their Relations to Mystical Experiences and Positive Emotionality

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Abstract

Paradoxically, psychedelics have long been used as models of both psychosis and therapy. After proposing mystical experiences as a link between these models for lysergic acid diethylamide (LSD), we aimed to extend and refine this framework for *N,N*-Dimethyltryptamine (DMT). In a randomised, placebo-controlled, double-blind, crossover study, 25 healthy participants received DMT (60mg) and an active placebo (0.6mg DMT), separated by two hours. Psychotic-like experiences were assessed via aberrant salience (Aberrant Salience Inventory [ASI]) and therapeutic-like experiences via suggestibility (Creative Imagination Scale [CIS]), including suggestion-induced mystical experiences. Psychedelic experiences were measured via the Six Dimensions and Eleven Factors of Altered States of Consciousness Questionnaire (6D-ASC and 11-ASC), Hallucinogen Rating Scale (HRS), and Mystical Experiences Questionnaire (MEQ). Compared to placebo, DMT increased all aberrant salience factors, most suggestibility modalities, including mystical experiences, and most 6D-ASC and HRS factors. Aberrant salience showed widespread correlations with psychedelic experiences, particularly mystical experiences (MEQ) and positive emotionality (e.g., Joyfulness [6D-ASC], Blissful State [11-ASC]). Suggestibility correlated with the same positive emotionality factors and inversely with negatively valenced aberrant salience (Heightened Emotionality [ASI]), emotionality (Dysphoria [HRS), and mystical experiences (Ineffability [MEQ]). In conclusion, DMT's effects on aberrant salience and suggestibility support its role both as a psychosis and therapy model. The models' link may be indirect with respect to mystical experiences, with emotionality playing a more crucial role. Importantly, suggestion-induced mystical experiences after DMT may suggest post-acute perceptual plasticity, informing the development of more tailored psychedelic treatments that induce, amplify, and guide therapeutic experiences.

Introduction

Classic or serotonergic psychedelics, including lysergic acid diethylamide (LSD) and *N,N*-dimethyltryptamine (DMT), induce profound perceptual, emotional, and cognitive alterations and have been explored both as therapeutic tools and psychosis model [1]. While psychedelic-assisted therapies show therapeutic potential across psychiatric conditions [2], psychedelics can also reproduce phenomenological features of psychosis [3, 4], raising longstanding questions about how these compounds may both alleviate and model psychopathology. Our previous LSD study addressed this paradox by proposing mystical experiences as conceptual bridge between psychosis and therapy models, showing close associations with psychosis-related measures and taking a central role in therapeutic outcomes [5]. Building on this, we now report a subsequent DMT study aimed at confirming and extending these insights.

DMT was selected for its remarkably short duration. While LSD effects last several hours, DMT effects subside after around 15 minutes. Inhaled DMT offers additional advantages of non-invasive administration, supporting potential widespread clinical use, for example in depression [6, 7]. At higher doses, DMT induces alterations in perception, self-experience, emotionality, and mystical experiences [8–11].

Regarding psychosis models, similarities between psychedelic and psychotic experiences have been documented early [12]. Phenomenological similarities include distorted perceptions of senses, reality, self, and body, distorted thinking, intensified emotionality, spiritual and meaningful experiences [3, 13, 14]. However, contemporary perspectives emphasise that psychedelic and psychotic experiences differ in important respects, including emotional valence (positive vs. negative), sensory modality (visual vs. auditory), and reality monitoring (preserved vs. impaired). Nevertheless, shared mechanistic pathways have been highlighted, including disturbed memory, attention, and pre-attentional processes such as salience [13–15].

Salience is the prominence of an external or internal stimulus (e.g., object or idea) that automatically catches attention – a red apple on a green tree – and is a fundamental mechanism to interact with the environment [16]. Aberrant salience is the excessive meaning attribution to irrelevant stimuli and thought to underlie the development of psychotic symptoms (e.g., hallucinations and delusions) [17–19]. Aberrant salience is associated with schizophrenia symptoms [20], psychotic experiences in first-episode psychosis [21], paranormal experiences in the general population [22]. We showed aberrant salience to increase under LSD [5], while other classic psychedelics remain unexplored.

Regarding therapy models, suggestibility is a crucial mechanism in patient–health professional interactions [23–26]. Suggestibility is the tendency to yield to suggestions, which are communications that shift perception, affect, cognition, or behaviour and are basic tools in hypnotherapy [27, 28]. Suggestibility can be increased by hypnosis [29] and long-acting psychedelics [26, 30].[1] Placebo-controlled research reported increased suggestibility under high LSD doses during the drug peak [31]. Furthermore, we demonstrated increased suggestibility under moderate LSD doses post-peak [5]. Here, we explored whether suggestibility increases with short-acting psychedelics post-acutely. Furthermore, we assessed suggestibility-induced mystical experiences. Mystical experiences commonly occur under psychedelics, have substantial personal and therapeutic impact [32, 33], and can be induced using hypnotic suggestions [34]. Considering the importance of mystical experiences to psychotic disorders [3, 35, 36], and their proposed bridging role between psychosis and therapy models [5], we examined suggestion-induced mystical experiences as a possible link between both models.

Materials and Methods

This work reports data from a previously published project on the safety and tolerability of inhaled DMT, including harms or unintended events [6].

Design

We used a randomised, double-blind, placebo-controlled, crossover design with two treatment sessions (DMT, active placebo), separated by a 2-hour washout period, which has previously yielded no residual physiological effects [8]. Participants were randomly assigned to the drug order (DMT–placebo, placebo–DMT), using simple randomisation (randomizer.org). The study received approval by the ethics committee (University Hospital Onofre Lopes [HUOL], Federal University of Rio Grande do Norte [UFRN]; #67.303.623.6.0000.5292), registered at clinicaltrials.gov (https://clinicaltrials.gov/study/NCT05901012, registered 02/06/2023), and conducted according to the Declaration of Helsinki, Good Clinical Practice (GCP), and psychedelic research guidelines [37]. No patients or members of the public were involved in the design, conduct, reporting, or dissemination of this study. No important changes to outcomes or analyses were made after trial commencement.

Participants

Using online advertisements and word of mouth, we recruited 26 healthy, right-handed volunteers (18 to 60 years) with at least one experience with DMT (04–07/2023). Sample size was estimated based on previous studies [8]. Candidates underwent a medical and psychiatric screening and selection criteria check [6]. Participants gave written informed consent and had to abstain from psychedelics for two weeks and from alcohol and other drugs for three days before study participation.

Drug

DMT (purity 98.9% ±0.18) was isolated from organically and regionally grown *Mimosa tenuiflora* tree roots. For inhalation, 60 mg DMT were vapourised (Volcano® Medic 2, Storz & Brickel GmbH & Co, Tuttlingen, Germany) at 200°C for 10 sec into a 2-L balloon. As an active placebo, a very small DMT dose (0.6 mg) was vapourised to minimally mimic smell and colour. Participants emptied the lungs, inhaled, and retained the vapour for 3 sec. Before the first treatment, the procedures were trained with air-filled balloons. Inhalation quality was satisfactory except for one session (DMT in subject #6).

Measurements

Psychedelic Experiences

Psychedelic experiences was measured regarding Intensity [5], the Five Dimensions, Six Dimensions, and Eleven Factors of Altered States of Consciousness Questionnaire (5D-, 6D- and 11-ASC) [38–40], Hallucinogen Rating Scale (HRS) [9], and Mystical Experiences Questionnaire (MEQ) [41] (**Supplemental Methods**). Most main drug effects for these scales are reported

elsewhere [6]; for this work, we correlated the deltas (Δ = DMT − placebo) of significantly altered measurement with aberrant salience and suggestibility.

Psychosis Model: Aberrant Salience

The Aberrant Salience Inventory (ASI) measures trait aberrant salience using 29 yes–no items [42], yielding a total score and five factors (Increased Significance, Senses Sharpening, Impending Understanding, Heightened Emotionality, Heightened Cognition). The Brazilian Portuguese translation and state measurement adaptation confirmed the five-factor structure beyond supporting a four-factor solution [43] (**Supplemental Methods**; **table S1**).

Therapy Model: Suggestibility

Suggestibility was measured by the Creative Imagination Scale (CIS) [44], comprising 10 guided imagery items of different sensory modalities (e.g., auditory, tactile), rated on a 5-point Likert scale (0 = not at all the same; 4 = almost exactly the same). We divided the items into two parallel versions (A and B) [5], applied in balanced order across participants and counterbalanced across treatments. The items yield a total score and the sensory modalities Weight, Sensation, Taste, External Ambience, Internal Ambience and an additional item Mystical, based on a previous hypnotic protocol [34] (for details on task adaptation, application, and mystical item, see **Supplemental Methods**).

Procedures

The study was conducted at the university hospital's Psychedelic Research Unit. The room was furnished in a modern living room style and at least one experienced researcher always remained with the participant.

Sessions started at 7:30 a.m. with baseline measurements. At 9:00 a.m., DMT or placebo was administered, followed by physiological and biochemical measurements, with acute DMT effects lasting around 20 min [6]. At 9:30 a.m., during the post-acute DMT phase, the suggestibility task was conducted, lasting 20 min. Afterwards, psychedelic experience and aberrant salience questionnaires were applied.

Hereafter, the second session repeated the same procedures. At 11:10 a.m., participants received the other corresponding drug. At 12:54 p.m., participants underwent final medical evaluations, received lunch, and were released into the care of a family member or friend.

Statistical Analysis

Each scale factor/item was analysed using a Repeated Measures General Linear Model (GLM) with the within-subject factor drug (DMT, placebo) and the between-subjects factor drug order (DMT–placebo, placebo–DMT). Main effects of drug, order, and session (drug×order) were evaluated. Effect sizes were estimated using partial eta squared (η_p^2).

Spearman correlations were calculated of DMT-induced aberrant salience and suggestibility with psychedelic experiences (Δ = DMT − placebo).

Significance level was α = 0.05, two-tailed. The *p*-values were Bonferroni-corrected *post hoc* for multiple testing by factor number plus total score, unless stated otherwise. No interim analyses or stopping guidelines were prespecified. Analyses were conducted using IBM SPSS Statistics (v.22). Additional exploratory and sensitivity analyses (e.g., correlations and alternative factor structures) were conducted and were not pre-specified.

Results

Participants

The first subject (order DMT–placebo) received a different inhalation volume and was therefore excluded from all analyses (for the CONSORT flow diagram, see **figure S1**). So, the final sample consisted of 25 subjects (age = 33 ± 6 years; female = 13; male = 12). These were predominantly White, single, highly educated, employed, non-religious but spiritual, and experienced with ayahuasca (14 ± 19 times) [6].

Psychedelic Experiences

Regarding 6D-ASC, DMT, compared to placebo, increased Oceanic Boundlessness, Dread of Ego Dissolution, Visionary Restructuralization, Joyfulness, and Auditory Alterations (all $p \leq 0.001$), but not Vigilance Reduction (Fig. 1A).

Regarding HRS, DMT increased Vision, Meaningfulness, Euphoria, Somesthesia, Auditory and Minor Senses (all $p \leq 0.001$), Dysphoria, and Liking (both $p \leq 0.030$), while the increases in Volition did not survive multiple testing correction (Fig. 1B).

No order or session effects reached significance. For detailed GLM values, estimated marginal means, and standard deviations, see Table 1.

Displayed are means (bars) ± SEM (error bars), and individual subject data (dots) in the following sample sizes: n = 25 (6D-ASC, HRS, ASI and CIS Weight, Sensation, and Taste), n = 21 (CIS External Ambience), n = 17 (CIS Internal Ambience and Mystical), and n = 15 subjects (CIS Total). *** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$ ((A-C) Bonferroni-corrected, (D) uncorrected).

6D-ASC, Six Dimensions of Altered State of Consciousness Questionnaire: OBN, Oceanic Boundlessness; DED, Dread of Ego Dissolution; VRS, Visionary Restructuralization; AUA, Auditory Alterations; VIR, Vigilance Reduction; JOY, Joyfulness. HRS, Hallucinogen Rating Scale: Meaning, Meaningfulness; Auditory Minors, Auditory and Minor Senses. ASI, Aberrant Salience Inventory: Significance, Increased Significance; Sharpening, Senses Sharpening; Understanding, Impending Understanding; Emotionality, Heightened Emotionality; Cognition, Heightened Cognition. CIS, Creative Imagination Scale.

Table 1
Drug effects on measures of psychedelic experience (6D-ASC, HRS), aberrant salience (ASI), and suggestibility (CIS).

Measurement	GLM values	Estimated marginal means ± SD
6D-ASC		
Oceanic Boundlessness	**$F(1,23) = 36.1$, $p < 0.001$, $\eta_p^2 = 0.61$**	DMT: 33.0 ± 27.4, Placebo: 4.2 ± 7.9
Dread of Ego Dissolution	**$F(1,23) = 23.8$, $p < 0.001$, $\eta_p^2 = 0.51$**	DMT: 12.3 ± 10.2, Placebo: 2.9 ± 5.3
Visionary Restructuralization	**$F(1,23) = 70.0$, $p < 0.001$, $\eta_p^2 = 0.75$**	DMT: 50.1 ± 24.7, Placebo: 6.7 ± 12.9
Auditory Alterations	**$F(1,23) = 19.6$, $p = 0.001$, $\eta_p^2 = 0.46$**	DMT: 15.0 ± 15.8, Placebo: 2.1 ± 4.8
Vigilance Reduction	$F(1,23) = 0.83$, $p = 0.372$, $\eta_p^2 = 0.04$	DMT: 27.7 ± 24.5, Placebo: 23.0 ± 21.5
Joyfulness	**$F(1,23) = 41.2$, $p < 0.001$, $\eta_p^2 = 0.64$**	DMT: 31.9 ± 23.1, Placebo: 6.4 ± 10.3
HRS		
Vision	**$F(1,23) = 87.5$, $p < 0.001$, $\eta_p^2 = 0.79$**	DMT: 1.97 ± 0.87, Placebo: 0.22 ± 0.32
Meaningfulness	**$F(1,23) = 28.7$, $p < 0.001$, $\eta_p^2 = 0.56$**	DMT: 0.89 ± 0.76, Placebo: 0.21 ± 0.23
Dysphoria	**$F(1,23) = 13.2$, $p = 0.011$, $\eta_p^2 = 0.37$**	DMT: 0.37 ± 0.42, Placebo: 0.06 ± 0.08
Euphoria	**$F(1,23) = 47.4$, $p < 0.001$, $\eta_p^2 = 0.67$**	DMT: 1.06 ± 0.67, Placebo: 0.25 ± 0.27
Somaesthesia	**$F(1,23) = 23.4$, $p = 0.001$, $\eta_p^2 = 0.51$**	DMT: 0.74 ± 0.63, Placebo: 0.21 ± 0.25
Auditory and Minor Senses	**$F(1,23) = 21.3$, $p = 0.001$, $\eta_p^2 = 0.48$**	DMT: 0.89 ± 0.81, Placebo: 0.18 ± 0.25
Liking	**$F(1,23) = 10.4$, $p = 0.030$, $\eta_p^2 = 0.31$**	DMT: 2.61 ± 0.82, Placebo: 1.97 ± 0.89
Volition	$F(1,23) = 5.70$, $p = 0.208$, $\eta_p^2 = 0.20$	DMT: 1.18 ± 0.56, Placebo: 0.83 ± 0.69
ASI		
Total	**$F(1,23) = 50.5$, $p < 0.001$, $\eta_p^2 = 0.69$**	DMT: 0.34 ± 0.22, Placebo: 0.04 ± 0.10
Increased Significance	**$F(1,23) = 19.1$, $p = 0.001$, $\eta_p^2 = 0.45$**	DMT: 0.25 ± 0.27, Placebo: 0.02 ± 0.09
Senses Sharpening	**$F(1,23) = 54.4$, $p < 0.001$, $\eta_p^2 = 0.70$**	DMT: 0.60 ± 0.33, Placebo: 0.08 ± 0.21
Impending Understanding	**$F(1,23) = 18.5$, $p = 0.002$, $\eta_p^2 = 0.45$**	DMT: 0.48 ± 0.52, Placebo: 0.04 ± 0.20
Heightened Emotionality	**$F(1,23) = 29.3$, $p < 0.001$, $\eta_p^2 = 0.56$**	DMT: 0.28 ± 0.22, Placebo: 0.03 ± 0.08
Heightened Cognition	**$F(1,23) = 23.9$, $p < 0.001$, $\eta_p^2 = 0.51$**	DMT: 0.28 ± 0.27, Placebo: 0.03 ± 0.09
CIS		
Total	**$F(1,13) = 21.6$, $p < 0.001$, $\eta_p^2 = 0.62$**	DMT: 2.20 ± 0.90, Placebo: 1.45 ± 0.70
Weight	**$F(1,23) = 4.96$, $p = 0.036$, $\eta_p^2 = 0.18$**	DMT: 2.32 ± 1.34, Placebo: 1.53 ± 1.24
Sensation	**$F(1,23) = 8.20$, $p = 0.009$, $\eta_p^2 = 0.26$**	DMT: 1.83 ± 1.08, Placebo: 1.11 ± 0.95
Taste	$F(1,23) = 0.41$, $p = 0.529$, $\eta_p^2 = 0.02$	DMT: 1.69 ± 1.00, Placebo: 1.80 ± 1.06
External Ambience	**$F(1,19) = 5.17$, $p = 0.035$, $\eta_p^2 = 0.21$**	DMT: 2.49 ± 1.13, Placebo: 1.95 ± 1.09

Measurement	GLM values	Estimated marginal means ± SD
Internal Ambience	**$F(1,15) = 13.4$, $p = 0.002$, $\eta_p^2 = 0.47$**	DMT: 2.54 ± 1.37, Placebo: 1.42 ± 0.82
Mystical	**$F(1,15) = 6.56$, $p = 0.022$, $\eta_p^2 = 0.30$**	DMT: 1.88 ± 1.55, Placebo: 1.16 ± 1.07

Note. Displayed are the values of the Repeated Measures General Linear Mixed Models (GLM), estimated marginal means, and standard deviations (SD). Significant effects are marked in **bold**. All *p*-values were Bonferroni-corrected by the number of factors plus total score, namely by n = 6 (6D-ASC), n = 8 (HRS), and n = 6 (ASI), while the CIS items were not corrected due to the exploratory nature of the analyses and for a better comparison with our previous LSD results.

6D-ASC, Six Dimensions Altered States of Consciousness Questionnaire. HRS, Hallucinogen Rating Scale; ASI, Aberrant Salience Inventory; CIS, Creative Imagination Scale; DMT, dimethyltryptamine.

Psychosis Model: Aberrant Salience

DMT, compared to placebo, increased total aberrant salience and the factors Senses Sharpening, Heightened Emotionality, Heightened Cognition, Increased Significance (all $p \leq 0.001$), and Impending Understanding ($p = 0.002$; Fig. 1C; Table 1). No order and session effects were observed.

The original English ASI factors and alternative Brazilian four factors showed overall similar results, with all factors increased under DMT and no order and session effects (**figure S2**; **table S2**).

Therapy Model: Suggestibility

Several subjects fell asleep, especially during later task items after approximately 15 min of eyes-closed suggestion exposure. Therefore, participants were asked whether they had fallen asleep (yes/no) and investigators independently evaluated sleep status (yes/unsure/no) and affected items. Items were excluded from analyses whenever participant or investigator indicated sleep, resulting in reduced sample sizes (item #4 External Ambience: n = 21; item #5 Internal Ambience and item #6 Mystical: n = 17; total scale: n = 15; for details, see **Supplementary Results**).

To enhance comparability with our previous LSD findings [5] and given the exploratory nature of the suggestion-induced mystical experiences, we initially explored uncorrected *p*-values. Compared to placebo, DMT increased total suggestibility ($p < 0.001$) and the modalities Internal Ambience ($p = 0.002$), Sensation ($p = 0.009$), Mystical ($p = 0.022$), External Ambience ($p = 0.035$), and Weight ($p = 0.036$), but not Taste (Fig. 1D; Table 1). No order or session effects were observed.

Corrected *p*-values were additionally analysed for comparison with aberrant salience and psychedelic scales (see **Supplementary Results**).

Correlations

Regarding aberrant salience, numerous moderate to high positive correlations emerged for the total score and factors (ΔASI) with psychedelic experiences (Δ6D-ASC, Δ11-ASC, ΔHRS, ΔMEQ), with r_s-values ranging from 0.52 to 0.89 (Table 2; for scatterplots of total scores, see Fig. 2A). This included relationships with mystical-type experiences (e.g., Oceanic Boundlessness, Experience of Unity, Sacredness) and positive emotionality (e.g., Joyfulness, Blissful State, Euphoria, Positive Mood; Fig. 2B).

For suggestibility, some moderate to high correlations emerged. The total score (ΔCIS) correlated positively with Joyfulness (Δ6D-ASC; $r_s = 0.79$, $p = 0.003$), Blissful State (Δ11-ASC; $r_s = 0.67$, $p = 0.038$), and Insightfulness (Δ11-ASC; $r_s = 0.70$, $p = 0.021$; Fig. 2C), indicating associations with positive emotionality similar to those observed for aberrant salience. Contrastingly, negative correlations emerged between External Ambience (ΔCIS) and Heightened Emotionality (ΔASI, $r_s = -0.68$, $p = 0.004$), between Internal Ambience (ΔCIS) and Dysphoria (ΔHRS, $r_s = -0.65$, $p = 0.029$), and between Sensation (ΔCIS) and Ineffability (ΔMEQ; $r_s = -0.60$, $p = 0.010$; Fig. 2D; Table 2), pointing to inverse relationships of suggestibility with negatively valenced aberrant salience, negative emotionality, and specific aspects of mystical experiences.

Given the associations of both aberrant salience and suggestibility with mystical experiences and positive emotionality, we developed a conceptual model linking the psychosis model, therapy model, and psychedelic experiences (Fig. 3).

Additionally, for comparison with previous studies, we correlated aberrant salience and suggestibility with earlier factor structures of 5D-ASC [38] and HRS [9, 45]. Moderate to high positive correlations emerged again between ΔASI and psychedelic scales (r_s=0.56 to 0.70), whereas a negative correlation appeared for ΔCIS Mystical with Agitation (ΔHRS; r_s=-0.73, p = 0.005; **table S3**). Moreover, to align with our previous LSD findings using the original ASI factor composition [5], we repeated the analyses with this structure. No correlations were found of ΔASI with ΔCIS, but with psychedelic scales similar to those observed for the Brazilian ASI (r_s=0.52 to 0.88; **table S4**).

DMT, dimethyltryptamine; ASI, Aberrant Salience Inventory; 6D-ASC, Six Dimensions of Altered States of Consciousness Questionnaire; 11-ASC, Eleven Factors of Altered States of Consciousness Questionnaire; MEQ, Mystical Experiences Questionnaire; CIS, Creative Imagination Scale.

Table 2
Significant relationships of DMT-induced aberrant salience (ΔASI) and suggestibility (ΔCIS) with psychedelic experience scales (Δ6D-ASC, Δ11-ASC, ΔHRS, ΔMEQ).

Psychedelic Experiences	**Aberrant Salience (ΔASI)**						**Suggestibility (ΔCIS)**			
	Total	**Signi-ficance**	**Shar-pening**	**Under-standing**	**Emo-tion**	**Cogni-tion**	**Total**	**Sensa-tion**	**External**	**Internal**
ΔASI										
Heightened Emotionality	-	-	-	-	-	-			**-0.68****	
Δ6D-ASC										
Total	**0.72*****		0.60**			0.66**				
Oceanic Boundlessness	0.72***	0.53*				0.76***				
Joyfulness	**0.62****		0.52*			0.66**	**0.79****			
Δ11-ASC										
Total	**0.74*****		0.56*			0.71***				
Experience of Unity	0.65**			0.54*		0.72***				
Spiritual Experience	0.64**			0.56*		0.63**				
Blissful State	**0.62****	0.55*				0.60**	**0.67***			
Insightfulness	0.59*					0.58*	**0.70***			
Disembodiment	0.62**				0.52*	0.63**				
Impaired Control & Cognition			0.53*							
Changed Meaning of Percepts	0.56*	0.61**				0.58*				
ΔHRS										
Vision			0.60**							
Meaningfulness	0.62**					0.62**				
Dysphoria										**-0.65***
Euphoria	**0.62****	0.58*		0.60**		0.54*				
Somaesthesia	0.54*				0.52*					
Auditory and Minor Senses			0.55*							
ΔMEQ										
Total	**0.88*****	0.55*	0.61**	0.57*		0.86***				
Mystical	0.84***	0.57*	0.54*	0.62**		0.83***				
Positive Mood	**0.74*****	0.54*	0.59*	0.52*		0.67***				

Psychedelic Experiences	Aberrant Salience (ΔASI)						Suggestibility (ΔCIS)			
	Total	Signi-ficance	Shar-pening	Under-standing	Emo-tion	Cogni-tion	Total	Sensa-tion	External	Internal
Transcendence of Time & Space	0.77***		0.55*			0.84***				
Ineffability			0.52*					**-0.60****		
Internal Unity	0.81***	0.59*		0.67**		0.84***				
External Unity	0.82***		0.54*			0.81***				
Noetic Quality	0.81***	0.72***		0.69***		0.82***				
Sacredness	0.89***	0.63**	0.60**	0.68***		0.78***				

Note. Displayed are Spearman's rank correlation coefficients for the total and factor scores in n = 25 (ASI, CIS Sensation), n = 21 (CIS External Ambience), n = 17 (CIS Internal Ambience), n = 15 subjects (CIS Total). For presentation purposes, only significant values are shown. Correlations in fields showing "-" were not evaluated. *** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$ (Bonferroni-corrected by the number or factors plus total score, i.e. n = 6 for ΔASI and ΔCIS). Correlations marked in **bold** are shown as scatterplots in Fig. 3.

Δ, difference between DMT and placebo. DMT, dimethyltryptamine. ASI, Aberrant Salience Inventory: Significance, Increased Significance; Sharpening, Senses Sharpening; Understanding, Impending Understanding; Emotion, Heightened Emotionality; Cognition, Heightened Cognition. CIS, Creative Imagination Scale: External, External Ambience; Internal, Internal Ambience. 6D-ASC, Six Dimensions of Altered States of Consciousness Questionnaire. 11-ASC, Eleven Factors of Altered States of Consciousness Questionnaire. HRS, Hallucinogen Rating Scale. MEQ, Mystical Experiences Questionnaire.

ASI, Aberrant Salience Inventory; 6D-ASC, Six Dimensions of Altered States of Consciousness Questionnaire; 11-ASC, Eleven Factors of Altered States of Consciousness Questionnaire; MEQ, Mystical Experiences Questionnaire; CIS, Creative Imagination Scale.

Discussion

To our knowledge, this is the first study to examine the link between the DMT psychosis and therapy models, beyond exploring the feasibility of inducing post-acute mystical experiences via suggestion. DMT robustly increased both aberrant salience and multimodal suggestibility, supporting the engagement of concurrent psychotic- and therapeutic-related processes. However, these processes appear phenomenologically distinct and partially dissociable with the altered state. Importantly, post-acute suggestions induced mystical experiences, highlighting potential strategies to optimise psychedelic treatments by amplifying and guiding therapeutic experiences.

Correlations between aberrant salience and psychedelic experiences further support a close link of psychotic-like features with mystical phenomenology and positive emotionality. Positive correlations of suggestibility with pleasant affect reveal novel connections between therapy model and positive emotionality, whereas negative correlations with emotional aberrant salience, dysphoria, and ineffability indicate associations with negatively valenced, psychosis- and mystical-related aspects. Together with our LSD results, the findings suggest generalised psychotic- and therapeutic-like dimensions across short- and long-acting psychedelics and reveal novel connections between psychosis and therapy models through mystical experiences and positive emotionality.

Psychedelic Experiences

DMT increased all 6D-ASC factors except Vigilance Reduction, replicating our previous 5D-ASC findings [6]. Again, Visionary Restructuralization and Oceanic Boundlessness were most pronounced, with weaker increases in Auditory Alterations and Dread of Ego Dissolution. The 6D-ASC more strongly captured visual and auditory dimensions, likely due to slightly modified item composition. The additional Joyfulness dimension on ecstasy, meaning, and well-being was comparable to Oceanic

Boundlessness levels. Similarly, survey data showed for DMT particularly strong visual, mystical, and joyful effects and less hypovigilance, anxious, and auditory experiences [40].

DMT increased all HRS factors except Volition, with pronounced visual and less somaesthetic effects, similar to previously factors [6]. Unlike earlier factors of overall Agitation/Affect [9, 45], the updated structure distinguished Euphoria and Dysphoria, with stronger increases in positive than negative affect. Liking was increased despite high placebo ratings. Auditory and Minor Senses covered a broader sensory range than previous factors, including smell, touch, and synaesthesia. Volition increases in one [9] but not another [45] nor the current structure, likely reflect item inversions – earlier items emphasised physiological control loss and current items acceptance, awareness, and control. Contrasting the earlier Quality of the Experience [45], Meaningfulness more directly captures meaning-making, a common feature of psychedelic experiences [46]. Overall, our findings align with multi-study data on diverse psychedelics [47], closely matching high-dose DMT on meaning and visual experiences, despite higher volition, liking, auditory, and somesthesia.

Psychosis Model: Aberrant Salience

DMT increased total aberrant salience and all factors, supporting its role as a psychosis model capturing salience disturbances and exaggerated meaning attribution. Effects are comparable to LSD [5], suggesting generalised aberrant salience alterations across psychedelics. However, DMT mean scores were slightly, possibly due to shorter durations or less well-remembered effects.

Both DMT and LSD most strongly increased Senses Sharpening, indicating enhanced sensory perception across short- and long-acting psychedelics, which is widely reported [48–53] and thought to contribute to noetic and insight experiences [54]. Total and Increased Significance were similarly strong expressed, reflecting core phenomena of aberrant salience and consistent with literature highlighting meaning-making as central psychedelic phenomenon [46]. Heightened Emotionality showed similar effects, aligning with euphoric and overwhelming feelings widely reported under psychedelics [33, 51].

Contrastingly, Impending Understanding was slightly weaker and Heightened Cognition stronger than in our LSD study. Contrastingly, the original factors showed comparable effects, suggesting psychometric rather than ontological differences, with the Brazilian ASI Impending Understanding consisting of only one item with most other items reassigned to Heightened Cognition (**table S1**, **S2**; **figure S1**) [42]. Clinically, these experiences resemble psychiatrist Klaus Conrad's concept of apophany in the prodromal phase of schizophrenia [55], characterised by pervasive senses of estrangement, neutral events acquiring personal significance, and disturbed boundaries between internal meaning attribution and external perception, but also by great apprehension.

The results implicate aberrant salience as a possible mechanism in psychedelic experiences. Aberrant salience is linked to psychosis-related symptoms across clinical, subclinical, and non-clinical populations [20–22, 56, 57] and modulated by external factors including cannabis use [58, 59] and meditation [60]. Such modulability may underlie psychedelic-induced sensory intensification and enhanced meaning-making. Similarly, the entropic processing framework proposes for psychedelic and psychotic phenomena that reduced sensory gating and loosened cognitive schemas increase information density and attentional scope, fostering altered salience, hyperassociative thinking and expanded meaning attribution [15].

Historically, psychedelic and psychosis research have emphasised different aspects, limiting their comparability. Psychedelic research focuses on mysticism, compassion, support, and context, whereas psychosis research emphasises symptomatologies, functioning, restraint, and safety concerns [61]. Nevertheless, comparative work highlights both convergences and distinctions. DMT best modelled positive symptoms (formal thought disorder, inappropriate affect), characteristic of early psychosis, while the non-classic psychedelic ketamine was more associated with negative symptoms (disturbed attention, distorted body perception, catatonia-like phenomena), resembling later or chronic psychosis [62, 63]. Psychedelic experiences involve more reality monitoring, visual alterations, positive affect, and transient durations, while clinical psychosis is marked by poorer reality monitoring, more auditory disturbances, negative affect, recurrent involuntary episodes, and functional impairment [3, 52]. The closest overlap may be strong existential or metaphysical meaning attribution [3]. Together with these findings, our results suggest that classic psychedelics – particularly DMT – best model positive

symptoms of early psychosis, including exaggerated internal and external meaning attribution, potentially mediated by aberrant salience.

Therapy Model: Suggestibility

DMT's effects on suggestibility support the simultaneous engagement of therapy-related processes. DMT-induced total and multi-modal suggestibility paralleled our LSD results [5] and are notable given DMT's shorter duration and the post-acute assessment. Together with similar results on acute, higher-dose LSD [31], this suggests robust psychedelic-induced suggestibility independent of substance, dose, and phase. This aligns with the proposed central role of suggestions in psychedelic research and therapy to unlock therapeutic benefits [26]. However, suggestibility likely only partially captures psychological processes in psychedelic-assisted treatments, which also include experiential avoidance, social bonding, emotional breakthrough, psychological flexibility, memory, symbolic thinking, and insight [64–70].

DMT and LSD similarly increased Weight, indicating substance-independent enhancements. Conversely, DMT showed weaker effects on External Ambience, and none on Taste, suggesting that imaginations of hearing music, age regression, and gustatory experiences require longer psychedelic durations or acute phases to unfold. DMT more strongly increased total suggestibility, Sensation, and Internal Ambience, suggesting potential therapeutic relevance for pain, somatic, and anxiety-related conditions, where suggestibility predicts hypnotherapeutic outcomes [71–74].

For the first time, we demonstrated that suggestions might post-acutely induce mystical experiences, indicating that psychedelic experiences may remain sensitive to contextual and interpersonal modulation. Given that mystical experiences predict therapeutic outcomes across psychedelic substances and conditions [32], post-acute suggestibility windows may enable more tailored interventions, with directed suggestions inducing, amplifying, and guiding therapeutically relevant experiences. This aligns with emerging clinical proposals emphasizing post-acute integration, including our recent DMT depression trial, with immediate, structured integrations to capitalise on this window of heightened experiential malleability [7].

Correlations: Connecting Psychosis Model and Therapy Model

DMT-induced aberrant salience showed widespread correlations with psychedelic – particularly mystical – experiences, underscoring a close link between psychosis model and mystical phenomena, especially sacredness. This aligns with the importance of mystical experiences in psychotic disorders [3, 35, 36] and extends our previous LSD findings [5]. Across substances, aberrant salience robustly correlated with psychedelic and mystical experiences, consistent with findings in psychosis patients, where thought disorder related to ASC measurements [75]. Notably, these relationships appeared stronger for DMT than LSD, with most ASI factors correlating with all MEQ factors.

Conversely, LSD showed several correlations of aberrant salience with Complex Imagery, whereas DMT only yielded one, suggesting a less generalised link with visual effects. Notably, Heightened Emotionality did not correlate with mystical experiences under either substance, suggesting that emotionally overwhelming aberrant salience is distinct from mystical phenomena. This aligns with the therapeutic aspect of mystical experiences and findings of reduced emotional aberrant salience following mindfulness training [60]. Contrastingly, aberrant salience correlated with positive affect (e.g., Joyfulness, Blissful State, Euphoria), indicating an additional link to pleasant emotionality, while also highlighting its limits given the typically distressing nature of clinical psychosis.

Suggestibility, unlike in our LSD study, correlated with psychedelic experiences, mainly with positive affect (e.g., Joyfulness, Blissful State), revealing novel links between the therapy model and positive emotionality and aligning with psychedelic studies linking these experiences to mental health benefits [76–78]. Additionally, suggestibility correlated negatively with Dysphoria, emotional aberrant salience, and ineffable mystical experiences, revealing inverse connections to unpleasant, inexplicable aspects of the psychosis model and mystical phenomena.

Suggestibility – including suggested mystical experiences – did not correlate with core mystical dimensions (MEQ), contrary to our hypotheses. Together with the associations between mystical experiences and aberrant salience, this suggests that mystical phenomena may represent a more indirect link between psychosis and therapy models. Conversely, positive

emotionality – associated with both aberrant salience and suggestibility – may provide a more direct link between the two models.

Limitations

Blinding was challenging due to DMT's characteristic vapour, odour, taste, and unmistakable subjective effects, potentially influencing suggestibility outcomes. Future studies should test improved placebos that better mimic vapour properties, such as combining inert smoke (e.g., glycerine) with very low DMT doses. The placebo (0.6 mg DMT) may have produced subjective and pharmacological effects. The 2-hour washout period limits exclusion of carryover effects, although none were statistically detected.

The small, homogeneous sample – predominantly young, White, single, well-educated, non-religious, and DMT-experienced – limits generalisability, highlighting the need for larger, diverse samples particularly in clinical populations.

Psychometric limitations also apply. The Intensity scale is unvalidated and the HRS lacks formal Portuguese validation [47]. Non-parallel suggestibility items, together with LSD- and DMT-induced increases in Weight, caution against overinterpretation due to potential measurement inequivalence. Splitting the long mystical item [34] may have reduced experience depth.

Conceptually, aberrant salience may capture only specific psychosis-related processes (e.g., hallucinations, delusions) rather than broader, emotional, cognitive, and behavioural dimensions. Similarly, suggestibility likely reflects only part of psychedelic therapeutic processes.

Participant exclusions due to sleep during later CIS items may introduce bias and reduced statistical power. The initial lack of multiple-testing correction to enhance comparability with our LSD results warrants cautious interpretation.

Conclusion

Overall, the DMT findings extend our LSD results, showing similar effects on aberrant salience and suggestibility and supporting the generalisation of concurrent psychotic- and therapeutic-like processes across short- and long-acting psychedelics. Correlations further confirm a close link between aberrant salience and mystical experiences across substances.

Furthermore, aberrant salience and suggestibility were associated with positive emotionality, suggesting a novel affective bridge between the psychosis and therapy models. Importantly, suggestions were able to induce post-acute mystical experiences, highlighting clinical potential for inducing, amplifying, and guiding therapeutically relevant psychedelic experiences.

Declarations

Data Availability Statement

The trial protocol, statistical analysis plan, data, and statistical code are available upon request from the corresponding author IW.

Author Contributions (CRediT)

Conceptualization and Resources: IW, MF, NGC, FPF, DBA

Methodology: IW, MF, DM, FPF, DBA

Software, Validation, Formal Analysis, Writing – Original Draft, and Visualization: IW

Investigation: IW, MF, SL, HB, FPF, DBA

Data Curation: IW, RB, MM, FPF

Writing – Review & Editing: MF, SL, HB, RB, MM, DM, NGC, FPF, DBA

Supervision and Project administration: IW, MF, FPF, DBA

Competing Interests

The authors have nothing to disclose.

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Footnotes

1. LSD-induced suggestibility among patients was reported to be higher in those with schizophrenia than with ‘neurosis’ or depression [79]. On the other hand, psychedelic-induced suggestibility in psychotherapy was proposed to reduce defences and increase acceptance and meaning, and promote health benefits, such as stress coping and alcohol abstinence [80–82]. Additionally, the combination of hypnosis with psychedelic psychotherapy, so-called hypnodelic therapy, has been proposed to boost the benefits of both techniques beyond those of each technique alone [83].
   From a cultural perspective, psychedelic-induced suggestibility in ritualistic and traditional contexts was proposed to be essential to shape social identity, bonding, and cohesion, as well as to reduce judgements and promote adaptation, conformity, insights, and fertility in initiation rituals [80–82]. These contexts include classic and non-classic psychedelics, including the peyote cult among the Navajo People in the Southwestern United States, ayahuasca churches such as the União do Vegetal in Brazil, *Tabernanthe iboga* use among the Bwiti people in Gabon, and *Datura* use among the Shangana-Tsonga people in Mozambique, but also other psychoactive substances such as the nicotine-containing *pituri* among the Aborigines in Australia.

Figures

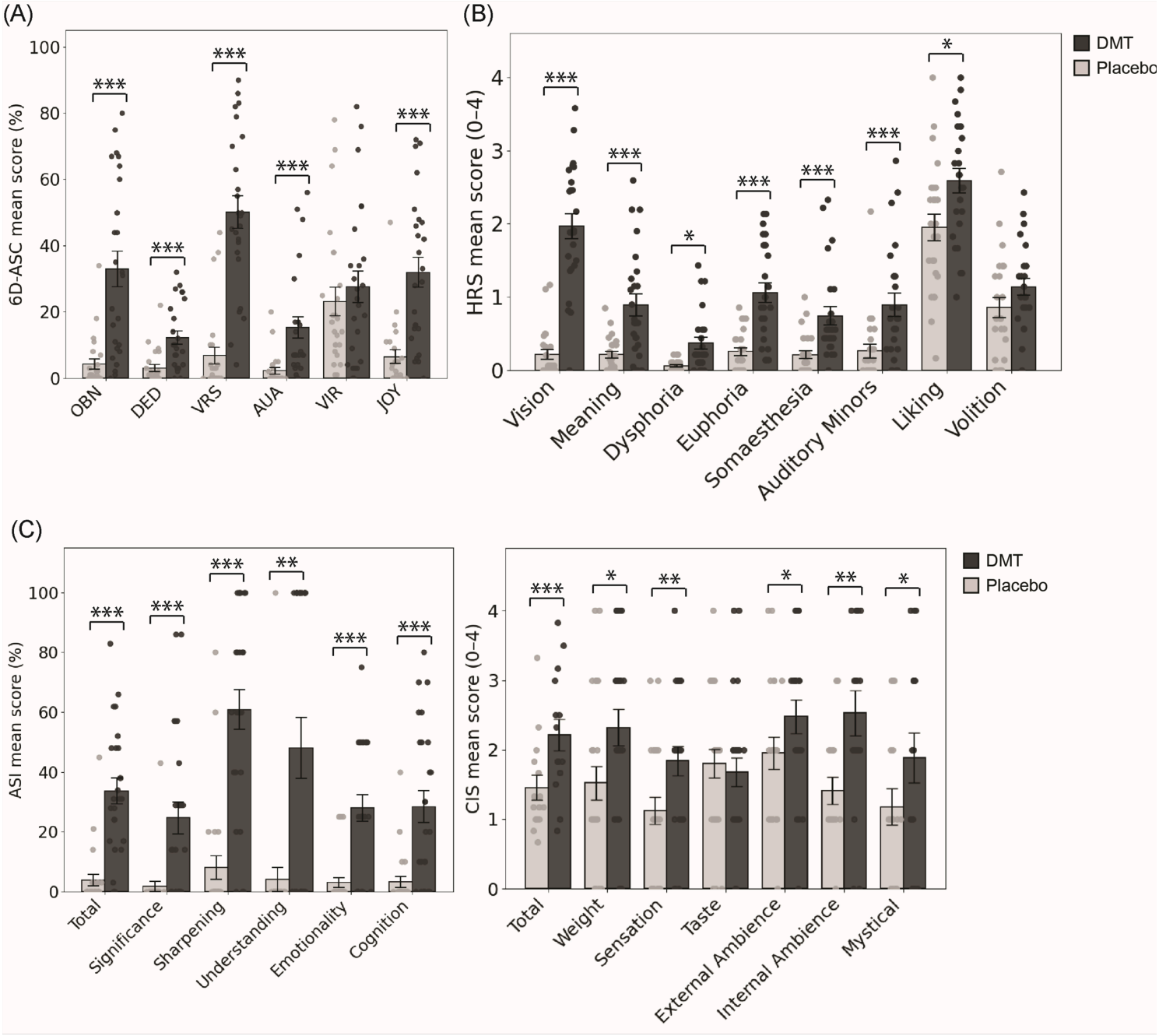


Figure 1

DMT, compared to placebo, induced psychedelic, psychotic- and therapeutic-like experiences.DMT increased psychedelic experiences, including (A) all 6D-ASC dimensions except for Vigilance Reduction and (B) all HRS factors except Volition. DMT also increased (C) psychotic-related experiences, as measured by total aberrant salience and all factors and (D) therapeutic-related effects, as measured by total suggestibility and the modalities Weight, Sensation, External and Internal Ambience and Mystical, but not Taste.

Displayed are means (bars) ± SEM (error bars), and individual subject data (dots) in the following sample sizes: n=25 (6D-ASC, HRS,ASI and CIS Weight, Sensation, and Taste), n=21 (CIS External Ambience), n=17 (CIS Internal Ambience and Mystical), and n=15 subjects (CIS Total). *** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$ ((A-C) Bonferroni-corrected, (D) uncorrected).

6D-ASC, Six Dimensions of Altered State of Consciousness Questionnaire: OBN, Oceanic Boundlessness; DED, Dread of Ego Dissolution; VRS, Visionary Restructuralization; AUA, Auditory Alterations; VIR, Vigilance Reduction; JOY, Joyfulness. HRS, Hallucinogen Rating Scale: Meaning, Meaningfulness; Auditory Minors, Auditory and Minor Senses. ASI, Aberrant Salience

Inventory: Significance, Increased Significance; Sharpening, Senses Sharpening; Understanding, Impending Understanding; Emotionality, Heightened Emotionality; Cognition, Heightened Cognition. CIS, Creative Imagination Scale.

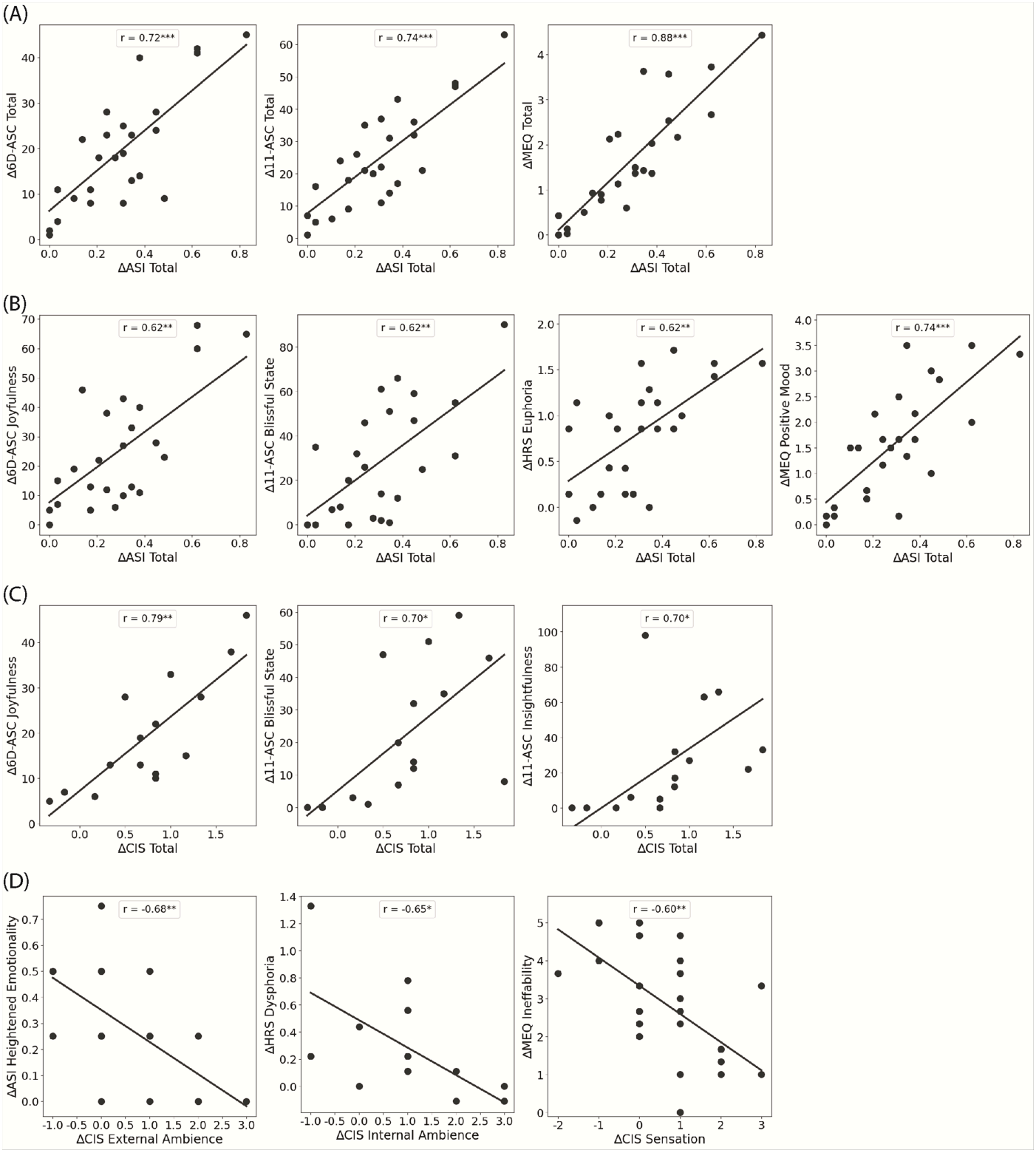


Figure 2

Relationships of psychosis model and therapy model with psychedelic experiences under DMT. (A) The psychosis model showed close relationships with psychedelic experiences, including high positive correlations of DMT-induced total aberrant salience (ΔASI Total) with total altered consciousness and mystical experiences (Δ6D-ASC, Δ11-ASC, and ΔMEQ Total). (B) Moreover, total aberrant salience correlated moderately to highly with pleasant emotional psychedelic experiences (Δ6D-ASC

Joyfulness, Δ11-ASC Blissful State, ΔHRS Euphoria, and ΔMEQ Positive Mood). (C) Similarly, the therapy model closely related to positive emotionality, including high positive correlations of DMT-induced suggestibility (ΔCIS Total) with Joyfulness (Δ6D-ASC) and Blissful State (Δ11-ASC), beyond Insightfulness (Δ11-ASC). (D) Specific suggestibility modalities also correlated inversely with unpleasant emotional aberrant salience (ΔASI Heightened Emotionality), negative emotionality (ΔHRS Dysphoria), and mystical experiences (ΔMEQ Ineffability). Displayed are scatterplots with each dot representing one subject. *** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$ (Bonferroni-corrected *post hoc* by n=6, respectively).

DMT, dimethyltryptamine;ASI, Aberrant Salience Inventory; 6D-ASC, Six Dimensions of Altered States of Consciousness Questionnaire; 11-ASC, Eleven Factors of Altered States of Consciousness Questionnaire; MEQ, Mystical Experiences Questionnaire; CIS, Creative Imagination Scale.

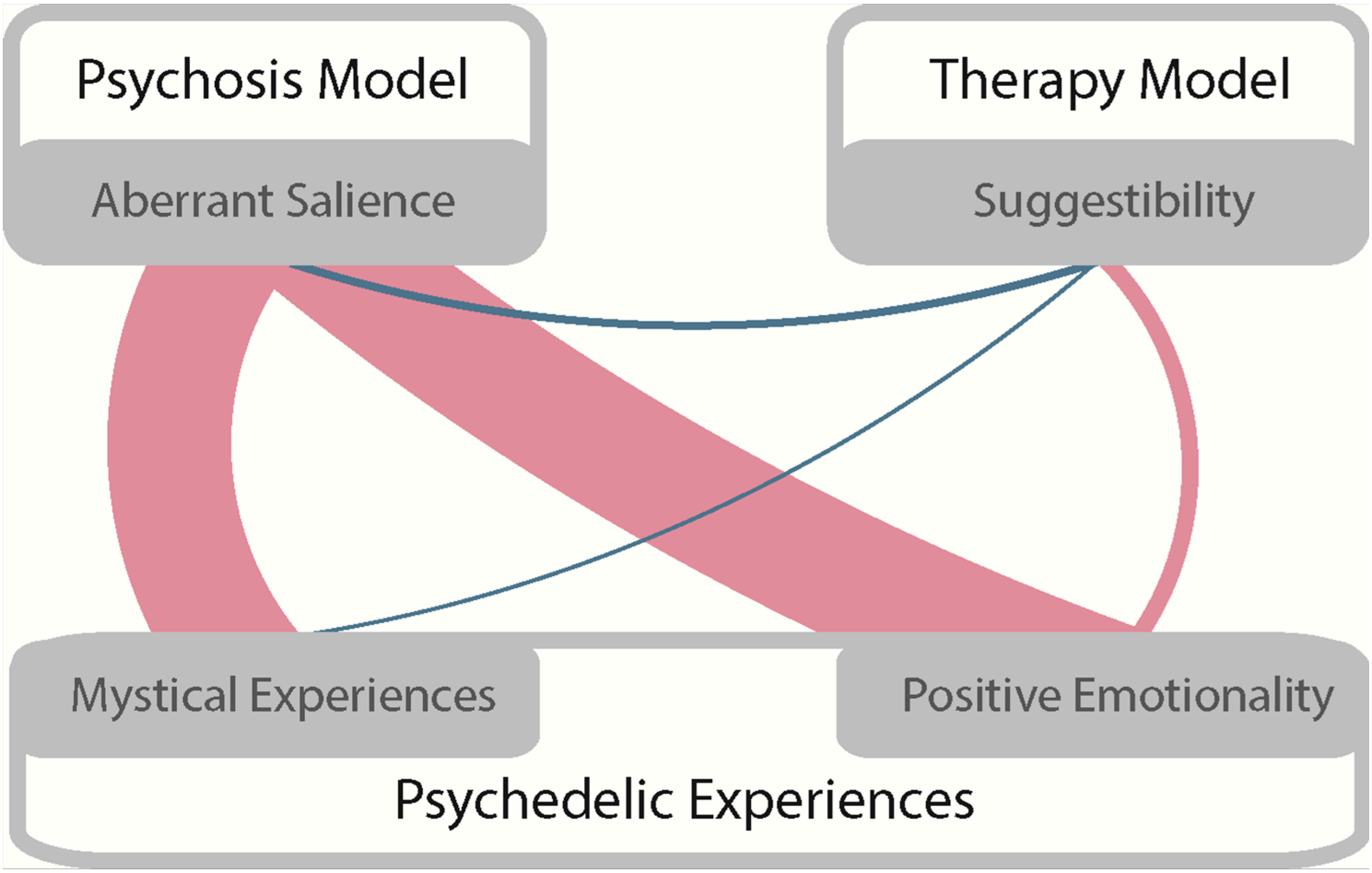


Figure 3

Relationships between psychosis model and therapy model. DMT-induced psychotic- and therapeutic-like experiences were both related to psychedelic experiences, yet occupied partially dissociable phenomenological spaces, with positive emotionality emerging as the key connecting dimension. Specifically, the psychosis model, as measured by aberrant salience (ASI), showed numerous high correlations with mystical-type experiences (such as Oceanic Boundlessness, Spiritual Experience, and most MEQ factors) as well as with positive emotionality (Joyfulness, Blissful State, Euphoria, Positive Mood). The therapy model, as measured by suggestibility (CIS), was similarly linked to positive emotionality (Joyfulness, Blissful State), while also showing inverse links to negative emotionality (Dysphoria), distressing aspects of the psychosis model (Heightened Emotionality), and inexpressible psychedelic experiences (Ineffability). The connecting lines represent significant correlations, with colour indicating the directions (positive = red, negative = blue) and thickness indicating the relative quantities.

ASI, Aberrant Salience Inventory; 6D-ASC, Six Dimensions of Altered States of Consciousness Questionnaire; 11-ASC, Eleven Factors of Altered States of Consciousness Questionnaire; MEQ, Mystical Experiences Questionnaire; CIS, Creative Imagination

Scale.

Supplementary Files

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- WiessnerDMTMadness260427supplNPP.pdf