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Beyond dose. Perceived group support as a person-level predictor of emotional breakthrough and psychological insight during DMT–harmine administration

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Beyond dose. Perceived group support as a person-level predictor of emotional breakthrough and psychological insight during DMT–harmine administration

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Abstract

Dose-escalation studies with dimethyltryptamine (DMT) show robust increases in emotional breakthrough, mystical experience, and psychological insight at higher doses, but with substantial inter-individual variability, suggesting factors beyond pharmacology shape response profiles. Growing evidence points to the clinical relevance of social factors, especially in group-based psychedelic therapy. Using data from a randomized-controlled trial, we investigated oromucosal DMT-harmine administration in a group setting and identified a three-layer architecture of acute psychedelic experience. First, dose scaled all three primary subjective outcomes. Second, perceived group support, reflecting stable between-person differences rather than session-to-session fluctuations, accounted for a substantial share of dose-independent between-subject variance in emotional breakthrough and psychological insight, though not in mystical-type experience. Third, pre-session affective personality, indexed by an approach-withdrawal composite, predicted group appraisal, with more approach-oriented profiles linked to more favorable perceptions of the group context. We situate these findings within the current research landscape and discuss the clinical implications of this three-layer framework for acute psychedelic experience.

1. Introduction

Besides the well-researched phenomenon of mystical-type experiences[1–3], other subjective effects like emotional breakthrough[4,5] or psychological insight experiences[6,7] have been suggested as clinical markers of positive therapeutic outcome following experiences with classic serotonergic psychedelics. Standardized psychometric assessments of the intensity and quality of these subjective experiences have been shown to predict long-term clinical outcomes more robustly than drug dose or plasma levels[8–11]. To advance the clinical utility of psychedelic interventions, it is therefore necessary to identify the factors that predict the intensity and quality of these clinically relevant subjective effects.

DMT, a hallucinogenic tryptamine alkaloid, is characterized by rapid onset, and short duration of action. Novel pharmacological formulations[12,13] make DMT a promising agent for psychedelic-assisted psychotherapy[14]. Recent dose-escalation studies indicate that higher DMT doses produce a robust increase in plasma concentration, along with increases in acute subjective intensity, mystical experiences, and ego dissolution [15–17]. Beyond intensity, DMT–harmine administration has been shown to elicit emotional breakthrough and psychological insight relative to placebo, with positive persisting effects at one- and four-month follow-up[13]. However, the strength of this relationship varies substantially across individuals[15,18]. Up to twofold variability in both plasma concentration and subjective intensity has been observed at identical doses[16,19]. Understanding which individual and contextual factors account for this residual variability is therefore an important next step toward more predictable psychedelic interventions.

Extra-pharmacological factors (*set* and *setting*) have long been thought to shape psychedelic effects[20–22], and recent work increasingly suggests they partly drive clinical outcomes by shaping both the acute experience and the subsequent integration of insights and emotional learning[23–26].

Within 'set,' stable individual differences are candidate sources of between-subject variability. Traits such as absorption, openness, and affective disposition predict the intensity and quality of acute experience[27–29], offering a plausible account of person-level variability. Whether these traits also blur the set–setting boundary remains unclear: how supportive a participant perceives a context may itself be shaped by disposition, meaning an apparent 'setting' appraisal could partly reflect 'set' rather than genuine, session-specific environmental features. The classical dichotomy cannot resolve this, and single-session designs are equally unable to disentangle the two. Separating a stable tendency to "feel supported" from a momentary, session-specific reading of context requires repeated within-subject measurement of perceived context alongside controlled dose variation.

Extra-pharmacological factors are inherently shaped by social dynamics[22,30], which has sparked growing clinical and economic interest in group-based psychedelic therapy[31–35].

Dedicated research has examined constructs such as communitas—a sense of shared togetherness during collective ritual[36]—linking it to increased psychological wellbeing, social connectedness, and deeper, more meaningful experiences among participants in psychedelic and group therapeutic settings[37]. This converges with recent consensus efforts identifying interpersonal and social factors, for example who is present during dosing, as core extra-pharmacological variables warranting systematic reporting[38,39]. Despite growing evidence for the therapeutic relevance of the social dimension of psychedelic use, established approaches to quantify the interpersonal dimension of a setting as experienced by individual participants remain scarce. Evidence is largely observational, retrospective, methodologically heterogenous, and studies endorse single-session designs, hence cannot disentangle contextual from dispositional contributions.

Here, we aimed to advance the identification of extra-pharmacological predictors of subjective experience. One valuable step in that direction could be to capture a participant's subjective appraisal of the interpersonal context at a given session, which, if shown to account for outcome variability beyond dose, would offer a measurable and session-specific operationalization of setting for future research designs.
The repeated-measures design allowed us to assess the strength and directionality of the association between perceived group support and acute subjective effects of DMT-harmine across different dose levels.

We hypothesized that (1) mystical-type experiences, emotional breakthrough, and psychological insight would increase with dose; (2) greater perceived group support would be associated with stronger subjective effects beyond dose; (3) this association likely reflects within-person, session-to-session variation rather than between-person differences; a distinction worth resolving, as it would narrow the space of candidate mechanisms and inform how interpersonal context is managed in future clinical protocols. We additionally undertook an exploratory, post-hoc examination of whether stable baseline dispositional (i.e., ‘set’) characteristics carried into every session could account for any person-level differences observed.

2. Methods

2.1 Study design

This study is a secondary analysis of psychometric data collected during a factorial dose-escalation trial of DMT and harmine in healthy volunteers[17]. The parent trial employed a within-subject, single-blind, randomized, balanced, crossover design. The study included a screening visit, six 11-h study days and brief (30 min) follow-up visits the next day (24 h post drug administration), and two online follow-ups at 1 week and 1 month after the last study day. Participants were randomly assigned to one of two possible dose-escalation axes. Axis 1 escalated harmine first (DMT fixed at 90 mg), then DMT (harmine fixed at 120 mg); Axis 2 had the reverse order (DMT escalation first, then harmine) (Figure 1). Seven dose conditions were administered, defined by the cumulative DMT (D) and harmine (H) dose in mg: 0(D)-120(H), 60(D)-120(H), 90(D)-0(H), 90(D)-60(H), 90(D)-120(H), 90(D)-180(H), and 120(D)-120(H). Each participant completed six dosing sessions, yielding 96 sessions in total. Only participants in axis 1 received the "DMT only" condition, whereas only participants in axis 2 received the "harmine only" condition. All DMT-harmine conditions included all 16 participants; DMT/harmine-only conditions included 8 participants each. Participants were blinded to the dosing scheme, except that they were informed that they would not receive the highest dose on the first study day. Experimenters present on dosing days were informed about the dosing scheme. The study drug was administered in three equal dose increments 20 min apart at 10:00 AM, 10:20 AM, and 10:40 AM. The washout period between any two intervention days was set to 1 week, with deviations from the schedule due to logistical reasons (range: 2–51 days, median: 7 days, mode: 7 days; there was a single occurrence of a 2-day washout period, and seven occurrences of a washout period >16 days). To preserve the group structure as far as possible, an alternative study day was scheduled whenever two or more participants were unable to attend. Two dosing sessions nevertheless had to be run with only two participants (one of dosing day 4 and one of dosing day 5). The study period, including dates of recruitment and follow-up, is reported in the parent publication[17].

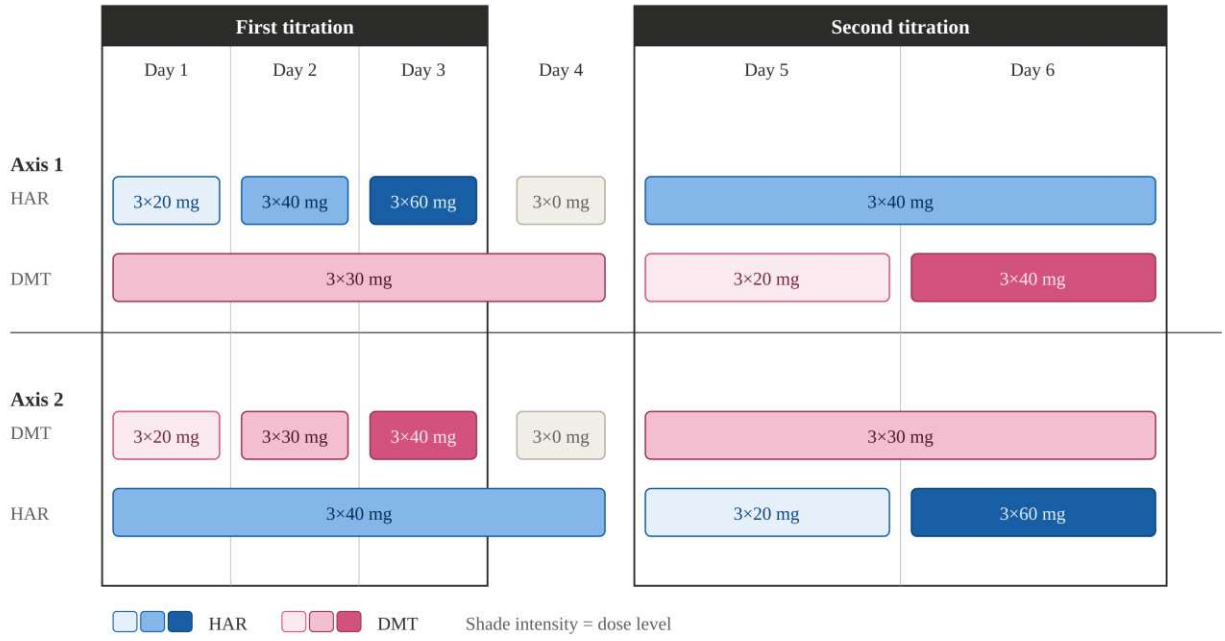


Figure 1: Study Design with two titration axes and respective dosing regimen
After enrollment, participants were randomized into one of two experimental axes, which determined their dose regimen on each study day. Axis 1 started with a titration of harmine over three study days (up to 3 × 60 mg) with a fixed DMT dose of 3 × 30 mg. Axis 2 started with a DMT titration over the first three study days (up to 3 × 40 mg) with a fixed harmine dose of 3 × 40 mg. On study day 4, participants received either only DMT (3 × 30 mg; axis 1) or only harmine (3 × 40 mg; axis 2). On study days 5 and 6, the missing doses from the respective other sequence were administered, so that all participants received the same five DMT + harmine combinations over the intervention days, but in differing order. The study drug was administered in three tablets of same dose at 20 min intervals. Study days were generally scheduled one week apart (refer to Egger et al., 2025 for details). Abbreviations: DMT = *N,N*-dimethyltryptamine, HAR = harmine.

2.2 Study setting

Dosing sessions took place in a spacious, living-room-style space at the University Hospital of Psychiatry Zurich, decorated with plants, carpets, colored cloths, and adjustable, primarily indirect lighting. Sessions were conducted in groups of 3 to 4 (two outlier sessions with only 2) participants lying on mattresses arranged in a circle, each with an individual sitter present throughout. At least one physician and 4–6 trained experimenters monitored participants and vital signs, with a board-certified psychotherapist or psychiatrist present or on-call. One of three standardized playlists

played throughout the day. Participants were encouraged to focus on internal processes. Study days ran from 8:30 AM to 7:30 PM in a fasted state, with a light lunch and possibility to share about their experience from 3:00 PM onwards. No formal preparation or integration sessions were included. Each dosing day began with a group check-in and guided mindfulness practice. Post-trial support remained available on request. See supplement 1 for an extensive description of the study setting following the ReSPECT Guidelines 2025[38].

2.3 Participants

Sixteen healthy volunteers (9 male, 7 female; mean age 35 ± 5.4 years, range 25–45; BMI 22.9 ± 2.1 kg/m²) were recruited through university online platforms and mailing lists, an internal research waiting list and public boards in the main buildings of Zurich Universities ETH and UZH and University Hospital Zurich. All were of Western European ethnicity and had prior experience with psychedelic substances (≥ 5 occasions), as required by the inclusion criteria. Full inclusion and exclusion criteria are reported in Supplement 2. No participants withdrew from the study; no sessions were excluded from analysis. The sample size of 16 participants was calculated to detect statistically significant between-dose differences in pharmacokinetic parameters; no independent power calculation was performed for the present secondary analysis. Full demographic characteristics can be found in Table S1.

The study was approved by the Cantonal Ethics Committee of the Canton of Zurich (BASEC-Nr. 2022–00973) and received regulatory approval from the Swiss Federal Office of Public Health (BAG-Nr. (AB)-8/5-BetmG-2022/018086). The trial was registered at ClinicalTrials.gov (NCT05829603). All participants provided written informed consent prior to enrolment.

2.4 Drug formulation

DMT and harmine were administered as fast-disintegrating orodispersible tablets via the oromucosal (transmucosal) route. The DMT was obtained by basic aqueous extraction from pulverized root bark of *Mimosa tenuiflora* (The Mimosa Shop, Brazil). Harmine hydrochloride (Harmine HCl, ≥98 % HPLC-tested) was procured from Santa

Cruz Biotechnology Inc. (Dallas, Texas 75220, USA). The tablets employed a microcarrier-based delivery system using template inverted particle (TIP) technology — calcium phosphate microparticles with a hollow, hydrophilic internal structure designed for rapid dispersion in the buccal cavity and enhanced transmucosal absorption, bypassing first-pass gastrointestinal metabolism[40]. To achieve a gradual transition into the psychedelic state, the total target dose for each session was divided into three equal tablets administered at 20-minute intervals[17]. The sublingual formulation was manufactured at the Institute of Regenerative Medicine (IREM) by a Swiss federal pharmacist with subsequent randomization (randomization list provided by the cantonal pharmacy Zurich (KAZ) and implemented in Wespirit); labeling and storage at the GMP-accredited Hospital Pharmacy of the University Hospital of Psychiatry Zurich.

2.5 Materials and measures

2.5.1 Outcome measures

Three retrospective psychometric instruments were administered after each dosing session to assess distinct dimensions of the subjective experience:

- **Emotional Breakthrough Inventory** (EBI[4])
- **Psychological Insight Scale** (PIS[6])
- **Mystical Experience Questionnaire** (MEQ[1])

These instruments capture qualitatively distinct aspects of the psychedelic experience – emotional processing (EBI), cognitive insight (PIS), and mystical-type phenomenology (MEQ) – extending beyond the acute intensity measures (e.g., 5D-ASC[41]) reported in the parent trial[17]. EBI and PIS were administered 240 minutes after the first dose (200 minutes after the final dose). MEQ was assessed 300 minutes after the first dose (260 minutes after the final dose). The staggered schedule was designed to reduce participant burden by spreading the psychometric battery across two timepoints rather than administering all instruments simultaneously. A description of the scales is available in Supplement 3.

2.5.2 Predictor measures

Perceived group support

Perceived group support (PGS) was operationalized using a single item from the Participant Feedback Form (PFF), a study-specific instrument developed to capture contextual aspects of participants' experiences not covered by the existing, validated outcome measures: "I believe that the group setting helped me to have a meaningful experience", rated on a 7-point Likert scale from −3 (strongly disagree) to +3 (strongly agree). This instrument was administered 300 minutes after the first dose (260 minutes after the final dose), alongside the MEQ. See Supplement 4 for all items of the PFF pertaining to participants' perception of contextual variables surrounding the experience.

Affective personality

The Affective Neuroscience Personality Scale (ANPS[42]) was administered once during medical screening, before the first dosing session. The ANPS yields scores on seven affective trait dimensions: Seeking, Play, Care, Fear, Sadness, Anger, and Spirituality. To place the dimensions on a common scale, each subscale score was z-standardized across participants in the analytic sample.

The primary Approach–Withdrawal Index (AWI) was calculated as the mean of the standardized Seeking, Play, and Care scores minus the mean of the standardized Fear, Sadness, and Anger scores:

$$AWI = mean[z(Seeking), z(Play), z(Care)] - mean[z(Fear), z(Sadness), z(Anger)] \quad (1)$$

For the sensitivity analysis, an extended index (AWI^{+}) was calculated by additionally including Spirituality in the approach component:

$$AWI^{+} = mean[z(Seeking), z(Play), z(Care), z(Spirituality)] - mean[z(Fear), z(Sadness), z(Anger)] \quad (2)$$

All dimensions were equally weighted within their respective components. Higher index values indicate a relatively more approach-oriented than withdrawal-oriented affective profile, whereas lower values indicate the reverse.

2.6 Statistical analysis

All analyses were conducted in Python 3.12. Linear mixed-effects models were fitted using statsmodels 0.14.4[43]; SciPy 1.12.0[44], pandas 2.2.3[45], and NumPy 1.26.4[46] were used for additional statistical computations and data processing. Statistical significance was set at $\alpha = .05$ unless otherwise noted. The psychometric analyses reported here are exploratory, arising from patterns observed in the parent dose-escalation dataset.

2.6.1 Dose effects on psychometric outcomes

For each outcome measure (EBI, PIS, MEQ), a baseline linear mixed-effects model was fitted with dose condition (7 levels) as a categorical fixed effect and participant as a random intercept. The reference condition was 0(D)-120(H), which was the harmine-active, DMT-absent condition selected to anchor the dose-escalation design. The omnibus effect of dose was tested by likelihood-ratio comparison of the baseline model against an intercept-only model retaining the participant random intercept. Condition-level coefficients (β, SE, 95% Wald CI) are reported descriptively. Intraclass correlation coefficients (ICCs) were computed from the baseline model to quantify the proportion of residual variance attributable to stable between-subject differences after accounting for dose.

2.6.2 Perceived group support as additional predictor

To test whether extra-pharmacological factors accounted for residual between-subject variability, the PGS item was incorporated into the dose model. Because a single-item state measure can carry both stable trait variance and session-level variance, a decomposition strategy was employed to separate between-subject and within-subject variance components[47]. This decomposition guards against aggregation bias — the risk that a combined predictor conflates stable person-level differences with session-level fluctuations, potentially masking the true direction or magnitude of the association[48]. Four nested models were compared for each outcome:

1. **Baseline model** — dose as fixed effect, participant random intercept.
2. **Combined model** — Baseline model plus undifferentiated (combined) PGS as a single additional fixed effect.

3. **Decomposed model** — Baseline model plus PGS decomposed into a between-subject component (participant mean across sessions) and a within-subject component (session-level deviation from participant mean), entered as two separate fixed effects.
4. **Between-subject model** — **Baseline model** plus between-subject PGS only (within-subject component removed).

The primary inferential test was the omnibus LR test comparing the decomposed model against the baseline model (2 df). A parsimony check — LR test of the decomposed model against the between-subject model (1 df) — assessed whether the within-subject component contributed meaningfully beyond the between-subject signal. Where the omnibus test and the 1-df comparison of the between-subject model against baseline led to different conclusions, the pre-specified omnibus test was treated as the primary criterion, and coefficients from the between-subject model were reported descriptively. All models were estimated with maximum likelihood (ML) to enable valid likelihood-ratio comparisons. Residual diagnostics (normality of residuals and random effects, homoscedasticity) were inspected for all linear mixed-effects models; no substantial violations were observed. Descriptive visualizations stratified participants at the condition-specific PGS median within each dose condition to illustrate the between-subject effect independently of dose-related variation in PGS ratings.

2.6.3 Personality and perceived group support

The between-subject component of PGS (participant mean across all sessions) served as the trait-level outcome variable. Participants were split at the median of their mean PGS scores (n = 8 per group), and their baseline ANPS dimension profiles were compared descriptively using Cohen's d. Pearson's r was used to assess correlation strength between the AWI and trait PGS. A sensitivity analysis additionally included Spirituality as a fourth approach dimension, yielding the extended index (AWI+).

3. Results

3.1 Dose effects on psychometric outcomes

We first quantified how EBI, PIS, and MEQ scores varied across the seven dose conditions, and how much of the outcome variability dose alone accounted for. Median scores on all three psychometric scales increased with dose across both the DMT and harmine escalation axes. At the highest combined doses, individual scores spanned nearly the full instrument range (Figure 2).

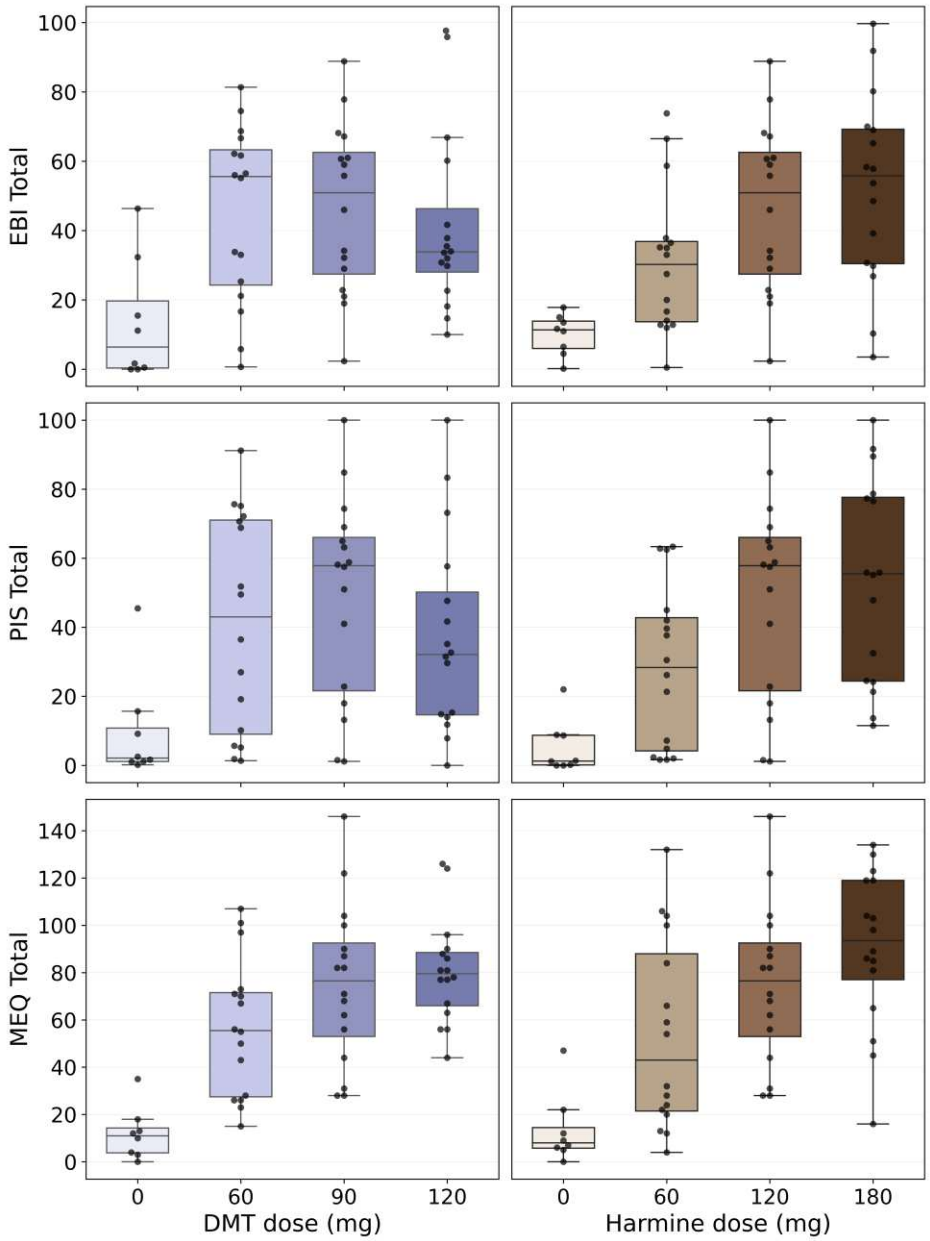


Figure 2. Dose-dependent effects on subjective experience measures.
Box plots with overlaid individual data points for Emotional Breakthrough Inventory (EBI; top row), Psychological Insight Scale (PIS; middle row), and Mystical Experience Questionnaire (MEQ; bottom row). Left column: DMT dose escalation with harmine fixed at 120 mg. Right column: harmine dose escalation with DMT fixed at 90 mg. Boxes indicate interquartile range with median line; whiskers extend to 1.5 × IQR. Each point represents one participant in a given dosing session. N ≈ 8 per condition for placebo/zero-dose conditions; N ≈ 16 for active dose conditions. At 90(D)-180(H), EBI ranged from 3.5 to 99.7, PIS from 11.5 to 100, and MEQ from 16 to 134, and at 120(D)-120(H), PIS scores covered the entire 0–100 scale.

3.2 Perceived Group Support stratification

To examine whether the observed person-to-person variation was structured by the perceived interpersonal context rather than by dose alone, we stratified participants within each dose condition at the condition-specific median of their perceived group support (PGS) rating. Splitting within each condition isolates differences in PGS from any dose-related variation in PGS ratings (Figure 3). Across both dose-escalation designs, participants with above-median PGS consistently showed higher median EBI, PIS, and MEQ scores than those below median. The size of that gap did not scale monotonically with dose but peaked at intermediate doses along each respective axis before narrowing at the highest doses tested.

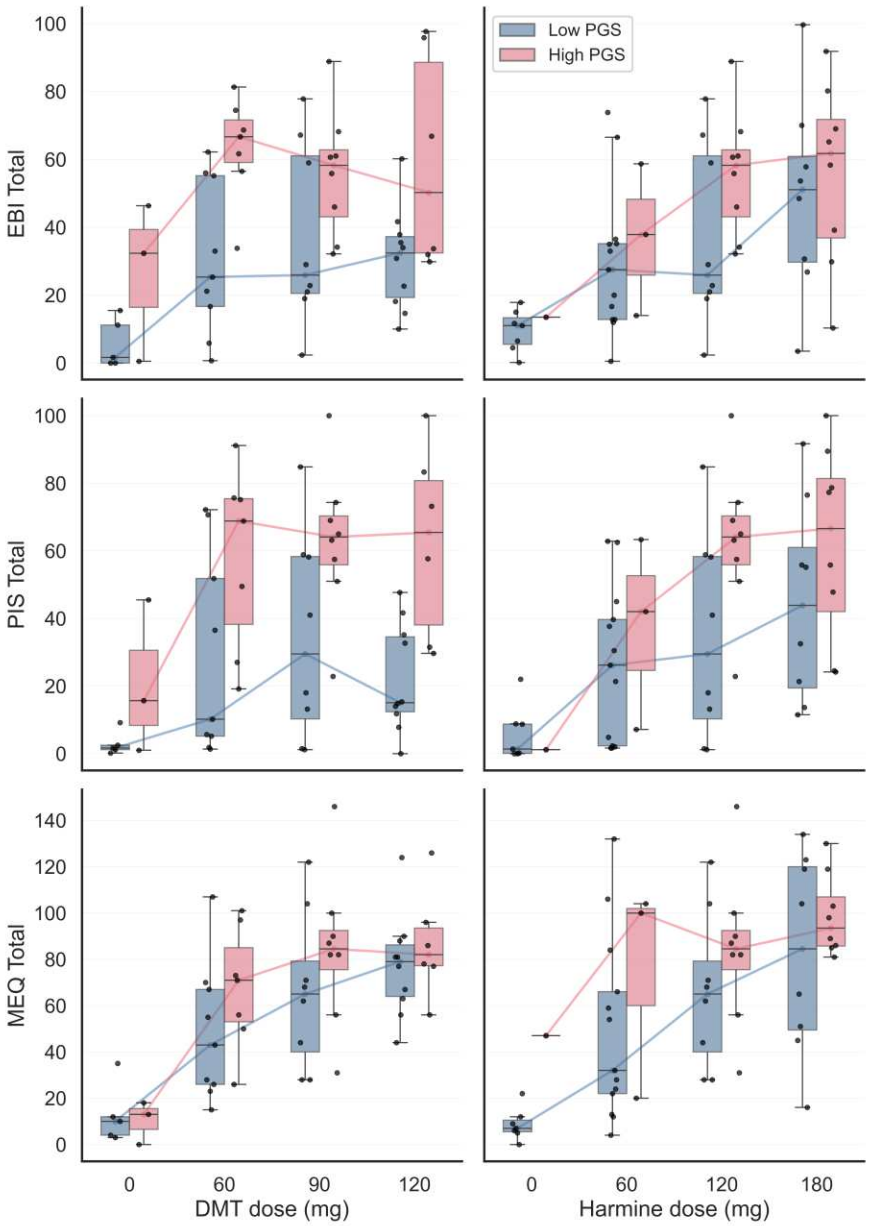


Figure 3. Perceived group support stratification within each dose condition. Box plots with overlaid individual data points for Emotional Breakthrough Inventory (EBI; top row), Psychological Insight Scale (PIS; middle row), and Mystical Experience Questionnaire (MEQ; bottom row). Left column: DMT dose escalation with harmine fixed at 120 mg. Right column: harmine dose escalation with DMT fixed at 90 mg. Boxes indicate interquartile range with median line; whiskers extend to 1.5 × IQR. Each point represents one participant in a given dosing session. Participants are stratified within each dose condition at the condition-specific median of the perceived group support (PGS) item. Red: above-median PGS rating; blue: below-median PGS rating. Within-condition median splitting ensures that the stratification captures PGS effects independent of dose-related variation in PGS ratings. N per subgroup ≈ 4 (placebo/zero-dose conditions) or ≈ 8 (active dose conditions). Along the DMT escalation axis (harmine fixed at 120 mg), the difference in median EBI scores between above- and below-median PGS participants (above minus below) was 30.7, 41.3, 32.3, and 17.8 at 0, 60, 90, and 120 mg, respectively; corresponding differences in median PIS scores were 14, 58.7, 34.6, and 50.3, and in median MEQ 3, 28, 19.5, and 3.

Along the harmine escalation axis (DMT fixed at 90 mg), differences in median EBI scores were 2.5, 10.3, 32.3, and 10.7 at 0, 60, 120, and 180 mg, respectively; corresponding PIS differences were −0.2, 15.8, 34.6, and 22.7, and MEQ differences 40, 68, 19.5, and 9.

3.3 Statistical modeling

To quantify these patterns, we fitted linear mixed-effect models (see Methods).

3.3.1 Dose effects on subjective outcomes

The baseline linear mixed-effects model included the seven dose conditions as a categorical fixed effect and participant as a random intercept. All dose coefficients therefore represent contrasts against this harmine-active, DMT-absent baseline.

The omnibus effect of dose condition was highly significant for all three instruments (EBI: $\chi^2(6) = 46.16$, $p < .001$; PIS: $\chi^2(6) = 47.12$, $p < .001$; MEQ: $\chi^2(6) = 71.00$, $p < .001$).

For EBI and PIS, most active dose conditions scored higher than the reference, with effects generally increasing along the DMT escalation axis before peaking at 90(D)-120(H) and then declining somewhat at 120(D)-120(H). The lowest active harmine condition (90(D)-60(H)) showed little separation from the reference, while the harmine-absent condition (90(D)-0(H)) scored below reference on both measures. For MEQ, all active dose conditions except 90(D)-0(H) showed large effects, roughly double those observed for EBI and PIS, with confidence intervals well above zero. The harmine-absent condition (90(D)-0(H)) showed little separation from the reference for MEQ (Table S2).

3.3.2 Residual between-subject variability

The baseline models revealed substantial between-subject variability after accounting for dose: the intraclass correlation coefficient (ICC) was 0.44 for EBI, 0.47 for PIS, and 0.36 for MEQ. That is, even after controlling for pharmacological dose, 36–47% of the remaining variance in subjective experience was attributable to stable individual differences.

3.3.3 Perceived group support beyond dose

The four nested models described in Methods were compared for each outcome measure. The combined model's PGS predictor did not reach significance for any outcome (EBI: $\beta = 1.84$, $p = .34$; PIS: $\beta = 1.71$, $p = .41$; MEQ: $\beta = 2.30$, $p = .29$). The effect of perceived group support was only detectable after decomposition into between- and within-subject components.

The omnibus test was highly significant for EBI ($\chi^2(2) = 14.98$, $p < .001$) and PIS ($\chi^2(2) = 13.77$, $p = .001$), confirming that perceived group support improved prediction of EBI and PIS beyond dose alone. The parsimony check confirmed that removing the within-subject component did not worsen fit (EBI: $\chi^2(1) = 0.39$, $p = .53$; PIS: $\chi^2(1) = 0.44$, $p = .51$), justifying the between-subject model as the primary model. In the between-subject model, each one-point increase in between-subject PGS was associated with an 11.0-point increase in EBI ($\beta = 11.01$, 95% CI [6.54, 15.48], $p < .001$) and a 12.5-point increase in PIS ($\beta = 12.45$, 95% CI [7.05, 17.85], $p < .001$), with the model absorbing most of the between-subject variance in both outcomes (72.5% for EBI, $\sigma^2(u)$: 233.1→64.1; 67.3% for PIS, $\sigma^2(u)$: 319.0→104.3; ΔAIC = +12.6 and +11.3, respectively) and reducing the residual ICC from 0.44 to 0.18 for EBI and from 0.47 to 0.22 for PIS.

For MEQ, the omnibus test did not reach significance ($\chi^2(2) = 4.51$, $p = .11$). The between-subject coefficient was nominally significant in the between-subject model ($\beta = 8.44$, 95% CI [1.17, 15.72], $p = .02$), but the model fit improvement was modest (31.2% of between-subject variance was absorbed; ΔAIC was 2.5), and the pre-specified omnibus test remains the reference for MEQ.

Full condition-level coefficients and model comparison statistics for all three outcomes are reported in Table S2.

Figure 4 displays the per-participant association between mean PGS and mean outcome scores across all six sessions. Perceived group support was strongly associated with EBI ($r = .77$, $p < .001$) and PIS ($r = .75$, $p < .001$), but not with MEQ ($r = .48$, $p = .06$), consistent with the LMM results. EBI and PIS were positively correlated (Figure S1).

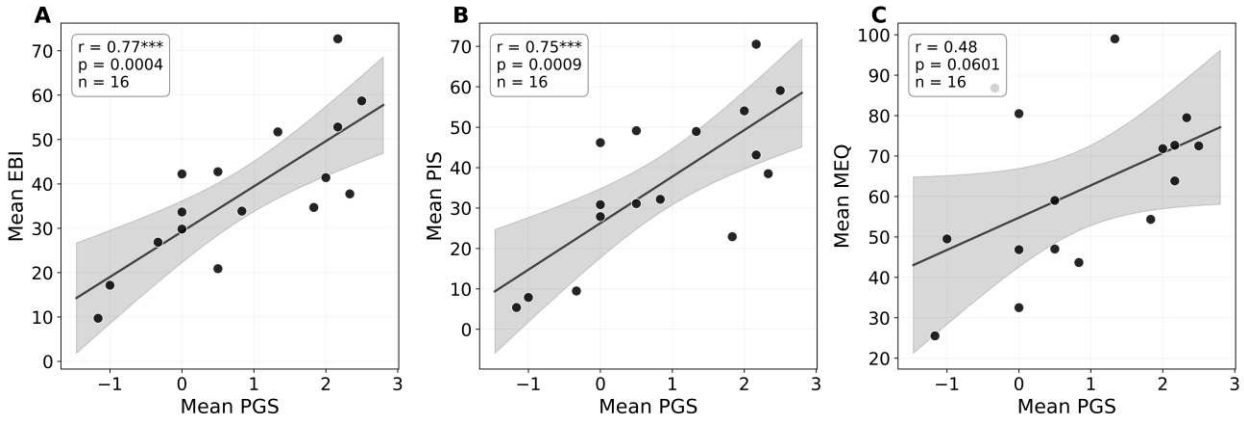


Figure 4. Between-subject association between perceived group support and subjective experience measures. Each point represents one participant's mean score across all dosing sessions (n = 16 participants, 6 sessions each). Horizontal axis: participant-mean perceived group support (pff_14; "I believe that the group setting helped me to have a meaningful experience"; -3 to +3 Likert scale). Vertical axis: participant-mean outcome score (**A**: Emotional Breakthrough Index; **B**: Psychological Insight Scale; **C**: Mystical Experience Questionnaire). Lines show linear regression fits with 95% confidence bands. Pearson correlation coefficients are annotated in each panel.

3.4 Approach-Withdrawal Index associated with Perceived Group Support

We next examined whether these stable individual differences were associated with pre-session affective personality, that is, whether baseline personality related to who perceived the group as more supportive. Participants were split at the median of their mean PGS scores (n = 8 per group), and baseline ANPS dimension profiles were compared between groups (Figure 5A).

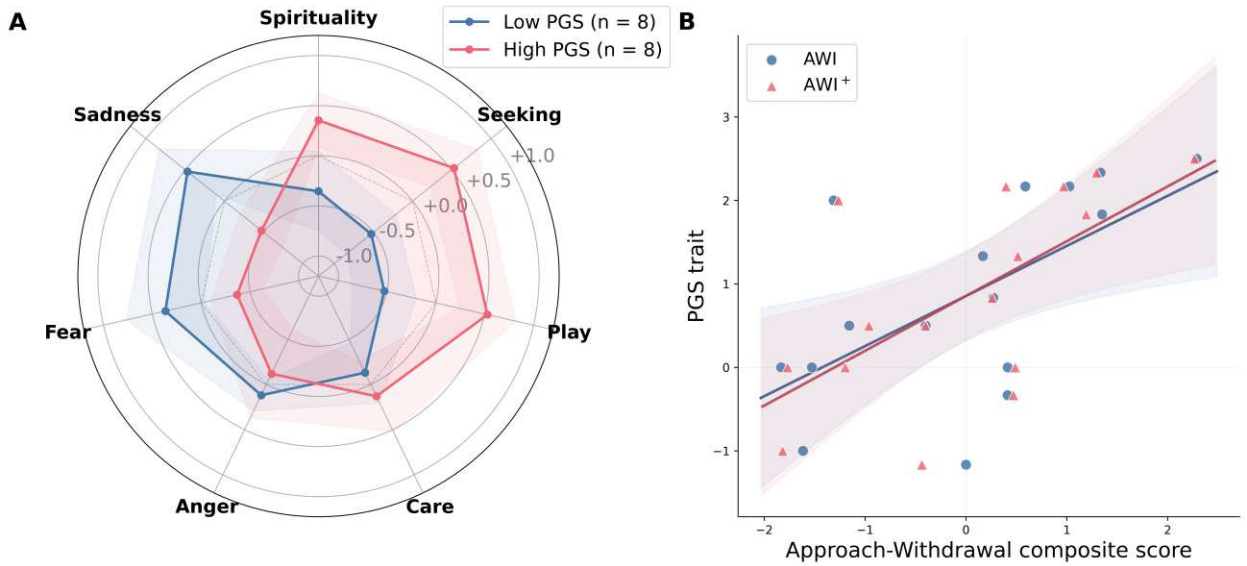


Figure 5. Baseline affective personality and perceived group support. A Radar plot of seven Affective Neuroscience Personality Scales (ANPS) dimensions for participants stratified by median split on PGS trait (participant mean across all six dosing sessions; n = 8 per group). Scores are z-standardized across the full sample (M = 0, SD = 1). Shaded bands represent ±1 standard error of the mean. Approach-related dimensions are located on the right side, withdrawal-related dimensions on the left side of the radar plot, with Spirituality shown at the top. **B** Association between the ANPS approach–withdrawal composite and PGS trait score. Each point represents one participant (N = 16). The horizontal axis shows the approach–withdrawal composite derived from the ANPS, computed as the mean of the approach-related dimensions minus the mean of the withdrawal-related dimensions; higher values indicate a more approach-weighted profile. The vertical axis shows the mean PGS trait score (averaged across dosing sessions). Two formulations are plotted (see legend): the Approach-Withdrawal Index (AWI; approach = Seeking, Play, Care; withdrawal = Fear, Sadness, Anger) and an extended index (AWI⁺) that additionally includes Spirituality as an approach dimension. Solid lines show ordinary least-squares regression fits; shaded bands indicate 95% confidence intervals.

Relative to the lower-PGS group, the higher-PGS group scored higher on the approach-related dimensions (most markedly Seeking, d = 1.22, and Play, d = 1.21) and on Spirituality (d = 0.73), and lower on the withdrawal-related dimensions (most markedly Sadness, d = −1.04); full descriptive statistics are reported in Table S3. Correlations for individual ANPS dimensions and PGS are reported in Figure S2. All approach dimensions showed positive correlations while all withdrawal dimensions showed negative correlations, consistent with a gradient along the approach-withdrawal axis. The AWI correlated significantly with PGS trait scores ($r = 0.60$, $p = .014$, $r^2 = 0.36$; Figure 5B), accounting for 36% of the variance in person-level perceived group support. A sensitivity analysis that additionally included Spirituality as an approach dimension

yielded a modestly stronger association ($r = 0.64$, $p = .008$, Figure 5B). AWI^+ was therefore carried forward.

Figure 5B established that AWI^+ tracked trait-level perceived group support. Because outcome scores differed systematically across dose conditions (Figures 2 and 3), correlations between AWI^+ and each outcome were computed separately within each dose level and resolved across the two titration series (Figure S3). AWI^+-outcome correlations strengthened with dose. For EBI, the correlation was positive and of similar magnitude in both highest dose conditions per titration series (120(D)-120(H): $r = 0.64$, 95% CI [0.21, 0.86]; 90(D)-180(H): $r = 0.59$, 95% CI [0.13, 0.84]). Of the three measures, EBI showed the most consistent positive association with AWI^+ across both escalation strategies (see Figure S4 for PIS and MEQ values).

4. Discussion

This repeated-measures dose-escalation study in a group setting examined why subjective responses to psychedelic interventions differ across individuals, and how these differences relate to therapeutic outcomes. We first characterized dose-related variation and then tested whether perceived group support, as an appraisal of the shared social context, accounted for additional differences in subjective response. Together, our findings delineate a three-layer account of psychedelic response within a group setting, spanning dose, perceived social context, and personality, and showing how variation beyond dose can become measurable and interpretable.

We confirm the dose dependency of characteristically psychedelic subjective effects, here induced by DMT-harmine, and reproduce the dose-response pattern documented in previous DMT dose-escalation studies using diverse administration routes[15–18,49] while extending this evidence to DMT-harmine administration in a group setting.

Across both the DMT and harmine escalation series, responses associated with higher perceived group support generally showed higher EBI and PIS scores than those associated with lower perceived group support, whereas the corresponding pattern for MEQ was less pronounced. Contrary to our hypothesis, removing session-to-session variation in PGS did not worsen model performance, meaning that the association was

carried by differences between participants rather than variation across sessions within participants.

Associations with mean PGS ratings differed by measure, being clearer for emotional breakthrough and psychological insight than for mystical-type experience. The MEQ may be less sensitive to social and interpersonal influences, reflecting aspects of acute psychedelic phenomenology that are more closely tied to drug intensity[15,50]. By contrast, breakthrough and insight capture more interpretive, affectively elaborated, and relationally embedded experiences that may covary more with perceived support and interpersonal attunement[11,37,51]. Nonetheless, residual between-person variability remained unexplained across all three outcomes.

We next explored whether participants' acute subjective effects ratings were related to personality measured before dosing. The association between baseline ANPS profiles and subsequent mean PGS ratings suggests that stable dispositional differences contributed to how participants perceived the group context. Spirituality aligned with the approach-related dimensions in our profile and correlation analyses, but it was not part of the original approach grouping. At the level of personality, this approach–withdrawal framing may also invite comparison with individual differences in experiential avoidance (EA), a transdiagnostic tendency to avoid unwanted internal experiences whose reduction has been proposed as an important mechanism of psychedelic-assisted therapy[52,53]. Whether EA represents a construct related to the affective approach–withdrawal profile captured by AWI+ was not assessed in our study and remains an open question.

Correlations between AWI+ and EBI generally strengthened with dose and remained positive at the highest-dose endpoints across both escalation series, indicating that participants with more approach-oriented affective profiles tended to report greater emotional breakthrough. Associations with PIS and MEQ were less consistent across conditions. Together, these findings suggest that pharmacological dose and baseline affective personality may contribute jointly to variation in acute subjective experience.

Personal predispositions have long been assumed to shape acute psychedelic experience, and although individual traits have repeatedly been associated with

subjective outcomes, the routes through which such predispositions might exert this influence have remained largely unresolved. Perceived group support may therefore be best characterized as an interface between set and setting; a set–setting construct in which the subjective appraisal of the environment partly reflects pre-existing affective personality. In this sense, the effects attributed to the social setting appeared to depend, in part, on the dispositions through which that setting was perceived. To our knowledge, this is the first evidence of such a person–context interaction in a controlled psychedelic dosing study. This interpretation is consistent with proposals that the set/setting dichotomy is less cleanly separable at the level of subjective experience than the classical dichotomy implies[38], and it suggests the practical possibility that what a setting contributes may become measurable before dosing, via personality, and session by session, via PGS.

As psychedelic-assisted therapy moves toward broader implementation, group-based delivery offers practical advantages, and group settings can give rise to collective experiences of meaningfulness, connection and profundity[32,37,54]. Withdrawal-dominant affective profiles resemble the anxious and depressive presentations most prevalent in the populations psychedelic therapies aim to serve, and experiential avoidance has been described as a transdiagnostic risk factor in these presentations[53,55,56]. The equitable approach would be to develop these measures to reliably identify individuals likely to benefit from additional preparation, more active facilitation of felt safety, and closer relational support before, during and after dosing. Future controlled studies could advance from a single rating of perceived support toward a working characterization of group processes moving the field closer to designing, rather than merely describing, the settings in which psychedelic experiences take place.

Interpreting these measures in a therapeutic frame nevertheless requires attention to timing and construct coverage. The EBI and PIS indexed acute experience, but therapeutic frameworks tend to emphasize the integration phase that follows[57,58], so insight or breakthrough emerging later in the therapeutic process falls outside the scope of our assessments. Likewise, challenging experiences, including those involving group constellation or setting, can transform into therapeutic benefits when met with appropriate therapeutic support[59,60]. The EBI and PIS scores reported here are therefore

best understood as early experiential markers within a longer arc of potential therapeutic change.

We disclose several limitations inherent to the study design and setting that may be difficult to disentangle from the measured data. 1) Participants knew they would receive an active dose each study day, and the dosing order was blinded. However, experimenters remained unblinded, potentially affecting psychometric outcomes. 2) Participants could share their experiences from 3:00 PM onwards as part of the group setting, potentially influencing the later MEQ and PGS but not the earlier EBI and PIS measurement. 3) The sample was small and limited to healthy individuals within normal limits on psychiatric and personality measures and of Western European ethnicity, rendering our findings exploratory and limiting their generalizability due to a likely underrepresentation of the tails of the approach–withdrawal distribution. 4) We did not contrast individual and group settings within our study, but we relied on between-study comparisons with previous dose-escalation studies conducted in 'single-participant' administration settings, potentially precluding direct claims about the benefits and drawbacks of group administration. 5) Collecting PGS and outcomes as same-session retrospective self-reports risks common-method variance and reverse causation (e.g., a stronger experience inflating PGS ratings), particularly as the single PGS item, like the primary outcomes, refers to the experience's meaningfulness.

Conclusion

Acute responses to DMT–harmine were shaped not only by dose, but also by stable individual differences in how participants perceived the group context. Perceived group support accounted for substantial dose-independent variation in emotional breakthrough and psychological insight, but not in mystical-type experience, and was associated with an approach-oriented affective disposition measured before dosing. These exploratory findings suggest that set and setting are not independent influences: the effects attributed to a social setting may partly depend on the dispositions through which that setting is perceived. If replicated in larger and clinically diverse samples, this person–context interaction could inform the design and individual tailoring of group-based psychedelic interventions. Our findings move beyond the general proposition that

"set and setting matter" by identifying a measurable pathway through which they may jointly shape acute psychedelic experience.

Data Availability

The data that support the findings of this study are available within the main article, the supplement, and the parent pharmacokinetic study (Egger et al., 2025). Additional information is available upon reasonable request.

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Conflict of Interests

JTTS, JD, KE, HDA, DM, FW, JJR, JM, JH, EAV have nothing to declare. MS and DAD declare that they co-founded Reconnect Labs. RR is an employee and shareholder of Reconnect Labs. JS is an affiliated researcher for Reconnect Labs.

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