Universidade Estadual de Campinas

Faculdade de Ciências Médicas

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Deconstruction and Reconstruction:
The Effects of LSD on Stream of Thought, Creativity, Cognition and Psychotic- and Therapeutic-Like Experiences

Desconstrução e Reconstrução:
Os Efeitos de LSD em Fluxo de Pensamento, Criatividade, Cognição e Experiências Similares à Psicose e Terapia

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Thesis presented to the School of Medical Sciences of the University of Campinas as part of the requirements demanded for the acquisition of the title Doctor in Sciences, in the concentration area Mental Health.

Tese apresentada à Faculdade de Ciências Médicas da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Doutora em Ciências, na área de concentração Saúde Mental.

Supervisor/*orientador*: Prof. Dr. Luís Fernando Farah de Tófoli

This work corresponds to the final version
of the thesis defended by the student Isabel Wießner
and oriented by Prof. Dr. Luís Fernando Farah de Tófoli.

Este trabalho corresponde à versão final da tese defendida pela aluna Isabel Wießner, e orientada pelo Prof. Dr. Luís Fernando Farah de Tófoli.

Campinas

2022

Ficha catalográfica
Universidade Estadual de Campinas
Biblioteca da Faculdade de Ciências Médicas
Maristella Soares dos Santos - CRB 8/8402

W637d

Wießner, Isabel, 1987-
Deconstruction and reconstruction : the effects of LSD on stream of thought, creativity, cognition and psychotic- and therapeutic-like experiences / Isabel Wießner. – Campinas, SP : [s.n.], 2022.

Orientador: Luís Fernando Farah de Tófoli.
Tese (doutorado) – Universidade Estadual de Campinas, Faculdade de Ciências Médicas.

1. Dietilamida do ácido lisérgico. 2. Pensamento. 3. Criatividade. 4. Cognição. 5. Psicoses. I. Tófoli, Luis Fernando Farah de, 1972-. II. Universidade Estadual de Campinas. Faculdade de Ciências Médicas. III. Título.

Informações para Biblioteca Digital

Título em outro idioma: Desconstrução e reconstrução : os efeitos de LSD em fluxo de pensamento, criatividade, cognição e experiências similares à psicose e terapia
Palavras-chave em inglês:
Lysergic acid diethylamide
Thinking
Creativity
Cognition
Psychoses
Área de concentração: Saúde Mental
Titulação: Doutora em Ciências
Banca examinadora:
Luís Fernando Farah de Tófoli [Orientador]
Patricia Moriel
Stevens Kastrup Rehen
André Brooking Negrão
Emilia Irene Gabrielle Sanabria
Data de defesa: 30-03-2022
Programa de Pós-Graduação: Ciências Médicas

Identificação e informações acadêmicas do(a) aluno(a)
- ORCID do autor: https://orcid.org/0000-0003-1653-2565
- Currículo Lattes do autor: http://lattes.cnpq.br/7108408451417888

Comissão Examinadora da Defesa de Doutorado

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A ata de defesa com as respectivas assinaturas dos membros encontra-se no SIGA/Sistema de Fluxo de Dissertação/Tese e na Secretaria do Programa da FCM.

Date of Defence: 30/03/2022

Dedication

To my beloved family and this wonderful country.

Acknowledgements

With deep gratitude, I wish to thank

the study participants for going through the experiment with endless patience, motivation and dedication to support psychedelic science in Brazil;

my supervisor Luís Fernando Farah de Tófoli for guiding me through this psychedelic journey and making this work possible with his inspiration and persistence;

the "psychedelic juniors" Marcelo Falchi, Fernanda Palhano-Fontes, Lucas Oliveira Maia, Dimitri Daldegan-Bueno, Rodolfo Olivieri and Luis Felipe Valêncio for riding with me on this journey as true friends, supporting me professionally and personally in uncountable moments and details of this work;

the "psychedelic seniors" Draulio Barros de Araujo, Sidarta Ribeiro and Natália Bezerra Mota for expanding my journey into Brazil's northeast and providing the intellectual, technical and institutional support for the refinements of this work; and Jaime Bruno Cirne de Oliveira and Sérgio Mota Rolim for providing the technical and everyday life basics for this northeast excursion;

Amanda Fielding, Valerie Bonnelle, Jon Sharp and the Beckley Foundation for promoting this journey with their organizational, conceptual and financial contributions;

the School of Medical Sciences of the University of Campinas and the Brain Institute of the Federal University of Rio Grande do Norte for providing the institutional bases of this journey.

The present work was realized with support of the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Finance Code 001.

With all my heart, I thank

my companion Raphael Egel for stimulating my thoughts, inspiring my work and encouraging me to realize my dream of a PhD in LSD;

my psychedelic son Yuma Wießner for making me see my work through the eyes of a child;

my parents Martin Wießner and Elke Schemm for their love, curiosity in my work and unconditional support without which I could not have gone on this journey;

my grandmother Erika Wießner for being my anchor and eternal spiritual and financial support;

Myriam and Thomas Egel-Goldschmidt and Dorothea Kowald for financially supporting the whole family on this psychedelic ride to Brazil;

Heidrun, Julia and Lisa Wilhelm for the fruitful talks on my research;

Carina Francischini and Hervé Yviquel for living this journey with us and enriching it with their company and advice on academic life in general and Brazilian culture in specific;

Camila and Martin Biebow for dedicated babysitting, for celebrating this psychedelic journey with us and making us feel at home;

Marie Lefèvre for true friendship, helpful advice and critical view in difficult questions on work and life.

Epigraph

Die Wahrheit ist eben kein Kristall, den man in die Tasche stecken kann, sondern eine unendliche Flüssigkeit, in die man hineinfällt.

- Rober Musil (Der Mann ohne Eigenschaften)

The psychotic drowns in the same waters in which the mystic swims with delight

- Joseph Campbell

A rosa tem dois galhos, olha quais eles são:
Um é a ilusão, o outro é o padrão.

- Uma monja num sonho

Resumo

História: A dietilamida de ácido lisérgico (LSD) tem uma história turbulenta desde a descoberta de suas propriedades psicoativas em 1943, sendo usada por psiquiatras como um modelo para a psicose, por psicoterapeutas como adjunto de tratamento, por artistas como amplificador de criatividade, por usuários de microdoses do Vale do Silício como estimulador cognitivo. O LSD muda profundamente a percepção, cognição e o comportamento, mas uma caracterização metodologicamente rigorosa dos efeitos no pensamento livre, desempenho criativo e cognição subaguda ainda não foi realizado e a relação entre o modelo de psicose e modelo de terapia não foi explorada.
Objetivo: Elucidar os efeitos do LSD em baixa dosagem em humanos saudáveis a respeito de fluxo de pensamento, criatividade, cognição, experiências psicodélicas, psicóticas e terapêuticas e a relação entre esses efeitos.
Métodos: Em um desenho aleatorizado, duplo-cego, placebo-controlado, cruzado, 24 voluntários saudáveis receberam 50 μg de LSD ou placebo inativo. O fluxo de pensamento foi avaliado por medidas de divagação mental e associação livre repetidamente após administração. A criatividade foi medida por tarefas de pensamento divergente e criatividade verbal e figural após o pico. A cognição foi avaliada por uma bateria de testes de memória visual e verbal, fluência verbal e figural, flexibilidade cognitiva, atenção sustentada e alternada, controle inibitório e organização perceptual na manhã após administração. Experiências psicóticas foram avaliadas por um questionário sobre saliência aberrante, experiências terapêuticas por medidas de sugestionabilidade e atenção plena e experiências psicodélicas por questionários sobre alterações de consciência e experiências místicas, desafiadoras e de dissolução do ego. As correlações entre os efeitos induzidos pelo LSD foram examinadas.
Resultados: O LSD, comparado com placebo, mudou o fluxo de pensamento induzindo caos, significados e sensações durante a divagação mental e um fluxo abstrato durante a associação livre. Respostas criativas foram caracterizadas por maior novidade, surpresa, distâncias semânticas, simbolismo e ambiguidade e menor utilidade, pensamento convergente e elaboração. A cognição subaguda demostrou melhor memória visuoespacial e fluência fonológica e pior flexibilidade cognitiva. O LSD evocou experiências psicóticas de saliência aberrante, experiências terapêuticas de sugestionabilidade mas não de atenção plena e experiências psicodélicas de alterações de consciência, experiências místicas, de dissolução do ego e moderadamente desafiadoras. A saliência aberrante induzida pelo LSD correlacionou-se altamente com imagiologia complexas, experiências místicas e dissolução do ego.
Conclusão: LSD em baixa dosagem afeta a mente humana em vários níveis. LSD evoca um fluxo de pensamento e desempenho criativo caracterizados por pensamento caótico, desorganizado e incoerente mas também carregado de significado, abstrato e simbólico, provoca um *afterglow* mas também uma ressaca cognitiva e induz experiências psicóticas mas também terapêuticas que podem estar ligados por experiências místicas. Globalmente, o LSD parece deslocar recursos perceptuais, cognitivos e comportamentais não só "longe do normal" mas também "para o novo", apontando para uma *desconstrução* e *reconstrução* geral induzida pelo LSD. Os resultados contribuem para o entendimento do estado psicodélico *per se*, pavimentam o caminho para uma melhor exploração de mecanismos e aplicações na terapia psicolítica e esperançosamente promovem uma imagem mais realista desta substância controversa na sociedade.

Palavras-chave: Dietilamida do Ácido Lisérgico; Divagação Mental; Associação Livre; Criatividade; Pensamento Divergente; Simbolismo; Cognição; Memória; Fluência Verbal; Funções Executivas; Modelo de Psicose; Saliência Aberrante; Terapia Assistida por Psicodélicos; Sugestão; Atenção Plena; Experiência Mística; Autopercepção.

Abstract

Background: Lysergic acid diethylamide (LSD) carries a turbulent history since the discovery of its psychoactive properties in 1943, being used by psychiatrists as psychosis model, by psychotherapists as treatment adjunct, by artists as creativity booster, by Silicon Valley's microdosers as cognitive enhancer. LSD fundamentally changes perception, cognition and behaviour, but a methodologically rigorous characterization of the effects on free thought, creative performance and sub-acute cognition is lacking and the relationship between the psychosis model and therapy model unexplored.
Objective: Elucidating the effects of low-dose LSD on healthy humans regarding the stream of thought, creativity, cognition and psychedelic, psychotic and therapeutic experiences and exploring the relationships between these effects.
Methods: In a randomized, double-blind, placebo-controlled, crossover design, 24 healthy volunteers received 50 µg LSD or inactive placebo. The stream of thought was assessed by mind-wandering and free association measurements repeatedly after drug administration. Creativity was measured by tasks on divergent thinking and verbal and figural creativity after drug peak. Cognition was assessed by a test battery on visual and verbal memory, verbal and design fluency, cognitive flexibility, sustained and switching attention, inhibitory control and perceptual organization the morning after drug administration. Psychotic experiences were assessed by an aberrant salience questionnaire, therapeutic experiences by suggestibility and mindfulness measurements and psychedelic experiences by questionnaires on alterations of consciousness and mystical, challenging and ego-dissolution experiences. Correlations between the LSD-induced effects were examined.
Results: LSD, compared to placebo, changed the stream of thought towards chaos, meaning and sensation during mind-wandering and an abstract flow during free association. Creative responses were characterized by increased novelty, surprise, semantic distances, symbolism and ambiguity and decreased utility, convergent thinking and elaboration. Cognition sub-acutely demonstrated improved visuospatial memory and phonological fluency and impaired cognitive flexibility. LSD evoked psychotic experiences of aberrant salience, therapeutic experiences of suggestibility but not mindfulness and psychedelic experiences of alterations of consciousness and mystical, ego-dissolution and mildly challenging experiences. LSD-induced aberrant salience correlated highly with complex imagery, mystical experiences and ego-dissolution.
Conclusion: Low-dose LSD affects the human mind on several levels. LSD evokes a stream of thought and creative performance characterized by chaotic, disorganized and incoherent thinking but also meaning-laden, abstract and symbolic thinking, provokes a cognitive afterglow but also hangover and induces psychotic but also therapeutic experiences which might be linked by mystical experiences. Altogether, LSD seems to shift the perceptual, cognitive and behavioural resources not only "away from normal" but also "towards the new", pointing to an overall LSD-induced *deconstruction* and *reconstruction*. The results contribute to the understanding of the psychedelic state *per se*, pave the way for a better exploration of mechanisms and applications in psycholytic therapy and hopefully promote a more realistic picture of this controversial substance in society.

Keywords: Lysergic Acid Diethylamide; Mind-Wandering; Free Association; Creativity; Divergent Thinking; Symbolism; Cognition; Memory; Verbal Fluency; Executive Functions; Psychosis Model; Aberrant Salience; Psychedelic-Assisted Therapy; Suggestion; Mindfulness; Mystical Experience; Self-Perception.

Zusammenfassung

Hintergrund: Lysergsäurediethylamid (LSD) hat eine turbulente Geschichte seit der Entdeckung seiner psychoaktiven Eigenschaften 1943, wurde von PsychiaterInnen als Psychosemodell verwendet, von PsychotherapeutInnen als Behandlungsergänzung, von KünstlerInnen als Kreativitätsbooster, von Silicon Valleys MicrodoserInnen als Kognitionsverstärker. LSD verändert Wahrnehmung, Kognition und Verhalten fundamental, jedoch steht eine methodisch rigorose Effektcharakterisierung bezüglich freien Denkens, kreativer Leistung und subakuter Kognition aus und die Beziehung zwischen Psychosemodell und Therapiemodell ist unerforscht.
Ziel: Darlegung der Effekte von niedrigdosiertem LSD auf gesunde Menschen bezüglich Gedankenstroms, Kreativität, Kognition und psychedelischen, psychotischen und therapeutischen Erfahrungen und der Beziehung zwischen diesen Effekten.
Methoden: In einem randomisierten, doppelblinden, placebokontrollierten Crossover-Design erhielten 24 gesunde Freiwillige 50 µg LSD oder inaktives Placebo. Der Gedankenstrom wurde nach Substanzverabreichung wiederholt mit Messungen zu Gedankenwandern und freier Assoziation untersucht. Kreativität wurde nach Substanzpeak mit Aufgaben zu divergentem Denken und verbaler und figürlicher Kreativität gemessen. Kognition wurde am Morgen nach Substanzverabreichung mit einer Testbatterie zu visuellem und verbalem Gedächtnis, verbaler und figürlicher Fluenz, kognitiver Flexibilität, anhaltender und wechselnder Aufmerksamkeit, inhibitorischer Kontrolle und Wahrnehmungsorganisation untersucht. Psychotische Erfahrungen wurden mit einem Fragebogen zu aberranter Salienz untersucht, therapeutische Erfahrungen mit Messungen zu Suggestibilität und Achtsamkeit und psychedelische Erfahrungen mit Fragebögen zur Bewusstseinsveränderung und mystischen, herausfordernden und Selbstauflösungs-Erlebnissen. Korrelationen zwischen den LSD-induzierten Effekten wurden untersucht.
Ergebnisse: LSD veränderte verglichen mit Placebo den Gedankenstrom in Richtung Chaos, Bedeutung und Sinneserleben während des Gedankenwanderns und abstrakten Gedankenflusses während der freien Assoziation. Kreative Antworten waren gekennzeichnet durch erhöhte Neuheit, Überraschung, semantische Distanzen, Symbolik und Mehrdeutigkeit sowie verminderte Nützlichkeit, konvergentes Denken und Ausarbeitung. Kognition zeigte subakut verbessertes visuell-räumliches Gedächtnis und phonologische Fluenz und beeinträchtigte kognitiven Flexibilität. LSD rief psychotische Erfahrungen von aberranter Salienz hervor, therapeutische Erfahrungen von Suggestibilität nicht aber Achtsamkeit und psychedelische Erfahrungen von Bewusstseinsveränderungen, mystischen, Selbstauflösungs- und leicht herausfordernden Erlebnissen. Die LSD-induzierte aberrante Salienz korrelierte hoch mit komplexem Bilderleben, mystischen Erfahrungen und Selbstauflösung.
Schlussfolgerung: Niedrigdosiertes LSD beeinflusst den menschlichen Geist auf mehreren Ebenen. LSD ruft einen Gedankenstrom und kreativen Leistung hervor, die gekennzeichnet sind durch chaotisches, unorganisiertes und inkohärentes Denken aber auch durch bedeutungsgeladenes, abstraktes und symbolisches Denken, erzeugt einen kognitiven Afterglow aber auch Hangover und induziert psychotische aber auch therapeutische Erfahrungen, die durch mystische Erlebnisse verbunden sein könnten. Insgesamt scheint LSD die Wahrnehmungs-, Kognitions- und Verhaltensressourcen nicht nur „weg vom Normalen“ sondern auch „hin zum Neuen“ zu verlagern, was auf eine allgemeine LSD-induzierte Dekonstruktion und Rekonstruktion hinweist. Die Ergebnisse tragen zum Verständnis des psychedelischen Zustandes an sich bei, ebnen den Weg für eine bessere Erforschung der Mechanismen und Anwendungen in der psycholytischen Therapie und fördern hoffentlich ein realistischeres Bild dieser kontroversen Substanz in der Gesellschaft.

Schlüsselwörter: Lysergsäurediethylamid; Gedankenwandern; Freie Assoziation; Kreativität; Divergentes Denken; Symbolismus; Kognition; Gedächtnis; Verbale Fluenz; Exekutivfunktionen; Psychosemodell; Aberrante Salienz; Psychedelika-Gestützte Therapie; Suggestion; Achtsamkeit; Mystische Erfahrung; Selbstwahrnehmung.

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1. Introduction

Lysergic acid diethylamide (LSD) is probably one of the substances that most underwent upheavals in society during its history, affecting psychiatry, science, politics and public opinion, evoking enthusiasm and frustration, representing opportunity and threat (1,2). These contrasting positions of LSD in society come along with its partially contrasting effects. LSD changes perception, cognition and emotion, including dose-dependent visual alterations, synaesthesia, distortions of the self, space and time, spiritual experiences and disorganized thoughts, insights and impaired concentration, euphoria and anxiety (1,3,4). Correspondingly, LSD has been applied for diverse purposes, by psychiatrists as a psychosis model to mimic psychotic experiences (5), by therapists as an adjunct to treat mood and substance use disorders (6,7), by artists to promote creativity (8), by the counterculture of the 1960s as a symbol of political resistance (2), by Silicon Valley's tech elite to boost cognitive performance (9,10).

In order to approximate the "psychedelic nature" of perception, cognition and behaviour *per se*, we need to look at the LSD effects from several perspectives relating to these application fields. One of the most fundamental cognitive processes we can look at is the mind when it is freely roaming, a mental state conceptualized as the "stream of thought" which is unconstrained, continuous and highly dynamic (11). Two forms of stream of thought are mind-wandering and free association, which are characterized by an unintentional, unaware nature and a stimulus-induced, output-generating nature, respectively (12,13). Mind-wandering accounts for around half of our daily mental activity, is associated with decreased mood and cognitive performance and can exert beneficial effects if modulated by spiritual or therapeutic techniques (14–18). Free association is a basic technique in psychoanalysis, requires to speak freely whatever comes to mind and intends to reveal unconscious structures based on the assumption that verbally connected content is also mentally connected (19,20). Overall, these facets of the stream of thought are being increasingly explored revealing fundamental aspects of mental functioning and carrying beneficial potential if applied as therapeutic tool. Yet, it is merely anecdotally reported how psychedelics, which fundamentally impact mental functioning, affect the freely roaming mind (21).

Creativity is a phenomenon closely intertwined with perception, cognition and behaviour and of major impact for diverse social spheres including art, education, mental health, science, technology, engineering and economy (22–25). Due to its

importance for society, attempts have been made to enhance creativity, for example, by means of training, new experiences, mindfulness, hypnosis or psychoactive substances (26–30). With the growing popularity and accessibility of LSD in the 1960s, several artists, scientists and entrepreneurs have designated the substance as a "wonder drug" to boost creative insights and performance (8,31–33). Yet, research on psychedelic-related creativity has been stumbling on conceptual and methodological shortcomings, limiting creativity assessments to self-reports, case studies or creative professionals, yielding inconclusive results (30).

Recently, the potential of psychedelics to promote cognition and well-being is gaining growing interest, especially regarding microdoses or sub-acute effects (34,35). Sub-acute cognitive improvements can comprise enhanced cognitive flexibility, convergent thinking and executive functions and are hypothesized to be related to psychedelic-induced neuroplasticity, neurogenesis and neuroprotective processes (36–40). However, a methodologically rigorous, comprehensive exploration of the LSD effects on sub-acute cognition, including memory, verbal and design fluency, cognitive flexibility, attention, executive functions and perceptual organization, is still lacking. Nevertheless, a better understanding of the modulation of these cognitive functions could provide new application perspectives for conditions involving cognitive declines such as natural ageing, brain injuries or psychiatric conditions (41).

Throughout its history, the most influential areas of LSD research and application involved two contrasting phenomena: the psychosis model exploring the psychotomimetic effects and the therapy model exploring the treatment effects (42). Within the psychosis model, psychiatrists applied LSD to themselves and to patients to understand and investigate treatment possibilities for psychotic disorders (5). LSD-induced similarities with the psychotic phenomenology involve an altered perception of senses, self, body and time, altered emotionality, impaired cognition, loss of intentionality, magical thinking and several behavioural and neurophysiological characteristics (43). Aberrant salience is the aberrant assignment of salience to external and internal percepts, a mechanism related to and possibly accounting for psychotic experiences (44–47), yet, the role of aberrant salience in the LSD psychosis model is still unknown. Within the therapy model, LSD was applied in psychedelic-assisted psychotherapy for the treatment of a variety of disorders, with promising results in mood and substance use disorders (48,49). Moreover, the potential of psychedelics to enhance suggestibility and mindfulness, mechanisms important for hypnosis- and mindfulness-

based treatments, might constitute promising complementary techniques in psychedelic-assisted treatments (50–54). Nevertheless, the paradox of how the same substance can concurrently induce and treat psychiatric symptoms has not yet been investigated properly.

Altogether, despite numerous early LSD studies with tens of thousands of participants, research on the LSD effects on the stream of thought, creativity, cognition, psychotic and therapeutic effects has yielded contradictory findings, mainly due to methodological limitations, political barriers, conceptual difficulties and insufficient exploration (1,2,42,55). Yet, a closer understanding of the LSD effects in these perceptual, cognitive and behavioural domains is necessary to better capture its phenomenology, explore its mechanisms of action and evaluate its therapeutic potential. Moreover, besides providing insights into the ontology of the human mind, a detailed effect characterization is probable to contribute to a more realistic positioning of this controversial substance in society, from psychiatry to public perception.

2. Objectives

This study aimed at elucidating the effects of a relatively low dose of LSD (50 μg) on the stream of thought, creativity, cognition, psychotic, therapeutic and psychedelic experiences in healthy humans.

Specifically, we aimed at exploring the LSD-induced effects on mind-wandering and free association (stream of thought), creativity factors, divergent and convergent thinking, semantic structure and special features (creativity), memory, verbal and design fluency, executive functions and perceptual organization (cognition), aberrant salience (psychotic-like experience), suggestibility and mindfulness (therapeutic-like experiences), altered state of consciousness, mystical, challenging and ego-dissolution experiences (psychedelic experiences) and the relationship between the LSD-induced effects.

Our hypotheses were that LSD affects these perceptual, cognitive and behavioural domains with changes in the stream of thought and increases in creativity, cognition, psychotic, therapeutic and psychedelic experiences and that LSD-induced psychotic and therapeutic experiences are connected.

3. Methods

3.1. Study Design

The study used a randomized, double-blind, placebo-controlled, crossover design with two treatments (LSD, placebo) and a washout period of 14 days between treatments. Participants were randomly assigned to treatment order. Where applicable, two parallel test versions (A, B) were applied to avoid learning effects, in balanced order across participants and counterbalanced order across treatments. This study was approved by the University Research Ethics Committee and the National Health Surveillance Agency and conducted according to safety guidelines for psychedelic research in humans (56).

3.2. Participants

Twenty-five healthy participants were recruited in a convenience sample. Inclusion criteria were: age above 21 years, at least one experience with LSD, abstinence from psychedelics for at least two weeks and from alcohol and other drugs for at least three days before each session and abstinence from tobacco and caffeine during the study days. Exclusion criteria were: the presence of psychiatric symptoms, personal or first-degree family member history of a psychotic disorder, use of psychiatric medication, history of severe complications after psychedelic use, alcohol or drug use disorder, heart disease or other relevant medical conditions, pregnancy and non-native speaking of Brazilian Portuguese. Participants provided written informed consent before participation. One participant ceased participation after the first session for personal reasons, resulting in a final sample of 24 subjects (8 women; age (mean ± SD) = 35 ± 11 years (range: 25–61)).

3.3. Drug

Participants received 50 µg of LSD (d-lysergic acid diethylamide; > 99 % purity on high performance liquid chromatography; dissolved in alcohol solution) or of an inactive placebo (alcohol solution). Either substance was diluted in 30 ml water for oral administration. The dose of 50 µg LSD is regarded as low (57,58) and was chosen to minimize the risk of adverse reactions and to exert noticeable effects without impairing the subjects' ability to complete the measurements. An absolute, non-weight adapted dose was chosen in accordance with recent LSD studies (59–62) and corresponded to a relative

dose of (mean ± SD) 0.69 ± 0.18 μg/kg body weight (range: 0.45–1.11). An alcohol solution was chosen as placebo to imitate the slight alcoholic taste of the LSD alcohol solution.

3.4. Measurements

3.4.1 Stream of Thought

The Stream of Thought was assessed by measurements of mind-wandering (Amsterdam Resting-State Questionnaire 2.0 (ARSQ)) (63) and free association (Forward Flow Task (FFT)) (13) repeatedly during the day of drug administration and the morning afterwards. For further details, see Methods of Article 1.

3.4.2. Creativity

Creativity was assessed by several tasks (Pattern Meaning Task (PMT) (64); Alternate Uses Task (AUT) (65); Picture Concept Task (PCT) (66); Creative Metaphors Task (MET); Figural Creativity Task (FIG) (67)) around drug peak. From these tasks, we extracted measurements of creativity factors (Novelty, Utility, Surprise), divergent thinking (Fluency, Originality, Flexibility, Elaboration), convergent thinking, semantic structure (Semantic Spread, Forward Flow, Flow Distance, Flow Steps) and data-driven special features. For further details, see Methods of Article 2.

3.4.3. Cognition

Cognition was assessed by measurements of visuospatial and auditory-verbal memory (Rey-Osterrieth Complex Figure (ROCF) (68,69); 2D Object-Location Memory Task (OLMT) (70); Rey Auditory-Verbal Learning Test (RAVLT) (71,72)), phonological and semantic verbal fluency (Verbal Fluency Task (VFT)) (73,74), design fluency (Design Fluency Task (DFT)) (75), cognitive flexibility (Wisconsin Card Sorting Test (WCST)) (76,77), sustained and switching attention (Trail Making Test (TMT)) (76,78), inhibitory control (Stroop Task (Stroop)) (78,79) and perceptual organization (Block Design Test (BDT)) (80,81) on the morning after drug administration. For further details, see Methods of Article 3.

3.4.4. Psychotic, Therapeutic and Psychedelic Experiences

Psychotic experiences were assessed by measurements of aberrant salience (Aberrant Salience Inventory (ASI)) (82), therapeutic experiences by measurements of

suggestibility (Creative Imagination Scale (CIS)) (83) and mindfulness (Five Facet Mindfulness Questionnaire (FFMQ) (84,85); Mindful Attention Awareness Scale (MAAS) (86,87); Experiences Questionnaire (EQ) (88)) and psychedelic experiences by measurements of intensity and valence (visual analogue scales), altered state of consciousness (Altered State of Consciousness Questionnaire (ASC)) (89), mystical experiences (Mystical Experiences Questionnaire (MEQ)) (90,91), challenging experiences (Challenging Experiences Questionnaire (CEQ)) (92,93) and ego-dissolution (Ego-Dissolution Inventory (EDI)) (94,95). For further details, see Methods of Article 4.

3.5. Study Procedures

The candidates for participation underwent a clinical and psychiatric interview including a screening of the inclusion and exclusion criteria, medical anamnesis, physical examination and check of a recent electrocardiogram. Complementary exams were consulted if indicated.

Each treatment session consisted of two study days (**figure 1**). Over both treatment sessions, the same investigators were present for each participant, a psychologist and a psychiatrist.

The day of drug administration started at 7:30 a.m. with baseline measurements including mindfulness (FFMQ, MAAS, EQ), memory (RAVLT, OLMT), free association (FFT) and mind-wandering (ARSQ). LSD or placebo was administered at 9:30 a.m. Intensity and valence of the drug effects was assessed in 15 min-intervals for two hours (+0h, +0.25h, +0.5h, +0.75h, +1h, +1.25h, +1.5h, +1.75h, +2h) and in 30 min-intervals for more six hours (+2.5h, +3h, +3.5h, +4h, +4.5h, +5h, +5.5h, +6h, +6.5h, +7h, +7.5h and +8h). Free association (FFT) and mind-wandering (ARSQ) were assessed in two hour-intervals (+2h, +4h, +6h, +8h). A standardized snack was served at 11:00 a.m. Creativity measurements were conducted from 12:00 p.m. to 1:15 p.m. Lunch was served at 1:40 p.m., suggestibility (CIS) tested at 2:15 p.m. Questionnaires on the psychedelic experience (ASC, MEQ, CEQ, EDI) were filled in by the end of the day, at 4:30 p.m. At 5:30 p.m., eight hours after drug administration, it was ensured that the participants were feeling well and stable before being left into the custody of a family member or friend.

On the next morning, the subjects returned at 8:00 a.m., completed measurements of mindfulness (FFMQ, MAAS, EQ), aberrant salience (ASI), free association (FFT), mind-wandering (ARSQ), memory (RAVLT, OLMT, ROCF), cognitive flexibility (WCST), sustained and switching attention (TMT), inhibitory control

(Stroop), verbal fluency (VFT), design fluency (DFT) and perceptual organization (BDT) and were released around 10:00 a.m.

Two weeks after the second session, the participants completed an online follow-up questionnaire including the mindfulness scales (FFMQ, MAAS, EQ). Four months after the second session, the last online follow-up contact was made with qualitative questions on study participation and possible long-term effects. No persisting side effects were reported.

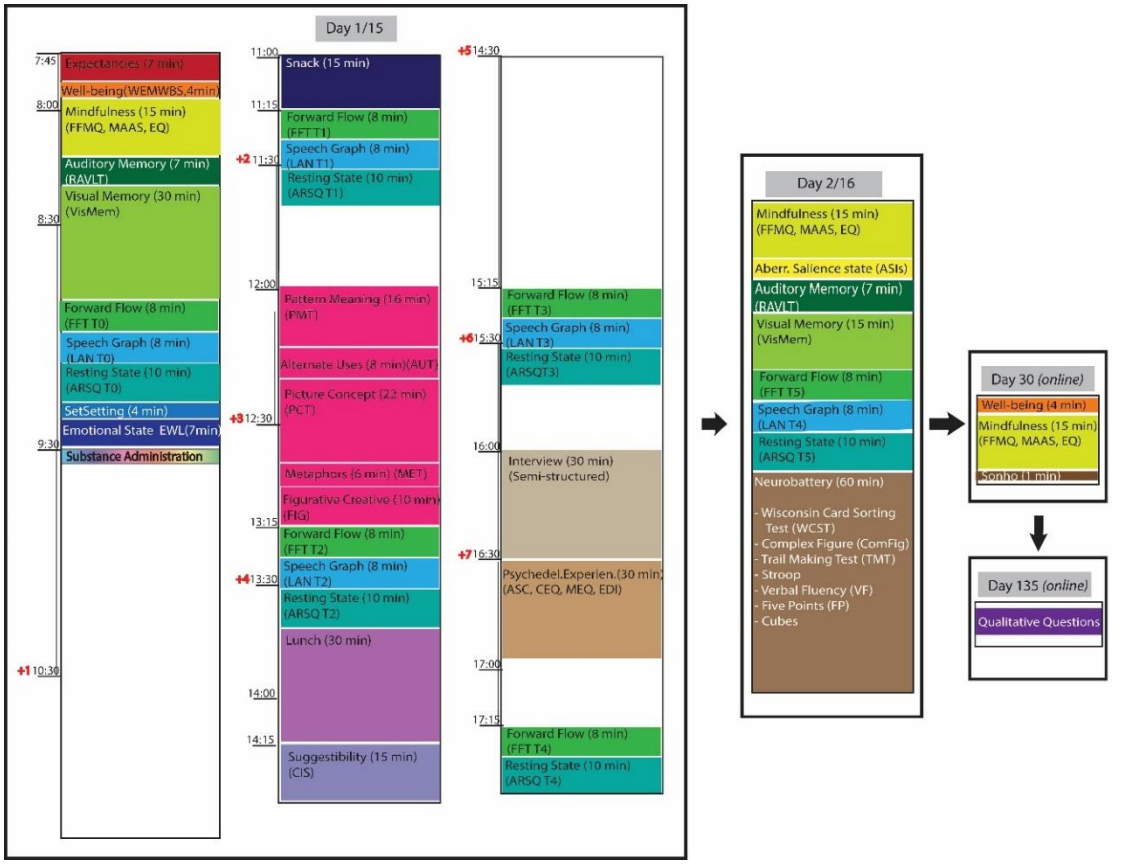

Figure 1. An illustration of the study procedures. On day 1, LSD or placebo was administered, together with a variety of baseline and post-administration questionnaires and tests throughout the day. On day 2, the morning after drug administration, sub-acute measurements were conducted. This procedure was repeated after a wash-out period of two weeks, on day 15 and 16. On day 30, two weeks after the second session, follow-up measurements were conducted by online questionnaires and on day 135, four months after the second session, the last follow-up contact was made by e-mail.

3.6. Data Analysis

The statistical analyses were performed with IBM SPSS Statistics (version 22). The treatment effects of LSD on the measurements, as compared to placebo, were analysed in repeated measures General Linear Models (GLMreps) with ‘treatment’ (LSD,

placebo) as within-subjects factor and ‘treatment order’ (LSD–placebo, placebo–LSD) as between-subjects factor. Effect sizes were estimated using partial eta squared (η_p^2). Spearman’s rank correlation coefficients (r_s) were calculated between the LSD-induced changes (Δ = LSD - placebo). For all measurements, significance level was set to α = 0.05, two-tailed. Corrections for multiple comparisons were conducted *post hoc* for pairwise comparisons and correlations.

4. Results

4.1. Article 1 – LSD and the Stream of Thought

Reference (96):

Wießner I, Falchi M, Palhano-Fontes F, Oliveira Maia L, Feilding A, Ribeiro S, Bezerra Mota N, Araujo DB, Tófoli, LF. Low-dose LSD and the stream of thought: Increased Discontinuity of Mind, Deep Thoughts and abstract flow. Psychopharmacology [Internet]. 2021;(Epub ahead of print):1–13. Available from: https://doi.org/10.1007/s00213-021-06006-3

Psychopharmacology
https://doi.org/10.1007/s00213-021-06006-3

ORIGINAL INVESTIGATION

Low-dose LSD and the stream of thought: Increased Discontinuity of Mind, Deep Thoughts and abstract flow

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Received: 31 March 2021 / Accepted: 7 October 2021

Abstract

Rationale Stream of thought describes the nature of the mind when it is freely roaming, a mental state that is continuous and highly dynamic as in mind-wandering or free association. Classic serotonergic psychedelics are known to profoundly impact perception, cognition and language, yet their influence on the stream of thought remains largely unexplored.

Objective To elucidate the effects of LSD on the stream of thought.

Methods In a randomized, double-blind, placebo-controlled, crossover study, 24 healthy participants received 50 µg lysergic acid diethylamide (LSD) or inactive placebo. Mind-wandering was measured by the Amsterdam Resting State Questionnaire (ARSQ), free association by the Forward Flow Task (FFT) for three seed word types (animals, objects, abstract words). ARSQ and FFT were assessed at +0 h, +2 h, +4 h, +6 h, +8 h and +24 h after drug administration, respectively.

Results LSD, compared to placebo, induced different facets of mind-wandering we conceptualized as "chaos" (Discontinuity of Mind, decreased Sleepiness, Planning, Thoughts under Control, Thoughts about Work and Thoughts about Past), "meaning" (Deep Thoughts, Not Sharing Thoughts) and "sensation" (Thoughts about Odours, Thoughts about Sounds). LSD increased the FFT for abstract words reflecting an "abstract flow" under free association. Overall, chaos was strongest pronounced (+2 h to +6 h), followed by meaning (+2 h to +4 h), sensation (+2 h) and abstract flow (+4 h).

Conclusions LSD affects the stream of thought within several levels (active, passive), facets (chaos, meaning, sensation, abstractness) and time points (from +2 h to +6 h). Increased chaos, meaning and abstract flow at +4 h indicate the utility of a late therapeutic window in psycholytic therapy.

Keywords LSD · Stream of thought · Resting state cognition · Mind-wandering · Free association · Forward flow · Abstract thinking · Semantic analysis

Introduction

What is the nature of mind? Over 130 years ago, William James described the freely roaming mind as a stream of thought: "If we could say in English 'it thinks,' as we say 'it rains' […], we should be stating the fact most simply and with the minimum of assumptions. As we cannot, we must simply say that *thought goes on*." (James 1890, p. 495). The stream of thought is a mental state that is relatively unconstrained, continuous and highly dynamic (James 1890). It can be "passive", task-unrelated, unintentional and unaware, when it is conceptualized as mind-wandering; or "active", task-related, stimulus-induced and output-generating, when it can be captured by free association (Christoff et al. 2016; Gray et al. 2019).

This article belongs to a Special Issue on Psychopharmacology on Psychedelic Drugs

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Published online: 28 October 2021

Mind-wandering spontaneously arises during the resting state and is multifaceted: It can be of a visual, verbal, somatic or emotional nature and oriented to the past, present, future, the self or others (Diaz et al. 2014; Smallwood et al. 2018; Zedelius and Schooler 2018). Mind-wandering is related to changes in emotion, cognition and behaviour, including decreased mood, changed executive functions and increased creativity (McVay and Kane 2010; Baird et al. 2012; Smallwood et al. 2018). Mind-wandering is altered in clinical conditions such as pain, depression, anxiety and dementia (Ottaviani et al. 2015; Kucyi 2018; O'Callaghan and Irish 2018; Seli et al. 2019) but, on the other hand, can be intentionally modulated to positively influence perception and behaviour, for example by relaxation (Stan and Christoff 2018), meditation (Eifring 2018) and cognitive behavioural therapy (Zedelius and Schooler 2018).

Free association is the "effort to speak the contents of one's mind free of conscious control" (Kris 2002, p. 829), a basic technique in Freud's psychoanalysis to unveil unconscious structures, based on the assumption that everything that comes to mind from a certain starting point is associated internally (Freud 1940). Freud's technique has later been more broadly applied, for example to map mental representations of risk or social relations, to conduct interviews about sensitive issues or to enhance creativity (Joffe and Elsey 2014; Marron et al. 2018). Also, his "targeted" free association around one seed concept (e.g. mother) has been modified towards a "chain" free association, where a chain of words is freely associated from a seed concept (Gray et al. 2019). This latter version of free association is intended to capture the evolution of thoughts over time and is quantified by forward flow, an index of semantic distances and a predictor of creativity (Gray et al. 2019).

Classic serotonergic psychedelics (also referred to as hallucinogens), such as lysergic acid diethylamide (LSD), psilocybin and ayahuasca, are known to change perception, cognition and emotion (dos Santos et al. 2016; Preller and Vollenweider 2016), but their effects on the stream of thought are sparsely explored. Early studies anecdotally observed an overall disintegration and disinhibition of thought processes under LSD, with less contextualized, targeted and coherent thinking and more pictorial, dreamlike and phantasy-prone thinking (Leuner 1962). This seems supported by recent findings of reduced convergent thinking and subjective control over thoughts and cognition, and increased divergent thinking, visual imagery, synaesthesia and mystical experiences under LSD, psilocybin and ayahuasca (Studerus et al. 2011; Kuypers et al. 2016; Valle et al. 2016; Wießner et al. 2021). Text and speech analyses suggest that LSD and psilocybin induce a semantically and syntactically more simple, stereotyped and unpredictable language and augment cognitive bizarreness and primary processes—a Freudian concept of automatic, associative, emotion-driven thinking (Amarel and Cheek 1965; Landon and Fischer 1970; Martindale and Fischer 1977; Kraehenmann et al. 2017a; Sanz et al. 2021). Moreover, LSD and psilocybin increase indirect semantic priming and semantically similar errors, pointing to disintegrated semantic information processing (Spitzer et al. 1996; Family et al. 2016).

These findings suggest that classic serotonergic psychedelics disorganize thinking and language towards more associative, bizarre and disinhibited processes. Yet, a more comprehensive, systematic investigation of their effects on the stream of thought is lacking. In light of this, our study aimed at exploring the time-dependent effects of LSD on passive and active stream of thought, as measured by mind-wandering and free association. Our hypotheses were: LSD time-dependently (1) changes mind-wandering during resting state and (2) increases forward flow during free association.

Methods

Study design

This study consisted of a randomized, double-blind, placebo-controlled, crossover design with two treatment sessions (LSD, placebo) and a washout period of 14 days between the sessions. Participants were randomly assigned to treatment order. The study was approved by the University Research Ethics Committee and conducted according to the guidelines for safety in psychedelic research (Johnson et al. 2008).

Participants

Twenty-five healthy volunteers were recruited by word-of-mouth. Candidates for participation underwent a complete medical history, including a detailed psychiatric anamnesis, family and medical health history, systems review, routine physical exam and mental exam. Normal intelligence level, lifestyle habits, use of medications/drugs, previous complementary exams, screening of personality (DSM-V), mental disorders (MINI) and inclusion/exclusion criteria were assessed. Inclusion criteria were as follows: ≥ 22 years, ≥ one experience with LSD, abstinence of at least 2 weeks from classic serotonergic psychedelics and 3 days from alcohol and other drugs before each session and from tobacco and caffeine during the study days. Exclusion criteria were as follows: presence of psychiatric symptoms, personal or first-degree family member history of psychotic disorders, use of psychiatric medication, history of severe complications after use of classic serotonergic psychedelics, alcohol or drug use disorder, heart disease or other relevant medical conditions, pregnancy and non-native speaking of Brazilian

Portuguese. All participants provided written informed consent before participation. One participant ended the participation after the first session for personal reasons, resulting in a final sample of 24 subjects (8 women; age (mean ± SD): 35 ± 11 years, range: 25–61). Detailed demographic information of the participants, including previous drug experiences, is reported elsewhere (Wießner et al. 2021).

Drug

Participants received 50 µg LSD (> 99% purity on high-performance liquid chromatography; dissolved in alcohol solution) or inactive placebo (alcohol solution). Both substances were diluted in 30 ml water and administered orally. This LSD dose is regarded as low (Passie et al. 2008).

Study procedures

This work is part of a larger study whose detailed procedures are reported elsewhere (Wießner et al. 2021). Each session consisted of 2 study days. On the day of drug administration, two investigators were present—a psychologist and a psychiatrist. Participants arrived at 7:30 a.m. in the study room furnished in a living room style, with a couch, chairs, a desk and a coffee table, and were informed about study aims and procedures. Since only subjects with previous LSD experience participated and received a relatively low dose, we provided no standardized information on possible drug effects to minimize suggestions and expectations, except for the written informed consent on possible discomforts and risks (e.g. transient mental/physical anxiety, psychotic symptoms). Baseline measurements of free association (FFT) and mind-wandering (ARSQ) were conducted at 8:50 a.m. and 9:08 a.m. (+0 h post-administration; see the "Measurements" section). Both measurements lasted around 8 min and were always applied in the same order to enhance their comparability. LSD or placebo was administered at 9:30 a.m., followed by measurement of subjective intensity and valence of drug effects in 15-min intervals for 2 h (+0 h, +0.25 h, +0.5 h, +0.75 h, +1 h, +1.25 h, +1.5 h, +1.75 h, + 2h) and in 30-min intervals for more 6 h (+2.5 h, +3 h, +3.5 h, +4 h, +4.5 h, +5 h, +5.5 h, +6 h, +6.5 h, +7 h, +7.5 h, +8 h). FFT and ARSQ were administered in 2-h intervals (+2 h, +4 h, +6 h, +8 h) and the morning after drug administration (+24 h). A standardized snack was served at 11:00 a.m. and lunch at 1:40 p.m. In task-free intervals, subjects were allowed to draw, write, look at photobooks and play with metallic and wooden puzzle games but not to listen to music, read, work or access the computer or internet. At 5:30 p.m.—8 h after drug administration—the investigators made sure that the subjects were feeling well and stable before releasing them into the custody of a family member or friend. The next morning, subjects returned at 8:00 a.m., completed FFT and ARSQ, among other tests and questionnaires, and were released at around 10:00 a.m.

Measurements

Intensity and valence

Intensity and valence of subjective drug effects over time were assessed by visual analogue scales (VASs), comprising a 10-cm horizontal line with the poles of 0 (no effect) and 100 (extremely intense effect) for intensity and −50 (extremely unpleasant effect) and 50 (extremely pleasant effect) for valence. The VASs were applied as paper-and-pencil versions to reduce the subjects' exposure to the computer monitor. Notably, the scales were created by our team and their psychometric properties need to be examined in future studies.

Mind-wandering

The Amsterdam Resting State Questionnaire 2.0 (ARSQ) measures mind-wandering during resting state via 55 questions on a 5-point Likert scale (1 = completely disagree; 5 = completely agree) (Diaz et al. 2014). For the resting state, participants were instructed to take off their glasses (if needed), relax and sit quietly on a couch with eyes closed and without falling asleep for 5 min. The researchers switched off the light (so only natural light entered the room) and silently remained in the room observing the participant, who was gently woken up if falling asleep. Afterwards, the participant sat in front of the computer—immediately and silently in order to interfere as little as possible with the memory of the resting state—and completed the ARSQ referring to the preceding 5 min. The ARSQ comprises ten factors ((1) Discontinuity of Mind, (2) Theory of Mind, (3) Self, (4) Planning, (5) Sleepiness, (6) Comfort, (7) Somatic Awareness, (8) Health Concern, (9) Visual Thought, (10) Verbal Thought) and 20 additional items on complementary thoughts and feelings, e.g. Deep Thoughts or Feeling Restless (Supplementary Methods, Table S1).

Chain free association

The Forward Flow Task (FFT) measures the evolution of thoughts over time based on semantic distances between words associated during "chain" free association (Gray et al. 2019). For this, the participant receives a seed word and is asked to type the first word that comes to mind from this seed word, followed by the first word that comes to mind from this first written word, and so on until reaching 20 words. Words were typed in boxes on a computer screen via the online survey tool LimeSurvey (Schmitz 2012). The

duration to complete the 20 words was recorded. Overall, three seed word types were given: animals (e.g. dog), objects (e.g. carpet) and abstract words (e.g. relationship). To avoid habituation effects, two seed word versions were used over both sessions (Table S2). Version order was balanced across participants and counterbalanced across treatments.

Semantic distances between words were estimated based on their co-occurrence in a Portuguese Wikipedia corpus by the Fast text method with the text similarity tool (TST; version 0.6.1) (Mota et al. 2020). For example, "ox" and "cow" have a lower semantic distance than "ox" and "journey", since the former combination co-occurs more frequently in the corpus. For processing details, see Supplementary Methods. With MATLAB (version R2015a; The MathWorks, Inc., Natick, MA, USA), different parameters were extracted from the 21 × 21 semantic distance matrices of each word chain: Forward Flow—the average distance of each word to all predecessors (Gray et al., 2019); Flow Distance—the average distance of the seed word to all subsequent words; and Flow Steps—the average distance between neighbouring words (Fig. S1). Notably, the latter two parameters were newly developed by our team and are therefore of an exploratory nature, intended to reflect different facets of free association, such as the length of the "semantic journey" (Flow Distance) and the size of the "journey steps" (Flow Steps). As an additional control, to rule out the possibility of a random spread of semantic distances, we furthermore calculated Semantic Spread, the average distance between all words.

Data analysis

Statistical analysis was performed with IBM SPSS Statistics (version 22). For intensity and valence, repeated measures General Linear Models (GLMreps) were implemented, with "treatment" and "time point" as within-subjects factors and "treatment order" as a between-subjects factor. For ARSQ (factors/items) and FFT (seed words/duration/semantic spread), an additional within-subjects factor "parameter" was added. Main effects of treatment (LSD, placebo), period (session 1, session 2) and order (LSD-placebo, placebo-LSD), interactions (treatment * time point) and pairwise comparisons for each time point and parameter were examined. Effect sizes were estimated using partial eta squared (η_p^2). Results were corrected *post hoc* for multiple comparisons by the Benjamini-Hochberg (BH) procedure (Benjamini and Hochberg 1995) to adjust more consistently over the different sizes of comparison families, namely, intensity and valence time points ($N = 21$), ARSQ factors ($N = 10$), ARSQ items ($N = 20$) and FFT parameters ($N = 3$). False discovery rate (FDR) was set to $q = \alpha = 0.05$.

Spearman's rank correlation coefficients (r_s) were calculated between LSD-induced changes (Δ = LSD − placebo) of intensity (ΔInt), valence (ΔVal), mind-wandering (ΔARSQ) and free association (ΔFFT). Significance level for correlations was set to $\alpha = 0.05$ and p-values were corrected *post hoc* for multiple comparisons by the number of scales ($N = 4$), as follows: $p_{\text{corrected}} = p_{\text{uncorrected}} * N$.

Results

Intensity and valence

For intensity, there was a significant main effect of treatment ($p < 0.001$) and interaction "treatment * time point" ($p = 0.008$), indicating LSD-induced time-dependent changes in subjective intensity (for detailed values of significant effects

Table 1 Values for the significant effects of treatment, period and order in the repeated measures General Linear Models (GLMrep) for intensity, valence and free association (Forward Flow Task, FFT)

Measurement[1]	GLMrep values	Means ± SD[2]
Treatment effects		
Intensity	$F(1,22) = 204.1, p < 0.001, \eta_p^2 = 0.90$	42.9 ± 12.8; 2.4 ± 3.4
Valence	$F(1,22) = 15.81, p = 0.001, \eta_p^2 = 0.42$	15.2 ± 14.1; 4.8 ± 13.0
Intensity (interaction treatment * time point)	$F(1,22) = 8.43, p = 0.008, \eta_p^2 = 0.28$	
Period effects		
Intensity	$F(1,22) = 8.22, p = 0.009, \eta_p^2 = 0.27$	26.7 ± 9.2; 18.6 ± 9.5
FFT animals	$F(1,22) = 5.98, p = 0.023, \eta_p^2 = 0.21$	0.75 ± 0.02; 0.74 ± 0.03
FFT objects	$F(1,22) = 4.75, p = 0.040, \eta_p^2 = 0.18$	0.75 ± 0.02; 0.74 ± 0.02
FFT duration	$F(1,22) = 7.21, p = 0.014, \eta_p^2 = 0.27$	109 ± 38; 96 ± 0.28
Order effects		
Intensity	$F(1,22) = 4.83, p = 0.039, \eta_p^2 = 0.18$	25.5 ± 8.8; 19.8 ± 8.8

[1]Main effects of treatment (LSD, placebo), period (session 1, session 2) and order (LSD-placebo, placebo-LSD) and interaction effects (treatment * time point) were evaluated

[2]Means and standard deviations (SD) are displayed for LSD and placebo (treatment effects), session 1 and session 2 (period effects) and treatment order LSD-placebo and placebo-LSD (order effects)

in all scales, see Table 1). For valence, there was a significant main effect of treatment ($p = 0.001$), but no interaction "treatment * time point", indicating LSD-induced overall changes in valence (for detailed values of non-significant effects in all scales, see Table S3). Pairwise comparisons revealed higher intensity for LSD, compared to placebo, from +0.5 h to +8 h (all $p \leq 0.025$) and more positive valence from +1 h to +4.5 h, at +5.5 h, and from +6.5 h to +7.5 h (all $p \leq 0.021$; Fig. 1). For intensity, there was a period effect ($p = 0.009$), with lower means in session 2 pointing to habituation effects, and an order effect ($p = 0.039$) with higher means in order LSD-placebo pointing to carryover effects. For valence, no period and order effects were observed.

Mind-wandering

For the ARSQ factors and items, there were no significant main effects of treatment, period and order and interactions "treatment * time point * parameter". Pairwise comparisons revealed for LSD, compared to placebo, increases in the factor Discontinuity of Mind at +2 h ($p < 0.001$), +4 h ($p = 0.002$) and +6 h ($p = 0.004$) and in the items Feeling Restless ($p < 0.001$), Not Sharing Thoughts ($p = 0.020$), Thoughts about Sounds ($p = 0.021$) and Thoughts about Odours ($p = 0.009$) at +2 h and Deep Thoughts at +2 h and +4 h (both $p \leq 0.001$) (Fig. 2, Fig. S2). Moreover, LSD decreased the factors Planning ($p = 0.009$) and Sleepiness ($p = 0.011$) at +2 h and the items Thoughts about Work ($p < 0.001$) and Thoughts about Past ($p = 0.005$) at +2 h, Feeling the Same and Thoughts under Control at +2 h and +4 h (all $p \leq 0.006$) and Feeling Bored at +4 h ($p = 0.009$). In order to condense these results, we grouped all significantly changed factors and items into qualitatively similar facets of mind-wandering based on the similarity of theme and denominated them by "chaos", "meaning" and "sensation" (Fig. 2, Table S4).

Chain free association

There was no treatment main effect or interaction for any seed word, duration or semantic spread (Fig. S3). Pairwise comparisons demonstrated increases under LSD, compared to placebo, in forward flow, flow distance and flow steps for abstract words at +4 h (all $p \leq 0.05$; Fig. 3). There were period effects for animals ($p = 0.023$), objects ($p = 0.040$) and duration ($p = 0.014$), with lower means in session 2 pointing to learning and habituation effects. No other period and order effect reached significance.

Correlations

Regarding intensity, ΔInt (+0.5 h to +1.5 h) correlated moderately positively with ΔVal (+1.5 h, +7 h, +7.5 h) and ΔARSQ Thoughts about Odours (+2 h) and moderately negatively with ΔFFT flow distance (+4 h) (Table 2). Regarding mind-wandering, there were moderate positive correlations between ΔARSQ Discontinuity of Mind and Feeling Restless (+2 h), between Planning and Thoughts about Work (+2 h), between Deep Thoughts at +2 h and +4 h and between Thoughts under Control at +2 h and +4 h, and a moderate negative correlation between Discontinuity

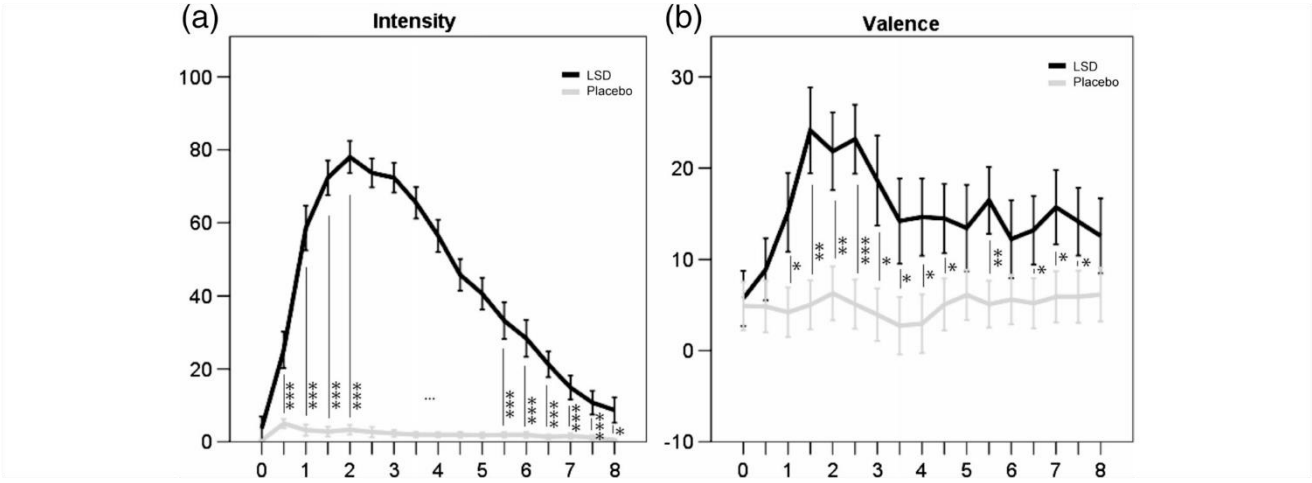
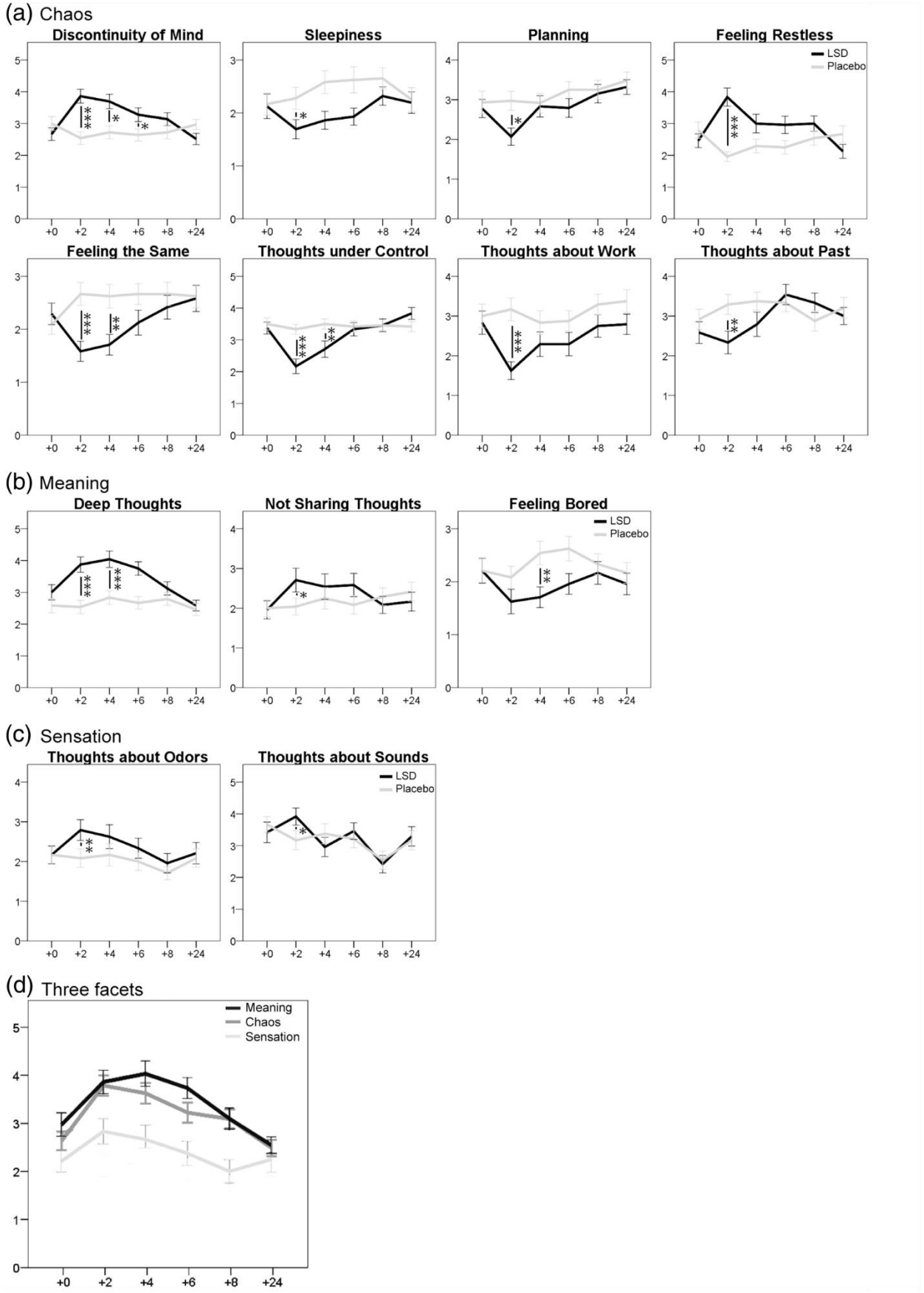


Fig. 1 Time course of subjective intensity and valence under 50 µg LSD and placebo. LSD, compared to placebo, increased **a** intensity from +0.5 h to +8 h, as rated on a visual analogue scale (VAS) from 0 (no effect) to 100 (extremely intense effect), and **b** valence from +1 h to +4.5 h, at +5.5 h, and from +6.5 h to +7.5 h, as rated on a VAS from −50 (extremely unpleasant effect) to 50 (extremely pleasant effect). Displayed are means (±SEM; *y*-axis) over the time course (hours after drug administration; *x*-axis) in 24 subjects. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (BH-corrected *post hoc* pairwise comparisons). For ease of comparison, only 30-min intervals are depicted


(a) Chaos
Discontinuity of Mind
Sleepiness
Planning
Feeling Restless
LSD
Placebo
Feeling the Same
Thoughts under Control
Thoughts about Work
Thoughts about Past
(b) Meaning
Deep Thoughts
Not Sharing Thoughts
Feeling Bored
(c) Sensation
Thoughts about Odors
Thoughts about Sounds
(d) Three facets
Meaning
Chaos
Sensation
+0 +2 +4 +6 +8 +24

◂**Fig. 2** The effects of LSD on mind-wandering, as measured by the Amsterdam Resting State Questionnaire (ARSQ). Overall, three facets of mind-wandering arose, including **a** a chaotic facet from +2 h to +6 h, **b** a meaningful facet from +2 h to +4 h, **c** and a sensory facet at +2 h; **d** the mind-wandering facets demonstrated different time courses, with chaos and sensation peaking at +2 h and meaning peaking later around +4 h (as exemplified by the time course of Discontinuity of Mind, Thoughts about Odours and Deep Thoughts, respectively). Displayed are means (±SEM) (0−4; *y*-axis) over the time course (hours after drug administration; *x*-axis) in 24 subjects. * $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.001$ (BH-corrected *post hoc* pairwise comparisons). Note that only factors and items with significant effects are displayed; for all factors and items, see Fig. S2

of Mind and Thoughts under Control (+4 h). Moreover, there were moderate to very high positive correlations within ΔFFT (Table 2), ΔInt and ΔVal (Table S5).

Discussion

Intensity and valence

The relatively low dose of 50 µg LSD elicited considerable subjective intensity and positive valence, which peaked around +2 h, lasting until +8 h. This is comparable to previous reports on higher LSD doses (75-200 µg) (Carhart-Harris et al. 2016; Dolder et al. 2017; Preller et al. 2017), besides an earlier peak and shorter duration in our study. The period effect (higher intensity in session 1) might be explained by higher expectations and insecurity regarding study procedures and drug effects, while the carryover effect (higher intensity in order LSD-placebo) indicates mid-term effects of LSD on the subjective experience. Both effects should be taken into consideration in treatment protocols for psycholytic therapy with doses around 50 µg (Buckman 1968). Specifically, lower doses might be indicated for the first session to accustom the patient to the setting, and for successive sessions with a short time lag (2 weeks) to avoid subjective exhaustion. Interestingly, early intensity measurements (+0.5 h to +1.5 h) correlated with effects at later time points, including positive relationships with valence (+1.5 h, +7 h, +7.5 h) and Thoughts about Odours (+2 h) and negative relationships with flow distance (+4 h). Put differently, stronger intensity before peak seemed to predict stronger positive valence at the beginning and the end, stronger sensory mind-wandering during peak and a shorter semantic journey after the peak. These findings point to a potential utility of early intensity to predict later emotion, perception and cognition and should be better explored in future studies.

Three facets of mind-wandering

The effects of LSD on mind-wandering seem to reflect three facets—a "chaotic", a "meaningful" and a "sensory" facet. The chaotic facet lasted from +2 h to +6 h and comprised increased Discontinuity of Mind and Feeling Restless and decreased Sleepiness, Planning, Feeling the Same, Thoughts under Control, Thoughts about Work and Thoughts about Past. The consistency within the chaotic facet is underlined by positive correlations between Discontinuity of Mind and Feeling Restless (+2 h), Planning and Thoughts about work (+2 h) and Thoughts under Control (+2 h and +4 h), and by a negative correlation between Discontinuity of Mind and Thoughts under Control (+4 h). The diverging effects of LSD on Discontinuity of Mind and Planning are opposed to the normally positive relationship between both factors (Diaz et al. 2014). The decreases in Planning and Thoughts about Past are in line with quantitative linguistic analyses and anecdotal findings reporting decreased time travel in mentation reports and storytelling (Rinkel et al. 1955; Speth et al. 2016) and might be related to distortions of time perception under LSD (Preller and Vollenweider 2016). Overall, the notion of more disorganized mind-wandering under LSD is coherent with anecdotal descriptions of a chase of loosened associations, flight of ideas and derailment of thoughts at the beginning of the effects (Leuner 1962, p. 36), subjective ratings of disinhibition and loss of control at +2 h and disconnected experiences and fast and difficult thinking at +5 h (Barr et al. 1972, p. 35). Moreover, recent LSD studies reported increased "cognitive bizarreness" (i.e. physically improbable/impossible elements) in mental imagery reports and subjectively impaired control and cognition (Schmid et al. 2015; Carhart-Harris et al. 2016; Kraehenmann et al. 2017b).

The meaningful facet lasted from +2 h to +4 h and comprised increased Deep Thoughts, Not Sharing Thoughts and reduced Feeling Bored. Notably, Not Sharing Thoughts was only increased at +2 h, but Deep Thoughts until +4 h. Similarly, previous findings observed increased subjective ratings of new meaning of and connections between experiences, better understanding and "talking more […] about personal things one would not usually talk about" at +5 h (Barr et al. 1972, p. 36). Changes in meaning are commonly observed under LSD (Preller et al. 2017; Wießner et al. 2021) and dose-dependently increased (Liechti 2017). Together with the second smaller peak of positive valence at +5.5 h in this study (Fig. 1B) and of trust, happiness, openness, closeness to others and wanting "to be with other people" at +3 h and +4 h in another study (Dolder et al. 2016), our results might point to a late therapeutic window in psycholytic therapy with decreased intensity and confusion, facilitated emotional processing, increased meaning, confidence and openness—allowing for a focus on psychotherapeutic work. Similarly, a previous work on LSD differentiated an earlier psychotic-like "stagnating-fragmented course" from a later "continuous-scenic course" with a stronger need to communicate and

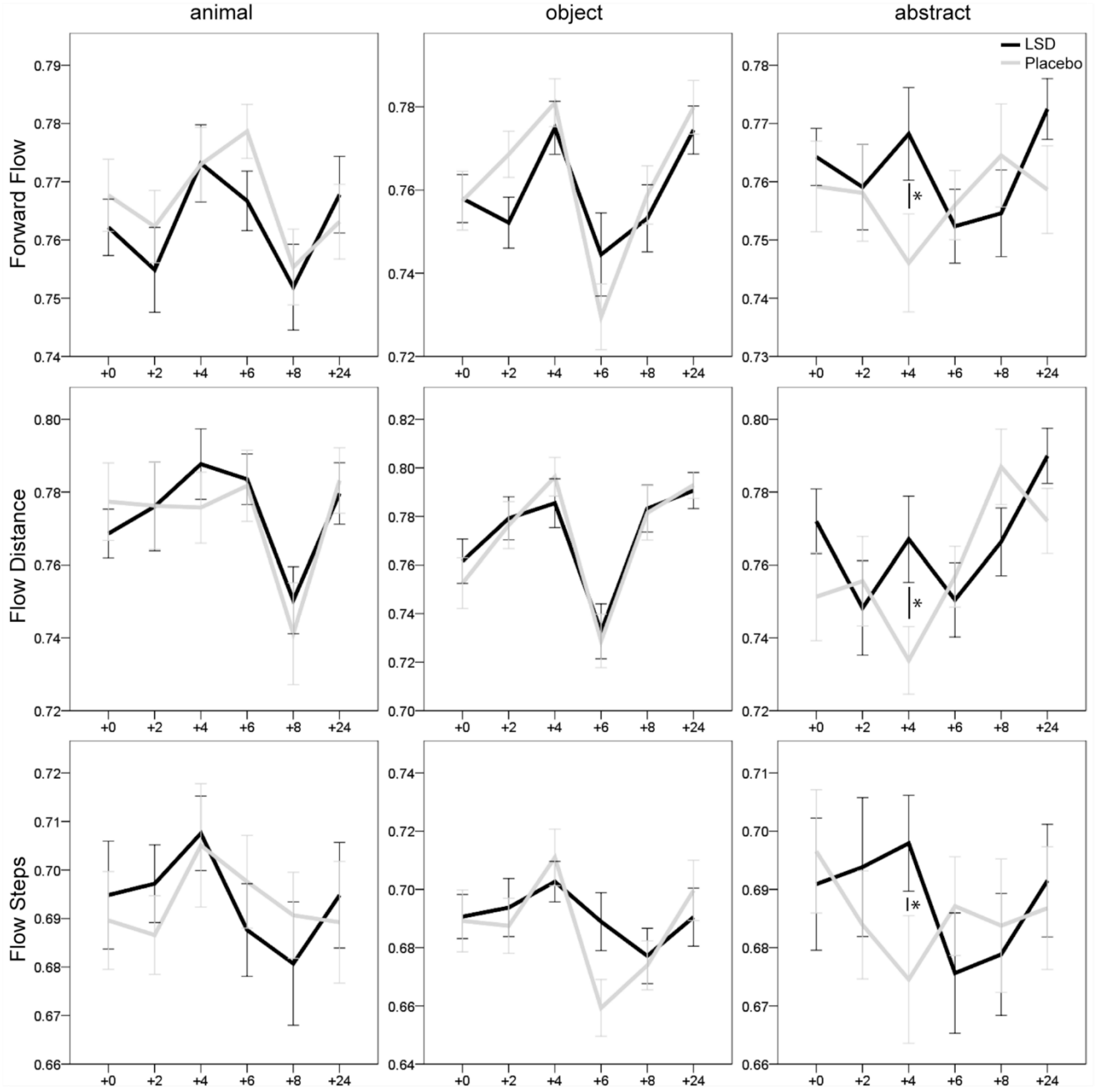


Fig. 3 The effects of LSD on free association, as measured by the Forward Flow Task (FFT) for different flow parameters and seed words (animals, objects, abstract). Flow parameters comprised forward flow, the average distance of each word to all predecessors, flow distance, the average distance of the seed word to all subsequent words and flow steps, the average distance between one word and its subsequent neighbour. Under LSD, all flow parameters were increased after abstract seed words at +4 h, while there were no effects for other seed words or time points. Displayed are means (±SEM) (0−1; *y*-axis) over the time course (hours after drug administration; *x*-axis) in 24 subjects. * $p \leq 0.05$ (BH-corrected *post hoc* pairwise comparisons)

more holistic experiences (e.g. childhood memories) that are guidable by a conversation (Leuner 1962, p. 75f, 186ff). Notably, some of these early LSD experiments were interrupted after 5-6 h by antipsychotic or sedative medication to economize time, which is why the therapeutic potential of this late phase needs to be better explored.

The sensory facet was expressed at +2 h, comprised Thoughts about Odours and Thoughts about Sounds and might reflect intensified sensory perception, a prominent, mostly anecdotally reported phenomenon under LSD and psilocybin (Preller and Vollenweider 2016; Kaelen et al. 2018; Wießner et al. 2021). Interestingly enough, the ARSQ

Table 2 Relationships between LSD-induced changes in intensity (ΔInt), valence (ΔVal), mind-wandering (ΔARSQ) and free association (ΔFFT)

		ΔInt			ΔARSQ										ΔFFT	
		+0.5	+1	+1.5	Disc +2	Plan +2	Deep +2	Rest +2	Odour +2	Work +2	Cont +2	Disc +4	Deep +4	Cont +4	Forw +4	Dist +4
ΔVal	+1.5	**0.55***	0.18	0.24												
	+7	0.35	**0.51***	**0.53***												
	+7.5	0.48	**0.62****	**0.61****												
ΔARSQ	Disc +2	0.20	0.16	0.10												
	Plan +2	−0.02	−0.13	−0.13	−0.12											
	Deep +2	−0.09	−0.28	−0.37	0.10	0.10										
	Rest +2	0.12	−0.09	−0.05	**0.61****	−0.28	0.05									
	Odour +2	**0.54***	0.40	0.36	−0.08	−0.01	−0.16	−0.17								
	Work +2	0.26	0.13	0.05	−0.15	**0.59***	0.19	−0.13	0.02							
	Cont +2	−0.21	−0.11	−0.04	−0.32	−0.14	0.08	−0.25	−0.09	−0.37						
	Disc +4	0.15	0.20	0.12	0.20	0.37	−0.17	−0.07	0.13	0.23	−0.34					
	Deep +4	−0.04	0.07	0.17	0.43	−0.04	**0.63****	0.28	−0.18	0.10	−0.00	−0.12				
	Cont +4	−0.16	−0.11	−0.04	−0.19	−0.21	0.08	−0.06	0.09	−0.40	**0.60****	**−0.58***	0.16			
ΔFFT	Forw +4	−0.07	−0.40	−0.40	−0.17	0.30	0.22	−0.20	−0.06	0.19	−0.11	−0.22	0.03	0.04		
	Dist +4	−0.31	**−0.60***	**−0.60****	−0.26	0.23	0.16	−0.23	−0.15	0.09	−0.13	−0.25	−0.22	0.09	**0.84*****	
	Step +4	0.06	−0.15	−0.21	0.15	0.14	0.00	−0.10	0.07	0.02	−0.14	−0.05	0.11	−0.06	**0.64****	0.47

Values depict Spearman's rank correlation coefficients in $n = 24$ subjects with significant correlations marked in **bold**. For presentation purposes, only variables yielding significant correlations are depicted. +2, at +2 h post-administration; +4, at +4 h post-administration

ARSQ Amsterdam Resting State Questionnaire; *Disc* Discontinuity of Mind; *Plan* Planning; *Deep* Deep Thoughts; *Rest* Feeling Restless; *Odour* Thoughts about Odours; *Work* Thoughts about Work; *Cont* Thoughts under Control; *FFT* Forward Flow Task; *Forw* forward flow for abstract words; *Dist* flow distance for abstract words; *Step* flow steps for abstract words

* $p \leq 0.05$

** $p \leq 0.01$

*** $p \leq 0.001$ (corrected)

factors Visual Thought, Somatic Awareness, Self and Theory of Mind were not affected (Fig. S2). This contradicts reports of LSD-induced changes in visual, body, self, other-perception (Dolder et al. 2016; Kometer and Vollenweider 2016; Liechti 2017; Wießner et al. 2021) and might be explained by the low dose. However, another explanation might lie in assessment differences, since these previous results were elicited by explicit eyes-open tests or overall, retrospective ratings, leaving room for stronger salience and memory biases than our immediate evaluation of short mind-wandering intervals.

Abstract flow during chain free association

LSD increased all flow parameters for abstract words but not for animals and objects, pointing to an LSD-induced "abstract flow". Notably, several early, mostly preliminary or anecdotal observations described changes in the use and understanding of abstract content under LSD and psilocybin, for example within experience reports or proverb interpretations (Silverstein and Klee 1958; Leuner 1962, p. 36; Young 1974). Our results support the notion that the processing of abstract content might be changed under LSD, indicating that abstract input augments unconstrained semantic processing under LSD.

Specifically, LSD increased forward flow, flow distance and flow steps but not semantic spread, indicating that semantic distances of words were meaningfully increased in relation to their predecessors, successors and neighbours but not overall, randomly spread. Similarly, LSD and psilocybin have been observed to change, but not completely disturb, semantic recognition and production. In word/picture recognition tasks, medium doses of psilocybin (0.2 mg/kg p.o.) and LSD (40-80 µg i.v.) were shown to enhance semantic priming of indirectly related (but not unrelated) words (Spitzer et al. 1996) and naming errors of semantically similar (but not different) pictures (Family et al. 2016). Analyses of natural speech rendered decreased predictability and increased variability of semantic content under high (100 and 200 µg) and moderate (75 µg) LSD doses, respectively (Amarel and Cheek 1965; Sanz et al. 2021). An explanation might be reduced attentional control and integration of contextual information, which are known to emerge under psilocybin (Umbricht et al. 2003; Carter et al. 2005). This would explain the lack of effects for concrete words (animals, objects), for which semantic processing might be more automatic and require less attentional control and contextual retrieval. This notion is supported by the period effects (lower animal flow and object flow in session 2), indicating habituation effects that did not arise for higher level abstract words.

Overall, our findings, together with previous results, indicate that LSD augments unconstrained semantic associations, possibly due to reduced control and integration mechanisms, and that these associations are meaningful and best induced by abstract input. The notion of an LSD-induced, meaningful abstract flow is in line with anecdotal reports of a "symbolic level" under LSD and related compounds, characterized by spontaneously arising, highly dynamic symbols (Masters and Houston 1966). These symbols were thought to express sensations, thoughts and emotions and be useful for guiding LSD-induced experiences and promoting therapeutically useful effects (Leuner 1962; Gasser et al. 2015). Similarly, Freud pointed to symbols in dreams being unintentional and highly problem-associated, underlining their importance in psychoanalytic processes (Freud 1940, p. 218). With this in mind, our results highlight the importance of examining the therapeutic potential of LSD-induced meaning-laden thinking in the freely wandering mind.

Relationships between mind-wandering and chain free association

Overall, LSD seemed to similarly affect the passive and active stream of thought towards deviant but meaningful thought patterns with increased chaos and meaning during mind-wandering and abstract flow during free association. Yet, the effects in mind-wandering arose earlier and were more pronounced than in free association, suggesting earlier and stronger modulations of spontaneous than stimulus-induced thought.

Specifically, the chaotic, meaningful and sensory mind-wandering facets were all pronounced near the subjective intensity and valence peak at +2 h. However, a remarkable time window emerged during decreasing intensity at +4 h, with lower chaotic and more meaningful mind-wandering, abstract flow and positive valence. These concurrent effects on thought processes and emotionality further support the notion that a late therapeutic window in psycholytic therapy deserves closer examination.

The stronger effects in mind-wandering than free association might suggest that the spontaneous stream of thought is more impacted than its stimulus-induced counterpart. In line with this, mind-wandering and free association effects were not correlated, pointing to two unrelated processes. In fact, mind-wandering is involuntary and internal, while free association is induced by a seed word and requires the expression of associations. However, an alternative explanation might lie in measurement differences (questionnaire vs. task, subjective evaluation vs. objective computation, direct self-reports vs. indirect semantic distances). This could imply that LSD changes more the subjective perception than the objective measurement of the stream of thought. Alternatively, self-reports might be more suitable for assessing

thought patterns than computations of semantic distances. These perspectives should be disentangled in future studies.

Limitations

Memory biases could have influenced self-reported mind-wandering especially under LSD, known to affect short-term memory (Pokorny et al. 2019), although the ARSQ validation factor did not indicate self-reported impaired motivation or capacity to evaluate the items (Fig. S2A). The ARSQ items (Fig. S2B) are non-factor items, and, despite correction for multiple comparisons, must be interpreted with caution. The grouping of ARSQ factors and items into mind-wandering facets is of explorative, qualitative nature and needs to be statistically confirmed in future studies. The free association parameters flow distance and flow steps are newly developed by our team, which is why their usefulness and relation to forward flow need to be assessed. The calculation of flow parameters depended on a Portuguese corpus which is not as extensive as its English counterpart, reducing the comparability across languages. The effects were less pronounced in free association than in mind-wandering, possibly due to differences in cognitive processes or assessment methods, but potentially indicating null results, despite correction for multiple testing and possibly related to the small sample size. Lastly, our results were elicited in healthy participants and need to be replicated in clinical populations.

Conclusion

This study aimed at elucidating the time-dependent changes in passive and active stream of thought using a low LSD dose, as previously used in psycholytic therapy. The results might have implications on a technical and therapeutic level. For the technical level, our time-specific, multifaceted investigation of free thought allowed us to approach the core of the LSD-induced phenomenology, in other words, the nature of the "psychedelic mind" *per se*, which seems to be characterized by chaos, meaning, sensation and abstract flow. As for the therapeutic level, LSD might provide a tool to modulate dysfunctional stream of thought patterns in clinical disorders. The concurrently increased valence, meaning and abstract flow during the later phase might open a valuable time window in psycholytic therapy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00213-021-06006-3.

Acknowledgements We thank Rodolfo Olivieri for his support in the data collection, Jon Sharp for the English language revision and Valerie Bonnelle for miscellaneous help.

Author contributions IW, LOM, DBA and LFT contributed to the study design. IW, MF and LFT recruited and selected the participants. IW and MF collected the data. IW, FPF and NBM analysed the data. IW wrote the manuscript. All authors revised the manuscript for intellectual content and approved its final version.

Funding This study received financial support from the Beckley Foundation and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) - Finance Code 001.

The study was approved by the Research Ethics Committee of the University of Campinas and conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent before participation.

Declarations

Conflict of interest The authors declare no competing interests.

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Supplementary Information

LSD and the Stream of Thought: Increased Discontinuity of Mind, Deep Thoughts and Abstract Flow

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Supplementary Methods

Mind-Wandering

Besides the ten regular, validated factors, the ARSQ contains one validation factor, which examines how well the participants felt able to respond to the questions, and 20 additional, non-factor single items, which were analyzed to gain insights into complementary phenomena. The ARSQ was translated into Brazilian Portuguese by our team; validation is currently in progress.

Free Association

For preprocessing, spelling errors were corrected by automatic spellchecking. Next, hyphens in composite words (e.g. arco-íris [rainbow]) were replaced with a space, as the software does not process special characters. In this way, average semantic distances in a chain were slightly modified (i.e. "arco íris" [rain bow]), but number of missing values could be reduced. Next, word chains were transformed into .txt files using MATLAB (version R2015a; The MathWorks, Inc., Natick, MA, USA). For easier handling, answers over all time points and sessions were merged into one .txt document per subject, resulting in 25 .txt documents. These documents were crossed with themselves in the Text Similarity Tool, yielding 25 word similarity matrices of (21 words x 6 time points x 2 sessions =) 252 x 252 dimension. In these similarity matrices, a value of 1 indicates absolute similarity (the word crossed with itself) and 0 indicates absolute distance. However, in practice, a value of 0 indicates an unprocessable word for the software because it is not contained in the underlying corpus. Therefore, the matrices were manually examined for 0-values, which were excluded from the analyses. Altogether, there were 115 unprocessable words out of a total of 6174 words (1.86%). In a next step, 21 x 21 similarity matrices (one seed word and 20 associated words) were extracted from the larger matrices for each subject, time point, and session using MATLAB. Missing values were interpolated and similarity matrices converted into distance matrices as follows: $value_{distance} = 1 - value_{similarity}$.

Supplementary Tables

Table S1. The abbreviations and content of the 20 non-factor items of the Amsterdam Resting State Questionnaire (ARSQ) that were analyzed in addition to the regular 10 factors

No.	Abbreviation	ARSQ item
31	Feeling Restless	I felt restless.
32	Enjoying Session	I enjoyed the session.
33	Negative Feelings	I had negative feelings.
34	Feeling Bored	I felt bored.
35	Feeling Nothing	I felt nothing.
36	Feeling the Same	I felt about the same throughout the session.
37	Thoughts about Work	I thought about my work/study.
38	Not Sharing Thoughts	I had thoughts that I would not readily share with others.
39	Similar Thoughts	I had similar thoughts throughout the session.
40	Pleasant Thoughts	I thought about pleasant things.
41	Thoughts under Control	I had my thoughts under control.
42	Thoughts about Experiment	I thought about the aim of the experiment.
43	Superficial Thoughts	I had superficial thoughts.
44	Thoughts about Past	I thought about the past.
45	Thoughts about Present	I thought about the present.
46	Deep Thoughts	I had deep thoughts.
47	Thoughts about Nothing	I thought about nothing.
48	Thoughts about Sounds	I thought about the sounds around me.
49	Thoughts about Odors	I thought about the odors around me.
55	Hear Music	In my thoughts I heard music.

Table S2. The two versions of seed words for the Forward Flow Task (FFT) applied over both sessions

Time point	Version A	Frequency	Version B	Frequency
Animal				
+0	Ox [boi]	10244	Horse [cavalo]	17484
+2	Tiger[tigre]	6447	Jaguar [onça]	4075
+4	Alligator [jacaré]	5525	Whale [baleia]	6302
+6	Birdie [passarinho]	2002	Butterfly [borboleta]	2662
+8	Dog [cachorro]	17231	Cat [gato]	16545
+24	Monkey [macaco]	6151	Bear [urso]	6248
Object				
+0	Sofa [sofá]	8925	Carpet [tapete]	8390
+2	Eraser [borracha]	10109	Rope [corda]	8863
+4	Vase [vaso]	3916	Hammer [martelo]	5103
+6	Sheet [lençol]	2836	Pillow [travesseiro]	1511
+8	Wheel [roda]	20604	Dish [prato]	24969
+24	Book [livro]	178056	Cube [dado]	109540
Abstract				
+0	Love [amor]	141911	Peace [paz]	99333
+2	Connection [conexão]	24063	Sensation [sensação]	46443
+4	Feeling [sentimento]	35901	Tought [pensamento]	31153
+6	Space [espaço]	372063	Time [tempo]	860268
+8	Sin [pecado]	7435	Vanity [vaidade]	4167
+24	Relationship [relação]	431373	Value [valor]	480527

Words for both versions were selected based on a balanced frequency in natural language, as calculated by a Portuguese corpus (https://www.corpusdoportugues.org/now/).

Table S3. Values for the non-significant effects of treatment, period and order in the repeated measures General Linear Models (GLMrep) for mind-wandering (Amsterdam Resting State Questionnaire, ARSQ) and free association (Forward Flow Task, FFT)

Measurement[1]	**GLMrep values**
Treatment effects	
ARSQ factor	$F(1,22)=0.66$, $p=0.424$, $\eta_p^2=0.03$
ARSQ items	$F(1,22)=0.88$, $p=0.359$, $\eta_p^2=0.04$
FFT animal	$F(1,22)=0.03$, $p=0.872$, $\eta_p^2<0.01$
FFT object	$F(1,22)=0.02$, $p=0.896$, $\eta_p^2<0.01$
FFT abstract	$F(1,22)=1.50$, $p=0.234$, $\eta_p^2=0.06$
FFT duration	$F(1,22)=0.03$, $p=0.874$, $\eta_p^2<0.01$
FFT Semantic Spread	$F(1,22)=0.17$, $p=0.687$, $\eta_p^2<0.01$
Valence (treatment*time)	$F(1,22)=0.04$, $p=0.835$, $\eta_p^2<0.01$
ARSQ factor (treatment * time point * parameter)	$F(1,22)=0.31$, $p=0.583$, $\eta_p^2=0.01$
ARSQ items (treatment * time point * parameter)	$F(1,22)=2.64$, $p=0.119$, $\eta_p^2=0.11$
FFT animal (treatment * time point * parameter)	$F(1,22)=3.04$, $p=0.095$, $\eta_p^2=0.12$
FFT object (treatment * time point * parameter)	$F(1,22)=1.04$, $p=0.319$, $\eta_p^2=0.05$
FFT abstract (treatment * time point * parameter)	$F(1,22)=0.03$, $p=0.877$, $\eta_p^2<0.01$
FFT duration (treatment * time point * parameter)	$F(1,22)=0.03$, $p=0.874$, $\eta_p^2<0.01$
FFT Semantic Spread (treatment * time point * parameter)	$F(1,22)<0.01$, $p=0.985$, $\eta_p^2<0.01$
Period effects	
Valence	$F(1,22)=2.73$, $p=0.113$, $\eta_p^2=0.11$
ARSQ factor	$F(1,22)=0.12$, $p=0.733$, $\eta_p^2=0.01$
ARSQ items	$F(1,22)=1.81$, $p=0.193$, $\eta_p^2=0.08$
FFT abstract	$F(1,22)=3.24$, $p=0.085$, $\eta_p^2=0.13$
FFT Semantic Spread	$F(1,22)=4.20$, $p=0.053$, $\eta_p^2=0.16$
Order effects	
Valence	$F(1,22)=3.18$, $p=0.088$, $\eta_p^2=0.13$
ARSQ factor	$F(1,22)=0.08$, $p=0.785$, $\eta_p^2<0.01$
ARSQ items	$F(1,22)=0.03$, $p=0.873$, $\eta_p^2<0.01$
FFT animal	$F(1,22)=0.43$, $p=0.517$, $\eta_p^2=0.02$
FFT object	$F(1,22)=0.01$, $p=0.933$, $\eta_p^2<0.01$
FFT abstract	$F(1,22)=0.49$, $p=0.492$, $\eta_p^2=0.02$
FFT duration	$F(1,22)=0.46$, $p=0.506$, $\eta_p^2=0.02$
FFT Semantic Spread	$F(1,22)=0.68$, $p=0.418$, $\eta_p^2=0.03$

[1] Main effects of treatment (LSD, placebo), period (session 1, session 2) and order (LSD-placebo, placebo-LSD) and interaction effects ('treatment * time point' for valence and 'treatment * time point * parameter' for ARSQ and FFT) were evaluated.

Table S4. The composition of the mind-wandering facets chaos, meaning and sensation from all ARSQ factors and non-factor items that demonstrated LSD-induced changes

Facet	**Type**	**Name of factor/non-factor item**	**ARSQ item(s) no.**
Chaos	factor	Discontinuity of Mind	1, 2, 3
	factor	Planning	10, 11, 12
	factor	Sleepiness	13, 14, 15
	item	Feeling Restless	31
	item	Feeling the Same	36
	item	Thoughts about Work	37
	item	Thoughts under Control	41
	item	Thoughts about Past	44
Meaning	item	Feeling Bored	34
	item	Not Sharing Thoughts	38
	item	Deep Thoughts	46
Sensation	item	Thoughts about Sounds	48
	item	Thoughts about Odors	49

Table S5. Relationships between LSD-induced changes within intensity (ΔInt) and valence (ΔVal) at several time points after drug administration

ΔInt

ΔInt	+0.5	+1	+1.5	+2	+2.5	+3	+3.5	+4	+4.5	+5	+5.5	+6	+6.5	+7	+7.5
+1	0.66**														
+1.5	0.43	0.87***													
+2	0.40	0.74***	0.88***												
+2.5	0.19	0.66**	0.82***	0.88***											
+3	0.21	0.52*	0.66**	0.82***	0.92***										
+3.5	0.29	0.59*	0.66**	0.82***	0.90***	0.95***									
+4	0.38	0.59**	0.57*	0.69***	0.75***	0.81***	0.92***								
+4.5	0.03	0.36	0.42	0.46	0.67***	0.70***	0.75***	0.83***							
+5	-0.02	0.37	0.40	0.49	0.58*	0.59**	0.71***	0.82***	0.90***						
+5.5	0.29	0.32	0.22	0.33	0.36	0.42	0.56*	0.72***	0.72***	0.77***					
+6	0.45	0.30	0.16	0.25	0.23	0.31	0.46	0.68***	0.63**	0.67**	0.94***				
+6.5	0.29	0.24	0.19	0.23	0.24	0.29	0.41	0.63**	0.67***	0.67***	0.81***	0.86***			
+7	0.31	0.24	0.19	0.20	0.25	0.29	0.40	0.60**	0.67***	0.63**	0.78***	0.83***	0.95***		
+7.5	0.35	0.21	0.13	0.07	0.13	0.19	0.25	0.44	0.56*	0.43	0.64**	0.70***	0.85***	0.93***	
+8	0.32	0.18	0.11	0.04	0.11	0.16	0.23	0.40	0.51*	0.39	0.62**	0.68***	0.79***	0.90***	0.99***

ΔVal

ΔVal	+1	+1.5	+2	+2.5	+3	+3.5	+4	+4.5	+5.5	+6.5	+7
+1.5	0.53*										
+2	0.283	0.79***									
+2.5	0.47	0.64**	0.62**								
+3	0.57*	0.66**	0.56*	0.69***							
+3.5	0.66**	0.58*	0.372	0.59**	0.89***						
+4	0.62**	0.7***	0.388	0.49	0.7***	0.76***					
+4.5	0.58*	0.49	0.204	0.57*	0.52*	0.66**	0.84***				
+5.5	0.5	0.312	0.161	0.45	0.254	0.46	0.55*	0.78***			
+6.5	0.41	0.381	0.308	0.277	0.347	0.45	0.59**	0.68***	0.8***		
+7	0.298	0.227	0.137	0.174	0.244	0.391	0.54*	0.67***	0.73***	0.89***	
+7.5	0.215	0.216	0.171	0.141	0.149	0.264	0.388	0.51*	0.71***	0.89***	0.91***

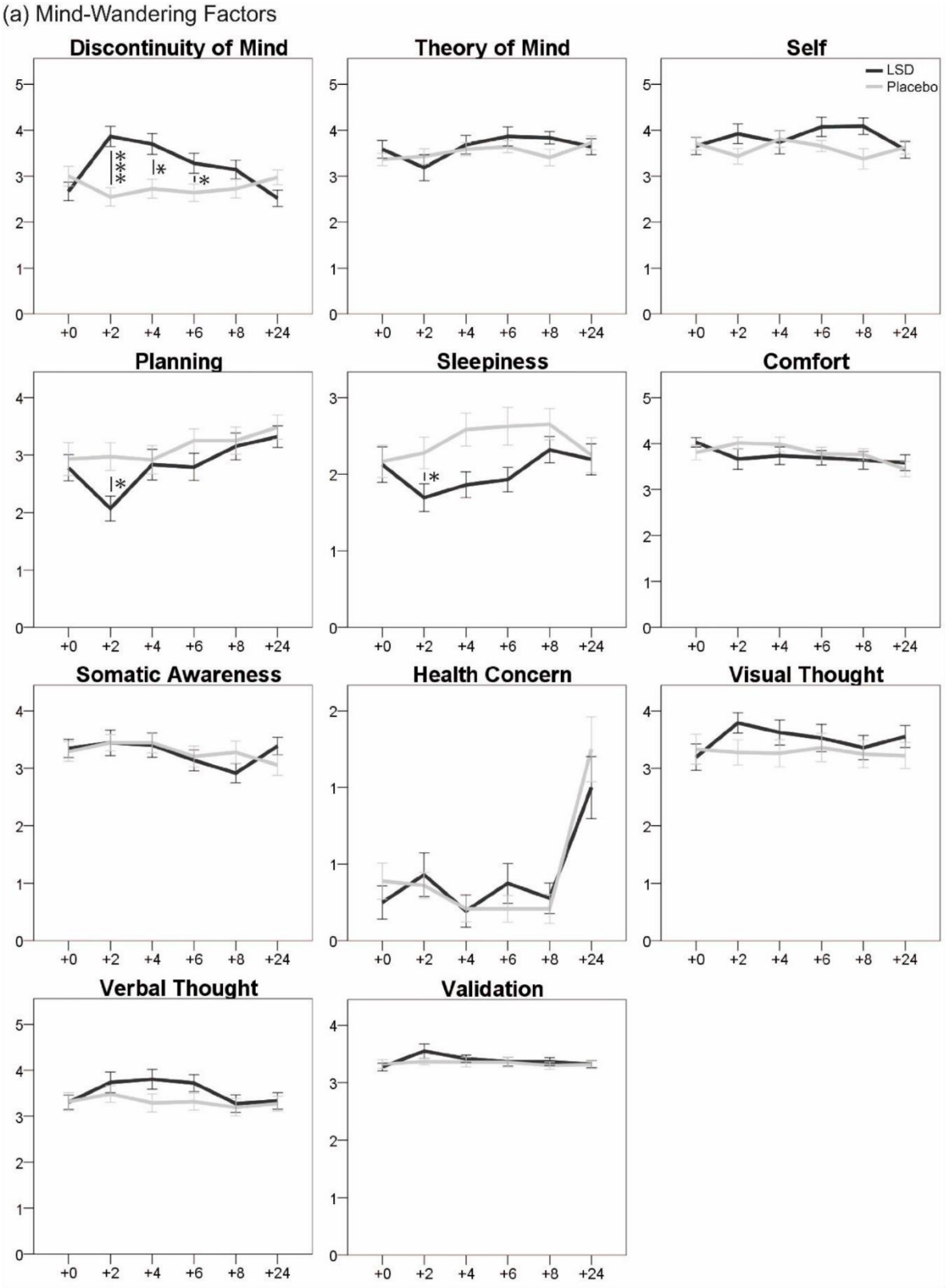
Values depict Spearman's rank correlation coefficients in n=24 subjects. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$ (corrected). For presentation purposes, only variables yielding significant correlations are depicted.

Supplementary Figures

		seed	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
seed	ox	0,00	0,52	0,60	0,86	0,87	0,89	0,85	0,82	0,88	0,78	0,76	0,67	0,83	0,66	0,74	0,72	0,77	0,72	0,74	0,66	0,72
1	cow	0,52	0,00	0,49	0,72	0,83	0,73	0,76	0,84	0,79	0,75	0,73	0,73	0,83	0,59	0,65	0,58	0,62	0,51	0,59	0,59	0,48
2	manure	0,60	0,49	0,00	0,75	0,86	0,73	0,60	0,82	0,78	0,66	0,62	0,78	0,91	0,57	0,63	0,56	0,68	0,66	0,65	0,60	0,53
3	mushroom	0,86	0,72	0,75	0,00	0,92	0,61	0,72	0,90	0,74	0,78	0,74	0,81	0,89	0,81	0,84	0,83	0,67	0,65	0,73	0,73	0,72
4	journey	0,87	0,83	0,86	0,92	0,00	0,81	0,98	0,88	0,92	0,90	0,87	0,81	0,80	0,90	0,86	0,72	0,83	0,91	0,95	0,84	0,93
5	hallucinogen	0,89	0,73	0,73	0,61	0,81	0,00	0,70	0,88	0,41	0,58	0,65	0,73	0,92	0,80	0,79	0,78	0,73	0,91	0,93	0,83	0,82
6	acid	0,85	0,76	0,60	0,72	0,98	0,70	0,00	0,88	0,78	0,62	0,73	0,81	1,00	0,74	0,90	0,86	0,85	0,76	0,80	0,80	0,64
7	paper	0,82	0,84	0,82	0,90	0,88	0,88	0,88	0,00	0,94	0,95	0,84	0,74	0,93	0,81	0,86	0,83	0,80	0,88	0,87	0,76	0,79
8	ayahuasca	0,88	0,79	0,78	0,74	0,92	0,41	0,78	0,94	0,00	0,63	0,68	0,78	0,96	0,77	0,72	0,82	0,92	0,90	0,92	0,88	0,79
9	vomit	0,78	0,75	0,66	0,78	0,90	0,58	0,62	0,95	0,63	0,00	0,77	0,89	0,99	0,78	0,78	0,70	0,83	0,84	0,87	0,82	0,75
10	snuff	0,76	0,73	0,62	0,74	0,87	0,65	0,73	0,84	0,68	0,77	0,00	0,68	0,86	0,65	0,75	0,80	0,72	0,81	0,75	0,75	0,59
11	indian	0,67	0,73	0,78	0,81	0,81	0,73	0,81	0,74	0,78	0,89	0,68	0,00	0,73	0,72	0,68	0,83	0,92	0,87	0,90	0,82	0,81
12	village	0,83	0,83	0,91	0,89	0,80	0,92	1,00	0,93	0,96	0,99	0,86	0,73	0,00	0,82	0,84	0,85	0,97	0,77	0,84	0,83	0,84
13	manioc	0,66	0,59	0,57	0,81	0,90	0,80	0,74	0,81	0,77	0,78	0,65	0,72	0,82	0,00	0,67	0,62	0,71	0,63	0,68	0,57	0,54
14	ant	0,74	0,65	0,63	0,84	0,86	0,79	0,90	0,86	0,72	0,78	0,75	0,68	0,84	0,67	0,00	0,67	0,79	0,76	0,84	0,72	0,68
15	food	0,72	0,58	0,56	0,83	0,72	0,78	0,86	0,83	0,82	0,70	0,80	0,83	0,85	0,62	0,67	0,00	0,59	0,61	0,60	0,51	0,60
16	cheesecake	0,77	0,62	0,68	0,67	0,83	0,73	0,85	0,80	0,92	0,83	0,72	0,92	0,97	0,71	0,79	0,59	0,00	0,60	0,63	0,58	0,57
17	cheese	0,72	0,51	0,66	0,65	0,91	0,91	0,76	0,88	0,90	0,84	0,81	0,87	0,77	0,63	0,76	0,61	0,60	0,00	0,37	0,46	0,36
18	ham	0,74	0,59	0,65	0,73	0,95	0,93	0,80	0,87	0,92	0,87	0,75	0,90	0,84	0,68	0,84	0,60	0,63	0,37	0,00	0,55	0,47
19	bread	0,66	0,59	0,60	0,73	0,84	0,83	0,80	0,76	0,88	0,82	0,75	0,82	0,83	0,57	0,72	0,51	0,58	0,46	0,55	0,00	0,45
20	butter	0,72	0,48	0,53	0,72	0,93	0,82	0,64	0,79	0,79	0,75	0,59	0,81	0,84	0,54	0,68	0,60	0,57	0,36	0,47	0,45	0,00
	Means		0,52	0,55	0,78	0,87	0,75	0,77	0,86	0,78	0,74	0,74	0,77	0,89	0,74	0,76	0,75	0,78	0,75	0,76	0,70	0,65

Semantic Spread
Forward Flow
Flow Distance
Flow Steps

Fig. S1 Calculation of different semantic distance indices, as exemplified by one subject's output (subject #1, session 1, time point +0h). The numbers display semantic distances between words. Forward Flow is calculated by the average of all column averages (red cells), i.e. the average distance of the current word from all preceding words, Flow Distance by the average distance of the seed word to all subsequent words (orange cells), Flow Steps by the average distance between neighbouring words (black-framed cells) and Semantic Spread by the average distance between all words (pink cells). For presentation purposes, the English translations of the words are displayed, but the depicted values were obtained for the original Portuguese material


(a) Mind-Wandering Factors
Discontinuity of Mind
Theory of Mind
Self
LSD
Placebo
Planning
Sleepiness
Comfort
Somatic Awareness
Health Concern
Visual Thought
Verbal Thought
Validation
+0
+2
+4
+6
+8
+24

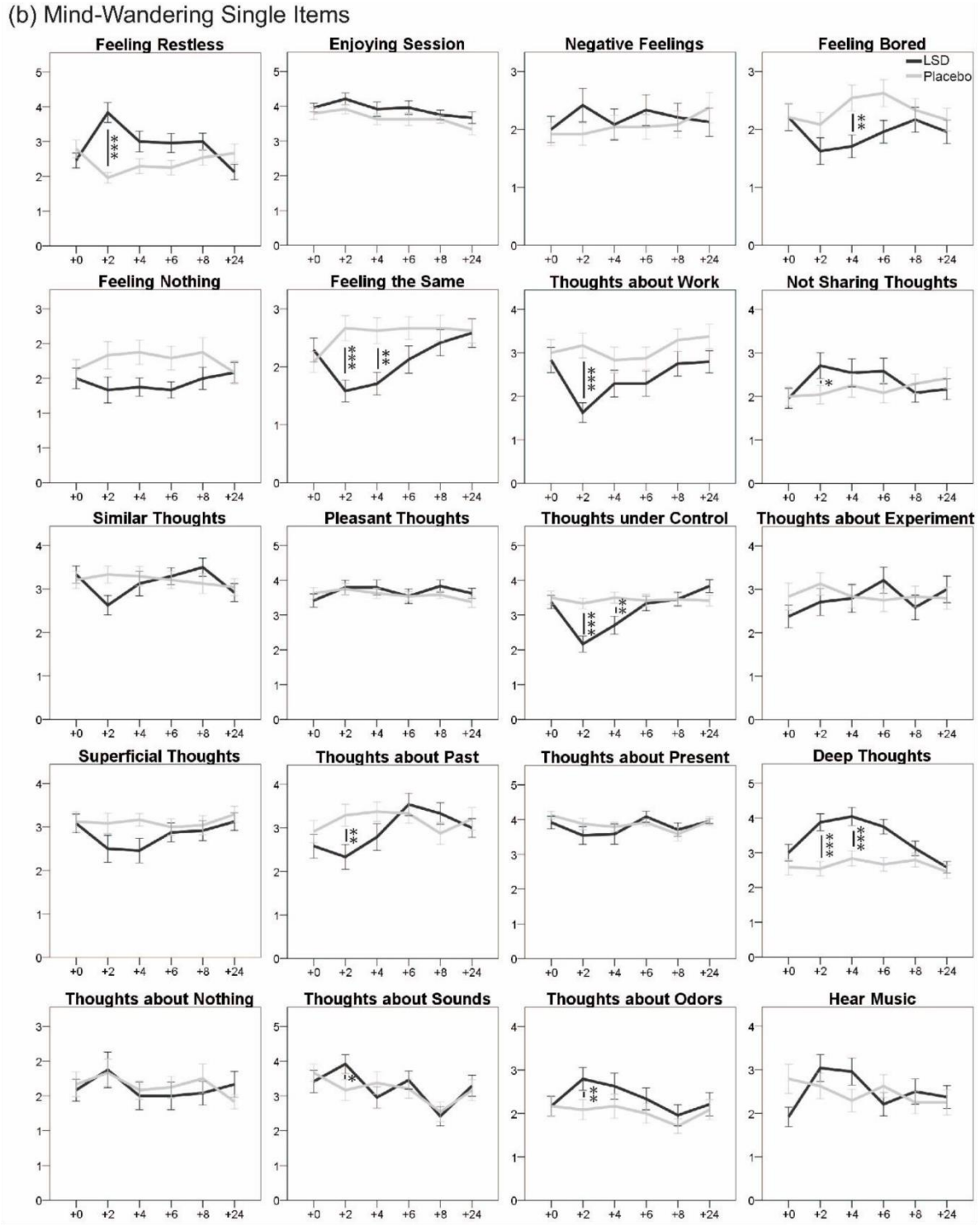


Fig. S2 Mind-wandering as measured by the Amsterdam Resting State Questionnaire (ARSQ) for (a) 10 factors and (b) 20 single items. Displayed are mean scores (0-4; y-axis) over the time course (hours after drug administration; x-axis). *p<0.05, **p<0.01, ***p≤0.001 (BH-corrected *post hoc* pairwise comparisons)

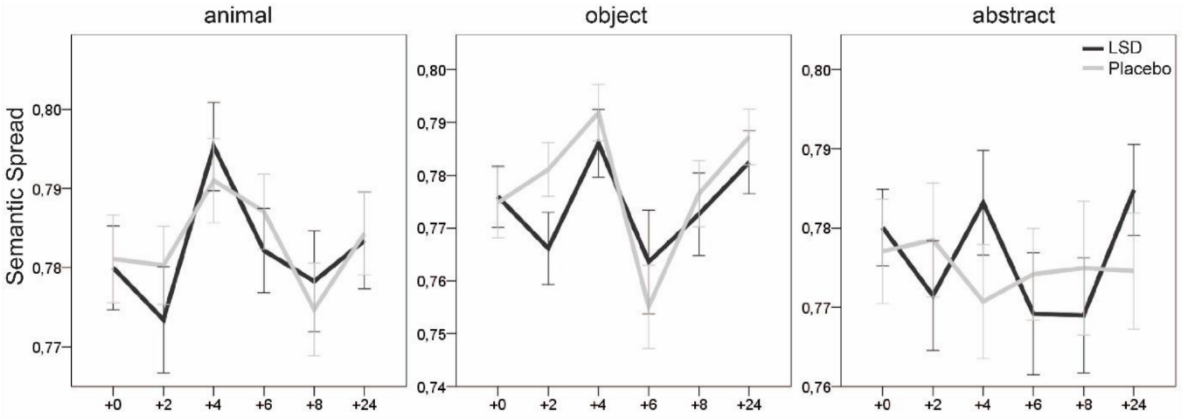


Fig. S3 Semantic Spread during free association, as measured by the average distance between all words in the Forward Flow Task (FFT), for three seed word types (animals, objects, abstract words). Displayed are mean scores (0-4; y-axis) over the time course (hours after drug administration; x-axis) in 24 subjects. *$p \leq 0.05$ (uncorrected)

4.2. Article 2 – LSD and Creativity

Reference (97):

Wießner I, Falchi M, Maia LO, Daldegan-Bueno D, Palhano-Fontes F, Mason NL, Ramaekers JG, Gross ME, Schooler JW, Feilding A, Ribeiro S, Araujo DB, Tófoli LF. LSD and creativity: Increased novelty and symbolic thinking, descreased utility and convergent thinking. J Psychopharmacol [Internet]. 01/02/2022. 2022;36(3):348–59. Available from: https://doi.org/10.1177/02698811211069113

Original Paper

Psychopharm

Journal of Psychopharmacology
2022, Vol. 36(3) 348–359

DOI: 10.1177/02698811211069113
journals.sagepub.com/home/jop
SAGE

LSD and creativity: Increased novelty and symbolic thinking, decreased utility and convergent thinking

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Abstract

Background: Controversy surrounds psychedelics and their potential to boost creativity. To date, psychedelic studies lack a uniform conceptualization of creativity and methodologically rigorous designs.

Aims: This study aimed at addressing previous issues by examining the effects of lysergic acid diethylamide (LSD) on creativity using multimodal tasks and multidimensional approaches.

Methods: In a randomized, double-blind, placebo-controlled, crossover study, 24 healthy volunteers received 50 µg of LSD or inactive placebo. Near drug peak, a creativity task battery was applied, including pattern meaning task (PMT), alternate uses task (AUT), picture concept task (PCT), creative metaphors task (MET) and figural creativity task (FIG). Creativity was assessed by scoring creativity criteria (novelty, utility, surprise), calculating divergent thinking (fluency, originality, flexibility, elaboration) and convergent thinking, computing semantic distances (semantic spread, semantic steps) and searching for data-driven special features.

Results: LSD, compared to placebo, changed several creativity measurements pointing to three overall LSD-induced phenomena: (1) 'pattern break', reflected by increased novelty, surprise, originality and semantic distances; (2) decreased 'organization', reflected by decreased utility, convergent thinking and, marginally, elaboration; and (3) 'meaning', reflected by increased symbolic thinking and ambiguity in the data-driven results.

Conclusion: LSD changed creativity across modalities and measurement approaches. Three phenomena of pattern break, disorganization and meaning seemed to fundamentally influence creative cognition and behaviour pointing to a shift of cognitive resources 'away from normal' and 'towards the new'. LSD-induced symbolic thinking might provide a tool to support treatment efficiency in psychedelic-assisted therapy.

Keywords

Psychedelics, creativity, divergent and convergent thinking, semantic distance, symbolic thinking

Introduction

Creativity promotes the prosperity of societies, from education, arts, technology and economy to therapy (Cropley, 2020; Desrochers, 2001; Florida, 2002; Snyder, 1997). Given its importance for society, numerous studies have attempted to promote creativity in individuals (Carson, 2014; Gino et al., 2010; Scott et al., 2004). Recent years have brought renewed interest in

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examining the potential of serotonergic psychedelics to promote creativity, which has long been anecdotally claimed by artists, scientists and entrepreneurs including Aldous Huxley, Kary Mullis and Steve Jobs (Huxley, 1954; Markoff, 2005; Mullis, 2000). However, early attempts to capture these effects were fraught with methodological shortcomings, including small sample sizes and unclear operational definitions of creativity (Iszáj et al., 2017).

An application-oriented approach reported low mescaline doses to facilitate problem-solving of professional issues (e.g. engineering, mathematics, architecture), as compared to baseline (Harman et al., 1966). Psychedelics and other psychoactive substances such as alcohol and cannabis are discussed to facilitate the creative process especially among artists (Iszáj et al., 2012, 2018). The probably most comprehensive long-term study examined the effects of repeated lysergic acid diethylamide (LSD) administration on 60 artists over 7 years. Over 250 drawings were rated as showing increased expressionism, sharpening of colour, mental freedom, syntactical organization and accessibility of past impressions (Dobkin De Rios and Janiger, 2003). Behavioural approaches suggested that psychedelics alter several creative domains. These include anecdotal descriptions of drawings and paintings being more simple, crude, distorted and bizarre, but also aesthetic and free, playing with colours, forms and styles (Berlin et al., 1955; Leuner, 1962; Mátéfi, 1952; Tonini and Montanari, 1955). Text and speech analyses observed language under psychedelics being more simple, short and concrete but also more unpredictable, stereotyped and bizarre (Amarel and Cheek, 1965; Kraehenmann et al., 2017b; Landon and Fischer, 1970; Sanz et al., 2021). Semantic-oriented approaches reported psychedelic-induced increases in semantic priming, semantic errors, semantic distances and originality of word associations pointing to disintegrated semantic information processing (Family et al., 2016; Spitzer et al., 1996; Wießner et al., 2021a; Zegans et al., 1967). Cognitive-oriented approaches focused on divergent and convergent thinking (necessary for creative generation and evaluation, respectively), often used naturalistic settings and baseline comparisons and yielded inconclusive results. While some studies reported psychedelics to increase fluency and originality, others reported decreased fluency, originality and convergent thinking (Frecska et al., 2012; Harman et al., 1966; Kuypers et al., 2016; Mason et al., 2021). This could be attributed to relatively high doses impairing cognitive processing, in line with findings of increased fluency, originality and convergent thinking after psychedelic ceremonies and under microdoses (Mason et al., 2019; Prochazkova et al., 2018; Uthaug et al., 2018, 2019).

Overall, these studies suggest that psychedelics change creativity-related aspects but comprise methodological limitations regarding design (e.g. lacking placebo-control), sample (e.g. artists), setting (e.g. ceremonies) or dose (e.g. impairing). Moreover, they followed different approaches using diverse methodologies, which reduce their comparability. In light of this, our study aimed at systematically mapping the effects of a relatively low dose of LSD (50 µg) on creativity in a methodologically rigorous design over diverse modalities and approaches. These include a multimodal task battery on several creative domains (e.g. visual/drawn, verbal/written) (Silvia et al., 2009) and an evaluation of task responses by a theory-driven approach scoring the creativity criteria 'novelty', 'utility' and 'surprise' (Simonton, 2012), a data-driven approach searching for special features (Elo and Kyngäs, 2008) and established parameters which are more objective, easy to measure and predictors of real-world creative achievements, namely divergent thinking (fluency, originality, flexibility, elaboration), convergent thinking and semantic indices (semantic distances between words) (Cropley, 2006; Gray et al., 2019; Kim, 2008).

Methods

This work is part of a larger study which is published elsewhere, including further information on participants, drug and procedures (Wießner et al., 2021a, 2021b).

Study design

The study used a randomized, double-blind, placebo-controlled, crossover design with two treatment sessions (LSD, placebo) and washout period of 14 days between sessions. Participants were randomly assigned to treatment order.

Participants

Twenty-five healthy participants were recruited in a convenience sample. Inclusion criteria were ⩾22 years, ⩾one experience with LSD, ⩾2 weeks of abstinence from psychedelics and 3 days from alcohol and other drugs before each session, abstinence from tobacco and caffeine during the study days. Exclusion criteria were presence of psychiatric symptoms, personal or first-degree family member history of psychotic disorder, use of psychiatric medication, history of severe complications after psychedelic use, alcohol or drug use disorder, heart disease or other relevant medical conditions, pregnancy and non-native speaking of Brazilian Portuguese. Participants provided written informed consent before participation. One participant ceased participation after the first session for personal reasons, resulting in a final sample of 24 subjects (8 women; age (mean ± SD) = 35 ± 11 years (range = 25–61)).

Study drug

Participants orally received 50 µg of LSD (dissolved in alcohol solution) or inactive placebo (alcohol solution) diluted in 30 mL of water. The low dose was chosen to minimize the risk of adverse reactions while exerting noticeable effects without impairing the ability to perform the tasks.

Study procedures

This study was approved by the National Health Surveillance Agency and Research Ethics Committee of the University of Campinas (CAAE: 04179918.2.0000.5404) and conducted following the Declaration of Helsinki and safety guidelines for psychedelic research in humans (Johnson et al., 2008). The study consisted of a screening interview, a day of drug administration and additional follow-up measurements. The day of drug administration began at 7:30 a.m. with baseline measurements. LSD or placebo was administered at 9:30 a.m. At 11:00 a.m., a standardized snack was served. Creativity measurements started after

drug peak at 12:00 p.m. and lasted until 1:15 p.m. Lunch was served at 1:40 p.m. The session ended 8 h after drug administration at 5:30 p.m. when it was ensured that subjects were feeling well before being left into the custody of a family member or friend.

Creativity tasks

Five tasks of diverse stimulus-response modalities were applied (for details, see Supplemental Methods). To avoid learning effects, two parallel task versions (A, B) were applied in balanced order across participants and counterbalanced across treatments.

The *pattern meaning task* (PMT) involves writing as many creative interpretations as possible for abstract line patterns (8 patterns, 2 min each) (Claridge and McDonald, 2009).

The *alternate uses task* (AUT) involves writing as many uncommon uses as possible for everyday objects (2 objects, 3 min each) (Guilford, 1967).

The *picture concept task* (PCT) involves (1) selecting pictures from slides which belong to a common group (convergent thinking) and (2) generating as many alternative, creative picture combinations as possible (divergent thinking) (17 slides, 1 min each) (Kuypers et al., 2016).

The *creative metaphors task* (MET), created by our team, involves writing up to 10 creative or poetic metaphors (5 min in total).

The *figural creativity task* (FIG) involves producing drawings based on simple line patterns on a sheet of paper and writing creative titles for them (2 patterns, 10 min in total) (Artola et al., 2012).

Creativity variables

Over all tasks, diverse variable groups were assessed, based on theory-driven (creativity criteria), established (divergent thinking, convergent thinking), semantic (semantic structure) and data-driven (special features) approaches (Figure S1). Examples for all variables are listed in Supplemental Table S1. Two trained, independent raters scored the subjectively evaluated variables (Silvia et al., 2008). Interrater reliability, as estimated by intraclass correlation coefficients (ICC) and 95% confident intervals (mean-rating (k=2), consistency, 2-way random-effects model; Koo and Li, 2016), ranged from moderate to excellent with few exceptions (Supplemental Table S2). For each task and variable, average scores over all responses and stimuli were calculated for statistical analysis.

Creativity criteria. *Novelty, utility* and *surprise* of each response was rated on a 3-point scale (0 = not at all; 2 = very much) based on how novel/useful/surprising responses were within the general socio-cultural context.

Relative novelty, utility and *surprise* were assessed by calculating the ratios to the number of total responses.

Divergent thinking. *Fluency* was calculated by the number of total responses (PMT, AUT, PCT, MET).

Originality was assessed by grouping the sample's responses for each stimulus into categories. In PMT, AUT and PCT, responses in categories containing more than 5% of all responses for the stimulus received zero points, those containing between 1% and 5% received one point and those containing less than 1% received two points of originality (Prochazkova et al., 2018). In FIG, assessments comprised stimulus originality (response points weighted inversely by category size), title originality (0 = without or just descriptive title; 2 = metaphoric, surprising title) and special details (one point per detail) (Artola et al., 2012).

Flexibility was assessed by calculating (PMT, AUT, PCT) and rating (MET) the number of different response categories per subject.

Elaboration was assessed by the number of details within one response (PMT, AUT, PCT, MET) (Guilford, 1967) and by rating FIG picture elaboration (0 = without special details; 2 = much elaboration and abundant details) and colour elaboration (0 = without colours and shadows; 2 = many colours and shadows) (Artola et al., 2012).

Relative originality, flexibility and *elaboration* were assessed by calculating the ratios to fluency.

Convergent thinking. Convergent thinking comprised the number of correct combinations in the PCT (Kuypers et al., 2016).

Semantic structure. Semantic distances between responses were calculated based on a Portuguese Wikipedia corpus by Fast text method in Text Similarity Tool (version 0.6.1) (Mota et al., 2020). For details on preprocessing, see Supplemental Methods. From each semantic distance matrix, two distance indices were calculated:

Semantic spread, the average distance over all responses;
Semantic steps, the average distance between two neighbouring responses (Wießner et al., 2021a).

Special features. To identify common, data-driven features within the responses, we applied a qualitative content analysis-inspired approach (Elo and Kyngäs, 2008). We first developed a categorization matrix and then coded the data according to the generated main categories and subcategories (for details, see Supplemental Methods). Four main categories (**bold**) subdivided into subcategories (*italic*) were created:

Content was assessed by assigning each response to content subcategories in MET (*symbols, nature, objects, persons, body parts, animals, characteristics, sensation, cognition, emotion*) and FIG (*symbols, nature, objects, persons, body parts, animals*).

Techniques were assessed by assigning each response to technique subcategories in MET (*union, exaggeration, contrast, wordplay*) and by rating techniques in FIG (*background, spatiality, symmetry, frame break, colours, connections*).

Ambiguity was evaluated based on whether the response (MET, FIG) was interpretable in different ways (0 = not at all; 2 = very much). Relative ambiguity was assessed by calculating the ratio to fluency.

Symbolic thinking was assessed by the number of symbolic or abstract responses (PMT, AUT, PCT), by the content subcategory *symbols* (MET) and by scoring (FIG) *title symbolism, picture symbolism* (0 = very concrete; 2 = very symbolic) and *colour*

abstractness (0 = very realistic; 2 = very abstract). Relative symbolic thinking was assessed by calculating ratios to fluency.

Data analysis

Statistical analyses were conducted by IBM SPSS Statistics (version 22). A repeated-measures general linear model (GLM) with 'treatment' as within-subjects factor and 'treatment order' as between-subjects factor was performed for each task and variable. Main effects of treatment (LSD, placebo), period (session 1, session 2) and order (LSD-placebo, placebo-LSD) were evaluated. Effect sizes were estimated using partial eta squared (η_p^2). Results were corrected post hoc for multiple comparisons within variable groups (creativity criteria, divergent thinking, semantic structure, special feature categories) by Benjamini–Hochberg (BH) procedure with false discovery rate (FDR) of $q = \alpha = 0.05$ (Benjamini and Hochberg, 1995). Spearman's rank correlation coefficients (r_s) were calculated between LSD-induced changes (Δ = LSD − placebo) with significance level corrected for multiple comparisons by the number of tasks ($\alpha = 0.05/5 = 0.01$).

Results

Detailed values for all treatment, period and order effects are shown in Table 1.

Creativity criteria

LSD, compared to placebo, increased novelty ($p = 0.038$), relative novelty ($p < 0.001$) and relative surprise in PMT ($p = 0.016$), while increased relative novelty in AUT ($p = 0.034$) did not survive correction for multiple testing. LSD decreased utility in PMT ($p = 0.021$) and relative utility in PMT ($p < 0.001$) and AUT ($p = 0.008$; Figure 1(a)).

In PCT, there were period effects for relative novelty ($p < 0.001$) and relative surprise ($p < 0.001$), with lower means in session 2 indicating habituation effects, and for relative utility ($p < 0.001$), with higher means in session 2 indicating learning effects. Two effects of period (PMT relative utility: $p = 0.043$) and order (AUT relative novelty: $p = 0.029$) did not survive correction for multiple testing. No other effects of treatment, period and order were observed.

Divergent thinking

LSD, compared to placebo, increased title originality in FIG ($p = 0.007$), while increased special details in FIG ($p = 0.031$) and relative originality in PMT ($p = 0.019$) did not survive correction for multiple testing. LSD decreased relative flexibility in MET ($p = 0.029$), elaboration in PMT ($p = 0.022$), AUT ($p = 0.043$) and FIG ($p = 0.025$) and relative elaboration in MET ($p = 0.033$), but these effects did not survive correction for multiple testing (Figure 1(b)).

There was a period effect for relative flexibility in PCT ($p < 0.001$), with higher means in session 2 indicating learning effects. Two order effects (FIG special details: $p = 0.039$; AUT relative flexibility: $p = 0.029$) did not survive correction for multiple testing.

Convergent thinking

LSD, compared to placebo, increased convergent thinking in PCT ($p = 0.023$; Figure 1(c)). There was no period and order effect.

Semantic structure

LSD, compared to placebo, increased semantic spread ($p = 0.047$) and semantic steps in PMT ($p = 0.025$; Figure 1(d)). No other treatment, period and order effect reached significance.

Special features

Content under LSD, compared to placebo, exhibited more *sensation* in MET ($p = 0.019$) and fewer *objects* in MET ($p = 0.011$) and FIG ($p = 0.023$), but these effects did not survive correction for multiple testing (Supplemental Figure S2).

Techniques demonstrated more *contrast* in MET ($p = 0.005$), while decreased *exaggeration* in MET ($p = 0.035$) and increased *frame break* in FIG ($p = 0.017$) did not survive correction for multiple testing (Supplemental Figure S2).

LSD increased ambiguity in MET ($p = 0.028$) and FIG ($p = 0.044$) and relative ambiguity in MET ($p = 0.039$).

LSD increased symbolic thinking in PMT ($p = 0.036$), AUT ($p = 0.022$) and FIG (*title symbolism:* $p = 0.011$; *picture symbolism:* $p = 0.022$; *colour abstractness:* $p = 0.001$) and relative symbolic thinking in PMT ($p = 0.018$) and AUT ($p = 0.033$), while increased symbolic thinking in PCT ($p = 0.032$) did not survive correction for multiple testing (Figure 1(e)).

There was a period effect for ambiguity in MET ($p = 0.021$) with lower means in session 2. Two period effects (MET *contrast:* $p = 0.018$; PCT symbolic thinking: $p = 0.048$) and two order effects (FIG *body parts:* $p = 0.043$; AUT relative symbolic thinking: $p = 0.043$) did not survive correction for multiple testing.

For an overview of the effects, see Figure 2. For an illustration of ambiguity and symbolic thinking in FIG, see Figure 3.

Correlations

There was a positive correlation of novelty with surprise, but negative correlations of both criteria with utility (PMT; Table 2). Utility correlated positively with elaboration (PMT) and negatively with symbolic thinking (AUT). Surprise (PMT) correlated positively with symbolic thinking (AUT). Title originality correlated positively with ambiguity (FIG) and symbolic thinking (FIG *title symbolism*, FIG *picture symbolism*). Elaboration correlated negatively (MET) and positively (FIG) with ambiguity and positively with symbolic thinking (PMT). Semantic steps (PMT) correlated negatively with ambiguity (FIG) and symbolic thinking (FIG *picture symbolism*). Techniques (MET *contrast*) correlated positively with ambiguity (MET) and symbolic thinking (PMT). Ambiguity (FIG) correlated positively with symbolic thinking (PMT, AUT, FIG *picture symbolism*, FIG *colour abstractness*).

Table 1. Values for the effects of treatment, period and order in the repeated-measures general linear models for the different creativity measurement approaches, variables and tasks.

Approach	Variable	Task	Results[a]	Means ± SD[b]
Treatment effects				
Creativity criteria	novelty	PMT	**$F(1,22) = 4.85$, $p = 0.038$, $\eta_p^2 = 0.18$***	Means ± SEM of treatment effects are displayed in **Figure 1**
	rel novelty	PMT	**$F(1,22) = 18.0$, $p < 0.001$, $\eta_p^2 = 0.45$***	
		AUT	$F(1,22) = 5.13$, $p = 0.034$, $\eta_p^2 = 0.19$	
	rel surprise	PMT	**$F(1,22) = 6.77$, $p = 0.016$, $\eta_p^2 = 0.24$***	
	utility	PMT	**$F(1,22) = 6.20$, $p = 0.021$, $\eta_p^2 = 0.22$***	
	rel utility	PMT	**$F(1,22) = 26.0$, $p < 0.001$, $\eta_p^2 = 0.54$***	
		AUT	**$F(1,22) = 8.60$, $p = 0.008$, $\eta_p^2 = 0.28$***	
Divergent thinking	title originality	FIG	**$F(1,22) = 8.87$, $p = 0.007$, $\eta_p^2 = 0.29$***	
	special details	FIG	$F(1,22) = 5.28$, $p = 0.031$, $\eta_p^2 = 0.19$	
	rel originality	PMT	$F(1,22) = 6.42$, $p = 0.019$, $\eta_p^2 = 0.22$	
	rel flexibility	MET	$F(1,22) = 5.43$, $p = 0.029$, $\eta_p^2 = 0.19$	
	elaboration	PMT	$F(1,22) = 6.07$, $p = 0.022$, $\eta_p^2 = 0.22$	
		AUT	$F(1,22) = 4.61$, $p = 0.043$, $\eta_p^2 = 0.17$	
		FIG	$F(1,22) = 5.78$, $p = 0.025$, $\eta_p^2 = 0.21$	
	rel elaboration	MET	$F(1,22) = 5.18$, $p = 0.033$, $\eta_p^2 = 0.19$	
Convergent thinking		PCT	**$F(1,22) = 5.99$, $p = 0.023$, $\eta_p^2 = 0.21$***	
Semantic structure	spread	PMT	**$F(1,22) = 4.44$, $p = 0.047$, $\eta_p^2 = 0.17$***	
	steps	PMT	**$F(1,22) = 5.76$, $p = 0.025$, $\eta_p^2 = 0.21$***	
Special features	cont *sensation*	MET	$F(1,22) = 6.38$, $p = 0.019$, $\eta_p^2 = 0.23$	
	cont *objects*	MET	$F(1,22) = 7.67$, $p = 0.011$, $\eta_p^2 = 0.26$	
		FIG	$F(1,22) = 5.94$, $p = 0.023$, $\eta_p^2 = 0.21$	
	tec *contrast*	MET	**$F(1,22) = 9.68$, $p = 0.005$, $\eta_p^2 = 0.31$***	
	tec *exagg*	MET	$F(1,22) = 5.02$, $p = 0.035$, $\eta_p^2 = 0.19$	
	tec *frame*	FIG	$F(1,22) = 6.67$, $p = 0.017$, $\eta_p^2 = 0.23$	
	ambiguity	MET	**$F(1,22) = 5.56$, $p = 0.028$, $\eta_p^2 = 0.20$***	
		FIG	**$F(1,22) = 4.57$, $p = 0.044$, $\eta_p^2 = 0.17$***	
	rel ambiguity	MET	**$F(1,22) = 4.85$, $p = 0.039$, $\eta_p^2 = 0.18$***	
	symb think	PMT	**$F(1,22) = 4.98$, $p = 0.036$, $\eta_p^2 = 0.18$***	
		AUT	**$F(1,22) = 6.05$, $p = 0.022$, $\eta_p^2 = 0.22$***	
		PCT	$F(1,22) = 5.21$, $p = 0.032$, $\eta_p^2 = 0.19$	
		FIG (tit)	**$F(1,22) = 7.63$, $p = 0.011$, $\eta_p^2 = 0.26$***	
		FIG (pic)	**$F(1,22) = 6.13$, $p = 0.022$, $\eta_p^2 = 0.22$***	
		FIG (col)	**$F(1,22) = 14.3$, $p = 0.001$, $\eta_p^2 = 0.39$***	
	rel symb think	PMT	**$F(1,22) = 6.50$, $p = 0.018$, $\eta_p^2 = 0.23$***	
		AUT	**$F(1,22) = 5.18$, $p = 0.033$, $\eta_p^2 = 0.19$***	
Period effects				
Creativity criteria	rel novelty	PCT	**$F(1,22) = 116$, $p < 0.001$, $\eta_p^2 = 0.84$***	1.51 ± 0.21; 0.51 ± 0.31
	rel surprise	PCT	**$F(1,22) = 29.8$, $p < 0.001$, $\eta_p^2 = 0.58$***	1.63 ± 0.84; 0.85 ± 0.29
	rel utility	PCT	**$F(1,22) = 59.4$, $p < 0.001$, $\eta_p^2 = 0.73$***	0.88 ± 0.29; 1.53 ± 0.17
		PMT	$F(1,22) = 4.63$, $p = 0.043$, $\eta_p^2 = 0.17$	1.53 ± 0.19; 1.63 ± 0.15
Divergent thinking	rel flexibility	PCT	**$F(1,22) = 85.0$, $p < 0.001$, $\eta_p^2 = 0.79$***	0.91 ± 0.04; 0.99 ± 0.02
Special features	tec *contrast*	MET	$F(1,22) = 6.48$, $p = 0.018$, $\eta_p^2 = 0.23$	1.67 ± 1.78; 0.92 ± 1.48
	ambiguity	MET	**$F(1,22) = 6.21$, $p = 0.021$, $\eta_p^2 = 0.22$***	6.58 ± 5.21; 5.02 ± 4.98
	symb think	PCT	$F(1,22) = 4.40$, $p = 0.048$, $\eta_p^2 = 0.17$	0.39 ± 0.35; 0.24 ± 0.22
Order effects				
Creativity criteria	rel novelty	AUT	$F(1,22) = 5.43$, $p = 0.029$, $\eta_p^2 = 0.20$	0.88 ± 0.28; 0.61 ± 0.28
Divergent thinking	special details	FIG	$F(1,22) = 4.82$, $p = 0.039$, $\eta_p^2 = 0.18$	0.51 ± 0.33; 0.22 ± 0.33
	rel flexibility	AUT	$F(1,22) = 5.43$, $p = 0.029$, $\eta_p^2 = 0.20$	0.97 ± 0.04; 0.93 ± 0.04
Special features	cont *body pts*	FIG	$F(1,22) = 4.63$, $p = 0.043$, $\eta_p^2 = 0.17$	0.27 ± 0.22; 0.06 ± 0.22
	rel symb think	AUT	$F(1,22) = 4.63$, $p = 0.043$, $\eta_p^2 = 0.17$	0.19 ± 0.15; 0.06 ± 0.15

rel: relative; spread: semantic spread; steps: semantic steps; cont: content; body pts: body parts; tec: technique; exagg: exaggeration; frame: frame break; symb think: symbolic thinking; tit: title symbolism; pic: picture symbolism; col: colour abstractness; PMT: pattern meaning task; AUT: alternate uses task; PCT: picture concept task; MET: creative metaphors task; FIG: figural creativity task; LSD: lysergic acid diethylamide.

[a]Significant effects (**bold***) after correction for multiple comparisons.

[b]Means and standard deviations are displayed for session 1 and session 2 (period effects) and treatment order LSD-placebo and placebo-LSD (order effects).

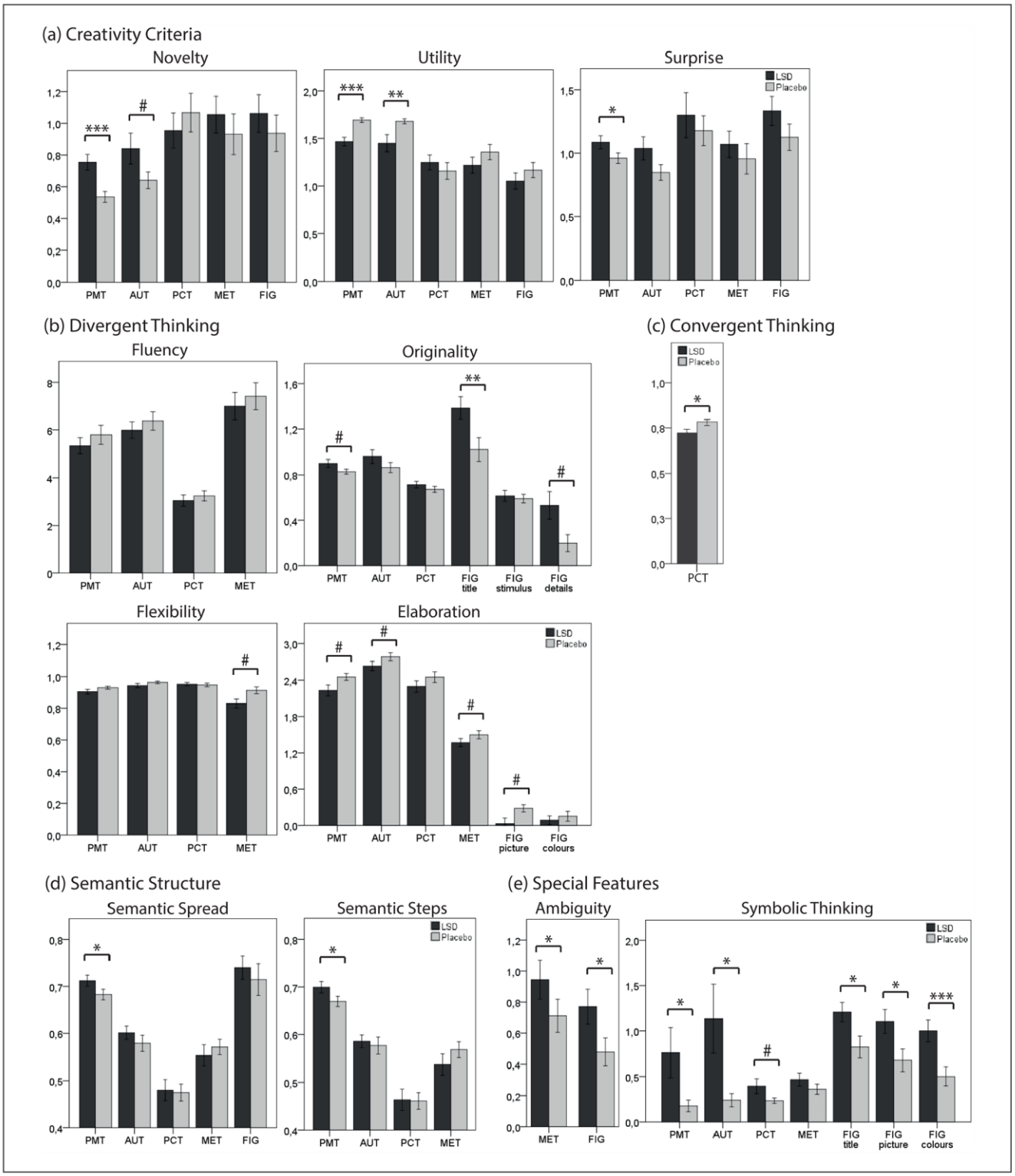

Figure 1. The effects of LSD on creativity as measured by several approaches within several tasks. Overall, LSD compared to placebo (a) changed creativity criteria, as measured by increased novelty and surprise and decreased utility (PMT, AUT); (b) changed divergent thinking towards increased originality (PMT, FIG) and decreased flexibility (MET) and elaboration (PMT, AUT, MET, FIG), but most effects did not survive correction for multiple testing; (c) decreased convergent thinking (PCT); (d) changed semantic structure, as measured by increased semantic spread and semantic steps (PMT); and (e) induced special features, as reflected by increased ambiguity (MET, FIG) and symbolic thinking (PMT, AUT, PCT, FIG). All values are displayed as means (±SEM) in 24 subjects. For presentation purposes, relative values are displayed wherever applicable, except for elaboration (PMT, AUT, PCT). Elaboration values were log-transformed. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ (corrected), $^{\#}p < 0.05$ (uncorrected).
PMT: pattern meaning task; AUT: alternate uses task; PCT: picture concept task; MET: creative metaphors task; FIG: figural creativity task; Originality: title: title originality; stimulus: stimulus originality; details: special details; Elaboration: picture: picture elaboration; colours: colour elaboration; Symbolic thinking: title: title symbolism; picture: picture symbolism; colour: colour abstractness.

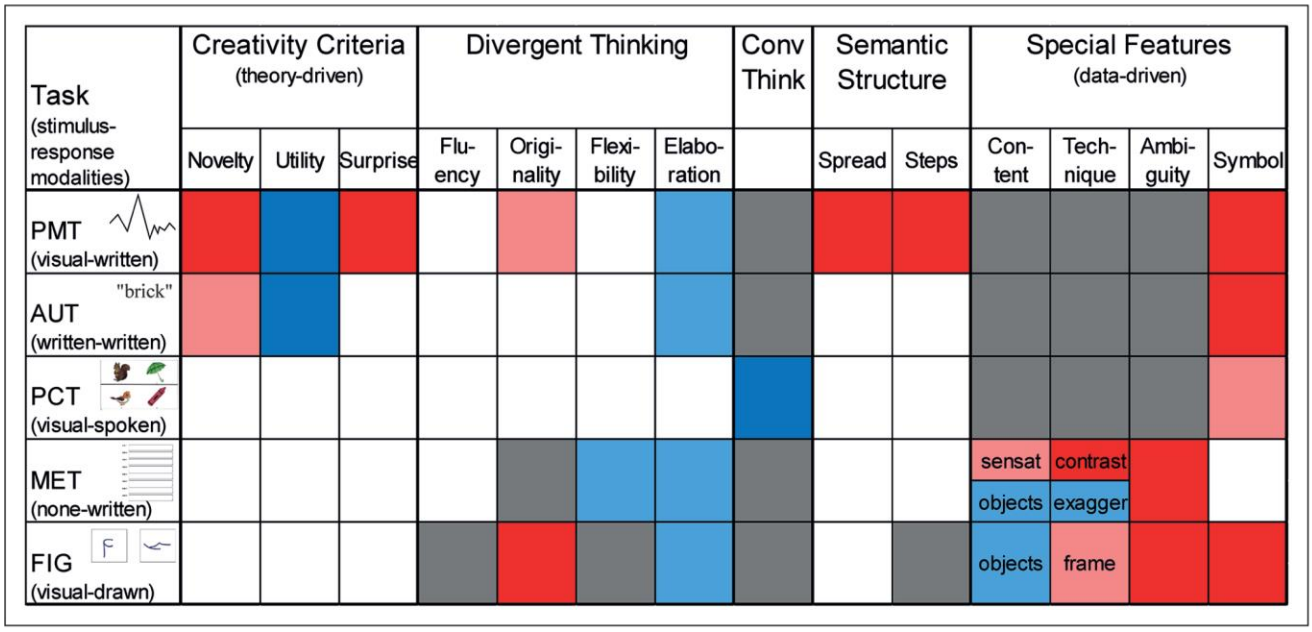

Figure 2. An overview of the effects of LSD, compared to placebo, on creativity, as measured by tasks of diverse stimulus-response modalities (lines) and by diverse approaches (columns). Overall, effects were most pronounced in PMT and for special feature symbolic thinking. Cells represent LSD-induced increases (dark red: corrected; light red: uncorrected) and decreases (dark blue: corrected; light blue: uncorrected) and no effects (white) for 24 subjects at $\alpha = 0.05$. Non-assessed variables are depicted in grey.
PMT: pattern meaning task; AUT: alternate uses task; PCT: picture concept task; MET: creative metaphors task; FIG: figural creativity task; Conv Think: convergent thinking; Spread: semantic spread; Steps: semantic steps; Symbol: symbolic thinking; sensat: sensation; exagger: exaggeration; frame: frame break.

Discussion

This study aimed at systematically mapping the effects of a relatively low dose of LSD on creativity across modalities and approaches. LSD, compared to placebo, changed creativity on several levels and seemed to elicit two opposing phenomena of 'pattern break', reflected by increased novelty (PMT), surprise (PMT), originality (FIG) and semantic distances (PMT), and decreased 'organization', reflected by decreased utility (PMT), convergent thinking (PCT) and, marginally but consistently across tasks, elaboration (PMT, AUT, MET, FIG; Figure 2). The consistency within both phenomena is underscored by positive correlations of novelty with surprise and utility with elaboration (Table 2). The inverse relationship between both phenomena is underlined by negative correlations of novelty and surprise with utility. Moreover, a data-driven phenomenon of 'meaning' seemed to arise, reflected by increased symbolic thinking (PMT, AUT, FIG), ambiguity (MET, FIG) and verbal techniques (MET *contrast*) (Figure 3). These effects correlated positively with each other, pointing to consistency within the phenomenon, and negatively with semantic distances and utility and positively and negatively with elaboration, pointing to contrasting relationships to the formerly described phenomena. Overall, the effects were specific to task and variable, pointing to influences of stimulus-response modalities and drug intensity, since results were most pronounced in PMT near drug peak.

Creativity criteria – LSD increases novelty and surprise and decreases utility

On a phenomenological level, LSD increased novelty and surprise and decreased utility of responses, indicating that responses were more remote and nonobvious but also 'chaotic' and less useful, while there was no change in the amount of highly creative responses, as measured by high novelty, utility and surprise (Simonton, 2012). Considering that novelty is regarded as essential for creativity, while usefulness adds merely additional value (Diedrich et al., 2015), our findings indicate that LSD provides a basis for creative thinking but impairs further sophisticated processes, similar to the proposal that psychedelics support creative generation but not creative evaluation (Girn et al., 2020). The notion of more 'chaotic' and 'less useful' thinking is in line with findings of LSD-induced cognitive bizarreness during mental imagery (Kraehenmann et al., 2017b) and chaos during mind-wandering (Wießner et al., 2021a).

Effects were pronounced in PMT and AUT, possibly due to stronger drug effects during these tasks and the medium task difficulty (in contrast to more demanding (PCT) or unconstrained tasks (MET, FIG)), indicating that acute, medium doses and medium task difficulties foster the creation of novel and surprising responses. Notably, novelty (FIG) and utility (PCT, MET, FIG) elicited partially poor interrater reliability (Supplemental Table S2), indicating that the evaluation of novelty (drawings) and utility (associations, metaphors, drawings) might yield unreliable results possibly obscuring effects. Therefore, future studies should complement novelty ratings with surprise ratings and refine evaluation frames of utility (e.g. utility regarding personal, aesthetic, societal or political value).

Divergent and convergent thinking – LSD decreases convergent thinking and elaboration

On a cognitive level, LSD increased title originality (FIG), while other originality parameters did not survive correction for

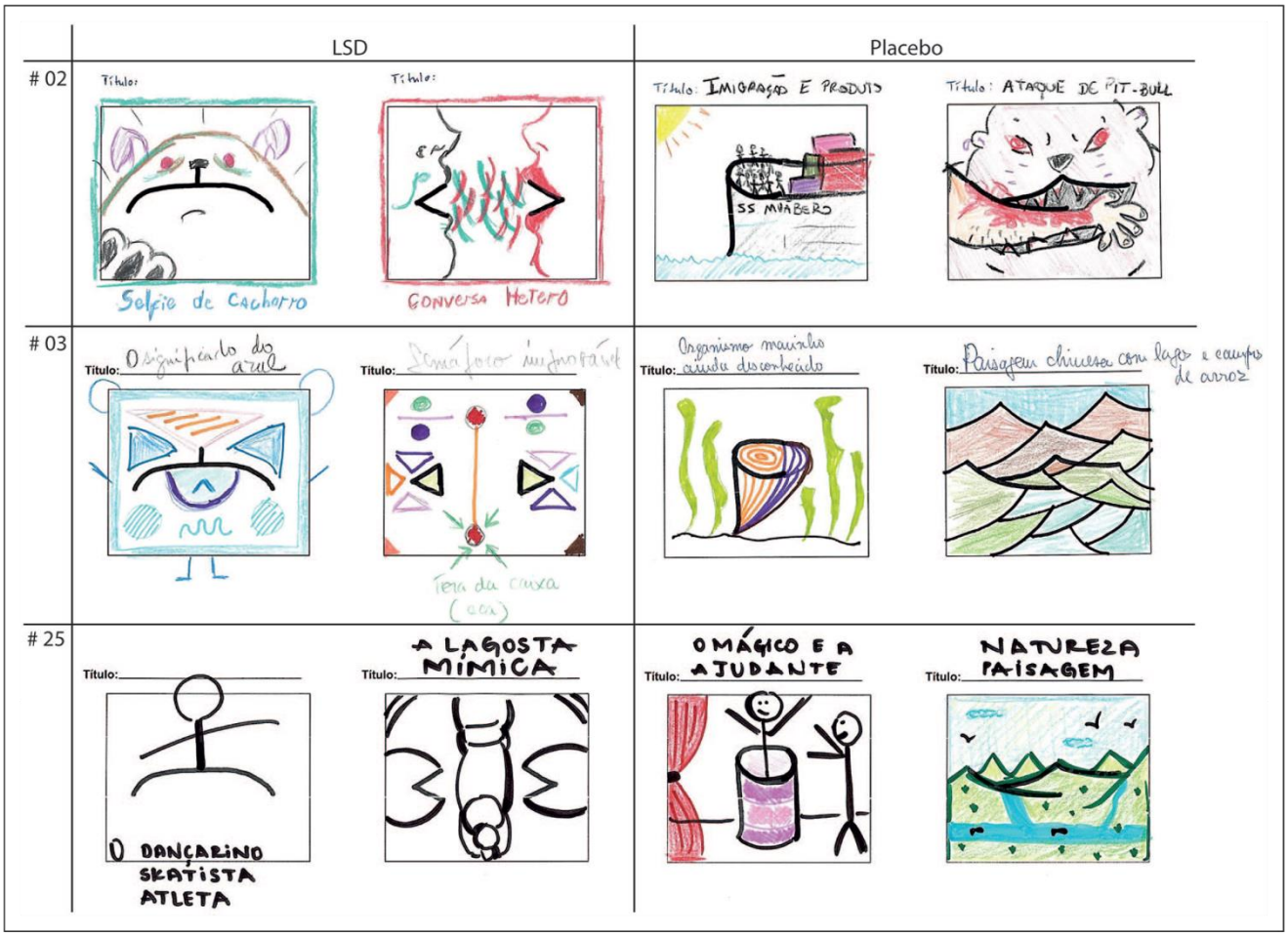

Figure 3. Drawings produced under LSD (left) and placebo (right) in the figural creativity task (FIG) as exemplified by three subjects (#02, #03 and #25). Symbolic thinking was enhanced as reflected by increased symbolism and abstractness in title, picture and colours. In a similar vein, ambiguity was enhanced reflecting increased interpretability of titles and drawings in several ways.
The translated titles are as follows, from left to right: #02: 'Dog selfie', 'Hetero conversation', 'Immigration and product', 'Pitbull attack'. #03: 'The meaning of blue', 'Improbable traffic light', 'Still unknown marine organism', 'Chinese landscape with lakes and rice fields'. #25: 'The skating athletic dancer', 'The mimic crayfish', 'The magician and the assistant', 'Nature landscape'.

multiple testing (FIG special details, PMT originality) or remained unchanged. Similarly, previous studies observed psychedelic-induced originality depending on task and parameter (Frecska et al., 2012; Kuypers et al., 2016; Zegans et al., 1967). Moreover, drug doses seem to influence effect directions, with increases under microdoses and decreases under high doses (Mason et al., 2021; Prochazkova et al., 2018). Together with these findings, our results suggest that psychedelics increase specific originality aspects, especially under lower doses.

Similarly, LSD decreased convergent thinking (PCT), in line with previous findings of impairments under regular doses (Kuypers et al., 2016; Mason et al., 2021) and improvements under microdoses (Prochazkova et al., 2018). LSD consistently decreased elaboration (PMT, AUT, MET, FIG at uncorrected level), similar to previous reports of psychedelic-induced impairments in technical execution of written and graphic productions, which was attributed to impaired psychomotricity and concentration (Bercel et al., 1956; Krippner, 1985; Landon and Fischer, 1970; Mátéfi, 1952). In line with this, effects emerged only for written (PMT, AUT, MET) and drawn (FIG) but not spoken (PCT) tasks. Notably, elaboration tended to decrease but fluency did not, indicating unchanged idea generation but less detail development. Altogether, these results might point towards impaired cognitive control, including selective (convergent thinking) and sustained (elaboration) attention and executive functions, important for divergent thinking (Zabelina and Ganis, 2018) and impaired under psychedelics (Pokorny et al., 2019; Umbricht et al., 2003; Vollenweider et al., 2007).

Semantic structure – LSD increases semantic spread and semantic steps

On a semantic level, LSD increased PMT semantic spread and semantic steps (distances between all and between neighbouring responses), indicating a random semantic spread of ideas. Contrastingly, LSD did not increase semantic spread but semantic distances to previous and subsequent words during free word association in this sample, pointing to meaningful but not randomly increased semantic distances between words (Wießner et al., 2021a). Altogether, these findings suggest that LSD-induced semantical dispersion is meaningful at simple task level (word

Table 2. Relationships between LSD-induced effects (Δ) on several creativity variables and tasks.

Approach			Creativity criteria						Divergent thinking				Sem	Tec	Ambiguity		
	Variable		nov	rel nov	utility	rel utility		rel surp	tit orig	elab[a]		rel elab	steps	contr		rel	
		Test	PMT	PMT	PMT	PMT	AUT	PMT	FIG	PMT	AUT	MET	PMT	MET	MET	MET	FIG
Creativity criteria	util	PMT	0.36	−0.45													
	rel util	PMT	**−0.60**	**−0.73**												1.0	
		AUT	−0.18	−0.42												0.8	
	rel surp	PMT	0.47	**0.87**	−0.32	**−0.79**	−0.37									0.6	
Divergent thinking	tit orig	FIG	0.11	0.15	0.12	−0.12	−0.31	0.19								0.4	
	elab	PMT	0.44	0.02	**0.58**	−0.11	−0.23	0.16	0.46							0.2	
		AUT	0.33	0.17	0.24	−0.20	−0.42	0.35	0.44							0.0	
	rel elab	MET	0.26	−0.14	0.46	0.15	0.28	0.04	0.09							−0.2	
Sem	steps	PMT	0.07	−0.12	0.13	0.15	0.07	−0.33	−0.46	−0.39	−0.23	−0.27				−0.4	
Tec	contr	MET	0.14	0.42	−0.16	−0.44	−0.32	0.39	0.34	0.18	0.09	−0.13	−0.32			−0.8	
Ambiguity		MET	−0.07	0.12	0.03	−0.09	−0.32	0.00	0.23	0.12	0.16	−0.34	−0.18	**0.61**		−1.0	
	rel	MET	−0.21	0.08	−0.21	0.06	−0.25	−0.26	0.00	−0.14	−0.15	**−0.59**	0.15	0.34			
		FIG	0.22	0.26	−0.02	−0.36	−0.50	0.39	**0.68**	0.39	**0.58**	0.04	**−0.54**	0.33			
Symbolic thinking		PMT	0.24	0.25	0.04	−0.39	−0.43	0.30	0.33	**0.52**	0.35	0.13	−0.46	**0.54**	0.47	0.22	**0.57**
	rel	PMT	0.23	0.31	−0.05	−0.45	−0.40	0.37	0.31	0.41	0.34	0.08	−0.45	**0.54**	0.44	0.20	**0.58**
		AUT	0.47	0.46	0.01	**−0.57**	**−0.59**	**0.53**	0.34	0.38	0.44	−0.13	−0.12	0.26	0.32	0.06	**0.55**
	rel	AUT	0.40	0.35	0.06	−0.49	**−0.53**	0.42	0.33	0.40	0.42	−0.15	−0.12	0.26	0.36	0.11	0.48
	title	FIG	−0.10	−0.27	0.25	0.16	−0.15	−0.18	**0.66**	0.46	0.06	0.13	−0.46	0.32	0.16	0.03	0.40
	picture	FIG	0.14	−0.06	0.31	0.00	−0.19	0.03	**0.74**	**0.53**	0.29	0.23	**−0.54**	0.35	0.21	0.05	**0.57**
	colour	FIG	0.42	0.26	0.23	−0.37	−0.49	0.45	0.48	**0.61**	**0.55**	0.21	−0.30	0.19	−0.01	−0.21	**0.66**

Approaches and variables: rel: relative variables as calculated by ratios to fluency; nov: novelty; util: utility; surp: surprise; tit orig: title originality; elab: elaboration; Sem: semantic structure; steps: semantic steps; Tec: Technique; contr: contrast; Symbolic thinking: title: title symbolism; picture: picture symbolism; colour: colour abstractness; Tasks: PMT: pattern meaning task; AUT: alternate uses task; FIG: figural creativity task; MET: creative metaphors task; PCT: picture concept task; LSD: lysergic acid diethylamide.

Displayed are Spearman's rank correlation coefficients for 24 subjects. **Bold** numbers indicate significant correlations at corrected significance level $\alpha = 0.01$. For presentation purposes, only variables with significant effects are depicted.

[a]Despite not surviving correction for multiple testing, elaboration was maintained in the correlation analysis for depicting consistent tendencies over most tasks, for a comprehensive understanding of the results.

association) and chaotic at complex level (idea generation), similar to findings of psychedelic-induced semantic priming and naming errors for semantically similar words/pictures (Family et al., 2016; Spitzer et al., 1996) and unpredictability of spontaneous speech (Amarel and Cheek, 1965). Notably, semantic distances increased for abstract (PMT) but not for concrete (AUT, PCT) or without (MET) stimuli. Similarly, semantic distances in free association increased for abstract but not concrete seed words (Wießner et al., 2021a), indicating that abstract, more than concrete, input stimulates the generation of semantically distinct thinking under LSD.

Special features – LSD affects content and technique in metaphors and drawings

On a behavioural level, metaphor and drawing content under LSD exhibited tendentially fewer *objects*, pointing to a weak but cross-modal phenomenon. Metaphors demonstrated tendentially more *sensation*, potentially related to the LSD-induced intensification and synaesthesia of senses (Leuner, 1962; Terhune et al., 2016; Wießner et al., 2021a). This implies that metaphors were influenced by and possibly used to express subjective experiences, similar to metaphors use in ayahuasca ceremonies and by people with psychotic disorders to express and handle subjective experiences (Mould et al., 2010; Shanon, 2002).

Metaphor techniques under LSD exhibited more *contrast* and tendentially less *exaggeration*, suggesting that the evaluation of semantic characteristics remains stable, while their associations shift from similarities to differences. Similarly, *contrast* correlated positively with ambiguity (MET) and symbolic thinking (PMT), suggesting an association between contrast-focused and meaning-laden thinking. Drawings under LSD showed unchanged colour quantity but increased *colour abstractness*, similar to previous observations on sharpened colours and changed colour combinations in drawings and paintings (Dobkin De Rios and Janiger, 2003; Tonini and Montanari, 1955). This might be related to psychedelic-induced visual effects (Kometer and Vollenweider, 2016; Wießner et al., 2021b), implying that subjective experiences might have been expressed by figural techniques.

Special features – LSD increases symbolic thinking and ambiguity

On an ontological level, symbolic thinking and ambiguity emerged as the most noticeable data-driven features. LSD increased metaphor and drawing ambiguity pointing to a cross-modal feature. Similarly, previous works observed logical contradictions in speech and paradoxical ideas and perceptions under psychedelics (Barr et al., 1972; Pahnke and Richards, 1966), reinforcing the notion that verbal and graphic means were spontaneously used to express subjective experiences. Drawing ambiguity correlated positively with title originality (FIG) and elaboration (AUT) and negatively with semantic steps (PMT), suggesting that figural ambiguity might be related to semantic organization. Contrastingly, metaphor ambiguity correlated negatively with elaboration (MET), suggesting that verbal ambiguity reflects condensed or reduced information, in line with findings of LSD-induced condensation of speech (Barr et al., 1972) and the notion of reduced cognitive control, as discussed above. Especially the latter notion seems supported by the period effect (lower ambiguity in session 2) pointing to learning effects (lower difficulties in creating metaphors in session 2), probably due to certain critical task procedures (e.g. few instructions, no training).

LSD increased symbolic thinking across modalities and tasks (PMT, AUT, FIG *title symbolism, picture symbolism, colour abstractness*). In the PCT, demanding procedures and concrete, child-like stimuli possibly restrained symbolization, in contrast to abstract patterns (PMT, FIG) and imagined objects (AUT), indicating that symbolic thinking is best induced by abstract stimuli. Remarkably, several anecdotal reports described psychedelics to induce a spontaneous 'symbolic level', with symbols that can be positive or negative, historical, mythical or religious, comprise eidetic images or complex scenes and influence figural creativity (Gasser et al., 2015; Leuner, 1962; Masters and El Houston, 1966; Mátéfi, 1952; Pahnke, 1967). Similarly, psychedelics seem to increase symbolism in Rorschach interpretations and mental imagery (Barr et al., 1972; Kraehenmann et al., 2017a), further supporting the notion that abstract and imagined stimuli promote LSD-induced symbolic thinking. In the therapeutic context, psychedelic-induced symbolization was hypothesized to unveil unconscious material, facilitate problem confrontation and solving, supporting psychological growth and maturation (Cohen, 1967; Eisner and Cohen, 1958; Gasser et al., 2015; Masters and El Houston, 1966). With this in mind, our results suggest that abstract stimuli and drawing tasks, for example within psychedelic-assisted psychotherapy or art therapy, might constitute intriguing techniques to stimulate symbolic thinking to express and process problems on personally meaningful level.

The correlations reveal insights into relationships of symbolic thinking with other processes. Negative correlations with utility (AUT) and positive correlations with originality (FIG), elaboration (PMT) and ambiguity (FIG) suggest that symbolic responses are perceived as less useful but original, require cognitive control and transmit multiple meanings. These contrasting relationships suggest that symbolic thinking and ambiguity constitute a third phenomenon of increased 'meaning', differentially related to 'pattern break' and decreased 'organization'. Meaning attribution under psychedelics is widely reported but poorly understood, being associated with psychedelic-induced symbolization, mystical experiences, creativity, psychotic-like and therapeutic effects (Hartogsohn, 2018; Leptourgos et al., 2020; Liechti et al., 2017; Masters and El Houston, 1966; Preller et al., 2017; Wießner et al., 2021b), pointing to a fundamental mechanism within the psychedelic phenomenology requiring further exploration.

Limitations

In order to provide a more comprehensive picture of the effects of psychedelics on creativity, a variety of variables were assessed using diverse methods including several exploratory procedures. Considering the relatively small sample size, this high number of variables increases the risk of false positives, despite correction for multiple comparisons, and the results should therefore be interpreted with caution. The special features were newly introduced variables, which is why their psychometric qualities need to be explored in future studies. Specifically, content and techniques might not reflect ideal material classifications with partly small group sizes (e.g. MET *body parts*, MET *wordplay*) and poor interrater reliability (e.g. FIG *symbols*). Moreover, cultural adequacy of the PCT pictures (e.g. sledges) was reduced within our Brazilian sample and possibly affected convergent thinking performance. Finally, due to the low amount of applicable responses, symbolic thinking remained a broadly defined concept including symbolic (e.g. use a pen 'to put in the shirt pocket of an adult to make him feel important'), abstract (e.g. 'to mark time and space'), poetic (e.g. 'to write real universes') or fantasy-like responses (e.g. 'support stick for gnomes'), with non-concreteness as common denominator. Future studies should carefully disentangle these constructs to specify underlying cognitive mechanisms and evaluate therapeutic applicability in clinical populations.

Conclusion

This study aimed at elucidating the psychedelic effects on creativity by diverse tasks and approaches. This diversity allows approximating the question of how psychedelics change creativity on different levels and provides insights into psychedelic creativity per se. On a phenomenological level, creativity criteria alterations seem to reflect more 'chaotic' and 'useless' ideas. On a cognitive level, divergent and convergent thinking changes may indicate decreased cognitive control. On a semantic level, associations seem to shift towards distances and differences. On a behavioural level, figural and verbal content and techniques might serve as tools to express subjective experiences. Overall, these effects point to elementary phenomena of 'pattern break' and decreased 'organization'. Furthermore, the data-driven approach unveiled a phenomenon of enhanced 'meaning', characterized by symbolic thinking and ambiguity. Therefore, on an ontological level, our findings suggest that psychedelics may not merely disrupt cognitive-behavioural processes 'away from normal', but relocate them 'towards the new'.

Acknowledgements

We thank Raphael Egel for his help in preparing the test material and Rodolfo Olivieri for his help in data collection.

Author contributions

I.W., L.O.M. and L.F.T. contributed to study design. I.W., M.F. and L.F.T. recruited and selected the participants. I.W. and M.F. collected the data. N.L.M., J.G.R., M.E.G. and J.W.S. provided technical support. I.W., M.F., L.O.M., D.D.-B. and F.P.-F. analysed the data. I.W. wrote the manuscript. M.F., L.O.M., D.D.-B., F.P.-F., N.L.M., J.G.R., M.E.G., J.W.S., A.F., S.R., D.B.A. and L.F.T. reviewed the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This study received financial support from the Beckley Foundation and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) – Finance Code 001.

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Data availability

The data underlying the analyses are available under https://osf.io/kuhgw/.

Supplemental material

Supplemental material for this article is available online.

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Journal of Psychopharmacology

Supplementary Information

LSD and Creativity: Increased Novelty and Symbolic Thinking, Decreased Utility and Convergent Thinking

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Supplementary Methods

Creativity Tasks

For all tasks, subjects were instructed to be as creative as possible to increase ceiling and variance of creativity scores and thus test validity (Silvia et al., 2008; Harrington, 1975).

In the **PMT**, the abstract line patterns were presented on slides on an 18.5″ monitor. Over both sessions, different line patterns were shown (version A and B). Responses were handwritten and transcribed by the researchers afterwards.

In the **AUT**, the stimuli were "pen" and "towel" (version A) and "knife" and "brick" (version B). Responses were handwritten and transcribed by the researchers afterwards.

In the **PCT**, the stimuli were presented on slides on an 18.5″ monitor. Each slide contained 4 to 12 coloured drawings grouped into 2 to 3 lines. The subjects always had to select one drawing from each line to make their correct combination and their alternative combinations. The selection of the alternative combinations had to be justified. Over both sessions, different drawings were shown (version A and B). Responses were audio-recorded and transcribed by the researchers afterwards. The responses of three subjects on overall five stimuli were lost due to technical problems, so averages over the remaining stimuli were calculated for these subjects.

In the **MET**, metaphors were typed in text boxes using the survey tool LimeSurvey (Schmitz, 2012).

In the **FIG**, the stimuli were presented in rectangles (86 x 71 mm, 32 mm apart) on a sheet of paper (DIN A4 landscape). The subjects were instructed to finish the drawings and to draw at least for 10 min. For this, coloured pencils and markers, eraser and sharpener were provided. In order to generate two parallel test versions (A and B), the four stimuli from the Prueba de Imaginación Creativa (Artola et al., 2012) were divided into two version.

Creativity Variables

Semantic structure

As for preprocessing, orthographic errors were corrected by automatic spellchecking. Next, punctuation was excluded and hyphens in composite words were replaced with a blank space. Using MATLAB (version R2015a; The MathWorks, Inc., Natick, MA, USA), the Excel spreadsheets were converted into 25 .txt files (one per subject) with one response per line. These 25 .txt files were crossed with themselves in Fast text, resulting in 25 similarity matrices with dimensions according to the total number of responses for each subject. For example, if one subject gave a total of 17 responses in the AUT on both stimuli in both sessions, the matrix had a dimension of 17x17 cells. In the next step, one small matrix for each stimulus was extracted using MATLAB. For example, if the subject created two uses for pen, seven for towel, three for brick and five for knife over both sessions, four stimuli matrices with the dimensions 2x2, 7x7, 3x3 and 5x5 were extracted. In these similarity matrices, a value of 1 indicates absolute similarity (the word crossed with itself) and 0 absolute distance. Therefore, if a subject gave just one answer for a stimulus, the stimulus matrix had a dimension of 1x1 with a value of 1. Therefore, all cases of less than two answers per stimulus were excluded from the analysis. Note that in the FIG, the matrices always had a dimension of 2x2 cells comprising the two titles for both drawings, which is why only one semantic index was extracted from this

task. Next, similarity matrices were converted into distance matrices as following: $value_{distance} = 1 - value_{similarity}$.

Special features

In order to identify common features between all responses, we applied an analysis based on the principles of the qualitative content analysis using a mixed inductive-deductive approach (Elo and Kyngäs, 2008). In a first, inductive step, all responses were read once without any a priori hypotheses to identify overall discernible features within the data, resulting in the generation of diverse main categories (details below in **bold**), subdivided into subcategories (details below in italic). In a next, deductive step, we assigned all responses to these subcategories to examine the effects of the treament on the expression of the subcategories.

Content: In the MET, the topic (what the metaphor is about) and tool (by which vehicle the metaphor is generated) were examined (Silvia and Beaty, 2012) and each assigned to one of ten subcategories (symbols, nature, objects, persons, body parts, animals, characteristics, sensation, cognition, emotion). For example, the metaphor "She is a hurricane" is about a woman (topic = "she"), who is compared to a natural phenomenon (tool = "hurricane"). Hence, the topic was assigned to the subcategory persons, while the tool was assigned to the subcategory nature. The value for each content subcategory was then assessed by the total number of topic and tool assignments for each subject.

In the FIG, the title and all drawing elements were examined regarding their content and each assigned to one of six subcategories (symbols, nature, objects, persons, body parts, animals). An example is the drawing entitled "Life" and depicting a hand holding a cup of coffee on a table and, in the background, a clock on the wall and a window with the sun and a tree. Here, the title was assigned to the subcategory symbols ("Life"), while the drawing elements were body parts (hand), object (cup, table, clock, window) and nature (sun, tree). The value for each content subcategory was then assessed by the total number of title and drawing element assignments for each subject.

Technique: In the MET, the technique used to create the metaphor was examined and assigned to one of four subcategories (union, exaggeration, contrast, wordplay).

Union comprised the unification of a topic and tool (e.g. "Love is the destination of life" unifies the topic "love" with the tool "destination of life").

Exaggeration comprised the use of a tool with extreme characteristics attributed to the topic (e.g. "My head is exploding" attributes the extreme characteristics of the tool "exploding" to the topic "my head").

Contrast comprised the use of a topic and tool with contrasting characteristics (e.g. "The universe is in a seed" puts in contrast the characteristics of the big "universe" and small "seed").

Wordplay comprised the use of a phonologically similar topic and tool (e.g. "The pain of rejection hurts more than an injection" uses the phonological similarity of "rejection" and "injection").

In the FIG, technique ratings were conducted on 3-point scales for background (0=none; 2=very elaborated), spatiality (0=very flat; 2=very spatial), symmetry (0=asymmetric; 2=symmetric) and frame (0=completely inside; 2=not considering the frame at all) and regarding the quantity of colours (one point per colour) and connections (one point per connection).

Symbolic thinking: A symbolic or abstract response was defined as not de facto executable object use (AUT), non-figural pattern interpretation (PMT) and non-concrete stimulus use for combinations (PCT).

Supplementary Tables

Table S1. Examples for the measured variables within different tasks

Variable Group	Variable	Example
Creativity criteria	novelty	The AUT responses to use a knife to "juggle" received zero points of novelty, while the response to use a knife to "play the piano" received two points of novelty.
	utility	The AUT responses to use a knife to "cut the air to feel the movement" received zero points of utility, while the response to use a knife to "unscrew screws" received two points of utility.
	surprise	The AUT responses to use a knife to "kill" received zero points of surprise, while the response to use a knife to "mark the page in a book" received two points of surprise.
Divergent thinking	originality (PMT, AUT, PCT)	The sample's AUT responses to use a knife to "draw […] in the clay", "draw in the bark of a tree", "draw in the earthen floor", "[…] draw in the sand" and "[…] write in the sand" were grouped in the category 'draw'. This category with 5 responses (out of 103 total responses for knife) contained 4.85% of total responses. Therefore, each response within this category received one point of originality.
	originality (FIG)	The sample's FIG uses of the line pattern < > to draw arms of humans, animals and fruits were grouped into the category 'arms'. This category contained 5 responses, of which each received 1/5 = 0.2 points of stimulus originality. Special details points were given for symmetry within the drawings, rotation, inversion, expansion or connection of the drawings or other special ideas. A drawing depicting a hand holding a cup of coffee entitled "Life" received two points of Title originality, while a drawing depicting a colourful hat entitled "party hat" received zero points.
	flexibility	One subject's AUT responses to use a knife to "draw […] in the clay" and "draw in the bark of a tree" were classified in the same category 'draw' and received overall one point of flexibility.
	elaboration	The AUT response to use a knife to "sculpt (1) a statue (2) in wood (3)" received three points of elaboration.
Semantic structure	semantic distances	The AUT responses to use a knife to "hunt" and "kill" show a lower semantic distance than the responses "hunt" and "sculpt", as the former combination co-occurs more frequently in the corpus.
Special features	content	The MET response "Life is a flower in constant bloom" was assigned to the topic *symbol* (life) and tool *nature* (flower).
	technique (MET)	The MET response "The universe is in a seed" was classified into the technique *contrast* (contrasting the big universe and a small seed); "My head is exploding" was classified into the technique *exaggeration* (exaggeration regarding the overworked head), "Love is the destination of life" was classified into the technique *union* (unifying love and the destination of life).
	technique (FIG)	The two drawings depicting two heads (1) in similar colours (2) entitled "Can we see?" and "Yes, we can" (3) received three points of *connections.*
	ambiguity	The MET response "faithful as a dog" received zero points, while "the philosopher is a hole in the ocean" received two points of ambiguity.
	symbolic thinking	The AUT response to use a knife to "separate nonsense from what is important", the PMT interpretation of a zigzag line as "the course of my thoughts" and the PCT combination key–sandwich by "the key for a good health is good alimentation" were considered symbolic responses.

Table S2. Interrater reliability estimates for all creativity tests and variables[1]

Variable	ICC	95% CI	*F*-value	*p*-value	Interpretation[2]
AUT					
novelty	0.934	0.884-0.963	15.26	<0.001	good to excellent
utility	0.957	0.957-0.986	41.27	<0.001	excellent
surprise	0.938	0.890-0.965	16.14	<0.001	good to excellent
rel novelty	0.919	0.857-0.954	12.36	<0.001	good to excellent
rel utility	0.917	0.853-0.953	12.06	<0.001	good to excellent
rel surprise	0.915	0.849-0.952	11.72	<0.001	good to excellent
fluency	0.993	0.987-0.996	135.30	<0.001	excellent
originality	0.864	0.759-0.923	7.35	<0.001	good to excellent
flexibility	0.969	0.945-0.982	32.04	<0.001	excellent
elaboration	0.735	0.530-0.850	3.77	<0.001	moderate to good
rel originality	0.833	0.704-0.906	6.00	<0.001	moderate to excellent
rel flexibility	0.672	0.419-0.815	3.05	<0.001	poor to good
rel elaboration	0.622	0.330-0.787	2.644	0.001	poor to good
symbolic thinking	0.943	0.900-0.968	17.67	<0.001	excellent
rel symbolic thinking	0.916	0.851-0.952	11.86	<0.001	good to excellent
PMT					
novelty	0.963	0.934-0.979	26.69	<0.001	excellent
utility	0.961	0.931-0.978	25.86	<0.001	excellent
surprise	0.943	0.898-0.968	17.44	<0.001	good to excellent
rel novelty	0.921	0.859-0.955	12.60	<0.001	good to excellent
rel utility	0.819	0.678-0.898	5.51	<0.001	moderate to good
rel surprise	0.882	0.790-0.933	8.46	<0.001	good to excellent
fluency	0.994	0.990-0.997	181.37	<0.001	excellent
originality	0.934	0.882-0.963	15.07	<0.001	good to excellent
flexibility	0.970	0.947-0.983	33.56	<0.001	excellent
elaboration	0.842	0.719-0.911	6.32	<0.001	moderate to excellent
rel originality	0.724	0.511-0.844	3.63	<0.001	moderate to good
rel flexibility	0.816	0.674-0.896	5.44	<0.001	moderate to good
rel elaboration	0.777	0.604-0.874	4.48	<0.001	moderate to good
symbolic thinking	0.996	0.993-0.998	263.63	<0.001	excellent
rel symbolic thinking	0.989	0.981-0.994	93.27	<0.001	excellent
PCT					
novelty	0.932	0.879-0.961	14.63	<0.001	good to excellent
utility	0.935	0.885-0.964	15.47	<0.001	good to excellent
surprise	0.935	0.885-0.963	15.35	<0.001	good to excellent
rel novelty	0.910	0.840-0.949	11.08	<0.001	good to excellent
rel utility	0.486	0.088-0.710	1.94	0.012	poor to moderate
rel surprise	0.891	0.808-0.939	9.21	<0.001	good to excellent
fluency	1.000	1.000-1.000	-	-	excellent
originality	0.993	0.987-0.996	138.64	<0.001	excellent
flexibility	0.999	0.999-1.000	1363.2	<0.001	excellent
elaboration	0.848	0.731-0.914	6.59	<0.001	good to excellent
rel originality	0.944	0.900-0.968	17.74	<0.001	excellent
rel flexibility	0.969	0.946-0.983	32.69	<0.001	excellent
rel elaboration	0.786	0.621-0.879	4.67	<0.001	moderate to good
symbolic thinking	0.810	0.664-0.893	5.28	<0.001	moderate to good
rel symbolic thinking	0.544	0.192-0.743	2.19	0.004	poor to moderate
MET					
novelty	0.921	0.860-0.956	12.68	<0.001	good to excellent
utility	0.808	0.660-0.892	5.21	<0.001	moderate to good
surprise	0.879	0.785-0.932	8.25	<0.001	good to excellent
rel novelty	0.888	0.802-0.937	8.94	<0.001	good to excellent
rel utility	0.552	0.206-0.747	2.23	0.003	poor to moderate
rel surprise	0.824	0.689-0.901	5.69	<0.001	moderate to excellent
fluency	1.000	1.000-1.000	-	-	excellent
flexibility	0.936	0.887-0.964	15.71	<0.001	good to excellent
elaboration	0.985	0.973-0.992	66.43	<0.001	excellent
rel flexibility	0.583	0.260-0.765	2.40	0.002	poor to good
rel elaboration	0.978	0.960-0.987	44.45	<0.001	excellent

cont *symbols*	0.931	0.878-0.961	14.51	<0.001	good to excellent
cont *nature*	0.949	0.909-0.971	19.50	<0.001	excellent
cont *objects*	0.971	0.949-0.984	34.75	<0.001	excellent
cont *persons*	0.734	0.528-0.850	3.76	<0.001	moderate to good
cont *body parts*	0.874	0.776-0.929	7.93	<0.001	good to excellent
cont *animals*	0.996	0.993-0.998	258.96	<0.001	excellent
cont *characteristics*	0.856	0.745-0.919	6.96	<0.001	moderate to excellent
cont *sensation*	0.873	0.775-0.928	7.86	<0.001	good to excellent
cont *cognition*	0.843	0.721-0.911	6.35	<0.001	moderate to excellent
cont *emotion*	0.761	0.575-0.865	4.18	<0.001	moderate to good
tec *union*	0.830	0.698-0.904	5.87	<0.001	moderate to excellent
tec *exaggeration*	0.838	0.713-0.909	6.18	<0.001	moderate to excellent
tec *contrast*	0.874	0.777-0.929	7.96	<0.001	good to excellent
tec *wordplay*	0.824	0.687-0.901	5.67	<0.001	moderate to excellent
ambiguity	0.897	0.817-0.942	9.71	<0.001	good to excellent
rel ambiguity	0.816	0.673-0.896	5.42	<0.001	moderate to good
symbolic thinking	0.931	0.878-0.961	14.51	<0.001	good to excellent
rel symbolic thinking	0.701	0.470-0.831	3.35	<0.001	poor to good
FIG					
novelty	0.711	0.487-0.837	3.46	<0.001	poor to good
utility	0.541	0.187-0.741	2.18	0.004	poor to moderate
surprise	0.768	0.588-0.869	4.31	<0.001	moderate to good
special details	0.766	0.584-0.868	4.27	<0.001	moderate to good
title originality	0.800	0.645-0.887	4.99	<0.001	moderate to good
picture elaboration	0.788	0.624-0.880	4.71	<0.001	moderate to good
colour elaboration	0.792	0.632-0.883	4.82	<0.001	moderate to good
cont *symbols*[3]	0.478	0.074-0.705	1.92	0.013	poor to moderate
cont *nature*[3]	0.686	0.444-0.823	3.19	<0.001	poor to good
cont *objects*[3]	0.819	0.679-0.898	5.52	<0.001	moderate to good
cont *persons*[3]	0.845	0.725-0.913	6.46	<0.001	moderate to excellent
cont *body parts*[3]	0.685	0.441-0.822	3.17	<0.001	poor to good
cont *animals*[3]	0.858	0.748-0.920	7.04	<0.001	moderate to good
tec *background*	0.872	0.774-0.928	7.83	<0.001	good to excellent
tec spatiality	0.736	0.532-0.851	3.79	<0.001	moderate to good
tec *symmetry*[3]	0.766	0.586-0.868	4.28	<0.001	moderate to good
tec *frame*	0.948	0.908-0.971	19.20	<0.001	excellent
tec *colours*	0.947	0.905-0.970	18.73	<0.001	excellent
tec *connection*	0.760	0.574-0.864	4.16	<0.001	moderate to good
ambiguity	0.632	0.347-0.792	2.72	<0.001	poor to good
title symbolism	0.824	0.688-0.901	5.69	<0.001	moderate to excellent
picture symbolism	0.800	0.646-0.887	5.00	<0.001	moderate to good
colour abstractness	0.744	0.545-0.855	3.90	<0.001	moderate to good

[1] Interrater reliability was estimated by intraclass correlation coefficients (ICC), lower and upper bound of 95% confidence intervals (CI), *F*- and *p*-values.
[2] Reliability was interpreted based on the guidelines for classification of the CI bounds as following: poor <0.5, moderate 0.5-0.75, good 0.75-0.9, excellent 0.9-1.0 (Koo and Li, 2016).
[3] Values for second rating after discussion and re-training.
PMT, Pattern Meaning Task. AUT, Alternate Uses Task. PCT, Picture Concept Task. MET, Creative Metaphors Task. FIG, Figural Creativity Task. rel, relative values as calculated by ratios to fluency. cont, content. tec, technique.

Supplementary Figures

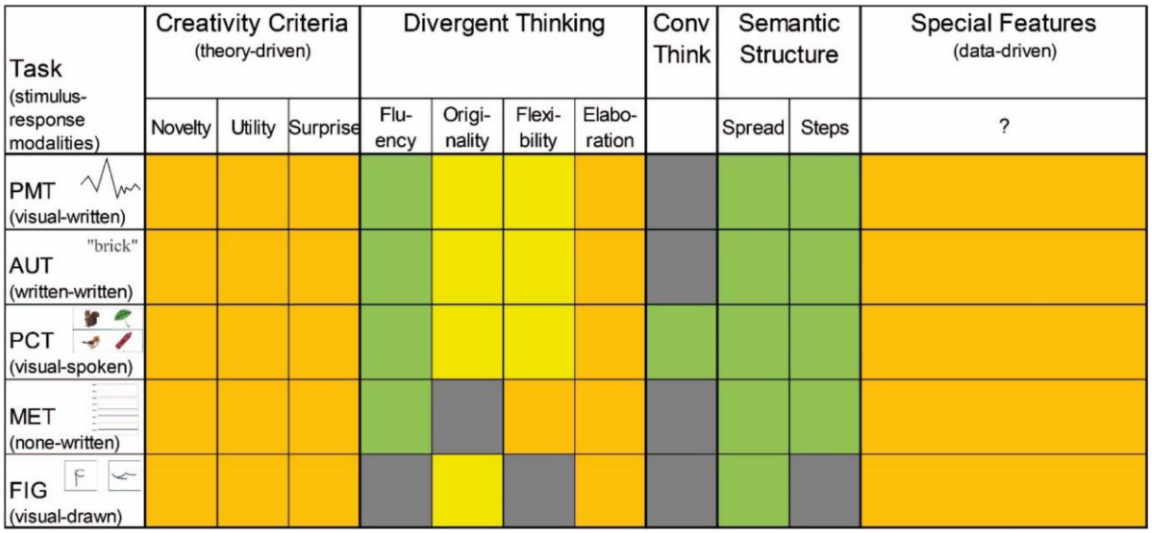

Figure S1. An overview of the diverse creativity tasks (lines) and approaches (columns). Altogether, five tasks of different stimulus-response modalities were applied (PMT, AUT, PCT, MET, FIG). Over all tasks, diverse variable groups of diverse approaches were examined, aimed at assessing parameters that were 1.) theory-driven, phenomenological-oriented (creativity criteria), 2.) established, cognitive-oriented (divergent thinking, convergent thinking), 3.) semantic-oriented (semantic structure) and 4.) data-driven, behavioural/ontological-oriented (special features). The cells represent variables that were subjectively scored by the researchers (orange), objectively scored by manual or automatic computations (green), first subjectively scored and then, based on these scorings, objectively computed (yellow) and not assessed due to theoretical or practical limitations (grey). Note that creativity criteria, convergent thinking, semantic structure and special features are evaluated in relation to the general sociocultural context, while divergent thinking is evaluated in relation to the study sample.

PMT, Pattern Meaning Task. AUT, Alternate Uses Task. PCT, Picture Concept Task. MET, Creative Metaphors Task. FIG, Figural Creativity Task. Conv Think, convergent thinking. Spread, semantic spread. Steps, semantic steps.

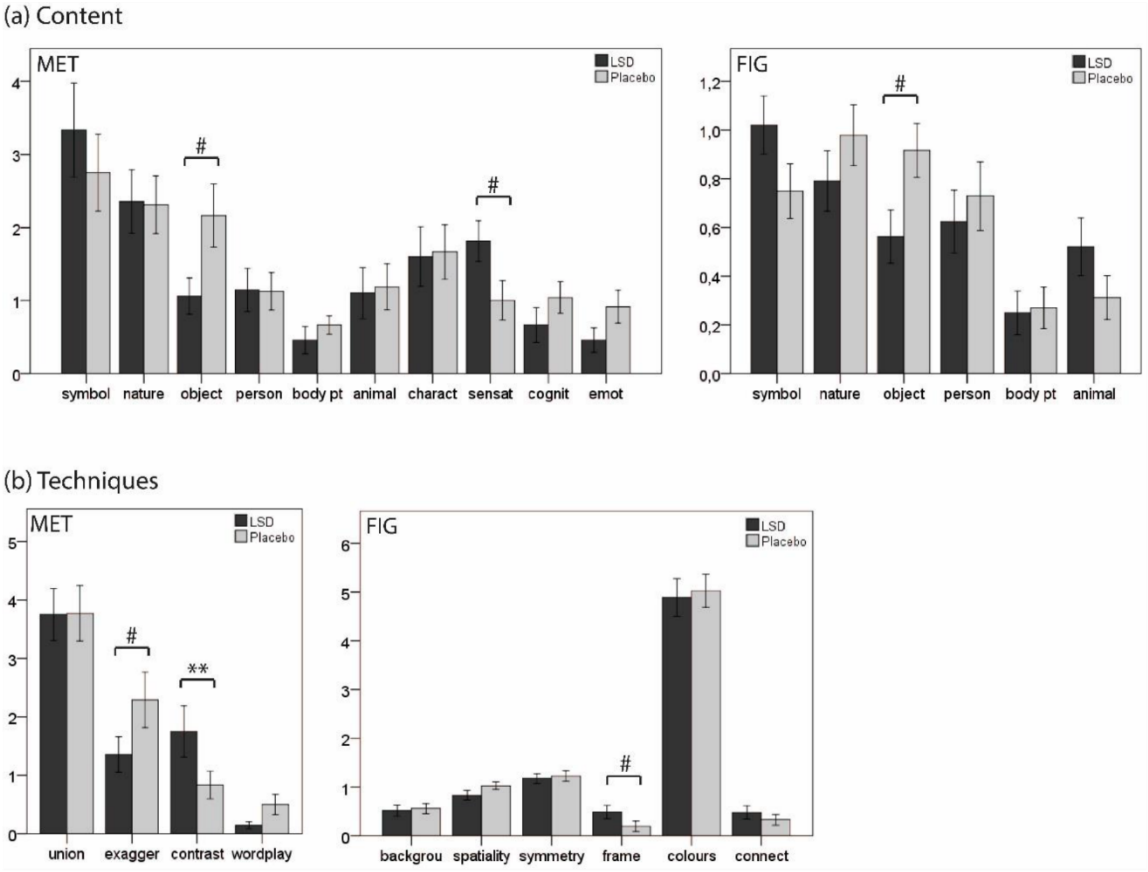

Figure S2. The effects of LSD, compared to placebo, on content and techniques in metaphors and drawings. (a) Content under LSD showed more sensation (MET) and fewer objects (MET, FIG), but these effects did not survive correction for multiple comparisons. (b) Techniques under LSD showed increased contrast (MET), while decreased exaggeration (MET) and increased frame break (FIG) did not survive correction for multiple testing. Values are displayed as means (±SEM) in 24 subjects. **$p<0.01$ (corrected), $^{\#}p<0.05$ (uncorrected).

MET, Creative Metaphors Task. FIG, Figural Creativity Task. content: symbol, symbols; object, objects; person, persons; body pt, body parts; animal, animals; charact, characteristics; sensat, sensation; cognit, cognition; emot, emotion. technique: exagger, exaggeration.

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4.3. Article 3 – LSD and Cognition

Reference (98):

Wießner I, Olivieri R, Falchi M, Palhano-Fontes F, Maia LO, Feilding A, Araujo DB, Ribeiro S, Tófoli LF. LSD, afterglow and hangover: Increased episodic memory and verbal fluency, decreased cognitive flexibility. Eur Neuropsychopharmacol [Internet]. 2022;58(May):7–19. Available from: https://doi.org/10.1016/j.euroneuro.2022.01.114

LSD, afterglow and hangover: Increased episodic memory and verbal fluency, decreased cognitive flexibility

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Word Count: **5,022**
Submitted to: *European Neuropsychopharmacology* as Research Article
Submission Date: 02 October 2021
Resubmission Date: 24 January 2022

Abstract

Psychedelics acutely impair cognitive functions, but these impairments decline with growing experiences with psychedelics and microdoses may even exert opposing effects. Given the recent evidence that psychedelics induce neuroplasticity, this explorative study aimed at investigating the potential of psychedelics to sub-acutely change cognition. For this, we applied a randomized, double-blind, placebo-controlled, crossover study with 24 healthy volunteers receiving 50µg lysergic acid diethylamide (LSD) or an inactive placebo. Sub-acute changes in cognition were measured 24 hours after dosing, including memory (Rey-Osterrieth Complex Figure, ROCF; Object-Location Memory Task, OLMT; Rey Auditory-Verbal Learning Test, RAVLT), verbal fluency (phonological; semantic; switch), design fluency (basic; filter; switch), cognitive flexibility (Wisconsin Card Sorting Test, WCST), sustained and switching attention (Trail Making Test, TMT), inhibitory control (Stroop Task) and perceptual reasoning (Block Design Test, BDT). The results show that when compared to placebo and corrected for Body Mass Index (BMI) and abstinence period from psychedelics, LSD sub-acutely improved visuospatial memory (ROCF immediate recall points and percentage, OLMT consolidation percentage) and phonological verbal fluency and impaired cognitive flexibility (WCST: fewer categories achieved; more perseveration, errors and conceptual level responses). In conclusion, the low dose of LSD moderately induced both “afterglow” and “hangover”. The improvements in visuospatial memory and phonological fluency suggest that LSD-assisted therapy should be explored as a novel treatment perspective in conditions involving memory and language declines such as brain injury, stroke or dementia.

Keywords: Sub-acute LSD Effects; Psycholytic Dose; Visuospatial Memory; Phonological Verbal Fluency; Cognitive Flexibility; Executive Functions.

1. Introduction

Increasing evidence suggests that psychedelics such as LSD, psilocybin and ayahuasca might constitute promising treatments in psychiatric conditions including mood, anxiety and substance use disorders (dos Santos et al., 2016; Krebs and Johansen, 2012). Beyond that, there is increasing interest in their therapeutic potential for other conditions including obsessive-compulsive disorders (OCD), post-traumatic stress disorders (PTSD), eating disorders, cluster headache and other pain conditions (Castellanos et al., 2020; Krediet et al., 2020; Lafrance et al., 2017; Moreno et al., 2006). Interestingly enough, psychedelic research has hitherto largely neglected clinical conditions involving sudden or gradual cognitive decline including brain injury, stroke or dementia. Merely one study on healthy older adults reported no effects of LSD microdoses on several cognitive domains, including reaction time, visual memory and learning, visual attention and spatial working memory (Family et al., 2020). However, psychedelics might exert benefits in conditions involving memory and language impairments given the recent findings of psychedelic-induced neuroplasticity, neurogenesis, neuroprotective and anti-inflammatory effects (Inserra et al., 2021; Shao et al., 2021). Moreover, the main target of psychedelics, serotonin 2A (5-HT_{2A}) receptors, play an important role in cognitive processes such as executive functions, learning, and memory (Lane et al., 2008; Zhang and Stackman, 2015).

During their acute effects, psychedelics seem to disturb perception, cognition and behaviour. Subjective and neurophysiological evidence indicates that psychedelics impair subjective cognitive functioning (Schmid et al., 2015; Studerus et al., 2011) and affect the brain's executive control and dorsal attention network (Tagliazucchi et al., 2014). Behavioural evidence suggests that psychedelics impair concentration skills including visual sustained attention, attentional tracking, disengaging and reorienting attention, and simple and complex arithmetic performance (Carter et al., 2005; Krus et al., 1963; Vollenweider et al., 2007); executive functions including working memory, cognitive flexibility and inhibitory control (Barrett et al., 2018; Bouso et al., 2013; Pokorny et al., 2019; Quednow et al., 2012); and learning and episodic memory including recall (drawing geometric figures, recalling objects, syllables, paired associate words and sentences) and recognition (letters) (Barr et al., 1972; Barrett et al., 2018; Jarvik et al., 1955; Silverstein and Klee, 1958).

However, the notion that psychedelics merely impair cognition has been challenged. Regular ayahuasca use has been associated with better executive functions and increased cortical thickness in the anterior cingulate cortex (ACC), a brain area important for attention and inhibitory control (Bouso et al., 2015, 2012). Acute impairments in executive functions (as measured by the Tower of London) were only observed in occasional but not experienced ayahuasca users, although the observed groups were small (Bouso et al., 2013). Microdoses were associated with increased attention (Hutten et al., 2020), convergent thinking (Prochazkova et al., 2018) and subjective cognition (Cameron et al., 2020; Lea et al., 2019), although other findings comprised unchanged overall cognitive performance (Szigeti et al., 2021), fluid intelligence (Prochazkova et al., 2018), working memory (Bershad et al., 2019) and cognitive control, and even impaired information processing and subjective control and cognition (Hutten et al., 2020). Studies in naturalistic settings found increased convergent thinking up to four weeks and increased subjective and behavioural cognitive flexibility at 24 hours after ceremonies with ayahuasca and 5-Methoxy-N,N-dimethyltryptamin (5-MeO-DMT) (Murphy-Beiner and Soar, 2020; Uthaug et al., 2019, 2018). Increased cognitive and neural flexibility was also observed in patients with depression up to four weeks after psilocybin therapy (Doss et al., 2021).

The mechanisms underlying acute psychedelic-induced changes in episodic memory are just beginning to be understood. For example, it has been unclear whether the episodic memory impairments were attributable to impaired encoding or retrieval. Psilocybin-induced decreased recall (of previously categorized words) was attributed to impaired encoding, since encoding

was conducted during drug peak and recall three hours afterwards, however, some persisting drug effects might still have impacted the recall (Barrett et al., 2018). The non-classic psychedelic 3,4-methylenedioxymethamphetamine (MDMA), exhibiting both psychedelic and stimulant effects, assessed encoding and retrieval separated by two days, found impaired encoding but not retrieval (emotional pictures), as compared to placebo (Doss et al., 2018). In mice, the 5-HT_{2A} psychedelic TCB-2 improved memory extinction (trace and delay fear) and recognition (novel objects) if applied between encoding and retrieval, pointing to psychedelic-induced improved memory consolidation (Zhang et al., 2013).

On receptor level, psychedelic-induced impairments in working and episodic memory, cognitive flexibility and inhibitory control are blocked by the 5-HT_{2A} antagonist ketanserin (Pokorny et al., 2019; Quednow et al., 2012; Van Wel et al., 2011), emphasizing the crucial role of serotonergic activity in psychedelic-induced cognitive processes. Here, the relationship between cognitive flexibility and the 5-HT_{2A} receptors, activated by psychedelics, is mixed. While the 5-HT_{2A} blockade is associated with impairments (Amodeo et al., 2017; Furr et al., 2012), no changes (Boulougouris and Robbins, 2010) and enhancements in rodents (Amodeo et al., 2017, 2014; Baker et al., 2011), the 5-HT_{2A} activation by psychedelics is principally associated with impairments in humans and rodents (Amodeo et al., 2020; Pokorny et al., 2019), although a recent rodent study reported no changes (Odland et al., 2021).

Overall, these findings suggest that psychedelics might enhance cognition under certain conditions, depending on previous experience, dose, and time point after intake. In light this, we aimed at examining the sub-acute effects of low-dose LSD on diverse aspects of cognition in an explorative, placebo-controlled, double-blind study.

2. Methods

This work is part of a larger study, details of which - including further information on participants, drug and procedures - is published elsewhere (Wießner et al., 2021a).

2.1. Study Design

This study used a randomized, double-blind, placebo-controlled, crossover design with two treatments (LSD, placebo) and a washout period of 14 days between treatments. Participants were randomly assigned to treatment order and half of them (n=12) received LSD first. Where indicated, parallel test versions (A, B; **table S1**) were used, which were applied in balanced order across participants and in counterbalanced order across treatments, i.e. half of the participants completed version A under LSD. This study was approved by the University Research Ethics Committee and conducted according to safety guidelines for psychedelic research in humans (Johnson et al., 2008).

2.2. Participants

Twenty-five healthy participants were recruited in a convenience sample. Inclusion criteria were: ≥ 22 years, ≥ one experience with LSD, abstinence of at least two weeks from psychedelics until the end of the study and of three days from alcohol and other drugs before each session, and abstinence from tobacco and caffeine during the study days. Exclusion criteria were: presence of psychiatric symptoms, personal or first-degree family member history of psychotic disorder, use of psychiatric medication, history of severe complications after psychedelic use, alcohol or drug use disorder, heart disease or other relevant medical conditions, pregnancy, and non-native speaking of Brazilian Portuguese. Participants provided written informed consent before participation. One participant ceased participation after the first session for personal reasons, resulting in a final sample of 24 subjects (8 women; mean (±SD) age=35 (±11) years, range=25–61). Notably, participants consumed on average 3 cups of coffee a day (±2; range=0–6) and one third of the sample consumed tobacco every third day to several

times a day, which is why we cannot rule out that a mere stimulating effect of LSD might account for the improvements over placebo.

2.3. Drug

Participants orally received 50µg LSD (dissolved in alcohol solution) or inactive placebo (alcohol solution) diluted in 30ml water. The low dose was chosen to minimize the risk of adverse reactions but exert noticeable effects in the participants.

2.4. Measurements

2.4.1. Episodic Memory

The Rey-Osterrieth Complex Figure (ROCF) measures visual perception, visuoconstructional abilities and spontaneous memory retention (Rey, 1999). First, participants are requested to copy a complex geometric figure (18 units of black lines) on a sheet of paper (copy). Then, the sheets are taken away and the participants asked to draw the figure from memory immediately afterwards (immediate recall) and after 20-30 min (delayed recall). Note that no instructions are given to memorize the figure, which is why the task is intended to measure what is spontaneously kept in mind. Measured variables are: copy, immediate recall and delayed recall points (one point for accuracy and location per unit); copy percentage (= copy points / maximum points); immediate recall percentage (= immediate recall points / copy points); delayed recall percentage (= delayed recall points / immediate recall points).

The 2D Object-Location Memory Task (OLMT) measures visuospatial memory consolidation (Rasch et al., 2007). In our paper version, 15 pairs of identical cards (4x4cm) with pictures of animals and objects are placed covertly on a board in a 5×6 matrix. During learning before drug administration, the first card of a pair is shown for 1 sec and then, the second card of the pair is additionally revealed for another 3 sec. Next, both cards are covered and no card is shown during an inter-stimulus interval of 3 sec. Afterwards, the next pair is shown correspondingly and so on, until revealing all 15 pairs. The whole set of 15 pairs is presented in two consecutive learning runs. During immediate recall (before drug administration), the first card of a pair is revealed and participants must turn the second card of the pair. Independent of the guess (correct/wrong), the correct pair is then shown for 2 sec, before getting to the next pair. Immediate recall runs are repeated until participants recall 60% of pair locations or reach a total of six runs. During final recall the morning after drug administration, the immediate recall procedure is repeated with a different pair order and without revealing correct locations. Measured variables are: consolidation points (number of recalled card locations in final recall) and consolidation percentage (= consolidation points / last immediate recall run points).

The Rey Auditory-Verbal Learning Test (RAVLT) (Malloy-Diniz et al., 2000) was aligned to the OLMT procedures to measure auditory-verbal memory consolidation. During learning before drug administration, participants hear a list of 15 nouns twice and then recall as many nouns as possible. List reading and recalling are repeated either six times or until participants recall all nouns (immediate recall). The morning after drug administration, participants are asked to recall as many nouns as they can (final recall) and recognize the 15 nouns from a larger list with phonological and semantic distractors (recognition). Measured variables are: consolidation points (number of recalled nouns in final recall), consolidation percentage (= consolidation points / last immediate recall run points), hits and false alarms (number of correctly and falsely recognized nouns during recognition).

2.4.2. Fluency

The Verbal Fluency Task (VFT) measures verbal fluency and shifting abilities (Lezak et al., 2004). In one minute, participants list as many words as possible of the same initial letter (phonological: F, A and S), of the same content (semantic: animals) and switching between two

contents (switch: female names and furniture). Measured variables are: total responses, correct responses and errors in phonological, semantic and switch.

The Design Fluency Task (DFT) measures design fluency as a nonverbal counterpart to verbal fluency (Baldo et al., 2001). On a sheet of paper, 5x7 rectangles are depicted containing patterns of black dots (basic) or black and white dots (filter and switch). In one minute, participants draw as many different designs as possible using four lines per rectangle connecting the black dots (basic), the white dots (filter) and a black and a white dot (switch). Measured variables are: total responses, correct responses and errors in basic, filter and switch.

2.4.3. Cognitive Flexibility

The Wisconsin Card Sorting Test (WCST) measures cognitive flexibility, including the formation, maintenance and shift of abstract concepts utilizing feedback (Heaton et al., 2005; Strauss et al., 2006). In each trial, participants assign a card with symbols of different colours (yellow, red, blue, green), forms (circle, triangle, cross, star) and numbers (one to four) to a *key card* according to the assumed correct dimension (colour, form or number), followed by feedback from the researcher (correct/wrong). After ten consecutive correct trials (one achieved category), the dimension changes. The test ends after achieving six categories or assigning all 128 cards. Measured variables are: the number of total trials, total correct responses, total errors, categories achieved, trials to complete the first category, conceptual level responses (sequences of at least three correct responses), failures to maintain set (sequences of at least five correct responses followed by one error) and learning to learn (average difference of percent errors between two consecutive categories). To evaluate perseveration, a "perseveration principle" is established corresponding to the dimension of the first error (e.g. colour; for details, see **Supplemental Methods**, Heaton et al., 2005). The perseveration principle changes if three consecutive errors of another dimension (e.g. number) are given. With this, we evaluated perseverative responses (any responses within the perseveration principle), perseverative errors type 1 (any errors within the perseveration principle), perseverative errors type 2 (two consecutive errors within the perseveration principle), perseverative errors type 3 (three consecutive errors within any prior or the current perseveration principle) and non-perseverative errors (= total errors − perseverative error type 1). Beyond that, the percentage of total errors, conceptual level responses, perseverative responses, perseverative errors and non-perseverative errors were calculated by the ratio to total trials.

2.4.4. Sustained and Shifting Attention

The Trail Making Test (TMT) measures sustained and shifting attention and visuomotor processing speed (Strauss et al., 2006). Participants receive a sheet of paper with circles containing numbers (basic) and numbers and letters (switch). They must connect the circles as fast as possible, without lifting the pencil, in ascending order of numbers (basic) and ascending/alphabetical order switching between numbers and letters (switch). Measured variables are: duration and errors in each condition and interference between both conditions (= [switch duration − basic duration] / basic duration).

2.4.5. Inhibitory Control

The Stroop Task (Stroop) measures inhibitory control, selective attention and visuoverbal processing speed (Regard, 1981). Participants see cards containing coloured rectangles (colours), coloured words (words) and colour names printed in incongruent colours (colour words) and must name the colours of each item as fast as possible. Note that we manually applied a non-computerized version with three printed cards, one for each condition (colours, words, colour words) and with each card containing 24 stimuli (6 rows with 4 stimuli in a row). The total duration to name the colours of all 24 stimuli on the card is assessed. Measured variables are: duration and errors in each condition, total interference between

conditions (= colour words duration − [(words duration + colours duration) / 2]), low interference (= words duration / colours duration) and high interference (= colour words duration / colours duration).

2.4.6. Perceptual Organization

The Block Design Test (BDT), a sub-test of the Wechsler Abbreviated Scale of Intelligence (WASI), measures perceptual organization including visuospatial reasoning and visuoconstructional abilities (Wagner et al., 2014). Participants receive cubes of red, white and red-white faces and must reconstruct patterns presented on a computer monitor as fast as possible. Measured variables are: total duration and errors.

2.5. Study Procedures

Candidates for participation underwent a clinical and psychiatric interview, including medical anamnesis, physical and mental state examination and a check of a recent electrocardiogram. If indicated, complementary exams were consulted.

Each session consisted of two study days. The day of drug administration started at 7:30 a.m. with baseline measurements. At 8:10 a.m., RAVLT and OLMT learning was conducted. LSD or placebo was administered at 9:30 a.m., followed by diverse tests and questionnaires throughout the day. Results of these additional measurements are reported elsewhere (Wießner et al., 2022, 2021a, 2021b). A standardized snack was served at 11:00 a.m., lunch at 1:40 p.m. Eight hours after substance administration, at 5:30 p.m., it was ensured that subjects were feeling stable and well before being released into the custody of a family member or friend.

The next morning, subjects returned at 8:00 a.m., performed RAVLT and OLMT final recall, WCST, ROCF, TMT, Stroop, VFT, DFT, BDT, among other tasks, and were released around 10:00 a.m.

2.6. Data Analysis

Data were analysed with IBM SPSS Statistics (version 22). A repeated measures General Linear Model (GLM) with 'treatment' as within-subjects factor and 'treatment order' as between-subjects factor was performed for each variable to assess effects of treatment, order (treatment order) and period (treatment*treatment order). In a next step, we complemented the models by the covariates 'abstinence from psychedelics' and 'Body Mass Index' (BMI) to control for abstinence periods and drug dose, which might impact psychedelic effects especially under LSD (Holze et al., 2021; Nichols, 2016; Schmid et al., 2015) although this is not necessarily always the case (Garcia-Romeu et al., 2021). Effect sizes were estimated using partial eta squared (η_p^2). Significance level was set to α=0.05, two-tailed. Given the exploratory nature of the study, *p*-values were not corrected for multiple comparisons.

3. Results

Data from one to two subjects were lost in OLMT, RAVLT, VFT and Stroop due to application errors. The GLM results without covariates are shown in **table S2** and **figure S1**. The GLM results with covariates are described below (for detailed values, see **table 1**, for estimated marginal means and standard errors of measurement, see **table S3**).

3.1. Episodic Memory

Compared to placebo, LSD increased ROCF immediate recall points (p=0.044) and percentage (p=0.018), indicating improved spontaneous visuospatial memory encoding and recall (**figure 1A**). Moreover, LSD increased OLMT consolidation percentage (p=0.022), indicating improved memory consolidation overnight as compared to immediate recall before drug administration (**figure 1B**, for single subject data on the immediate recall performance,

see **figure 2**). No treatment effects were observed for ROCF copy and delayed recall points and percentage, OLMT consolidation points and RAVLT variables (**figure 2, S2**).

There was no order effect but a period effect for ROCF immediate recall points (p=0.006) and percentage (p=0.002) and delayed recall points (p=0.008) with higher means in session 2 indicating practice effects. Note that the subjects were not instructed to memorize the figure, which might have facilitated memory performance in the second session, when they were already aware of the procedures.

3.2. Fluency

LSD increased VFT phonological total responses (p=0.036) and correct responses (p=0.027) and marginally decreased VFT switch errors (p=0.058; **figure 1C**), indicating improved phonological and tendentially switching abilities. No treatment effects were observed for other VFT variables (phonological, semantic, switch) and DFT variables (basic, filter, switch; **figure S2**).

There was a period effect for VFT phonological total (p=0.010) and correct responses (p=0.008) and for DFT basic total (p=0.001) and correct responses (p<0.001) with higher means in session 2 pointing to practice effects. There was an order effect for VFT switch total (p=0.047) and correct responses (p=0.016) with higher means in order placebo–LSD pointing to better switching abilities if placebo was applied before LSD.

3.3. Cognitive Flexibility

LSD decreased WCST categories achieved (p=0.010) and conceptual level responses percentage (p=0.017) indicating impairments in overall performance and insight into the correct dimension. LSD increased total errors (absolute: p=0.011; percentage: p=0.009), conceptual level responses (p=0.021), perseverative responses (absolute: p=0.013; percentage: p=0.022), perseverative errors type 1 (absolute: p=0.013; percentage: p=0.015), type 3 (absolute: p=0.006; percentage: p=0.004) and marginally type 2 (absolute: p=0.056) and non-perseverative errors (absolute: p=0.020; percentage: p=0.031), pointing to overall increased errors and perseveration (**figure 1D**). No treatment effects were observed for total trials, total correct responses, trials to complete first category, failures to maintain set, learning to learn and perseverative errors type 2 percentage (**figure S2**). There was no order effect but a period effect for conceptual level responses (p=0.046) with lower means in session 2.

3.4. Sustained and Shifting Attention

In TMT, there was no treatment effect (**figure S2**) and order effect but a period effect for basic duration (p=0.032) with lower values in session 2 indicating practice effects.

3.5. Inhibitory Control

In Stroop, there was no treatment effect (**figure S2**) and order effect but a period effect for duration in colours (p=0.007), words (p=0.013) and colour words (p=0.049) with lower values in session 2 indicating practice effects.

3.6. Perceptual Organization

In BDT, there was no effect of treatment, order and period (**figure S2**).

4. Discussion

To our knowledge, this is the first study to assess the sub-acute effects of psychedelics on cognition in a randomized, double-blind, placebo-controlled design. Overall, the effects of the low 50µg dose were not strong in the morning after drug administration and mixed with period and order effects but provide insights into prolonged LSD-induced effects on cognitive processes. The results indicate that LSD, compared to placebo, sub-acutely improved visual

memory (immediate retrieval (ROCF), overnight consolidation (OLMT)) and phonological verbal fluency (VFT). On the other hand, LSD seemed to sub-acutely impair cognitive flexibility (fewer achieved categories, more errors and perseveration (WCST)). There were no sub-acute effects in design fluency (DFT), sustained and shifting attention (TMT), inhibitory control (Stroop) and perceptual reasoning (BDT). This underlines the specificity of prolonged LSD-induced processes and suggests that the previously reported acute impairments in these areas might return to normal after an overnight sleep.

4.1. LSD sub-acutely improves episodic memory and verbal fluency

LSD enhanced specific aspects of memory, including recall of visuospatial locations (OLMT) but not auditory-verbal nouns (RAVLT) learned before drug administration, indicating improved visuospatial but not auditory-verbal consolidation overnight. Similarly, a mice study reported improved memory fear extinction and object recognition for psychedelics applied after encoding and before retrieval, pointing to psychedelic-induced improvements in memory consolidation (Zhang et al., 2013). Together with these finding, our study suggests that psychedelics seem to similarly support memory consolidation in humans and rodents. Furthermore, LSD enhanced immediate but not delayed recall of complex figures (ROCF) learned the morning after drug administration, suggesting improved encoding and spontaneous retrieval but not enduring storage of new visuospatial content (Shin et al., 2006). Visuospatial memory relies on the 5-HT_{2A} receptor-rich hippocampus (Shin et al., 2006; Stickgold, 2005). Therefore, our results point to LSD-induced improvements in visuospatial consolidation (pre-drug content), encoding, and short-term maintenance (post-drug content) possibly related to hippocampal serotonergic action. The activation of 5-HT_{2A} receptors has been associated hitherto with non-spatial memory consolidation (Zhang and Stackman, 2015), which is why our findings might point to a broader functional mechanism of 5-HT_{2A} action in memory processes.

LSD improved phonological fluency (VFT), although this form of fluency is generally more difficult than semantic fluency, which was not affected (Schmidt et al., 2017). While both fluency types rely on semantic memory retrieval, phonological fluency depends more on efficient strategies, including syllabification of initial letters for phonological memory search, and is associated with frontal brain functions (Henry and Crawford, 2004; Lezak et al., 2004; Schmidt et al., 2017). In contrast, semantic fluency depends more on conceptual knowledge, including the creation of sub-categories for semantic memory search, and is associated with temporal brain functions (Henry and Crawford, 2004; Lezak et al., 2004; Schmidt et al., 2017). Therefore, the results suggest that LSD facilitates phonological, frontal-based strategic retrieval but not semantic, temporal-based conceptual retrieval. Beyond that, the order effect in switch fluency (more correct responses in order placebo-LSD) might indicate that LSD hampers unpractised switching abilities (session 1) but improves them after repetition (session 2), in other words, after a “sober training session”. In a similar line are the findings of hampered cognitive flexibility (WCST, see next section) and improved consolidation of previously learned material (OLMT, see above). Notably, similar to the memory effects, fluency improvements depended on the sensory domain, with improvements for verbal but not design fluency, pointing to domain-specific effects of LSD on fluency.

4.2. LSD sub-acutely impairs cognitive flexibility

LSD impaired most aspects of cognitive flexibility (WCST), represented by decreased categories achieved and percent conceptual level responses, and increased errors and perseveration, suggesting impaired executive control, insight into correct dimensions and ability to relinquish old for new categories (Strauss et al., 2006). No changes arose in trials to complete the first category, failures to maintain set, and learning to learn, indicating unchanged initial conceptual ability, ability to maintain a successful strategy, and conceptual efficiency (Strauss et al., 2006). Notably, conceptual level responses were increased in absolute terms but

decreased in relation to the total trials. Together with the period effect (fewer conceptual level responses in session 2), this seems to indicate that LSD-induced increased conceptual level responses reflect a form of perseveration, reducing in session 2 with increased practice, a notion in line with the overall increased perseveration.

Regarding perseveration, preservative errors type 3 (three consecutive errors within any prior or the current perseveration principle) were most pronounced, followed by type 1 (any errors within the current perseveration principle) and marginally type 2 (two consecutive errors within the current perseveration principle). Note that the type 3 errors reflect the least strict form of perseveration (or a more longer-term perseveration mixed with other processes), since they consider errors of any prior internally established rule which might lie several minutes in the past and therefore not merely reflect perseveration, i.e. actively insisting on a wrong rule, but also other processes such as working memory or short-term memory. In other words, the subjects might have simply forgotten that they already tried a dimension that resulted to be wrong. In contrast, type 1 and type 2 errors merely consider errors of the current internally established wrong rule. Type 1 errors might still be affected by influences of working memory, since they consider any errors within the current rule regardless of a potentially high amount of intervening responses within other rules. However, type 2 errors reflect the purest form of perseveration (or a short-term perseveration) since they merely consider two consecutive errors within the current rule, i.e. clearly insisting on a rule that has just resulted to be wrong. Overall, these findings indicate that the LSD-induced impairments do not reflect a pure form of perseveration but are mixed with other processes such as impaired attention, working memory or short-term memory.

In a similar vein, a previous study found increased total errors and response latency for dimension shifts under acute LSD effects, reflecting perseveration and difficulties in attentional shifting (Pokorny et al., 2019). Together with these findings, our results suggest that the LSD-induced impaired cognitive flexibility, mediated by 5-HT_{2A} activation (Amodeo et al., 2020; Pokorny et al., 2019), might remain pronounced up to 24h post-administration. However, it seems improbable that these impairments persist enduringly, considering that several studies found unchanged or even increased WCST performance in regular psychedelic ritual attendees (Bouso et al., 2012; Halpern et al., 2005) and up to 4 weeks after psychedelic-assisted therapy (Doss et al., 2021). However, these divergences might also be explained by particularities of substance (ayahuasca, peyote, psilocybin), sample (regular users, patients), setting (ritual, therapy), comparison method (baseline, other groups) or dose, which is why future studies on longer-lasting psychedelic effects on cognitive flexibility should carefully disentangle these influences in placebo-controlled designs.

4.3. Implications for Therapy and Research

Our findings of improved visual memory and verbal fluency, together with previous reports on psychedelic-induced neuroplasticity (Inserra et al., 2021), suggest that future studies should more closely examine psychedelics as preventive or treatment measures in conditions related to progressive or sudden cognitive decline. Specifically, LSD effects might constitute protective and regenerative mechanisms in conditions related to impaired memory consolidation and retrieval, including mild cognitive impairment, dementia, OCD, attention-deficit/hyperactivity disorder (ADHD), epilepsy, multiple sclerosis (MS), stroke or traumatic brain injury (Chen et al., 2012; Fuermaier et al., 2017; Helmstaedter, 2002; Lezak et al., 2004; Rao et al., 1989; Shin et al., 2004) and in conditions related to impaired phonological fluency, including frontal brain lesions, vascular dementia, ADHD, autism, MS, Huntington's disease or Parkinson's disease (Andreou and Trott, 2013; Butters et al., 1986; Canning et al., 2004; Ellfolk et al., 2014; Henry and Crawford, 2004; Rao et al., 1989; Schmidt et al., 2017; Spek et al., 2009). The most promising conditions might comprise those involving concurrent memory and verbal fluency impairments such as dementia, MS, brain injury and stroke patients. First

support for this comes from animal studies reporting that N,N-dimethyltryptamine (DMT) reduces infarct size and improves functional recovery after brain ischemia (Nardai et al., 2020).

The disadvantageous sub-acute effects of LSD on cognitive flexibility also need to be addressed. Although these impairments are unlikely to be of enduring nature, from a practical perspective, they imply potentially reduced performance monitoring abilities, which should be taken into consideration the day following LSD consumption in psychotherapy, research or recreational contexts. Specifically, these impairments might entail a reduced ability to execute demanding tasks or operate machines and require a resting day scheduled after psychedelic therapies and recreational use. Moreover, they point to potential adverse effects related to LSD consumption in psychotic populations, since schizophrenia has long been associated with reduced cognitive flexibility (Kelly et al., 2021; Waltz, 2017).

4.4. Limitations

The results were not corrected for multiple comparisons due to the exploratory nature of the study, which is why our results need to be replicated in future studies with larger samples. Our results comprised several period effects, which highlight the importance of well-designed parallel test versions and careful data interpretation considering the influence of task practice effects. Note that a relatively low dose was applied, while higher LSD doses might be more suitable to elicit stronger effects that are better distinguishable from practice effects. Moreover, the results were corrected for BMI and abstinence period from psychedelics, while the analyses without these covariates yielded few treatment and many period effects. This suggests that dose and washout period fundamentally modulate the sub-acute effects of LSD on cognition, which should be more closely examined in future research and taken into consideration in protocols for psychedelic-assisted therapy regarding the patient's metabolism, treatment dose and treatment intervals. Finally, our results were elicited from healthy participants and need to be replicated in clinical conditions to fully evaluate the beneficial potential of psychedelics in cognitive processes.

4.5. Conclusion

The day after LSD administration is cognitively mixed. The effects of 50µg LSD on cognition seemed to last up to 24h and comprise improvements and impairments, in other words, "afterglow" and "hangover". The results prompt two considerations. On the one hand, sub-acutely impaired cognitive flexibility should be taken into account for therapy purposes, research or everyday life functionality. On the other hand, this study provides original evidence that LSD might sub-acutely enhance certain aspects of visuospatial memory and verbal fluency. In this light, our findings point to the potential of psychedelics to improve functions related to memory and language, which might provide new treatment perspectives in previously overlooked conditions such as brain injury, stroke and dementia.

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Contributors

IW, RO, LOM, SR and LFT contributed to the study design. IW, MF and LFT recruited and selected the participants. IW, RO and MF collected the data. IW, RO, FPF and DBA contributed to data analysis and interpretation. IW wrote the manuscript. IW and FPF created the figures. RO, MF, FPF, LOM, AF, DBA, SR and LFT reviewed the manuscript.

Acknowledgements

We thank Eliana Falchi Parra Carvalho da Silva, Flavia Ribeiro, Hervé Yviquel, Jens G. Klinzing and Raphael Egel for their support with the test material, Jon Sharp for the English language revision and Valerie Bonnelle for miscellaneous help. Funding for this study was provided by the Beckley Foundation, the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) - Finance Code 001, the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (grants 308775/2015-5 and 408145/2016-1) and the Sao Paulo Research Foundation (grants 2013/07699-0 (Neuromathematics), 2014/10068-4).

Role of Funding Source

IW received funding from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES; Finance Code 001), SR received funding from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (grants 308775/2015-5 and 408145/2016-1) and the Sao Paulo Research Foundation (grants 2013/07699-0 (Neuromathematics) and 2014/10068-4). These funding sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. AF is the director of the Beckley Foundation, which supported the implementation of the study.

Conflict of Interest

SR declares the following patent application as a competing interest: a) Patent applicants (The Beckley Foundation, Universidade Federal do Rio Grande do Norte); b) Name of inventors: Not yet listed; c) Application number: 1 911 024.6; d) Status of application: pending.

Tables

Table 1. Values for the significant effects of treatment, order and period in the cognition tasks for the GLMs covarying for BMI and abstinence

Task	Condition	Variable	Results	Direction[1]
Treatment effects				
ROCF	immediate recall	points	$F(1,20)=4.63$, $p=0.044$, $\eta_p^2=0.19$	LSD ↑
	immediate recall	percentage	$F(1,20)=6.62$, $p=0.018$, $\eta_p^2=0.25$	LSD ↑
OLMT	consolidation	percentage	$F(1,19)=6.23$, $p=0.022$, $\eta_p^2=0.25$	LSD ↑
VFT	phonological	total	$F(1,20)=5.08$, $p=0.036$, $\eta_p^2=0.20$	LSD ↑
		correct	$F(1,20)=5.69$, $p=0.027$, $\eta_p^2=0.22$	LSD ↑
	switch	errors	$F(1,19)=4.06$, $p=0.058$, $\eta_p^2=0.18$	LSD ↓
WCST		TE	$F(1,20)=7.86$, $p=0.011$, $\eta_p^2=0.28$	LSD ↑
		CA	$F(1,20)=8.11$, $p=0.010$, $\eta_p^2=0.29$	LSD ↓
		CL	$F(1,20)=6.32$, $p=0.021$, $\eta_p^2=0.24$	LSD ↑
		PR	$F(1,20)=7.53$, $p=0.013$, $\eta_p^2=0.27$	LSD ↑
		PE1	$F(1,20)=7.38$, $p=0.013$, $\eta_p^2=0.27$	LSD ↑
		PE2	$F(1,20)=4.12$, $p=0.056$, $\eta_p^2=0.17$	LSD ↑
		PE3	$F(1,20)=9.55$, $p=0.006$, $\eta_p^2=0.32$	LSD ↑
		NE	$F(1,20)=6.43$, $p=0.020$, $\eta_p^2=0.24$	LSD ↑
		%TE	$F(1,20)=8.35$, $p=0.009$, $\eta_p^2=0.30$	LSD ↑
		%CL	$F(1,20)=6.78$, $p=0.017$, $\eta_p^2=0.25$	LSD ↑
		%PR	$F(1,20)=6.19$, $p=0.022$, $\eta_p^2=0.24$	LSD ↑
		%PE1	$F(1,20)=7.16$, $p=0.015$, $\eta_p^2=0.26$	LSD ↑
		%PE3	$F(1,20)=10.3$, $p=0.004$, $\eta_p^2=0.34$	LSD ↑
		%NE	$F(1,20)=5.36$, $p=0.031$, $\eta_p^2=0.21$	LSD ↓
Order effects				
VFT	switch	total	$F(1,19)=4.50$, $p=0.047$, $\eta_p^2=0.19$	LSD-placebo ↓
		correct	$F(1,19)=6.94$, $p=0.016$, $\eta_p^2=0.27$	LSD-placebo ↓
Period effects				
ROCF	immediate recall	points	$F(1,20)=9.52$, $p=0.006$, $\eta_p^2=0.32$	session 2 ↑
		percentage	$F(1,20)=12.9$, $p=0.002$, $\eta_p^2=0.39$	session 2 ↑
	delayed recall	points	$F(1,20)=8.57$, $p=0.008$, $\eta_p^2=0.30$	session 2 ↑
VFT	phonological	total	$F(1,20)=8.16$, $p=0.010$, $\eta_p^2=0.29$	session 2 ↑
		correct	$F(1,20)=8.55$, $p=0.008$, $\eta_p^2=0.30$	session 2 ↑
DFT	basic	total	$F(1,20)=14.3$, $p=0.001$, $\eta_p^2=0.42$	session 2 ↑
		correct	$F(1,20)=20.0$, $p<0.001$, $\eta_p^2=0.50$	session 2 ↑
WCST		CL	$F(1,20)=4.53$, $p=0.046$, $\eta_p^2=0.19$	session 2 ↓
TMT	basic	duration	$F(1,20)=5.31$, $p=0.032$, $\eta_p^2=0.21$	session 2 ↓
Stroop	colours	duration	$F(1,18)=9.21$, $p=0.007$, $\eta_p^2=0.34$	session 2 ↓
	words	duration	$F(1,18)=7.59$, $p=0.013$, $\eta_p^2=0.30$	session 2 ↓
	colour words	duration	$F(1,18)=4.46$, $p=0.049$, $\eta_p^2=0.20$	session 2 ↓

[1] Arrows indicate the effect direction of LSD compared to placebo (treatment effect), LSD-placebo compared to placebo-LSD (order effect) and session 1 compared to session 2 (period effect).
ROCF, Rey-Osterrieth Complex Figure. OLMT, 2D Object-Location Memory Task. VFT, Verbal Fluency Task: total, total responses; correct, correct responses. WCST, Wisconsin Card Sorting Test: TE, total errors; CA, categories achieved; CL, conceptual level responses; PR, perseverative responses; PE1, perseverative errors type 1; PE2, perseverative errors type 2; PE3, perseverative errors type 3; NE, non-perseverative errors; %TE, total errors percentage; %CL, conceptual level responses percentage; %PR, perseverative responses percentage; %PE1, perseverative errors type 1 percentage; %PE2, perseverative errors type 2 percentage; %PE3, perseverative errors type 3 percentage; %NE, non-perseverative errors percentage. DFT, Design Fluency Task: total, total responses; correct, correct responses. TMT, Trail Making Test. Stroop, Stroop Task.

Figures

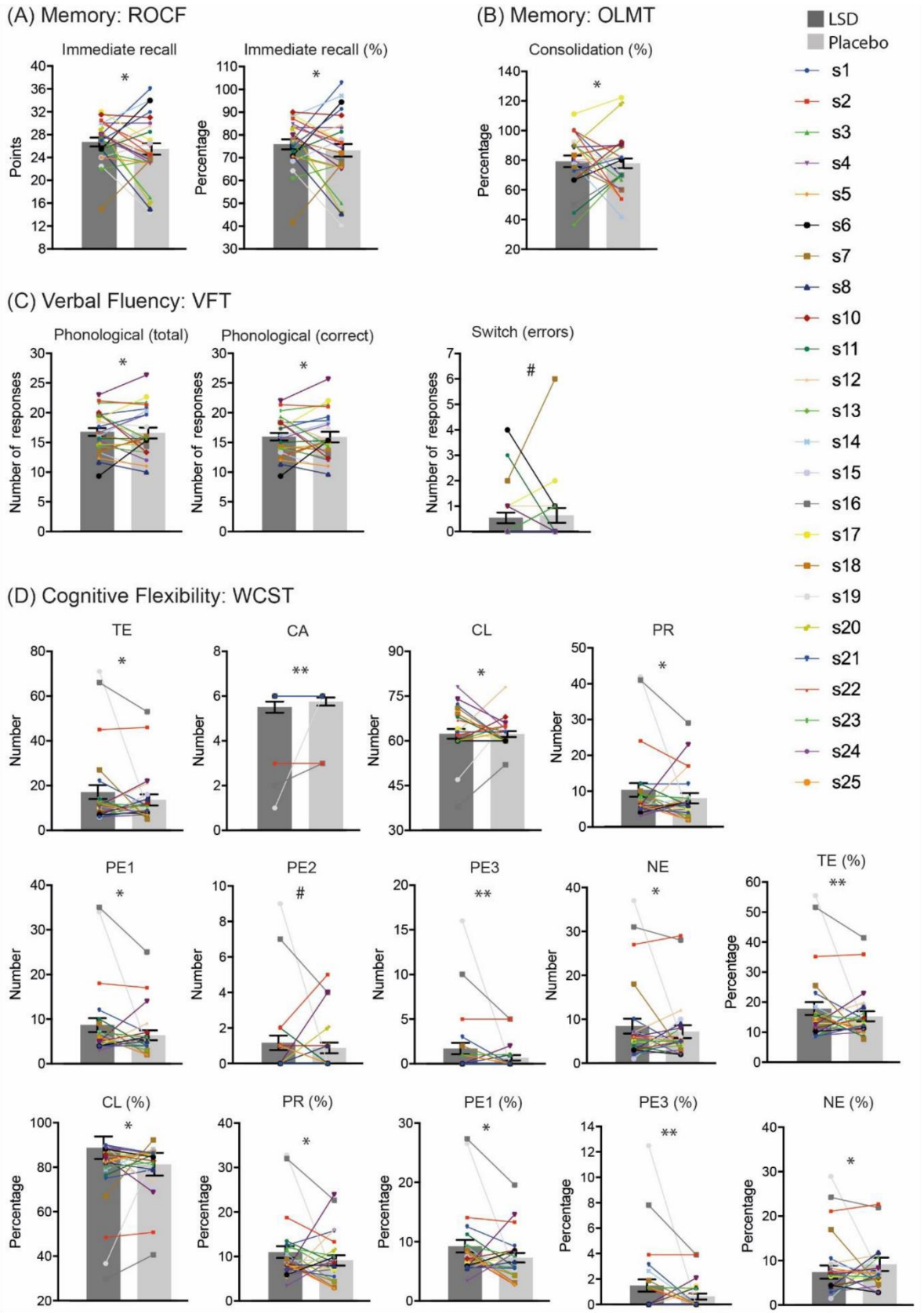
(A) Memory: ROCF
Immediate recall
Points
Immediate recall (%)
Percentage
(B) Memory: OLMT
Consolidation (%)
Percentage
LSD
Placebo
s1
s2
s3
s4
s5
s6
s7
s8
s10
s11
s12
s13
s14
s15
s16
s17
s18
s19
s20
s21
s22
s23
s24
s25
(C) Verbal Fluency: VFT
Phonological (total)
Number of responses
Phonological (correct)
Number of responses
Switch (errors)
Number of responses
(D) Cognitive Flexibility: WCST
TE
CA
CL
PR
PE1
PE2
PE3
NE
TE (%)
CL (%)
PR (%)
PE1 (%)
PE3 (%)
NE (%)
Number
Percentage

Figure 1. The effects of 50µg LSD on cognition as measured the morning after drug administration. LSD sub-acutely improved visuospatial episodic memory with increased (A) spontaneous encoding and recall and (B) overnight consolidation. Moreover, LSD sub-acutely (C) improved phonological and tendentially improved switch verbal fluency and (D) impaired cognitive flexibility. Displayed are estimated marginal means (bars) ± SEM (error bars) and paired single subject data (connected dots) for (A, C, D) 24 and (B) 23 subjects. $^{\#}p \leq 0.06$, $^{*}p \leq 0.05$, $^{**}p \leq 0.01$.

ROCF, Rey-Osterrieth Complex Figure. OLMT, 2D Object-Location Memory Task. VFT, Verbal Fluency Task: total, total responses; correct, correct responses. WCST, Wisconsin Card Sorting Test: TE, total errors; CA, categories achieved; CL, conceptual level responses; PR, perseverative responses; PE1, perseverative errors type 1; PE2, perseverative errors type 2; PE3, perseverative errors type 3; NE, non-perseverative errors; %TE, total errors percentage; %CL, conceptual level responses percentage; %PR, perseverative responses percentage; %PE1, perseverative errors type 1 percentage; %PE3, perseverative errors type 3 percentage; %NE, non-perseverative errors percentage. s, subject number.

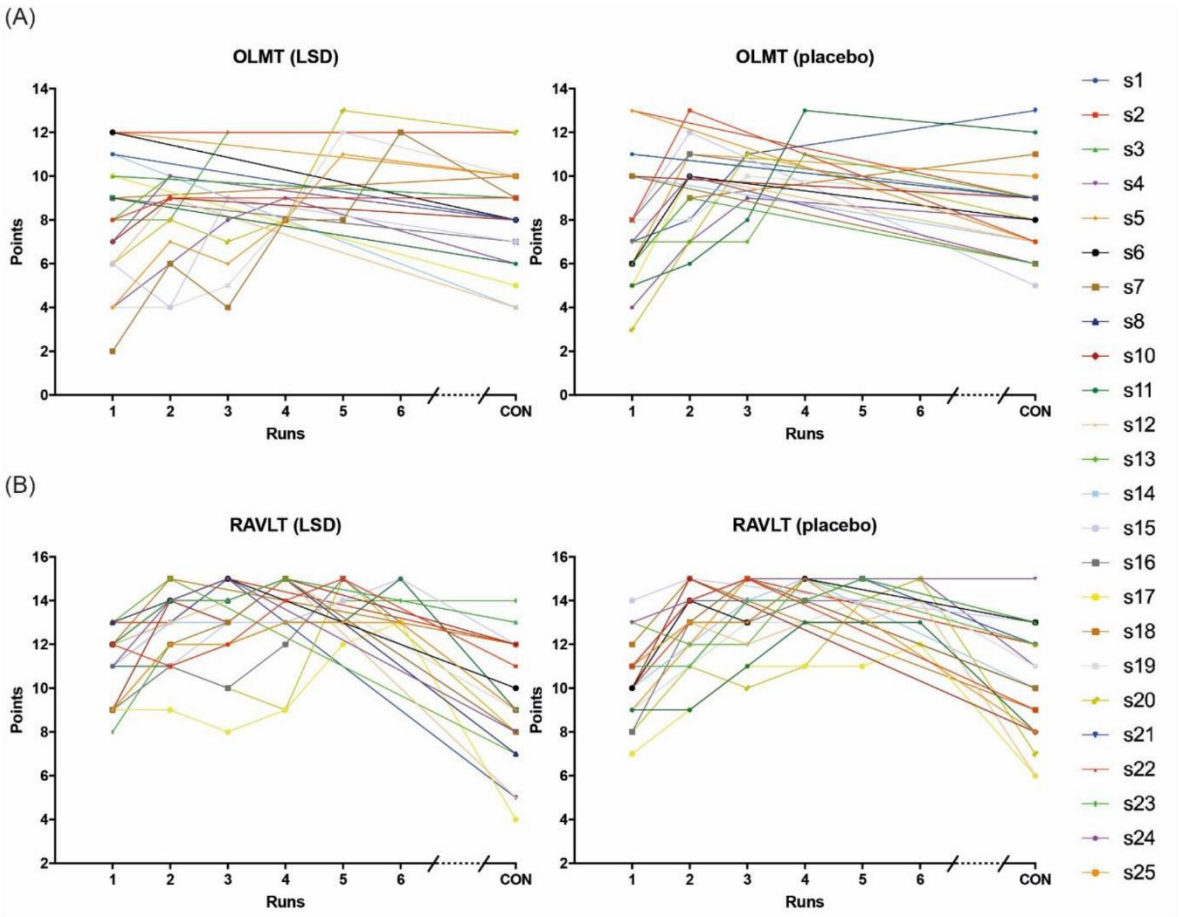

Figure 2. The effects of LSD and placebo on (A) visuospatial and (B) auditory-verbal episodic memory consolidation. Displayed are single subject data for the performance (y-axis; points) during memory encoding before drug administration (x-axis; immediate recall runs 1-6) and during the final recall the morning after drug administration (x-axis; CON). Note that each

subject underwent a different number of runs, depending on the performance, with a threshold set to (A) 60% correctly remembered card locations and (B) 100% correctly remembered words.

OLMT, 2D Object-Location Memory Task. RAVLT, Rey Auditory-Verbal Learning Test. CON, consolidation points in the final recall. s, subject number.

European Neuropsychopharmacology

Supplementary Material

LSD, afterglow and hangover: Increased episodic memory and verbal fluency, decreased cognitive flexibility

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Supplemental Methods

Cognitive Flexibility

Perseverative responses and perseverative errors type 1 were assessed according to the manual's instruction (Heaton et al., 2005). Specifically, the first (unambiguous) error in a category opens a "perseveration principle" (e.g. colour). Any subsequent (correct/wrong) response that falls in the perseveration principle is counted as a perseverative response, even if other responses (e.g. according to the dimension form) are given between them. Alike, any subsequent error falling in the perseveration principle is counted as a perseverative error type 1. The perseveration principle changes if three consecutive (unambiguous) errors of another dimension (e.g. number) are given. Notably, after the successful completion of a category, the first (unambiguous) error of the same dimension as the completed category is also classified as perseverative error type 1, intending to measure if the participant is aware of the periodic rule changes.

Perseverative errors type 2 were defined as the number of times in which two consecutive, unambiguous errors were made based on the current perseveration principle.

Perseverative errors type 3 were defined as the number of times in which three consecutive errors were made based on any prior or the current perseveration principle (adapted after Doss et al., 2021). Notably, the three errors could be unambiguous or ambiguous, as long as all dimensions of the error fell in any prior or current perseveration principle.

Supplemental Tables

Table S1. Description of the parallel test versions applied in each cognitive task

Task	Parallel test versions
ROCF	Version B: Modified Taylor Complex Figure (MTCF) (Hubley and Tremblay, 2002)
OLMT	Version B: different pictures at different locations
RAVLT	Version B: an updated version of the RAVLT (Malloy-Diniz et al., 2007)
VFT	Version B: P, M, R; food; male names and clothes
DFT	Version B: dot patterns mirrored along horizontal and vertical axis
WCST	Version A: colour, form, number; Version B: number, form, colour
BDT	Version A: figures 4, 6, 8, 10, 12; Version B: figures 5, 7, 9, 11 (from Wechsler Abbreviated Scale of Intelligence; WASI; Wagner, Alves Camey, & Marceli Trentini, 2014)

ROCF, Rey-Osterrieth Complex Figure. OLMT, 2D Object-Location Memory Task. RAVLT, Rey Auditory-Verbal Learning Test. VFT, Verbal Fluency Task. DFT, Design Fluency Task. WCST, Wisconsin Card Sorting Test. BDT, Block Design Test.

Table S2. Values for the significant effects of treatment, order and period in the cognition tasks for the GLMs without covarying for BMI and abstinence

Task	Condition	Variable	Results	EMM (±SEM)	
Treatment effects				**LSD**	**Placebo**
ROCF	copy	points	$F(1,22)=4.53$, $p=0.045$, $\eta_p^2=0.17$	35.2 (0.19)	34.6 (0.25)
		percentage	$F(1,22)=4.53$, $p=0.045$, $\eta_p^2=0.17$	97.8 (0.54)	96.2 (0.70)
DFT	filter	errors	$F(1,22)=5.68$, $p=0.026$, $\eta_p^2=0.21$	2.92 (0.58)	1.83 (0.32)
Period effects				**Session 1**	**Session 2**
ROCF	immediate recall	points	$F(1,22)=5.91$, $p=0.024$, $\eta_p^2=0.21$	24.7 (0.99)	27.4 (0.97)
		percentage	$F(1,22)=7.22$, $p=0.013$, $\eta_p^2=0.25$	70.6 (2.77)	78.6 (2.72)
	delayed recall	points	$F(1,22)=5.94$, $p=0.023$, $\eta_p^2=0.21$	23.8 (0.98)	26.4 (1.03)
OLMT	consolidation	points	$F(1,22)=6.82$, $p=0.016$, $\eta_p^2=0.25$	8.96 (0.50)	7.65 (0.36)
		percentage	$F(1,22)=6.06$, $p=0.023$, $\eta_p^2=0.22$	84.1 (3.81)	73.2 (3.71)
RAVLT	recognition	hits	$F(1,20)=7.19$, $p=0.014$, $\eta_p^2=0.26$	14.3 (0.16)	13.6 (0.24)
		false alarms	$F(1,20)=6.94$, $p=0.016$, $\eta_p^2=0.26$	1.27 (0.37)	2.46 (0.43)
DFT	basic	total	$F(1,22)=19.2$, $p<0.001$, $\eta_p^2=0.47$	12.0 (0.69)	15.5 (1.16)
		correct	$F(1,22)=22.8$, $p<0.001$, $\eta_p^2=0.51$	10.6 (0.61)	13.2 (0.79)
	filter	correct	$F(1,22)=6.98$, $p=0.015$, $\eta_p^2=0.24$	11.6 (0.63)	13.0 (0.76)
WCST		TT	$F(1,22)=5.53$, $p=0.028$, $\eta_p^2=0.20$	85.8 (4.09)	78.3 (3.43)
		PE1	$F(1,22)=4.40$, $p=0.048$, $\eta_p^2=0.17$	8.96 (1.52)	6.08 (1.41)
		TE (%)	$F(1,22)=4.34$, $p=0.049$, $\eta_p^2=0.17$	18.7 (2.30)	14.4 (2.01)
		PE1 (%)	$F(1,22)=5.67$, $p=0.026$, $\eta_p^2=0.21$	9.53 (1.03)	6.99 (2.01)
TMT	basic	duration	$F(1,22)=8.57$, $p=0.008$, $\eta_p^2=0.28$	34.8 (2.61)	29.3 (1.69)
	switch	duration	$F(1,22)=4.99$, $p=0.036$, $\eta_p^2=0.19$	50.0 (3.58)	45.4 (3.58)
Stroop	colours	duration	$F(1,22)=11.1$, $p=0.003$, $\eta_p^2=0.36$	17.5 (1.03)	15.4 (0.76)
	words	duration	$F(1,22)=11.7$, $p=0.003$, $\eta_p^2=0.37$	18.0 (0.90)	15.7 (0.76)
	colour words	duration	$F(1,22)=4.75$, $p=0.041$, $\eta_p^2=0.19$	21.3 (1.02)	20.0 (1.07)

ROCF, Rey-Osterrieth Complex Figure. OLMT, 2D Object-Location Memory Task. RAVLT, Rey Auditory-Verbal Learning Test. DFT, Design Fluency Task: total, total responses; correct, correct responses. WCST, Wisconsin Card Sorting Test: TT, total trials; PE1, perseverative errors type 1; TE (%), total errors percentage; PE1 (%), perseverative errors type 1 percentage. TMT, Trail Making Test. Stroop, Stroop Task.

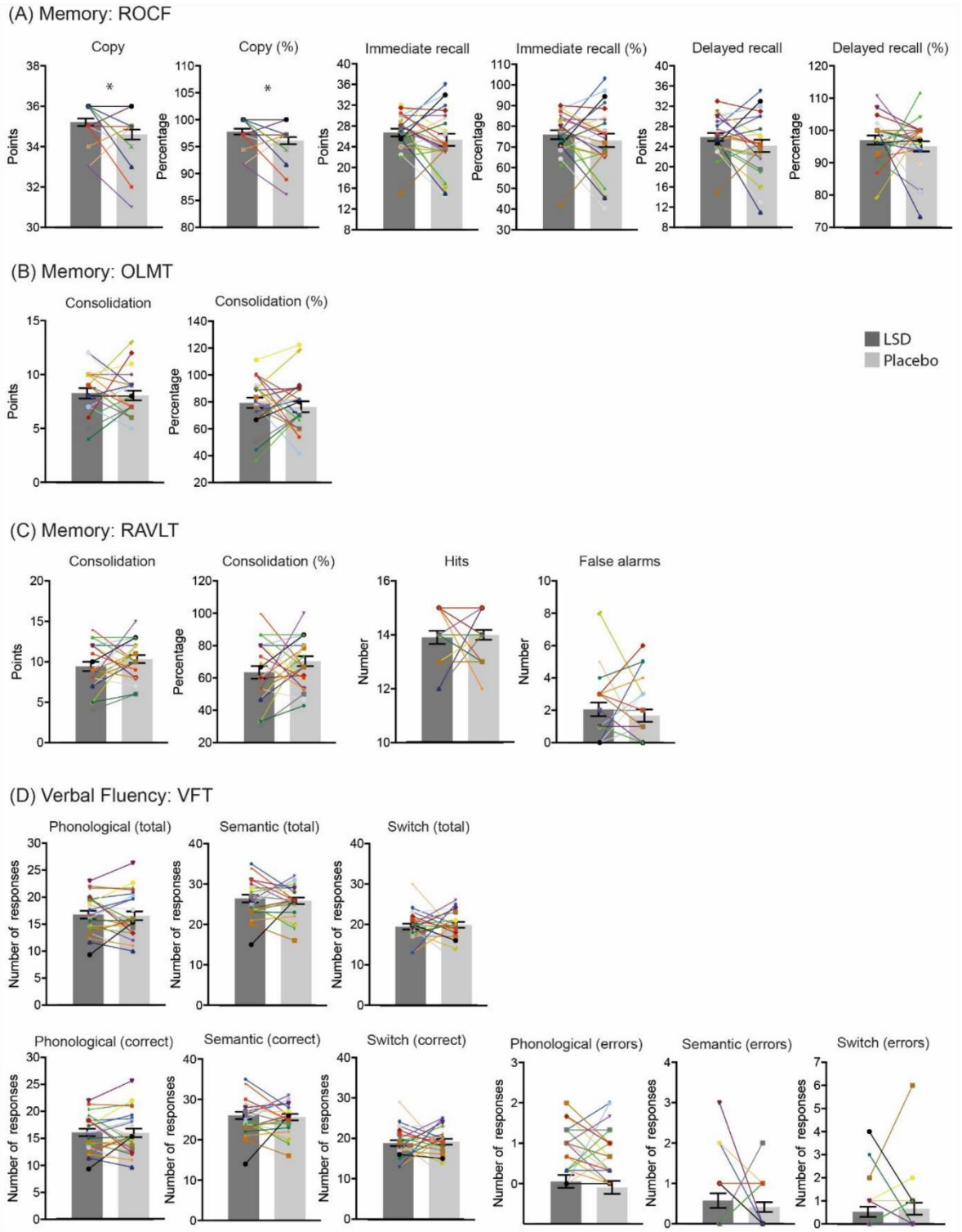
Table S3. Estimated marginal means (EMM) and standard errors (SEM) for significant effects of treatment, order and period in the cognition tasks for the GLMs covarying for abstinence and BMI

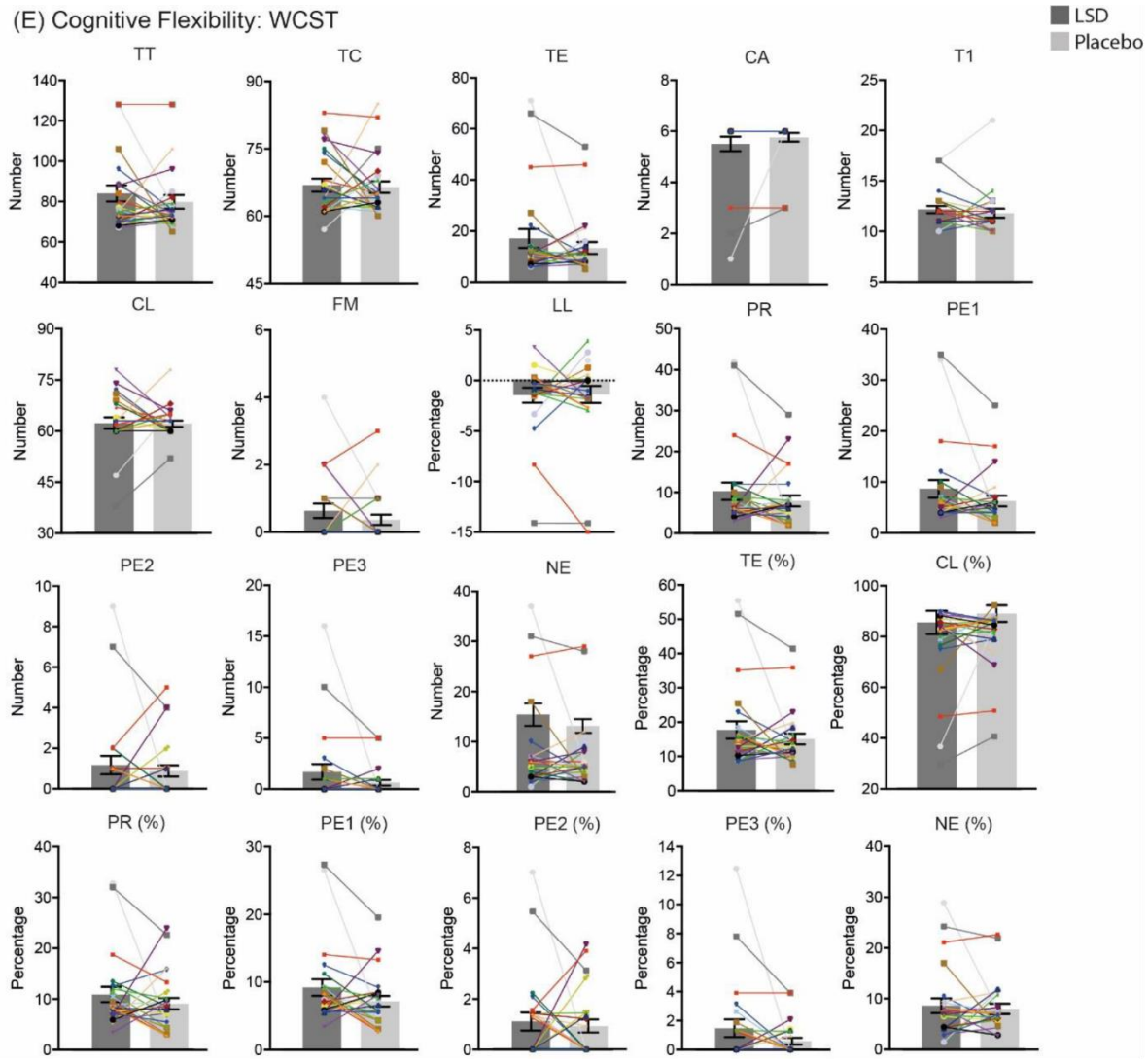
Task	Condition	Variable		EMM (±SEM)	
Treatment effects				**LSD**	**Placebo**
ROCF	immediate recall	points		26.71 (0.77)	25.49 (0.99)
	immediate recall	percentage		75.92 (2.21)	73.29 (2.76)
OLMT	consolidation	percentage		79.25 (3.9)	77.90 (3.29)
VFT	phonological	total		16.75 (0.67)	16.58 (0.91)
		correct		15.96 (0.62)	15.90 (0.88)
	switch	errors		0.55 (0.21)	0.65 (0.29)
WCST		TE		17.13 (3.13)	13.54 (2.49)
		CA		5.50 (0.25)	5.75 (0.18)
		CL		62.33 (1.63)	62.21 (0.99)
		PR		10.33 (1.89)	8.00 (1.42)
		PE1		8.67 (1.55)	6.38 (1.11)
		PE2		1.17 (0.41)	0.88 (0.30)
		PE3		1.71 (0.63)	0.67 (0.30)
		NE		8.46 (1.68)	7.17 (1.47)
		TE (%)		17.89 (2.14)	15.29 (1.69)
		CL (%)		81.62 (3.82)	76.05 (3.82)
		PR (%)		10.98 (1.32)	9.12 (1.17)
		PE1 (%)		9.23 (1.06)	7.28 (0.80)
		PE3 (%)		1.49 (0.48)	0.62 (0.24)
		NE (%)		7.42 (1.50)	9.15 (1.50)
Order effects				**LSD-placebo**	**placebo-LSD**
VFT	switch	total		18.72 (0.68)	20.94 (0.71)
		correct		17.89 (0.66)	20.57 (0.69)
Period effects[1]				**Session 1**	**Session 2**
ROCF	immediate recall	points	LSD	26.22 (1.17)	27.20 (1.17)
			placebo	22.41 (1.52)	28.38 (1.52)
		percentage	LSD	74.06 (3.39)	77.79 (3.39)
			placebo	64.81 (4.23)	81.76 (4.23)
	delayed recall	points	LSD	25.18 (1.20)	26.62 (1.20)
			placebo	21.62 (1.65)	26.98 (1.65)
VFT	phonological	total	LSD	14.86 (1.02)	18.64 (1.02)
			placebo	16.60 (1.40)	16.57 (1.40)
		correct	LSD	14.20 (0.96)	17.72 (0.96)
			placebo	15.78 (1.34)	16.03 (1.34)
DFT	basic	total	LSD	12.63 (1.57)	14.54 (1.57)
			placebo	11.31 (1.46)	16.52 (1.46)
		correct	LSD	11.00 (1.14)	12.83 (1.14)
			placebo	10.03 (1.11)	13.72 (1.11)
WCST		CL	LSD	65.05 (2.49)	59.62 (2.49)
			placebo	63.30 (1.52)	61.12 (1.52)
TMT	basic	duration	LSD	36.23 (3.40)	28.06 (3.40)
			placebo	33.07 (3.50)	30.93 (3.50)
Stroop	colours	duration	LSD	17.87 (1.45)	15.81 (1.31)
			placebo	17.25 (1.05)	14.77 (1.16)
	words	duration	LSD	18.23 (1.04)	15.78 (0.94)
			placebo	17.59 (1.32)	15.77 (1.46)
	colour words	duration	LSD	21.79 (1.56)	19.93 (1.41)
			placebo	20.85 (1.19)	19.91 (1.32)

[1] Period effects were evaluated by the interaction treatment*treatment order, with values for session 1 assessed by the values for LSD*LSD-placebo and placebo*placebo-LSD and values for session 2 assessed by the values for placebo*LSD-placebo and LSD*placebo-LSD, respectively.

ROCF, Rey-Osterrieth Complex Figure. OLMT, 2D Object-Location Memory Task. VFT, Verbal Fluency Task: total, total responses; correct, correct responses. WCST, Wisconsin Card Sorting Test: TE, total errors; CA, categories achieved; CL, conceptual level responses; PR, perseverative responses; PE1, perseverative errors type 1; PE2, perseverative errors type 2; PE3, perseverative errors type 3; NE, non-perseverative errors; TE (%), total errors percentage; CL (%), conceptual level responses percentage; PR (%), perseverative responses percentage; PE1 (%), perseverative errors type 1 percentage; PE3 (%), perseverative errors type 3 percentage; NE (%), non-perseverative errors percentage. DFT, Design Fluency Task: total, total responses; correct, correct responses. TMT, Trail Making Test. Stroop, Stroop Task.

Supplemental Figures




(E) Cognitive Flexibility: WCST
LSD
Placebo
TT
TC
TE
CA
T1
CL
FM
LL
PR
PE1
PE2
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PR (%)
PE1 (%)
PE2 (%)
PE3 (%)
NE (%)
Number
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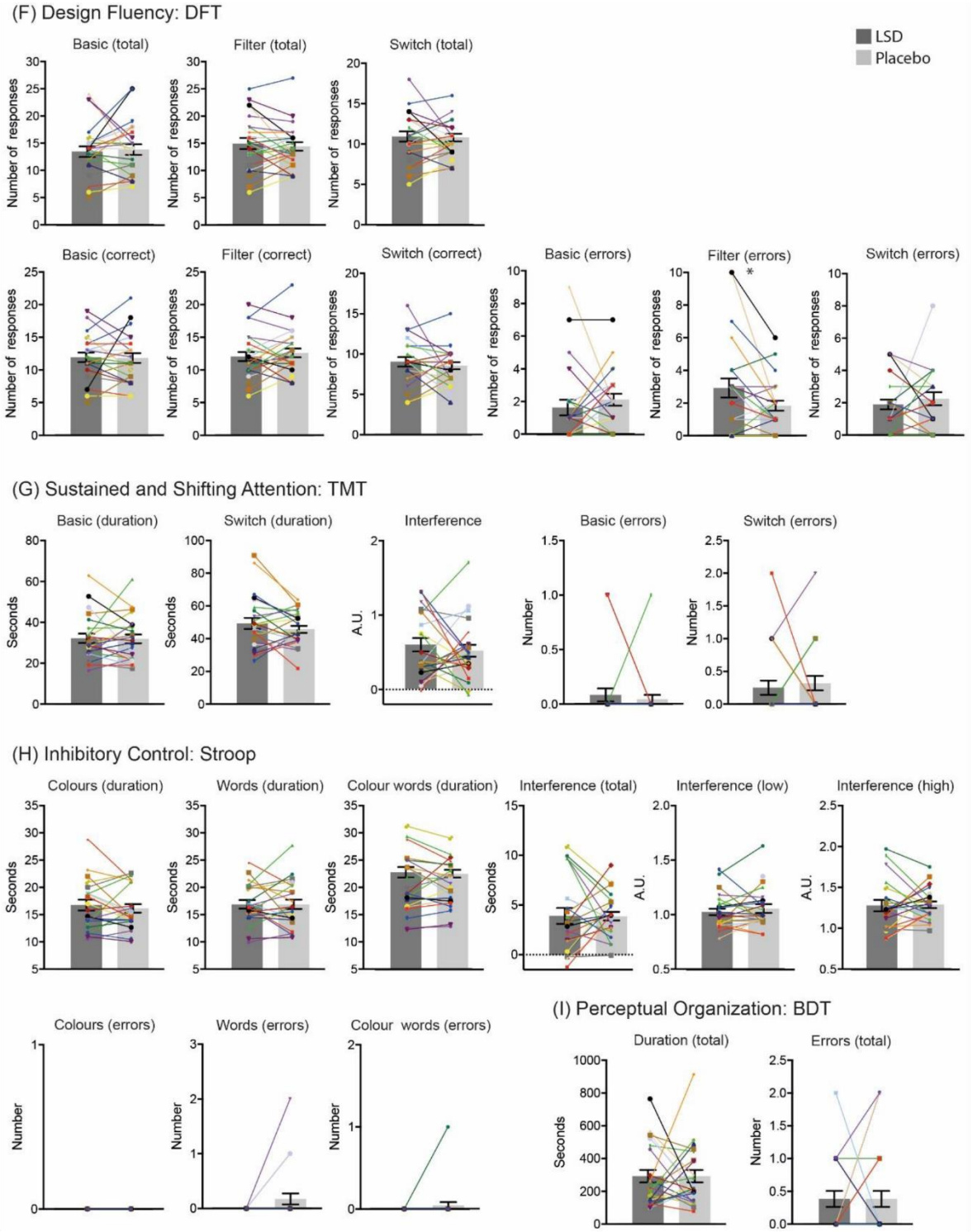
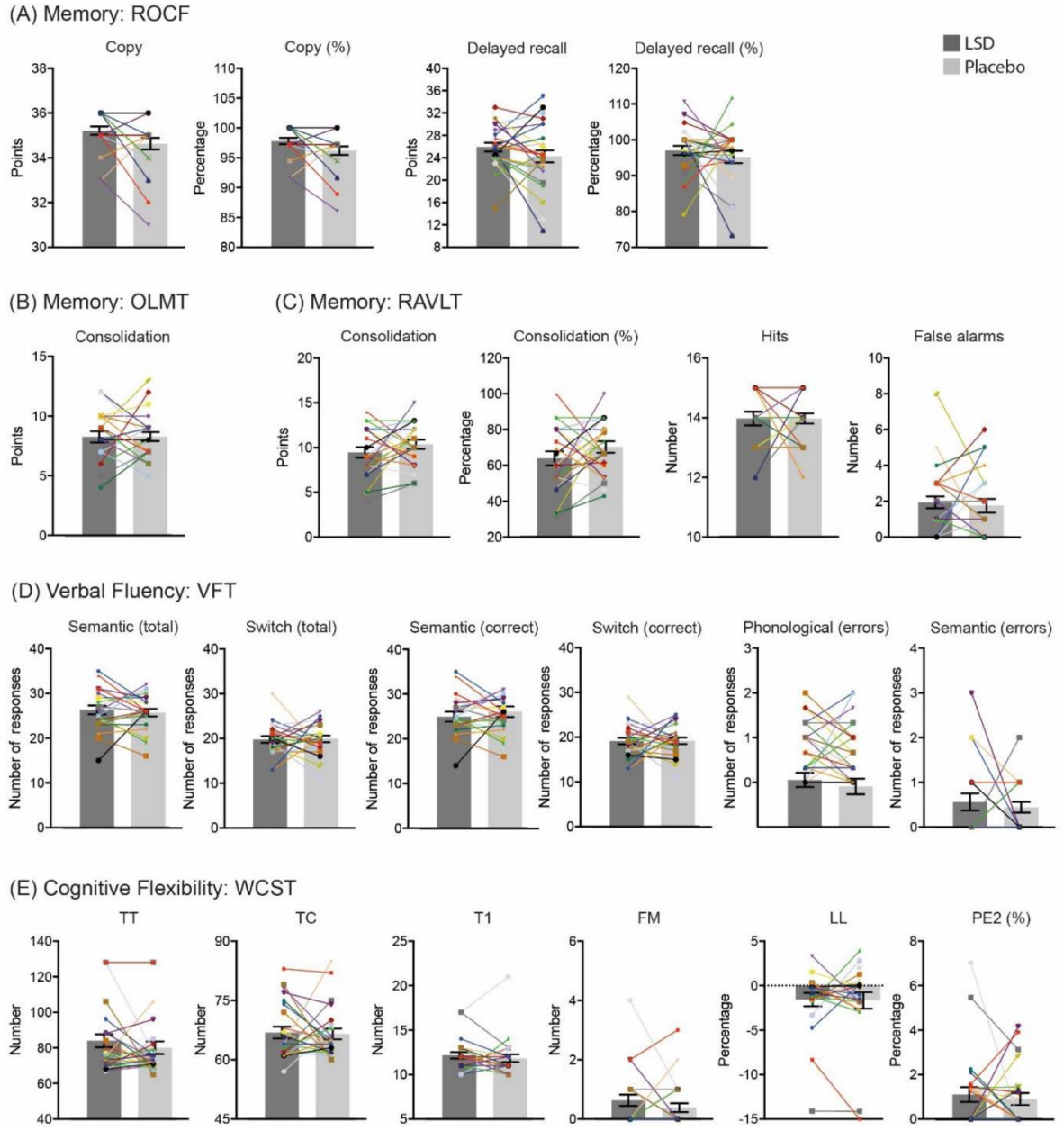


Figure S1. The treatment effects for the GLMs without covarying with BMI and abstinence period. LSD sub-acutely improved (A) copy and (F) aspects of design fluency performance (filter errors). There were no changes in (A-C) memory performance, (D) verbal fluency, (E) cognitive flexibility, (G) attention, (H) inhibitory control, and (I) perceptual organization. Displayed are means (bars) ± SEM (error bars) and paired single subject data (connected dots) for 23 (OLMT, RAVLT, WCST LL), 22 (Stroop) and 24 subjects (all others). *$p \leq 0.05$.

ROCF, Rey-Osterrieth Complex Figure. OLMT, 2D Object-Location Memory Task. RAVLT, Rey Auditory-Verbal Learning Task. VFT, Verbal Fluency Task: total, total responses; correct, correct responses. WCST, Wisconsin Card Sorting Test: TT, total trials; TC, total correct responses; TE, total

errors; CA, categories achieved; T1, trials to complete the first category; CL, conceptual level responses; FM, failures to maintain set; LL, learning to learn; PR, perseverative responses; PE1, perseverative errors type 1; PE2, perseverative errors type 2; PE3, perseverative errors type 3; NE, non-perseverative errors; TE (%), total errors percentage; CL (%), conceptual level responses percentage; PR (%), perseverative responses percentage; PE1 (%), perseverative errors type 1 percentage; PE2 (%), perseverative errors type 2 percentage; PE3 (%), perseverative errors type 3 percentage; NE (%), non-perseverative errors percentage. DFT, Design Fluency Task: total, total responses; correct, correct responses. TMT, Trail Making Test: A.U., arbitrary unit. Stroop, Stroop Task: A.U., arbitrary unit. BDT, Block Design Test.


(A) Memory: ROCF
Copy
Copy (%)
Delayed recall
Delayed recall (%)
LSD
Placebo
Points
Percentage
(B) Memory: OLMT
Consolidation
(C) Memory: RAVLT
Consolidation
Consolidation (%)
Hits
False alarms
Number
(D) Verbal Fluency: VFT
Semantic (total)
Switch (total)
Semantic (correct)
Switch (correct)
Phonological (errors)
Semantic (errors)
Number of responses
(E) Cognitive Flexibility: WCST
TT
TC
T1
FM
LL
PE2 (%)

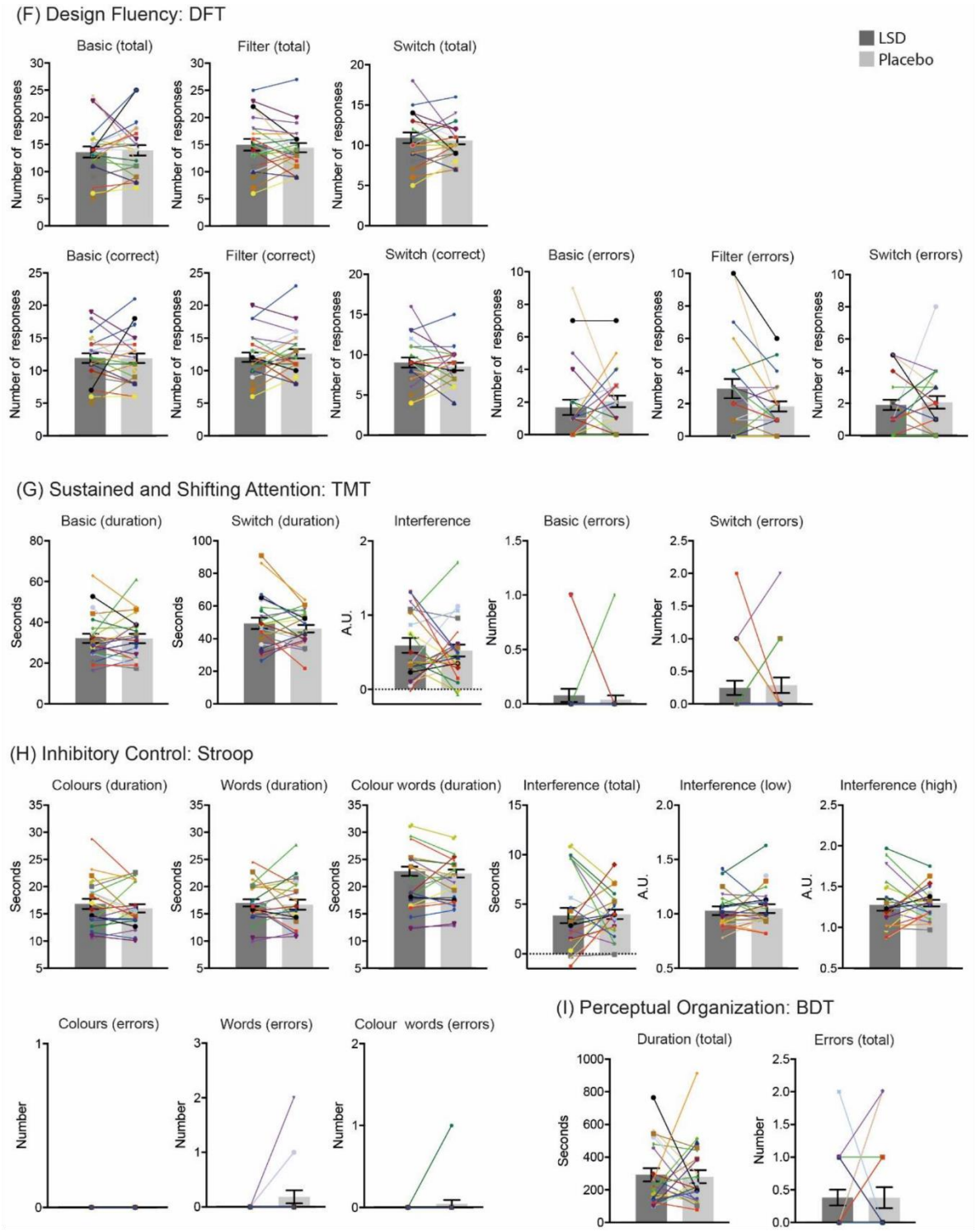


Figure S2. The treatment effects for the GLMs covarying with BMI and abstinence period. LSD did not sub-acutely change certain aspects of (A) visual memory recall, (B) visual memory consolidation, (C) auditory-verbal memory consolidation, (D) verbal fluency, and (E) cognitive flexibility. Also, LSD did no change overall (F) design fluency, (G) sustained and shifting attention, (H) inhibitory control and (I) perceptual organization. Displayed are estimated marginal means (bars) ± SEM (error bars) and paired single subject data (connected dots) for 24 (ROCF, VFT phonological errors, DFT, WCST, TMT, BDT), 23 (OLMT, RAVLT consolidation, VFT, WCST LL) and 22 subjects (RAVLT hits, false alarms, Stroop).

ROCF, Rey-Osterrieth Complex Figure. OLMT, 2D Object-Location Memory Task. RAVLT, Rey Auditory-Verbal Learning Test. VFT, verbal fluency task: total, total responses; correct, correct responses. WCST, Wisconsin Card Sorting Test: TT, total trials; TC, total correct responses; T1, trials to complete the first category; FM, failures to maintain set; LL, learning to learn; PE2 (%), perseverative errors type 2 percentage. DFT, Design Fluency Task: total, total responses; correct, correct responses. TMT, Trail Making Test: A.U., arbitrary unit. Stroop, Stroop Task: A.U., arbitrary unit. BDT, Block Design Test.

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4.4. Article 4 – LSD, Psychotic, Therapeutic and Psychedelic Experiences

Reference (99):

Wießner I, Falchi M, Palhano-Fontes F, Feilding A, Ribeiro S, Tófoli LF. LSD, madness and healing: Mystical experiences as possible link between psychosis model and therapy model. Psychol Med. 2021;(Epub ahead of print):1–15. Available from: https://doi.org/10.1017/S0033291721002531

LSD, Madness and Healing: Mystical Experiences as Possible Link between Psychosis Model and Therapy Model

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Word Count (text body): 4,491
Submitted to: *Psychological Medicine* as Original Article
Submission Date: 25th February 2021
Resubmission Date: 02nd June 2021

Financial support
This study received financial support from the Beckley Foundation and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) - Finance Code 001.

Abstract

Background: For a century, psychedelics have been investigated as models of psychosis for demonstrating phenomenological similarities with psychotic experiences and as therapeutic models for treating depression, anxiety, and substance use disorders. This study sought to explore this paradoxical relationship connecting key parameters of the psychotic experience, psychotherapy, and psychedelic experience.
Methods: In a randomized, double-blind, placebo-controlled, crossover design, 24 healthy volunteers received 50µg d-lysergic acid diethylamide (LSD) or inactive placebo. Psychotic experience was assessed by aberrant salience (Aberrant Salience Inventory, ASI), therapeutic potential by suggestibility (Creative Imagination Scale, CIS) and mindfulness (Five Facet Mindfulness Questionnaire, FFMQ; Mindful Attention Awareness Scale, MAAS; Experiences Questionnaire, EQ), and psychedelic experience by four questionnaires (Altered State of Consciousness, ASC; Mystical Experiences, MEQ; Challenging Experiences, CEQ; Ego-Dissolution, EDI). Relationships between LSD-induced effects were examined.
Results: LSD induced psychedelic experiences, including alteration of consciousness, mystical experiences, ego-dissolution, and mildly challenging experiences, increased aberrant salience and suggestibility, but not mindfulness. LSD-induced aberrant salience correlated highly with complex imagery, mystical experiences, and ego-dissolution. LSD-induced suggestibility correlated with no other effects. Individual mindfulness changes correlated with aspects of aberrant salience and psychedelic experience.
Conclusions: The LSD state resembles a psychotic experience and offers a tool for healing. The link between psychosis model and therapeutic model seems to lie in mystical experiences. The results point to the importance of meaning attribution for the LSD psychosis model and indicate that psychedelic-assisted therapy might benefit from therapeutic suggestions fostering mystical experiences.

Keywords: LSD; Psychedelics; Aberrant Salience; Suggestibility; Mindfulness; Mystical Experiences; Ego-Dissolution; Psychosis Model; Psycholytic Therapy

Introduction

Since the discovery of its psychedelic properties, d-lysergic acid diethylamide (LSD) has carried a paradoxical history. On one hand, LSD was applied as a psychosis model, owing to its similarity to the schizophrenic phenomenology (Geyer & Vollenweider, 2008). On the other hand, it was applied as a therapeutic tool for conditions including alcoholism and mood disorders (Krebs & Johansen, 2012; Reiff et al., 2020). This study sought to bridge the gap between these parallel research lines by examining key parameters of both areas: aberrant salience reflecting psychosis model and suggestibility and mindfulness reflecting therapeutic models.

Regarding psychosis model, there are remarkable similarities between psychedelic and psychotic experiences, namely altered perception of senses, self, body, time, altered emotions, impaired cognition, loss of intentionality, magical thinking, among other behavioral and neurophysiological phenomena (De Gregorio, Comai, Posa, & Gobbi, 2016; Geyer & Vollenweider, 2008; Vollenweider & Geyer, 2001). To explain the generation of psychotic experiences, schizophrenia research has emphasized salience processing. Salience is the quality of an element that makes it stand out from its environment and thereby catch attention, like a red dot on a wall (stimulus-driven) or a journal's impact factor for scientists (goal-directed) (Paulus, Rademacher, Schäfer, Müller-Pinzler, & Krach, 2015). Salience prioritizes relevant information and influences perception and behavior, including knowledge activation (Higgins, 1996), attribution of causality (Taylor & Fiske, 1978), decision making (Tversky & Kahneman, 1974), and self- and other-perception (Callero, 1985).

Aberrant salience is the "aberrant assignment of salience to external objects and internal representations" (Kapur, 2003, p.15) and possibly accounts for hallucinations and delusions in psychotic phenomena. It is related to delusions and negative symptoms in schizophrenia (Roiser et al., 2019) and psychotic experiences in first-episode psychosis and, to a lesser extent, healthy controls (Reininghaus et al., 2016). Aberrant salience predicts anomalous experiences and paranormal attributions (Irwin, Schofield, & Baker, 2014), increases with cannabis use (Bernardini et al., 2018), and mediates the cannabis-induced development of schizotypal symptoms (O'Tuathaigh et al., 2020). Altogether, these findings indicate a crucial role of aberrant salience in psychotic experiences. To evaluate the suitability of psychedelics as a psychosis model, an investigation of their effects on aberrant salience is therefore essential.

Regarding the therapeutic model, promising approaches to date seem to lie in psychedelic-induced suggestibility and mindfulness (Lemercier & Terhune, 2018; Walsh & Thiessen, 2018). Suggestibility is the tendency to react to suggestions. Suggestions influence cognition and behavior by guiding perception and assigning significance and support therapeutic processes (Gheorghiu, 2000; Kirsch & Low, 2013; Michael, Garry, & Kirsch, 2012). In hypnotherapy, suggestions induce cognitive, emotional, behavioral, and physiological changes (Peter, 2011) and suggestibility predicts treatment outcome in cases of pain, anxiety, somatization, asthma, and nicotine addiction (Lynn, Shindler, & Meyer, 2003; Montgomery, Duhamel, & Redd, 2000). Suggestibility can be increased by hypnosis (Kirsch et al., 2011), training (Gorassini & Spanos, 1986), and psychedelics, including LSD, mescaline, and psilocybin (Carhart-Harris et al., 2015; Middlefell, 1967; Sjoberg & Hollister, 1965). Considering that psychedelics and hypnosis enhance suggestibility and share other similarities, a combination of both tools might potentially boost treatment efficiency (Lemercier & Terhune, 2018).

Mindfulness is the "intentional self-regulation of attention from moment to moment [and] detached observation" (Kabat-Zinn, 1982, p.34). Mindfulness techniques are associated with improvements in mental health, depression, anxiety, stress, and pain management (Marchand, 2012). Mindfulness-related capacities can be increased by psychedelics, including psilocybin (Madsen et al., 2020), ayahuasca (Murphy-Beiner & Soar, 2020; Sampedro et al., 2017), and 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) (Uthaug et al., 2019).

Remarkably, mindfulness increases seem to facilitate the therapeutic action of psychedelics in mood and substance use disorders (Mian, Altman, & Earleywine, 2020; Walsh & Thiessen, 2018; Watts, Day, Krzanowski, Nutt, & Carhart-Harris, 2017). However, to the best of our knowledge, the effects of LSD on mindfulness have not yet been investigated.

This study aimed at exploring the suitability of LSD as a psychosis model, as measured by aberrant salience, and as a therapy model, as measured by suggestibility and mindfulness, as well as the relationship between both models and the psychedelic experience. Our hypotheses were: 1. LSD increases aberrant salience; 2. LSD increases suggestibility and mindfulness; 3. there are positive correlations between LSD-induced aberrant salience, suggestibility, mindfulness, and psychedelic experience.

Methods

Study Design

The study used a randomized, double-blind, placebo-controlled, crossover design with two treatments (LSD; placebo) and a washout period of 14 days between treatments. Participants were randomly assigned to treatment order. This study was approved by the University Research Ethics Committee and the National Health Surveillance Agency and conducted according to safety guidelines for psychedelic research in humans (Johnson, Richards, & Griffiths, 2008).

Participants

Twenty-five healthy participants were recruited in a convenience sample. Inclusion criteria were: age above 21 years, at least one experience with LSD, abstinence of at least two weeks from psychedelics and three days from alcohol and other drugs before each session and from tobacco and caffeine during the study days. Previous drug use was assessed by self-report questionnaires. Exclusion criteria were: presence of psychiatric symptoms, personal or first-degree family member history of psychotic disorder, use of psychiatric medication, history of severe complications after psychedelic use, alcohol or substance use disorder (according to DSM-5), heart disease or other relevant medical conditions, pregnancy, and non-native speaking of Brazilian Portuguese. Participants provided written informed consent before participation. One participant ceased participation after the first session for personal reasons, resulting in a final sample of 24 subjects. For demographic characteristics of the participants, see **table 1**.

Drug

Participants received 50µg LSD (> 99% purity on high-performance liquid chromatography; dissolved in alcohol solution) or inactive placebo (alcohol solution). Either substance was administered orally diluted in 30ml water. The dose of 50µg LSD is regarded as low and was chosen to minimize the risk of adverse reactions and exert noticeable effects without impairing the subjects' ability to complete the measurements (Holze et al., 2021; Majić, Schmidt, & Gallinat, 2015; Passie, Halpern, Stichtenoth, Emrich, & Hintzen, 2008). The absolute dose corresponded to a relative dose of (mean±SD) 0.69±0.18 µg/kg body weight (range=0.45–1.11).

Measurements

Psychedelic Experience

Subjective intensity and valence of drug effects were assessed by visual analog scales from 0 (no effect) to 100 (extremely intense effect) for intensity and from -50 (extremely unpleasant effect) to 50 (extremely pleasant effect) for valence. Both scales were applied as paper-and-pencil versions in 15 min-intervals for two hours, followed by 30 min-intervals for six hours. Maximum intensity (Int_{max}), maximum and minimum valence (Val_{max}, Val_{min}), area

under the curve for intensity (Int_{AUC}) and positive and negative valence (Val_{AUCpos}, Val_{AUCneg}) were calculated.

The LSD-induced experience was self-rated using Brazilian Portuguese versions of the Altered State of Consciousness Questionnaire (ASC) (Dittrich, 1998; Studerus, Gamma, & Vollenweider, 2010), Mystical Experiences Questionnaire (MEQ) (MacLean, Leoutsakos, Johnson, & Griffiths, 2012; Schenberg, Tófoli, Rezinovsky, & Da Silveira, 2017), Challenging Experiences Questionnaire (CEQ) (Barrett, Bradstreet, Leoutsakos, Johnson, & Griffiths, 2016; Schenberg, n.d.), and Ego-Dissolution Inventory (EDI) (Bienemann et al., 2020; Nour, Evans, Nutt, & Carhart-Harris, 2016). The ASC contains 11 factors (Experience of Unity; Spiritual Experience; Blissful State; Insightfulness; Disembodiment; Impaired Control and Cognition; Anxiety; Complex Imagery; Elementary Imagery; Audio-Visual Synaesthesia; Changed Meaning of Percepts), the MEQ four factors (Mystical; Positive Mood; Transcendence of Time and Space; Ineffability), and the CEQ seven factors (Fear; Grief; Physical Distress; Insanity; Isolation; Death; Paranoia; compare **Supplemental Methods**).

Aberrant Salience

The Aberrant Salience Inventory (ASI) measures the trait aberrant salience using 29 items in yes-no format (Cicero, Kerns, & McCarthy, 2010). The items form five factors (Increased Significance; Senses Sharpening; Impending Understanding; Heightened Emotionality; Heightened Cognition) and total score of all yes-responses (Total). For this study, the trait scale was adapted to a state scale by converting items from present tense ("do you ever feel") into past tense ("did you feel") referring to the last 24 hours. The English scale was translated into Brazilian Portuguese by our team; validation is currently in progress.

Suggestibility

The Creative Imagination Scale (CIS) measures suggestibility (Wilson & Barber, 1978). Participants are instructed to sit comfortably, close their eyes, and imagine as vividly as possible the suggestions read by the investigator. The protocol contains 10 items of different modalities (e.g. auditory, tactile, olfactory). Afterward, participants rate their imagined experience compared to a real experience on a 5-point Likert scale from 0 (not at all the same) to 4 (almost exactly the same). The material was translated by our team and split into two parallel versions (see **Supplemental Methods**). Version order was balanced across participants and counterbalanced across treatments, i.e. half of the participants completed version A under LSD.

All items are summed to a total score (Total). Additionally, the different modalities were explored by grouping similar items to the modality areas Weight (arm heaviness; hand levitation), Sensation (finger anesthesia; hot hand), Taste (water; orange), Extern Ambience (music; age regression), Intern Ambience (time distortion; relaxation). Notably, this analysis was exploratory because the scale is not intended to and might not adequately distinguish between modalities, especially within our split version.

Mindfulness

Mindfulness was measured by Brazilian Portuguese versions of the Five Facet Mindfulness Questionnaire (FFMQ) (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006; De Barros, Kozasa, De Souza, & Ronzani, 2014), Mindful Attention Awareness Scale (MAAS) (Brown & Ryan, 2003; De Barros, Kozasa, De Souza, & Ronzani, 2015), and Experiences Questionnaire (EQ) (Fresco et al., 2007). The Brazilian FFMQ contains seven factors (Observe; Describe–Positive; Describe–Negative; Act with Awareness–Autopilot; Act with Awareness–Distraction; Nonjudge; Nonreact). MAAS and EQ are unifactorial measuring Awareness and Decentering, respectively (see **Supplemental Methods**). All scales were rated referring to the last 24 hours (Soler et al., 2016) and applied before drug administration (T0), 24 hours afterward (T1), and two weeks afterward (T2).

Study Procedures

Candidates for participation underwent a clinical and psychiatric interview including screening of the inclusion/exclusion criteria, medical anamnesis, physical examination, and check of a recent electrocardiogram. If indicated, complementary exams were consulted.

Each session consisted of two study days. On the day of drug administration, two investigators were present, a psychologist and a psychiatrist. At least one of them was continuously in the same room as the subject, who was only allowed to leave for visiting the bathroom. For each participant, the same investigators were present in both sessions and continuously available for questions and doubts via e-mail and phone.

At 7:30 a.m., the session started. The researcher explained the study aims and procedures, addressed questions, asked the subject to switch off their cell phone, and initiated the baseline measurements including mindfulness scales (FFMQ, MAAS, EQ at T0). LSD or placebo was administered at 9:30 a.m., followed by diverse tests and questionnaires throughout the day. Results of these additional measurements will be reported elsewhere. During task-free intervals, participants were allowed to draw, write or spend time with provided photobooks and metallic and wooden puzzle games but not to listen to music, read, work or access the internet or computer. A standardized snack was served at 11:00 a.m. and lunch at 1:40 p.m. Suggestibility (CIS) was tested at 2:15 p.m. lasting around 18 min. At 4:30 p.m., seven hours after drug administration, participants completed questionnaires on the psychedelic experience (ASC, MEQ, CEQ, EDI). At 5:30 p.m., eight hours after drug administration, the researcher ensured that the subject was feeling emotionally and physically well, answered possible questions and released the subject into the custody of a family member or friend. Next morning, the subject returned at 8:00 a.m., completed measurements of mindfulness (FFMQ, MAAS, EQ at T1) and aberrant salience (ASI), among others, and was released around 10:00 a.m.

All questionnaires were presented on a monitor via online survey tool LimeSurvey (Schmitz, 2012). Two weeks after the second session, participants completed online follow-up measurements including mindfulness scales (T2). Four months after the second session, the last follow-up e-mail contact was made including qualitative questions on study participation and possible long-term effects. No persisting side effects were reported.

Data Analysis

Statistical analysis was performed with IBM SPSS Statistics (version 22). A repeated measures General Linear Model (GLMrep) with 'treatment' (LSD, placebo) as within-subjects factor and 'treatment order' as between-subjects factor was performed for each scale. For scales with several factors or time points, GLMreps were complemented by respective within-subject factors. Main effects of treatment, period, and carryover were examined, followed by pairwise comparisons for each factor and time point. Effect sizes were estimated using partial eta squared (η_p^2).

Spearman's rank correlation coefficients (r_s) were calculated between LSD-induced changes (Δ=LSD-placebo) on psychedelic experience (ΔInt, ΔVal, ΔASC, ΔMEQ, ΔCEQ, ΔEDI), aberrant salience (ΔASI), suggestibility (ΔCIS), and mindfulness (ΔFFMQ, ΔMAAS, ΔEQ).

Significance level was set to α=0.05, two-tailed. Results were Bonferroni-corrected *post hoc* for multiple comparisons unless stated otherwise. Therefore, *p*-values were corrected by the number of factors or time points for pairwise comparisons and the number of scales (n=11) for correlations, as follows: $p_{corrected}=p_{uncorrected}$*n.

Results

Psychedelic Experience

Intensity and positive valence were increased under LSD compared to placebo, as measured by Int_{max} ($F(1,22)=195.42$, $p<0.001$, $\eta_p^2=0.90$), Int_{AUC} ($F(1,22)=203.16$, $p<0.001$, $\eta_p^2=0.90$), Val_{max} ($F(1,22)=42.96$, $p<0.001$, $\eta_p^2=0.66$), and Val_{AUCpos} ($F(1,22)=20.80$, $p<0.001$, $\eta_p^2=0.49$). There was a significant, though weaker, period effect for Int_{AUC} ($F(1,22)=7.02$, $p=0.015$, $\eta_p^2=0.24$; $mean_{session1}\pm SD=209.4\pm203.2$, $mean_{session2}\pm SD=153.3\pm167.3$; **figure S1**), which might be explained by higher expectations and insecurity regarding study procedures and drug effects in the first session. There were no other effects of period and carryover.

ASC ratings of one subject were lost due to a storage error, so n=23 ratings were analyzed. There was a significant ASC main effect ($F(1,21)=99.01$, $p<0.001$, $\eta_p^2=0.83$), with higher scores for LSD than placebo in Total and all factors (all $p\leq0.001$) except for Anxiety (p=n.s.). Likewise, there was a main effect in MEQ ($F(1,22)=137.61$, $p<0.001$, $\eta_p^2=0.86$), with higher scores for LSD than placebo in Total and all factors (all $p<0.001$). There was a significant, though weaker, main effect for CEQ ($F(1,22)=32.63$, $p<0.001$, $\eta_p^2=0.60$). Pairwise comparisons revealed increases in Total, Grief, Physical Distress (all $p<0.001$), Insanity ($p=0.040$), and Isolation ($p=0.048$). Moreover, EDI was significantly increased under LSD compared to placebo ($F(1,22)=32.21$, $p<0.001$, $\eta_p^2=0.59$). No effects of period or carryover were observed. Means (±SEM) are presented in **figure 1.**

Aberrant Salience

ASI scores were significantly increased under LSD compared to placebo ($F(1,22)=55.00$, $p<0.001$, $\eta_p^2=0.71$), with no effects of period or carryover. Pairwise comparisons revealed higher ratings for Total, Increased Significance, Senses Sharpening, Impending Understanding, Heightened Emotionality (all $p<0.001$), and Heightened Cognition ($p=0.002$; **figure 2A**).

Suggestibility

CIS ratings were significantly increased under LSD compared to placebo ($F(1,22)=12.03$, $p=0.002$, $\eta_p^2=0.35$). Pairwise comparisons revealed increases in the modalities Extern Ambience ($p=0.004$), Weight ($p=0.024$), Sensation ($p=0.047$), and, marginally, Taste ($p=0.053$), but not Intern Ambience (p=n.s.; due to the exploratory nature of the modality analysis, p-values were not corrected for multiple comparisons; **figure 2B**). No effects of period or carryover were observed.

Mindfulness

For FFMQ, MAAS and EQ, no main effect or pairwise comparison reached significance (**table S1**, **figure S2**).

Correlations

Regarding aberrant salience, ΔASI Total was highly correlated with ΔASC Total ($r_s=0.71$, $p=0.002$), ΔMEQ Total ($r_s=0.72$, $p=0.001$), and ΔEDI ($r_s=0.82$, $p<0.001$; **figure 3**). Furthermore, there were several moderate to high factor correlations of ΔASI with ΔInt, ΔASC, ΔMEQ, and ΔEDI (**table 2**). Regarding suggestibility, ΔCIS was not correlated with other LSD-induced effects (**table 2**). Despite the lack of main effects in mindfulness, correlations of LSD-induced individual changes (ΔFFMQ, ΔMAAS, ΔEQ) were examined to gain insights into complementary phenomena. Interestingly, psychedelic experiences correlated positively with mindfulness at T1 (ΔASC and ΔMEQ with ΔEQ), but negatively with mindfulness at T2 (ΔASC, ΔMEQ, ΔEDI, and ΔASI with ΔEQ and ΔFFMQ Nonreact; **table 2, figure S3**).

Regarding psychedelic experience, there were several moderate to high correlations for ΔASC, ΔMEQ, and ΔEDI, few correlations for ΔVal, ΔCEQ, and none for ΔInt (**table S2**).

Discussion

To the best of our knowledge, this is the first study attempting to bridge the gap between psychedelics as a psychosis model and as a therapeutic model. We explored aberrant salience, as measure of the psychosis model, and suggestibility and mindfulness, as measures of the therapy model, as well as diverse facets of the psychedelic experience. Our hypotheses were: 1. LSD increases aberrant salience; 2. LSD increases suggestibility and mindfulness; 3. there are positive correlations between LSD-induced aberrant salience, suggestibility, mindfulness, and psychedelic experience. LSD induced a psychedelic experience including alterations of consciousness, mystical experiences, ego-dissolution and mildly challenging experiences. Regarding the psychosis model, as hypothesized, LSD significantly increased aberrant salience. Regarding the therapeutic model, our hypothesis was partially supported, with LSD significantly increasing suggestibility but not mindfulness. Regarding the relationship between both models, as expected, psychedelic experiences were correlated moderately to highly positively with aberrant salience and moderately positively with mindfulness at T1 but, contrary to our expectations, there were moderate negative correlations of psychedelic experiences with mindfulness at T2 and no correlations for suggestibility.

Psychedelic Experience

The low dose of LSD (50µg) was utilized in psycholytic therapy in the past (Majić et al., 2015) and is poorly investigated in modern studies. This dose exerted principally positive effects, as indicated by increased positive valence, Positive Mood (MEQ), only slightly increased Grief, Physical Distress, Insanity, and Isolation (CEQ), and unaltered negative valence, Anxiety (ASC), Fear, Death, and Paranoia (CEQ), supporting the notion that lower doses of LSD induce predominantly positive emotions (Carhart-Harris et al., 2016; Dolder, Schmid, Müller, Borgwardt, & Liechti, 2016; Holze et al., 2021; Schmid et al., 2015). This dose also induced mystical experiences and ego-dissolution, which seem to play a critical role in therapeutic processes. Psilocybin-induced mystical experiences induce personal and spiritual significance which account for long-term enhancements in openness, positive attitudes, and prosocial behaviors (Griffiths et al., 2018; Griffiths, Richards, McCann, & Jesse, 2006; MacLean, Johnson, & Griffiths, 2011), are related to increased alcohol and smoking abstinence (Bogenschutz et al., 2015; Johnson, Garcia-Romeu, & Griffiths, 2017) and reduced anxiety and depression in patients with life-threatening cancer (Griffiths et al., 2016; Ross et al., 2016). Ego-dissolution might support an altered perspective on the self and increased self-acceptance (Fischman, 2019). A "psychedelic peak experience", including ego-dissolution, transcendence of time and space, and meaningful insights, was suggested as an important mechanism in LSD-assisted psychotherapy (Gasser, Kirchner, & Passie, 2015). Our results indicate that even a low dose of LSD evokes this peak experience and, therefore, is of potential therapeutic value.

Psychosis Model

LSD increased all aberrant salience factors, namely Senses Sharpening (reflecting thalamic sensory gating), Impending Understanding (feeling of the importance of one's own reasoning), Increased Significance (salience attribution to external or internal stimuli), Heightened Emotionality (the urge to make sense of this significance), and Heightened Cognition (the feeling of being part of something mystically or intellectually important) (Cicero et al., 2010). The results support the suitability of the psychosis model especially regarding meaning attribution. This is consistent with previously reported subjective, behavioral, and neurophysiological similarities between psychedelic experiences and acute, early phases of psychosis (Geyer & Vollenweider, 2008; Hermle & Kraehenmann, 2016; Pienkos et al., 2019;

Vollenweider & Geyer, 2001), especially regarding meaning attribution: "There is a charismatic aspect to the experience of the LSD-intoxicated and schizophrenic patients, giving rise to the feeling that they are approaching the truth or gaining a true awareness of the world" (Savage & Cholden, 1956, p.409f) (Bowers & Freedman, 1966; Gouzoulis-Mayfrank et al., 1998; Leptourgos et al., 2020).* Conversely, emotional aspects of aberrant salience and psychedelic experience showed few correlations, pointing to the limits of the psychosis model, since psychotic experiences exhibit strong, principally negative emotionality (Geyer & Vollenweider, 2008; Hermle & Kraehenmann, 2016; Young, 1974). Moreover, aberrant salience correlated highly with Complex Imagery, emphasizing the importance of psychedelic-induced visions for meaning attribution, while psychotic experiences are characterized by more auditory hallucinations (Hermle & Kraehenmann, 2016). Altogether, our findings highlight the potential of low psychedelic doses to induce psychotic-like, meaning-laden experiences, including hallucinations (Senses Sharpening) and delusions (Impending Understanding, Increased Significance, Heightened Cognition).

Beyond that, the correlations of aberrant salience with mystical experiences and ego-dissolution might point to common mechanisms for psychotic, therapeutic and psychedelic experiences. Specifically, LSD-induced aberrant salience might increase significance attribution and reduce ego boundaries and defense mechanisms, allowing for therapeutic changes in perspectives and attitudes (Fischman, 2019). Similarly, aberrant salience exerts a modulatory role within psychotic experiences related to cannabis use and self-concept clarity (Cicero, Docherty, Becker, Martin, & Kerns, 2015; O'Tuathaigh et al., 2020). Moreover, considering that salience impacts attention, causality attribution, decision making, self-concept, role-identity, and moral reasoning (Bordalo, Gennaioli, & Shleifer, 2012; Callero, 1985; Taylor & Fiske, 1978; Trémolière, Neys, & Bonnefon, 2012), aberrant salience might provide an intriguing perspective to explain psychedelic phenomena including altered cognition, logical thinking, self- and other-perception, empathy, and prosocial attitudes.

Therapy Model

LSD increased suggestibility in a manner similar to previous results (Carhart-Harris et al., 2015) despite the lower dose and later time point, when intensity had almost halved (means±SD: ΔInt_{max}=72±27; ΔInt_{+5h}=39±22). This might point to a "late therapeutic window" in psycholytic therapy, with reduced intensity, cognitive impairment, emotional instability, and

* Other similarities include distorted perception of senses, time, space, self, and body, thought disturbances, perceived loss of control (Bercel, Travis, Olinger, Dreikurs, & Polos, 1956; Carhart-Harris et al., 2016; Gouzoulis-Mayfrank et al., 1998, 2005; Osmond & Smythies, 1952; Rinkel, Hyde, Solomon, & Hoagland, 1955; Vardy & Kay, 1983; Young, 1974), reduced organization and adjustment of behavior (Bercel et al., 1956; Rinkel et al., 1955; Savage & Cholden, 1956), impaired cognition (attention, concentration, inhibition), disorganized language (Carter et al., 2005; Krus, Wapner, Freeman, & Casey, 1963; Sanz et al., 2021; Sloane & Doust, 1954; Spitzer et al., 1996) and several neurophysiological parameters (Carhart-Harris et al., 2013; Carter et al., 2007; Heekeren et al., 2008; Hermle et al., 1992; Quednow, Kometer, Geyer, & Vollenweider, 2012; Schmid et al., 2015; Vollenweider, Csomor, Knappe, Geyer, & Quednow, 2007; Vollenweider et al., 1997). Most studies compared psychedelic effects in healthy subjects to experiences of patients with psychotic disorders (Bercel et al., 1956; Bowers & Freedman, 1966; Carhart-Harris et al., 2016; B. D. Cohen, 1962; S. Cohen, 1966; Gouzoulis-Mayfrank et al., 1998, 2005; Guttmann, 1936; Klüver, 1928; Middlefell, 1967; Osmond & Smythies, 1952; Rinkel et al., 1955; Savage & Cholden, 1956; Vardy & Kay, 1983; Young, 1974). Interestingly, a number of studies even administered psychedelics to patients with, or people with predisposition to, schizophrenia. These groups demonstrated stronger effects or reactivations of undesirable symptoms including withdrawal, preoccupation, and impaired concentration, as compared to the same groups without psychedelics and to healthy controls with and without psychedelics (Anastasopoulos & Photiades, 1962; Hermle & Kraehenmann, 2016; Hoch, 1951; Krus et al., 1963; Sloane & Doust, 1954). Similarly, animal models with chronic LSD administration seemed to mimic chronic symptoms of schizophrenia including irritability, hyperactivity, anhedonia, and withdrawal, which persisted even after cessation of LSD treatment and were reversed by antidopaminergic medication (Marona-Lewicka, Nichols, & Nichols, 2011).

increased disposition to engage in therapeutic dialogue, similar to findings of a second LSD-induced peak in trust, happiness, openness, and wanting "to be with other people" (Dolder et al., 2016). LSD increased the modalities Extern Ambience, Weight, Sensation, and, marginally, Taste. The modulated Extern Ambience indicates application potential for mood disorders, where positive memories and imagery exert therapeutic benefits (Holmes, Lang, & Shah, 2009; Serrano, Latorre, Gatz, & Montanes, 2004). Moreover, the results indicate application possibilities in hypnotherapeutic areas concerning memory integration (e.g. post-traumatic stress disorder), somatization, pain, and eating disorders (Godoy, 1999; Lynn et al., 2003; Montgomery et al., 2000). Notably, psychedelic-induced suggestibility needs to be prudently applied, since suggestions can engender potentially harmful results, including false memories (Michael et al., 2012; Paddock & Terranova, 2001). Future studies should confirm our exploratory results by focusing on psychedelic-induced mystical experiences, which act therapeutically in similar areas and might boost treatment efficacy if guided and potentiated by suggestions.

In contrast with previous findings, LSD did not increase mindfulness,. This might be explained by previous studies assessing mindfulness in naturalistic settings (Murphy-Beiner & Soar, 2020; Smigielski et al., 2019; Soler et al., 2018, 2016; Uthaug et al., 2019) or with baseline comparisons (Madsen et al., 2020; Sampedro et al., 2017), allowing for setting or placebo effects which fundamentally influence psychedelic experiences (J. A. Olson, Suissa-Rocheleau, Lifshitz, Raz, & Veissière, 2020). Moreover, our study applied no mindfulness-enhancing procedures, but assessed spontaneous changes. Alternatively, our low dose might not have exerted effects, while ritual doses are generally higher. Lastly, substance differences might account for the discrepancy, since the naturally-derived ayahuasca (DMT), toad secretion (5-MeO-DMT), and mushrooms (psilocybin) contain diverse psychoactive components (Chen & Kovariková, 1967; Domínguez-Clavé et al., 2016; Tylš, Páleníček, & Horáček, 2014). Future studies should carefully disentangle influences of substance, dose, setting, and placebo effect.

Connecting Psychedelic Experience, Psychosis Model, and Therapy Model

Suggestibility was not correlated with other effects, contradicting the concern that psychedelic-induced suggestibility biases the psychedelic experience *per se* (Johnson et al., 2008) and indicating that therapeutic suggestions act independently of the psychedelic experience. Contrastingly, mindfulness changes were correlated with mystical experiences and ego-dissolution, positively in the short term and negatively in the mid-term. Similarly, previous findings reported positive relationships between ayahuasca-induced ego-dissolution and sub-acute mindfulness (Uthaug et al., 2018) and negative relationships between psilocybin-related effects and long-term mindfulness (Madsen et al., 2020). Overall, these results might indicate that psychedelic experiences facilitate spontaneous mindfulness in the short term but hinder it in the long term. However, due to the lack of main effects, conclusions must be drawn with caution.

Aberrant salience showed no correlations with suggestibility and few with mindfulness, indicating no close connection between the psychosis model and these specific therapeutic models. However, aberrant salience robustly correlated with mystical and ego-dissolution experiences, which are fundamental within psychedelic-assisted treatments (compare section "Psychedelic Experience") and psychotic experiences. Psychotic experiences are associated with self-distortions (Cicero et al., 2015; Nordgaard & Parnas, 2014), although these seem to differ quantitatively and qualitatively from psychedelic-induced self-distortions (Vollenweider & Geyer, 2001). Mystical experiences are common in the psychotic phenomenology, comprise religious and mystical hallucinations and delusions, including a sense of noesis, heightened perception, and communion with the 'divine', and are phenomenologically similar to non-psychotic and psychedelic-induced mystical experiences (Buckley, 1981; Clarke, 2010; Hermle

& Kraehenmann, 2016; Leptourgos et al., 2020; Lukoff, 1985; Parnas & Henriksen, 2016; Stifler, Greer, Sneck, & Dovenmuehle, 1993).[†]

The concurrency of mystical and psychotic experiences is reframed in some non-Western cultures as spiritual trance and shamanism (Castillo, 2003; McClenon, 2012). Similarly, the psychedelic use in shamanic rituals and psychedelic-assisted psychotherapy underlies different conceptions of illness and healing (Metzner, 1998). With this in mind and considering the capacity of humans to experience mystical states (Buckley, 1981) and the importance of mystical experiences for therapeutic processes, our results suggest that mystical experiences might constitute the link between the psychosis model and therapy model. Consequently, a stronger cultural integration of mystical experiences might promote the understanding and improvement of mental health, in line with the call of a consciousness culture (*Bewusstseinskultur*) for a social dialogue on consciousness and promotion of self-awareness, from education in school (meditation, lucid dreaming, guided imagery) to the public stance towards psychiatric disorders, euthanasia, and the human striving for altered states of consciousness (Metzinger, 2006; Fink, 2018).

Limitations

Several limitations should be considered when interpreting the results. I) Design: Blinding was difficult to realize, although the low dose permitted a certain degree of blinding especially in less experienced subjects. The randomization method led to imbalanced education levels across groups (**table 1**). The crossover design, chosen to reduce the sample size, carries risks of potentially undetected carryover effects, emphasizing the need for larger sample sizes. II) Sample: The convenience sampling method led to underrepresented women, non-Caucasian ethnicities and low-educated people, reducing the generalizability to the wider Brazilian population. Results within our healthy participants need to be replicated in clinical populations. The lack of drug screening potentially led to disrespected abstinence periods. III) Measurements: Aberrant salience does not directly measure psychotic symptoms and should be complemented by additional measurements in future studies (e.g. Psychotomimetic States Inventory). These should also include pharmacological and neurophysiological assessments, since the brain mechanisms underlying our effects remain unclear. Moreover, future research should specify how mystical experiences are comparable in quality and quantity within the psychosis model and therapy model.

Conclusions

This study aimed at bridging the gap between psychedelics as a psychosis model and therapeutic model. The low dose of LSD is poorly explored in modern studies and provides insights for psychosis research and psycholytic therapy. LSD increased suggestibility but not mindfulness, suggesting that psychedelics act therapeutically if applied as a tool but are not necessarily therapeutic *per se*. Contrastingly, LSD spontaneously increased aberrant salience,

[†] Accordingly, spirituality is important for many patients with schizophrenia, influences their attitudes towards medical treatment, and promotes their coping with challenging symptoms (Borras et al., 2007; Clarke, 2010; Huguelet, Mohr, Borras, Gillieron, & Brandt, 2006; Jackson, 2010). Strikingly, mental health professionals differentiate religious experiences from psychopathology not regarding their content but their deviation from conventional beliefs and practices (Sanderson, Vandenberg, & Paese, 1999). Yet, the conception of psychosis as disorder is culture-specific, influences public and personal attitudes and the unfavorable progression of symptoms (Angermeyer, Buyantugs, Kenzine, & Matschinger, 2004; Brekke & Barrio, 1997; Castillo, 2003; Jackson, 2010; Kirmayer, 2006; Williams & Steer, 2011). In contrast, traditional non-Western cultures consider psychotic symptoms as transient crisis of life and expression of what cannot be put into words and emphasize the importance to integrate the treatment in the spiritual and cultural context (Higgs, 2020; Silverman, 1967; Waxler, 1979). Alike, contemporary views claim the shift of psychiatric and public awareness from diagnostic categorizations as "psychosis" to transdiagnostic, experience-orientated, culture-specific approaches (Harnack, 2011; Hermle & Kraehenmann, 2016; Higgs, 2020; M. Olson, Seikkula, & Ziedonis, 2014; Pienkos et al., 2019).

indicating a greater weight of psychosis- than therapy-related aspects in the psychedelic phenomenology. In other words, the LSD state resembles a psychotic experience and offers a tool for healing. The results suggest that psychedelic and psychotic experiences share a mystical and ego-dissolution phenomenology which, as previously shown, is also important in therapeutic processes, pointing to mystical experiences as possible links between the psychosis model and therapy model. Future studies should explore suggestions guiding and promoting mystical experiences to boost efficiency of psychedelic-assisted therapy.

Supplemental Material

Supplemental material is available online.

Author Contributions

IW designed and coordinated the study, acted as psychological cover of the study, collected and analyzed data, and wrote the manuscript. MF conducted clinical interviews, selected participants, collected data, and served as psychiatric cover of the study. FPF contributed to data analysis. LFT designed the study, recruited and selected participants, and served as psychiatric cover of the study. All authors reviewed the manuscript.

Financial Support

This study received financial support from the Beckley Foundation and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) - Finance Code 001.

Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Acknowledgements

We wish to thank all our participants for their study participation and Dr. Martin Wießner for his support in the area under the curve analysis.

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Tables

Table 1. Demographic characteristics of the study participants

Characteristic [a]	**Categories**	**Total**	**LSD first** [b]	**Placebo first** [b]
Participants		24 (100%)	12 (50%)	12 (50%)
Age	years (mean±SD; range)	35±11; 25–61	35±11; 25–61	35±12; 25–61
Sex	female	8 (33%)	3 (25%)	5 (42%)
	male	16 (67%)	9 (75%)	7 (58%)
Ethnicity	not declared	2 (8%)	1 (8%)	1 (8%)
	black	1 (4%)	0 (0%)	1 (8%)
	pardo	3 (13%)	3 (25%)	0 (0%)
	Caucasian	17 (71%)	8 (67%)	9 (75%)
	oriental	1 (4%)	0 (0%)	1 (8%)
Marital status	single	10 (42%)	5 (42%)	5 (42%)
	married/cohabitation	13 (54%)	6 (50%)	7 (58%)
	divorced/separated	1 (4%)	1 (8%)	0 (0%)
Living	alone	3 (13%)	3 (25%)	0 (0%)
arrangements	with partner/children	12 (50%)	4 (33%)	8 (67%)
	with parents/siblings	3 (13%)	1 (8%)	2 (17%)
	with housemates/friends	6 (25%)	4 (33%)	2 (17%)
Education [c]	years (mean±SD; range)	19±3; 15–24	20±3; 16–24	17±2; 15–20
Profession	Researcher/Professor	10 (42%)	6 (50%)	4 (33%)
	Journalist	5 (21%)	0 (0%)	5 (42%)
	Lawyer	2 (8%)	2 (17%)	0 (0%)
	Architect	2 (8%)	1 (8%)	1 (8%)
	Psychologist	1 (4%)	0 (0%)	1 (8%)
	Physician	2 (8%)	1 (8%)	1 (8%)
	Teacher	2 (8%)	2 (17%)	0 (0%)
Employment status	unemployed	1 (4%)	0 (0%)	1 (8%)
	employed	19 (79%)	10 (83%)	9 (75%)
	occasionally employed	4 (17%)	2 (17%)	2 (17%)
Household Income	<1 minimum wage	1 (4%)	1 (8%)	0 (0%)
	1-3 minimum wages	5 (21%)	3 (25%)	2 (17%)
	>3 minimum wages	18 (75%)	8 (67%)	10 (83%)
Religion	none/atheist/agnostic	17 (71%)	8 (67%)	9 (75%)
	Catholic/Spiritist	2 (8%)	2 (16%)	0 (0%)
	Umbanda/Candomblé	2 (8%)	1 (8%)	1 (8%)
	Santo Daime	3 (13%)	1 (8%)	2 (17%)
Spirituality	not sure	5 (21%)	3 (25%)	2 (17%)
	yes	16 (67%)	8 (67%)	8 (67%)
	no	3 (13%)	1 (8%)	2 (17%)
Tobacco use	never	6 (25%)	3 (25%)	3 (25%)
	<1 time/month	5 (21%)	2 (17%)	3 (25%)
	1–10 times/month	4 (17%)	2 (17%)	2 (17%)
	11–30 times/month	5 (21%)	3 (25%)	2 (17%)
	>30 times/month	4 (17%)	2 (17%)	2 (17%)
Cannabis use	never	2 (8%)	2 (17%)	0 (0%)
	<1 time/month	5 (21%)	2 (17%)	3 (25%)
	1–10 times/month	4 (17%)	1 (8%)	3 (25%)
	11–30 times/month	5 (21%)	4 (33%)	1 (8%)
	>30 times/month	8 (33%)	3 (25%)	5 (42%)
Coffee use	cups/day (mean±SD; range)	3±2; 0–6	3±2; 0–6	3±2; 1–6
Alcohol use	units/moth (mean±SD; range)	13±15; 1–60	14±16; 2–60	12±16; 1–60
MDMA	lifetime (mean±SD; range)	12±14; 0–50	13±18; 0–50	11±10; 0–30
Stimulants	lifetime (mean±SD; range)	23±45; 0–200	33±60; 0–200	13±18; 0–60
Opioids	lifetime (mean±SD; range)	3±10; 0–50	5±14; 0–50	1±1; 0–3
Sedatives	lifetime (mean±SD; range)	8±22; 0–100	14±30; 0–100	1±3; 0–10
LSD	lifetime (mean±SD; range)	17±15; 1–50	18±18; 1–50	16±12; 1–40
Psilocybin	lifetime (mean±SD; range)	6±7; 0–25	7±7; 0–25	6±6; 0–20
Ayahuasca	lifetime (mean±SD; range)	69±131; 0–500	87±122; 0–300	50±142; 0–500
DMT	lifetime (mean±SD; range)	1±2; 0–5	1±2; 0–5	1±2; 0–5
Mescaline	lifetime (mean±SD; range)	0±1; 0–2	1±1; 0–2	0±0; 0–1

[a] Data is based on self-reported information, including drug use experience and frequency.

[b] The two treatment order groups did not significantly differ on demographic characteristics, unless stated otherwise.

[c] Higher means in the group “LSD first”, as indicated by an independent samples t-test.

Table 2. Relationships between LSD-induced changes in aberrant salience (ΔASI), suggestibility (ΔCIS), mindfulness (ΔFFMQ, ΔMAAS, ΔEQ), and psychedelic experience (ΔInt, ΔVal, ΔASC, ΔMEQ, ΔCEQ, ΔEDI)

			Aberrant Salience						**Sug**	**Mindfulness**			
			ΔASI						**ΔCIS**	**ΔFFMQ**	**ΔMAAS**	**ΔEQ**	
			Total	**Sign**	**Shar**	**Unde**	**Emo**	**Cog**	**any**	**NReac T2**	**any**	**T1**	**T2**
Sug	**ΔCIS**	**any**	n.s.										
Mindfulness	**ΔFFMQ**	**any**	n.s.						n.s.				
	ΔMAAS	**any**	n.s.										
	ΔEQ	**T1**	0,33	0,22	0,38	0,23	0,24	0,33					
		T2	-0,49	-0,50	-0,30	**-0,65****	-0,45	-0,29					
Psychedelic Experience	**ΔInt**	**Max**	0,56	**0,59***	0,41	0,41	0,50	0,19	n.s.	n.s.			
	ΔVal	**any**	n.s.						n.s.	n.s.			
	ΔASC	**Total**	**0,71****	0,56	**0,66****	**0,60***	0,53	**0,73*****	n.s.	-0,25	n.s.	0,47	-0,40
		Unit	**0,79*****	**0,68****	**0,67****	**0,72****	**0,60***	**0,73*****		-0,31		0,36	-0,51
		Spirit	0,54	**0,59***	**0,62***	0,30	0,17	**0,58***		-0,15		0,31	-0,24
		Bliss	0,55	0,56	0,47	0,40	0,41	0,45		-0,43		0,25	-0,56
		Insig	**0,65****	**0,71****	0,49	**0,68****	0,39	0,45		-0,41		0,20	**-0,65****
		Disem	0,43	0,20	0,37	0,42	0,43	**0,60***		-0,19		**0,60***	-0,39
		Impair	0,33	0,13	0,33	0,37	0,44	0,32		-0,09		0,22	-0,15
		Anxi	0,05	-0,19	0,03	0,10	0,08	0,18		0,26		0,38	0,26
		CImag	**0,76*****	**0,80*****	**0,58***	**0,59***	0,49	**0,58***		**-0,59***		0,47	**-0,62***
		EImag	0,55	0,39	0,55	0,39	0,46	0,52		-0,33		0,34	-0,26
		Synae	0,52	0,46	0,49	0,37	0,32	0,56		-0,03		0,41	-0,12
		Mean	0,56	0,51	**0,62***	0,43	0,41	0,55		-0,19		0,25	-0,30
	ΔMEQ	**Total**	**0,72****	**0,62***	**0,57***	**0,63***	0,49	**0,76*****	n.s.	-0,33	n.s.	0,48	-0,51
		Mystic	**0,70****	**0,65****	0,47	**0,65****	0,46	**0,79*****		-0,29		0,41	-0,47
		Mood	0,50	**0,59***	0,45	0,40	0,35	0,30		-0,36		0,21	**-0,61***
		Transc	0,52	0,32	0,47	0,44	0,37	**0,67****		-0,19		**0,56***	-0,23
		Ineffa	0,39	0,29	0,49	0,19	0,30	0,19		-0,23		0,33	-0,12
	ΔCEQ	**any**	n.s.						n.s.	n.s.			
	ΔEDI	**Total**	**0,82*****	**0,75*****	**0,66****	**0,69****	**0,59***	**0,73*****	n.s.	n.s.	n.s.	0,40	**-0,62***

Values depict Spearman's rank correlation coefficients for total and factor scores in n=23 subjects (ΔASC) and n=24 (all others), with significant correlations in bold. * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, Bonferroni-corrected.
Sug, Suggestibility. any, any scale factor. n.s., not significant. T1, 24 hours after drug administration. T2, two weeks after drug administration. ASI, Aberrant Salience Inventory: Sign, Increased Significance; Shar, Senses Sharpening; Unde, Impending Understanding; Emo, Heightened Emotionality; Cog, Heightened Cognition. CIS, Creative Imagination Scale. FFMQ, Five Facet Mindfulness Questionnaire: NReact, Nonreact. MAAS, Mindful Attention Awareness Scale. EQ, Experiences Questionnaire. Int, intensity. Val, valence. ASC, Altered State of Consciousness Questionnaire: Unit, Experience of Unity; Spirit, Spiritual Experience; Bliss, Blissful State; Insig, Insightfulness; Disem, Disembodiment; Impair, Impaired Control and Cognition; Anxi, Anxiety; CImag, Complex Imagery; EImag, Elementary Imagery; Synae, Audio-Visual Synaesthesia; Mean, Changed Meaning of Percepts. MEQ, Mystical Experiences

Questionnaire: Mystic, Mystical; Mood, Positive Mood; Transc, Transcendence of Time and Space; Ineffa, Ineffability. CEQ, Challenging Experiences Questionnaire. EDI, Ego-Dissolution Inventory.

Figures

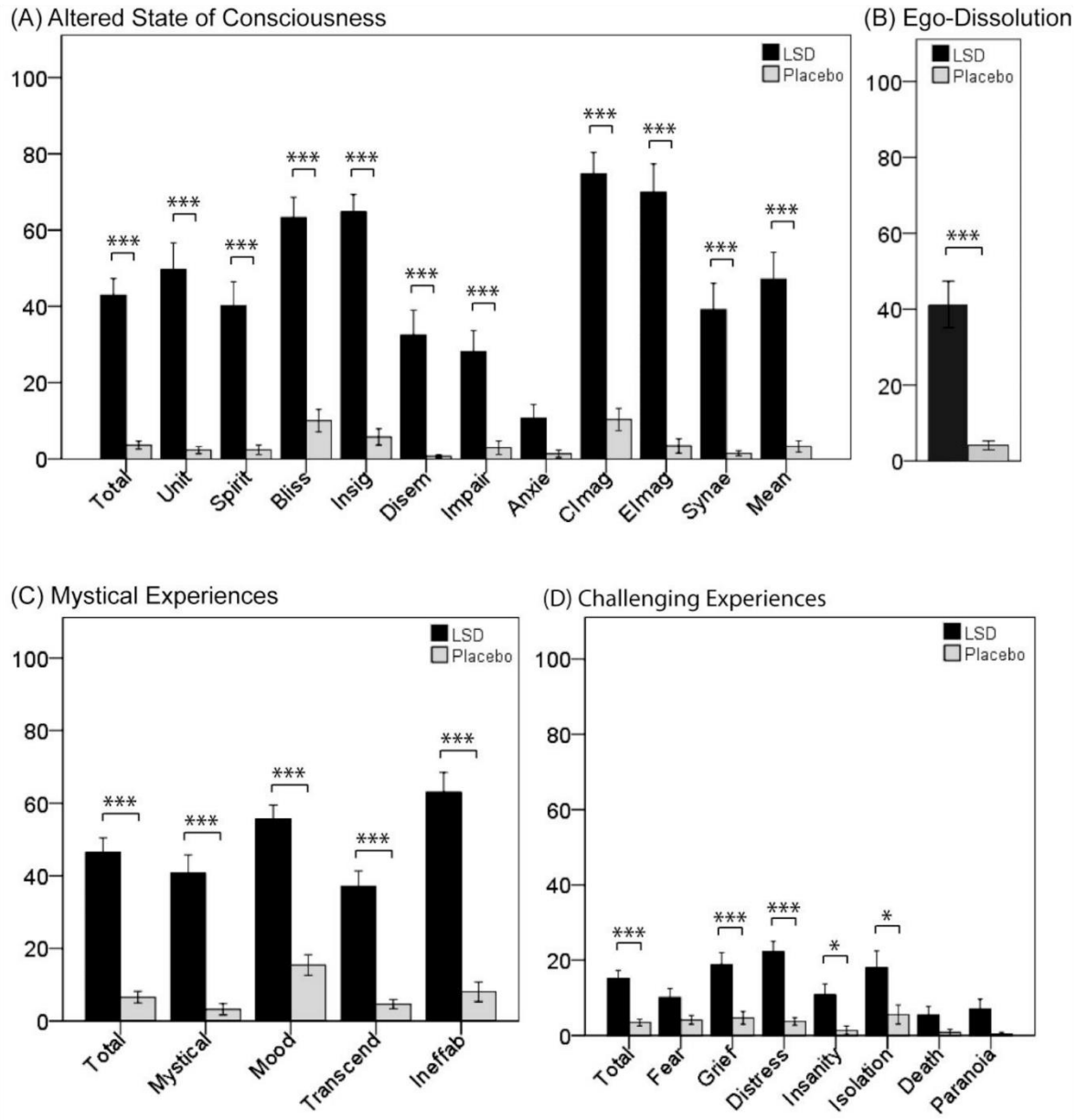

Figure 1. LSD, compared to placebo, induced psychedelic experiences as measured by (A) Altered State of Consciousness Questionnaire (ASC) for all factors except for Anxiety, (B) Ego-Dissolution Inventory (EDI), (C) Mystical Experiences Questionnaire (MEQ) for all factors, and (D) Challenging Experiences Questionnaire (CEQ) for the factors Grief, Physical Distress, Insanity, and Isolation but not in Fear, Death, or Paranoia. Scores are displayed as mean (±SEM) percentage of scale maximum in (A) 23 and (B-D) 24 subjects. * $p \leq 0.05$, *** $p \leq 0.001$ (Bonferroni-corrected *post hoc* pairwise comparisons).

ASC: Unit, Experience of Unity; Spirit, Spiritual Experience; Bliss, Blissful State; Insig, Insightfulness; Disem, Disembodiment; Impair, Impaired Control and Cognition; Anxie, Anxiety; CImag, Complex Imagery; EImag, Elementary Imagery; Synae, Audio-Visual Synaesthesia; Mean, Changed Meaning of Percepts. MEQ: Mood, Positive Mood; Transcend, Transcendence of Time and Space; Ineffab, Ineffability. CEQ: Distress, Physical Distress.

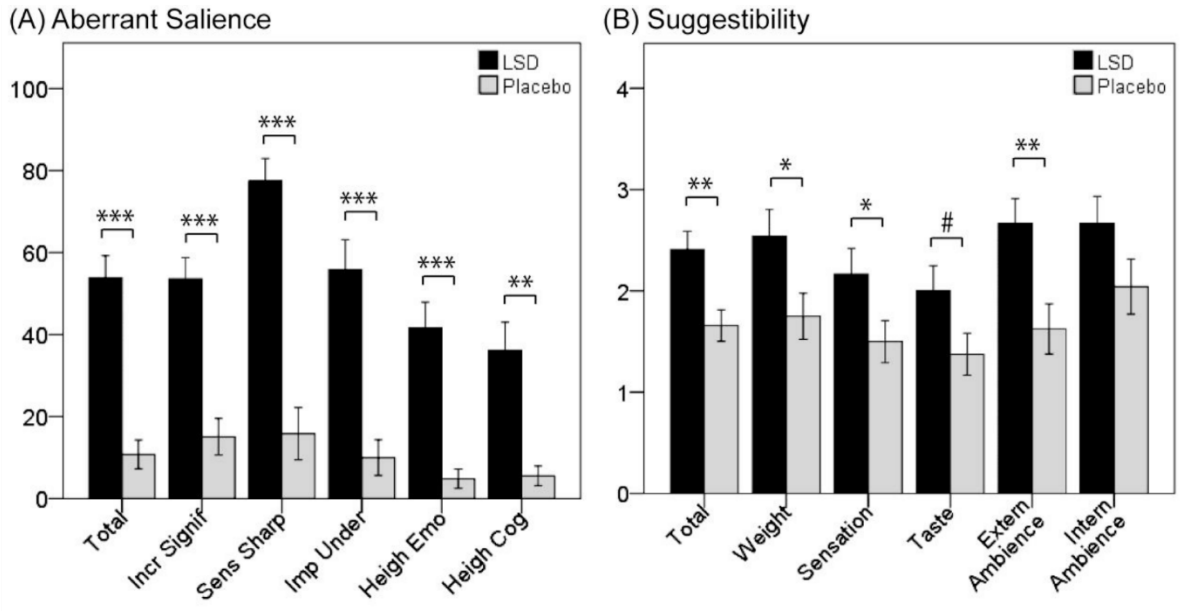

Figure 2. LSD, compared to placebo, induced psychotic- and therapeutic-like experiences, respectively, as measured by increased (A) aberrant salience (Aberrant Salience Inventory, ASI) for all factors, with strongest effect in Senses Sharpening, and (B) suggestibility (Creative Imagination Scale, CIS) for different modalities, with strongest effects in Extern Ambience, followed by Weight, Sensation, and, marginally, Taste, but not Intern Ambience. Scores are displayed as (A) mean (±SEM) percentage of maximum and (B) mean (±SEM) in 24 subjects. # $p \leq 0.06$, * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ ((A) Bonferroni-corrected *post hoc* pairwise comparisons, (B) uncorrected).

ASI: Incr Signif, Increased Significance; Sens Sharp, Senses Sharpening; Imp Under, Impending Understanding; Heigh Emo, Heightened Emotionality; Heigh Cog, Heightened Cognition.

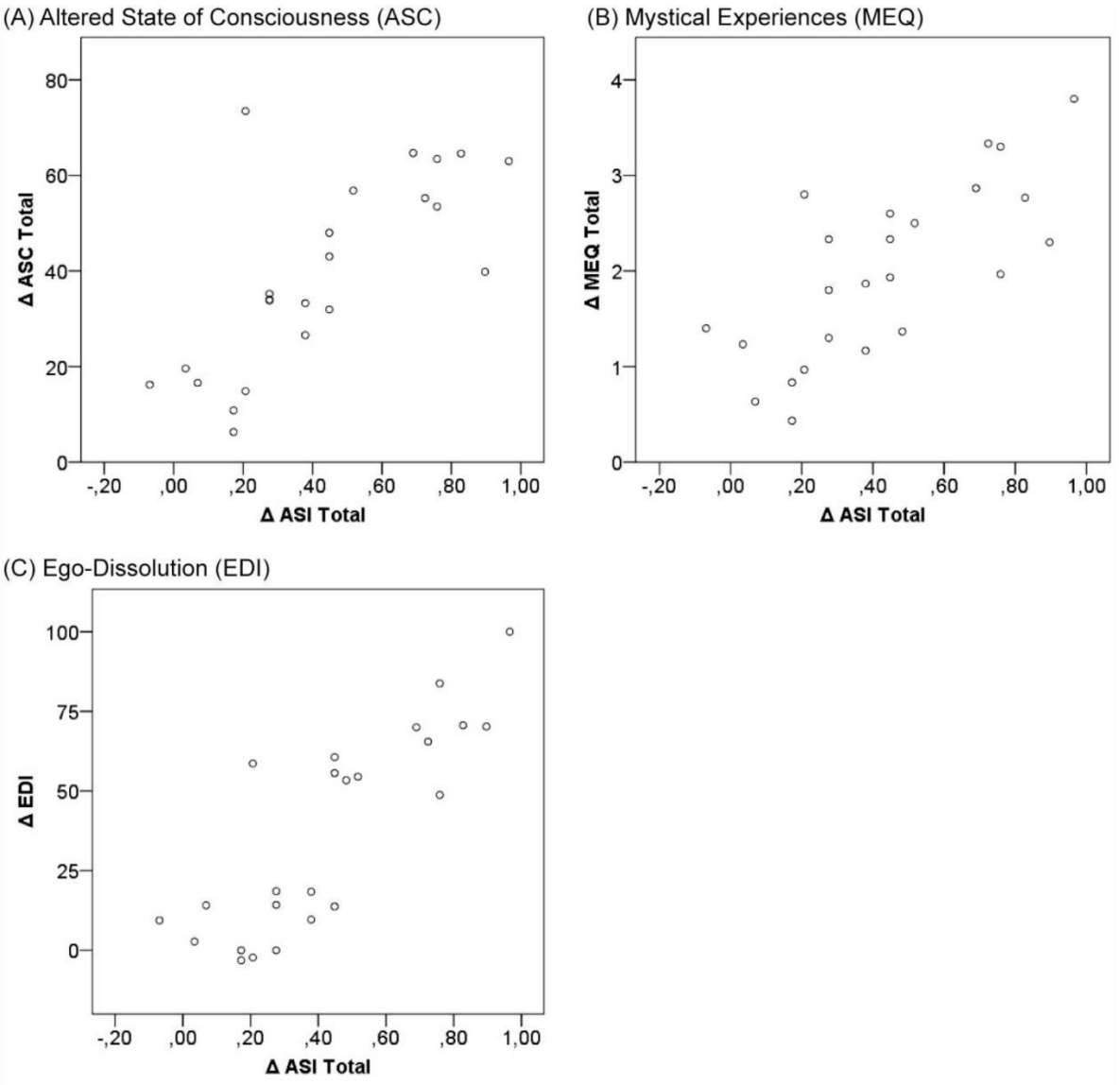

Figure 3. Scatterplots depicting relationships between aberrant salience and psychedelic experience. LSD-induced aberrant salience (ΔASI Total, x-axis) correlated highly with (A) altered state of consciousness (ΔASC Total, y-axis; r_s=0.71, p=0.002, n=23), (B) mystical experiences (ΔMEQ Total, y-axis; r_s=0.72, p=0.001, n=24), and (C) ego-dissolution (ΔEDI, y-axis; r_s=0.82, p<0.001, n=24). All p-values were Bonferroni-corrected *post hoc* for multiple comparisons.

ASI, Aberrant Salience Inventory. ASC, Altered State of Consciousness Questionnaire. MEQ, Mystical Experiences Questionnaire. EDI, Ego-Dissolution Inventory. Total, total score.

Supplemental Material

LSD, Madness and Healing: Mystical Experiences as Possible Link between Psychosis Model and Therapy Model

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Supplemental Methods

Altered State of Consciousness

The Altered States of Consciousness Questionnaire (ASC) assesses psychedelic-induced altered states of consciousness and is rated on a visual analogue scale (VAS) from 0 (No, not more than usual) to 100 (Yes, much more than usual) (Dittrich, 1998; Dittrich, Lamparter, & Maurer, 2006). The ASC contains 42 items that load on 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 Synaesthesia; 11) Changed Meaning of Percepts (Studerus, Gamma, & Vollenweider, 2010). Additionally, the 42 items were summed to a total score (Total). Notably, we applied the most extensive version with 94 items comprising five dimensions (Oceanic Boundlessness; Dread of Ego Dissolution; Visionary Restructuralization; Vigilance Reduction; Auditive Alteration) (Dittrich, 1998; Dittrich et al., 2006). However, for the purpose of this study, only the items relevant for the lower 11 factors demonstrating desirable psychometric properties (Studerus et al., 2010) are reported.

As there was no version in Portuguese available, we translated the scale following the guidelines for translation and cross-cultural adaptation (Douglas & Craig, 2007; Guillemin, 1995). Therefore, two independent native speakers translated the scale into Brazilian Portuguese and two independent native speakers back-translated these versions into American English. Discrepancies between versions were discussed to reach a final version. Validation of the scale is currently in progress.

Mystical Experiences

The Mystical Experiences Questionnaire (MEQ) measures mystical experiences elicited by psychedelics (Pahnke & Richards, 1966). The revised version comprises 30 items rated on a 6-point Likert scale from 0 (none, not at all) to 5 (extreme, more than ever before in my life) (MacLean, Leoutsakos, Johnson, & Griffiths, 2012). The questionnaire contains four factors: 1) Mystical; 2) Positive Mood; 3) Transcendence of Time and Space; 4) Ineffability. Additionally, a total score (Total) is calculated throughout all items. A Brazilian Portuguese version was applied (Schenberg, Tófoli, Rezinovsky, & Da Silveira, 2017).

Challenging Experiences

The Challenging Experiences Questionnaire (CEQ) was developed to characterize challenging experiences with psilocybin (Barrett, Bradstreet, Leoutsakos, Johnson, & Griffiths, 2016). The 26 items are rated on a 6-point Likert scale from 0 (none, not at all) to 5 (extreme, more than ever before in my life). The CEQ contains seven factors: 1) Fear; 2) Grief; 3) Physical Distress; 4) Insanity; 5) Isolation; 6) Death; 7) Paranoia. A total score (Total) is calculated over all items. A translated and validated version was applied (Schenberg, n.d.).

Ego-Dissolution

The Ego-Dissolution Inventory (EDI) measures psychedelic induced ego-dissolution (Nour, Evans, Nutt, & Carhart-Harris, 2016). The single factor instrument consists of eight items rated on a VAS from 0 (No, not more than usually) to 100 (Yes, entirely or completely). A translated version was applied; validation is currently in progress (Bienemann et al., 2020).

Suggestibility

The Creative Imagination Scale (CIS) (Wilson & Barber, 1978) was translated by a Brazilian Portuguese native speaker and back-translated by an American English native speaker. Discrepancies between original and back-translation were used to discuss the Portuguese translation and develop a final version (available upon request with the author).

To avoid learning effects, the scale was split into two versions with similar modalities applied over both sessions: Version A – Items 1. arm heaviness; 3. finger anesthesia; 4. water taste; 6. hearing music; 8. time distortion. Version B – Items 2. hand levitation; 7. hot hand; 5. orange smell and taste; 9. age regression; 10. mind-body relaxation.

To assure that the item split yielded parallel versions, the subjects' ratings in both version (A and B) were analyzed independently of treatment or treatment order. For this, a repeated measures General Linear Model (GLMrep) was conducted with 'version' as within-subject factor and 'version order' as between-subjects factor. There was no significant main effect ($F(1,22)=2.51$, p=n.s.), indicating comparable means in both versions and, therefore, both versions being parallel.

Mindfulness

The Five Facet Mindfulness Questionnaire (FFMQ) consists of 39 items (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006). The Brazilian Portuguese version is rated on a 5-point Likert scale from 1 (never or rarely true) to 5 (almost always or always true) (Barros, Kozasa, Souza, & Ronzani, 2014) and loads on seven factors: 1) Observe; 2) Describe–Positive; 3) Describe–Negative; 4) Act with Awareness–Autopilot; 5) Act with Awareness–Distraction; 6) Nonjudge; 7) Nonreact. Additionally, a total factor (Total) is calculated over all items. The Mindful Attention Awareness Scale (MAAS) consists of 15 items rated on a 6-point Likert scale from 1 (almost always) to 6 (almost never) (Brown & Ryan, 2003). Just as in the original version, the Brazilian MAAS measures awareness as a single factor (De Barros, Kozasa, De Souza, & Ronzani, 2015). The Experiences Questionnaire (EQ) consists of 20 items rated on a 5-point Likert scale from 1 (never) to 5 (all the time) (Fresco et al., 2007). Of these, 11 items load on one factor Decentering. The unifactorial structure was confirmed for the Brazilian version, but the results have not yet been published (P. Lucena-Santos, personal communication, 29 June 2020).

Supplemental Tables

Table S1. Details on the repeated measures GLM for each mindfulness scale

Scale	Main effect of treatment
FFMQ	$F(1,22)=1.60$, $p=0.219$, $\eta_p^2=0.07$
MAAS	$F(1,22)=0.34$, $p=0.568$, $\eta_p^2=0.02$
EQ	$F(1,22)=2.97$, $p=0.099$, $\eta_p^2=0.12$

FFMQ, Five Facet Mindfulness Questionnaire. MAAS, Mindful Attention Awareness Scale. EQ, Experiences Questionnaire.

Table S2. Spearman's rank correlation coefficients between total and factor scores on psychedelic experience scales

		ΔMEQ					ΔCEQ				ΔEDI	ΔInt	ΔVal	
		Total	**Mystic**	**Mood**	**Transc**	**Ineffa**	**Total**	**Fear**	**Insan**	**Others**	**Total**	**any**	**Min**	**AUCn**
ΔASC	**Total**	**0,86*** **	**0,73*** **	0,50	**0,78*** **	0,56	0,43	0,32	0,35		**0,81*** **			-0,21
	Unit	**0,84*** **	**0,83*** **	0,52	**0,63***	0,41	0,24	0,07	0,18		**0,86*** **			-0,34
	Spirit	**0,72****	**0,72****	0,55	0,43	0,35	0,14	0,08	-0,19		**0,61***			-0,37
	Bliss	**0,67****	0,55	**0,72****	0,44	0,55	0,09	-0,08	-0,04		**0,66****			-0,25
	Insig	**0,58***	**0,65****	**0,69****	0,18	0,15	-0,06	-0,19	-0,34		**0,58***			**-0,64***
	Disem	**0,74*** **	0,57	0,39	**0,81*** **	0,44	0,42	0,29	0,36	n.s.	**0,63***	n.s.	n.s.	-0,17
	Impair	0,35	0,18	0,04	0,56	0,19	0,56	0,54	**0,64***		0,39			0,13
	Anxi	0,30	0,15	0,01	0,42	0,32	**0,58***	**0,59***	**0,73*** **		0,06			0,01
	CImag	**0,73*** **	**0,69****	**0,72****	0,45	0,52	0,00	-0,10	-0,23		**0,76*** **			-0,47
	EImag	0,48	0,30	0,13	**0,60***	**0,68****	0,11	0,00	0,17		0,50			-0,07
	Synae	**0,59***	0,52	0,19	0,55	0,40	0,48	0,48	0,41		0,55			0,19
	Mean	**0,72****	**0,69****	0,32	0,52	0,39	0,45	0,37	0,29		**0,62***			0,02
ΔMEQ	**Total**						0,32	0,24	0,17		**0,88*** **			
	Mystic						0,27	0,18	0,11		**0,83*** **			
	Mood						0,11	-0,03	-0,28	n.s.	**0,65****	n.s.	n.s.	n.s.
	Transc						0,23	0,27	0,25		**0,71****			
	Ineffa						0,10	-0,01	0,16		0,33			
ΔCEQ	**Total**												-0,34	
	Fear												-0,32	
	Grief												-0,26	
	Distr												-0,04	
	Insan										n.s.	n.s.	-0,38	n.s.
	Isola												**-0,58***	
	Death												0,06	
	Paran												-0,29	

Values are depicted for n=23 (ΔASC) and n=24 subjects (all others). Bold numbers indicate significant correlations. * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, Bonferroni-corrected.

ASC, Altered State of Consciousness Questionnaire: Unit, Experience of Unity; Spirit, Spiritual Experience; Bliss, Blissful State; Insig, Insightfulness; Disem, Disembodiment; Impair, Impaired Control and Cognition; Anxi, Anxiety; CImag, Complex Imagery; EImag, Elementary Imagery; Synae, Audio-Visual Synaesthesia; Mean, Changed Meaning of Percepts. MEQ, Mystical Experiences Questionnaire: Mystic, Mystical; Mood, Positive Mood; Transc, Transcendence of Time and Space; Ineffa, Ineffability. CEQ, Challenging Experiences Questionnaire: Distr, Physical Distress; Insan, Insanity; Isola, Isolation; Paran, Paranoia. EDI, Ego-Dissolution Inventory. Int, Intensity: any, any parameter. Val, Valence: Min, Minimum score; AUCn, Area under the curve for negative scores.

Supplemental Figures

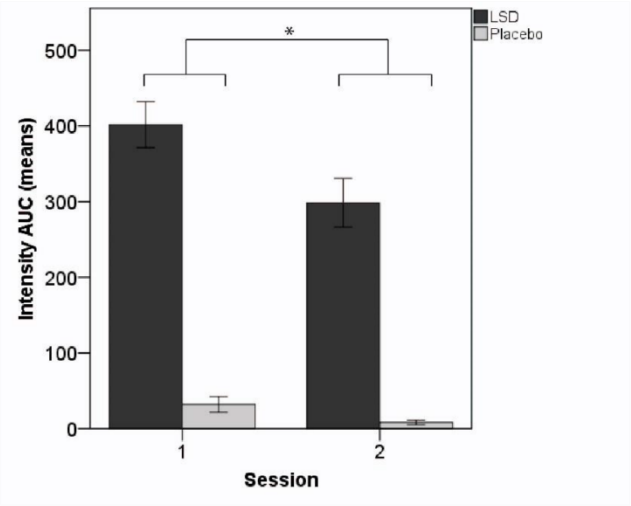


Figure S1. Period effect for Intensity Area under the Curve (AUC). There were higher overall ratings in the first than in the second session independent of treatment, probably pointing to increased expectations and insecurity regarding the forthcoming drug effects.

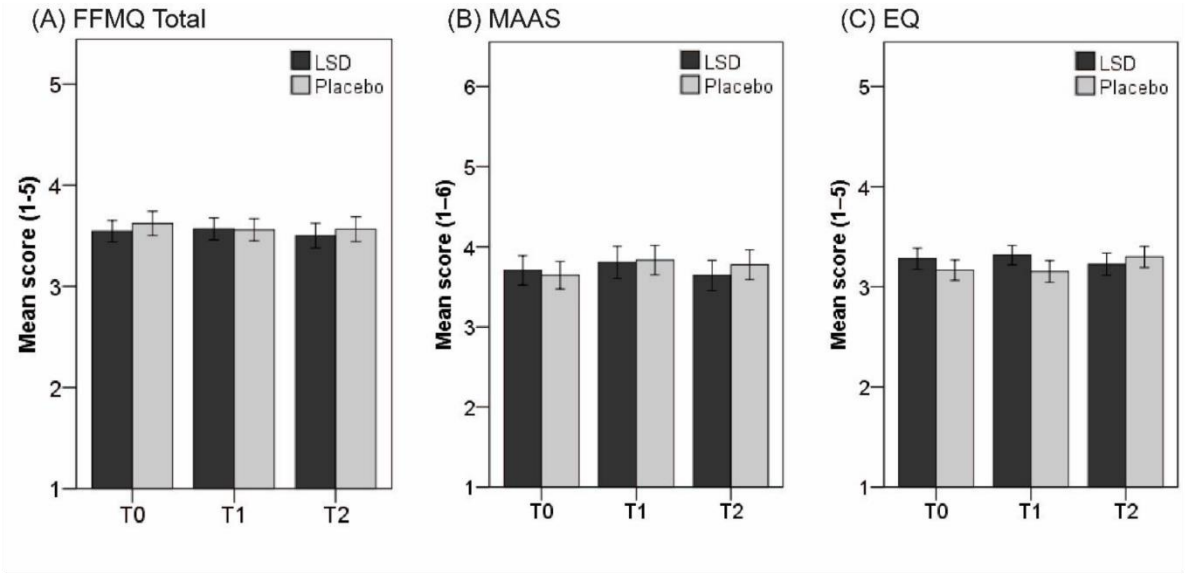
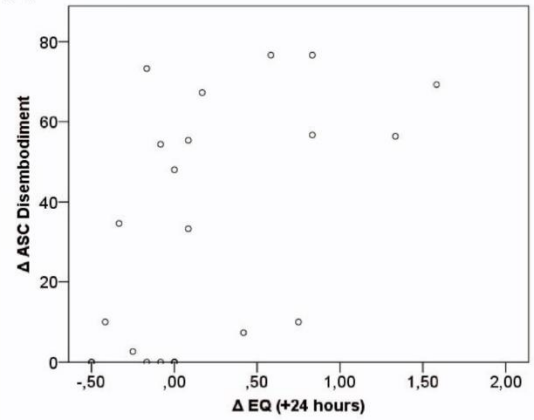


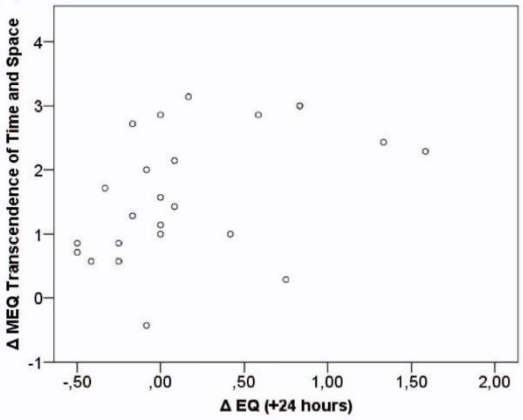
Figure S2. Mindfulness ratings for LSD and placebo before treatment (T0), 24 hours after treatment (T1), and two weeks after treatment (T2). (A) Five Facet Mindfulness Questionnaire (FFMQ) (only total score displayed), (B) Mindful Attention Awareness Scale (MAAS), and (C) Experiences Questionnaire. Mean scores (±SEM) are displayed for 24 subjects. No main effects or differences in pairwise comparisons were observed (all $p>0.05$, Bonferroni-corrected *post hoc* pairwise comparisons).

Decentering at 24 hours post-administration

(A)

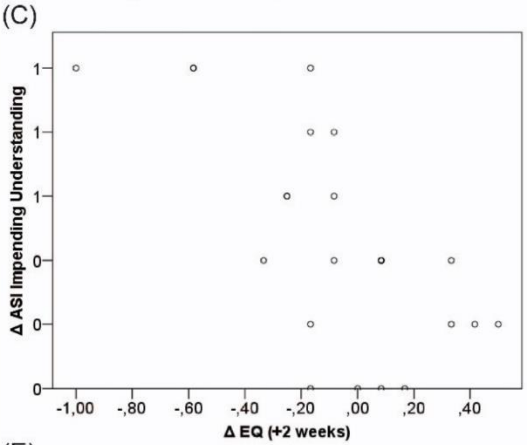


(B)

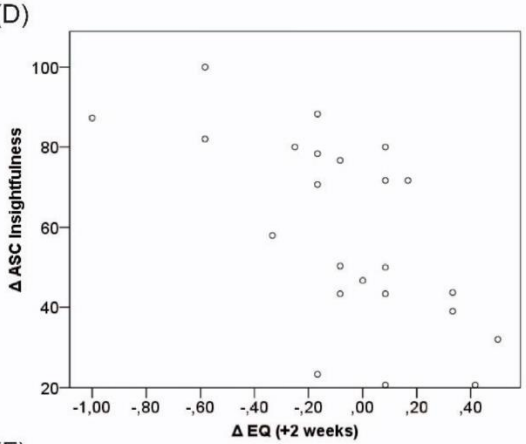


Decentering at 2 weeks post-administration

(C)



(D)



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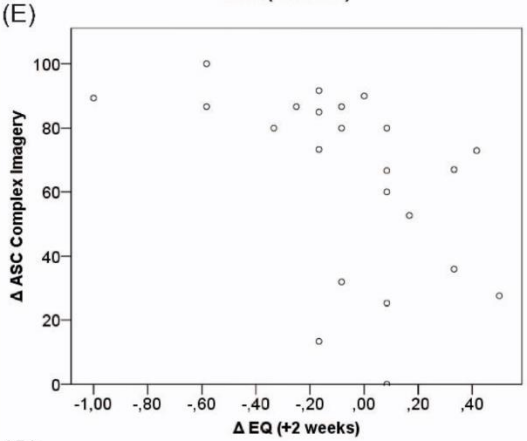
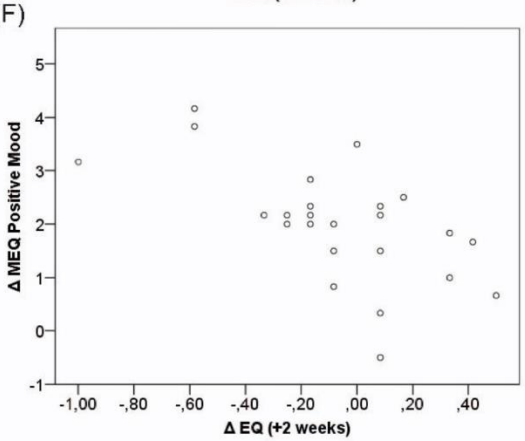


(F)



(G)

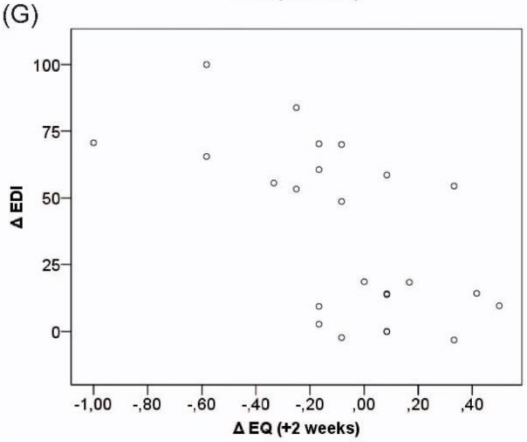


Figure S3. Scatterplots depicting the relationship between LSD-induced psychedelic experiences (ΔASC, ΔMEQ, ΔEDI), aberrant salience (ΔASI), and individual changes in mindfulness scale Decentering (ΔEQ) at 24 hours and 2 weeks after drug administration. Decentering at +24 hours (x-axis) was moderately positively correlated with (A) Disembodiment (ΔASC, y-axis; r_S=0.60, n=23, p=0.030) and (B) Transcendence of Time and Space (ΔMEQ, y-axis; r_S=0.56, n=24, p=0.048). In contrast, Decentering at +2 weeks (x-axis) was moderately negatively correlated with (C) Impending Understanding (ΔASI, y-axis; r_S=-0.65, n=24, p=0.006), (D) Insightfulness (ΔASC, y-axis; r_S=-0.65, n=23, p=0.008); (E) Complex Imagery (ΔASC, y-axis; r_S=-0.62, n=23, p=0.019); (F) Positive Mood (ΔMEQ, y-axis; r_S=-0.61, n=24, p=0.016); and (G) ego-dissolution (ΔEDI, r_S=-0.62, n=24, p=0.014; all p-values Bonferroni-corrected *post hoc* for multiple comparisons).
ASC, Altered States of Consciousness Questionnaire. MEQ, Mystical Experiences Questionnaire. EDI, Ego-Dissolution Inventory. ASI, Aberrant Salience Inventory. EQ, Experiences Questionnaire.

Supplemental References

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5. General Discussion

5.1. Condensation

This study aimed at examining the effects of low-dose LSD (50 µg) on healthy humans. One outstanding feature of this relatively low does is that is has been widely applied within psycholytic therapy in the last century (58) but not explored in modern studies with rigorous methodological designs. Overall, our study elicited a variety of results on different levels. We looked at perceptual, cognitive, emotional and behavioural effects under LSD and placebo. We examined time points before drug administration, during the peak, in the afterglow and mid-term. This variety of measurements allows for a comprehensive perspective on the effects of low-dose LSD and approach to the core of the "psychedelic mind" *per se*.

Nevertheless, this variety of measurements hampers the comparison between the diverse processes and gives rise to a range of new questions, based on the answers to the old questions. Are there similar effects of LSD on creativity in the mid-term and on cognition during drug the peak? When are mystical experiences and aberrant salience increased, during the intensity peak or during the post-peak phase with deep thoughts and suggestibility? Are there similar processes underlying the meaning enhancements in mind-wandering, creativity and the psychosis model? While these open questions remain to be explored in future studies, certain general observations can be made and conclusions can be drawn based on the present work.

LSD affected the basic default processes of the unintentionally and unawarely freely roaming mind up to the higher-order control processes of intentional and conscious convergent thinking and concept formation. LSD changed the subjective perception, inducing altered state of consciousness and psychedelic experience, and the objective behaviour, including semantic distances and creative content and techniques. LSD exerted remarkable effects during the drug peak but also during the sub-acute phase of this low dose. LSD decreased parameters related to structured, organized, rational thinking and increased others related to meaningful, associative, symbolic thinking.

Regarding the four explored domains of stream of thought, creativity, cognition and psychosis and therapy model, diverse facets of results emerged and attempts have been made to qualitatively resume these facets in the four articles presented in this thesis. The stream of thought was affected on several levels (mind-wandering; free association) over the course of time, with strongest effects at +2h and +4h. The variety of

results seem to reflect principally four facets of increased chaos, meaning, sensation and abstract thought. Creativity during drug peak was affected across diverse modalities and measurement approaches. Across all ratings, classifications and computations, the results seem to reflect three distinguishable phenomena of pattern break, disorganization and meaning. Cognition was affected the morning after drug administration, as measured by a comprehensive neuropsychological test battery. The results pointed to both "afterglow" and "hangover", with increased visual memory and verbal fluency and decreased cognitive flexibility. The LSD psychosis model and therapy model seemed both supported, with increases in aberrant salience and suggestibility. A connection between both models seemed to arise in mystical and ego-dissolution experiences, known to play an important role in psychotic experiences and psychedelic-assisted therapy.

Importantly, similarities between the four explored domains of stream of thought, creativity, cognition and the LSD models can also be observed. These emerged in the form of three main facets, namely chaos, meaning and sensation. The overall most pronounced chaotic facet was assessed within several measurements and time points. In the stream of thought, the chaotic facet was reflected by discontinuity of mind and less control over thought and most pronounced during drug peak (+2h). Similarly, creativity seemed characterized by a pattern break and disorganization, as measured by increased novelty and surprise and decreased utility, elaboration and convergent thinking after drug peak (+2.5h to +3.75h). The overall psychedelic experience was characterized by subjectively impaired control and cognition (ASC). Moreover, the cognitive flexibility to form, maintain and shift abstract concepts (WCST) was decreased the morning after LSD administration, indicating that the chaos and disorganization exerted influence beyond the acute effects, up to the next morning (+24h).

The most noticeable facet in terms of therapeutic implications certainly consists of meaning making. Increased meaning was found in the stream of thought, as reflected by deep thoughts, and strongest pronounced in the post-peak phase around +4h. Likewise, the creative productions in most tasks expressed meaningfulness, as reflected by symbolic thinking and ambiguity, although these were already pronounced near drug peak from +2.5h. In this sense, it might be interesting to explore whether symbolic thinking is more pronounced in the post-peak phase (around +4h), a finding that would further underpin the notion of a late therapeutic window. The notion of overall increased meaning over the LSD session is supported by subjective evaluations of the psychedelic experience by changed meaning of percepts (ASC) and of the psychotic experience by

increased significance (ASI). Along similar lines as an LSD-induced meaning is the central role of abstract stimuli for the LSD effects. While concrete stimuli evoked no effects in free association and few in creativity, abstract stimuli enhanced semantic distances in free association and novelty, surprise and semantic distances in creativity. Altogether, these findings suggest that LSD not only promotes meaning making and symbolic and abstract thought, but also exerts the clearest effects when stimulated by abstract content.

A less pronounced facet emerged in the form of sensation, which merely evoked medium effect sizes and arose for specific parameters, but was expressed over a variety of perceptual and behavioural measurements and time points. Specifically, the sensory facet was expressed by thoughts about smelling and hearing during mind-wandering (+2h), the use of sensation-related content in creative metaphors (+3.5h) and tactile suggestibility (CIS) (+5h). Moreover, imagery (ASC), synaesthesia (ASC) and a sharpening of senses (ASI) over the LSD session were experienced, altogether pointing to a consistent, multimodal phenomenon of medium extent over diverse domains.

Overall, the facets of chaos, meaning and sensation were observed in all domains, the stream of thought, creativity, cognition, psychedelic, therapeutic- and psychotic-like experiences. It is interesting to note that previous works mapped out similar aspects characterizing the psychedelic experience. For example, Masters and Houston hypothesized four major levels, namely a sensory, a recollective-analytic, a symbolic and an integral level (96, p. 110ff). Similar to our sensory facet, their sensory level is characterized by altered perceptions of the senses, the body, space and time. Similarities to our meaningful facet can be observed in the other three levels. The recollective-analytic level is characterized by analysing and having insights on personal problems and goals; the symbolic level is characterized by experiencing archetypal images and scenes representing the own life and allowing for personal growth; the integral level is characterized by profound, religious-like experiences of self-understanding and -transformation, mystical union and enlightenment. However, there seem to be no strong similarities with the chaotic facet. A form of chaos is described by Leuner, who characterized the earlier course of the psychedelic experience as a “stagnating-fragmented course” with psychotic-like, overwhelming and dissociated experiences (21, p. 80ff). This “extremely psychotic form” of experience is opposed to a later “quasi-normal form” and “continuous-scenic course” of experience with sensorial alterations, dreamlike and holistic experiences and a need for communication. Broadly, these two forms correspond

to our chaotic facet on the one hand and the meaningful and sensory facets on the other hand.

Taken these previous works and our results together, the psychedelic experience seems to reflect at least two main patterns which are quite paradoxical in nature. One pattern could be denominated as a "deconstructive" pattern characterized by the chaotic facet and effects of dissociation, disorganization and incoherence. The other could be designated as a "reconstructive" pattern characterized by the meaningful and sensory facets and effects of association, reconnection and significance attribution. **Figure 2** depicts an attempt to classify the principal findings of this study into the psychedelic patterns of *deconstruction* and *reconstruction*. Despite their paradoxicality, both patterns share a fundamental alteration of perceptual, cognitive, affective and behavioural resources. While the deconstructive pattern disrupts previously established concepts and processes (e.g. the self, rational thinking, mind-wandering about work or the past), the reconstructive pattern intensifies and realigns previously unrelated concepts and processes (e.g. deep thoughts, novel ideas, ambiguous and symbolic thinking, phonological fluency).

5.2. Mechanisms

Which mechanisms might underlie the LSD-induced *deconstruction* and *reconstruction*? To discuss this question, a variety of processes from the molecular to the brain connectivity level can be explored. This section will shed light on the potential neurochemical and neurophysiological processes underlying our findings within 1.) the stream of thought, 2.) creativity, 3.) cognition and 4.) the LSD models including psychotic, therapeutic and psychedelic experiences.

First, regarding the stream of thought, there might be an association between the chaotic, meaningful and sensory mind-wandering and the time-dependent neurotransmitter and brain network activity.

The chaotic facet combines with findings of disrupted cognitive functioning and disintegrated cortico-cortical networks, including the Central Executive Network (CEN), which are related to a prefrontal serotonin 2A (5-HT_{2A}) receptor activation (101–103). Moreover, the chaos might point to a disintegration of the brain's Default Mode Network (DMN), known to be activated during mind-wandering and disintegrated under psychedelics (104,105). In line with this, our findings of decreased Thoughts about Past and Planning correspond to previous findings of decreased mental time travel which

correlated with DMN disintegration under LSD (106). Moreover, the chaotic facet is time-dependent (from +2h to +6h) and strongest pronounced at drug peak, when also the DMN disintegration under psychedelics is observed. Based on these assumptions, the time course of the chaotic facet suggests that these cognitive and network disruptions might peak concurrently with subjective intensity around +2h and last until +6h.

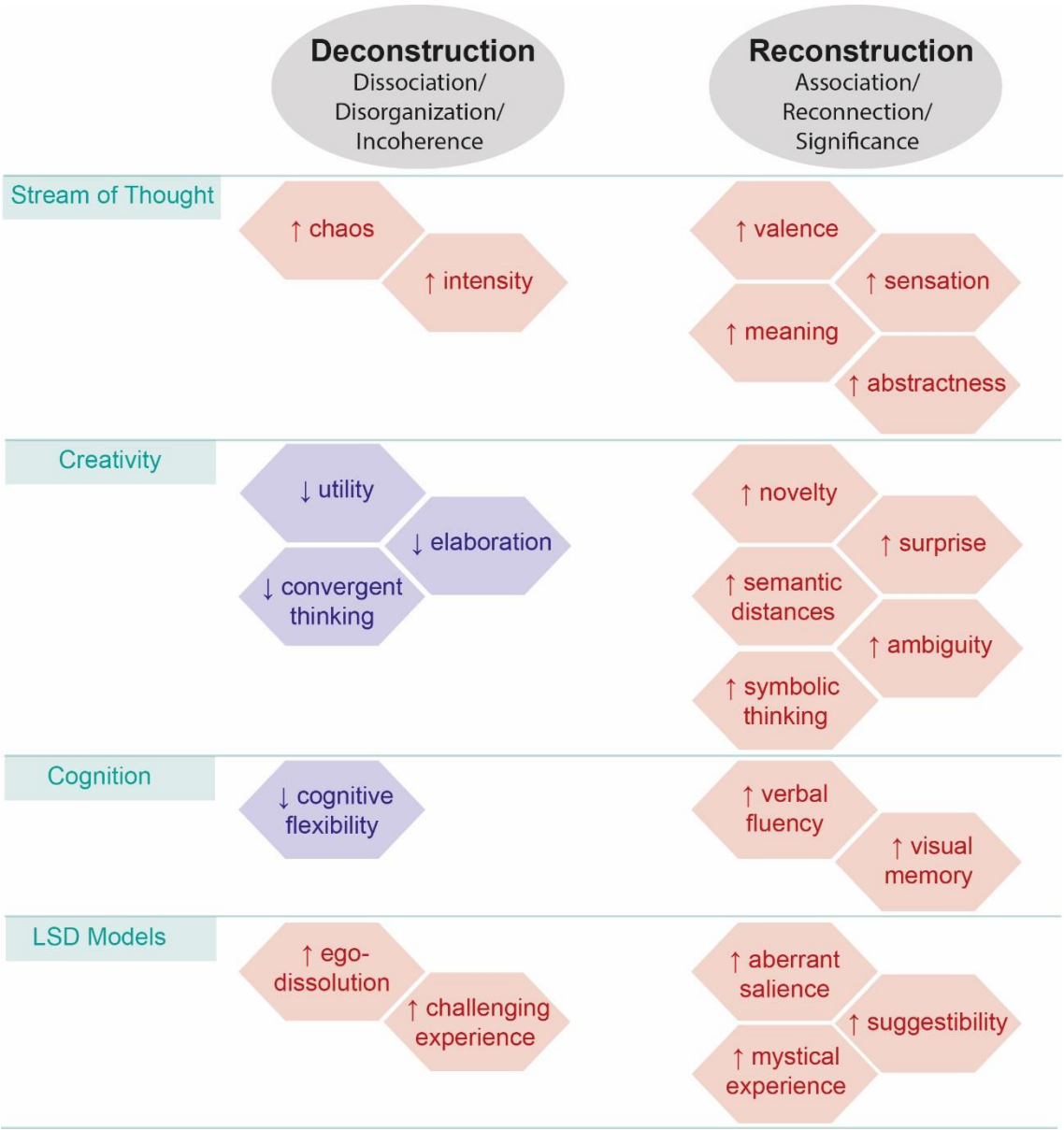

Figure 2. The effects of low-dose LSD (50 µg) on the domains of stream of thought, creativity, cognition and psychotic, therapeutic and psychedelic experiences. Within each domain, diverse increases (red) and decreases (blue) were observed under LSD compared to placebo. Over all domains, two contrasting patterns of *deconstruction* and *reconstruction* seemed to arise.

The meaningful facet is coherent with findings of aberrant salience and attribution of self-relevance to meaningful stimuli, which are possibly mediated by

dopaminergic activity in the striatum during the later time course of LSD (44,101,107–110). Consequently, the meaningful facet might represent this later dopaminergic phase peaking to a similar degree as the chaotic facet but later around +4h. In a similar vein, the abstract flow peaked at +4h. The effects depended on stimulus (abstract not concrete) and parameter (meaningful not chaotic), indicating that the abstract flow seems to reflect divergent but meaningful abstract-related thinking. Thus, the abstract flow might rely on similar mechanisms as the meaningful facet, including striatal dopamine during the post-peak phase.

The sensory facet is consistent with findings of increased thalamo-cortical functioning and synchronization of sensory networks which are mediated by glutamatergic and serotonergic projections (102). The sensory facet is less pronounced than the chaotic and the meaningful facet, indicating that the thalamo-cortical activation is less expressed and merely around +2h. Notably, the thalamus and the striatum form part of the salience network (SN), responsible for the integration of sensory input and relocation of attention to salient stimuli (111). This further strengthens the notion that the meaningful and the sensory facet belong to a common pattern of *reconstruction* with common cognitive and neurophysiological characteristics.

Based on these assumptions, our time-dependent measurements suggest that the glutamatergic-serotonergic thalamo-cortical action (sensory facet) peaks around +2h, while the dopaminergic striatal action (meaningful facet and abstract flow) peaks afterwards around +4h and the serotonergic cortico-cortical disruption (chaotic facet) remains pronounced until +6 h. Yet, these assumptions need to be explored in time-dependent, concurrent measurements of mind-wandering, neurotransmission and brain connectivity. Specifically, future studies should disentangle these processes by selectively blocking the 5-HT_{2A} receptors (ketanserin) and dopamine 2 (D_2) receptors (haloperidol) and put an emphasis on different components of abstract thinking, such as the pragmatic knowledge, reasoning schemes, metacognition and execution (112).

Second, regarding creativity, we might speculate about the cognitive mechanisms and brain activity underlying the phenomena of pattern break, disorganization and meaning.

The creative process can be divided at least into two stages of idea *generation* and *evaluation*. *Generation* is the production of novel ideas, associated with divergent thinking, suspended cognitive control and striatal and medial temporal activations

(12,113,114). *Evaluation* is the judgement of the usefulness of ideas, associated with convergent thinking and CEN and DMN activations (12,113).

In this light, our findings of an increased pattern break (increased novelty, surprise, originality, semantic distances) and increased meaning (ambiguity and symbolic thinking) suggest that the *generation* is improved, possibly related to striatal and medial temporal activations. On the other hand, the disorganization (decreased utility, convergent thinking, elaboration) suggests that the *evaluation* is impaired, possibly due to deactivations or disintegrations of CEN and DMN regions. Along the same lines are observations of psychedelic-induced increased striatal dopamine and medial temporal activity (110,115) and decreased frontal control and DMN activity (116,117). Interestingly enough, this is in line with the above discussed role of striatal dopamine for meaningful mind-wandering and CEN and DMN disintegrations for chaotic mind-wandering, strengthening the notion of common mechanisms underlying the LSD-induced *deconstruction* and *reconstruction*.

Third, regarding cognition, we can have a glimpse into possible mechanisms underlying the sub-acute LSD effects, in other words, the "afterglow" and "hangover".

As for the afterglow, we detected two phenomena, improvements in visual memory and verbal fluency, which seem to be unrelated processes underlain by different brain mechanisms (76). LSD improved visuospatial (OLMT) but not auditory-verbal (RAVLT) memory consolidation overnight. In line with this, visuospatial more than auditory-verbal memory consolidation is sleep-dependent (118). Visuospatial (vs. verbal) memory relies more on 5-HT_{2A} (vs. 5-HT_{1A}) receptors and the right (vs. left) hippocampus (118–122). Therefore, our findings might point to LSD-induced 5-HT_{2A} action supporting right hippocampal memory consolidation overnight.

Moreover, LSD facilitated the phonological but not semantic verbal fluency (VFT). This points to improved phonological search strategies, associated with CEN activity, including the dorsolateral prefrontal cortex (dlPFC) (74,123–125). On the other hand, there seemed to be no changes in semantic memory activation, associated with medial temporal activity, a finding in line with the unchanged semantic retrieval in the RAVLT. Moreover, LSD enhanced verbal but not design fluency (DFT), related to more left (vs. right) frontal activations (74,75)

As for the "hangover", LSD hampered cognitive flexibility, as measured by all types of errors and perseveration in the WCST. This finding might be related to 5-HT_{2A} receptor activity, known to mediate the cognitive flexibility impairments under

acute LSD (103), and to disturbed frontoparietal activity (dlPFC, anterior cingulate cortex (ACC), inferior parietal lobule (IPL)), known to be important for the WCST and related to attention and executive functions (126).

Overall, the increases in visual memory and phonological fluency and decreases in cognitive flexibility indicate modulations of memory, attentional and frontal control mechanisms. In line with this are psychedelic-induced acute and long-term changes in cognitive control, frontoparietal activity and frontal cortical structure (103,127–129). Notably, the frontal control was altered in different tasks (VFT and WCST) towards different directions, underlining the specificity of the LSD effect. Similarly, the 5-HT_{2A} receptors, known to be activated by psychedelics and important for executive functions, attention, learning and memory (122,130–133), might have played a specific role, with visual memory improvements and cognitive flexibility impairments.

Fourth, regarding the LSD models, we might try to bridge the gap between the psychedelic experience, therapy model and psychosis model from neurotransmitter to brain network level.

As for the psychedelic experience, the improved mood and altered state of consciousness under psychedelics are known to depend on 5-HT_{2A} receptor activation (109,134–136), especially in the ACC, a key region of the SN, and the medial PFC (mPFC), a key region of the DMN (137). Similarly, mystical experiences seem to rely on DMN disintegrations (mPFC, posterior cingulate cortex (PCC), parahippocampal cortex (PHC)) (138). Ego-dissolution is associated with 5-HT_{2A} receptor activity (62) and correlates with increased SN connectivity (insula) and changed DMN connectivity (decreased: PHC with retrosplenial cortex (RSC); increased: temporo-parietal junction (TPJ)) (139,140).

As for the therapy model, LSD-induced suggestibility might underlie extensive network changes, since suggestibility in the context of experimental and therapeutic hypnosis is related to increased SN-CEN connectivity (IPL, ACC, dlPFC), increased DMN-CEN connectivity (PCC/precuneus) and decreased thalamus-CEN connectivity (141). In line with this, these networks show altered connectivity under LSD, possibly related to 5-HT_{2A} receptor activity (102,140,142).

As for the psychosis model, aberrant salience, the aberrant assignment of meaning to stimuli, is related to striatal dopamine in healthy people, people with high schizotypy trait and people with high risk of psychosis (143–145). Similarly, dopamine seems to be important for the LSD effects, especially for increased meaning attribution

(107–110), overall pointing to a role of striatal dopamine for LSD-induced aberrant salience.

Overall, the effects of LSD on psychedelic, therapeutic and psychotic experiences seem to point to changes in two neurotransmitters (serotonin, dopamine) and three brain networks (DMN, SN, CEN). While the relationship between serotonergic activity and psychedelic experiences is well established, dopaminergic activity seems to be of particular relevance for the psychotic-related phenomenology. While the DMN seems to be essential for the psychedelic experiences (altered state of consciousness, mystical experiences, ego-dissolution), the CEN seem to play a fundamental role for the therapeutic effects (suggestibility) and the SN for the psychotic effects (aberrant salience).

This section intended to shed light on possible mechanisms underlying the LSD-induced *deconstruction* and *reconstruction*, as reflected within our four domains of stream of thought, creativity, cognition and psychedelic, therapeutic and psychotic experiences. Altogether, the chaotic facet (chaotic mind-wandering, disorganized creativity, subjectively impaired control, impaired cognitive flexibility), seems to be associated with a disintegrated DMN under the acute effects and a disintegrated CEN up to the next morning. The meaningful facet (meaningful mind-wandering, ambiguous and symbolic creativity, subjectively changed meaning of percepts, aberrant salience), seems to be associated with dopaminergic activity in the striatum. The sensory facet (sensory mind-wandering, sensory metaphors, sensory suggestibility, sharpening of senses, subjective imagery and synaesthesia) seems to be associated with altered thalamo-cortical connectivity and increased sensory network synchrony. Together with the considerations in the previous section, these observations point to cognitive, neurochemical and neurophysiological commonalities, with LSD-induced *deconstruction* being related to a disruption of concepts, processes and networks (DMN, CEN) and *reconstruction* being related to an intensification and realignment of concepts, processes and network activity (SN).

5.3. Implications

The results of this study might have implications on 1.) ontological, 2.) therapeutic and 3.) societal level.

First, the ontological implications comprise a more philosophical approach and technical view on the results with respect to our four domains in particular, the psychedelic state *per se* and human consciousness in general.

As for the four domains in particular, regarding the stream of thought, our results of changed mind-wandering and free association imply that measuring the freely wandering mind under psychedelics might yield insight into the resting brain, considering that the subjective and neurophysiological resting state seem to be closely intertwined (146,147), and that an integrative assessment has been largely neglected in psychedelic research (148). Together with the important role of the stream of thought and resting state brain function within perception, cognition, behaviour and clinical disorders (149–153), these insights will certainly allow for a more profound understanding of who we are and where we go.

Regarding creativity, our results of increased pattern breaking and meaning and decreased organization imply that LSD does not enhance but change creative behaviour, possibly in favour of creative *production* but not *evaluation*, in line with previous considerations (154). In other words, LSD makes thinking but not revising outside the box. The advantages and disadvantages of this double-edged sword have to be considered when exploring and applying psychedelics to boost creativity.

Regarding cognition, the results of enhanced memory and verbal fluency and impaired cognitive flexibility suggest that LSD induces changes beyond the acute effects, which are measurable even after a low dose and overnight recuperation and restructuration of the brain. This is in line with previous reports of sub-acute and long-term psychedelic effects on cognition (35,128,155,156) and implies the potential of LSD to modulate cognitive patterns more enduringly in healthy subjects and potentially clinical conditions.

Regarding the LSD models, our results of psychedelic, psychotic- and therapeutic-like experiences imply the utility of LSD to study the whole range of mental health, from “madness” to “healing”. This particularly includes mystical experiences, which might constitute a potential link between these two poles of mental health. By exploring the modulation of and connection between these poles, we might get an insight into the nature of mental health and its significance for consciousness.

As for the psychedelic state *per se*, the notion of LSD-induced *deconstruction* and *reconstruction* over diverse parameters and timepoints might point to common cognitive and neural processes underlying the LSD state. Consequently, the notion of

deconstruction and *reconstruction* might be applied to an even wider range of psychedelic-induced effects, such as attitudes, personality, age-related declines, clinical dysfunctions and brain connectivity, to derive predictions on possible short- and long-term effects. Importantly, the notion of *reconstruction* extends previous models of purely deconstructive, "chaotic", entropic effects of psychedelics on behaviour and brain (157–159) and adds a constructive, regenerative, creative aspect to the model of psychedelic mechanisms of at least equal importance. Moreover, the notion of *deconstruction* and *reconstruction* highlights the advantage of low psychedelic doses, in contrast to high doses and microdoses, to examine two contrasting poles and thereby the full range of possible effects and actions.

As for the human consciousness in general, the notion of LSD-induced *deconstruction* and *reconstruction* implies that consciousness is a transient state that can be altered in opposite directions. In contrast to non-drug-induced altered states of consciousness induced through, for example, yoga, hypnosis and holotropic breathwork, the advantage of drug-induced states is that we can regulate in a finely graded way the dose and, consequently, time course and variety of effects in a wide range of subjects, including unexperienced ones. Moreover, the notion of *reconstruction* implies that consciousness is not necessarily a default state that returns to "normal" after alteration, but might undergo changes through experiences, developments, learning, motivation and challenges in the course of life.

Overall, the ontological implications of our study demonstrate that psychedelics in general and low-dose LSD in particular can teach us about the human mind, the fragility of how we perceive the world and the chances of escaping our cage of consciousness and having a glimpse into what an alternative or "external reality" might look like.

Second, the therapeutic implications comprise a more application-oriented approach and practical view on the results and certainly elicit most interest in research, practitioners, media, economy and society.

Regarding the stream of thought, our results might open intriguing perspectives on the treatment of disorders which exhibit dysfunctional stream of thought patterns (12). Specifically, the chaotic facet of mind-wandering might support the disruption of dysfunctional patterns in depression, anxiety, obsessive compulsive disorder (OCD) and substance abuse, characterized by restraint attentional focus and excessive rumination (160,161). The meaningful facet might foster the creation of coping

mechanisms in post-traumatic stress disorder (PTSD) and grief (162,163). The sensory facet might promote introspection, body and self-awareness in somatosensory and eating disorders. Beyond that, the beneficial effects of free association on mental, emotional and physical health (164–167) might be further facilitated by an LSD-induced abstract flow. As for the time course, especially the post-peak effects around +4h point to a late therapeutic window, in which positive mood, chaos, meaning and abstract flow might foster a reduced constraint to share thoughts, a disruption of habitual thought patterns, an adoption of different perspectives and an elaboration of abstract topics in a therapeutic dialogue.

Regarding creativity, our results of increased pattern break, meaning and disorganization might provide new perspectives in the treatment of clinical conditions related to rigid or restrictive thinking and behaviour, such as OCD and autism (168). Moreover, the spontaneous generation of symbolic ideas points to a more universal therapeutic applicability, since symbolization has long been associated with psychotherapeutic processes (20,169). Symbolic representations are thought to express mental states (21,165), abstract ideas (166), the unconscious (172) and dreams (168), be of unintentional, unintelligible and highly problem-associated nature (173,174) and unveil unconscious material in a "psychodynamic experience", promoting self-understanding and self-transformation (59,100,174–176).

Regarding cognition, our results of sub-acute increases in visuospatial memory and phonological fluency might yield novel treatment perspectives in conditions related to concurrent memory and fluency impairments, such as brain injury, stroke, multiple sclerosis (MS), dementia and attention deficit hyperactivity disorder (ADHD) (74,76,177–180). Moreover, impairments in visuospatial memory are observed in OCD (181), while impairments in (phonological) fluency are observed in degenerative disorders such as Parkinson (182), pointing to future exploratory directions.

Regarding the LSD models, the results of increased ego-dissolution and mystical experiences might point to therapeutic mechanisms of low-dose LSD in psycholytic therapy, since these experiences are associated with beneficial effects in mood and substance use disorders, including depression, anxiety, alcohol and smoking addiction (183–187). The results of increased suggestibility indicate that therapeutic suggestions might exert effects even within low doses and post-peak phases, strengthening the notion of a late therapeutic window in psycholytic therapy. As for the modalities, suggestions might be most efficient in age regression (memory integration),

body perception (pain, somatization) and, potentially, olfaction/gustation (eating disorders). Broadly, these modalities are consistent with the increased sensory mind-wandering and sub-acute memory, pointing to distinguishable possible therapeutic mechanisms.

Overall, the therapeutic implications of our study point to the potential of psychedelics, particularly low-dose LSD, to exert beneficial effects in diverse mental health conditions by diverse mechanisms, including novel, meaningful and symbolic thinking at drug peak, suggestibility at post peak and ego-dissolution and mystical experiences in psychedelic-assisted psychotherapy in general, acutely intensified sensation in conditions related to somatization, body and self-awareness and sub-acutely improved memory and verbal fluency in clinical disorders and age-related cognitive decline.

Third, the societal implications comprise a more systemic approach and holistic view on the results, considering the turbulent history of LSD in society and its potential for treating some disorders and mimicking others.

Regarding creativity, the results of increased pattern break and meaning might point to the utility of psychedelics in professional sectors, not only in arts as prominently proclaimed in the last century (8,31), but also education, design, science, technology, entrepreneurship and economy, where creativity plays a crucial role and might be stimulated by psychedelics (22–25,32,33,168,188). Yet, our results of decreased organization highlight the limits of this potential, considering the important interplay between generation and evaluation for the final creative product. Therefore, application possibilities might lie more during phases of problem search, brain storming, idea generation, model creation and development of the product or service but not during the selection of the most significant problem or idea, model refinement and improvement of the product or service. Put differently, LSD might be called a “wonder drug” to boost creative insight but not enduring performance. Beyond that, special attention might be paid on the implications of LSD-induced symbolic thinking for society. Symbols transmit meaning and convey content in a non-rational, non-verbal, intuitive language and thereby affect thinking, reasoning and learning (189,190). Symbols guide our attention and orientation and thereby exert influence in almost any social field, including education, religion, art, literature, philosophy, politics and economy (191). This points to a variety of areas in which psychedelic-induced symbolic thinking might be applied to modulate our perception, cognition and behaviour.

Regarding cognition, the results of improved memory and fluency point to the general potential to apply psychedelics for sustained cognitive enhancement, although these enhancements might be weak, depend on specific cognitive processes and be accompanied by substantial impairments in other cognitive domains (cognitive flexibility). Therefore, together with its potential for creativity enhancement, the ethical, moral and societal implications of LSD as performance booster need to be highlighted, should these substances be promoted as tools for personal, professional and social optimisation. For example, this might pose risks of work-related or societal pressure to maximize individual health, well-being, work performance, competitivity and conformity as a productive, well-balanced member of society, similarly to the developments observed in Silicon Valley's tech elite (9,192).

Regarding the LSD models, the results of alterations of consciousness and mystical experiences under our low dose were partially higher than previously reported for 75, 100 or 200 µg LSD (3). These differences might demonstrate culture-specific effects since Brazilian populations are unexplored in modern LSD research and might differ from European populations (cf. 3). In fact, spirituality is deeply embedded in Brazilian culture and has undergone influences from indigenous, European, African and Asian cultures leading to syncretic religions including ayahuasca churches (193,194). This highlights the importance of cross-cultural research to better determine the influence of socio-cultural characteristics on psychedelic experiences. The most striking societal implications certainly lie in the notion of LSD-induced mystical experiences bridging the gap between the psychosis model and therapy model, pointing to the importance of mystical experiences for mental health. Therefore, a better exploration of the quality and quantity of mystical experiences might contribute to a better characterization of mental disorders in psychiatry and the health system, but also to a better understanding, awareness and self-empowerment of our mind and consciousness. In the same vein, the concept of a *Bewusstseinskultur* (consciousness culture) recently emerged from the unsolved Western problem of "how to deal properly with the brain" (192, p.13,193). The *Bewusstseinskultur* claims a stronger cultural integration of consciousness-related domains in our society, for example by educating techniques to expand consciousness (meditation, hypnosis), exploring the limits of consciousness (coma, artificial intelligence) and a public discourse on the human need for altered states of consciousness.

5.4. Limitations

Several limitations have to be considered when interpreting the results of this study. Regarding the design, robust blinding in psychedelic studies is notoriously difficult to achieve due to the characteristic psychedelic effects on perception and behaviour. Nevertheless, the low dose permitted that subjects and researchers remained unsure about the administered drug in some sessions, especially in subjects with few psychedelic experiences and if placebo was applied first. This highlights the advantage of unexperienced subjects and low doses for more efficient blinding, especially if compared to active placebos (197). The study design comprised many questionnaires and tasks applied before, during and after the LSD effects. This amount of measurements was experienced by several subjects as tedious (under placebo) and annoying (under LSD) and might have influenced the performance and motivation. Similarly, some subjects reported feeling the lack of music during the LSD effects, since they were not allowed to listen to music but strongly primed with musical background during previous psychedelic experiences such as ayahuasca rituals. The within-subjects design resulted in several effects of period (intensity, creativity, cognition) and order (intensity, cognition), indicating influences of learning, habituation and motivation and blurring the treatment effects. This underlines the importance of carefully prepared parallel test versions to minimize the interferences with the treatment.

Regarding the sample, we applied a non-probabilistic convenience recruitment, leading to a non-representative sample in terms of sex (male), ethnicity (Caucasian), education (high), income (high), religiosity (none) and drug use (high for cannabis and ayahuasca). Of note, this is the first modern LSD-study in a Brazilian population. Overall, the results (psychedelic experience) are comparable to those elicited in European populations (London, Basel, Zürich). The sample size was relatively small, possibly weakening the reliability of the results and masking existing effects (semantic distances, divergent thinking, creative content and techniques, sub-acute cognition). The LSD effects were elicited in healthy participants and need to be replicated in psychiatric conditions to evaluate whether the observed phenomena and potential therapeutic implications apply for patient populations as well.

Regarding the measurements, several tasks were translated by our team (CIS, ASI, ASC, creativity tasks) and split into two versions (CIS, creativity tasks, verbal fluency), some variables are newly created (semantic distances, creative special phenomena) and not previously validated (ARSQ single questions, PMT, PCT, MET),

which is why the psychometric properties and cultural adequacy of these measurements need to be explored. Certain results (suggestibility, cognition) were not corrected for multiple testing due to their exploratory nature. Several interpretations to condense the results remain qualitative (mind-wandering facets, creativity phenomena, cognitive afterglow/hangover) and need to be quantitatively determined. Some measurements do not reflect representative or comprehensive parameters of the explored areas (ASI for psychosis model, CIS for therapy model, creativity criteria) and need to be complemented by more direct measurements (psychotic symptoms, salience attribution task, well-being, real-world creativity). A high number of variables was measured within the domains (ARSQ, creativity tasks) to map the sparsely explored psychedelic effects in these areas. This increases the risk of false positives, despite correction for multiple comparisons, which is why these measurements should be interpreted in a more explorative manner. Finally, this study applied self-report and behavioural measurements, but the brain mechanisms underlying the effects need to be explored with neurochemical and neurophysiological measurements.

6. Conclusion

This is Brazilian's first systematic placebo-controlled, double-blind, human study on LSD. We explored the effects of low-dose LSD (50 µg) on healthy humans in a variety of domains, including the stream of thought, creativity, cognition and the LSD psychosis model and therapy model, and a variety of time points, including the peak, post-peak and sub-acute phase. The results suggest that LSD fundamentally changes the freely wandering mind towards chaos, meaning and sensation; gives rise to creative productions characterized by pattern break, meaning and disorganization; induces both an "afterglow" and "hangover" in sub-acute cognitive performance; and evokes psychedelic, therapeutic- and psychotic-like experiences, which might be linked by mystical experiences. Overall, these results seem to reflect two fundamental patterns of *deconstruction* and *reconstruction*, expressed over all domains and time points. The findings might point to ontological, therapeutic and societal implications. Specifically, the findings provide insights into the psychedelic state in particular and human consciousness in general, highlight new research paths on mechanisms of action and application possibilities in psychedelic-assisted therapy and hopefully contribute to a more realistic picture of this controversial substance in society, from psychiatry to politics and economics to public perception.

7. References

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8. Appendices

8.1. Appendix 1 – Informed Consent Form

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Os efeitos de um agonista do receptor 5-HT_{2A} na cognição de indivíduos saudáveis

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Você está sendo convidado a participar como voluntário de um estudo. Este documento, chamado Termo de Consentimento Livre e Esclarecido, visa assegurar seus direitos e deveres como participante e é elaborado em duas vias, uma que deverá ficar com você e outra com o pesquisador.

Por favor, leia com atenção e calma, aproveitando para esclarecer suas dúvidas. Se houver perguntas antes ou mesmo depois de assiná-lo, você poderá esclarecê-las com o pesquisador. Se preferir, pode levar para casa e consultar seus familiares ou outras pessoas antes de decidir participar. Se você não quiser participar ou retirar sua autorização, a qualquer momento, não haverá nenhum tipo de penalização ou prejuízo.

Justificativa e objetivos:

Doses baixas e médias de dietilamida do ácido lisérgico (LSD) foram utilizadas no passado para facilitar processo de psicoterapia através do que foi chamado de terapia psicolítica. Tais doses, que não configuram experiências psicodélicas (alucinógenas) completas com a substância, aparentemente poderiam ser capazes de aumentar a capacidade de criatividade durante o seu efeito e, após o término, a cognição e a capacidade de focar no momento atual (atenção plena, ou *mindfulness*, em inglês). A pesquisa com esta substância ficou parada durante muitos anos e agora vem sendo retomada no mundo. No entanto, ainda não há estudos que tenham investigado o efeito de doses baixas de LSD na memória, no raciocínio, na linguagem, na criatividade e na atenção plena (*mindfulness*). Este estudo tem como objetivo investigar tais efeitos em participantes saudáveis que já tenham tido experiências prévias com substâncias psicodélicas tais quais LSD, psilocibina (cogumelos 'mágicos'), DMT, ayahuasca, mescalina (peiote e San Pedro), etc.

Procedimentos:

Você será convidado a participar de duas sessões de coletas de dados com um intervalo de duas semanas entre as sessões. Nos dias das sessões, você deverá chegar às 8:00h, preencher alguns questionários e realizar alguns testes. Às 9:30h você irá receber, para ingestão, 50 microgramas de LSD ou um placebo inerte. Nem você nem os pesquisadores realizando o experimento saberão qual dose foi escolhida para cada sessão, que será determinada por sorteio.

A partir daí, uma série de medidas serão realizadas, incluindo a gravação de relatos seus a partir da estimulação de imagens, o preenchimento de um questionário por algumas vezes, após ficar cinco minutos com os olhos fechados, um teste de sugestionabilidade e testes de criatividade. Você deverá almoçar em torno de 13:40h (o

almoço será realizado no mesmo local do estudo e fornecido pela equipe de pesquisa), realizará mais alguns testes, gravará uma entrevista sobre a experiência e será dispensado em torno de 17:30h. Você deve combinar de voltar para casa acompanhado e não dirigir.

No dia seguinte, vinte e quatro horas após a administração da substância, você deverá chegar às 8:00h novamente, preencher alguns questionários e realizar algumas testagens neuropsicológicas, incluindo testes de memória, atenção, raciocínio, etc. e será dispensado em torno de 10:15h.

Na segunda sessão, você receberá a substância que não recebeu anteriormente, ou seja, se você recebeu LSD na primeira sessão, receberá o placebo inerte na segunda sessão, e vice versa. Os testes e atividades serão os mesmos ou equivalentes, durando o mesmo tempo e sendo liberado na mesma hora e com as mesmas condições.

Algumas das atividades acima mencionadas serão gravadas por áudio e, em alguns poucos testes, por vídeo. Ao assinar esse termo, você concorda com tais gravações. Esses materiais não serão divulgados em hipótese alguma. Caso algum trecho da sua entrevista seja citado em artigo científico oriundo deste estudo, sua identidade será mantida em sigilo e não será revelada nenhuma informação que permita a sua identificação.

Desconfortos e riscos:

Você **não** deve participar deste estudo se se enquadrar em quaisquer das situações a seguir: a) presença sintomas psiquiátricos ou histórico pessoal de transtornos psiquiátricos diagnosticados; b) presença de histórico familiar imediato de transtornos psicóticos; c) histórico de intercorrência grave (transtorno mental, internação psiquiátrica ou necessidade de atendimento em pronto-socorro) induzida por experiência com psicodélico; d) presença de doenças cardíaca ou qualquer condição médica que torne você inapto(a) a participar do estudo; e) gravidez; f) uso problemático de álcool ou outras drogas; g) uso de medicamentos psiquiátricos ou inibidores de monoaminoxidase. Estes itens serão investigados por avaliação médica competente.

Participando deste estudo você está sujeito a alguns estados mentais desagradáveis ou patológicos associados ao uso do LSD. Poderá haver sintomas e sinais de ansiedade, tanto do ponto de vista psicológico quanto físico, embora estes sejam provavelmente transitórios e fáceis de manejar devido às doses relativamente baixas que serão utilizadas. No caso do LSD, embora remoto, por se tratar de uma dose baixa, há o risco do aparecimento de sintomas psicóticos. Como se trata de dosagem única e baixa, o risco do desenvolvimento de quadros psiquiátricos permanentes é considerado baixo, porém não pode ser completamente descartado. Da mesma forma, é pouco provável que você venha a apresentar um quadro de dependência ou abuso de drogas devido à participação neste projeto de pesquisa. Ainda assim, você deve levar em consideração que esse risco pode estar presente, e não deve participar desta pesquisa se achar que está sob risco de uso abusivo de drogas. Em caso de qualquer desconforto ou problema de saúde você receberá acompanhamento médico.

Também contaremos com a sua paciência e atenção para responder os questionários utilizados na pesquisa, embora você não seja obrigado a respondê-los. Cada bateria de questionários leva um certo tempo para ser respondido e isso exige dedicação, o que para algumas pessoas pode ser desconfortável. Além disso, o conteúdo dos

questionários pode lhe fazer refletir sobre a sua vida e o seu bem-estar, o que pode ser um pouco incômodo para algumas pessoas.

Benefícios:

Não estão previstos benefícios diretos a você, embora não possa ser descartada uma sensação de empatia e bem-estar transitória causada pelo uso do LSD que é relatada na literatura de psicoterapia com doses psicolíticas. Do ponto de vista científico, o estudo poderá trazer benefícios na compreensão da ação do LSD e de seu potencial uso para o aumento da performance cognitiva ou em futuras terapias assistidas com esta substância.

Acompanhamento e assistência:

Durante todo o período do estudo e após o encerramento ou interrupção da pesquisa, você terá acesso aos pesquisadores responsáveis pelo estudo, que estarão à disposição para esclarecer dúvidas e conversar sobre a pesquisa. Caso sejam detectadas situações que indiquem a necessidade de uma intervenção médica, psicológica ou psicossocial, você será informado adequadamente e orientado pelos pesquisadores para cuidados adequados. No item "Contato" abaixo você encontrará o telefone da pesquisadora principal e do orientador deste projeto, e que estarão disponíveis para acolher suas demandas causadas pelo projeto a qualquer momento.

Sigilo e privacidade:

Você tem a garantia de que sua identidade será mantida em sigilo e nenhuma informação será dada a outras pessoas que não façam parte da equipe de pesquisadores. Na divulgação dos resultados desse estudo, seu nome não será citado. O vídeo e o áudio de suas entrevistas e gravações serão descartados após a publicação dos resultados da pesquisa ou após cinco anos de sua gravação, o que acontecer antes.

Ressarcimento e Indenização:

Você tem direito a receber ressarcimento pelo deslocamento de sua casa até a Faculdade de Ciências Médicas e para o retorno em cada uma das vezes que comparecer para participar neste estudo. A equipe de pesquisa arcará com os custos da alimentação durante a execução do protocolo. Você terá garantia do direito a indenização diante de eventuais danos decorrentes da pesquisa.

Contato:

Em caso de dúvidas sobre o estudo, você poderá entrar em contato com Isabel Wiessner pelo telefone telefone (19) 99397-0935 e o email isabel.wiessner@gmail.com ou com Luís Fernando Tófoli pelo telefone (19) 99988-7663 e o email lftofoli@gmail.com. Em caso de denúncias ou reclamações sobre sua participação no estudo, você pode entrar em contato com a secretaria do Comitê de Ética em Pesquisa (CEP): Rua Tessália Vieira de Camargo, 126, CEP 13083-887, Campinas–SP, telefone (19)3521-8936, fax (19)3521-7187, e-mail cep@fcm.unicamp.br.

Consentimento livre e esclarecido:

Após ter sido esclarecimento sobre a natureza da pesquisa, seus objetivos, métodos, benefícios previstos, potenciais riscos e o incômodo que esta possa acarretar, aceito participar:

Nome do(a) participante: _____

_____ Data: ____/_____/_____.

(Assinatura do/a participante)

Responsabilidade do(a) Pesquisador(a):

Asseguro ter cumprido as exigências da resolução 466/2012 CNS/MS e complementares na elaboração do protocolo e na obtenção deste Termo de Consentimento Livre e Esclarecido. Asseguro, também, ter explicado e fornecido uma cópia deste documento ao participante. Informo que o estudo foi aprovado pelo CEP perante o qual o projeto foi apresentado. Comprometo-me a utilizar o material e os dados obtidos nesta pesquisa exclusivamente para as finalidades previstas neste documento ou conforme o consentimento dado pelo participante.

_____ Data: ____/_____/_____.

(Assinatura do/a pesquisador/a)

9. Annexes

9.1. Annex 1 – Ethics Committee Approval

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PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Os efeitos de um agonista do receptor 5-HT2A na cognição de indivíduos saudáveis

Pesquisador: Isabel Wiessner
Área Temática:
Versão: 1
CAAE: 04179918.2.0000.5404
Instituição Proponente: FACULDADE DE CIÊNCIAS MÉDICAS - CEP/CHS
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.096.823

Apresentação do Projeto:
INTRODUÇÃO:
1. HistóricoOs receptores 5-HT2A têm um papel importante em processos cognitivos, como aprendizagem (Harvey, 2003), consolidação de memória (Wingen et al., 2007b), atenção e controle motor (Wingen et al., 2007a), mas também estão envolvidos na depressão e na ação terapêutica de antidepressivos (Eison & Mullins, 1995). Substâncias psicodélicas, como a psilocibina, mescalina ou N,N-dimetiltriptamina (DMT), têm uma ação agonista principal aos receptores 5-HT2A (Vollenweider et al., 2007; Smith et al., 1998; Preller et al., 2018). Dentre os agonistas clássicos deste receptor, a substância mais potente é a dietilamida do ácido lisérgico (do alemão: Lysergsäurediethylamid – LSD), um produto semissintético derivado do fungo Claviceps purpurea (Passie et al., 2008). Logo após a descoberta de suas propriedades psicodélicas em 1943, o LSD e outras substâncias psicodélicas foram investigadas em termos do seus efeitos na cognição, emoção, percepção do ego e potencial terapêutico, principalmente no tratamento de ansiedade e depressão associadas a estágios terminais de câncer, alcoolismo e os transtornos denominados antigamente como “neuroses” (Passie et al., 2008; Das et al., 2016). Os resultados promissores desses estudos indicavam que o LSD e outros agonistas 5-HT2A poderiam ser administrados de forma segura em contextos controlados e que era clinicamente útil no tratamento de variadas condições psiquiátricas (Gasser, 2007; Tylš et al., 2014). Porém, no final dos anos 60, as substâncias psicodélicas foram proibidas em resposta ao crescente movimento político de

Endereço: Rua Tessália Vieira de Camargo, 126
Bairro: Barão Geraldo **CEP:** 13.083-887
UF: SP **Município:** CAMPINAS
Telefone: (19)3521-8936 **Fax:** (19)3521-7187 **E-mail:** cep@fcm.unicamp.br

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1269459.pdf	06/12/2018 15:48:26		Aceito
Projeto Detalhado / Brochura Investigador	Projeto_5HT2A.pdf	06/12/2018 15:13:41	Isabel Wiessner	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_5HT2A.pdf	06/12/2018 14:53:03	Isabel Wiessner	Aceito
Folha de Rosto	Folha_de_Rosto_assinada_Projeto_5HT2A.pdf	06/12/2018 00:18:17	Luís Fernando Tófoli	Aceito
Outros	Comprovante_de_vinculo_com_UNICAMP.pdf	03/12/2018 18:54:38	Isabel Wiessner	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

CAMPINAS, 20 de Dezembro de 2018

Assinado por:
Renata Maria dos Santos Celeghini
(Coordenador(a))

9.2. Annex 2 – Editorial Authorization for Article 1 (LSD and Stream of Thought)

Gmail **Isabel Wiessner <isabel.wiessner@gmail.com>**

Journalpermissions <journalpermissions@springernature.com> 16 November 2021 at 08:54
To: "isabel.wiessner@gmail.com" <isabel.wiessner@gmail.com>
Cc: SNCS Author Support <authorsupport@springernature.com>

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9.3. Annex 3 – Editorial Authorization for Article 2 (LSD and Creativity)

Gmail **Isabel Wiessner <isabel.wiessner@gmail.com>**

RP-6803 Republication of article in my doctoral thesis
3 messages

Craig Myles <permissions@sagepub.com> 6 January 2022 at 13:14
Reply-To: rights.permissions@sagepub.com
To: isabel.wiessner@gmail.com

———————
Reply above this line.

Craig Myles commented:

Dear Isabel Wießner,

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9.4. Annex 4 – Editorial Authorization for Article 3 (LSD and Cognition)

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LSD, afterglow and hangover: Increased episodic memory and verbal fluency, decreased cognitive flexibility

Corresponding author Mrs. Isabel Wießner
E-mail address isabel.wiessner@gmail.com
Journal European Neuropsychopharmacology
Our reference NEUPSY12166
PII S0924-977X(22)00124-9

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Grant numbers: 001

Conselho Nacional de Desenvolvimento Científico e Tecnológico
Grant numbers: 308775/2015-5, 408145/2016-1

State of Sao Paulo Research Foundation
Grant numbers: 2013/07699-0, 2014/10068-4

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9.5. Annex 5 – Editorial Authorization for Article 4 (LSD, Madness and Healing)

Gmail **Isabel Wiessner <isabel.wiessner@gmail.com>**

Inclusion of article in doctoral thesis

4 messages

Isabel Wiessner <isabel.wiessner@gmail.com> 11 November 2021 at 10:25
To: authorcontracts_journals@cambridge.org

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