A Quantitative and Qualitative Report of Psilocybin Induced Mystical-Type Experiences and Their Relation to Lasting Positive Effects

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Abstract

Psychedelic drugs such as psilocybin are under investigation for the treatment of several psychiatric conditions. They also have the remarkable property of producing persisting positive psychological changes in healthy volunteers for at least several months. In this study, 35 medium-high doses of psilocybin were administered to 28 healthy volunteers (12 females). By the end of the dosing day, participants reported the intensity of their acute experience using the 30-item Mystical Experience Questionnaire (MEQ) and an open-form qualitative report from home. Persisting psychological effects attributed to the psilocybin experience were measured using the Persisting Effects Questionnaire (PEQ) three-months after administration. Using a linear latent-variable model we show that the MEQ total score is positively associated with the later emergence of positive PEQ effects ($p = 3 \times 10^{-5}$). Moreover, the MEQ subscales "Positive Mood" ($p_{corr} = 4.1 \times 10^{-4}$) and "Mysticality" ($p_{corr} = 2.0 \times 10^{-4}$) are associated with positive PEQ whereas the subscales "Transcendence of Time and Space" ($p_{corr} = 0.38$) and "Ineffability" ($p_{corr} = 0.45$) are not. Using natural language pre-processing, we provide the first qualitative descriptions of the "Complete Mystical Experience" induced by orally administered psilocybin in healthy volunteers, revealing themes such as a sense of connection with the universe, familial love, and the experience of profound beauty. Combining qualitative and quantitative methods, this paper expands understanding of the acute psilocybin induced experience in healthy volunteers and suggests an importance of the type of experience in predicting lasting positive effects.

1. Introduction

Psilocybin is a prodrug to the 5-HT2A agonist psilocin (Passie, Seifert, Schneider, & Emrich, 2002), which is the drug responsible for the psychoactive effects of "magic mushrooms". Preliminary evidence from the last 15 years suggest that psilocybin has a rapid and potent positive treatment effect in affective and addictive disorders (Anderson et al., 2020; Bogenschutz et al., 2015; R. Carhart-Harris et al., 2021; R. L. Carhart-Harris et al., 2018; Davis et al., 2020; Garcia-Romeu et al., 2019; Roland R. Griffiths et al., 2016; Grob et al., 2011; Johnson, Garcia-Romeu, & Griffiths, 2017; Moreno, Wiegand, Taitano, & Delgado, 2006; Ross et al., 2016). In healthy individuals and patients, psilocybin has been associated with long-lasting positive psychological effects and self-reported positive changes in mood, behaviour (Barrett, Doss, Sepeda, Pekar, & Griffiths, 2020; Roland R. Griffiths et al., 2011) and personality (e.g., increased openness; (Erritzoe et al., 2018; Kettner et al., 2021; MacLean, Johnson, & Griffiths, 2011; Martin Korsbak Madsen et al., 2020; Schmid & Liechti, 2018), while no association with persisting effects on cognition has been observed (Rucker et al., 2021).

The subjective effects of psychedelics vary between individuals (Stenbæk et al., 2020) and are substantially affected by dose, CYP2D6 phenotype (Vizeli et al., 2021) and non-pharmacological factors like emotional "set", i.e., a person's current psychological state, and environmental "setting", i.e., the immediate surroundings (Hartogsohn, 2017; Hyde, 1960; Strickland, Garcia-Romeu, & Johnson, 2021). The acute effects of medium-high oral doses (i.e., > 0.2 mg/kg) of psilocybin last approximately four to six hours (Hasler, Grimberg, Benz, Huber, & Vollenweider, 2004; Martin K. Madsen et al., 2019, 2021; Passie et al., 2002; Preller et al., 2018; Stenbæk et al., 2020) though psilocybin may produce a misjudged perception of time on behalf of the recipient of the drug (Wackermann, Wittmann, Hasler, & Vollenweider,

68 2008). Subjective psychedelic effects are characterised by changes in bodily experience,

69 cognition, and alterations in the visual field (Hirschfeld & Schmidt, 2021; Preller &

70 Vollenweider, 2018), and by pseudohallucinations but not "true hallucinations" (sensory

71 phenomena indistinguishable from reality) (Sanati, 2012). The typical experience induced by

72 a medium-high dose of psilocybin has a plateau of maximum subjective intensity which for

73 some participants can occasion transient, profound alterations in consciousness described as a

74 sense of unity with all things accompanied by dissolution of ego or personhood, blissful mood

75 and ecstasy, and aberrant sense of time and space (Preller & Vollenweider, 2018; Stenbæk et

76 al., 2020). Despite extensive quantitative characterisation, no papers so far have reported a

77 qualitative description of the subjective experience of orally administered psilocybin in healthy

78 volunteers, though the effects of 2mg of intravenous psilocybin in an MR scanning

79 environment have been reported (Turton, Nutt, & Carhart-Harris, 2014).

80 At maximum intensity psychedelic experiences can share many similar features with traditional

81 'mystical-type' or 'peak' experiences which have a potential for psychological transformation

82 (R. R. Griffiths, Richards, McCann, & Jesse, 2006; Roland R. Griffiths et al., 2011; Lyvers &

83 Meester, 2012; Maslow, 1959). The most intense of these, known as "Complete Mystical

84 Experiences" (CME) are hypothesised to be instrumental in the lasting positive effects of

85 psychedelics (Yaden & Griffiths, 2021). The magnitude of psilocybin-induced mystical-type

86 experience has shown positive correlations with improvements in subjective life quality,

87 meaning in life, and mood in patients suffering from anxiety and depression associated with

88 life threatening cancer (Roland R. Griffiths et al., 2016; Ross et al., 2016), cigarette addiction

89 (Garcia-Romeu, Griffiths, & Johnson, 2015) and major depressive disorder (Davis et al., 2020;

90 Roseman, Nutt, & Carhart-Harris, 2018). In healthy volunteers, the degree of mystical

91 experience has been positively associated with increases in personality-domain openness up to

92 14-months after psilocybin (R. Griffiths, Richards, Johnson, McCann, & Jesse, 2008; Roland

93   R Griffiths et al., 2018; MacLean et al., 2011) and self-rated persisting positive effects 12-

94   months after psilocybin (Schmid & Liechti, 2018). Despite replicated research investigating

95   the acute effects of psychedelics, comparatively little is known about the relation between the

96   character of the acute psychedelic experience (i.e., the way the experience feels, not simply the

97   intensity) and the persisting changes in mood, behaviour, and personality.

98   Qualitative research so far has provided insight into themes that patients report as important in

99   the lasting effects of psychedelic therapy including increased aesthetic appreciation and

100   experiences of interconnectedness (Noorani, Garcia-Romeu, Swift, Griffiths, & Johnson,

101   2018), movement from disconnection to connection with senses, self, others and the world, and

102   from emotional avoidance or numbness to emotional acceptance (Watts, Day, Krzanowski,

103   Nutt, & Carhart-Harris, 2017). In terminally ill patients, themes observed to be associated with

104   clinical improvement include reconciliation with death and reconnection with life (Swift et al.,

105   2017). Patients' qualitative reports also describe meaningful aspects of the acute experience

106   including altered perception of relationships and the appearance of meaningful visual

107   phenomena (Belser et al., 2017) as well as acutely felt motivation and commitment to

108   behavioural change (Nielson, May, Forcehimes, & Bogenschutz, 2018). However, qualitative

109   analyses are particularly susceptible to investigator bias, as quote selection can be driven by

110   the investigator's proposed narrative (Galdas, 2017). We aimed to control for this for by first

111   pre-analysing data using an unbiased natural language processing (NLP) script to steer

112   qualitative analyses.

Aims and hypotheses

In this study, we contribute to the ongoing research concerning the relation between the acute subjective effects of psilocybin and their lasting effects. We do so by examining whether the self-reported intensity of the mystical-type experience is associated with persisting effects reported three months later in healthy volunteers. Further, we examined whether NLP of qualitative reports can be used to differentiate participants who have a CME compared to those who do not. We also expand the literature describing the subjective mystical-type experience induced by psilocybin by providing curated quotes from the qualitative reports guided by NLP results.

We hypothesise that there will be a positive association between intensity of the mystical-type experience and persisting positive effects attributed to the psilocybin experience at three-month follow-up. In addition, we provide NLP of qualitative reports to describe the experiences of participants who have a CME compared to those who do not.

2. Methods

2.1 Participants

2.1.1 Recruitment

We recruited 28 healthy participants (12 females) ≥18 years of age from a list of individuals that expressed interest in participating in a psilocybin neuroscience study. Individuals participated in at least one of three sub-projects (sub-project 1 (n=4), sub-project 2 (n=10) and sub-project 3 (n=21)) for a total of 35 psilocybin administrations (i.e., seven participants took part in two sub-projects). The sample included in this study only included those who had completed the Qualitative Experience Report as described below, and received at least 12 mg of psilocybin.

All participants underwent screening for somatic illness, including a medical examination, an ECG, blood screening for somatic disease, and screening for psychiatric disorders using the Mini International Neuropsychiatric Interview, Danish translation version 6.0.0 (Sheehan et al., 1998). Exclusion criteria for all sub-projects were: (1) present or previous primary psychiatric disease (DSM axis 1 or WHO ICD-10 diagnostic classifications) or in first-degree relatives; (2) present or previous neurological condition/disease, significant somatic condition/disease; (3) intake of drugs suspected to influence test results; (4) non-fluent Danish language skills; (5) vision or hearing impairment; (6) previous or present learning disability; (7) pregnancy; (8) breastfeeding; (9) magnetic resonance imaging (MRI) contraindications; (10) alcohol or drug abuse; (11) allergy to test drugs; (12) significant exposure to radiation within the past year (e.g., medical imaging investigations); (13) intake of QT-prolonging medication or electrocardiogram (ECG) results indicative of heart disease, (14) blood donation less than 3 months before project participation; (15) bodyweight less than 50 kg; (16) low plasma ferritin levels (< 12 μg/L).

150 *2.1.2 Ethics*

151 Written informed consent was obtained from all individuals before inclusion. The study was

152 conducted in accordance with the Declaration of Helsinki. The study was approved by the

153 ethics committee for the Capital Region of Copenhagen (journal identifier: H-16028698,

154 amendments: 56023, 56967, 57974, 59673, 60437, 62255 and Danish Medicines Agency

155 (EudraCT identifier: 2016-004000-61, amendments: 2017014166, 2017082837, 2018023295).

156 The study was also preregistered at ClinicalTrials.gov (identifier: NCT03289949).

157

158 **2.2 Psilocybin Intervention**

159 Prior to the intervention day, all participants attended a preparatory consultation with the study

160 psychologists who would assist them on the intervention day. In all three sub-projects,

161 psilocybin was administered orally in 3 mg capsules with a glass of water. Dose was adjusted

162 for bodyweight: mean (SD) [range] = 0.26 (0.04) [0.19-0.31] mg/kg, absolute dose: mean (SD)

163 [range] = 19.4 (3.7) [12–30] mg. Interpersonal support was provided throughout the

164 interventions in all three sub-projects by the same leading psychologist (DSS) assisted by

165 psychologist trainees. Likewise, the same medical doctor was involved in all three sub-projects

166 (MKM). A light lunch and beverages (i.e., water + juice) were offered to the participants on all

167 intervention days. Among the 35 sessions, four were conducted in the context of up to two

168 positron emission tomography (PET) scans on the intervention day in sub-project 1 (Martin K.

169 Madsen et al., 2019), 10 sessions were conducted in a comfortable hotel-room-like setting in

170 sub-project 2 (Martin Korsbak Madsen et al., 2020; Stenbæk et al., 2020), and 21 were

171 conducted in the context of MRI scans on the intervention day in sub-project 3 (Martin K.

172 Madsen et al., 2021). All participants returned one day after the intervention day for a post-

173 session consultation with the assisting psychologists.

174

2.3 Data collection and outcome measures

2.3.1. Baseline Psychometrics

The outcome measures used in this study consisted of qualitative and questionnaire data collected on the day of psilocybin intervention and at three-months follow-up. At baseline, we also collected descriptive information about depressive symptoms, perceived stress and sleep quality with the Major Depression Inventory (MDI) (Bech, Rasmussen, Olsen, Noerholm, & Abildgaard, 2001), Cohen's Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983) and Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), respectively.

2.3.2. Mystical Experience Questionnaire

At the end of the psilocybin intervention (~six to eight hours after ingestion of psilocybin), participants completed the self-report revised 30-item Mystical Experience Questionnaire (MEQ) (Barrett, Johnson, & Griffiths, 2015). The MEQ is a validated questionnaire comprising 30 items that capture the essential elements of a mystical-type experience relating to a single, discrete event (e.g., one psilocybin administration). The MEQ was derived from the MEQ43 which in turn was developed from the States of Consciousness Questionnaire based on classical descriptive work on mystical experiences and the psychology of religion (Pahnke, 1969; Richards, 1975; Stace, 1960). Items in the MEQ are rated using a 6-point Likert scale from 0 (none, not at all) to 5 (extreme, more than any other time in my life and more than a rating of 4). It has four sub-scales: Mysticality, Positive Mood, Transcendence of Time and Space and Ineffability (e.g., MEQ items: "Experience of unity with ultimate reality", "Experience of ecstasy", "Loss of your usual sense of time" and "Sense that the experience cannot be described adequately in words", respectively (MacLean & Griffiths, 2013)). The threshold for a CME is a score of >60% on all sub-scales (Barrett et al., 2015). This threshold was used to divide data into CME and non-CME. MEQ total score was calculated as the mean of all items.

2.3.3 Mandala drawing

Following completion of the MEQ, participants were asked to draw a mandala of their experience using coloured pencils. Mandala is the Sanskrit word for 'circle', and it is typically interpreted as symbolising a transcendent function in the psyche (Bailer, 2020). Practically, participants were given a paper with a circle represented on it and asked to draw their psilocybin experience within the circle using coloured pencils.

2.3.4 Qualitative Experience Report

In the evening on the day of psilocybin intervention, participants completed a qualitative report describing their experience in free writing using a secured online survey system (https://www.limesurvey.org/). There were no constrains and no minimum or maximum length to the experience report, only that it had to be completed before the participants went to sleep.

2.3.5 Persisting Effects Questionnaire

Approximately three months following the psilocybin sessions, participants completed the Persisting Effects Questionnaire (PEQ) (R. R. Griffiths et al., 2006). The PEQ is used to measure long-lasting positive and negative effects attributed directly to the psychedelic experience. The PEQ is a non-validated self-report questionnaire that has been used, among others, by Griffiths et al. (2006, 2008, 2011, 2016) to assess persisting effects of psychedelics as well as long-term positive effects attributable to "naturally occurring" mystical-type experiences (Roland R. Griffiths, Hurwitz, Davis, Johnson, & Jesse, 2019). The PEQ comprises 145 questions that describe how the participants perceive changes in their life that they feel are "due to the experiences during your last session [of psilocybin] and your contemplation of those experiences". Items are rated using a 6-point Likert scale from 0 (none, not at all) to 5 (extreme, more than any other time in my life and more than a rating of 4). It has 12 subscale-themes,

225 namely a positive and a negative change in: Attitudes About Life, Attitudes About Self, Mood

226 Changes, Social Effects, Behavioural Changes, and Spirituality (e.g., Attitudes about life: "You

227 have more joy in your life" & "You have less joy in your life", Social Effects: "You express

228 more love toward others" & "You express more hatred toward others"). Subscale scores were

229 converted to percentage of maximum score as performed in previous analyses (Roland R.

230 Griffiths et al., 2016, 2011). For the statistical analyses within study, we used the positive

231 subscales only since very few persisting negative effects were rated. See **Figure 2**.

232 *2.3.6 Plasma Psilocin Levels*

233 In sub-project 3 plasma samples were drawn before and approximately 40, 80, 110, 160, 190

234 and 340 mins post-psilocybin administration, and plasma psilocin levels (PPL) were evaluated

235 as described in (Martin K. Madsen et al., 2019). Peak values were chosen as the MEQ specifies

236 "at any time during that session you experienced the following phenomena".

2.4 Descriptive Analyses

Differences at baseline between those who experienced a CME and did not experience a CME (non-CME) on the MDI, PSS, PSQI, age differences, bodyweight, dose administered, and naivety to psychedelic experiences were compared using a random intercept model to take into account that some participants participated twice. Sex differences in MEQ subscale and total score were also estimated using a similar model. Associations between the highest PPL value, i.e., representing peak effects of the drug, for each participant and MEQ total score or PPE_{LV} were evaluated using univariate linear models. There were no repeated observations in this subgroup.

2.5 Association between MEQ and PEQ

The association between the MEQ and the PEQ, was investigated with linear latent variable models (LVMs) using the "lava" package for R (Holst & Budtz-Jørgensen, 2013). LVMs can be seen as an extension of linear mixed models for the analysis of multiple repeated measurements. While linear models parameterised with a random slope assume a constant correlation between measurements, LVMs relax this assumption allowing certain measurements to be more correlated than others (i.e., measurements from certain subscales can be more intercorrelated than others). LVMs were evaluated using the 'modelsearch' function from the lava package and typically structured as shown in **Figure 1** with some variation in covariance as described in section 3.2.1. A latent variable representing the six subscales of the PEQ was constructed and termed Positive Persisting Effects (PPE_{LV}). The association between the MEQ total and PPE_{LV} was evaluated within this model. Post hoc analyses of the associations between MEQ subscale scores and PPE_{LV} were also evaluated, each in a separate model. In order to calculate the potential direct and indirect mediation effects of the co-variates "Age", "Sex", "Dose", "Project 2" and "Project 3", both direct regressions of these onto PPE_{LV}

and indirect effects of these via MEQ total or subscales were calculated in each model. "Sex-Female" and "Project 1" are reported as the intercept in the analysis of these co-variates. We report loadings (i.e., parameter for the association subscale-latent variable, denoted by "β" in figure 1) and confidence intervals of each PEQ subscale onto PPE_{LV} with "life-positivity" arbitrarily chosen as a reference. To control for the small sample size and repeated measures, robust standard error was used (Ozenne, Fisher, & Budtz-Jørgensen, 2020). The MEQ total model was evaluated first as a primary hypothesis and the p-value for the relation between the MEQ score and PPE_{LV} is reported. Subsequent tests investigating the subscales report the p-value for the same interaction in the model, corrected using the Bonferroni method for a family of four tests (Dunn, 1961).
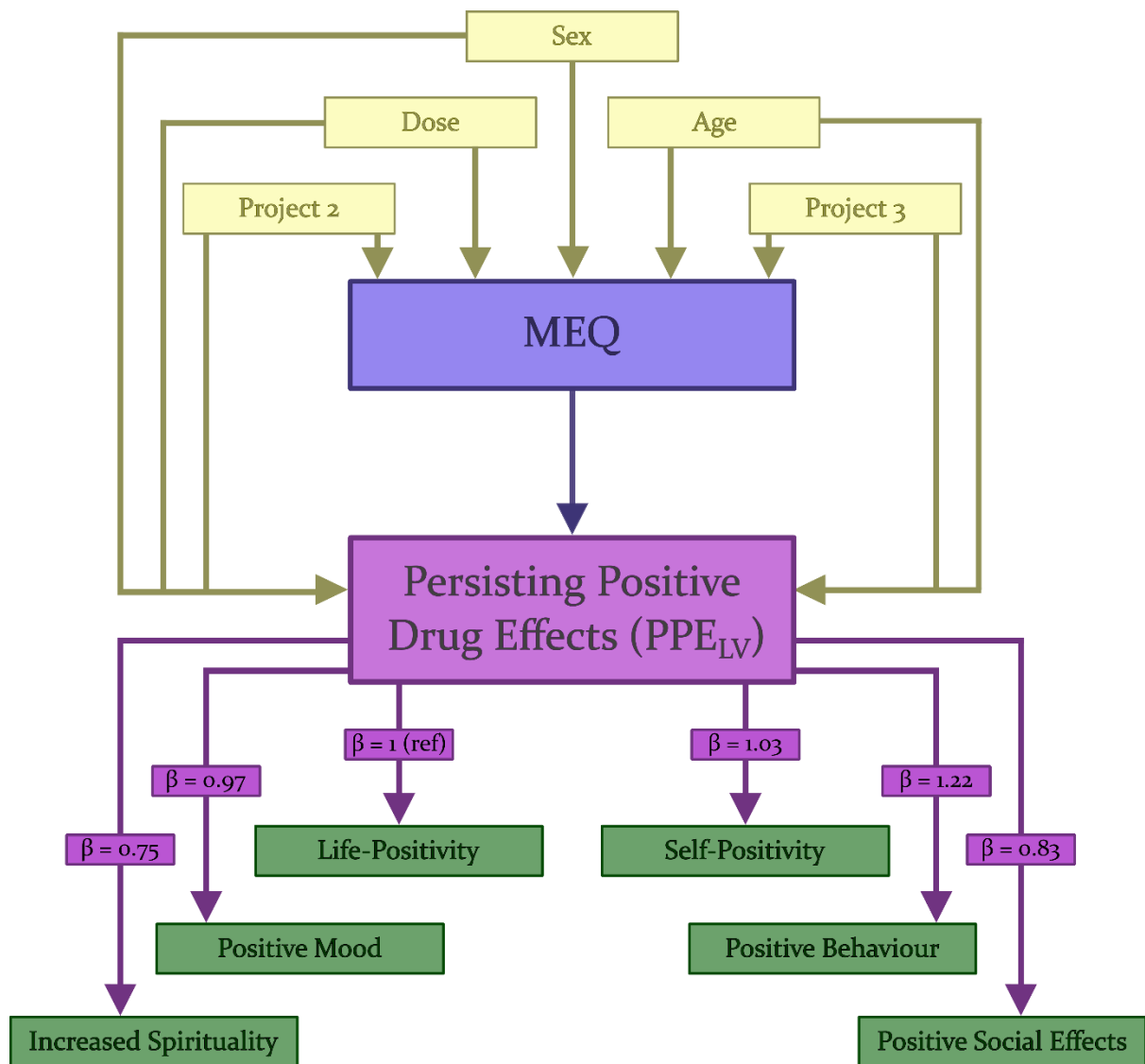
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Figure 1: Latent Variable Model. Schematic diagram describing the structure of the LVM used in the analysis of the relation between MEQ and the latent variable PPE$_{LV}$. 'MEQ' (blue) represents either the MEQ total score or one of the four different subscales of the MEQ. Each was analysed using a different model; therefore, regression outputs are not reported in this figure and are instead reported in **Table 2**. Loadings of the individual positive subscales of the PEQ are stable between models and are thus reported on the lines between PPE$_{LV}$ and the subscales. Loadings of co-variates are reported in **Supplementary Table 3**.

2.6 Language pre-processing

2.6.1 Lemmatisation

All evaluations were performed on the untranslated Danish text. Instances of words and quotes presented in this paper were independently translated by two bilingual individuals and recombined by a native English speaker and a third bilingual person.

In order to pre-process the qualitative data for this analysis, words were lemmatised using the python package 'lemmy' v 2.1.0 (https://github.com/sorenlind/lemmy). Lemmatisation is the process of converting a word back to its root (i.e., "running" "ran" and "runs" would each be lemmatised to "run"). Danish words are not easily lemmatised as any given word may represent different cases for several different roots. For example, "slappe" (relax) could be lemmatised to "slappe" (relax), "slap" (loose), or "slippe" (drop). In order to control for this, the first lemma for each word was selected and others discarded. Upon random manual checking, this was accurate in all instances.

2.6.2 tf-idf analyses

In this paper we attempt to control for investigator-narrative bias by utilising term-frequency inverse document frequency (tf-idf) to identify distinguishing themes in the text prior to qualitative analysis (Ramos, 2003). The corpus of all reports was split into two documents containing reports from either CME or non-CME. Tf-idf is a statistic that reflects the importance of a term to a specific subset of documents within a wider corpus. Term frequency is the number of times the word appears in each document divided by the total number of words in that document. Inverse document frequency is the log of the total number of documents divided by the number of documents containing the word, and tf-idf is the product of these. Reports were pre-processed by lemmatisation as described above, but stop-words (e.g., "the", "if", "and" etc.) were not removed as the tf-idf process accounts for these. Tf-idf scores were

304   computed for each term within CME and non-CME documents. Analyses were performed

305   using the R package "tidytext" (Silge & Robinson, 2016).

306    $$\text{tf-idf} = \frac{incidence\ of\ x\ in\ document}{total\ length\ of\ document} \times log_{10}\left(\frac{total\ number\ of\ documents}{number\ of\ documents\ containing\ x}\right)$$

307   *2.6.3 Post-hoc qualitative analyses*

308   To further investigate the terms with the highest tf-idf scores, we manually searched through

309   all reports and extracted quotes that included each of the five highest tf-idf terms. We first

310   checked that each term was not driven by a single report that used the word repeatedly. We

311   then selected quotes that reflected the most representative thematic usages of these terms.

312   *2.6.4 Mandala assignment*

313   To further illustrate our qualitative findings, available mandala drawings were located that

314   aligned with the qualitative reports presented. Those interpreted as aligning with the themes of

315   the associated qualitative report were selected, and the five participants were contacted to

316   ensure that perception of depicted themes was accurate. These are presented in the results

317   alongside their respective quotes.

318   *2.6.5 Code availability*

319   All   R   and   python   scripts   used   in   analyses   are   available   at

320   https://github.com/Pneumaethylamine/MysticalPEQ

321   *2.6.6 Statistical Inference*

322   Throughout the paper statistical significance was considered at an alpha of $p < 0.05$ following

323   Bonferroni correction for multiple comparisons where appropriate (Haynes, 2013). We report

324   corrected and uncorrected p-values, estimates and 95% confidence intervals.

3. Results

Measure	All	CME	Non-CME	P value
Participants (no.)	28	16*	12*	NA
Psilocybin sessions (no.)	35	21	14	NA
Project 1 (PET) (no.)	4	1	3	0.31
Project 2 (no.)	10	7	3	0.21
Project 3 (MRI) (no.)	21	13	8	0.28
Female (%)	15 (43%)	8 (38%)	7 (50%)	0.50
Mean age (SD) (years)	31.7 (7.0)	30.8 (4.9)	33.1 (9.4)	0.45
Mean weight (SD) (kg)	72.4 (12.2)	75.5 (11.9)	72.7 (12.7)	0.44
Psychedelic Naïve (no. (%))	23 (66%)	14 (67%)	9 (64%)	0.89
Mean dose (SD) (mg)	19.4 (3.7)	19.3 (3.5)	19.5 (4.2)	0.80
Mean dose (SD) (mg/kg)	0.26 (0.04)	0.26 (0.04)	0.27 (0.04)	0.34
Mean baseline MDI	4.2 (2.4)	4.1 (2.6)	4.3 (2.2)	0.94
Mean baseline PSS	6.8 (3.8)	6.7 (3.6)	7.1 (4.1)	0.70
Mean baseline PSQI	3.7 (1.7)	3.3 (1.5)	4.3 (1.9)	0.18

Table 1: Descriptive statistics of the participants split by Complete Mystical Experience (CME). All descriptive statistics are mean (Standard Deviation) unless otherwise stated. These describe the baseline characteristics including Major Depressive Inventory (MDI), Perceived Stress Scale (PSS), and Pittsburgh Sleep Quality Index (PSQI), aspects of the acute experience including dose of psilocybin administered (*per os*) and subproject. P-values for projects were calculated using a chi-squared test. All other p-values were calculated using a linear mixed-effects model controlling for participant ID as a random variable. PET: Positron Emission Tomography, MRI: Magnetic Resonance Imaging. *All individuals observed twice had either a CME or non-CME both times.

3.1 Descriptive Analyses

336

337 In total 35 reports from 28 individual participants were recorded as seven participants took part

338 in two projects. Of the 35 reports, the mean age (SD) was 31.7 (7.0) [range = 24.3 to 58.8]

339 years, and 15 were from female subjects. One participant had missing PEQ data at three-month

340 follow-up. Therefore, this dataset was not included in the analyses involving the PEQ.

341 Individual doses, sex, MEQ total and subscale scores are reported in **Supplementary Table 1**.

342 Descriptive statistics of participants, psilocybin sessions, project, sex, age, weight, naivety to

343 psychedelics, dose, and baseline psychometrics for all participants combined and split by CME

344 and non-CME are shown in **Table 1**, indicating no significant differences in these metrics

345 between groups. PEQ subscale scores split by CME are presented in **Figure 2**. MEQ total and

346 subscale scores are reported in **Supplementary Table 2**. A linear mixed effects model

347 comparing MEQ total score and subscales between males and females, accounting for

348 participant as a random variable and treating 'Female' as the intercept showed no significant

349 sex difference in any score ($p_{corr} > 0.31$). A description of the direct and indirect mediation

350 effects of sex and other co-variates on PPE_{LV} can be found in **Supplementary Table 3**. No

351 relation was observed between peak PPL and MEQ total score ($p = 0.88$, uncorrected) or PPE_{LV}

352 ($p = 0.35$, uncorrected). **See Supplementary Figure 2.**

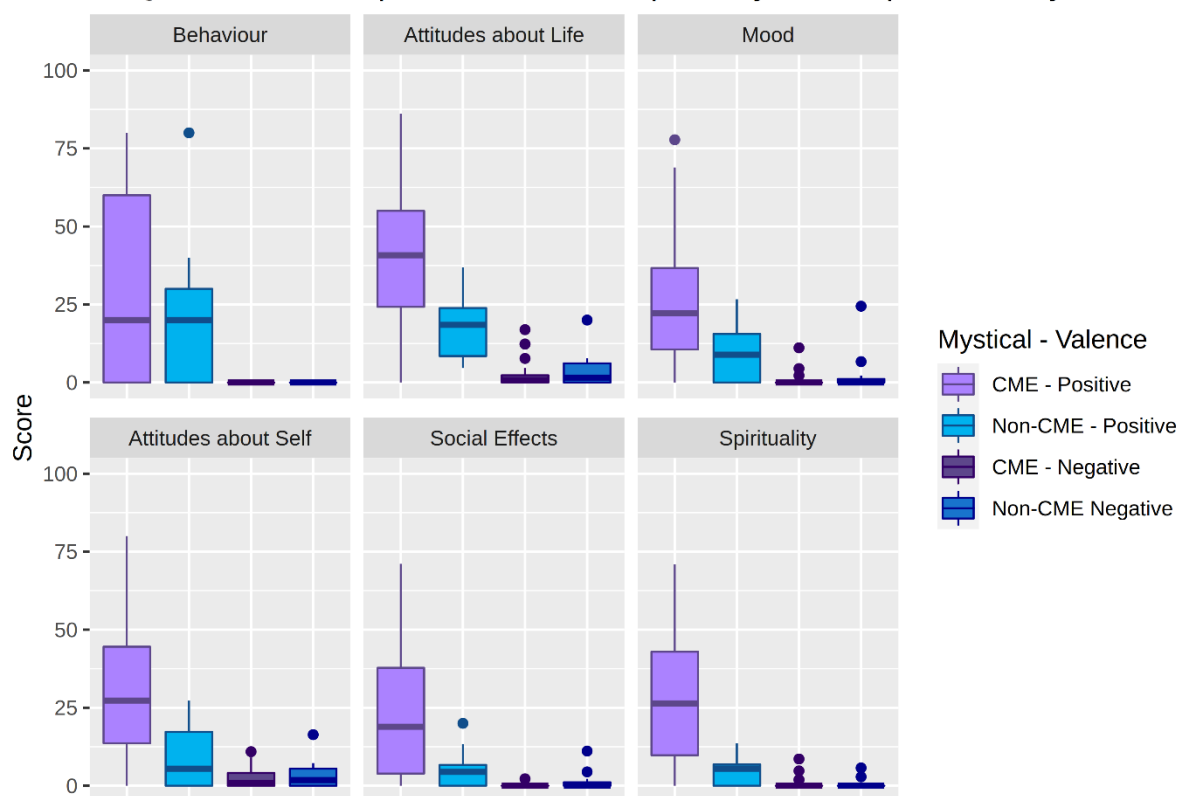PEQ scores for Complete and Non-Complete Mystical Experiences by Subscale

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Figure 2: Boxplots showing Persisting Effect Questionnaire (PEQ) scores relating to either Complete
Mystical Experiences (CME) (Purple) or non-CME (Blue). Each plot represents the positive (lighter
colours, left) and negative (darker colours, right) aspects of each PEQ subscale. The middle line in
each box represents the median. Lower and upper hinges represent first and third quartiles. Datapoints
more than 1.5 interquartile range beyond the hinges are plotted as outliers.

3.2 Association between MEQ and PEQ

3.2.1 Latent-variable model construction

All six positive subscales of the PEQ loaded well onto the latent variable PPE_{LV} (Estimate range = 0.75:1.22, p < $1.1x10^{-10}$ for all subscales). All subscale loadings for each model are reported in **Supplementary Table 4**. No additional covariances were modelled in the main analysis evaluating MEQ total. The models for subscales Ineffability, Transcendence of Time and Space, and Mysticality contained covariance between the PEQ subscales 'Positive Attitudes about Life' and 'Positive Attitudes about Self' whereas the model investigating the Positive Mood subscale contains a covariance between the MEQ subscale Positive Mood and the PEQ subscale 'Increased Spirituality'.

3.2.2 Association between PEQ and MEQ

The LVM investigating the association between MEQ total score and PPE_{LV} showed a statistically significant positive association (ß = 14.8, 95% CI = 8.66:20.96, p = $3x10^{-5}$). The subsequent LVMs investigating effects of the MEQ subscales on PPE_{LV} showed significant positive association with Positive Mood (ß = 14.5, 95% CI = 7.90:21.11, p_{corr} = $4.1x10^{-4}$), as did the LVM evaluating Mysticality (ß = 10.8, 95% CI = 6.14:15.51, p_{corr} = $2.0x10^{-4}$). However, no significant associations were observed for Transcendence of Time and Space (ß = 9.4, 95% CI = -1.72:20.56, p_{corr} = 0.38) or Ineffability (ß = 11.2, 95% CI = -2.75:25.14, p_{corr} = 0.45). See **Table 2** for a full summary of the LVM results and **Figure 3** for a graphical representation. LVM model summaries are reported in **Supplementary Table 4**. Direct and indirect mediation effects of covariates are reported in **Supplementary Table 2**. No indirect effects of any covariate via MEQ were significant (all p > 0.1, uncorrected). Scatter plots of MEQ total and subscales by PPE_{LV} are reported in **Supplementary Figure 1**.

Variable	ß	95% CI	P-value	P-value (corrected)
MEQ total	14.8	8.66:20.96	3.0×10^{-5}	3.0×10^{-5}
Positive Mood	14.5	7.90:21.11	1.0×10^{-4}	4.1×10^{-4}
Mysticality	10.8	6.14:15.51	5.1×10^{-5}	2.0×10^{-4}
Transcendence of Time and Space	9.4	-1.72:20.56	0.094	0.377
Ineffability	11.2	-2.75:25.14	0.111	0.446

383
384 Table 2: Results from the Latent Variable Model analyses for Mystical Experience Questionnaire
385 (MEQ) total score and subsequent subscale analyses. ß and 95% CI indicate effect size and 95%
386 confidence interval in units of the latent variable PPE_{LV} which represents persisting positive effects
387 attributable to the drug experience as a % of maximum possible score.
388

Relation Between MEQ and Persisting Positive Effects Attributed to Psilocybin
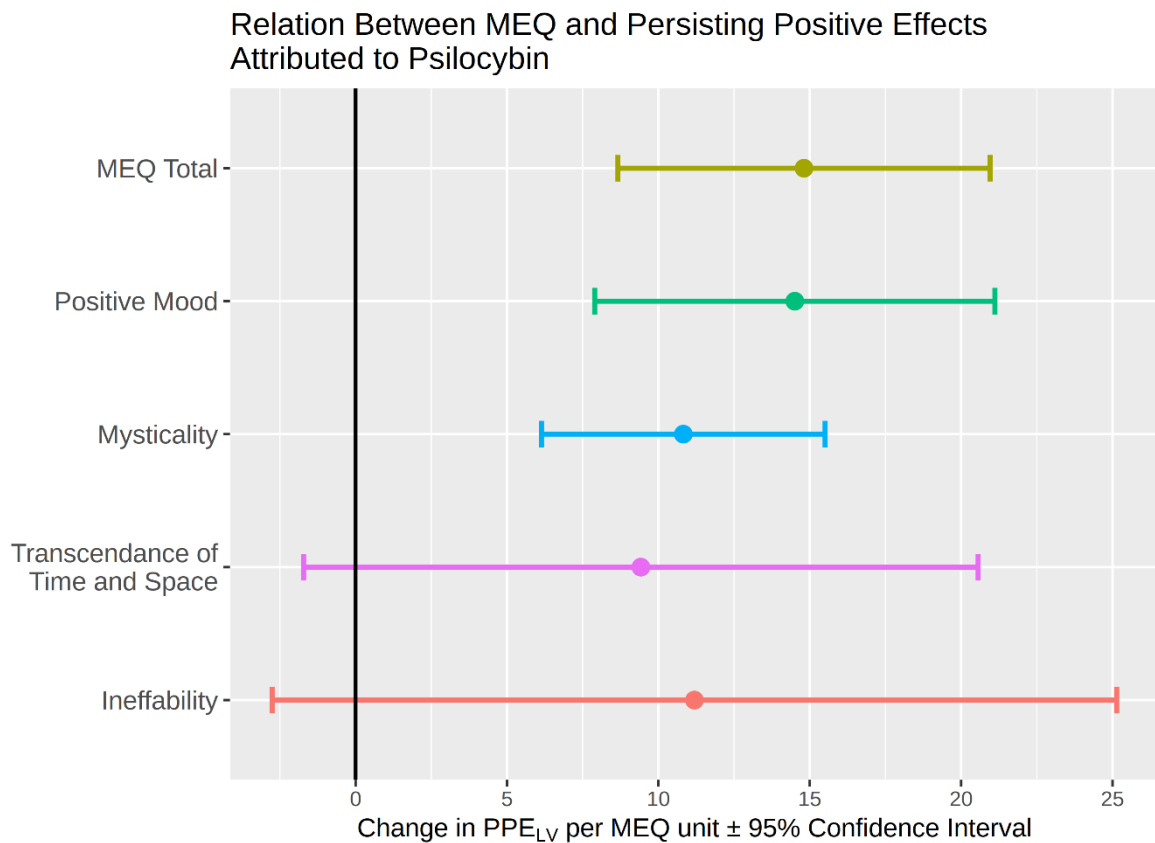
389
390 Figure 3: Results of the latent variable model describing the estimate of effect of the MEQ total and
391 subscale scores measured on the day of psilocybin on PPE_{LV} measured three months after psilocybin.
392 The y-axis represents each individual subscale while the x-axis provides an estimate of the difference
393 in PPE_{LV} associated with a one-unit increase in the indicated MEQ subscale.

3.3 Language differences in mystical and non-mystical experiences

3.3.1 Natural Language Processing

Of the 35 reports analysed, 21 met the criteria for a CME i.e., scoring at least 60% on all subscales of the MEQ. The words with the highest tf-idf score from CME Qualitative Experience Reports indicating the greatest distinction from the overall corpus, were "universe", "dad", "MR" (Magnetic Resonance), "beautiful", "simultaneous", "infinite", "purple", "in relation to", "ray", "happy", and "brother" (See **Figure 4**). The highest tf-idf scores from non-CME reports were "gloomy", "cycle", "evil", "cold" and "need". To expand on these findings, these words were identified in text and a selection of quotes are presented below. Notably, as there are only two documents within the corpus (CME and non-CME), any word which appears in both documents has a tf-idf score of zero. Thus, tf-idf scores distinguish words that only appear in one document set (CME or non-CME).
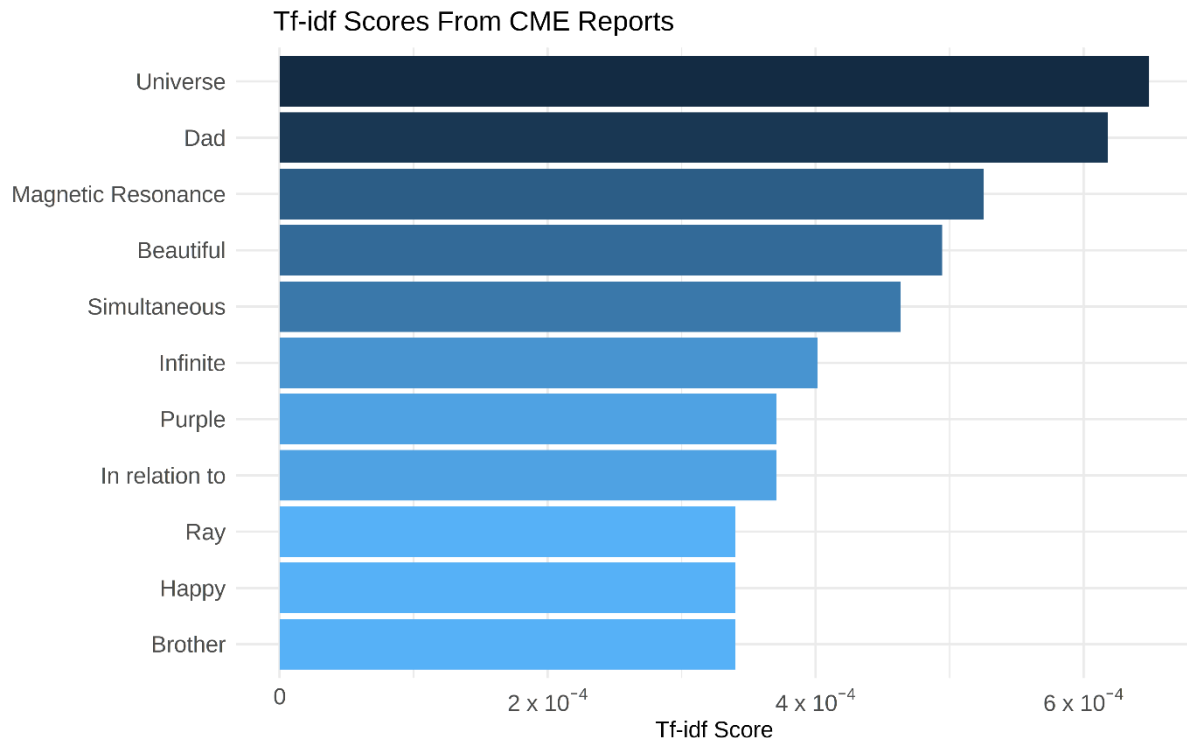

Figure 4: Bar chart displaying the term-frequency inverse document frequency (tf-idf) values for the words that only appear in "Complete Mystical Experience" (CME) reports. Analyses were performed on Danish words and are only translated into English for display in this figure.

411 *3.3.2 Qualitative reports of the Complete Mystical Experience*

412 By manually searching through the document body, we confirmed that high tf-idf scores were

413 not driven by single individuals utilising the identified word multiple times. The word with the

414 highest tf-idf score from the CME reports was "universe". Viewed in context, these references

415 to the universe appear to relate to feelings of unity and connectedness, analogous to MEQ item

416 14 "Freedom from the limitations of your personal self and feeling a unity or bond with what

417 was felt to be greater than your personal self", as well as a wonderment around the complexity

418 of conscious experience.

419 *The trip was mostly concerned with the love pertaining to the different*
420 *relations in my life, but also the love that exists between human beings in*
421 *general, to the planet and to the universe.*
422 **Report 3, female, CME, MEQ total 3.9**

423 *The light of love brings clarity to everything. I get a deep feeling of purity*
424 *and feel that everything is beautiful, and that love is what makes up the*
425 *world and the universe and connects everything like a network of roots.*
426 **Report 22, female, CME, MEQ total 3.9**

427 *Several times during the trip, I found myself laughing in sheer admiration*
428 *of the impressive and wonderous universe of human consciousness.*
429 **Report 10, male, CME, MEQ total 4.7**
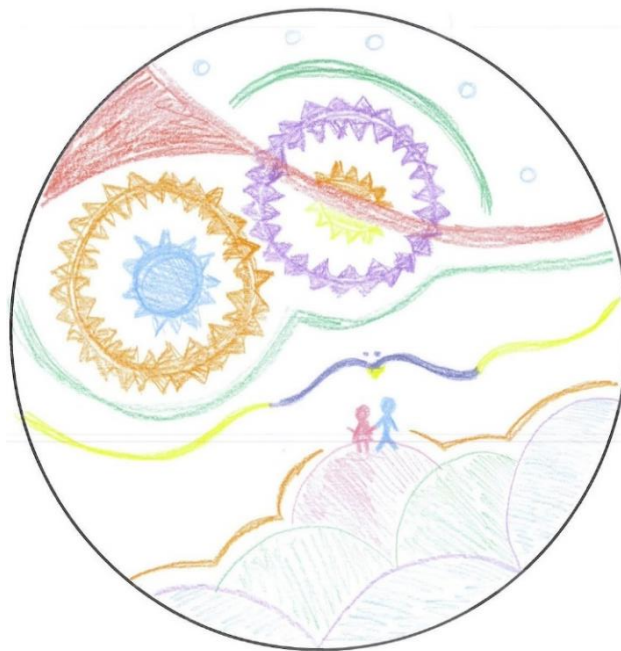
430 *When I close my eyes, I am in a fantastic world. Suspended in the whole*
431 *universe. Stretched across the cosmos. When I open my eyes, I am being*
432 *prepared for the MR-scanner. […] I can hear the sounds of the scanner*
433 *which influence my universe, white and silver lines unfold, make sudden*
434 *angles and travel onwards abruptly.*
435 **Report 31, male, CME, MEQ total 4.2**

436   One report juxtaposes the profound noetic quality of the experience with the tasks that

437   participants were asked to perform in the scanner environment. This aligns with item 9 of the

438   MEQ i.e., "Certainty of encounter with ultimate reality (in the sense of being able to "know"

439   and "see" what is really real at some point during your experience)."

440   *I have the answer to the riddle of the universe,*

441   *but I'm forced to look into a TV-screen.*

442   **Report 31, male, CME, MEQ total 4.2**

443   The word that next-best distinguished the CME was "dad". The reports describe feelings of

444   gratitude, love and respect for the participants' fathers. There are no items of the MEQ that

445   reflect this theme directly. Notably, references to the participants mothers appeared in both

446   CME and non-CME reports and thus had a tf-idf score of zero.

447

448   *I had the feeling that I was experiencing the world through myself as a*

449   *little girl holding her dad's hand. My dad and I were observing what was*

450   *happening around us. I think we saw something that resembled beautiful*

451   *nature and charming castles.*

452   **Report 6, female, CME, MEQ total 3.9**

My mum and dad are opposites, red and white, cold and warm, but they are

like a perfect yin-yang melting together, like my drawing shows, and their

dynamic dance of east and west creates a space in the middle where it is

purple – I am purple – I am both of them.

Report 14, female, CME, MEQ total 4.5

In two cases, the participants describe a desire to share this experience with their fathers specifically.

The tears run down my cheeks as I feel an enormous sense of closeness and

connectedness. I feel an enormous sense of love towards my dad, his way of

being and his patience. I want my dad to experience the feeling of ultimate

love as I do, and for him to have the same experience.

I wish to share my love with him.

Report 12, male, CME, MEQ total 4.9

The word with the third highest tf-idf score was "MR" referring to the MRI scanner. In several cases, participants found the intense noises of the scanner influenced their experience, in some cases inducing synaesthesia-like experiences. More broadly, this represents the profound impact of the environment on the experience.

The sounds from the MR scanner each cast a specific hue, with high-frequency tones giving a

yellowish tinge and low-frequency tones having a purple tinge.

Report 22, female, CME, MEQ total 3.9

The MR environment was the setting for 21 out of the 35 experiences collected (sub-project 3). Some felt that it played a positive role in the experience, as described in item 6 of the MEQ "Experience of oneness or unity with objects and/or persons perceived in your surroundings."
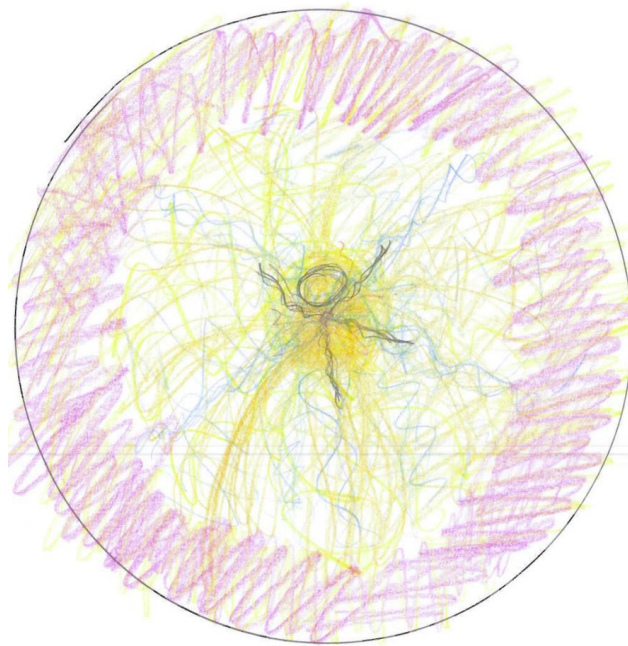
477

478 *I felt a sense of no longer being connected to my own body. The MRI scanner and I stepped*

479 *into a different reality together. With colours, and shapes, and figures.*

480 **Report 32, female, CME, MEQ total 4.7**

481 The word with the fourth highest score was "beautiful". This particular excerpt below

482 combines the themes of universality, family and beauty that appear repeatedly in the CME

483 reports. This report also aligns with item 8 in the MEQ "Feelings of tenderness and

484 gentleness".

485

486

487

488　　　　　*The feeling of joy and love was the energy in the universe, completely*
489　　　　　*intense and multiplied by 100. It was like taking those two emotions and*
490　　　　　*concentrating them, to have them in their purest form without any worries*
491　　　　　*or other troubles that can come with everyday reality. Everything else*
492　　　　　*ceased to matter while those two emotions were so pure – they made*
493　　　　　*everything incredibly beautiful. When I was soaring through the*
494　　　　　*soundwaves with this energy, I could see all the people close to me in my*
495　　　　　*life appear. My partner, my sister and her boyfriend and their new-born*
496　　　　　*son, my mother, my amazing friends. I felt immensely privileged to be part*
497　　　　　*of this universe / community, to be able to feel those feelings in such a pure*
498　　　　　*form, to have such deep emotions in my body – and I was overwhelmed*
499　　　　　*with gratitude for this world. That everything simply is. And with that I was*
500　　　　　*overtaken by a desire to protect it all, to show the world how beautiful it is*
501　　　　　*and to take care of it.*
502　　　　　**Report 3, female, CME, MEQ total 3.9**

503

504 Several reports refer to the beauty of the closed eye visual effects and the participants

505 interactions with them. Perceptual effects are not measured by the MEQ.

506 *Beautiful, beautiful geometrical shapes – and I spin around, do backflips –*
507 *for a moment I just enjoy doing summersaults. My body diffuses into rays*
508 *of sand/light and disappear, but as soon as they're completely gone and I*
509 *think to myself 'oh, all gone, oh well', they remanifest themselves into a*
510 *new meaningful picture.*
511 **Report 14, female, CME, MEQ total 4.5**

512

513 *My inner vision became the universe, filled with colourful waterfalls,*
514 *glistening like stars, not bound by gravity. They floated in the air and*
515 *folded around each other. Totally quiet. The streams were infinite and*
516 *beautiful.*
517 **Report 15, female, CME, MEQ total 3.5**

518   Some of the reports of beauty refer to participants experiences of reflecting on the nature of

519   their consciousness and emotions.

520   *It gave me insights into consciousness as an abstract type of cake:*

521   *Normally, unaffected, you see it as a beautiful object with all of its whipped*

522   *cream and frosting, but throughout the experience it was as if you entered*

523   *the different layers; all of them had their own contents to offer; and one*
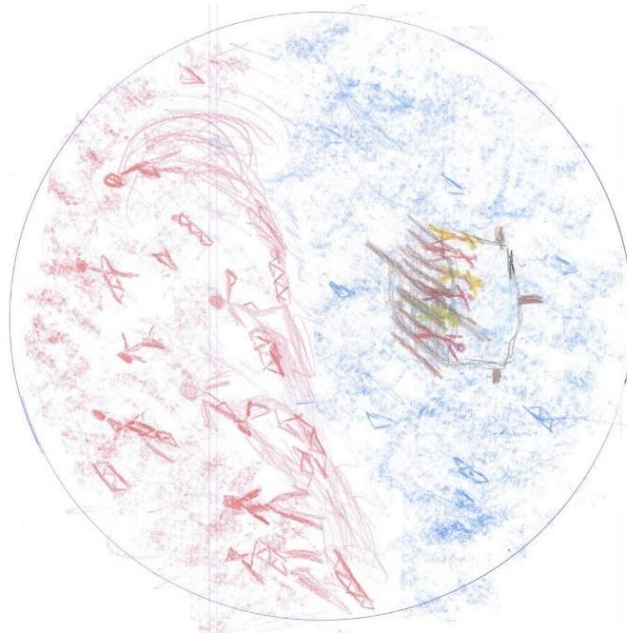
524   *only had to choose.*

525   ***Report 13, male, CME, MEQ total 3.6***

526   *I think it is absurd that we try to examine this phenomenon. That we are*

527   *scanning my brain to figure out what's happening. I know that we can't*

528   *understand it, that we can't put an equation on it and figure it out. I feel it*

529   *is human arrogance, trying to tame all the beauty. I think,*

530   *"Scan me then! We won't get any closer to the truth!"*

531   ***Report 31, male, CME, MEQ total 4.2***

Finally, many participants who had CMEs describe the beauty of the world and universe

around them, both natural and interpersonal. This is reflected in MEQ item 27 "sense of awe

or awesomeness"

With high spirits and a child-like excitement, I started to think about how

the Norwegian adventurer Thor Heyerdahl crossed the Pacific Ocean on a

raft to prove that life was big and beautiful. I see long realistic passages

that made me laugh and feel a great inner joy.

Report 19, male, CME, MEQ total 3.8

The fifth highest tf-idf word was "simultaneous". These quotes largely refer to a duality of

experience (e.g., perceived disconnection of body and mind) wherein participants report feeling

several, sometimes conflicting, emotions at the same time or reflect on their experience as it is

ongoing. No specific items in the MEQ match these themes.

In my thoughts, mentally, physically, and bodily. I desire the togetherness of being a pair, but

simultaneously I feel a togetherness with the whole world and all people.

Report 12, male, CME, MEQ total 4.9

548   *The next sequence was a mixture of thinking about different relationships and at the same*

549   *time being present on a different level of consciousness,*

550   *which transcended my body and my mind.*

551   **Report 16, male, CME, MEQ total 4.6**

552   *I open my eyes and cry with happiness. I am completely one with the past, the future and the*

553   *present - stretched, but at the same time not in my body.*

554   **Report 31, male, CME, MEQ total 4.2**

555

556   *3.3.3 Qualitative Reports of the Non-Complete Mystical Experience*

557   Upon inspection, many of the words that had high tf-idf values from non-CME reports were

558   driven primarily by one or two reports that used the words repeatedly. Thus, we did not feel

559   that they provided a sound reflection of the themes within the non-CME. The only exception

560   was the word "gloomy" which was used 6 times in non-CME reports, never in CME reports,

561   and was reported by several individuals. In context this referred largely to interpretation of

562   music.

563   *The physical insecurities I have about myself and the gloomy music made me feel uneasy*

564   **Report 7, female, non-CME, MEQ total 2.8**

4. Discussion

4.1 Summary

This study investigated how persistent positive effects of psilocybin attributed to the psychedelic experience are associated with the self-reported "mystical" nature of the experience in healthy volunteers. Analyses showed that the intensity and character of mystical-type experiences were associated with these, a relation which could be considered predictive as MEQ was collected approximately three months before PEQ. We provide qualitative lexical and pictorial descriptions of the psilocybin-induced Complete Mystical Experience (CME) describing themes such as connection to the universe, familial love, beauty, and highlighting the importance of setting. Beyond replicating the relation between MEQ and PEQ in healthy volunteers, this paper shows that the character of mystical-type experience may be important for lasting positive effects in healthy volunteers and provides a qualitative description of the psilocybin experience in healthy volunteers that can be used to inform practice and future research around the administration of psilocybin in this population.

4.2 Relation between MEQ and PEQ

Previous research suggests that the mystical-type experience is qualitatively linked to patient outcomes (Belser et al., 2017; Nielson et al., 2018; Noorani et al., 2018; Swift et al., 2017) as well as being quantitatively linked to positive persisting effects in healthy volunteers (R. R. Griffiths et al., 2006; R. Griffiths et al., 2008; Roland R. Griffiths et al., 2011; Roland R Griffiths et al., 2018; Schmid & Liechti, 2018) and patients (Davis et al., 2020; Garcia-Romeu et al., 2015; Roland R. Griffiths et al., 2016; Ross et al., 2016). In this study we provide quantitative estimates of these effects in a population of carefully screened healthy Danish individuals. We also show that the degree to which these experiences were described as positively emotionally valanced i.e., MEQ item 17 "Experience of ecstasy" or as feelings of

590   connectedness i.e., MEQ item 28 "Experience of unity with ultimate reality" were robustly

591   associated with lasting positive effects. However, the degree to which the experiences were

592   described as beyond typical comprehension of space and time, i.e., MEQ item 7 "Loss of your

593   usual sense of space" or difficult to describe i.e., MEQ item 10 "Feeling that you could not do

594   justice to your experience by describing it in words" were not significantly associated with

595   persisting positive effects. Importantly, the effect sizes for each subscale were similar, but the

596   variance of the latter two subscales was too broad to conclude a significant association between

597   these subscale scores and positive persisting effects. Although other papers have shown a

598   relation between MEQ total score and persisting positive effects of psilocybin (Roland R.

599   Griffiths et al., 2011; Schmid & Liechti, 2018), this is the first paper to show a subscale-specific

600   effect. Our results indicate that the subjective nature of the psychedelic experience is indeed

601   linked to lasting positive outcomes, though it is argued that such links may be mere

602   epiphenomena (Hibicke, Landry, Kramer, Talman, & Nichols, 2020; Olson, 2021). Due to the

603   lack of adequate controls and mechanistic antagonists, our study design is not suited to test

604   whether the persisting positive effects of psilocybin are caused by the subjective or non-

605   subjective effects of psilocybin. We did not observe a relation between peak plasma psilocin

606   levels and MEQ score or persisting positive effects in the 20-participant subgroup for whom

607   such data was available.

608

609   Given the above findings we may consider how to optimise the conditions that permit mystical-

610   type experiences to unfold safely and allow patients to surrender to the experience (Aday,

611   Davis, Mitzkovitz, Bloesch, & Davoli, 2021), since this has been consistently associated with

612   persisting positive outcomes. These may be modulated by parameters such as dose (Holze et

613   al., 2021), choice of psychedelic compound, as preliminary literature suggests differential

614   phenomenology between compounds (Metzner, 2015; Papaseit et al., 2018; Richards, 1975;

615 Shulgin & Shulgin, 1991, 1997), or "set" and "setting" (Hartogsohn, 2017, 2021; Kettner et

616 al., 2021; Perkins et al., 2021; Strickland et al., 2021). Notably, despite previous research

617 showing that the scanning environment was strongly associated with negative reactions

618 (Studerus, Gamma, Kometer, & Vollenweider, 2012), our mediation analysis showed no

619 overall mediation effect of sub-project on persisting effects. A weak direct negative effect of

620 sub-project 2 (comfortable environment) and sub-project 3 (MR scanner) was observed on

621 lasting effects, compared to sub-project 1 (PET scanner). However, these associations do not

622 survive multiple comparisons correction. Curiously, the term "MR" only appeared in CME

623 reports and not in non-CME reports.

624

625 **4.3 Qualitative findings**

626 In this paper, we provide the first published qualitative descriptions of the subjective

627 experience of healthy volunteers given medium-high doses of oral psilocybin in a research

628 environment. The tf-idf analyses revealed themes in open-ended reports that aligned with items

629 of the MEQ such as 1) connection with the universe: "Experience of the fusion of your personal

630 self into a larger whole." (MEQ item 26), 2) A sense of infinity: "Feeling that you experienced

631 eternity of infinity" (MEQ item 5) and 3) Wonderment/beauty: "Sense of reverence" (MEQ

632 item 21) and "Sense of awe or awesomeness" (MEQ item 27) (Barrett et al., 2015). Despite

633 playing prominent roles in the CME open-ended reports, certain themes emerged that are not

634 described in the MEQ such as familial love, gratitude, and the simultaneous presence of

635 contradictory feelings. The themes of family (Breeksema, Niemeijer, Krediet, Vermetten, &

636 Schoevers, 2020) and gratitude are also described in other qualitative reports (Noorani et al.,

637 2018; Watts et al., 2017), and while not "mystical" in nature these may reliably co-emerge with

638 the CME. None of the themes identified in the CME reports have connotations of the

639 'challenging' or 'dysphoric' experiences that have been reported in the qualitative literature of

patient experiences (Belser et al., 2017; Nielson et al., 2018; Swift et al., 2017). Although this may be in part driven by the Positive Mood criteria of the CME, it still highlights the distinction between experiences in healthy volunteers and patients that deserves further investigation. We were not able to distinguish themes that surround non-mystical experiences, likely due to greater descriptive variability among these states relative to CME.

4.4 Ineffability

One notable finding from the descriptive analyses was that even those who had non-CME had an average MEQ subscale Ineffability score of 3.9 out of 5, and every participant surpassed the threshold of 3 for CME relating to Ineffability. Some experts consider ineffability to be an essential component of an authentic CME (Papanicolaou, 2021), yet the idea that psychedelic phenomena are particularly ineffable is at odds with the idea that all phenomena are inherently ineffable, thus there is nothing special about psychedelia phenomena (Nagel, 1974). If we consider other phenomena to be "effable", then describing psychedelic phenomena as ineffable can be considered scientifically pessimistic, and contribute to the culture of "psychedelic exceptionalism" (Johnson, 2021; Sanders & Zijlmans, 2021). What is it about a psychedelic experience i.e., "Being in a realm with no space boundaries" (MEQ item 19) that is judged to be more ineffable than the inability to describe the colour blue, without resorting to comparison? It has been argued that "effability" is the product of shared experience and the subsequent production of language (Millikan, 2005), which is why "blueness" is easy to convey, at least to those who have experienced it (Jackson, 1982, 1986). Therefore, the ineffability of these CME may reflect the novel nature of the experience to individuals without indicating any epistemic truth about the experience. If many people underwent high dose psychedelic experiences, then we might expect a new language to emerge that facilitates the description of such experiences between individuals. An example of this is the term "ego-

665 dissolution" which is now widely used across psychedelic science (Lebedev et al., 2015; Mason

666 et al., 2020; Nour, Evans, Nutt, & Carhart-Harris, 2016; Preller & Vollenweider, 2018).

667

668 **4.5 Criticism of "mystical-type experience" science**

669 The focus of this paper is the investigation of the mystical-type experience, an area of inquiry

670 with which some researchers have taken issue (Sanders & Zijlmans, 2021). Critics highlight

671 the pervasive culture of mysticism in psychedelic science (including the MEQ itself) which

672 may bias participants towards interpreting their experiences through a supernatural,

673 unscientific, or spiritual lens where they may not have done so otherwise. It has been argued

674 that the epistemic status of metaphysical conclusions drawn from psychedelic experiences are

675 relevant to whether we should endorse psychedelics as a means to lasting positive

676 psychological changes (Flanagan & Graham, 2017). Following psychedelic experiences,

677 individuals may draw comfort from beliefs that are not veridical, which may be considered

678 troublesome. This stance is known as the "Comforting Delusion Objection" and is discussed

679 and objected to in detail by Letheby (2021). Nevertheless, psychedelic drugs reliably induce

680 the sorts of experiences wherein individuals feel that statements such as "Certainty of encounter

681 with ultimate reality" (MEQ item 9) and "Sense of being at a spiritual height" (MEQ item 15)

682 accurately describe a component of their experience (Barrett et al., 2015; R. R. Griffiths et al.,

683 2006; MacLean, Leoutsakos, Johnson, & Griffiths, 2012). As participants feel justified in

684 describing their experiences with such language, the framework of "mystical-type experiences"

685 is a useful one for describing a cluster of co-occurring experiences, independent of ontological

686 judgement of their content, especially given the apparent predictive utility of such experiences.

687

688

4.6 Limitations

In the latent variable model analyses, we attempted to control the type-1 error at its nominal level using a method described by Ozenne, Fisher, & Budtz-Jørgensen (2020). Additionally, we accounted for individuals who took part in two projects using robust standard error (section 6 of Ozenne, Fisher and Budtz-Jørgensen). Despite these corrections, it is still noteworthy that the type-1 error may be inflated by the sample size and we urge independent replication with larger samples, especially given these scales are widely used in psychedelic research.

This study was not blinded and did not account for expectancy effects which have been theorised to be mediate some of the persisting positive effects of psychedelics (Muthukumaraswamy, Forsyth, & Lumley, 2021). Rigorous future work should aim to replicate these findings with such controls and evaluate the role of expectancy in the intensity and character of mystical-type experiences induced by psilocybin. By performing a mediation analysis, it may be possible to delineate the degree to which expectancy is either related to persisting positive effects and whether independent of or via MEQ. The PEQ specifically asks participants to evaluate changes that are *due to* the experience, thus further work could aim to investigate the subjectively experienced causal link between the content of the experience and persisting positive effects. Additionally, we do not collect data on whether participants recreationally consume psilocybin between administration within the study and 3-month follow up, which has the potential to bias evaluation of persisting effects.

The PEQ scores that we report are similar in value to those reported by a group based in Basel, Switzerland for a comparable dose of LSD (Schmid & Liechti, 2018). Curiously, these scores are equal to the PEQ scores reported for the placebo group from studies at Johns Hopkins in the USA, and far lower than the PEQ scores reported following similar doses of psilocybin

714   (Roland R. Griffiths et al., 2011). This suggests that there may be a relevant difference between

715   studies, such as recruitment basis, age, preparation, setting, and integration practices, or

716   cultural differences that should be taken into account when considering the generalisability of

717   these findings. Notably, the PEQ has not been robustly compared to other measures of

718   persisting psychological change, or undergone factor analyses. Our sample is drawn from three

719   separate settings, namely PET scanning, a comfortable environment, and MRI scanning. This

720   adds heterogeneity to our sample, though our mediation analysis did not show a significant

721   effect of setting on PEQ either directly or via MEQ. Nevertheless, analyses comparing the

722   mystical-type experience to persisting positive effects could be repeated with a more

723   homogenous setting.

724

725   Due to the lack of generalisability of the terms within the corpus of non-CME reports, we did

726   not feel that these were sufficient to provide a qualitative characterisation of non-CME. The

727   only exception was "gloomy" that referred in several cases to the music, a sentiment that has

728   been identified in previous qualitative psychedelic research (Watts et al., 2017).

729

730   Qualitative analyses are often limited by biased selection of quotes that fit the narrative of the

731   paper (Galdas, 2017). We attempted to control for this by utilising a natural language

732   processing procedure, tf-idf, to delineate themes without a priori criteria. However, quotes

733   selected after this filtering step are not entirely unbiased, as not all quotes are reported.

734   Additionally, although tf-idf analyses account for total corpus length, they are susceptible to

735   bias from a single report containing a specific word repeatedly. We attempted to control for

736   this bias by manually searching to ensure each word described was used in multiple reports.

737   Tf-idf analyses are limited in cases where there are only two document bodies as a single

738   incidence of the term in both bodies results in a tf-idf value of zero. Therefore, the high tf-idf

739   scores reported above represent the most frequently used terms that only appear in the CME

740   reports, though this may also be considered a strength of these findings. Further collection of

741   these open-form reports on the night of the session will allow for more nuanced natural

742   language processing of the data, as there were several analyses that we were unable to perform

743   due to a small sample (e.g., thematic analyses, n-gram analyses, splitting into smaller

744   subgroups). These may provide a deeper understanding of the phenomenology of the

745   psychedelic experience.

746

747   **4.7 Conclusion**

748   In this paper we show a relation between the intensity of the psilocybin-induced mystical-type

749   experience and lasting positive psychological effects and extend previous work by showing

750   that the MEQ subscales Mysticality and Positive Mood were more closely associated with

751   lasting positive effects than Transcendence of Time and Space or Ineffability. This suggests

752   that the phenomenology of the psychedelic experience is relevant to lasting positive effects.

753   Additionally, we provide the first qualitative descriptions of orally administered psilocybin in

754   healthy volunteers revealing themes including universal connectedness, experience of beauty,

755   and familial love that may be used to inform future research utilising psilocybin in healthy

756   volunteers.

768   Bibliography

769   Aday, J. S., Davis, A. K., Mitzkovitz, C. M., Bloesch, E. K., & Davoli, C. C. (2021). Predicting
770   Reactions to Psychedelic Drugs: A Systematic Review of States and Traits Related to Acute
771   Drug Effects. *ACS Pharmacology & Translational Science*, *4*(2), 424–435.
772   https://doi.org/10.1021/acsptsci.1c00014

773   Anderson, B. T., Danforth, A., Daroff, P. R., Stauffer, C., Ekman, E., Agin-Liebes, G., … Woolley, J.
774   (2020). Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men:
775   An open-label safety and feasibility pilot study. *EClinicalMedicine*, *27*, 100538.
776   https://doi.org/10.1016/j.eclinm.2020.100538

777   Bailer, L. W. (2020). *Encyclopedia of Psychology and Religion*. (D. A. Leeming, Ed.) (3rd ed.).
778   Cham: Springer International Publishing. https://doi.org/10.1007/978-3-030-24348-7

779   Barrett, F. S., Doss, M. K., Sepeda, N. D., Pekar, J. J., & Griffiths, R. R. (2020). Emotions and brain
780   function are altered up to one month after a single high dose of psilocybin. *Scientific Reports*,
781   *10*(1), 1–14. https://doi.org/10.1038/s41598-020-59282-y

782   Barrett, F. S., Johnson, M. W., & Griffiths, R. R. (2015). Validation of the revised Mystical
783   Experience Questionnaire in experimental sessions with psilocybin. *Journal of
784   Psychopharmacology*, *29*(11), 1182–1190. https://doi.org/10.1177/0269881115609019

785   Bech, P., Rasmussen, N.-A., Olsen, L. R., Noerholm, V., & Abildgaard, W. (2001). The sensitivity
786   and specificity of the Major Depression Inventory, using the Present State Examination as the
787   index of diagnostic validity. *Journal of Affective Disorders*, *66*(2–3), 159–164.
788   https://doi.org/10.1016/S0165-0327(00)00309-8

789   Belser, A. B., Agin-Liebes, G., Swift, T. C., Terrana, S., Devenot, N., Friedman, H. L., … Ross, S.
790   (2017). Patient Experiences of Psilocybin-Assisted Psychotherapy: An Interpretative
791   Phenomenological Analysis. *Journal of Humanistic Psychology*, *57*(4), 354–388.
792   https://doi.org/10.1177/0022167817706884

793   Bogenschutz, M. P., Forcehimes, A. A., Pommy, J. A., Wilcox, C. E., Barbosa, P., & Strassman, R. J.
794   (2015). Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. *Journal
795   of Psychopharmacology*, *29*(3), 289–299. https://doi.org/10.1177/0269881114565144

796   Breeksema, J. J., Niemeijer, A. R., Krediet, E., Vermetten, E., & Schoevers, R. A. (2020). Psychedelic
797   Treatments for Psychiatric Disorders: A Systematic Review and Thematic Synthesis of Patient
798   Experiences in Qualitative Studies. *CNS Drugs*, (0123456789). https://doi.org/10.1007/s40263-
799   020-00748-y

800   Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh
801   sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry
802   Research*, *28*(2), 193–213. https://doi.org/10.1016/0165-1781(89)90047-4

803   Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., …
804   Nutt, D. J. (2021). Trial of Psilocybin versus Escitalopram for Depression. *New England Journal
805   of Medicine*, *384*(15), 1402–1411. https://doi.org/10.1056/nejmoa2032994

806   Carhart-Harris, R. L., Bolstridge, M., Day, C. M. J., Rucker, J., Watts, R., Erritzoe, D. E., … Nutt, D.
807   J. (2018). Psilocybin with psychological support for treatment-resistant depression: six-month
808   follow-up. *Psychopharmacology*, *235*, 399–408.

809   Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A Global Measure of Perceived Stress. *Journal of
810   Health and Social Behavior*, *24*(4), 385. https://doi.org/10.2307/2136404

811   Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., …
812   Griffiths, R. R. (2020). Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder A
813   Randomized Clinical Trial. *JAMA Psychiatry*, *Published*, 1–9.

814   https://doi.org/10.1001/jamapsychiatry.2020.3285

815 Dunn, O. J. (1961). Multiple Comparisons among Means. *Journal of the American Statistical*
816   *Association*, *56*(293), 52–64. https://doi.org/10.1080/01621459.1961.10482090

817 Erritzoe, D., Roseman, L., Nour, M. M., MacLean, K., Kaelen, M., Nutt, D. J., & Carhart-Harris, R.
818   L. (2018). Effects of psilocybin therapy on personality structure. *Acta Psychiatrica*
819   *Scandinavica*, *138*(5), 368–378. https://doi.org/10.1111/acps.12904

820 Flanagan, O., & Graham, G. (2017). Truth and Sanity: Positive Illusions, Spiritual Delusions, and
821   Metaphysical Hallucinations. https://doi.org/10.7551/mitpress/9780262035484.003.0013

822 Galdas, P. (2017). Revisiting Bias in Qualitative Research. *International Journal of Qualitative*
823   *Methods*, *16*(1), 160940691774899. https://doi.org/10.1177/1609406917748992

824 Garcia-Romeu, A., Davis, A. K., Erowid, F., Erowid, E., Griffiths, R. R., & Johnson, M. W. (2019).
825   Cessation and reduction in alcohol consumption and misuse after psychedelic use. *Journal of*
826   *Psychopharmacology*, *33*(9), 1088–1101. https://doi.org/10.1177/0269881119845793

827 Garcia-Romeu, A., Griffiths, R., & Johnson, M. (2015). Psilocybin-Occasioned Mystical Experiences
828   in the Treatment of Tobacco Addiction. *Current Drug Abuse Reviews*, *7*(3), 157–164.
829   https://doi.org/10.2174/1874473708666150107121331

830 Griffiths, R. R., Richards, W. A., McCann, U., & Jesse, R. (2006). Psilocybin can occasion mystical-
831   type experiences having substantial and sustained personal meaning and spiritual significance.
832   *Psychopharmacology*, *187*(3), 268–283. https://doi.org/10.1007/s00213-006-0457-5

833 Griffiths, R., Richards, W., Johnson, M., McCann, U., & Jesse, R. (2008). Mystical-type experiences
834   occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance
835   14 months later. *Journal of Psychopharmacology*, *22*(6), 621–632.
836   https://doi.org/10.1177/0269881108094300

837 Griffiths, Roland R., Hurwitz, E. S., Davis, A. K., Johnson, M. W., & Jesse, R. (2019). Survey of
838   subjective "God encounter experiences": Comparisons among naturally occurring experiences
839   and those occasioned by the classic psychedelics psilocybin, LSD, ayahuasca, or DMT. *PLOS*
840   *ONE*, *14*(4), e0214377. https://doi.org/10.1371/journal.pone.0214377

841 Griffiths, Roland R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B.
842   D., … Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in
843   depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial.
844   *Journal of Psychopharmacology*, *30*(12), 1181–1197.
845   https://doi.org/10.1177/0269881116675513

846 Griffiths, Roland R., Johnson, M. W., Richards, W. A., Richards, B. D., McCann, U., & Jesse, R.
847   (2011). Psilocybin occasioned mystical-type experiences: Immediate and persisting dose-related
848   effects. *Psychopharmacology*, *218*(4), 649–665. https://doi.org/10.1007/s00213-011-2358-5

849 Griffiths, Roland R, Johnson, M. W., Richards, W. A., Richards, B. D., Jesse, R., MacLean, K. A., …
850   Klinedinst, M. A. (2018). Psilocybin-occasioned mystical-type experience in combination with
851   meditation and other spiritual practices produces enduring positive changes in psychological
852   functioning and in trait measures of prosocial attitudes and behaviors. *Journal of*
853   *Psychopharmacology*, *32*(1), 49–69. https://doi.org/10.1177/0269881117731279

854 Grob, C. S., Danforth, A. L., Chopra, G. S., Hagerty, M., McKay, C. R., Halberstad, A. L., & Greer,
855   G. R. (2011). Pilot study of psilocybin treatment for anxiety in patients with advanced-stage
856   cancer. *Archives of General Psychiatry*, *68*(1), 71–78.
857   https://doi.org/10.1001/archgenpsychiatry.2010.116

858 Hartogsohn, I. (2017). Constructing drug effects: A history of set and setting. *Drug Science, Policy*
859   *and Law*, *3*, 205032451668332. https://doi.org/10.1177/2050324516683325

860 Hartogsohn, I. (2021). Set and Setting in the Santo Daime. *Frontiers in Pharmacology*, *12*.
861   https://doi.org/10.3389/fphar.2021.651037

862 Hasler, F., Grimberg, U., Benz, M. A., Huber, T., & Vollenweider, F. X. (2004). Acute psychological
863   and physiological affects of psilocybin in healthy humans: A double-blind, placebo-controlled
864   dose-effect study. *Psychopharmacology*, *172*(2), 145–156. https://doi.org/10.1007/s00213-003-
865   1640-6

866 Haynes, W. (2013). Bonferroni Correction. In *Encyclopedia of Systems Biology* (pp. 154–154). New
867   York, NY: Springer New York. https://doi.org/10.1007/978-1-4419-9863-7_1213

868 Hibicke, M., Landry, A. N., Kramer, H. M., Talman, Z. K., & Nichols, C. D. (2020). Psychedelics,
869   but Not Ketamine, Produce Persistent Antidepressant-like Effects in a Rodent Experimental
870   System for the Study of Depression. *ACS Chemical Neuroscience*, *11*(6), 864–871.
871   https://doi.org/10.1021/acschemneuro.9b00493

872 Hirschfeld, T., & Schmidt, T. T. (2021). Dose–response relationships of psilocybin-induced
873   subjective experiences in humans. *Journal of Psychopharmacology*, *35*(4), 384–397.
874   https://doi.org/10.1177/0269881121992676

875 Holst, K. K., & Budtz-Jørgensen, E. (2013). Linear latent variable models: the lava-package.
876   *Computational Statistics*, *28*(4), 1385–1452. https://doi.org/10.1007/s00180-012-0344-y

877 Holze, F., Vizeli, P., Ley, L., Müller, F., Dolder, P., Stocker, M., … Liechti, M. E. (2021). Acute
878   dose-dependent effects of lysergic acid diethylamide in a double-blind placebo-controlled study
879   in healthy subjects. *Neuropsychopharmacology*. https://doi.org/10.1038/s41386-020-00883-6

880 Hyde, R. W. (1960). The dynamics of psychiatric drug therapy.

881 Jackson, F. (1982). Epiphenomenal Qualia. *The Philosophical Quarterly*, *32*(127), 127.
882   https://doi.org/10.2307/2960077

883 Jackson, F. (1986). What Mary Didn't Know. *The Journal of Philosophy*, *83*(5), 291.
884   https://doi.org/10.2307/2026143

885 Johnson, M. W. (2021). Consciousness, Religion, and Gurus: Pitfalls of Psychedelic Medicine. *ACS*
886   *Pharmacology & Translational Science*, *4*(2), 578–581.
887   https://doi.org/10.1021/acsptsci.0c00198

888 Johnson, M. W., Garcia-Romeu, A., & Griffiths, R. R. (2017). Long-term follow-up of psilocybin-
889   facilitated smoking cessation. *American Journal of Drug and Alcohol Abuse*, *43*(1), 55–60.
890   https://doi.org/10.3109/00952990.2016.1170135

891 Kettner, H., Rosas, F. E., Timmermann, C., Kärtner, L., Carhart-Harris, R. L., & Roseman, L. (2021).
892   Psychedelic Communitas: Intersubjective Experience During Psychedelic Group Sessions
893   Predicts Enduring Changes in Psychological Wellbeing and Social Connectedness. *Frontiers in*
894   *Pharmacology*, *12*. https://doi.org/10.3389/fphar.2021.623985

895 Lebedev, A. V., Lövdén, M., Rosenthal, G., Feilding, A., Nutt, D. J., & Carhart-Harris, R. L. (2015).
896   Finding the self by losing the self: Neural correlates of ego-dissolution under psilocybin. *Human*
897   *Brain Mapping*. https://doi.org/10.1002/hbm.22833

898 Letheby, C. (2021). *Philosophy of psychedelics* (1st ed.). Oxford: Oxford University Press. Retrieved
899   from https://global.oup.com/academic/product/philosophy-of-psychedelics-
900   9780198843122?cc=dk&lang=en&#

901 Lyvers, M., & Meester, M. (2012). Illicit Use of LSD or Psilocybin, but not MDMA or
902   Nonpsychedelic Drugs, is Associated with Mystical Experiences in a Dose-Dependent Manner.
903   *Journal of Psychoactive Drugs*, *44*(5), 410–417. https://doi.org/10.1080/02791072.2012.736842

904 MacLean, K. A., & Griffiths, R. R. (2013). Factor Analysis of the Mystical Experience Questionnaire:

Study of Experiences Occasioned by the Hallucinogen Psilocybin. *Journal for the Scientific Study of Religion*, *51*(4), 721–737. https://doi.org/10.1111/j.1468-5906.2012.01685.x.Factor

MacLean, K. A., Johnson, M. W., & Griffiths, R. R. (2011). Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. *Journal of Psychopharmacology*, *25*(11), 1453–1461. https://doi.org/10.1177/0269881111420188

MacLean, K. A., Leoutsakos, J.-M. S., Johnson, M. W., & Griffiths, R. R. (2012). Factor Analysis of the Mystical Experience Questionnaire: A Study of Experiences Occasioned by the Hallucinogen Psilocybin. *Journal for the Scientific Study of Religion*, *51*(4), 721–737. Retrieved from http://www.jstor.org/stable/23353829

Madsen, Martin K., Fisher, P. M., Burmester, D., Dyssegaard, A., Stenbæk, D. S., Kristiansen, S., … Knudsen, G. M. (2019). Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. *Neuropsychopharmacology*, *44*(7), 1328–1334. https://doi.org/10.1038/s41386-019-0324-9

Madsen, Martin K., Stenbæk, D. S., Arvidsson, A., Armand, S., Marstrand-Joergensen, M. R., Johansen, S. S., … Fisher, P. M. (2021). Psilocybin-induced changes in brain network integrity and segregation correlate with plasma psilocin level and psychedelic experience. *European Neuropsychopharmacology*, *50*, 121–132. https://doi.org/10.1016/j.euroneuro.2021.06.001

Madsen, Martin Korsbak, Fisher, P. M. D., Stenbæk, D. S., Kristiansen, S., Burmester, D., Lehel, S., … Knudsen, G. M. (2020). A single psilocybin dose is associated with long-term increased mindfulness, preceded by a proportional change in neocortical 5-HT2A receptor binding. *European Neuropsychopharmacology*, *33*, 71–80. https://doi.org/10.1016/j.euroneuro.2020.02.001

Maslow, A. H. (1959). Cognition of Being in the Peak Experiences. *The Journal of Genetic Psychology*, *94*(1), 43–66. https://doi.org/10.1080/00221325.1959.10532434

Mason, N. L., Kuypers, K. P. C., Müller, F., Reckweg, J., Tse, D. H. Y., Toennes, S. W., … Ramaekers, J. G. (2020). Me, myself, bye: regional alterations in glutamate and the experience of ego dissolution with psilocybin. *Neuropsychopharmacology*. https://doi.org/10.1038/s41386-020-0718-8

Metzner, R. (2015). *Allies for awakening, guidelines for productive and safe experiences with entheogens* (1st ed.). Regent Press.

Millikan, R. G. (2005). *Language: A Biological Model*. Oxford University Press. https://doi.org/10.1093/0199284768.001.0001

Moreno, F. A., Wiegand, C. B., Taitano, E. K., & Delgado, P. L. (2006). Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *Journal of Clinical Psychiatry*, *67*(11), 1735–1740. https://doi.org/10.4088/JCP.v67n1110

Muthukumaraswamy, S. D., Forsyth, A., & Lumley, T. (2021). Blinding and expectancy confounds in psychedelic randomized controlled trials. *Expert Review of Clinical Pharmacology*, 1–20. https://doi.org/10.1080/17512433.2021.1933434

Nagel, T. (1974). What Is It Like to Be a Bat? *The Philosophical Review*, *83*(4), 435. https://doi.org/10.2307/2183914

Nielson, E. M., May, D. G., Forcehimes, A. A., & Bogenschutz, M. P. (2018). The psychedelic debriefing in alcohol dependence treatment: Illustrating key change phenomena through qualitative content analysis of clinical sessions. *Frontiers in Pharmacology*. https://doi.org/10.3389/fphar.2018.00132

Noorani, T., Garcia-Romeu, A., Swift, T. C., Griffiths, R. R., & Johnson, M. W. (2018). Psychedelic therapy for smoking cessation: Qualitative analysis of participant accounts. *Journal of*

951   *Psychopharmacology.* https://doi.org/10.1177/0269881118780612

952   Nour, M. M., Evans, L., Nutt, D., & Carhart-Harris, R. L. (2016). Ego-dissolution and psychedelics:
953   Validation of the ego-dissolution inventory (EDI). *Frontiers in Human Neuroscience*, *10*(June),
954   1–13. https://doi.org/10.3389/fnhum.2016.00269

955   Olson, D. E. (2021). The Subjective Effects of Psychedelics May Not Be Necessary for Their
956   Enduring Therapeutic Effects. *ACS Pharmacology & Translational Science*, *4*(2), 563–567.
957   https://doi.org/10.1021/acsptsci.0c00192

958   Ozenne, B., Fisher, P. M., & Budtz-Jørgensen, E. (2020). Small sample corrections for Wald tests in
959   latent variable models. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*,
960   *69*(4), 841–861. https://doi.org/10.1111/rssc.12414

961   Pahnke, W. N. (1969). The Psychedelic Mystical Experience in the Human Encounter with Death.
962   *Harvard Theological Review*, *62*(1), 1–21. https://doi.org/10.1017/S0017816000027577

963   Papanicolaou, A. C. (2021). *A Scientific Assessment of the Validity of Mystical Experiences:*
964   *Understanding Altered Psychological and Neurophysiological States*. Routledge.

965   Papaseit, E., Farré, M., Pérez-Mañá, C., Torrens, M., Ventura, M., Pujadas, M., … González, D.
966   (2018). Acute Pharmacological Effects of 2C-B in Humans: An Observational Study. *Frontiers*
967   *in Pharmacology*, *9*. https://doi.org/10.3389/fphar.2018.00206

968   Passie, T., Seifert, J., Schneider, U., & Emrich, H. M. (2002). The pharmacology of psilocybin.
969   *Addiction Biology*, *7*(4), 357–364. https://doi.org/10.1080/1355621021000005937

970   Perkins, D., Schubert, V., Simonová, H., Tófoli, L. F., Bouso, J. C., Horák, M., … Sarris, J. (2021).
971   Influence of Context and Setting on the Mental Health and Wellbeing Outcomes of Ayahuasca
972   Drinkers: Results of a Large International Survey. *Frontiers in Pharmacology*, *12*.
973   https://doi.org/10.3389/fphar.2021.623979

974   Preller, K. H., Burt, J. B., Ji, J. L., Schleifer, C. H., Adkinson, B. D., Stämpfli, P., … Anticevic, A.
975   (2018). Changes in global and thalamic brain connectivity in LSD-induced altered states of
976   consciousness are attributable to the 5-HT2A receptor. *ELife*, *7*, 1–31.
977   https://doi.org/10.7554/eLife.35082

978   Preller, K. H., & Vollenweider, F. X. (2018). Phenomenology, structure, and dynamic of psychedelic
979   states. In *Current Topics in Behavioral Neurosciences*. https://doi.org/10.1007/7854_2016_459

980   Ramos, J. (2003). Using tf-idf to determine word relevance in document queries. In *Proceedings of*
981   *the first instructional conference on machine learning* (Vol. 242, pp. 29–48). Citeseer.

982   Richards, W. A. (1975). *Counseling, peak experiences and the human encounter with death: An*
983   *empirical study of the efficacy of DPT-assisted counseling in enhancing the quality of life of*
984   *persons with terminal cancer and their closest family members*. The Catholic University of
985   America.

986   Roseman, L., Nutt, D. J., & Carhart-Harris, R. L. (2018). Quality of Acute Psychedelic Experience
987   Predicts Therapeutic Efficacy of Psilocybin for Treatment-Resistant Depression. *Frontiers in*
988   *Pharmacology*, *8*. https://doi.org/10.3389/fphar.2017.00974

989   Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., … Schmidt, B. L. (2016).
990   Rapid and sustained symptom reduction following psilocybin treatment for anxiety and
991   depression in patients with life-threatening cancer: A randomized controlled trial. *Journal of*
992   *Psychopharmacology*, *30*(12), 1165–1180. https://doi.org/10.1177/0269881116675512

993   Rucker, J., Young, A., Bird, C., Harrison, J., Marwood, L., Mistry, S., … Malievskaia, E. (2021). The
994   effects of COMP360 (psilocybin formulation) on cognitive function: Results from a randomized,
995   placebo-controlled trial in healthy participants. In *American Society of Clinical*

996   *Psychopharmacology Annual Meeting*.

997 Sanati, A. (2012). Pseudohallucinations: a critical review.

998 Sanders, J. W., & Zijlmans, J. (2021). Moving Past Mysticism in Psychedelic Science. *ACS*
999   *Pharmacology & Translational Science*, *4*(3), 1253–1255.
1000   https://doi.org/10.1021/acsptsci.1c00097

1001 Schmid, Y., & Liechti, M. E. (2018). Long-lasting subjective effects of LSD in normal subjects.
1002   *Psychopharmacology*, *235*(2), 535–545. https://doi.org/10.1007/s00213-017-4733-3

1003 Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. C.
1004   (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and
1005   validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. In *Journal*
1006   *of Clinical Psychiatry*.

1007 Shulgin, A., & Shulgin, A. (1991). *Phenethylamines I Have Known And Loved: A Chemical Love*
1008   *Story* (1st ed.). Transform Press.

1009 Shulgin, A., & Shulgin, A. (1997). *Tryptamines I Have Known And Loved: The Continuation* (1st
1010   ed.). Transform Press.

1011 Silge, J., & Robinson, D. (2016). tidytext: Text Mining and Analysis Using Tidy Data Principles in R.
1012   *The Journal of Open Source Software*, *1*(3), 37. https://doi.org/10.21105/joss.00037

1013 Stace, W. T. (1960). *Mysticism and Philosophy*. *St. Martin's Press*.

1014 Stenbæk, D. S., Madsen, M. K., Ozenne, B., Kristiansen, S., Burmester, D., Erritzoe, D., … Fisher, P.
1015   M. (2020). Brain serotonin 2A receptor binding predicts subjective temporal and mystical effects
1016   of psilocybin in healthy humans. *Journal of Psychopharmacology*, 1–10.
1017   https://doi.org/10.1177/0269881120959609

1018 Strickland, J. C., Garcia-Romeu, A., & Johnson, M. W. (2021). Set and Setting: A Randomized Study
1019   of Different Musical Genres in Supporting Psychedelic Therapy. *ACS Pharmacology &*
1020   *Translational Science*, *4*(2), 472–478. https://doi.org/10.1021/acsptsci.0c00187

1021 Studerus, E., Gamma, A., Kometer, M., & Vollenweider, F. X. (2012). Prediction of psilocybin
1022   response in healthy volunteers. *PLoS ONE*, *7*(2). https://doi.org/10.1371/journal.pone.0030800

1023 Swift, T. C., Belser, A. B., Agin-Liebes, G., Devenot, N., Terrana, S., Friedman, H. L., … Ross, S.
1024   (2017). Cancer at the Dinner Table: Experiences of Psilocybin-Assisted Psychotherapy for the
1025   Treatment of Cancer-Related Distress. *Journal of Humanistic Psychology*, *57*(5), 488–519.
1026   https://doi.org/10.1177/0022167817715966

1027 Turton, S., Nutt, D. J., & Carhart-Harris, R. L. (2014). A qualitative report on the subjective
1028   experience of intravenous psilocybin administered in an fMRI environment. *Current Drug*
1029   *Abuse Reviews*. https://doi.org/10.2174/1874473708666150107120930

1030 Vizeli, P., Straumann, I., Holze, F., Schmid, Y., Dolder, P. C., & Liechti, M. E. (2021). Genetic
1031   influence of CYP2D6 on pharmacokinetics and acute subjective effects of LSD in a pooled
1032   analysis. *Scientific Reports*, *11*(1), 10851. https://doi.org/10.1038/s41598-021-90343-y

1033 Wackermann, J., Wittmann, M., Hasler, F., & Vollenweider, F. X. (2008). Effects of varied doses of
1034   psilocybin on time interval reproduction in human subjects. *Neuroscience Letters*, *435*(1), 51–
1035   55. https://doi.org/10.1016/j.neulet.2008.02.006

1036 Watts, R., Day, C., Krzanowski, J., Nutt, D., & Carhart-Harris, R. (2017). Patients' Accounts of
1037   Increased "Connectedness" and "Acceptance" After Psilocybin for Treatment-Resistant
1038   Depression. *Journal of Humanistic Psychology*, *57*(5), 520–564.
1039   https://doi.org/10.1177/0022167817709585

1040 Yaden, D. B., & Griffiths, R. R. (2021). The Subjective Effects of Psychedelics Are Necessary for
1041   Their Enduring Therapeutic Effects. *ACS Pharmacology & Translational Science*, *4*(2), 568–
1042   572. https://doi.org/10.1021/acsptsci.0c00194

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Report	Gender	Dose (mg)	Dose (mg/kg)	Mystical Experience Questionnaire Subscale (out of 5)				Persisting Effects Questionnaire Subscale (out of 100)					
				Mystical	Positive Mood	Transcendance of Time and Space	Ineffability	Attitudes About Life (Positive)	Attitudes About Self (Positive)	Mood Changes (Positive)	Altruistic/Positive Social Effects	Behaviour Changes (Positive)	Increased Spirituality
1	Male	15	0.20	2.9	2.5	1.8	3.7	23	5	11	9	20	5
2	Male	18	0.20	1.3	2.2	2.0	4.0	22	18	20	20	40	11
3	Female	12	0.20	3.8	3.3	4.5	4.0	23	5	11	0	0	4
4	Male	18	0.20	4.7	4.8	4.5	5.0	71	69	78	64	80	70
5	Male	21	0.19	4.1	3.7	4.7	5.0	14	0	9	0	0	0
6	Female	12	0.19	3.7	3.3	4.5	5.0	42	33	33	38	60	15
7	Female	18	0.27	2.8	3.8	1.8	3.0	37	27	11	4	80	7
8	Male	18	0.25	4.3	4.0	2.7	4.3	28	18	13	0	0	9
9	Female	24	0.29	0.9	2.2	4.5	4.3	5	2	0	2	0	0
10	Male	21	0.28	4.8	4.8	4.3	5.0	46	29	31	24	40	57
11	Male	30	0.31	3.0	2.8	3.7	3.7	54	53	69	58	80	7
12	Male	24	0.30	4.9	4.7	5.0	5.0	37	22	22	18	20	30
13	Male	21	0.27	3.1	3.2	4.7	5.0	54	44	22	11	60	24
14	Female	24	0.27	4.5	4.8	4.5	4.0	77	67	60	42	80	71
15	Female	15	0.19	3.3	3.7	4.0	3.0	0	0	0	0	0	0
16	Male	18	0.23	4.5	4.3	5.0	5.0	54	27	24	20	40	56
17	Female	15	0.24	2.0	2.8	2.3	4.0	34	22	27	4	40	14
18	Male	21	0.28	5.0	5.0	5.0	5.0	86	80	69	49	80	42
19	Male	21	0.28	3.7	4.5	3.5	3.3	40	27	18	7	0	37
20	Male	21	0.28	3.7	4.0	4.3	5.0	42	16	13	4	0	9
21	Female	18	0.29	2.0	2.7	4.2	4.7	25	11	9	13	20	5
22	Female	18	0.30	3.9	3.5	4.5	3.7	9	0	2	0	0	1
23	Male	21	0.27	0.7	1.0	3.8	4.0	14	0	7	0	0	0
24	Female	18	0.30	2.4	3.2	3.5	4.0	18	16	27	0	20	6
25	Male	21	0.27	3.5	3.7	3.0	4.0	58	55	47	71	60	29
26	Female	18	0.28	3.2	3.7	4.8	4.0	29	22	22	27	20	14
27	Female	18	0.28	4.6	5.0	5.0	5.0						
28	Male	21	0.27	3.2	3.2	5.0	5.0	25	15	0	2	0	24
29	Female	18	0.31	1.7	2.5	4.2	3.7	5	0	0	4	0	0
30	Female	15	0.26	1.4	3.5	2.7	3.0	8	0	0	0	0	5
31	Male	24	0.30	4.1	4.0	4.3	4.7	31	35	16	38	20	30
32	Female	15	0.26	4.6	4.8	4.8	5.0	66	47	60	38	60	46
33	Male	21	0.27	3.7	3.5	3.7	4.0	17	11	9	7	20	10
34	Male	24	0.27	1.7	2.8	3.3	4.7	9	0	0	0	0	0
35	Male	21	0.30	2.7	3.7	3.7	3.3	60	33	40	16	40	20

Table S1 Individual MEQ and PEQ scores

Subscale Mean (SD)	All	CME	Non-CME
MEQ total	3.6 (0.9)	4.2 (0.5)	2.7 (0.6)
Mysticality	3.3 (1.2)	4.0 (0.6)	2.1 (0.9)
Positive Mood	3.6 (0.9)	4.1 (0.7)	2.8 (0.8)
Transcendence of Time and Space	3.9 (1.0)	4.5 (0.5)	3.2 (0.9)
Ineffability	4.3 (0.7)	4.5 (0.7)	3.9 (0.5)

Table S2 MEQ total and subscale scores as split by CME and non-CME

Table S3 (LVM mediation analysis results) and S4 (Complete descriptions of LVMs) are provided as standalone excel files
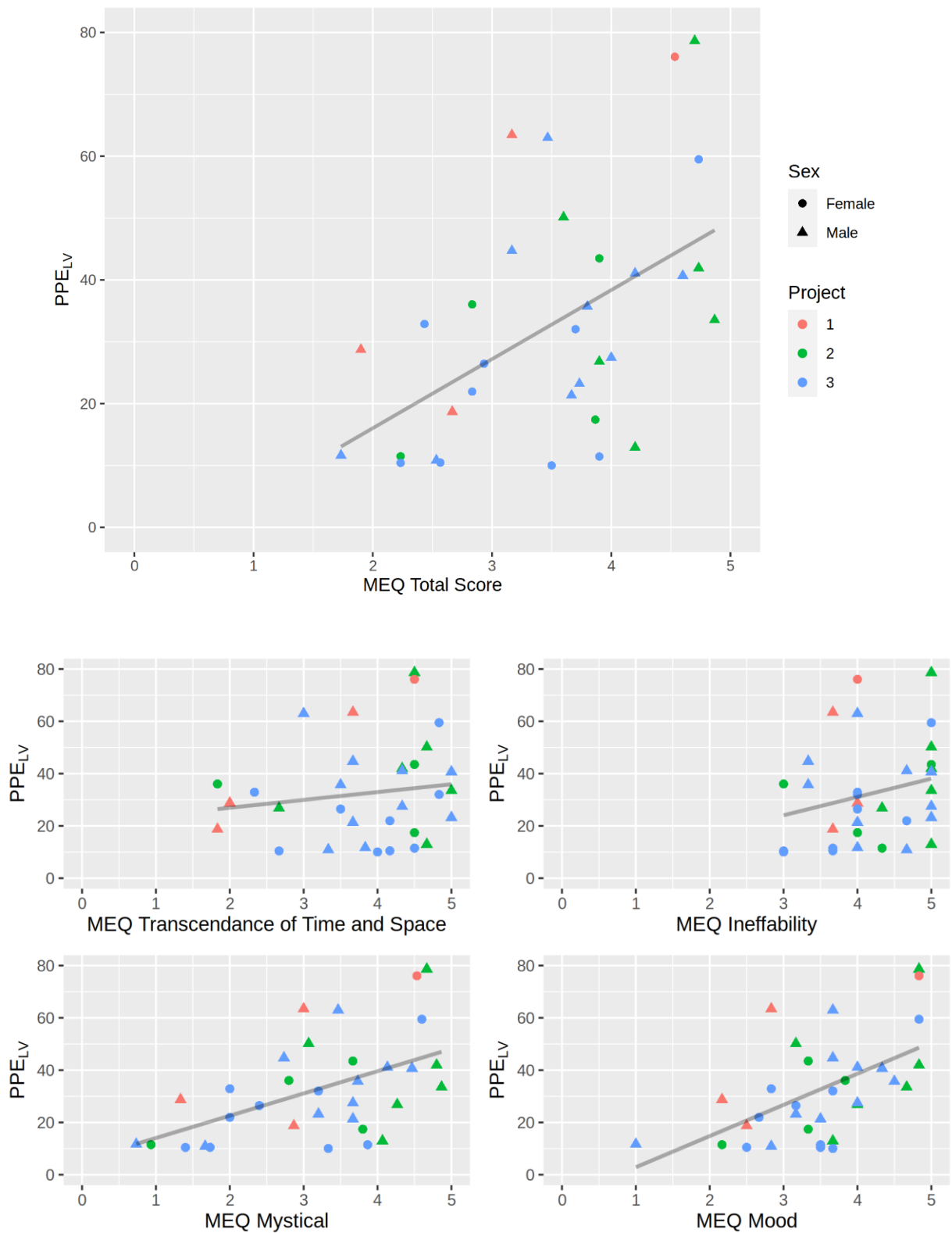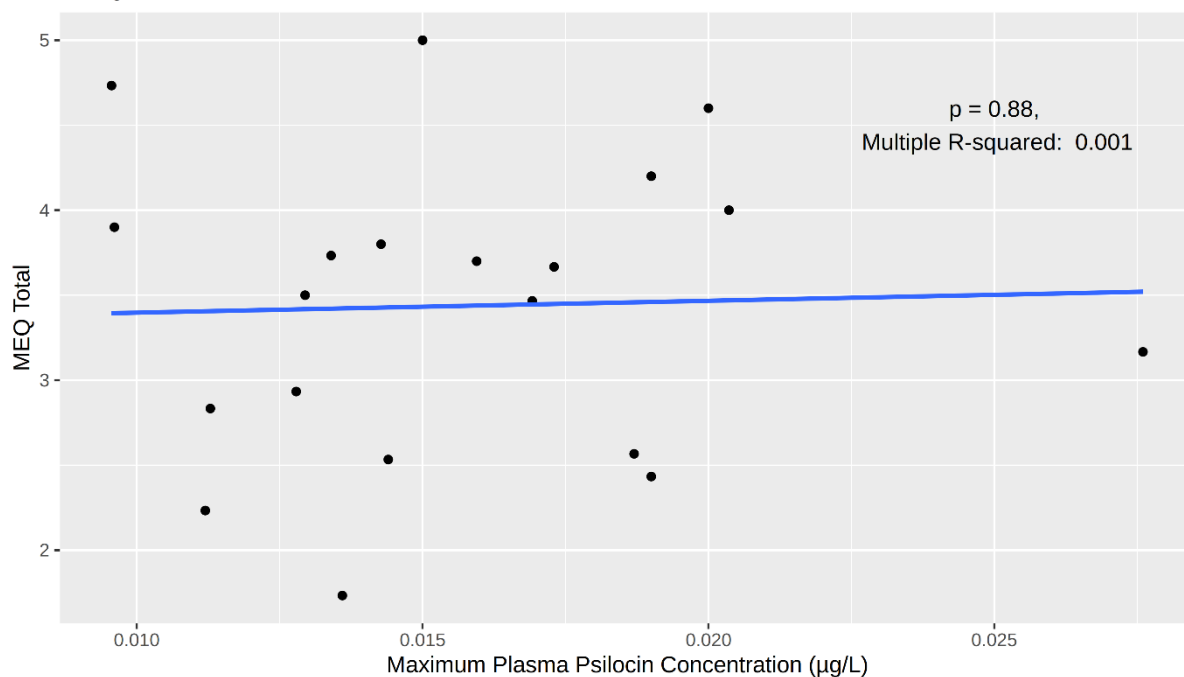
Figure S1: Scatter plots showing MEQ total score or subscale scores and PPE$_{LV}$ and a univariate linear model. Colour denotes subproject involvement and shape denotes the sex of the participant. No formal statistics were evaluated as these plots are only for visualisation purposes.

A: Relation Between Peak Plasma Psilocin Concentration and MEQ total score

B: Relation Between Peak Plasma Psilocin Concentration and Persisting Positive Effects
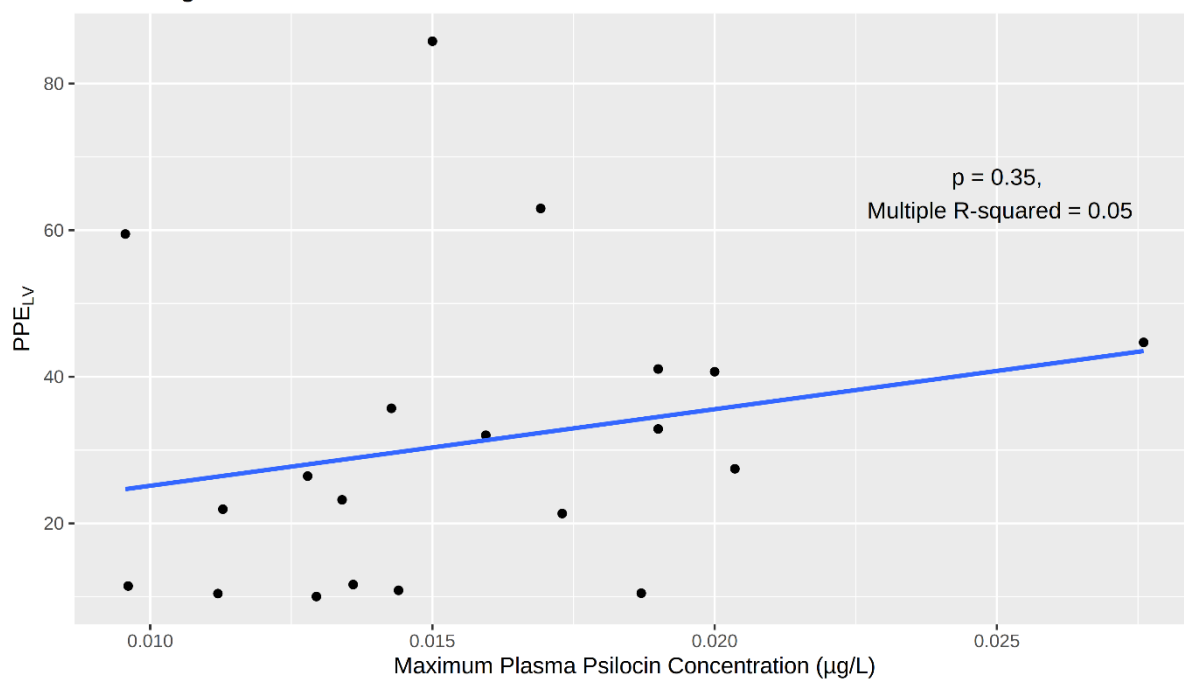
Figure S2: Scatter plots showing (A) MEQ total score or (B) PPE_{LV} and Maximum plasma psilocin concentrations for the 20 participants from project 3 with complete data. Neither association is statistically significant.