Dose-response relationships of LSD-induced subjective experiences in humans

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Abstract

Lysergic acid diethylamide (LSD) is a potent classic serotonergic psychedelic, which facilitates a variety of altered states of consciousness. Here we present the first meta-analysis establishing dose-response relationship estimates of the phenomenological states induced by LSD. Data extracted from articles identified by a systematic literature search following PRISMA guidelines were obtained from the Altered States Database. The psychometric data comprised ratings of subjective effects from standardized and validated questionnaires: the Altered States of Consciousness Rating Scale (5D-ASC, 11-ASC) and the Mystical Experience Questionnaire (MEQ30). We used a meta-regression approach to obtain estimates for linear dose-response relationships of questionnaire ratings after LSD administration to healthy, highly selected study participants in controlled settings for a dosage range between 25 µg and 200 µg. LSD doses positively correlated with ratings on most factors and scales of the questionnaires, with strongest responses for visionary phenomena such as audio-visual synesthesia and altered imagery, followed by positively perceived ego dissolution comprising depersonalization and derealization phenomena. Measures referring to mystical experiences exhibited weak modulations by dose. The established dose-response relationships in the given range may be used as general references for future experimental and clinical research on LSD with low to moderate dosages to relate observed with expected subjective effects and to elucidate phenomenological differences between psychedelics.

Introduction

D-lysergic acid diethylamide (LSD) is the prototype of classic serotonergic psychedelics, a group of substances which unfold their psychoactive properties predominantly via the serotonin 2A (5-HT_{2A}) receptor [1]. Psychedelics embrace structurally heterogenous subgroups like phenethylamines (e.g., mescaline) and tryptamines (e.g., psilocybin, *N,N*-dimethyltryptamine (*N,N*-DMT)) [2], as well as substances from the ergoline subgroup (e.g., LSD and lysergic amide (LSA)) which have been characterized as “rigidified tryptamines” [3]. The term ‘psychedelics’ is also used in a broader sense, including non-serotonergic drugs like Ketamine, PCP or MDMA. The term ‘psychedelic experience’ is used in an even broader sense, not limited to the effects induced by specific substances, instead referring to a group of psychological effects. However, there is no clear definition on the exact set of consciousness alterations that define a psychedelic experience. Here, we will refer to classic serotonergic psychedelics and the effects they induce when using the term ‘psychedelics’ or ‘psychedelic experience’. Several studies suggest that qualitatively, LSD might not be differentiated from other psychedelics with regard to the induced psychologic effects [4–6]. On the other hand, anecdotal reports mention differences in subjective experiences regarding different substances [7], and LSD somewhat differs from pharmacodynamical profiles of other 5-HT_{2A} agonists, including a broader variety of receptor targets [3].

After its initial synthesis in 1938, LSD’s psychedelic properties have accidentally been discovered in 1943 by the Swiss pharmacologist Albert Hofmann [8]. Ever since, LSD has been the most extensively investigated psychedelic from the 1950s to the 1970s, with more than 1,000 scientific papers published in the context of basic science, as well as in clinical research as a therapeutic tool [9–11]. Most intensively studied indications included, among others, alcoholism [12] and existential distress in life-threatening physical illness [13].

After a hiatus of more than 20 years, during which regulatory hurdles prevented research on psychedelics, research eventually resumed in the 1990s, with a focus shifting from LSD to other substances like psilocybin [1] and *N,N*-dimethyltryptamine (*N,N*-DMT) [14]. This shift might have taken place due to political aspects given a somewhat notorious image of LSD [15], as well as pragmatic considerations, as

psychoactive effects of LSD display longer duration than the latter substances [3]. In recreational underground use, however, LSD is still by far the most frequently used psychedelic worldwide [16], and dosages of psychedelics are often compared to LSD equivalents by users.

LSD has recently been re-evaluated for the treatment of different mental health conditions, like anxiety and depression in patients with [17,18] and without life-threatening illness [17]. Psychological effects of psychedelics underlie specific temporal dynamics [9], including (acute) psychedelic experiences, subacute effects ("afterglow phenomena" or "carry-over effects") and long-term (enduring) effects [19]. There is some evidence that the quality and intensity of acute psychedelic effects might predict therapeutic outcome [20]. Thus, the classification and description of acute psychedelic experiences appear to be of high importance when it comes to optimizing treatment interventions regarding efficacy and safety. In order to determine the optimal dosing ranges of LSD for future clinical studies, first and most importantly the influence of the LSD dosage on the nature and intensity of acute subjective effects needs characterization. Of note, the range of LSD dosages employed in current research is on average markedly below the dosages administered in studies from the 1950-1970s, where sometimes dosages of 1,000 ug and more have been administered [12].

Only few studies to date have investigated the dose dependency of altered states induced by LSD [21–23] or have compared therapeutic effects in different dosages of psychedelics (e.g. [24]). As LSD has only recently returned to basic and clinical research, only few studies have been carried out according to modern research standards, while the studies from the 1950s to the 1970s exhibit strong methodological limitations and do not appear suited for study overarching comparisons. Over the last decades some gold standards for the assessment of altered states phenomena have been established in terms of several well-validated questionnaires for an retrospective assessment of altered experiences [9,25–27]. Such standardized assessment allows meta-analytic comparisons, as recently presented to establish dose-response relationships for altered experiences induced by psilocybin [26]. To date there is no meta-analysis available investigating dose-response relationships for the subjective experiences of LSD.

With the present meta-analysis, we aim to obtain estimates of the relationship between LSD dosages and the intensity and quality of psychedelic experiences in healthy

subjects. The data stem from the Altered States Database (ASDB, *http://alteredstatesdb.org*, [28]), which is a regularly updated database with questionnaire data extracted from articles identified by systematic literature research, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement Guidelines [29]. Available data was found for the Altered States of Consciousness Rating Scale (5D-ASC, 11-ASC) and the Mystical Experience Questionnaire (MEQ30), as well as for a dosage range of 25 ug to 200 ug.

Methods

Included data

Psychometric questionnaire data on the subjective experience of LSD were included in this meta-analysis. The data has been retrieved from the ASDB repository on Open Science Framework (OSF; *https://osf.io/8mbru*, version: "ASDB-v2.0_12-2021"), which contains data from MEDLINE-listed studies published from 1975 until 2021-12-31. The ASDB data is based on a systematic literature review following PRISMA standards [29] as described in Prugger et al. (2022). Here, only datasets investigating the subjective effects of LSD were retrieved. To include most recent data, the described literature review was extended to contain data published until 2022-06-31. Further information on the search strategy and the PRISMA flowchart showing the process of item identification and screening can be found in Supplementary Material.

Data were excluded if experimental conditions comprised applications of combinations of substances [21,30,31] such as pre-treatments with ketanserin; if the application of LSD was reported as microdosing (< 25 µg) [22,32–36], if the LSD dosage was unclear [37], and if data were about recreational LSD usage [38]. Two studies [39,40] have been excluded as they reported on previously published data [30,41]. From studies reporting multiple questionnaire applications at different time points during the same day of the experimental session [34,40], only the final and complete questionnaire application was included describing the overall experience. In addition, unpublished original data were obtained from the authors [35] of ratings on the 11-ASC dimensions *Changed Meaning of Percepts* and *Elementary Imagery* which were not reported in the original publication. Also, after consultation with the authors, the LSD dose in a series of reports [23,30,31,34,42] were adjusted as suggested in [21,43], due to administration of capsules containing an unstable LSD formulation leading to dispersion of lower than presumed LSD doses.

Additionally, one dataset reporting on LSD application in a population of patients with anxiety associated with life-threatening diseases (N = 11, MEQ30, 140 µg) [34] was found, however not included in the analysis.

Questionnaires

This meta-analysis included psychometric data from commonly applied questionnaires to assess the phenomenology of altered states of consciousness, namely from two

versions of the Altered States of Consciousness Rating Scale (the 5D-ASC and the 11-ASC), and from the Mystical Experience Questionnaire (MEQ30).

The Altered States of Consciousness Rating Scale [44–46] is a self-report questionnaire with 94 items rated on a visual analog scale. Two different analysis schemata are in use: In the 5D-ASC version ("5-Dimensional Altered States of Consciousness Rating Scale" [47,48]), items are assigned to five core dimensions: (1) *Auditory Alterations*, (2) *Dread of Ego Dissolution*, (3) *Oceanic Boundlessness*, (4) *Visionary Restructuralization*, and (5) *Vigilance Reduction*. In the more recent 11-ASC version ("11-factor Altered States of Consciousness Rating Scale" [49]) only 42 of the 94 questionnaires items are used in the analysis, where item scores are summarized along 11 factors: (1) *Experience of Unity*, (2) *Spiritual Experience*, (3) *Blissful State*, (4) *Insightfulness*, (5) *Disembodiment*, (6) *Impaired Control and Cognition*, (7) *Anxiety*, (8) *Complex Imagery*, (9) *Elementary Imagery*, (10) *Audio-Visual Synesthesia*, and (11) *Changed Meaning of Percepts*. Both analysis schemes have been validated and demonstrate good reliability (5D-ASC: Hoyt 0.88–0.95 [48,50]); 11-ASC: mean Cronbach's alpha of 0.83 [49]).

The Mystical Experience Questionnaire, in its latest version the MEQ30 [51], consists of 30 items assigned to four scales: (1) *Mystical*, (2) *Positive Mood*, (3) *Transcendence of time and space*, and (4) *Ineffability*. This factor structure is currently recommended for analyses and has been assessed for reliability, yielding very good scores for all four subscales (Cronbach's alpha: 0.80 to 0.95) [52,53].

A more detailed description of the questionnaires can be found in Schmidt and Majić [25], Majić et al. (2015) [9] and in a recent review by de Deus Pontual et al. (2022) [27].

Statistical analyses

The statistical analyses were conducted as previously applied in Hirschfeld and Schmidt (2021) [26]: Due to a lack of data for minimum and maximum doses, a linear meta-regression for each factor and scale of the respective questionnaires was performed to approximate the dynamic range of a dose-response relationship, which is usually best described by a sigmoid function. Intercept and slope parameters were obtained with a random effects model to address between-study variance. To account for statistical dependencies resulting from within-subject designs with repeated measures, the robust variance estimation (RVE) framework [54] with small sample adjustment [55] was used. The RVE framework permits the inclusion of multiple effect size estimates from a study without the knowledge of the underlying covariance

structure by assuming a common correlation p (0-1) between within-study effect sizes (p= .8 was used as the recommended default value [56]). To test whether the choice of p affected the obtained parameter estimates, a sensitivity analysis was performed. The weights were calculated using the correlated effects model with the inverse of the sampling variance in combination with a method of moments estimator [54]. Heterogeneity was assessed by estimating the degree of inconsistency across studies using I^2 [57,58] and the between-study variance with Tau^2 [59]. Analyses were performed using the robumeta package [60] in R version 4.2.1 [61]. To provide an overview of results, radar charts for each questionnaire were computed using the fmsb package [62]. Additionally, for each scale dose-response relationships were computed using the plot function in R version 4.2.1 [61].The individual effect sizes are shown as circles corresponding to the magnitude of the calculated weight of a study sample. All syntax is provided on Github (*https://github.com/TimHirschfeld/doseresponse_LSD*).

Results

Data description

Eleven studies from the ASDB were included in the analysis. The additional literature search identified three studies. Thus, a total of 14 studies in healthy participants (overall N = 322) were included (See Table 1) comprising 13 datasets, or questionnaire applications, from seven samples of participants for the 5D-ASC; 18 datasets from 11 samples for the 11-ASC (except for the scales *Spiritual Experience*, *Blissful State*, *Disembodiment*, *Elementary Imagery*, and *Changed Meaning of Percepts* with 19 datasets from 12 samples); and 12 datasets from 6 samples for the MEQ30.

Table 1. Summary of studies included in the meta-regression analysis.

Table 1 displays the studies included in the meta-regression analysis, with sample size of study participants, study description (study design, additional conditions, physiological assessment and additional measurements), questionnaire used to report data, and LSD administration method. Several studies contain multiple observations (e.g., from repeated measurements).
ECG: electrocardiogram; EEG: electroencephalogram; fMRI: functional magnetic resonance imaging; MDMA: 3,4-methylenedioxy-methamphetamine; MEG: Magnetoencephalography

Study	Sample size	Study description	Data report	LSD administration
Müller et al., 2017[42]	*N* = 20	- double-blind, placebo-controlled, randomized, cross-over - plasma LSD levels, fMRI (resting state)	5D-ASC	Oral administration, Dosage: (1) 70 µg
Schmid et al., 2015[23]	*N* = 16	- double-blind, placebo-controlled, randomized, cross-over - blood pressure, heart rate, psychomotor performance, further questionnaire assessment	5D-ASC, 11-ASC	Oral administration, Dosage: (1) 70 µg
Liechti et al., 2017[34]	*N* = 24	- double-blind, placebo-controlled, cross-over - plasma LSD levels, further questionnaire assessment	5D-ASC, 11-ASC	Oral administration, Dosage: (1) 70 µg
	N = 16		MEQ30	Oral administration, Dosage: (1) 140 µg
Holze et al., 2020[70]	*N* = 28	- double-blind, placebo-controlled, cross-over, double-dummy - additional conditions: 125 mg MDMA, 40 mg d-amphetamine - blood pressure, heart rate, plasma LSD levels, fMRI (will be published elsewhere), further questionnaire assessment	5D-ASC, 11-ASC, MEQ30	Oral administration, Dosage: (1) 100 µg
Holze et al., 2021[21]	*N* = 16	- double-blind, placebo-controlled, cross-over - additional condition: 200 µg LSD 1 h after 40 mg ketanserin administration - blood pressure, heart rate, plasma LSD levels, further questionnaire assessment	5D-ASC, 11-ASC, MEQ30	Oral administration, Dosage: (1) 25 µg (2) 50 µg (3) 100 µg (4) 200 µg
Holze et al., 2022[5]	*N* = 28	- double-blind, placebo-controlled, cross-over - additional conditions: 15 mg psilocybin, 30 mg psilocybin - blood pressure, heart rate, plasma LSD levels, further questionnaire assessment	5D-ASC, 11-ASC, MEQ30	Oral administration, Dosage: (1) 100 µg (2) 200 µg
Family et al., 2022[63]	(1) *N* = 12 (2) *N* = 7 (3) *N* = 3	- phase 1 proof-of-concept, single-center (part 1: open-label dose-escalation study in psychedelic non-naïve participants; part 2: double-blind, placebo-controlled, randomized study in psychedelic naïve participants) - additional conditions: placebo followed by 75 µg LSD, 50 µg LSD followed by 75 µg LSD - blood pressure, pulse rate, plasma LSD levels, ECG, further questionnaire assessment	5D-ASC, MEQ30	Oral administration, Dosage: (1) 50 µg (2) 75 µg (3) 100 µg
Carhart-Harris et al., 2016[41] (subsample: Carhart-Harris et al., 2016[39])	*N* = 20	- placebo-controlled, cross-over, within-subject, balanced-order, double-dummy - fMRI and MEG (data published in other study [39]), further questionnaire assessment	11-ASC	Intravenous administration, Dosage: (1) 75 µg

Kraehenmann et al., 2017[31]	*N* = 25	- double-blind, placebo-controlled, cross-over, within-subject - additional condition: 40 mg ketanserin + 100 µg LSD - mental imagery task, primary and secondary process thinking	11-ASC	Oral administration, Dosage: (1) 70 µg
Preller et al., 2017[30] (same sample: Preller et al., 2018[40])	*N* = 22	- double-blind, placebo-controlled, randomized, cross-over - additional condition: 100 µg LSD after 40 mg ketanserin - fMRI (music paradigm)	11-ASC	Oral administration, Dosage: (1) 70 µg
Bershad et al., 2019[36]	*N* = 20	- double-blind, placebo-controlled, within-subject - additional conditions: 6.5 µg LSD, 13 µg LSD - heart rate, blood pressure, dual *n*-back task, digit symbol substitution task, cyberball task, emotional images task, remote associations task, further questionnaire assessment	11-ASC	Sublingual administration, Dosage: (1) 26 µg
Murray et al., 2021[35]	*N* = 22	- double-blind, placebo-controlled, within-subject - additional condition: 13 µg LSD - blood pressure, heart rate, EEG (broadband oscillatory power during resting state, event-related potentials during oddball task), further questionnaire assessment	11-ASC	Oral administration, Dosage: (1) 26 µg
de Wit et al., 2022[68]	*N* = 19	- double-blind, placebo-controlled, randomized - additional condition: 13 µg LSD - blood pressure, heart rate, digital symbol substitution task, *n*-back task, cyberball task, emotional images task, emotional faces task, further questionnaire assessment	11-ASC	Sublingual administration, Dosage: (1) 26 µg (2) 26 µg (3) 26 µg (4) 26 µg
Wießner et al., 2021[72]	*N* = 24	- double-blind, placebo-controlled, randomized, cross-over - further questionnaire assessment	11-ASC, MEQ30	Oral administration, Dosage: (1) 50 µg

Dose-response relationship

Regression coefficients for the dose-response analyses and heterogeneity parameters are summarized in Table 2.

Table 2. Meta-regression estimates for all included questionnaires with respective factors/dimensions/subscales.

Coefficients (Coeff.) are presented with 95% confidence intervals (CIs) and standard errors (SE). The t-test statistic determines whether a linear relationship exists under the null hypothesis that the slope is equal to zero. Tau² indicates the between-study variance and I² indicates the degree of inconsistency across studies in percent. Intercept estimates are rounded to the first decimal. Slope estimates are rounded to the third decimal considering its greater sensitivity to increasing dose.

Outcome	Intercept			Slope						
	Coeff.	(95% CI)	SE	Coeff.	(95% CI)	SE	*t* (df)	*p*	*Tau²*	*I²*
5D-ASC										
Auditory Alterations	13.8	(-7.5–35.1)	6.92	0.009	(-0.153–0.171)	0.0455	0.2 (2.5)	.858	27.2	73.3
Oceanic Boundlessness	31.2	(3.6–58.8)	9.66	0.103	(-0.149–0.354)	0.0736	1.4 (2.7)	.267	154.5	87.4
Dread of Ego Dissolution	14.5	(-6.8–35.8)	7.05	0.063	(-0.109–0.235)	0.0459	1.4 (2.3)	.285	63.1	79.8
Vigilance Reduction	31.4	(3.5–59.3)	9.69	0.035	(-0.176–0.246)	0.0609	0.6 (2.6)	.612	97.1	86.8
Visionary Restructuralization	33.0	(2.7–63.3)	10.59	0.148	(-0.143–0.439)	0.0864	1.7 (2.7)	.195	127.6	85.1
11-ASC										
Anxiety	0.9	(-3.4–5.2)	1.49	0.087	(0.007–0.166)	0.0252	3.4 (3.1)	.040	2.3	18.5
Audio-Visual Synesthesia	2.4	(-24.7–29.5)	10.68	0.504	(0.112–0.897)	0.143	3.5 (4.1)	.023	129.1	90.3
Blissful State	16.6	(-2.4–35.7)	7.98	0.233	(-0.033–0.499)	0.0959	2.4 (4.0)	.072	145.4	75.0
Changed Meaning of Percepts	11.0	(-4.3–26.3)	6.25	0.253	(-0.031–0.536)	0.1020	2.5 (4.0)	.069	110.4	79.1

Complex Imagery	17.8	(-11.4–47.0)	11.95	0.306	(0.006–0.607)	0.1090	2.8 (4.1)	.047	325.9	87.9
Disembodiment	13.0	(-6.1–32.0)	7.89	0.222	(-0.016–0.459)	0.0864	2.6 (4.1)	.061	225.5	84.5
Elementary Imagery	15.8	(-14.2–45.8)	12.43	0.398	(0.039–0.757)	0.1310	3.0 (4.2)	.037	384.5	91.7
Experience of Unity	12.3	(-5.6–30.2)	7.30	0.248	(0.043–0.454)	0.0750	3.3 (4.1)	.028	147.7	78.1
Impaired Control & Cognition	7.4	(-4.1–19.0)	4.68	0.198	(0.028–0.368)	0.0610	3.2 (4.0)	.032	90.1	81.2
Insightfulness	14.6	(-6.3–35.5)	8.61	0.174	(-0.025–0.372)	0.0717	2.4 (4.0)	.072	160.2	81.1
Spiritual Experience	7.6	(-1.7–16.9)	3.77	0.128	(0.016–0.239)	0.0389	3.3 (3.7)	.034	38.8	60.9
MEQ30										
Ineffability	50.7	(6.7–94.7)	13.90	0.196	(-0.135–0.528)	0.1000	2.0 (2.8)	.151	127.9	79.0
Mystical	28.1	(-19.7–75.9)	12.46	0.059	(-0.245–0.362)	0.0778	0.8 (2.2)	.522	73.8	52.9
Positive Mood	46.2	(9.0–83.4)	11.49	0.057	(-0.210–0.325)	0.0819	0.7 (2.9)	.537	155.8	82.1
Transcendence of Time & Space	32.3	(-5.2–69.8)	11.49	0.188	(-0.090–0.466)	0.0839	2.2 (2.8)	.117	183.0	82.7

Ratings on all factors and scales of the included questionnaires positively correlated with the LSD dose. Radar charts for each questionnaire and the dose-response relationships for each factor and scale of the respective questionnaires are presented in Figure 1 (5D-ASC and 11-ASC) and Figure 2 (MEQ30).

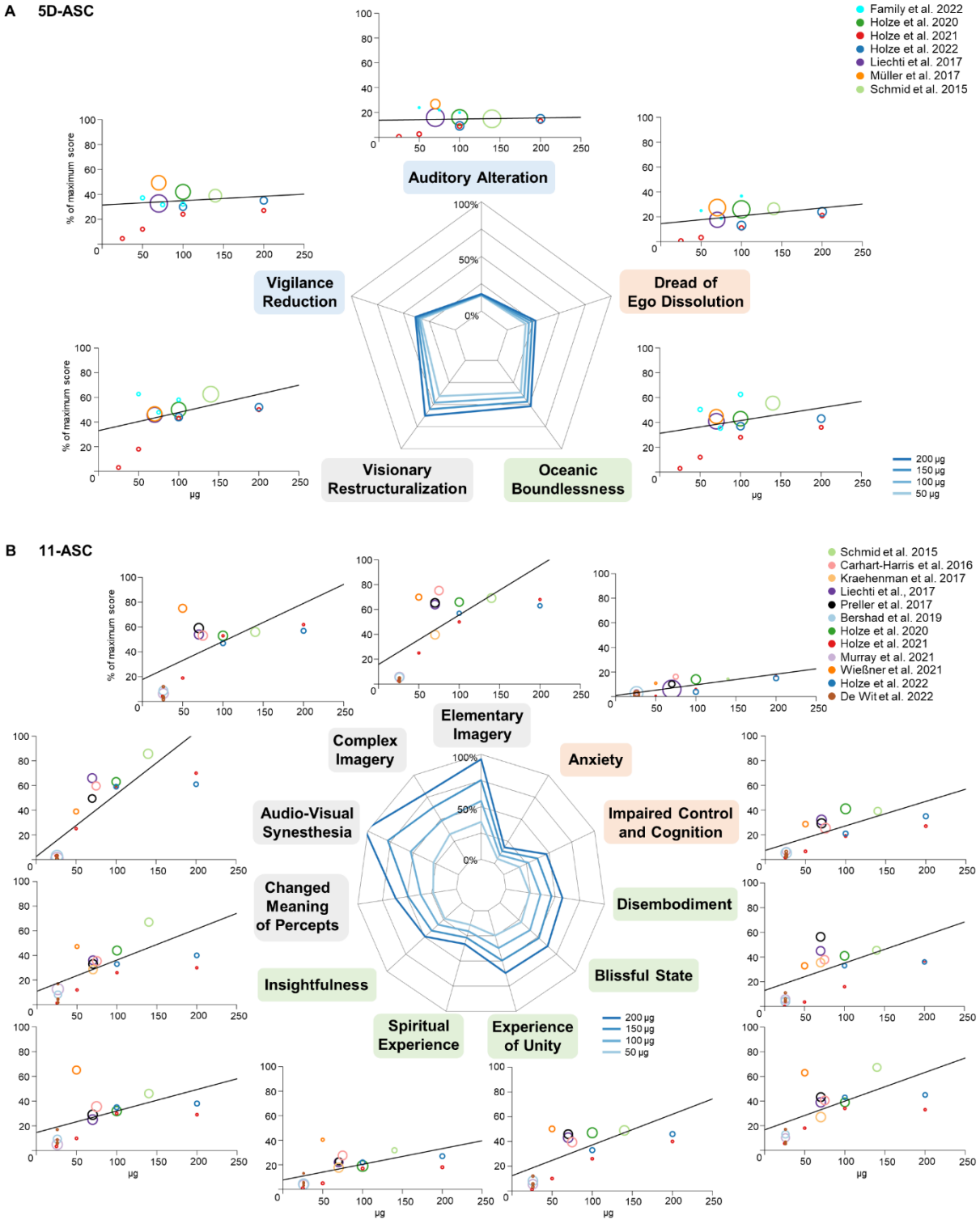

Figure 1. Dose-response relationships for the Altered States of Consciousness Rating Scale.

A Dose-specific subjective effects of LSD measured with the Altered States of Consciousness Rating Scale, where questionnaire items are organized into five factors, called 'dimensions' of ASC experiences (5D-ASC). **B** A finer-grained quantification of specific aspects of subjective experiences is obtained when the questionnaire is analyzed according to the 11-factors schema. These 11 factors can be considered subscales of the three core dimensions of the 5D-ASC (see corresponding colors of the subscale names). Doses are given in microgram, as absolute dosages not normalized to body weight; effects are given as the percentage score of the maximum score on each factor (questionnaire items were anchored with 0% for 'No, not more than usual' and 100% for 'Yes, much more than usual'). Circle color indicates from which article the data was obtained, where the same color of two circles corresponds to statistically dependent data; circle size represents the weight of the data based on study variance

(see Methods). Radar charts present the estimated dose-responses for 50-200 µg, corresponding to the range of doses that were included in the respective analyses. The color of individual scales corresponds to the primary dimensions and the respective subscales.

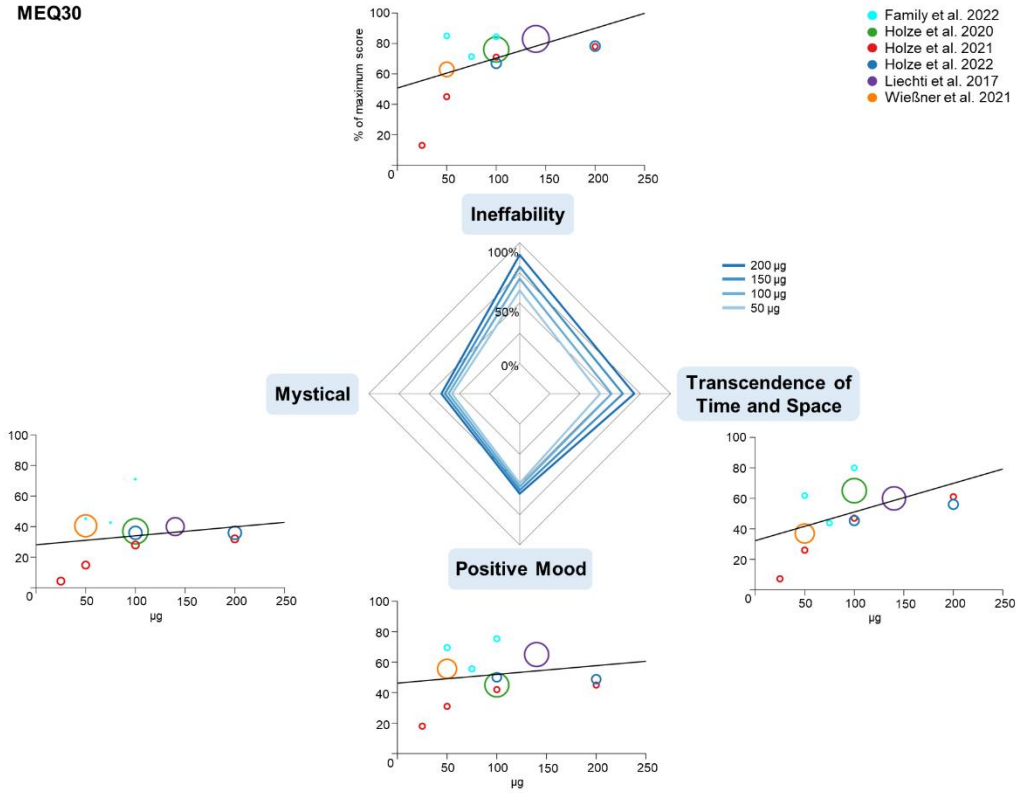

Figure 2. Dose-response relationships for the MEQ30.

Dose-specific subjective effects of LSD measured with the Mystical Experience Questionnaire (MEQ30). Absolute doses are given in microgram. Effects on the MEQ30 are presented as the percentage score of the maximum score. Circle color indicates from which article the data was obtained, where the same color of two circles corresponds to statistically dependent data; circle size represents the weight of the data based on study variance (see Methods). Radar charts present the estimated dose-responses for 50-200 µg, corresponding to the range of doses that were included in the respective analyses.

Sensitivity analyses

To test the robustness of the estimated RVE parameters (intercept and slope), different values of p (0-1) were examined. Across all analyses, intercept parameters differed only in the range of 0 to 0.09, and slope parameters differed only in the range of 0 to 0.0005. Therefore, in line with Tipton (2015) [55], the sensitivity analyses produced robust effect size estimates for different values of p.

Discussion

A meta-analysis on psychometric data was performed to estimate dose-response relationships of subjective effects of LSD. The analyses revealed positive correlations of effects and doses for most factors and scales of the 5D-ASC, the 11-ASC, and the MEQ30.

On the 5D-ASC, our results indicate strongly experienced *Visionary Restructuralization* (visual hallucinations, synesthesia, altered perception, or facilitated imagination) and *Oceanic Boundlessness* (depersonalization and derealization phenomena associated with positive emotional states or euphoria), whereas *Vigilance Reduction* and *Auditory Alterations* and interestingly also *Dread of Ego Dissolution* (anxiety and fearful delusions, arising from ego-disintegration, loss of self-control, and thought disorder) exhibited generally small effect sizes. Correspondingly, the analysis of the 11-ASC subscales revealed strongest dose-responses for *Audio-Visual Synesthesia*, *Elementary Imagery*, and *Complex Imagery*, accompanied by relatively strong modulation for *Changed Meaning of Percepts*, *Experience of Unity*, *Blissful State*, and *Disembodiment*, whereas ratings for *Anxiety* were low.

With regards to mystical-type experiences, we found that the MEQ30 scales, *Ineffability* and *Transcendence of Time and Space* show strong modulations by dose, whereas *Positive Mood*, and specifically the *Mystical* scale showed comparably smaller effect sizes and weak dose-modulation. Barrett et al. (2015) have suggested that full mystical experiences are reached with scores of ≥60% on each of the four factors of the questionnaire [53]. According to the obtained results, such experiences are not likely to occur with LSD applications at doses up to 200 µg, as the maximum reached score on the factor *Mystical* is around 40% with 200 µg. Similar findings of rarely occurring full mystical experiences at LSD doses of 200 µg were previously reported by Liechti et al. (2017), who noted that the subjective effects of LSD may not be primarily characterized by mystical and spiritual experiences, with the possible explanation that these findings are highly depend on the set and setting used in the study [34]. In contrast, the study by Family et al. (2022) suggests that doses as low as 50 µg may already evoke full mystical-type experiences in certain individuals, depending on the set and setting [63]. Taken together, mystical-type experiences may be less predicted by LSD dose than by extra-pharmacological factors.

Influences on subjective experiences

Not only the LSD dose (*substance*), but also the environment of substance administration (*setting*) as well as each substance user's personality and the preparation, expectation and intention of substance use (*set*) are essential factors in shaping the subjective experience induced by psychedelics [64,65] and can lead to considerable inter- and intra-individual variability [66,67]. The experimental settings of the included studies are highly different. Bershad et al. (2019) reports of "living-room style" environments with possibilities to relax, read or watch movies between measurements [36], similar to Kraehenmann et al. (2017) ("in an esthetic living-room-like room") [31] and de Wit et al. (2022) [68]. In other studies, however, participants were also given tasks during LSD applications that involved greater effort, potentially inhibiting the manifestation of effects [69]. Previous work indicated that spatially constrained neuroimaging procedures may be demanding for some individuals and could increase the likelihood of challenging experiences [19]. Carhart-Harris et al. (2016) reported on fMRI and MEG measurements of over 60 min each, as well as previous MRI environment habituation and a subsequent battery of cognitive and behavioral tests [41]. From the studies included, also Holze et al. (2020) [70] and Müller et al. (2017) [42] reported of fMRI measurements during the experimental session. In contrast, Schmid et al. (2015) [23], Liechti et al. (2017) [34], Holze et al. (2021 [21], 2022 [5]) reported on "quiet standard hospital patient room" environments, and the study procedure by Family et al. (2022) [63] included a 60-minutes breathing exercise. Additional factors influencing the psychedelic experience and thereby increasing the variability within and between the given datasets may involve subject's age, previous experience with psychedelics or other mind-altering substances, as well as differences in individual pharmacokinetics [71]. The study by Family et al. (2022) for instance reports of applications of 50 µg LSD to predominantly (9 of 12) psychedelic-naïve participants, and 75 and 100 µg LSD to psychedelic-non-naïve participants, resulting in higher questionnaire ratings on all factors of the 5D-ASC and MEQ30 in the 50 µg cohort compared to the 75 µg cohort, and higher ratings on most factors in the 50 µg cohort compared to the 100 µg cohort [63]. A similar case is demonstrated in the study by Wießner et al. (2021) with relatively high 5D-ASC scores, especially for the factors *Insightfulness*, *Spiritual Experience*, *Blissful State*, and *Complex Imaginary*, compared to other study results investigating the same LSD dose [72]. This may be due to relatively high lifetime use of other psychedelics or mind-altering substances among

study participants (particularly ayahuasca, with a mean lifetime use of 69 ± 131 S.D.), as well as the fact that most participants (67%) considered themselves spiritual. In summary, *set* and *setting* also influence the effects of LSD but could not be considered in this dose-response relationship estimation.

Comparison with previous dose-response reports

Only few dose-response reports are available to date. A within-subjects design study by Holze et al. (2021) reported on the effects of LSD at doses of 25 µg, 50 µg, 100 µg, and 200 µg and found a potential ceiling effect at LSD doses of > 100 µg with regard to its positive subjective effects [21]. The here presented meta-analysis is not appropriate for examining the ceiling effects mentioned, as included LSD doses did not cover the upper and lower bounds sufficiently to estimate a sigmoid curve. However, as reflected in our analysis, Holze et al. (2021) reported that the 200 µg dose led to significantly greater *Dread of Ego Dissolution* and *Anxiety*, as well as higher ratings of *Blissful State*, *Insightfulness*, and *Changed Meaning of Percepts* compared to the 100 µg dose. They suggest that doses > 100 µg can be used to elicit experiences of ego dissolution or disembodiment, and that doses < 100 µg may be useful to elicit a moderately intense and predominantly positive psychedelic experience [21]. A dose-escalation study by Family et al. (2022) evaluated safety, tolerability, and pharmacokinetics of LSD doses of 50 µg, 75 µg, and 100 µg and reports on a higher percentage of participants meeting criteria for a full mystical experience after 50 µg (25%) and 100µg (33.3%) of LSD [63], in contrast to the results of this meta-analysis. In summary, the results of the few dose-response reports available to date are largely consistent with those presented here.

Comparison to dose-response relationships of psilocybin-induced subjective experiences

Psilocybin and LSD are both classic psychedelics primarily targeting the 5-HT_{2A} receptor neurotransmission, so it is thought that they share typical psychedelic effects [39,63–66]. The meta-analysis presented here yielded an overall relatively similar pattern of response to those of the psilocybin meta-analysis [26]. The strongest dose-responses were found for the scales *Visionary Restructuralization* and *Oceanic Boundlessness* in both the LSD and psilocybin analyses. Noteworthy are the less pronounced LSD modulations for *Spiritual Experience* on the 11-ASC and *Mystical* on the MEQ30, contrasting findings by Holze et al. 2022 [5] and a survey of subjective

God encounter experiences by Griffiths et al. 2019 [38]. As discussed above, such experiences seem to be particularly influenced by set and setting and warrant further research. Interestingly, our findings seem to indicate that LSD is more prone to evoke *Audio-Visual Synesthesia* compared to psilocybin, supporting previous reports that LSD is highly effective in inducing synesthesia [73,74]. In a survey among recreational psychedelic users, the highest incidence rate of drug-induced synesthesia was reported for LSD [75] and a study comparing the effects of LSD (1 µg/kg) and psilocybin (150 µg/kg) also found significantly more synesthesia in the LSD group [4]. Considering that LSD not only interacts with serotonin receptors, but also with dopaminergic and adrenergic receptors [76,77], our results could be interpreted in line with evidence that drug-induced synesthesia is not exclusively a result of serotonergic activation [75]. LSD's pronounced modulation of *Audio-Visual Synesthesia* via non-5-HT_{2A} mechanism of action may be associated with the etiology of the rarely occurring hallucinogen-persistent perception disorder (HPPD). The vast majority of case reports on HPPD have been associated with LSD, even if it has to be taken into account that LSD is also the most frequently used psychedelic worldwide [16,78–81]. Generally, observed differences between LSD and psilocybin could either be attributed to extra-pharmacological factors such as set and setting or pharmacological differences resulting from molecular structures with different profiles of receptor activity, durations of action, and potentially different functional selectivity and potency [38,84].

Limitations

The estimation of dose-response relationships of subjective LSD experiences is associated with different challenges. First, the assessment of subjective experiences always faces problems associated with the quantification of personal and private inner states, relying on self-reporting. This makes its assessment more difficult than that of other physiological parameters [9]. The unexplained variance in subjective responses was relatively large, so that the influences of set and setting should be considered when interpreting or applying the results of this analysis. A more standardized assessment of factors other than substance dose could improve comparability of future studies. Also, the generalizability of the results presented here is limited due to the small number of studies available and the results obtained do not necessarily apply to the general population or to recreational use outside controlled laboratory experiments. Moreover, although RVE allows the inclusion of statistically dependent effect sizes

(due to repeated measures) to obtain reliable meta-regression estimates, it is not designed to provide precise variance parameter estimates or to test null-hypotheses related to heterogeneity parameters [85]. Another limitation of this meta-analysis is that, while LSD was administered orally in most studies, it was administered intravenously in one study [41] and sublingually in another study [36]. There were no different treatments in the analysis depending on substance administration method or substance formulation, although it has been indicated that different administration methods and substance formulations can have different physiological and subjective effects [43]. Also, the included LSD doses did not sufficiently cover the upper and lower bounds to estimate a sigmoid curve, so responses at very high and very low doses cannot be predicted by applying the models identified in this analysis.

The robustness of the obtained estimates, have been discussed in the previous meta-analysis on the effects of psilocybin by Hirschfeld and Schmidt (2021) [26]. With 12 to 19 datasets, the amount of available data in the present analysis was in the recommended range [86]. The between-study variance, Tau^2, was rather small for most factors and scales (see Table 2). The degree of inconsistency across studies, I^2, is considered small to moderate if < 60% [59], which was the case only for *Anxiety* on the 11-ASC and *Mystical* on the MEQ30. For the other factors and scales considerable inconsistencies were found (60 – 91%). Until more data are available for these scales, the corresponding dose-response estimates need to be treated with caution, and confidence intervals should be considered.

Conclusion

LSD administration in healthy, highly selected study participants in a controlled setting intensified almost all characteristics of ASC assessed with the two given questionnaires. The subjective experience of small to moderate dosages of LSD was mainly characterized by alterations in visual perception and positively experienced ego dissolution. Compared to psilocybin, LSD elicits very similar effects, however it seems to evoke larger effects with stronger dose-modulation for audio-visual synesthesia and smaller effects with weaker dose-modulation for spiritual or mystical-type experiences. Despite extra-pharmacological differences between included studies, we established relative robust dose-response relationships for most factors and scales. Results may be used as a general reference to relate observed with expected dose-specific effects.

Author contributions

TTS initiated and conceptualized the work. JP conducted the literature search. JP and TH performed the analyses with contributions of TTS. JP, TH, TM, and TTS jointly wrote, edited, and approved the final version of the manuscript.

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Competing interests

The authors declare no competing interests.

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