

Abigail Elizabeth Calder

**Effects of Psychedelics on
Markers of Neuroplasticity in
Humans**

Faculty of Science and Medicine

DOI : <https://doi.org/10.51363/unifr.sth.2026.073>

Abigail Elizabeth Calder  <https://orcid.org/0000-0001-9528-404X>

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Department of Medicine
University of Fribourg (Switzerland)

**Effects of Psychedelics on Markers
of Neuroplasticity in Humans**

THESIS

presented to the Faculty of Science and Medicine of the University of Fribourg
(Switzerland) in consideration for the award of the academic grade of
Doctor of Philosophy in Medical Sciences

by

Abigail Elizabeth Calder

from

Rock Island, IL, United States of America

Thesis No: 8158
UniPrint
2026

Accepted by the Faculty of Science and Medicine of the University of Fribourg
(Switzerland) upon the recommendation of Prof. Boris Quednow and Prof. Gregor Rainer.

Fribourg, 22 January 2026

Thesis supervisor



Prof. Gregor Hasler

Dean



Prof. Michael Walch

Any man could, if he were so inclined, be the sculptor of his own brain.

- Santiago Ramón y Cajal

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Summary

A growing number of studies suggest that serotonergic psychedelics, including lysergic acid diethylamide (LSD), can rapidly and lastingly stimulate various aspects of neuroplasticity. Neuroplasticity is the nervous system's fundamental ability to reorganize itself in order to adapt to its environment, and it involves both changes in brain structure and changes in how the brain functions. It is also fundamental for learning in the broadest sense. Drugs which stimulate neuroplasticity may have important clinical uses, and promising data from animal studies has given psychedelics the moniker of *psychoplastogens* for their rapid, circuit-specific, and lasting effects on neuroplasticity. However, data in humans is scarcer due to the relative difficulty of measuring neuroplasticity non-invasively. It remains unclear how psychedelics impact neuroplasticity in humans and, if they do, what this might mean. The aim of this thesis is to investigate whether psychedelics, and particularly the potent psychoplastogen LSD, can stimulate neuroplasticity in humans. It consists of three papers exploring this question from different angles.

The first paper (Chapter II) reviews existing evidence that psychedelics enhance neuroplasticity as preparation for conducting a study in humans. We aimed for a nuanced examination of the evidence broken down into several key questions: *Which* aspects of neuroplasticity respond to psychedelics? *How* do psychedelics impact neuroplasticity? *Where* in the brain does this occur, *what dose* is required, *how long* does it last – and finally, what does it *mean*? We conclude that some aspects of neuroplasticity (e.g. synaptogenesis) are more reliably enhanced after psychedelics than others (e.g. neurogenesis), and that this appears to largely depend on 5-HT_{2A} receptor signaling cascades. The neocortex appears to be the most strongly affected, and larger doses are probably more effective. Increases in neuroplasticity may appear within hours and last for a week or more, depending on substance, dose, and outcome measure. Finally, we discuss whether enhanced neuroplasticity might explain some of psychedelics' lasting effects in humans, as well as the implication that enhanced neuroplasticity could make people more sensitive to their environments – for better or worse.

The second paper (Chapter III) is a pre-registered systematic review and meta-analysis evaluating the effects of various psychoplastogens, including LSD, ketamine, and others, on peripheral levels of brain-derived neurotrophic factor (BDNF) in humans. BDNF is the most commonly used marker of neuroplasticity in human studies with psychedelics, and we also intended to use it in our study of LSD (Chapter IV). However, previous studies had observed conflicting results and its merits as a biomarker were unclear. We used an exceptionally

thorough search strategy to identify relevant studies (N = 29) and analyzed all available effect sizes (N = 104). We included all available information on drug, dose, blood fraction, and measurement timepoint, as well as participant characteristics and aspects of study design. There was no significant effect of psychoplastogens on BDNF overall, as well as no effect for serotonergic psychedelics or ketamine when analyzed individually. The strongest moderators were related to study design such that studies with more rigorous designs reported smaller effect sizes for BDNF. We discuss several possible explanations for these findings and conclude that if psychedelics enhance neuroplasticity in humans, it will likely not be seen in peripheral BDNF.

The third paper (Chapter IV) forms the core of this thesis and consists of a randomized, placebo-controlled crossover trial investigating the effects of 100µg LSD on neuroplasticity and motor learning up to one week after dosing in healthy subjects (N = 45). We used a multimodal approach to assess neuroplasticity and its possible consequences, combining neurophysiological markers with a motor learning task and measurements of perceived stress and cognitive flexibility. Neurophysiological markers of neuroplasticity included auditory tetanization with electroencephalography (EEG) to measure plasticity in the sensory domain, a transcranial magnetic stimulation (TMS) protocol to measure motor cortical excitability and plasticity, and peripheral BDNF. A key, novel finding from this study is that LSD enhanced motor learning one day after dosing, specifically *offline* motor learning during rest, consistent with an effect of LSD on synaptic plasticity. LSD also decreased perceived stress and increased some aspects of cognitive flexibility one week after dosing. Neurophysiological measures had evident limitations as markers of neuroplasticity, but EEG measures showed that LSD modulated auditory processing both acutely and post-acutely. This study is also the first to demonstrate that LSD acutely increases corticomotor excitability measured with TMS.

Together, these research projects form a well-rounded investigation of the effects of psychedelics on neuroplasticity in humans. Behavioral evidence, particularly from the motor learning task but also from measures of cognitive flexibility and stress, was consistent with the theory that LSD enhances cortical neuroplasticity for a short time even after acute drug effects subside. Finding neurophysiological evidence for enhanced neuroplasticity proves more challenging, but this thesis offers a critical contribution to the discussion of how best to measure it in human subjects. The promising findings on psychedelics and learning open up an exciting and as-yet barely explored avenue of research with many conceivable practical and clinical implications.

Zusammenfassung

Eine zunehmende Zahl von Studien deutet darauf hin, dass serotonerge Psychedelika, darunter Lysergsäurediethylamid (LSD), verschiedene Dimensionen der Neuroplastizität rasch und nachhaltig stimulieren können. Unter Neuroplastizität versteht man die grundlegende Fähigkeit des Nervensystems, sich neu zu organisieren und so an seine Umwelt anzupassen. Sie umfasst sowohl strukturelle Veränderungen des Gehirns als auch Modifikationen seiner Funktionsweise und bildet zugleich die Grundlage für Lernen im weitesten Sinne. Substanzen, die die Neuroplastizität fördern, besitzen daher ein hohes klinisches Potenzial. Vor allem tierexperimentelle Befunde sind vielversprechend und haben Psychedelika aufgrund ihrer schnellen, schaltkreisspezifischen und anhaltenden Wirkungen den Namen *Psychoplastogene* eingetragen. Im Menschen sind entsprechende Nachweise bislang jedoch seltener, da sich Neuroplastizität nicht-invasiv nur schwer erfassen lässt. Ungeklärt ist folglich, in welcher Weise Psychedelika die Neuroplastizität beim Menschen beeinflussen und welche Bedeutung sich daraus ergeben könnte. Ziel der vorliegenden Dissertation ist es, zu untersuchen, ob Psychedelika – und insbesondere das potente Psychoplastogen LSD – die Neuroplastizität beim Menschen steigern können. Die Arbeit umfasst drei Studien, die diese Fragestellung aus unterschiedlichen Perspektiven beleuchten.

Der erste Beitrag (Kapitel II) gibt einen Überblick über die bisherige Evidenz zur durch Psychedelika verstärkten Neuroplastizität und dient als Vorbereitung einer Humanstudie. Die Befunde wurden differenziert entlang zentraler Fragen aufgearbeitet: *Welche* Aspekte der Neuroplastizität sprechen auf Psychedelika an? *Wie* wirken sie? *Wo* im Gehirn zeigen sich Veränderungen, *welche Dosierung* ist erforderlich, *wie lange* halten die Effekte an – und schließlich: *Was bedeutet* das? Die Auswertung legt nahe, dass einzelne Facetten der Neuroplastizität (etwa die Synaptogenese) zuverlässiger gesteigert werden als andere (wie die Neurogenese) und dass diese Effekte im Wesentlichen auf Signalwege des 5-HT_{2A}-Rezeptors zurückzuführen sind. Am stärksten betroffen scheint der Neokortex, wobei höhere Dosen wahrscheinlich wirksamer sind. Erste Veränderungen lassen sich bereits nach Stunden beobachten und können, abhängig von Substanz, Dosis und Messparametern, eine Woche oder länger anhalten. Abschließend wird diskutiert, inwieweit eine erhöhte Neuroplastizität die langfristigen Wirkungen von Psychedelika beim Menschen erklären könnte, und ob sie Menschen zugleich empfänglicher für Umwelteinflüsse macht – im positiven wie im negativen Sinn.

Der zweite Beitrag (Kapitel III) präsentiert eine vorregistrierte systematische Übersichtsarbeit mit Meta-Analyse, in der die Effekte verschiedener Psychoplastogene – darunter LSD, Ketamin und andere – auf periphere Konzentrationen des *brain-derived neurotrophic factor* (BDNF) beim Menschen untersucht werden. BDNF ist in Humanstudien der am häufigsten eingesetzte Marker für Neuroplastizität und sollte auch in unserer eigenen LSD-Studie (Kapitel IV) verwendet werden. Frühere Arbeiten hatten jedoch widersprüchliche Ergebnisse geliefert, sodass der Wert dieses Biomarkers unklar blieb. Mithilfe einer besonders umfassenden Suchstrategie wurden 29 relevante Studien identifiziert und insgesamt 104 Effektstärken analysiert. Dabei flossen sämtliche Informationen zu Substanz, Dosierung, Blutfraktion, Messzeitpunkt sowie zu Teilnehmermerkmalen und Studiendesign ein. Es zeigte sich kein signifikanter Gesamteffekt von Psychoplastogenen auf BDNF, ebenso wenig ein Effekt für serotonerge Psychedelika oder Ketamin in der Einzelanalyse. Die deutlichsten Moderatoren betrafen das Studiendesign: Je methodisch stringenter die Studien angelegt waren, desto kleiner fielen die berichteten Effekte aus. Als Fazit lässt sich ziehen, dass sich eine mögliche Steigerung der Neuroplastizität durch Psychedelika beim Menschen vermutlich nicht im peripheren BDNF abbildet.

Der dritte Beitrag (Kapitel IV) bildet den Kern dieser Arbeit und umfasst eine randomisierte, placebokontrollierte Cross-over-Studie zur Untersuchung der Wirkungen von 100µg LSD auf Neuroplastizität und motorisches Lernen bis zu einer Woche nach Einnahme bei gesunden Probandinnen und Probanden (N = 45). Zum Einsatz kam ein multimodaler Ansatz, der neurophysiologische Marker mit einer motorischen Lernaufgabe sowie Messungen von wahrgenommenem Stress und kognitiver Flexibilität kombinierte. Zu den neurophysiologischen Indikatoren der Neuroplastizität zählten eine auditive Tetanisierung mit Elektroenzephalographie (EEG) zur Erfassung sensorischer Plastizität, ein Protokoll mit transkranieller Magnetstimulation (TMS) zur Bestimmung der motorisch-kortikalen Erregbarkeit und Plastizität sowie peripheres BDNF. Ein zentrales und neuartiges Ergebnis der Studie besteht darin, dass LSD das motorische Lernen einen Tag nach Einnahme verbesserte – insbesondere das *offline* Lernen in Ruhephasen – und damit womöglich auf synaptische Plastizitätsprozesse verweist. Darüber hinaus verringerte LSD den empfundenen Stress und steigerte bestimmte Aspekte der kognitiven Flexibilität noch eine Woche nach Einnahme. Die neurophysiologischen Maße erwiesen sich zwar als nur begrenzt geeignet, Neuroplastizität zuverlässig abzubilden, doch EEG-Messungen zeigten, dass LSD die auditive Verarbeitung sowohl akut als auch postakut modulierte. Zudem konnte erstmals belegt werden, dass LSD die kortikomotorische Erregbarkeit, gemessen mittels TMS, akut erhöht.

Insgesamt ergibt sich aus diesen Forschungsarbeiten eine facettenreiche Untersuchung der Wirkungen von Psychedelika auf die Neuroplastizität beim Menschen. Verhaltensevidenz – insbesondere aus der motorischen Lernaufgabe, aber auch aus Messungen zu kognitiver Flexibilität und Stress – stützt die Annahme, dass LSD die kortikale Neuroplastizität kurzfristig erhöhen kann, selbst nachdem die akuten Substanzeffekte abgeklungen sind. Schwieriger gestaltet sich der Nachweis neurophysiologischer Korrelate, doch liefert die vorliegende Dissertation einen wichtigen Beitrag zur methodischen Diskussion, wie sich Neuroplastizität beim Menschen adäquat erfassen lässt. Die vielversprechenden Befunde zum Zusammenhang zwischen Psychedelika und Lernen eröffnen ein spannendes und bislang kaum erforschtes Feld mit vielfältigen praktischen wie klinischen Implikationen.

Contributions

I contributed as the lead author of all publications presented in this thesis. With the help and supervision of Prof. Gregor Hasler, I led the conceptualization, data collection, analysis, and manuscript writing of all three papers. Additionally, the second paper (Chapter III) was completed with the assistance of Dr. Adrian Hase in data collection, analysis, and manuscript editing. The third paper (Chapter IV) was completed with the support of various other research group members, students, and interns who assisted with data collection and analysis. All work was conducted in the Molecular Psychiatry Lab of Prof. Gregor Hasler at the University of Fribourg, Switzerland.

List of abbreviations

5-HT2A(R)	Serotonin 2A (receptor)
5-HT1A(R)	Serotonin 1A (receptor)
5-MeO-DMT	5-methoxy N,N-dimethyltryptamine
5D-ASC	5-Dimensional Altered States of Consciousness Questionnaire
ACC	Anterior cingulate cortex
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APB	Abductor pollicis brevis
BASEC	Business Administration System for Ethics Committees
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BPD	Bipolar depression
CFI	Cognitive Flexibility Inventory
CONSORT	Consolidated Standards of Reporting Trails
DMT	N,N-dimethyltryptamine
DOI	2,5-dimethoxy-4-iodoamphetamine
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalography
ELISA	Enzyme-linked immunosorbent assay
ERP	Event-related potential
FDR	False discovery rate
GABA	Gamma-aminobutyric acid
HPPD	Hallucinogen persisting perceptual disorder
IEG	Immediate early gene
LTD	Long-term depression
LTP	Long-term potentiation
LSD	Lysergic acid diethylamide
mBDNF	Mature brain-derived neurotrophic factor
MDD	Major depressive disorder
MDMA	3,4-Methylenedioxymethamphetamine
MEP	Motor-evoked potential
MEQ	Mystical Experience Questionnaire
mRNA	Messenger ribonucleic acid
mTOR	Mammalian target of rapamycin
N1	Negative event-related potential occurring ca. 100ms after stimulus onset
NMDA	N-methyl-D-aspartate
OCD	Obsessive-compulsive disorder
P2	Positive event-related potential occurring ca. 200ms after stimulus onset
PAS	Paired associative stimulation
PET	Positron emission tomography
PFC	Prefrontal cortex
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Perceived Stress Scale

ROBINS-I	Risk Of Bias In Non-randomised Studies - of Interventions
RPM	Rotations per minute
SAE	Serious adverse event
SCID-5-CV	Structured Clinical Interview for DSM-5, Clinician Version
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SMD	Standardized mean difference
SPSI	Swiss Psychedelic Side Effects Inventory
ST	Sensory tetanization
SV2A	Synaptic vesicle glycoprotein 2A
T	Time of drug intake
TMS	Transcranial magnetic stimulation
TRD	Treatment-resistant depression
TrkB	Tropomyosin receptor kinase B

Chapter I General introduction

We have all sometimes wished it was easier to change. Sometimes we feel stuck with stubborn bad habits or recurring negative thoughts, or we fail to learn something as quickly or as well as we would like. But what if we could change our ability to change – and quickly, perhaps even within hours? This provocative question has inspired two decades of research into psychedelic drugs and their purported effects on neuroplasticity, though more questions than answers still remain. The present doctoral thesis examines the theory that psychedelics enhance neuroplasticity in detail and encompasses a search for evidence of this in humans.

The focus of this dissertation is a study of the effects of the psychedelic drug lysergic acid diethylamide (LSD) on neuroplasticity in human subjects (Chapter IV). As preparation for this study, we reviewed the existing literature establishing the theory that LSD and other psychedelics enhance certain aspects of neuroplasticity (Chapter II). Additionally, we conducted a systematic review and meta-analysis examining the effects of psychedelics on peripheral levels of brain-derived neurotrophic factor (BDNF), a common marker of neuroplasticity in human studies (Chapter III). In this first chapter, I will lay the groundwork for these studies and describe how we chose to investigate psychedelic-induced neuroplasticity in the manner that we did.

1. Neuroplasticity

Neuroplasticity is a core feature of the central nervous system which allows it to adapt to an ever-changing environment. The umbrella term “neuroplasticity” encompasses many distinct but related processes which can be described at multiple levels of analysis, from molecular to cellular to brain networks and behavior (1). Neuroplasticity is fundamental for learning in the broadest sense (2). It underlies deliberate learning of new skills and information, such as learning to play the piano or mastering a new language (3, 4). Beyond explicit forms of learning, neuroplastic changes also underlie less intentional learning processes such as conditioning, learned emotional responses (e.g. how one responds to stress), or the ability to flexibly adapt one’s habits and ways of thinking to new situations (5). Crucially, though the brain always maintains some degree of plasticity, its susceptibility to neuroplastic changes can vary: the brain may be more or less able to change, and thus the individual more or less able to adapt and learn (6).

In general, one can differentiate between processes related to structural and functional neuroplasticity, both of which are supported by changes in gene transcription and the activity of neurotrophic factors (5). Structural neuroplasticity refers to physical changes in neural architecture. It encompasses the formation and maturation of new neurons (neurogenesis), dendrites (dendritogenesis), and synapses (synaptogenesis). When it is adaptive, for example during neural development, pruning of neurons and dendrites is also part of structural neuroplasticity. Myelin, astrocytes, and other glial cells can also change their structure. At the whole brain level, changes in neurons and synapses summate to alterations in neural networks and the density of grey and white matter.

Functional neuroplasticity is a closely intertwined process and refers to alterations in neuronal signaling behavior. It includes changes in synaptic efficacy (e.g. LTP, LTD) and neuronal excitability, as well as reorganization of connectivity between brain regions. LTP may be the most widely researched neuroplastic process and its properties are well understood (8). Briefly, rapid stimulation of an excitatory synapse (accomplished experimentally with rapid electrical stimulation called tetanus) increases the strength of signaling at that synapse for hours or even days. This LTP effect is saturable, meaning it cannot be increased indefinitely, and it is also specific to the stimulated synapse(s). Though there are many forms of LTP, it generally depends on post-synaptic activation of NMDA receptors and subsequent trafficking of AMPA receptors to the membranes of dendritic spines. This results in a structural thickening of those spines and an increase in the post-synaptic neuron's sensitivity to further glutamatergic signaling at that synapse. Herein lies a key principle of neuroplasticity: the brain changes in response to its environment. Neuroplastic processes evolved to allow the nervous system to adapt to its surroundings, and they are fundamentally intertwined with one's experiences.

2. Psychedelics and neuroplasticity

Recent research has shown that it may be possible to manipulate neuroplasticity pharmacologically (7). Preclinical studies in animals have suggested that psychedelics, in particular, may be able to rapidly and lastingly promote neuroplasticity after a single dose in particular cortical circuits (8). The serotonergic psychedelic LSD appears particularly potent (9). This opens up the possibility that LSD could be used to promote neuroplasticity in humans, possibly explaining some of its known lasting effects and suggesting new possibilities for harnessing its properties.

2.1 Lysergic acid diethylamide

LSD is a highly potent psychedelic (“mind-manifesting” (10)) drug with far-reaching and unusual effects on conscious experience. The altered state of consciousness induced by LSD varies highly with characteristics of the individual and their environment, and it encompasses complex alterations in perception, emotion, cognition, and self-concept (11, 12). Since its discovery in 1943, LSD has been both maligned for its purported dangers and valued for its use in therapy, personal growth, and recreation (13). Together with drugs like psilocybin and N,N,-dimethyltryptamine (DMT), LSD belongs to a class of drugs called the *serotonergic psychedelics* (alternatively, *classic psychedelics*), so named because their psychoactive and neurobiological effects primarily depend on activity at serotonin 2A receptors (5-HT_{2A}Rs) (14, 15).

LSD is a scientifically fascinating substance for many reasons, but one of the most compelling is its unusually long-lasting effects. At fully psychedelic doses (starting at only ~100µg), LSD’s acute effects last for approximately 12 hours, and it is cleared from the bloodstream within 24 hours (16). However, when taken in a safe and supportive setting, LSD can cause positive changes in well-being, life satisfaction, and even psychiatric symptoms lasting up to a year or even longer (16-19). Lasting negative effects, though rarer, are also possible, particularly after frightening LSD experiences in unsafe settings (20). How can a drug’s effects outlast its presence in the body by such a large margin? Effects on neuroplasticity are a plausible underlying mechanism: LSD might catalyze neuroplastic changes or neuronal growth which remains even after the drug is gone (21).

The question of whether LSD really enhances the brain’s natural ability to change itself forms the core of my doctoral research. Crucially, though it is a leading hypothesis of psychedelic drug action (15), there is as yet very little evidence of psychedelic-induced neuroplasticity in humans. I will briefly describe how the theory came to be in animal research, then elucidate how we will attempt to translate preclinical findings to human subjects.

2.2 Preclinical studies of LSD and neuroplasticity

The theory that LSD might upregulate neuroplasticity grew from rodent gene expression studies in the early 2000s (22). In rats, a single dose of LSD increases the expression of genes related to synaptic plasticity and memory, particularly in the prefrontal cortex (PFC) (23-25). Later research demonstrated that most serotonergic psychedelics could stimulate structural and functional neuroplasticity, with LSD appearing particularly potent (9). Psychedelics stimulate dendritic and synaptic growth in cortical neurons (9, 26), possibly persisting for several days

after exposure (27, 28). They may also enhance the efficiency of long-term potentiation (LTP), a molecular basis of learning (29). Additionally, psychedelics may promote BDNF signaling by directly increasing brain BDNF expression (9, 30) or modulating the activity of tropomyosin kinase B (TrkB) receptors (31, 32). Like most of its subjective effects, LSD's effects on neuroplasticity likely depend on 5-HT_{2A}R activity (33, 34) and primarily affect cortical neurons (25, 35), distinguishing them from the neuroplastic effects of addictive drugs (36).

Though serotonergic psychedelics are not the only drugs to affect neuroplasticity, they do so in a relatively unique manner. Firstly, their effects are relatively specific to neural circuits involving layer 5 pyramidal neurons expressing 5-HT_{2A}R; this means they are particularly strong in the neocortex, including in the PFC and other regions critical for regulating mood (37). Secondly, upregulation of neuroplasticity is rapid, beginning within hours and peaking around 24-72 hours later (9, 28). Thirdly, this increase may last at least a few days and up to a few weeks after a single dose, depending on the specific substance (27, 38). These unique properties have led to the term *psychoplastogen* being widely adopted to describe small molecules which rapidly and lastingly promote neuroplasticity in cortical circuits after a single dose, including serotonergic psychedelics but also substances like ketamine and 3,4-Methylenedioxymethamphetamine (MDMA), which have some psychedelic-like molecular and psychoactive properties (8, 39).

The theory of psychedelic-induced neuroplasticity, as it is currently understood, contains two main propositions:

- 1) After a single (large enough) dose of a psychedelic, specific cortical circuits in the brain show a period of enhanced growth and capacity for neuroplastic restructuring, sometimes called the *window of neuroplasticity*. This includes enhanced dendritogenesis, synaptogenesis, LTP, and neurotrophic signaling.
- 2) Within the window of neuroplasticity, the affected circuits are more responsive to their environment (38, 40). This means that the brain's sensitivity to events within the window exceeds sensitivity to normal everyday experience (41). As an example, this could mean someone is more capable of learning new things during the window of neuroplasticity.

The neuroplasticity theory of psychedelic drug action is attractive not only because of evidence from preclinical studies, but also because it is compatible with and even complementary to other psychological and neurobiological theories of psychedelic drug effects for which there is some evidence (see Vollenweider & Preller 2020 for a review (15)). Importantly, however, most direct evidence for psychedelic-induced neuroplasticity comes from animal research.

Comparatively few studies have attempted to look for the window of neuroplasticity in humans,

and this important research gap is a focus of the current thesis. We chose to focus our attention on LSD because it is a particularly potent and well-studied psychoplastogen (9, 28).

3 Measuring neuroplasticity in human subjects

Once we had decided to study the effects of LSD on neuroplasticity, we had to decide how to measure neuroplasticity in human subjects. This is challenging because animal research on neuroplasticity largely relies on invasive molecular techniques that can only be indirectly translated to humans (42). Nevertheless, we considered the attempt to measure human neuroplasticity with neurophysiological methods worthwhile. Neurophysiological methods are relatively objective and robust to placebo effects, which are a particularly critical problem in psychedelic research (43). To balance out the limitations of different methods, we opted for a multimodal approach combining three purported neurophysiological markers of neuroplasticity with assessments of learning, cognitive flexibility, and perceived stress. The rationale for choosing each of these methods is described below.

3.1 Brain-derived neurotrophic factor

One of the most commonly used biomarkers for neuroplasticity in humans is peripheral brain-derived neurotrophic factor (BDNF) (44). BDNF can be measured in plasma or serum with a simple blood draw, making it attractive as a biomarker for both basic research and clinical purposes (45). Though it is secreted from platelets and various organs apart from the brain, peripheral BDNF is thought to at least partially reflect levels of brain BDNF (46).

BDNF is the most important neurotrophic factor in the central nervous system, where its expression and activity supports various neuroplastic processes (47). It is essential for regulation of synaptic plasticity and supports structural changes to dendritic spines, formation of synapses, dendrites, and neurons, and LTP (48). BDNF is excreted into the synapse in response to neural activation, where its activity at post-synaptic TrkB receptors triggers signaling cascades that support synaptic plasticity (49, 50).

Preclinical studies suggest that LSD may increase cortical BDNF levels, and that BDNF signaling is important for their neuroplastic effects (9, 31). However, previous studies measuring peripheral BDNF after LSD administration in humans have found mixed results (51, 52). Given its accessibility and potential usefulness as a biomarker, we decided to include peripheral BDNF as a marker of neuroplasticity. In addition, however, we noted that enough studies already

existed which measured peripheral BDNF levels in human subjects after administration of LSD or another psychoplastogen. In order to make sense of the varying results from different studies, we decided to conduct a systematic review and meta-analysis investigating changes in BDNF after psychoplastogens in humans (Chapter III).

Though BDNF is a commonly used marker of neuroplasticity, it has certain limitations. Firstly, it can only offer a global index of neuroplasticity, though LSD-induced neuroplasticity is probably specific to certain brain regions (8). Secondly, we were not sure whether BDNF would be sensitive enough to detect changes in brain BDNF, especially given the mixed results we observed in previous studies. We thus chose to add other measures of neuroplasticity as well.

3.2 Stimulation-based methods

Recent years have seen the development of several protocols which combine non-invasive brain stimulation with electrophysiology to index experience-dependent neuroplasticity in humans (53). These were developed as translational measures of LTP-like or Hebbian plasticity, perhaps the most well-studied aspect of neuroplasticity in animals. Measures of LTP-like plasticity have been viewed as a promising new frontier in studies of psychedelics because they measure functional aspects of neuroplasticity in response to environmental stimuli, an underexplored area in human subjects (54). We were drawn to using stimulation-based methods to investigate plasticity because they seemed well-suited to measuring whether the brain's sensitivity to its environment has changed after an intervention (i.e., LSD). We chose to two protocols assessing LTP-like plasticity in different brain regions: 1) sensory tetanization (ST) using electroencephalography (EEG) in the auditory system and 2) paired associative stimulation (PAS) using transcranial magnetic stimulation (TMS) in the motor cortex. These methods and the rationale behind our choices are described below.

3.2.1 Sensory tetanization (ST)

ST (Figure 1) was developed as a translational method for measuring LTP-like plasticity in the human auditory or visual system using EEG (55). It attempts to mimic molecular studies, in which LTP is often induced using rapid electrical stimulation (*tetanus*) at a particular synapse, increasing signaling efficacy at that synapse (56). LTP typically occurs when repeated excitation lastingly increases the efficacy of future excitation at that synapse, strengthening communication between the two neurons over time (57). The underlying principle of LTP is often summarized as “*neurons that fire together, wire together,*” (58) and it is a core molecular

mechanism underlying learning and memory (57). Techniques for studying LTP in humans are of great interest because it is one of the best-studied mechanisms of neuroplasticity in animals (59).

ST attempts to induce an LTP-like effect in human sensory systems by using rapid sensory stimulation rather than direct electrical stimulation (59). Notably, ST also works in animals and may be a more ecologically valid measure of sensory plasticity than direct electrical stimulation of neurons (53). Like LTP studied at the synapse, there is some evidence that the LTP-like potentiation of brain signals after ST is rapidly induced and long-lasting (>1 hour), preventable by blocking N-methyl-D-aspartate (NMDA) receptors, and specific to the stimulus and neural circuit of interest (i.e., not due to generally increased neural excitability) (55, 59, 60).

Additionally, the efficacy of ST at inducing LTP appears to vary with participant characteristics already known to be related to neuroplasticity, including physical exercise, age, depressive symptoms, and memory performance (53, 60). LTP-like plasticity is relevant to studies of psychedelics because animal studies have suggested that LSD and other psychedelics may enhance the magnitude of LTP (29, 61).

We had the choice to perform ST with either visual or auditory stimuli. Visual ST was developed first, and its body of existing literature is somewhat larger than that of auditory ST (62). However, we intended to perform ST six hours after dosing participants with LSD, which gave us two concerns about using visual tetanus. The first was practical: participants can look away from visual images, and participants on LSD may be less able to keep their gaze on the computer due to LSD's acute impairment of concentration and executive function (63); this would not be a problem with auditory stimuli. Secondly, LSD can in rare cases cause lasting changes in visual perception, which in the most severe cases become hallucinogen persisting perceptual disorder (HPPD) (64). We were unable to assess whether stimulating LTP-like plasticity in the visual system during an LSD experience would exacerbate the risk of HPPD, which is typically visual. Auditory ST has been observed to induce LTP-like effects in multiple studies, and despite the smaller body of research it appeared similarly robust to visual LTP (56, 60, 65). We thus chose to use the auditory version.

Briefly, the procedure for auditory ST is as follows: EEG is recorded while participants listen to pure tones over headphones. The brain's reaction to the tones is recorded in the form of auditory event-related potentials (ERPs). We chose to analyze both the N1 and P2 components of the auditory ERP because both had been potentiated in previous ST studies (66). In the first part of the experiment, baseline ERP amplitudes are recorded in response to the tones. Next,

participants hear very rapid tones (i.e., tetanus), typically played at 13Hz, which are theoretically fast enough to stimulate short-term upregulation of synaptic strength in the auditory system (60). After tetanus, ERPs in response to the same tones are recorded again over the course of half an hour; they are now typically larger in amplitude than they were before tetanus. Similar to previous studies, we measured auditory ERPs at 2, 17, and 32 minutes after ST; peak potentiation of auditory ERPs may occur around 20 minutes after ST (66). The degree of potentiation of ERP amplitudes is thought to reflect the capacity for neuroplastic changes in the auditory system.

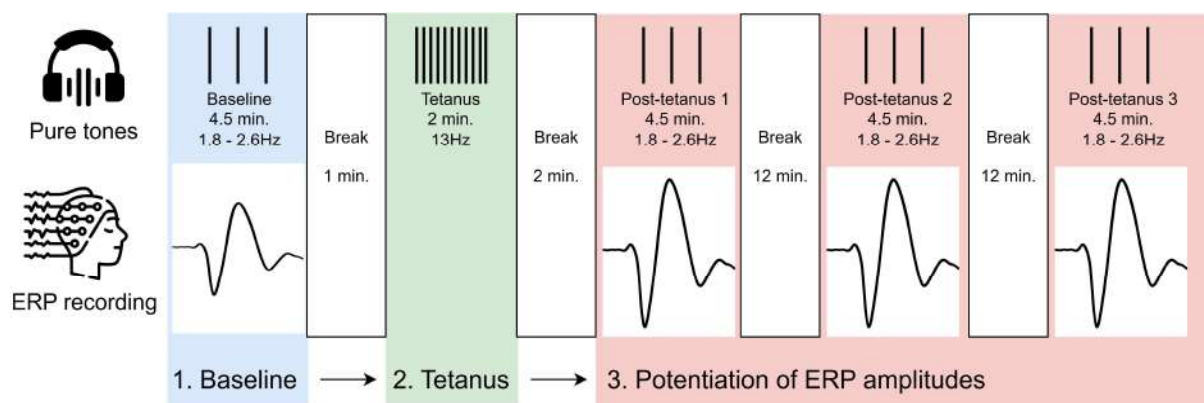


Figure 1. Procedures for assessing LTP-like plasticity using sensory tetanization (ST). ST uses rapid tones to potentiate auditory signals measured with electroencephalography (EEG). The degree of increase in ERP amplitude after ST is thought to reflect LTP-like plasticity in the auditory domain. Auditory event-related potentials (ERPs) are recorded with EEG in response to pure 1000Hz tones (1). Next, rapid tones (ST) are played at 13Hz in order to potentiate the amplitude of auditory ERPs (2). Finally, ERPs are measured again over the course of 30 minutes, during which their amplitudes should be larger (3).

3.2.2 Paired associative stimulation (PAS)

PAS (Figure 2) was originally developed as a method to measure LTP-like changes in the primary motor cortex (67). The procedure follows a similar logic to ST but utilizes *paired stimulation* instead of tetanus to temporarily strengthen synaptic efficacy. Prototypically, participants receive TMS to the area of the motor cortex which controls the abductor pollicis brevis (APB) muscle of their right hand. At the same time, they receive a weak electrical pulse to the median nerve of the right hand. These two stimuli (i.e. the paired stimulation) are timed so that both arrive at pyramidal cells of the motor cortex simultaneously (68). Before and after paired stimulation, we assess the responsiveness of the right APB to single TMS pulses by measuring motor-evoked potentials (MEPs) using electromyography. Like with ST, MEP amplitudes are typically larger after PAS and the degree of MEP potentiation is thought to reflect the capacity for

neuroplasticity in the motor cortex (69). To put it succinctly, we make a group of neurons “fire together” and then measure how well they “wire together” (58).

PAS is thought to reflect LTP-like changes in the primary motor cortex and, like ST, its effects are thought to share certain principles with LTP. The effect of PAS on MEPs can be blocked with NMDA receptor antagonists which block LTP, and it has some specificity to the muscles and nerves being targeted (70). Additionally, MEP potentiation can be induced rapidly and lasts for over an hour, while also being reversible (71). The timing of the TMS and electrical stimuli can be manipulated to produce either LTP-like changes or changes resembling long-term depression (LTD), which behave similarly to the LTP and LTD observed in molecular studies (68). Some studies also suggest that PAS effects vary with characteristics known to be related to motor cortical plasticity, including age (72, 73), physical exercise (74), motor skills (e.g. in professional musicians or athletes) (75, 76), and depressive symptoms (77).

We had a choice of several different TMS protocols which are thought to index neuroplasticity, including PAS with single TMS stimuli but also protocols using rapid TMS, such as theta burst stimulation. Previous studies suggested that PAS was the most effective protocol available (78-80), and so we established the method in our laboratory. Additionally, previous studies of PAS suggest it is more effective in the afternoon (81), perhaps because neuroplasticity can fluctuate throughout the day (82). Because of this, we decided to perform all experiments in the LSD study in the afternoon.

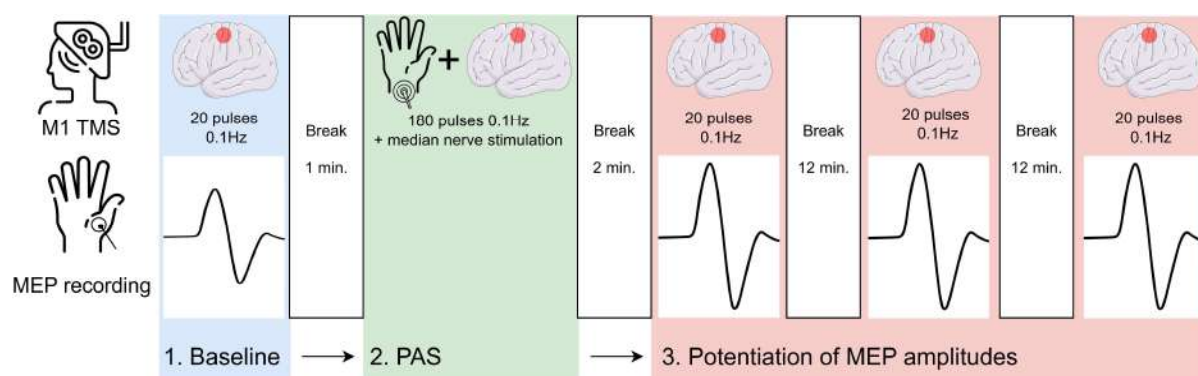


Figure 2. Procedures for assessing LTP-like plasticity using paired associative stimulation (PAS). PAS combines transcranial magnetic stimulation (TMS) over the primary motor cortex (M1) with median nerve stimulation in order to potentiate the amplitude of motor-evoked potentials (MEPs) measured with electromyography at the right abductor pollicis brevis. The degree of increase in MEP amplitude after PAS is thought to reflect LTP-like plasticity of M1. First, MEPs are recorded in response to TMS pulses over M1 (1). Next, TMS pulses are combined with right median nerve stimulation so that both stimuli are conducted to M1 simultaneously (2). Finally,

MEPs are measured again over the course of 30 minutes, during which their amplitudes should be larger (3).¹

3.2.3 Advantages of stimulation-based methods

There were a few additional reasons why both ST and PAS were appealing to us for studying neuroplasticity during and after LSD experiences. Firstly, ST and PAS are able to measure neuroplasticity non-invasively and over relatively short timescales (e.g. within hours), and they can both be repeated over multiple experimental days because the effects of both are thought to dissipate within two hours (66, 83). Secondly, both ST and PAS have some specificity to particular neural circuits. Auditory ST indexes neuroplasticity in the auditory system, with MRI data suggesting that it potentiates neural responses originating in the primary auditory cortex (65). The LTP-like changes induced by PAS, on the other hand, originate in the motor cortex (69).

Choosing these two methods meant that we could investigate LTP-like plasticity in two different neural circuits which could potentially react differently to LSD. According to preclinical studies, LSD should affect neuroplasticity proportionally to the expression of 5-HT_{2A}R in a given brain region or circuit. Auditory ST indexes neuroplasticity in the auditory system, where 5-HT_{2A}R expression is particularly strong according to PET studies with human subjects (84). PAS, by contrast, indexes LTP-like plasticity in the primary motor cortex, which has some 5-HT_{2A}R expression but comparatively less (84). (Notably, LSD barely alters motor function in comparison to its strong effects on visual and auditory processing.) Investigating LTP-like plasticity in two cortical regions with varying levels of 5-HT_{2A}R expression was therefore particularly intriguing.

Finally, apart from measuring LTP-like plasticity, ST and PAS also provide information about the excitability of the relevant circuits in the nervous system before any LTP-like changes are induced. Particularly for TMS, there was no existing data on corticomotor excitability after LSD exposure. The use of TMS thus served a basic research function of characterizing LSD's effects on the motor system.

3.3 Motor learning

Is neuroplasticity just something we can measure, or does it also have practical consequences? We considered it imperative to relate neurophysiological measures of neuroplasticity to

¹ Cortex image provided by Servier Medical Art (<https://smart.servier.com/>), licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>)

behavioral outcomes, and learning is the primary correlate of neuroplasticity (2). We thus chose to include a learning task in our study of LSD. In choosing a learning task, we sought a well-established and feasible paradigm that would match our neuroplasticity measures, thus allowing exploration of correlations between learning outcomes and physiological markers of neuroplasticity. We decided that motor learning, specifically a keyboard-based sequence learning task, would be the best fit.

3.3.1 Choice of motor learning paradigm

Motor learning refers to improvement in the execution of motor movements with practice, a process which requires structural and functional reorganization of brain networks (3). Motor learning as a behavioral outcome reflecting neuroplasticity is an ideal complement to PAS of the primary motor cortex. Repeated practice of new behaviors triggers LTP at the relevant synapses, a process which is particularly well-studied in the domain of motor learning (85). Furthermore, in humans, previous studies have shown a clear relationship between TMS measures of LTP in the motor cortex and motor learning, including PAS, suggesting not only that LTP underlies motor learning but that this process can be accessed with TMS (68, 86-90). Apart from its clear connection to PAS, motor learning is a complex process also involving neuroplastic adaptations in sensory systems, giving motor learning tasks a plausible connection to our ST paradigm (91). Lastly, BDNF levels are elevated during learning, and particularly convincing data exists for a role of cortical BDNF supporting motor learning (48).

Motor learning can be operationalized in various ways, but pertinent to the current thesis are sequence typing tasks, some of the most well-established measures of motor learning in human studies (92). Lab-based sequence learning tasks have been shown to have moderate ecological validity, offering basic insights into how motor skills are learned in the real world (93). Studies relating motor learning to LTP-like plasticity in humans have often employed sequence learning, in which participants learn to execute a particular series of motor movements quickly and accurately (86, 87). Participants are typically asked to practice a motor sequence (e.g. typing numbers in a certain order on a keyboard) as quickly and accurately as possible (92). They practice for a certain period of time (e.g. 30 minutes) and show reliable improvements in movement speed and/or accuracy with practice, which eventually reach an asymptote. The degree and speed of improvement over time is thought to reflect learning ability, and by proxy neuroplasticity.

We chose to have participants practice a typed sequence on a keyboard, which was a particularly good fit for PAS because both involve motor movement in the hands and activity the corresponding neural circuits. Because it is important that the learning task and PAS not interfere with each other (94), we elected to only recruit right-handed participants and use the right (dominant) hand for PAS and the left (non-dominant) hand for motor learning. Both sequence learning gains and PAS-induced LTP-like changes are specific to the region being studied, and so a learning task performed with the one hand should not interfere with PAS in the other.

3.3.2 Online and offline learning

Additionally, many previous studies of sequence learning have investigated the temporal dynamics of learning gains not only during, but also *after* practice of a motor skill. After as little as a few minutes of rest, participants often show substantial improvement in motor performance which exceeds the improvement they previously showed between blocks of active practice (95). While fast improvement during practice (*online learning*) reflects early acquisition of a motor skill, slower gains after rest (*offline learning*) are thought to reflect later structural and functional processes of synaptic consolidation.

Online and offline learning may involve somewhat different neuroplastic processes, and I was intrigued by the possibility that LSD might affect one more strongly than the other. Online and offline learning involve overlapping and distinct patterns of neural activation and plasticity involving the motor cortex, but also the somatosensory cortex and various subcortical regions (cerebellum, basal ganglia, and others) (96). I was particularly intrigued by a study using TMS to investigate neuroplastic processes in the motor cortex and cerebellum which suggested that neuroplastic changes in the motor cortex were particularly important for offline learning, while neuroplasticity in the cerebellum was more important for online learning (97). Because cortical regions like the motor cortex show high 5-HT_{2A}R expression compared to most subcortical regions, including the cerebellum (84), this raised the possibility that LSD's enhancement of neuroplasticity may particularly benefit offline learning.

To study LSD's effects on online and offline motor learning, we developed an in-house computer-based sequence typing task based on those used in previous studies. To maximize the potential for learning gains in healthy participants, who often show ceiling effects in similar tasks, we copied the common practice of having participants perform the task with the non-dominant hand. Furthermore, we chose a 9-digit sequence instead of the more typical 5-digit

sequence employed in previous studies in order to maximize the potential for learning gains in this healthy population, which we knew may be prone to ceiling effects. Additionally, we were aware that some degree of motivation to improve performance was probably necessary for learning gains. We thus programmed the task so that participants would receive audiovisual feedback on their performance at regular intervals, as well as encouragement to beat previous high scores.

Importantly, our motor learning task was designed to measure both online and offline learning gains. The online learning period consisted of 30 minutes of practice with brief (one minute) breaks in which participants received feedback on their performance. We chose the 30 minute practice time based both on previous studies of sequence learning in humans and the temporal dynamics of LTP. LTP stabilizes after approximately 30 minutes (98), making it plausible that learning gains persisting for longer than 30 minutes could reflect later phases of LTP consolidation.

After practice, two test blocks assessed early and late offline learning gains after breaks of 10 and 80 minutes. We chose these timepoints because previous studies showed that resting for 5-15 minutes is already sufficient to induce substantial offline learning gains (95, 99). It is unclear when offline learning gains peak, though they decay within a couple of hours without additional practice. The second test block 80 minutes after practice was influenced by practical considerations involving other experiments, but was still within the plausible window of observable offline learning gains (95). In the first 10-minute break between practice and test blocks of the motor learning task, participants rested with eyes closed. During the rest of the 80-minute break, participants performed other experiments not dissimilar to non-motor distractor tasks used in previous studies of offline learning (questionnaires, passive EEG measurements) (99). Judging from previous studies, it seemed that interference with motor memory consolidation would be minimal.

3.4 Possible psychological correlates of neuroplasticity

In addition to learning, we were curious about whether LSD's effects on neuroplasticity would have any subjective correlates in our subjects. Though far from proven, it has been speculated that the brain's general degree of neuroplasticity may have some correlates in subjective experiences – in other words, that people can feel how adaptable their brains are to the world around them (100). The connection to neuroplasticity is not nearly as robustly established for subjective correlates as for learning. Nevertheless, we found it worthwhile to carefully choose

plausible subjective correlates of neuroplasticity so that we could explore correlations between them and our neurophysiological measures. The theory that neuroplasticity underlies psychedelics' lasting subjective effects has become widely influential, and we saw an opportunity to test it (101).

Specifically, we assessed perceived stress and cognitive flexibility. We chose these two measures because they are relevant to both healthy and clinical populations, have been shown to change after psychedelic experiences in previous studies, and have some plausible connection to LSD-induced neuroplasticity. The rationale for each is explained below.

3.4.1 Perceived stress

One of the core molecular findings regarding LSD's effects on neuroplasticity is that it may catalyze a burst of synaptic and dendritic growth in cortical pyramidal neurons, particularly in PFC circuits important for mood regulation. Reduced neuroplasticity in the PFC is associated with reduced ability to cope with stress (102). It has thus been theorized that psychedelics lastingly enhance the ability of the PFC to exert top-down regulation over limbic areas, including responses to stress (8). Better stress regulation could underlie both LSD's lasting effects on well-being in healthy people and its beneficial effects in stress-related mood disorders, particularly depression and anxiety (100, 101). Relatedly, studies suggest some protective effects of psychedelics against subsequent stress in both animals (103) and humans (104), and amygdala reactivity in response to negative stimuli may be favorably altered for at least one week after exposure to a psychedelic (105). We thus included the Perceived Stress Scale (PSS) as a measure of perceived stress in our research, surmising that subjective stress would decrease after LSD and possibly be related to changes in neuroplasticity.

3.4.2 Cognitive flexibility

Cortical synaptic and dendritic growth may not only underlie changes in mood regulation, but also cognitive flexibility. Cognitive flexibility denotes the ability to flexibly adapt to changing environmental conditions (106). It relies heavily on frontal cortical function (107), and impairments in cognitive flexibility have been associated with impaired neuroplasticity in the PFC (102). Intriguingly, animal studies have suggested that serotonergic psychedelics can post-acutely enhance cognitive flexibility – but perhaps only *after* an initial burst of neuroplastic growth in the cortex, i.e. one week but not as early as one day after treatment (108). In this vein, a study in healthy subjects found no change in cognitive flexibility one day after LSD treatment

(109), but another study found enhanced cognitive flexibility at one and four weeks after treatment with psilocybin (110). Additionally, people who use psychedelics in naturalistic settings may show lasting enhancements of cognitive flexibility, though a causal relationship cannot be established (111, 112).

Together, previous studies suggest that LSD could improve cognitive flexibility after a short delay (113), and the possibility that this delay constitutes the time required for neuroplastic growth in the cortex is intriguing. We thus included a measure of cognitive flexibility in our study. One additional important consideration is that the term *cognitive flexibility* is used to denote two related but different constructs in the literature. On the one hand, it denotes an executive function underlying performance when switching tasks (107). On the other hand, the same term is often used to denote one's subjective perception of how well one adapts to changing environmental demands (114). Self-reported cognitive flexibility is more related to the similar construct of psychological flexibility, or the ability to pursue one's goals even in the presence of difficulty or distress, than to performance on set-shifting tasks (115). The abovementioned studies of psychedelics have used both operationalizations of cognitive flexibility in approximately equal measure. After some consideration, we chose to measure self-reported cognitive flexibility because of its positive relationship to clinical outcomes in psychedelic-assisted therapy (116, 117).

3.5 Timing of experiments

A final and critical consideration when measuring the effects of LSD on neuroplasticity was *when* to measure it. When, exactly, should we expect to find a window of neuroplasticity after LSD treatment? In preparation for my doctoral research, I searched for a literature review which would answer this question. Though informative reviews existed, none examined the temporal dynamics of psychedelic-induced neuroplasticity in the way we needed. I thus reviewed the literature myself so that we could write the review we wished existed.

In order to answer essential questions about timing and solidify our plans for the LSD study, we conducted a thorough literature review of (mostly preclinical) research assessing the effects of psychedelics on neuroplasticity (Chapter II). Among other things, this review would focus on the temporal dynamics of the window of neuroplasticity. In short, preclinical studies led us to hypothesize that LSD-induced upregulation of neuroplasticity would be visible within six hours (9), peak within 24-72 hours (9, 27, 28), and last for at least 7 days (27, 38, 105) (see also Chapter II).

Based on our findings from the review, we conducted measurements at three timepoints thought to fall within the window of neuroplasticity after LSD exposure: 6-8 hours after dosing, one day later, and one week later. Additionally, we chose to measure motor learning only the day after LSD treatment because learning was increased at this time in previous studies and it coincided with the possible peak of enhanced neuroplasticity (118). Cognitive flexibility and perceived stress were only measured one week after LSD because of the delayed effects seen for these trait-level variables in the literature (109) (110).

4. Thesis aims and outline

The overarching aim of this thesis is to investigate changes in neuroplasticity after exposure to LSD in humans. **Chapter II** summarizes current scientific understanding of how serotonergic psychedelics affect neuroplasticity, including which brain regions are likely to be affected, how long the effects might last, and what open questions remain. Reviewing the evidence for psychedelic-induced neuroplasticity allowed us to plan the methodology we would use for studying neuroplasticity after LSD, and it particularly allowed us to choose timepoints at which plasticity was most likely to be elevated.

Chapter III is a meta-analysis of the most commonly used marker of neuroplasticity in human studies of psychedelics, namely peripheral BDNF. As we prepared to study the effects of LSD on neuroplasticity, it became clear that previous studies reported contradictory findings on BDNF, with some finding an increase after LSD, others a decrease, and no clear pattern regarding the dose. This pattern of mixed results was also present for other psychoplastogens, most particularly ketamine. The meta-analysis compiles data from all available psychoplastogens to test the hypothesis that psychoplastogens increase peripheral BDNF in humans.

Chapter IV presents data from a randomized, double-blind crossover trial of LSD in 45 healthy subjects. It investigates the effects of LSD on two markers of LTP-like plasticity, namely ST and PAS, as well as peripheral BDNF. It also includes a motor learning task and measures of cognitive flexibility and perceived stress in order to test the effects of LSD in possible behavioral correlates of neuroplasticity. We report significant changes in motor learning, cognitive flexibility, and perceived stress, in addition to some unexpected findings for the EEG and TMS measures. Finally, **Chapter V** summarizes the findings and conclusions from this thesis and provides a general discussion of their significance, limitations, and implications for future research.

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Chapter II Towards an understanding of psychedelic-induced neuroplasticity

Abigail E. Calder¹ & Gregor Hasler¹, M.D. Ph.D.

¹ Center for Psychiatric Research, University of Fribourg, Fribourg, Switzerland

Neuropsychopharmacology, 2022, Vol. 48: 104 – 112

REVIEW ARTICLE **OPEN**



Towards an understanding of psychedelic-induced neuroplasticity

Abigail E. Calder¹✉ and Gregor Hasler¹✉

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Classic psychedelics, such as LSD, psilocybin, and the DMT-containing beverage ayahuasca, show some potential to treat depression, anxiety, and addiction. Importantly, clinical improvements can last for months or years after treatment. It has been theorized that these long-term improvements arise because psychedelics rapidly and lastingly stimulate neuroplasticity. The focus of this review is on answering specific questions about the effects of psychedelics on neuroplasticity. Firstly, we review the evidence that psychedelics promote neuroplasticity and examine the cellular and molecular mechanisms behind the effects of different psychedelics on different aspects of neuroplasticity, including dendritogenesis, synaptogenesis, neurogenesis, and expression of plasticity-related genes (e.g., brain-derived neurotrophic factor and immediate early genes). We then examine where in the brain psychedelics promote neuroplasticity, particularly discussing the prefrontal cortex and hippocampus. We also examine what doses are required to produce this effect (e.g., hallucinogenic doses vs. “microdoses”), and how long purported changes in neuroplasticity last. Finally, we discuss the likely consequences of psychedelics’ effects on neuroplasticity for both patients and healthy people, and we identify important research questions that would further scientific understanding of psychedelics’ effects on neuroplasticity and its potential clinical applications.

Neuropsychopharmacology; <https://doi.org/10.1038/s41386-022-01389-z>

INTRODUCTION

Recent decades have seen renewed scientific interest in classic psychedelics, which include lysergic acid diethylamide (LSD), psilocybin, 2,5-dimethoxy-4-iodoamphetamine (DOI), 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), and N,N-dimethyltryptamine (DMT), the psychedelic compound in the Amazonian ayahuasca brew [1]. Classic psychedelics have been shown to catalyze relatively long-lasting improvements in mental health after a small number of doses, especially when combined with psychotherapy [2]. In patients suffering from depression, anxiety disorders, and addiction, the benefits of psychedelic-assisted psychotherapy can last for many months or years [3–10]. Additionally, healthy subjects report increased well-being up to a year after administration of psychedelics in a safe and supportive setting [11–13].

One leading theory of psychedelics’ lasting effects categorizes them as “psychoplastogens” which rapidly stimulate a period of enhanced neuroplasticity, as well as enduring neuroplastic changes [14, 15]. Neuroplasticity denotes the nervous system’s ability to reorganize its structure and function and adapt to its dynamic environment [16]. Throughout the lifespan, neuroplasticity is essential for learning, memory, and recovery from neurological insults, as well as adapting to life experiences [17]. The theory that psychedelics open a window of neuroplasticity would explain how long-term effects outlast the drug’s presence in the body, and it is also attractive because disruptions in neuroplasticity are present in mood disorders and addiction [18].

Neuroplasticity can be investigated at multiple levels of analysis. At the molecular level, it comprises changes in gene and protein expression, as well as post-translational modifications [19]. Of particular importance is brain-derived neurotrophic factor (BDNF), a neurotrophin that regulates neuronal growth and synaptic plasticity [20]. Changes in gene and protein expression give rise to morphological changes, including the formation and modification of synapses and dendrites [21]. In particular regions, most notably the hippocampus, neuroplasticity also comprises neurogenesis [22]. These processes modify neural circuits, ultimately manifesting in learning, memory, and changes in adaptive behavior [19]. Neuroplasticity is crucially activity-dependent at the cellular level, which translates into experience-dependence at the level of cognition and behavior: people learn both passively and actively from their experiences, adjusting patterns of thought, emotion, and behavior accordingly [17, 23].

In order to effectively harness the potential of psychedelics, it is imperative to understand how they affect neuroplasticity, as well as the clinical relevance of these effects. In the present review, we first evaluate the available evidence concerning whether psychedelics enhance neuroplasticity. We then discuss where in the brain this likely happens, what doses are capable of this, how long the effects may last, and whether they have meaningful consequences for emotion, cognition, and behavior, as well as therapeutic use. Finally, we discuss the advantages and challenges that psychedelic-induced neuroplasticity presents and identify important directions for future research.

¹University Center for Psychiatric Research, University of Fribourg, Fribourg, Switzerland. ✉email: abigail.calder@unifr.ch; gregor.hasler@unifr.ch

Received: 13 May 2022 Revised: 10 July 2022 Accepted: 12 July 2022
Published online: 19 September 2022

DO PSYCHEDELICS ENHANCE NEUROPLASTICITY?

Classic psychedelics are thought to catalyze a period of accelerated neuronal growth, enhancing the brain's capacity for neuroplastic changes. Studies in animals have shown that LSD, psilocybin, DMT, and DOI promote the expression of genes related to synaptic plasticity, including immediate early genes (IEGs) and *BDNF* [24–34]. Furthermore, they catalyze a burst of synaptic and dendritic growth and can increase the strength of long-term potentiation (LTP) [27, 35–40]. Regarding neurogenesis, results have been mixed: LSD and DOI had no effect on adult neurogenesis in rats, and psilocybin was shown to slightly reduce it in mice [41–43]. By contrast, studies in mice using both DMT and 5-MeO-DMT observed increased neurogenesis [44, 45].

In humans, studies have often relied on peripheral BDNF as a marker of neuroplasticity, yielding mixed results. Though ayahuasca increased BDNF levels in both healthy and depressed people in one study, another found no change [46, 47]. Several studies have measured the effects of LSD on BDNF, with some finding an increase [48, 49] and others no change [50, 51]. In two studies in healthy subjects, comparable doses of psilocybin did not elevate plasma BDNF in one [50], but did so in the other [52]. This variability may be partially due to the limitations of peripheral BDNF as a biomarker in pharmacological studies. Though blood BDNF has been shown to predict brain BDNF under normal conditions, psychoplastogens may cause an increase in peripheral BDNF levels without any increase in brain BDNF [53, 54]. Furthermore, BDNF may not correlate with other measures of cortical neuroplasticity in humans, and blood platelets can store and release BDNF independently of neurons [55, 56]. Beyond measuring BDNF levels, neuroimaging studies have found evidence of altered neural connectivity following treatment with psilocybin and ayahuasca, which is interpreted as evidence of drug-induced neuroplastic changes [57–59].

Taken together, animal studies offer moderately strong evidence that psychedelics promote genes related to neuroplasticity, synaptic strength, and dendritic growth, including *BDNF*. However, analyses of peripheral BDNF protein in human studies have thus far been inconclusive. Future studies in humans could benefit from protocols which do not rely only on peripheral markers, but also induce LTP-like changes to index neuroplasticity, such as paired associative stimulation [60–62] or tetanic sensory stimulation [63, 64], as well as PET studies with markers of synaptic density, such as SV2A [65].

HOW DO PSYCHEDELICS ENHANCE NEUROPLASTICITY?

The complex molecular signaling underlying psychedelic-enhanced neuroplasticity has been thoroughly discussed elsewhere [66–69], but we will briefly review the most important aspects. Psychedelics appear to enhance neuroplasticity via the 5-HT_{2A} receptor, which also mediates most of their subjective effects [70–72]. Though relatively low doses of the selective 5-HT_{2A} receptor antagonist ketanserin do not fully block psychedelic-induced neuroplasticity [37, 73], higher doses of ketanserin block it completely [36]. Furthermore, the affinity of different psychedelic drugs for the 5-HT_{2A} receptor predicts their individual potency as psychoplastogens, and 5-HT_{2A} receptor knockout mice show no signs of enhanced neuroplasticity following treatment with psychedelics [24, 27, 36].

Psychedelics stimulate 5-HT_{2A} receptors found post-synaptically on layer 5 and 6 pyramidal neurons, as well as on GABAergic interneurons [72]. The net effect appears to be excitation of layer 5 pyramidal neurons and increased levels of extracellular glutamate, resulting in greater stimulation of AMPA receptors [35, 72, 74]. The precise molecular pathways which may modify neuroplasticity after 5-HT_{2A} receptor stimulation are not fully understood. However, one leading hypothesis suggests that the aforementioned AMPA receptor stimulation triggers a positive feedback

loop: Stimulation of AMPA receptors may enhance BDNF secretion, which would stimulate TrkB receptors and mTOR, which in turn would stimulate further BDNF production and sustained AMPA activation [36, 38]. Sustained activation of both AMPA receptors and mTOR appears to be necessary for the enhanced dendritic growth following stimulation with psychedelics [35]. Additionally, activity involving both 5-HT_{2A} and glutamate receptors, particularly mGlu₂, may be essential for psychedelics' effects on neuroplasticity [66, 75, 76]. These effects likely remain specific to synapses and circuits expressing 5-HT_{2A} receptors, as BDNF acts locally and does not diffuse far after release [20, 77].

In addition to 5-HT_{2A} receptors, the effects on neurogenesis seen with DMT and 5-MeO-DMT could potentially involve other receptors [42, 43]. DMT has low but functionally significant affinity for the sigma-1 receptor, an orphan receptor involved in neuroprotection and neurogenesis [78]. Sigma-1 receptor antagonists block DMT's effects on hippocampal neurogenesis [44, 79], and sigma-1 receptor activity has also been shown to stimulate neurogenesis in previous studies [80–82]. The affinity of DMT for sigma-1 receptors may also not only its effects on neurogenesis, but also DMT's neuroprotective effects in a rat model of stroke [83].

Concerning 5-MeO-DMT, this molecule is unusual among psychedelics in that it has a nearly 1000-fold higher affinity for 5-HT_{1A} than 5-HT_{2A} receptors, and many of its effects are mediated by 5-HT_{1A} receptors [79, 84–87]. Hippocampal 5-HT_{1A} receptors may drive neurogenesis, suggesting that the effects of 5-MeO-DMT on neurogenesis could conceivably occur via potent, relatively selective activation of 5-HT_{1A} receptors [88, 89]. Additionally, 5-HT_{1A} receptors are generally inhibitory and tend to have opposite effects on downstream signaling pathways than 5-HT_{2A} receptors [90–93]. Many psychedelics show binding affinity for both 5-HT_{2A} and 5-HT_{1A} receptors [94]. Furthermore, some of psychedelics' effects on attention and the visual system may be mediated by the 5-HT_{1A} receptor [95, 96]. The excitatory and neuroplastic effects of different psychedelic drugs in any particular brain region could conceivably depend on whether that region is richer in 5-HT_{2A} or 5-HT_{1A} receptors [79, 97–101].

WHERE DO PSYCHEDELICS ENHANCE NEUROPLASTICITY?

Because psychedelics promote synapse and dendrite growth in a 5-HT_{2A} receptor-dependent manner, the greatest effects would be expected in regions with high 5-HT_{2A} receptor expression, i.e., the neocortex [72, 91, 102]. Data from animal studies thus far supports this theory, showing relatively robust effects in cortical regions and smaller, less consistent effects on neuroplasticity elsewhere.

Neocortex

Psychedelics have been shown to enhance dendritic growth, including spinogenesis, in cortical neurons [36, 40]. In the frontal lobe specifically, animal studies show that psychedelics upregulate plasticity-related genes and promote the growth of synapses and dendritic spines [25, 27, 36, 37, 103]. In the prefrontal cortex (PFC), several psychedelics have been shown to rapidly upregulate genes related to neuroplasticity [25, 26, 104]. Pigs exposed to a hallucinogenic dose of psilocybin showed increased presynaptic density in the PFC [39]. In humans, PET imaging has shown that psilocybin increases glutamate signaling in the PFC, which is theorized to be important for psychedelic-enhanced plasticity [105].

Other cortical regions likely also show enhanced neuroplasticity as a function of 5-HT_{2A} receptor density. DOI enhanced expression of the plasticity-related *Arc* gene in the whole cortex, as well as in the parietal cortex specifically [28, 106]. A recent unpublished study in mice examined expression of *c-Fos*, an early marker of neuroplastic processes, after treatment with psilocybin, revealing strong upregulation in most cortical regions. These included

sensory visual, auditory, somatosensory, and gustatory areas, as well as motor and association areas, the anterior cingulate cortex (ACC), and the insula [107].

Hippocampus

Several studies have focused on the hippocampus, but many found modest effects compared to the cortex. In the rodent hippocampus, psilocybin treatment upregulated fewer plasticity-related transcripts in the hippocampus than in the cortex, and LSD failed to upregulate immediate early genes associated with neuroplasticity [24, 25]. Similarly, DOI failed to enhance expression of *Arc* in the hippocampus [106]. Treatment with DOI may even decrease the expression of *BDNF* in the dentate gyrus, leaving it unchanged in the rest of the hippocampus [28]. In line with this, the abovementioned PET study in humans found reduced glutamate activity in the hippocampus after psilocybin [105]. However, the cortex and hippocampus do not always show this opposite pattern. Pigs exposed to a hallucinogenic dose of psilocybin showed increased presynaptic density in both the hippocampus and the PFC [39]. Additionally, psilocybin has been shown to strengthen cortico-hippocampal synapses [73].

The reduced tendency toward neuroplastic effects in the hippocampus might be explained by its greater density of 5-HT_{1A} than 5-HT_{2A} receptors [90, 102]. It is possible that LSD, DOI, and psilocybin, and perhaps other psychedelics, have pro-neuroplastic effects in the cortex and other regions richer in 5-HT_{2A} than 5-HT_{1A} receptors, but tend to have modest or even inhibitory effects in 5-HT_{1A} receptor-dominant areas like the hippocampus.

Other subcortical regions

Some preliminary unpublished evidence suggests that psychedelics may enhance neuroplasticity in a few subcortical regions. In the aforementioned study of *c-fos*, psilocybin increased *c-fos* expression in the claustrum, locus ceruleus, lateral habenula and some areas of the thalamus, amygdala, and brainstem [107]. The pattern of expression changes correlated with 5-HT_{2A} receptor distribution [107]. Given that *c-fos* is a relatively unspecific marker, however, these results should be interpreted with caution, and more research is necessary to determine how psychedelics affect neuroplasticity in subcortical regions.

The mesolimbic pathway warrants particular attention due to its role in addiction. Addiction to drugs of abuse is driven by neuroplastic changes in dopaminergic neurons of the mesolimbic pathway [108]. Notably, however, psychedelics do not cause dependence or addiction [108]. Important mesolimbic areas for addiction, including the ventral tegmental area, nucleus accumbens, and striatum, express relatively few 5-HT_{2A} receptors and are therefore unlikely to be much affected by psychedelic-induced plasticity [102, 109]. Additionally, inhibitory neurons projecting from the PFC to areas of the mesolimbic pathway are much richer in 5-HT_{2A} receptors [102, 110], and enhanced dendritic growth in these PFC neurons could conceivably contribute to the anti-addictive effect observed with psychedelics [3, 10, 111].

At what dose do psychedelics enhance neuroplasticity?

Several studies have investigated how different doses of psychedelic drugs affect neuroplasticity. In rats, 0.2 mg/kg LSD promoted neuroplasticity-related changes in gene expression, and the efficacy increased up to a dose of 1 mg/kg, although some genes showed a peak effect at lower doses [31–33]. For psilocybin, a dose of 4 mg/kg was required to induce neuroplasticity-related changes in gene expression, and the effect also increased in a dose-dependent manner [25]. DOI also shows a dose-dependent effect on neuroplasticity [28]. Finally, a presumably sub-hallucinogenic dose of 1 mg/kg DMT increased functional plasticity in rat cortical slices, as measured by the frequency and amplitude of excitatory post-synaptic currents [36].

Though these studies suggest that psychedelics probably promote neuroplasticity in a dose-dependent manner, clear dose-response effects on neuroplasticity have not been established in humans. Sub-hallucinogenic doses of between 5 and 20 µg LSD produced significant short-term enhancements in plasma *BDNF* [48]. However, a similar study using doses of between 25 µg and 200 µg LSD only found significant effects on *BDNF* at 200 µg [49], and another failed to find significant changes even at this dose [50]. Perhaps using different methods, future research should seek to clarify the minimum and optimal doses for stimulating neuroplasticity with different psychedelics. The prospect of non-hallucinogenic “microdoses” which enhance neuroplasticity is attractive for certain clinical applications, including stroke, brain injury, and neurodegenerative disorders [15].

Particularly regarding microdoses, a discussion of dosing frequency is warranted. While large doses of psychedelics are not taken chronically due to their intense subjective effects, microdoses can be taken regularly and have been hypothesized to enhance neuroplasticity [48, 112]. Chronic dosing with LSD has been associated with enhanced eyeblink conditioning, as well as improved avoidance learning and reversal of stress-induced deficits in synaptogenesis in rodent models of depression [103, 113, 114]. However, chronic dosing with DMT may cause retraction of dendritic spines [115]. Additionally, chronic LSD dosing was associated with upregulation in genes related to neuroplasticity, but also to schizophrenia [104]. Many animal studies investigating chronic dosing have not differentiated between microdoses and hallucinogenic doses, which may be an important distinction. Nevertheless, further studies should investigate whether chronic dosing, particularly chronic microdosing, has different effects on neuroplasticity than single doses.

For how long do psychedelics enhance neuroplasticity?

In order to take advantage of a “window of plasticity,” it is essential to know when this window opens and closes. Evidence of enhanced neuroplasticity appears within several hours after exposure to psychedelics (Fig. 1). The earliest changes involve upregulation of neuroplasticity-related transcripts, which can occur within one hour [24, 34]. In rats, both LSD and psilocybin upregulated genes associated with neuroplasticity after 1.5 hours, particularly in the PFC [25, 33]. *BDNF* mRNA may become upregulated slightly later: one study found no change 1.5 hours after treatment with psilocybin, but others have found increased expression 2 and 3 hours after treatment with DOI [25, 28, 116].

Changes in cellular morphology have been observed starting 6 hours after stimulation with psychedelics [35]. One study found no changes in dendritic growth 1 hour after stimulating primary rat neuronal cultures with LSD, but observed significant changes in dendritic growth, synaptogenesis, and spinogenesis at several later time points [35]. In humans, increases in peripheral *BDNF* levels have earliest been seen 4 hours after oral administration of LSD [48, 49].

Though neuroplasticity may increase within several hours, the peak effect may come some time later. In rat cortical neurons, the observed increase in synaptogenesis was greater at 24 hours than at 6 hours post-stimulation, and in female mice, the rate of dendritic spine formation 3 days after psilocybin treatment is greater than the rate seen just 1 day after treatment [36, 37]. Other work has shown that a significant neuronal growth phase occurs in the 72 hours after initial exposure to psychedelics [35].

Enhanced neuroplasticity may also last for several days. In mice treated with psilocybin, the rate of dendritic spine formation remained elevated for 3 days, returning to baseline by 5 days post-treatment [37]. In humans, both healthy volunteers and depressed patients show elevated peripheral *BDNF* levels 2 days following treatment with ayahuasca [46]. Finally, a study that treated mice with LSD every other day for 1 month observed long-term upregulation of neuroplasticity-related genes, including *BDNF*, in

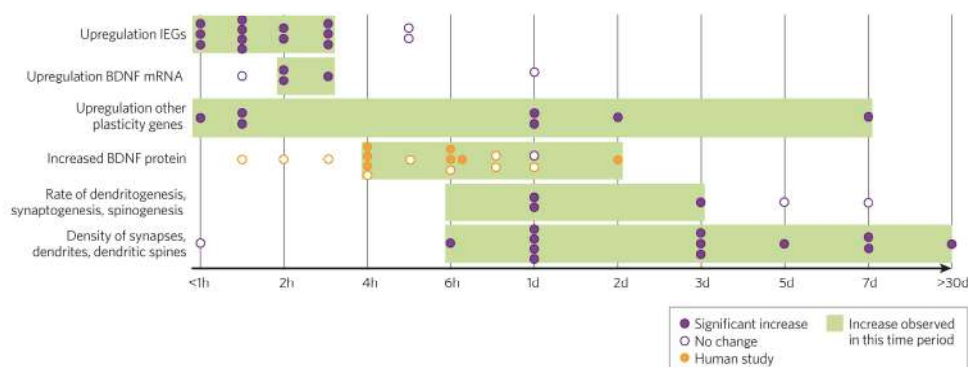


Fig. 1 Timeline showing the earliest and latest observations of various changes in neuroplasticity following treatment with a single dose of the serotonergic psychedelics LSD, psilocybin/psilocin, DMT, or DOI. One dot represents one study and time point. Human studies are shown in yellow; animal and in vitro studies are shown in purple. BDNF = brain-derived neurotrophic factor, IEGs = immediate early genes. Based on data for synaptic density, it is assumed that rates of dendritogenesis and synaptogenesis also increase at 6 h post-treatment. See Table S1 for citations.

the medial PFC 4 weeks after treatment cessation [104]. Additionally, specific markers of neuroplasticity may have different “windows.” Though *BDNF* mRNA can become upregulated within 2 hours, the effect may already be gone 24 hours later, and it is unclear what this means for *BDNF* protein expression [36]. Upregulation of other plasticity-related genes follows various time courses, with some genes showing peak expression within a few hours, others at around 48 hours, and still others at 7 days after administration [27, 31, 32].

Crucially, new dendrites and synapses formed during the window of enhanced neuroplasticity can outlast the window itself. Increased synaptic and dendritic density has been observed at 72 hours post-treatment in multiple studies [27, 37, 39]. Furthermore, though mice treated with psilocybin returned to baseline levels of dendritic spine formation within 5 days, new dendrites formed during that period survived for at least 1 month [37]. In humans, research has uncovered changes in brain function which lasted at least 1 month after treatment with psilocybin, suggesting the presence of lasting neuroplastic changes [57].

These data suggest that various signs of enhanced neuroplasticity arise within 1–6 hours, with changes in gene expression appearing earliest and changes in cell morphology and synapse organization arising later. The increased rate of dendritogenesis may taper off within 5 days, however, neuroplastic changes which arise during this period of neural growth may last for at least 1 month. However, important questions about the window of neuroplasticity remain, and future research should aim to define the temporal dynamics of enhanced neuroplasticity in humans, as this may be crucial for the timing of psychotherapeutic interventions.

Consequences of enhanced neuroplasticity

Is enhanced neuroplasticity simply something we can measure, or does it also have meaningful consequences? Answering this question is essential for understanding the basis of psychedelics’ long-term effects, however, few studies have related changes in neuroplasticity directly to behavioral outcomes. In chronically stressed mice, psilocybin both strengthened cortico-hippocampal synapses and reduced anhedonia, which may be the result of improved synaptic strength in reward circuits [73]. Additionally, DMT has been seen to enhance both neurogenesis and memory performance [44]. Other studies have reported improvements in fear extinction learning and reductions in anxious behaviors and learned helplessness following exposure to psychedelics, while also observing increased dendritic spine density in separate cohorts of animals [27, 37, 103]. Finally, the enhanced spinogenesis induced by ketamine, which is also a psychoplastogen, has been associated with reductions in depression-related behaviors

[117, 118]. More research is needed to determine whether the same could be true for classic psychedelics, and to confirm or deny the associations between neuroplastic and behavioral effects suggested in the literature thus far.

In humans, one study found that depressed patients treated with ayahuasca had elevated *BDNF* levels which correlated with their clinical improvements [46]. In another study, psilocybin lastingly increased connectivity between the PFC and other brain areas, including limbic and subcortical regions, and these increases occurred alongside decreases in negative affect and anxiety [57]. However, one limitation of many of these studies is the lack of causal inference: though changes in neuroplasticity and changes in cognition or behavior may occur simultaneously, whether neuroplasticity mediated those changes remains an open question for future studies to address.

Further outcomes possibly explained by enhanced neuroplasticity

Changes in neuroplasticity may also partially explain some other long-term effects of psychedelics. Psychedelics, combined with psychotherapy, have shown clinical efficacy in trials for mood disorders and addiction, and healthy participants also report improved mood after taking psychedelics [3–6, 10, 119–123]. Enhanced dendritic and synaptic growth in PFC neurons may be a plausible explanation for this: the PFC is essential for emotional regulation via its connections with the amygdala and other subcortical regions [124, 125]. Depression in particular is characterized by reduced cortical neuroplasticity [56, 126–128], synapse atrophy in the PFC [18, 129–131], and a reduced ability of the PFC to regulate limbic areas [132, 133]. Additionally, PTSD, social anxiety disorder, and generalized anxiety have been associated with fewer synaptic connections between the medial PFC and the amygdala, compromising the PFC’s ability to regulate fear responses [134–136]. In addition, neuroplasticity in the circuits between the PFC and the nucleus accumbens, striatum, and limbic system becomes impaired, reducing PFC modulation of these regions [137]. Relatively selective dendritic growth on neurons originating in the PFC may help reverse these deficits, restoring signaling balance and top-down control over the limbic system.

Other modest cognitive improvements found after treatment with psychedelics may also be explained by enhanced neuroplasticity in cortical regions. In animal studies, chronic LSD treatment has been associated with improvements in learning [113, 114, 138]. In humans, LSD has improved frontal-dependent memory retrieval, and unpublished data suggests that it may also improve reinforcement learning, possibly by enhancing reward sensitivity [139, 140]. Cognitive flexibility also involves several

circuits originating in the PFC [141, 142], and ayahuasca and psilocybin have been shown to promote certain aspects of cognitive flexibility [143–147]. Regular ayahuasca users additionally perform better on tests of behavioral inhibition, cognitive flexibility, working memory, and executive functioning [147]. Ayahuasca and psilocybin have also been shown to increase mindfulness, one form of attentional regulation for which the PFC, but also the ACC is essential [13, 58, 143, 148–150]. It is possible that dendritic growth in PFC and ACC neurons is responsible for these effects [59].

Finally, neuroplasticity may not only play a role in positive long-term effects of psychedelics, but also undesirable ones. Drug-induced neuroplastic changes in sensory regions could conceivably be a factor in psychedelic-induced flashbacks, as well as the rarer and more severe hallucinogen persisting perceptual disorder (HPPD), in which some drug effects, including hallucinations and psychological distress, persist after the drug has been metabolized [108, 151].

Experience-dependent neuroplasticity

Neuroplastic changes occur in an activity- and experience-dependent manner [16]. This is an important consideration when discussing psychedelic-enhanced neuroplasticity, because psychedelics themselves can catalyze intense experiences [2]. The beginning of the window of plasticity falls within the timeline of many psychedelic drugs' subjective effects, meaning that at least some of the psychedelic experience takes place within a highly plastic brain [1, 152].

Because of this, the experiences people have under psychedelics may have more power to re-shape neural circuitry than everyday occurrences. This possibility comes with opportunities and challenges. In a safe and supportive setting, psychedelic drugs can cause personally meaningful, emotionally salient experiences which can lead to lasting improvements in well-being [11]. Both patients and healthy volunteers report insights into personal problems, emotional breakthroughs, reprocessing of traumatic memories, and feelings of connectedness and empathy for oneself and others [7, 12, 123, 153–156]. Sometimes this can take the form of a "helioscope effect" in which people seem to perceive their experiences in more detail, but are also able to work through difficult material without becoming overwhelmed [157]. These effects are commonly described in terms of learning experiences [154, 158]. Furthermore, mystical experiences, emotional breakthroughs, and insights correlate significantly with positive long-term effects, independently from the overall intensity of drug effects [155, 159]. There may be a synergy between enhanced neuroplasticity and these positive, therapeutic experiences.

However, especially in unsafe settings, psychedelics can also cause "bad trips" involving intense physical and psychological distress [160]. Negative psychedelic experiences, in particular longer ones, are sometimes associated with subsequent negative changes in well-being, and feelings of anxiety during a psychedelic experience correlate negatively with therapeutic effects [12, 160–162]. Along these lines, most people who develop HPPD report that distressing symptoms appeared after a frightening acute psychedelic experience [163]. Crucially, not all negative experiences lead to decreases in well-being; in fact, most do not, and long-term negative effects are rare [12, 161]. In a survey of people who had had a challenging experience while on psilocybin, the duration of the challenging experience was significantly and negatively correlated with changes in well-being [161]. This suggests that challenging experiences which resolve relatively quickly are less likely to cause undesirable neuroplastic changes, perhaps because overcoming difficult feelings becomes a positive learning experience. However, prolonged experiences of anxiety and distress during a state of heightened plasticity have the potential to be damaging.

Finally, the psychedelic experience itself is not the only important experience in psychedelic therapy. Enhanced neuroplasticity may also make people more responsive to other therapeutic interventions, including psychotherapy, but potentially also neurorehabilitation after stroke or brain injury [14]. Therapeutic interventions combined with antidepressants, which also modestly promote neuroplasticity, have been shown to be more effective than either intervention alone, and the same is likely true of psychedelics [164, 165]. Enhanced neuroplasticity, coupled with a psychedelic experience in a safe setting and accompanying psychotherapy, could ultimately generate a therapeutic effect that is more than the sum of its parts.

CONCLUSIONS

Significant progress has been made toward understanding how psychedelics affect neuroplasticity. Data thus far supports the theory that psychedelics stimulate dendritogenesis, synaptogenesis, and the upregulation of plasticity-related genes in a 5-HT_{2A} receptor-dependent manner, affecting the cortex in particular. The window of neuroplasticity appears to open within a few hours and may last a few days, although neuroplastic changes occurring during this time may survive for at least a month. Because neuroplastic changes occur in an experience-dependent manner, experiences people have during this time may have a greater psychological impact than they otherwise would. Future research should attempt to confirm preclinical findings in humans, clarify optimal doses and specific neuroplastic effects for different psychedelic compounds, and further explore the consequences of psychedelic-enhanced neuroplasticity for both patient groups and healthy people.

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ACKNOWLEDGEMENTS

This work was supported by the University of Fribourg.

AUTHOR CONTRIBUTIONS

Both AEC and GH conceptualized the scope and content of this review. AEC drafted the manuscript, and GH critically revised the manuscript and approved the final version to be published.

FUNDING

Open access funding provided by University of Fribourg.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41386-022-01389-z>.

Correspondence and requests for materials should be addressed to Abigail E. Calder or Gregor Hasler.

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Supplementary Table S1: Citations for Figure 1 by time point and neuroplasticity marker

Legend: black = no change green = upregulation

Outcomes	Timepoints							
	≤1h	1.5h	2h	3h	4h	5h	6h	7h
Upregulation IEGs	Gonzalez-Maeso 2007 Gonzalez-Maeso 2003 Nichols et al 2003	Jefsen et al., 2020 Nichols & Sanders-Bush 2004 Nichols et al., 2003 Nichols & Sanders-Bush, 2002	Benekareddy et al., 2013 Desouza et al 2021	Nichols et al., 2003 Davoudian et al, 2022 Nichols & Sanders-Bush, 2004		Nichols et al., 2003 Nichols et al 2004		
BDNF mRNA		Jefsen et al., 2020	Gewirtz et al, 2002 Desouza et al 2021	Vaibya et al., 1997				
Upregulation other plasticity-related genes	Nichols & Sanders-Bush, 2004	Jefsen et al, 2020 Nichols & Sanders-Bush, 2004						
BDNF protein (mBDNF and/or proBDNF)		Rocha et al, 2021	Hutten et al, 2020	Holze et al, 2019	Hutten et al, 2020 Becker et al, 2021 Holze et al, 2021 Holze et al, 2022 Rocha et al, 2021	Holze et al, 2019	Hutten et al, 2020 Becker et al, 2021 Holze et al, 2021 Holze et al, 2022	Becker et al, 2021
Rate of synaptogenesis, dendritogenesis								
Synaptic and dendritic spine density	Ly et al, 2020						Ly et al, 2020	

Outcomes	Timepoints						
	12h	1d	2d	3d	5d	7d	≥30d
Upregulation IEGs							
BDNF mRNA		Ly et al., 2018					
Upregulation other plasticity-related genes		de la Fuente Revenga et al., 2021 Dacic et al, 2017	de la Fuente Revenga et al., 2021			de la Fuente Revenga et al., 2021	
BDNF protein (mBDNF and/or proBDNF)	Holze et al, 2021 Holze et al, 2022	Ly et al, 2018 Holze et al, 2021	de Almeida et al., 2019				
Rate of synaptogenesis, dendritogenesis		Shao et al., 2021 Cameron et al, 2021		Shao et al., 2021	Shao et al., 2021	Shao et al., 2021	
Synaptic and dendritic spine density		Ly et al., 2018 Ly et al., 2020 Shao et al., 2021 Raval et al., 2020		Ly et al., 2018 Ly et al., 2020 Shao et al., 2021	Shao et al., 2021	Raval et al., 2020 Shao et al., 2021	Shao et al., 2021

Chapter III Effects of psychoplastogens on blood levels of brain-derived neurotrophic factor (BDNF) in humans: a systematic review and meta-analysis

Calder A.E.¹, Hase A.¹, & Hasler G.^{1,2,3}

¹ Molecular Psychiatry Lab, Department of Medicine, University of Fribourg, Switzerland

² Freiburg Mental Health Network, Chemin du Cardinal-Journet 3, 1752 Villars-sur-Glâne, Switzerland

³ Lake Lucerne Institute, Vitznau, Switzerland

Molecular Psychiatry, 2025, Vol. 30(2): 763 – 776

SYSTEMATIC REVIEW OPEN



Effects of psychoplastogens on blood levels of brain-derived neurotrophic factor (BDNF) in humans: a systematic review and meta-analysis

Abigail E. Calder¹, Adrian Hase¹ and Gregor Hasler^{1,2,3}✉

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BACKGROUND: Peripheral levels of brain-derived neurotrophic factor (BDNF) are often used as a biomarker for the rapid plasticity-promoting effects of ketamine, psychedelics, and other psychoplastogens in humans. However, studies analyzing peripheral BDNF after psychoplastogen exposure show mixed results. In this meta-analysis, we aimed to test whether the rapid upregulation of neuroplasticity seen in preclinical studies is detectable using peripheral BDNF in humans.

METHODS: This analysis was pre-registered (PROSPERO ID: CRD42022333096) and funded by the University of Fribourg. We systematically searched PubMed, Web of Science, and PsycINFO to meta-analyze the effects of all available psychoplastogens on peripheral BDNF levels in humans, including ketamine, esketamine, LSD, psilocybin, ayahuasca, DMT, MDMA, scopolamine, and rapastinel. Risk of bias was assessed using Cochrane Risk of Bias Tools. Using meta-regressions and mixed effects models, we additionally analyzed the impact of several potential moderators.

RESULTS: We included 29 studies and found no evidence that psychoplastogens elevate peripheral BDNF levels in humans ($SMD = 0.024$, $p = 0.64$). This result was not affected by drug, dose, blood fraction, participant age, or psychiatric diagnoses. In general, studies with better-controlled designs and fewer missing values reported smaller effect sizes. Later measurement timepoints showed minimally larger effects on BDNF.

CONCLUSION: These data suggest that peripheral BDNF levels do not change after psychoplastogen administration in humans. It is possible that peripheral BDNF is not an informative marker of rapid changes in neuroplasticity, or that preclinical findings on psychoplastogens and neuroplasticity may not translate to human subjects. Limitations of this analysis include the reliability and validity of BDNF measurement and low variation in some potential moderators. More precise methods of measuring rapid changes in neuroplasticity, including neuroimaging and stimulation-based methods, are recommended for future studies attempting to translate preclinical findings to humans.

Molecular Psychiatry; <https://doi.org/10.1038/s41380-024-02830-z>

INTRODUCTION

In the late 1990s, the surprising discovery of ketamine's antidepressant effects spurred a search for the underlying mechanisms [1]. Preclinical research revealed enhanced structural and functional plasticity, particularly in the neocortex, as promising candidates [2]. Relatedly, depressive episodes in both unipolar and bipolar depression are associated with reductions in neuroplasticity at multiple levels of analysis [3, 4]. Research on classic psychedelics and 3,4-Methylenedioxymethamphetamine (MDMA) followed a similar trajectory: the discovery of rapid and sustained therapeutic effects in humans [5] inspired preclinical research which identified promotion of dendritogenesis, synaptogenesis, and increased neurotrophic signaling as potential underlying mechanisms [6–9]. These neuroplastic effects have been most reliably found in the cortex, and specific neural circuits involving the prefrontal cortex appear particularly important [10]. Other regions, including the hippocampus, may also be affected

[11]. Psychoplastogens are distinct from other classes of plasticity-promoting drugs due to their rapid, sustained effect and their specificity for particular cortical circuits. Other antidepressants, including selective serotonin reuptake inhibitors and tricyclic antidepressants, also promote neuroplasticity but act more slowly and require chronic administration [12]. Additionally, psychoplastogens are distinct from drugs of abuse that rapidly promote neuroplasticity in dopaminergic neurons and the mesolimbic system, including cocaine and methamphetamine [13]. To distinguish their specific pattern of effects, the term *psychoplastogen* was coined to describe small molecules which rapidly (i.e., within 24 h) and sustainably promote neuroplasticity after a single dose, particularly in prefrontal cortical circuits [14–16]. This rapid, circuit-specific effect is thought to be a therapeutic mechanism in psychedelic-assisted therapy [11, 12].

Psychoplastogens, which may or may not have psychoactive effects, include classic psychedelics such as lysergic acid

¹Molecular Psychiatry Lab, Department of Medicine, University of Fribourg, Fribourg, Switzerland. ²Fribourg Mental Health Network, Chemin du Cardinal-Journet 3, 1752 Villars-sur-Glâne, Switzerland. ³Lake Lucerne Institute, Vitznau, Switzerland. ✉email: gregor.hasler@unifr.ch

Received: 12 March 2024 Revised: 1 November 2024 Accepted: 5 November 2024

Published online: 29 November 2024

diethylamide (LSD), psilocybin and psilocin, N,N-dimethyltryptamine (DMT), and 5-MeO-DMT, as well as the entactogen MDMA, NMDA receptor ligands such as ketamine and rapastinel, and the muscarinic receptor antagonist scopolamine [8, 14, 17]. Their neuroplasticity-promoting effects have been associated with behavioral effects relevant to depression and PTSD in animal models [18, 19], as well as reopening of critical learning periods [20]. Further preclinical research has supported the theory that psychoplastogens promote metaplasticity, making the brain more sensitive to environmental inputs and thus to synaptic remodeling [20]. They may also shift the cortex into a hyperplastic state, in which dendritogenesis and synaptogenesis are upregulated for a period of several days, producing new dendrites that can survive for even longer [6, 15]. Nearly all psychoplastogens are thought to have antidepressant effects, and remodeling of the extracellular matrix may be a common mechanism of psychoplastogens from different drug classes [20, 21].

Despite promising preclinical data, testing whether psychoplastogens promote neuroplasticity in humans – and whether this underlies their lasting psychological effects – remains challenging. Many studies with psychoplastogens have used peripheral levels of brain-derived neurotrophic factor (BDNF) as a simple and accessible marker of neuroplasticity [22, 23]. BDNF is one of the most widely expressed and well-studied neurotrophins supporting neuroplasticity, and it has important roles in synaptic and dendritic growth, neuronal maturation, and neuroprotection [24, 25]. Both mature BDNF (mBDNF) and its precursor pro-BDNF may be secreted, and they are both important for various neuroplastic processes [25]. BDNF signaling in the brain is an essential facilitator of learning and memory, and it appears to be important for the action of antidepressant drugs [24]. Increases in BDNF expression in the brain have been observed in rodents after treatment with ketamine, LSD, psilocin, MDMA, and other psychoplastogens [6, 7, 19].

Assessing central BDNF levels is too invasive for most human studies, but BDNF is also present in the bloodstream [23]. Platelets store most of the peripheral BDNF secreted from various tissues, including but not limited to the brain, and a small amount of free BDNF is also present in plasma [26]. Rapid changes in circulating BDNF levels, as might be expected after psychoplastogen administration, may be more detectable in plasma than serum because serum BDNF may mostly be inherited from megakaryocytes at the beginning of platelets' 7–10 day lifespan [27, 28]. Some studies suggest that brain and peripheral BDNF may correlate with each other and be associated with greater brain volume in the prefrontal cortex, hippocampus, and other regions [29]. However, exactly how much peripheral BDNF originates from the brain remains a matter of debate [30]. BDNF is a relatively large, charged molecule which is tightly regulated at the synapse, though a small amount appears to travel across the blood-brain barrier [31, 32]. However, BDNF produced in other tissues also contributes to peripheral BDNF levels, including the heart, muscle, liver, and platelet precursor cells [30]. Additionally, peripheral BDNF levels show high variability and can be impacted by age, sex, diet, platelet activation, time of day, and handling of blood samples, as well as lifestyle factors such as sleep, exercise, smoking, and drinking [33, 34]. There is also substantial inter-assay variation in many commercial immunoassays used to quantify BDNF [35].

Despite uncertainty about how well peripheral BDNF reflects brain BDNF, it is one of the most widely used markers of neuroplasticity in human studies and seems related to several known correlates of neuroplasticity, including psychiatric disease, stress, and exercise. Studies using peripheral BDNF as a marker have found that it is reduced in depression, anxiety, and several other psychiatric disorders [25, 36, 37], as well as after stroke [38] and in neurodegenerative disorders [39, 40]. Peripheral BDNF levels also increase after aerobic exercise, in line with findings that

exercise enhances neuroplasticity in the brain [41], and they may be a marker of exposure to psychosocial stress [42]. Furthermore, BDNF levels normalize after remission from psychiatric disease, particularly in depression but also potentially in other psychiatric diseases, such as eating disorders [43–45]. Several meta-analyses pooling various antidepressant treatments, including pharmacological (selective serotonergic reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants) and non-pharmacological treatments (repetitive transcranial magnetic stimulation, vagus nerve stimulation, electroconvulsive therapy), have demonstrated a significant increase in peripheral BDNF after treatment [46–48], though one such analysis – and the only one to include a psychoplastogen, ketamine – also found no change [49]. Generally, BDNF is treated as a sufficient marker of neuroplasticity and is widely used in studies investigating depression and other topics for which neuroplasticity is relevant.

Studies investigating the effects of psychoplastogens on peripheral BDNF have shown mixed results, with some studies showing increases in BDNF after treatment and others showing no change [11]. A recent meta-analysis examined the effects of ketamine and esketamine on peripheral BDNF and other blood-based biomarkers in 11 studies of depressed patients [50]. They reported a significant longitudinal change in BDNF levels amongst treatment responders which was absent in non-responders. Preclinical research using healthy animals suggests that neuroplastic effects may not only be visible in patients, however, and that psychoplastogens other than ketamine should also increase BDNF. Another recent meta-analysis investigated changes in peripheral BDNF after classic psychedelic administration in seven independent samples, mostly healthy subjects. Using a reductionist approach [51] and analyzing only the largest effect size reported from each study (personal communication), they reported an overall increase [52].

Despite their strengths and contributions, previous systematic reviews and meta-analyses have had some limitations. Firstly, none have summarized findings across multiple psychoplastogens. Secondly, authors of some previous meta-analyses reported difficulty in retrieving data from several relevant publications, many of which found no change in BDNF. Finally, some important moderators have not yet been considered, including the timing of BDNF measurements, dose of medications, and aspects of study methodology. Given these limitations, the current analysis includes all available psychoplastogens and several important moderators, as well as a comprehensive search strategy to ensure inclusion of null results. We aimed to thoroughly test the hypothesis that the rapid upregulation of neuroplasticity seen after psychoplastogen administration in preclinical studies is detectable using peripheral BDNF in humans.

METHODS

Pre-registration

This systematic review was pre-registered in the PROSPERO database before beginning the search process (Record ID: CRD42022333096) [53]. It was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [54].

Inclusion criteria

We searched for clinical studies in adult human subjects which evaluated changes in peripheral BDNF after administration of a psychoplastogen. We included all psychoplastogens which have been shown to promote neuroplasticity in animal studies, including LSD, psilocybin and psilocin, DMT (including ayahuasca), 5-MeO-DMT, subanesthetic ketamine, MDMA, scopolamine, and rapastinel. Though we were primarily interested in effects within the first 24 h, we included all available timepoints for completeness. To provide specificity, we excluded studies in which the

psychoplastogen was systematically combined with another pharmacological or neurophysiological intervention in all treatment arms, for example other antidepressants, electroconvulsive therapy, or transcranial magnetic stimulation. Studies incorporating psychotherapy or psychological support were not excluded, nor were studies in which participants continued pre-existing psychiatric medications. Additionally, we excluded studies in which there was no comparison group (either placebo or baseline). We only included English language studies published in peer-reviewed journals since the year 1982, the year in which BDNF was first identified [55].

Search strategy

The initial search was conducted on May 25th, 2022 and updated on June 13th, 2023. We searched the electronic databases PubMed, Web of Science, and PsycINFO. Where possible, we tailored the search to each database to filter by our inclusion criteria. For all three databases, we used the filters for English language and peer-reviewed journals and restricted the publication date to after 1982. In PubMed, we additionally used the filters for clinical studies and human subjects.

We used broad inclusion criteria for our initial search because we had observed that some clinical studies of psychoplastogens which measured BDNF did not appear in search results when filtering by the keyword “BDNF”, “neurotrophic”, or other terms related to neuroplasticity, even when search filters were set to “all fields”. This appeared to occur most often for studies which did not report a significant result for BDNF, particularly when BDNF was not a main outcome and thus did not feature in the abstract. We therefore decided to first identify all clinical studies in human subjects in which any psychoplastogen had been administered, then manually search the full text for keywords related to BDNF. First, we searched databases for articles containing the following keywords in the title or abstract: “psychedelic” OR “psilocybin” OR “psilocin” OR “LSD” OR “lysergic acid diethylamide” OR “DMT” OR “N,N dimethyltryptamine” OR “5-MeO-DMT” OR “5-methoxy-N,N dimethyltryptamine” OR “ketamine” OR “MDMA” OR “3,4-methylenedioxymethamphetamine” OR “ayahuasca” OR “rapastinel” OR “scopolamine” OR “psychoplastogen”. We retrieved the title and abstract of all relevant articles.

Second, two reviewers (AEC and AH) filtered the results by title and abstract using a combination of automatic and manual searching. The goal was to identify studies in which a psychoplastogen was administered to human subjects which could then be manually searched for keywords related to BDNF. Automatic filters were applied to remove articles with common keywords in the title demonstrating that the study could not be included. These included keywords only seen in titles of animal studies (e.g. “rat”, “mouse”, “horse”), keywords related to pediatrics (“pediatric”, “children”), keywords related to the use of concomitant interventions (e.g. “propofol”, “fentanyl”, “opioid”), and keywords related to surgical interventions (e.g. “anesthetic”, “anesthesia”, “surgical”). The remaining articles were filtered manually using both the title and the abstract. Discrepancies were resolved by discussion.

Finally, the same two reviewers retrieved and electronically searched the full text of remaining articles for keywords related to markers of BDNF (namely, “neurotrophic” and “BDNF”). We included all articles which assessed BDNF in adult humans after treatment with a psychoplastogen and included a control group (placebo and/or baseline BDNF levels). Discrepancies were resolved by discussion.

Risk of bias assessment

We performed a risk of bias assessment using the Cochrane Risk of Bias Tools for parallel group and crossover designs [56], as well as the ROBINS-I tool for open-label trials [57]. The assessment was performed by two authors (AEC and AH) separately, and discrepancies were resolved by discussion.

Data extraction

The main outcome of this analysis was change in peripheral BDNF after treatment with a psychoplastogen. From each paper, we recorded the sample size and the mean and standard deviation for BDNF values. Many papers reported multiple effect sizes for different drugs, doses, and timepoints. We chose an integrative meta-analytic approach in order to analyze the impact of potential moderators, because BDNF values are known to be variable and meta-analyses can be strongly affected by choices to only include particular effect sizes [51]. We thus extracted data for all available psychoplastogens, doses, and timepoints. When the required BDNF data was not present in a publication, we requested it from the authors. If data could not be obtained this way, we extracted it from plots using WebPlotDigitizer (Version 4.6). If the required data could still not be obtained, the affected study was excluded from the meta-analysis.

Additionally, we extracted data concerning participant characteristics (age, gender, diagnoses), the specific psychoplastogen(s) and doses used, blood fraction used (i.e., serum or plasma), study design, percentage of missing data, and the timing of each BDNF measurement, including whether it was taken after a single dose or after repeated doses, which was common in open-label ketamine studies. Some studies involving ketamine also divided the sample into responders and non-responders. When possible, we analyzed a single effect size for the whole sample, otherwise we included all effect sizes available in the mixed effects model. We chose this route firstly because an analysis of BDNF in ketamine responders and non-responders has recently been done [50], and secondly because preclinical studies report an overall increase in BDNF without dividing samples. Additionally, studies varied in their choices of controls, with some using only a baseline BDNF measurement, some a comparison to placebo, and some both. We included the strongest control available, with placebo control relativized to baseline being the strongest and placebo control alone the second strongest. Baseline only was considered the weakest control because BDNF levels tend to decrease throughout the day [33] and follow-up measurements were often taken later in the day than baseline.

Statistical analyses

Using Hedges' g as the standardized mean difference (SMD), we configured a mixed effects meta-analysis with random effects for each individual study and effect size. Test statistics and confidence intervals were obtained with cluster robust variance estimation. We first performed a meta-analysis for all psychoplastogens together, then individually for each drug that was represented by at least three independent studies (namely ketamine, LSD, and psilocybin). Additionally, we analyzed all classic psychedelics together in an attempt to replicate results from a previous meta-analysis [52]. When sufficient data were available, we also performed subgroup analyses and meta-regressions to analyze the impact of potential moderators. Subgroup analyses were conducted for plasma and serum because rapid changes in BDNF might appear sooner in plasma. Further subgroup analyses were conducted for healthy subjects and depressed patients, including those with bipolar depression, because the reduced neuroplasticity observed in depressive episodes may affect the response to psychoplastogens. Meta-regressions were used to analyze the impact of the following variables: (1) timing of post-treatment BDNF measurements in hours; (2) average participant age; (3) type of control group, i.e. baseline only, placebo only, or both; (4) overall study design, i.e. parallel group design, crossover, or non-randomized (i.e., open-label); (5) whether BDNF was measured after a single dose or after repeated dosing; (6) immunoassay specificity to mBDNF, pro-BDNF, or both; (7) overall risk of bias rating; (8) percentage of missing BDNF values; and (9) dose, for the analyses involving single drugs and routes of administration. Publication bias was assessed using Egger's tests combined with

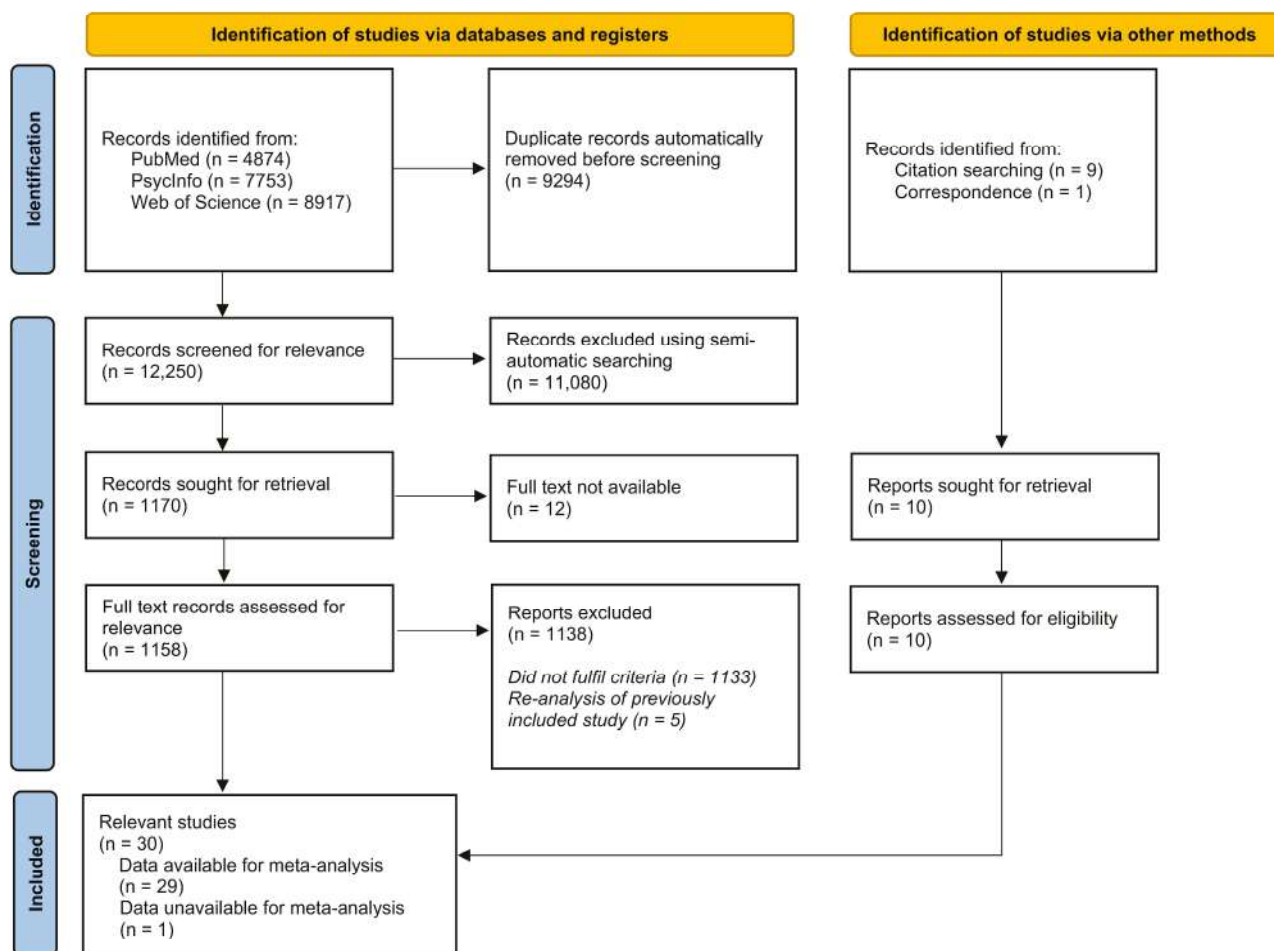


Fig. 1 PRISMA diagram showing the search process.

visual inspection of funnel plots. All statistical analyses were done in R (Version 4.2.3) using the metafor package (Version 4.4.0) [58]. Forest plots were generated using the meta package [59].

RESULTS

Included studies

The initial search identified 13,094 records after removal of duplicates (Fig. 1). Of these, 1170 were identified as clinical studies in which psychoplastogens were administered to adult human subjects. We identified 29 studies which measured BDNF levels after psychoplastogen administration, compared these to a control condition, and had available data for meta-analysis (Table 1). A total of 104 effect sizes from these 29 studies were included in the meta-analysis. Studies contributing multiple effect sizes ($N = 22$) had effect sizes for different timepoints, doses, and/or drugs.

The majority of these studies administered ketamine ($N = 17$), though some also used LSD ($N = 7$), psilocybin ($N = 3$), ayahuasca ($N = 2$), MDMA ($N = 2$), and other psychoplastogens ($N = 1$ each for esketamine, DMT, mescaline, rapastinel, and scopolamine). Most studies analyzed BDNF levels after a single dose of a psychoplastogen, but six studies analyzed BDNF after repeated infusions (range: 3–7) of ketamine ($N = 5$) or rapastinel ($N = 1$). Fourteen studies involved healthy subjects and 16 involved patient groups, including patients with depression ($N = 12$), bipolar depression ($N = 3$), anxiety disorders ($N = 2$), and OCD ($N = 1$). Most studies measured BDNF in the first 48 h after drug administration ($N = 25$), and a few ketamine studies measured it

between 7 and 26 days later ($N = 6$). We could find information on the specificity of immunoassays for mBDNF and pro-BDNF for 23 studies, of which 13 assessed total BDNF and 10 (all from the same research group) used an assay specific to mBDNF (Table S1).

Risk of bias assessment

Results of the risk of bias assessment are shown in Supplementary Fig. S1. For the 12 randomized crossover trials, one was rated as high risk of bias, and the rest were rated as low risk. For the nine randomized parallel trials, four were rated as low risk, three as having some concerns, and two as high risk. The most problematic domains involved missing outcome data and potential for selection of the reported result. For non-randomized trials, all eight studies received a high/serious risk of bias rating, largely due to the potential for baseline confounding and potential for bias in the selection of the reported result.

Effects of psychoplastogens on BDNF

Results from all analyses, including subgroup analyses and metaregressions, are summarized in Table 2. The combined effect size across all psychoplastogens was not significant ($SMD = 0.024$, $p = 0.64$). There was a relatively low level of heterogeneity ($I^2 = 22.64\%$) and no evidence of publication bias ($p = 0.15$, Supplementary Fig. S2). Subgroup analyses found no significant effects for plasma or serum alone, as well as no effect for healthy subjects or depressed patients alone. Because of the possibility that short-term changes in BDNF (<7 days post-treatment) may be better visible in plasma and long-term changes (≥ 7 days post-treatment) may be better visible in serum, we repeated the

Table 1. Studies included in the meta-analysis. N is the sample size included in this analysis.

Study	N	Drug	Dose	Timepoints	Sample	Blood fraction	BDNF change
Allen et al. [102]	16	ketamine	0.5 mg/kg	2, 24 h; 7 d	TRD	serum	No change except at 7 d in responders
Becker et al. [103]	23	psilocybin	25 mg	4, 7 h	healthy	plasma	Increase
Becker et al. [62]	24	LSD	100 µg	6, 9, 12 h	healthy	plasma	Increase
Caliman-Fontes et al. [104]	27	esketamine	0.25 mg/kg	24 h, 7 d	TRD	serum	No change
		ketamine	0.5 mg/kg				
de Almeida et al. [105]	69	ayahuasca	1 mL/kg	48 h	healthy, TRD	serum	Increase
Duncan et al. [106]	29	ketamine	0.5 mg/kg	4 h	MDD	plasma	Increase
Glue et al. [107]	6	ketamine	60, 120, 240 mg p.o.	24 h	healthy	serum	No change
Glue et al. [108]	12	ketamine	0.25, 0.5, 1 mg/kg	0.25, 0.5, 1, 2 h	anxiety	serum	No change
Glue et al. [109]	7	ketamine	60 mg p.o.	2-96 h	TRD, anxiety	serum	No change
Grunebaum et al. [110]	46	ketamine	0.5 mg/kg	4 h	MDD	plasma	No change
Grunebaum et al. [111]	9	ketamine	0.5 mg/kg	4 h	BPD	plasma	No change
Haile et al. [112]	15	ketamine	0.5 mg/kg	4 h	TRD	plasma	Increase in responders only
Holze et al. [60]	27	LSD	100 µg	3, 5 h	healthy	plasma	No change
		MDMA	100 mg				
Holze et al. [113]	16	LSD	25, 50, 100, 200 µg	6, 12, 24 h	healthy	plasma	Increase after 200 µg LSD only
Holze et al. [114]	28	LSD	100, 200 µg	4, 6, 12 h	healthy	plasma	No change
		psilocybin	15, 30 mg				
Hutten et al. [63]	10	LSD	5, 10, 20 µg	2, 4, 6 h	healthy	plasma	Increase after 5 and 20 µg LSD only
Kang & Vasquez [115]	10	ketamine	0.5 mg/kg	7 d	TRD	serum	No change
Ley et al. [116]	32	LSD	100 µg	3, 6, 12 h	healthy	plasma	No change
		psilocybin	20 mg				
		mescaline	300, 500 mg				
Linkovski et al. [117]	7	ketamine	0.5 mg/kg	0.67, 2, 4 h	OCD	serum	Decrease in rapastinel group
		rapastinel	10 mg/kg	0.67, 2, 4 h			
Machado-Vieira et al. [118]	23	ketamine	0.5 mg/kg	4 h	healthy	plasma	No change
Medeiros et al. [119]	38	ketamine	0.5 mg/kg	4, 24, 72 h	MDD	plasma	No change
Park et al. [120]	23	scopolamine	4 µg/kg	2.5 h	MDD	plasma	No change
Rocha et al. [121]	15	ayahuasca	1 mL/kg	2, 4 h	healthy	plasma	No change
Rybakowski et al. [122]	25	ketamine	0.5 mg/kg	7, 14 d	BPD	serum	Decrease in non-responders only
Straumann et al. [61]	24	LSD	100 µg	3, 6, 9, 12, 24 h	healthy	serum	No change
		MDMA	100 mg				
Vogt et al. [123]	27	DMT		1.5, 2.5 h	healthy	plasma	No change
Wang et al. [124]	127	ketamine	0.5 mg/kg	13, 26 d	BPD, MDD	serum	Increase in responders at day 14 only
Woelfer et al. [125]	36	ketamine	0.5 mg/kg	2, 24 h	healthy	plasma, serum	Increase
Zheng et al. [126]	75	ketamine	0.5 mg/kg	13, 26 d	MDD	plasma	Increase
Total	826						

Timepoints refers to the timing of blood draws used for BDNF analysis. BDNF change refers to the change compared to the control condition used for this analysis.

TRD treatment-resistant depression, MDD major depressive disorder, BPD bipolar depression, OCD obsessive compulsive disorder.

Table 2 Summary of all results from subgroup analyses and meta-regression models analyzing the effects of psychoplastogens on peripheral BDNF.

Subgroup analyses						
	Overall	Healthy	Depression	Plasma	Serum	
All psychoplastogens	0.02 [-0.08 to 0.13]	-0.01 [-0.17 to 0.14]	0.10 [-0.06 to 0.26]	0.05 [-0.09 to 0.19]	-0.04 [-0.21 to 0.13]	
Ketamine	0.03 [-0.11 to 0.17]	-0.08 [-0.25 to 0.08]	0.10 [-0.07 to 0.27]	0.09 [-0.17 to 0.34]	-0.05 [-0.26 to 0.17]	
Classic psychedelics	0.05 [-0.16 to 0.26]	-	-	0.04 [-0.20 to 0.28]	0.09 [-4.15 to 4.33]	
Meta-regressions						
	Dose	Timing (h)	Age	Missing values	mBDNF	Multiple infusions
All psychoplastogens	-	0.0005* [0-0.001]	-0.0008 [-0.01 to 0.01]	0.77* [0.13-1.42]	0.007 [-0.26 to 0.27]	-
Ketamine	-	0.0007* [0.0002-0.001]	-0.003 [-0.02 to 0.01]	0.76 [-0.18 to 1.70]	0.10 [-0.14 to 0.34]	0.26 [-0.05 to 0.56]
Classic psychedelics	-	0.01 [-0.01 to 0.03]	0.005 [-0.08 to 0.09]	0.68 [-2.01 to 3.37]	-0.32 [-1.43 to 0.79]	-
LSD	0.002 [-0.01 to 0.01]	0.02 [-0.04 to 0.09]	-0.03 [-0.09 to 0.03]	0.59 [-1.26 to 2.44]	-	-
Psilocybin	0.006 [-0.37 to 0.38]	-0.06 [-0.33 to 0.22]	0.09 [-0.32 to 0.51]	7.06 [-3.43 to 17.56]	-	-
Design		Control group		Risk of bias		
Crossover RCT	Parallel RCT	Placebo	Baseline + placebo	Some concerns	High	
All psychoplastogens	-0.18 [-0.44 to 0.08]	-0.13 [-0.38 to 0.11]	-0.006 [-0.27 to 0.25]	-0.31* [-0.55 to -0.06]	-0.005 [-0.23 to 0.22]	0.26* [0.05-0.46]
Ketamine	-0.46 [-1.12 to 0.20]	-0.26* [-0.48 to -0.04]	-0.19 [-1.53 to 1.15]	-	0.04 [-0.22 to 0.31]	0.32* [0.02-0.62]
Classic psychedelics	-0.32 [-1.43 to 0.79]	-	0.005 [-1.07 to 1.08]	-0.40 [-1.19 to 0.39]	-	0.35 [-0.04 to 0.74]
LSD	-	-	0.13 [-0.45 to 0.71]	-0.32 [-0.91 to 0.28]	-	0.34 [-0.02-0.71]

Missing fields indicate insufficient data available for analysis. Data are shown as standardized mean difference with 95% confidence intervals. In the moderator analyses, contrasts were as follows: mBDNF vs. total BDNF; multiple vs. single infusions; crossover or parallel RCT vs. non-randomized open-label trials; placebo control groups vs. baseline only control; and some concerns or high risk of bias vs. low risk of bias. * $p < 0.05$.

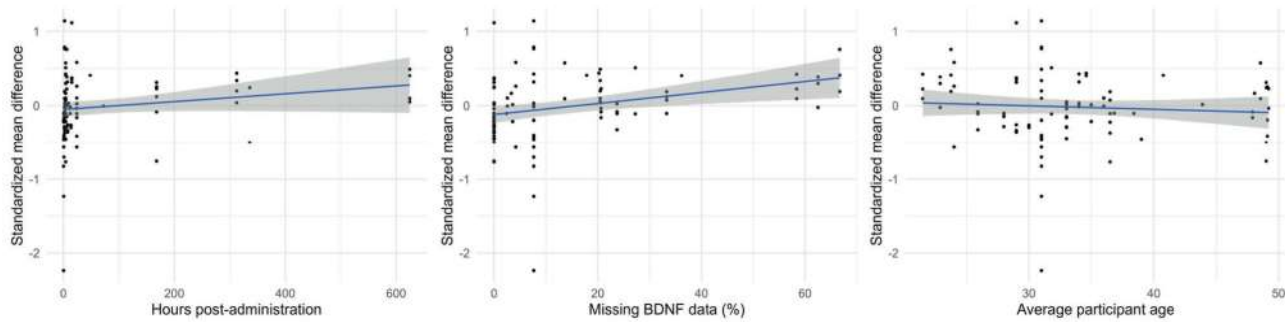


Fig. 2 Relationship between effect sizes and the continuous variables of timing, percentage of missing values, and average participant age for studies administering any psychoplastogen. Shading shows 95% confidence intervals. The effect of hours post-administration was significant but minimal ($SMD = 0.0005$, $p = 0.038$). Studies with a higher percentage of missing data reported significantly greater effect sizes ($SMD = 0.77$, $p = 0.028$).

analyses using only data on short-term changes in plasma and long-term changes in serum; this did not change any of the results. Meta-regressions found no significant effect of age, study design, BDNF immunoassay sensitivity, or overall risk of bias on change in BDNF. Later BDNF measurements were associated with minimally larger effect sizes ($SMD = 0.0005$, $p = 0.038$, Fig. 2). Studies comparing change from baseline BDNF between a treatment and placebo group reported significantly lower effect sizes than studies using only a baseline BDNF measurement as a control group ($SMD = -0.31$, $p = 0.031$). Additionally, studies with a higher percentage of missing data reported greater effect sizes ($SMD = 0.77$, $p = 0.029$), and studies with a high overall risk of bias rating showed significantly greater effect sizes than studies with a low rating ($SMD = 0.26$, $p = 0.017$).

For ketamine, the overall effect size was not significant ($SMD = 0.03$, $p = 0.65$, Fig. 3). Subgroup analyses found no effect for plasma or serum, as well as no effect for healthy subjects or depressed patients (Table 2). There was no significant effect of age, missing values, control group, immunoassay sensitivity, or repeated infusions. Randomized trials using a parallel design reported significantly smaller effect sizes than non-randomized open-label trials ($SMD = -0.26$, $p = 0.03$), and trials with a high risk of bias rating reported significantly higher effect sizes than those with a low rating ($SMD = 0.32$, $p = 0.04$). Later BDNF measurements showed minimally larger effect sizes ($SMD = 0.0007$, $p = 0.02$, Supplementary Fig. S3).

Classic psychedelics, when analyzed together, also had no significant effect on BDNF ($SMD = 0.048$, $p = 0.62$, Fig. 4). There was also no effect for either plasma or serum alone (Table 2). Meta-regressions showed no significant effect of timing, age, study design, missing values, control condition, or immunoassay specificity. When analyzing individual psychedelics, we also found no significant effect for LSD ($SMD = 0.01$, $p = 0.93$, Supplementary Fig. S4) or psilocybin ($SMD = 0.007$, $p = 0.97$, Supplementary Fig. S5). For LSD, meta-regressions showed no significant effect of dose, timing, control group, age, or missing values (Supplementary Fig. S6), although there was a trend toward studies with higher risk of bias having greater effect sizes than studies with low risk ($SMD = 0.34$, $p = 0.06$).

DISCUSSION

This meta-analysis found no evidence that a single dose of any psychoplastogen, including ketamine, LSD, psilocybin, and others, rapidly increased peripheral BDNF levels in human subjects. This is the first meta-analysis to consider all available psychoplastogens and timepoints, as well as both patients and healthy people, when investigating effects of psychoplastogens on peripheral BDNF. Furthermore, a major strength of this analysis is the particular care given to searching for null results which might otherwise be

under-represented, as well as the use of mixed effects models including all reported effect sizes in published papers and the consideration of moderators.

The impact of psychoplastogens on BDNF did not change based on specific drugs or drug classes, dose, blood fraction, psychiatric diagnoses, or average participant age. We were not able to replicate previous reports suggesting that classic psychedelics elevate peripheral BDNF levels [52]. This may be due to our inclusion of all available means for all drugs, doses, and timepoints in each study, as well as the inclusion of four additional studies of classic psychedelics [60–63] and differences in statistical choices when selecting data for calculating standardized mean differences.

We found a small but significant effect of timing, so that a greater amount of time between the psychoplastogen intervention and blood collection was associated with slightly larger effect sizes. Though the effect was minimal, it would be consistent with a previous meta-analysis suggesting that responders to ketamine treatment for depression showed greater longitudinal increases in peripheral BDNF over time [50]. Preclinical studies suggest that psychoplastogens induce rapid and sustained upregulation in brain BDNF signaling which is maintained via prolonged mTOR activation [16]. Assuming a similar process occurs in humans, it may take time for the increase in neural BDNF to be reflected in the periphery, and peripheral BDNF may thus not reflect the nearly immediate antidepressant effects of ketamine or other psychoplastogens. It is also possible that late increases in peripheral BDNF do not originate from the brain and instead reflect an effect of psychoplastogens on BDNF in megakaryocytes, from which platelets appear to inherit most of their stored BDNF at the beginning of their 7–10 day lifespan [27]. Overall, though we found no evidence of a rapid increase in BDNF, previous research suggests that slow increases in peripheral BDNF may be specifically associated with successful antidepressant treatment.

Other moderators showing significant effects suggested that reported effects of psychoplastogens on BDNF were reduced with more rigorous study designs. In the analysis of all psychoplastogens, studies with more missing BDNF values tended to report bigger effect sizes. Additionally, studies calculating changes in BDNF using both a placebo control and change from baseline reported lower effect sizes, and studies with a high risk of bias rating showed bigger effect sizes than studies with a low risk of bias. For ketamine studies, those using randomized controlled designs reported lower effect sizes than non-randomized open-label trials. Taken together, these findings suggest that more rigorously controlled studies tend to find reduced effects of psychoplastogens on BDNF.

Preclinical research suggests that psychoplastogens can enhance BDNF levels and other aspects of neuroplasticity in the brain within a few hours of exposure [11]. The lack of an effect on

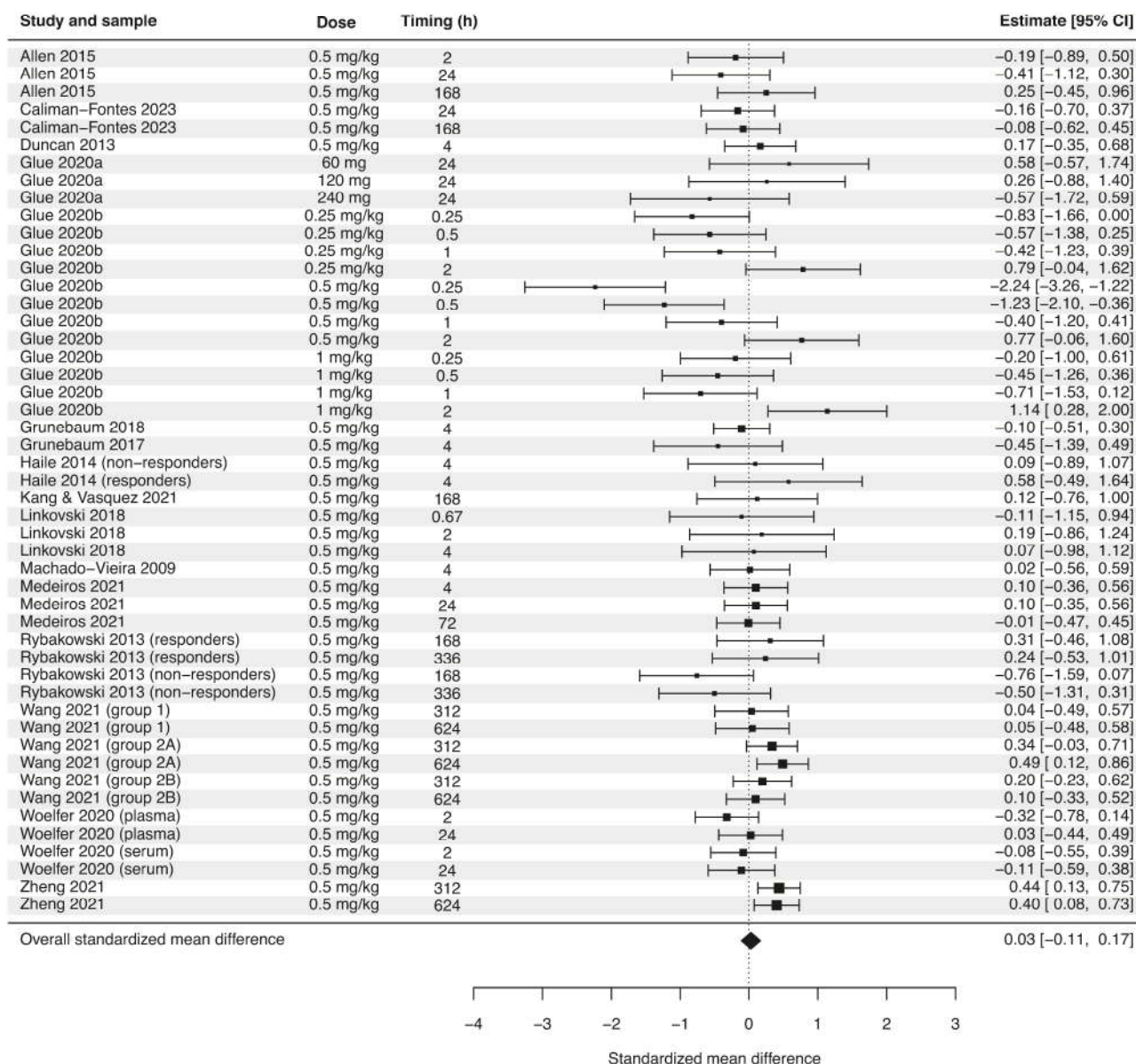


Fig. 3 Forest plot showing overall effect size estimates of the change in BDNF after administration of ketamine. There was no significant effect of ketamine on BDNF.

peripheral BDNF in humans may thus seem unexpected. We propose two potential explanations. Firstly, it is possible that peripheral BDNF levels are not valid or reliable markers of short-term changes in brain BDNF and are thus unsuitable for measuring the purportedly rapid effects of psychoplastogens on neuroplasticity. Alternatively, it is possible that the pro-neuroplastic effects of psychoplastogens observed in animals may not occur in humans, or not to the same degree. Below we discuss both of these possibilities, as well as the limitations of this analysis and avenues for future research assessing rapid neuroplasticity changes after psychoplastogen intake in humans.

Reliability and validity of peripheral BDNF as a marker of drug-induced neuroplasticity

There are several reasons to doubt peripheral BDNF as an informative biomarker in studies of psychoplastogen-induced neuroplasticity. Many commercially available BDNF assays, including some used in the studies we analyzed, show high inter-assay variability [35]. This is in addition to the questionable reliability of

BDNF itself, which can vary strongly with sample handling (e.g. storage time, hemolysis), experimental parameters (e.g. time of day), and unavoidable fluctuations in participant characteristics (e.g. hormones, sleep deprivation, exercise, or recent smoking and drinking) [33, 34, 64]. Plasma BDNF also may be less reliable than serum BDNF, though it is questionable whether rapid changes in BDNF can be assessed in serum at all because most serum BDNF may be inherited from megakaryocytes [27, 65]. Studies can control for some of these factors, for example by instructing participants to avoid certain activities, including covariates in analyses, or excluding outlier values which might be due to hemolysis. However, it is difficult to account for all of these factors, and most studies used in this analysis did not describe how they handled outliers or managed known covariates of BDNF. One potential avenue for future research would be to more consistently distinguish between pro-BDNF and mBDNF, which may show different or even opposite associations with depressive symptoms and neuroplastic processes and may thus respond differently to psychoplastogens [66].

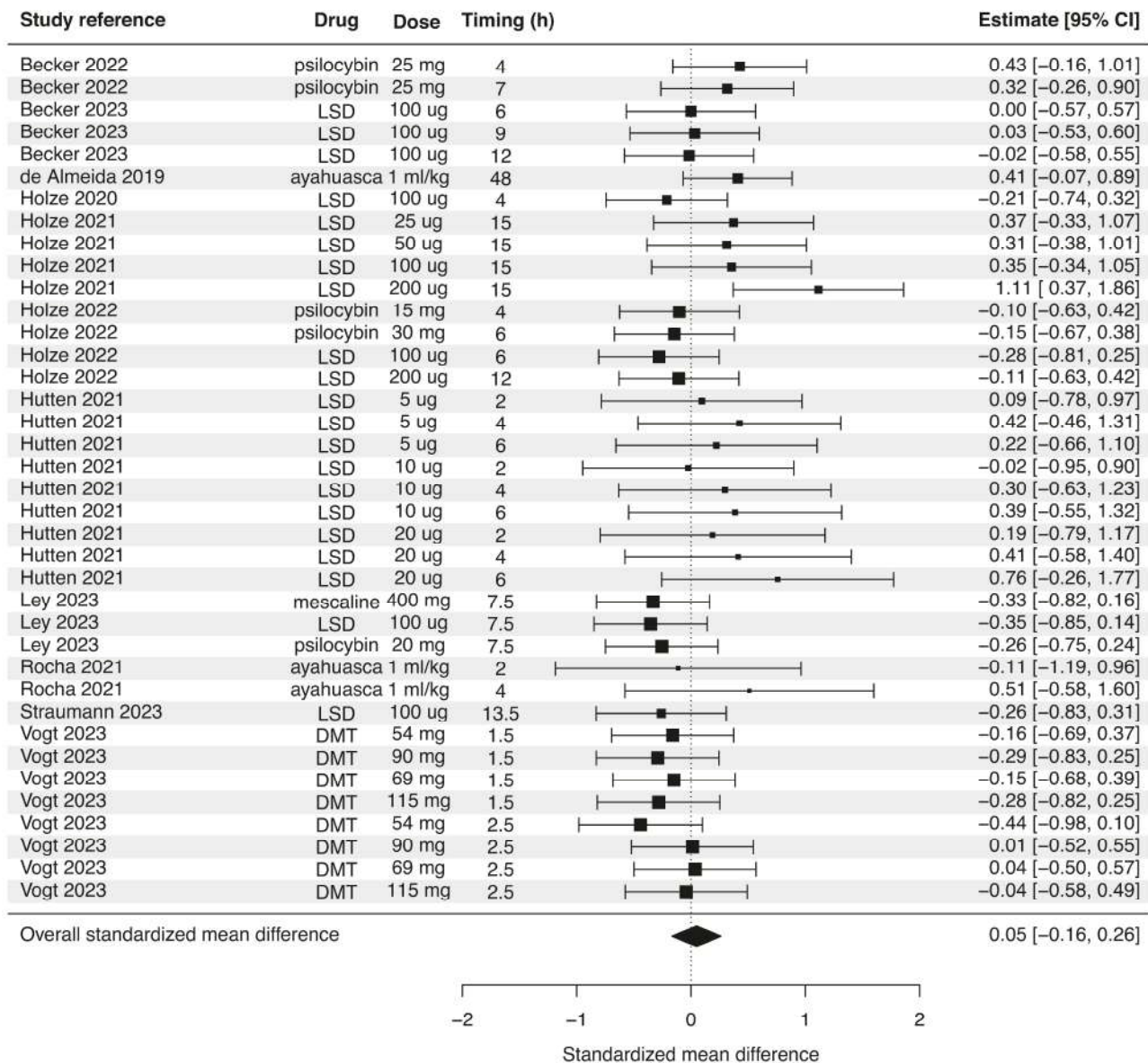


Fig. 4 Forest plot showing overall effect size estimates of the change in BDNF after administration of classic psychedelics. There was no significant effect of psychedelics on BDNF.

Furthermore, the validity of peripheral BDNF for reflecting brain BDNF is uncertain because it is not clear how much peripheral BDNF originates in the brain, and the proportion may be quite low. BDNF is a large molecule which does not diffuse easily across the blood-brain barrier, and the amount transported into the bloodstream may be very small [32]. Peripheral BDNF reflects secretions from other organs than the brain, and it is also mostly stored in platelets and thus affected by platelet count and activation [67]. Additionally, there is some evidence that serum BDNF mostly originates from megakaryocytes [27]. In rats and pigs, peripheral and hippocampal BDNF levels moderately correlate with each other [68]. However, several studies have failed to find overall correlations between central (i.e., cerebrospinal fluid) and peripheral BDNF in humans [69, 70]. In rodents, ketamine is also able to rapidly increase plasma BDNF levels without a corresponding increase in brain BDNF [71]. Peripheral BDNF may not be sensitive enough to reflect changes in BDNF expression in brain tissue at all, and platelets contain 100-1000-fold more BDNF than brain tissue [27, 72]. Thus, it may

be that peripheral BDNF levels do not allow much inference about brain BDNF in the first place.

Another possibility is that peripheral BDNF levels correlate with brain BDNF under normal circumstances but do not reflect rapid changes in plasticity, such as those induced by psychoplastogens in animals. Rather, they may reflect longer-term changes in plasticity and BDNF homeostasis [73]. Psychoplastogens have rapid antidepressant effects and are thought to rapidly (<24 h) stimulate neuroplasticity, including BDNF expression [7]. However, if this is the case in the human brain, it may not be immediately reflected in peripheral BDNF. Overall, it is possible that peripheral BDNF does not reflect brain BDNF very well in humans, or that it is at least unsuitable for assessing rapid changes in brain BDNF.

The “rat park” problem of drug-induced neuroplasticity

Another potential explanation for our results is that findings from animal research on psychoplastogens may not translate well to humans at all, at least not under all circumstances.

Neurophysiological differences between species are always a possible explanation for differences between preclinical and human studies, though it is notable that BDNF structure and function are highly conserved across vertebrates [74]. Another possible confounder is laboratory conditions, specifically the stark differences in environment between laboratory animals and human study participants. To the best of our knowledge, no preclinical studies have reported examining psychoplastogen-induced neuroplasticity under anything other than standard conditions [7, 9, 15]. Standard laboratory conditions for animal studies consist of relatively small cages with bedding and access to food and water, and animals may be housed alone or with a few same-sex animals. However, this unstimulating environment may negatively impact neuroplasticity compared to an animal's natural setting, as seen in studies of enriched environments. Enriched environments, originally developed in from the "rat park" studies of drug dependence, are larger than standard cages and provide novel objects and toys, exercise equipment, and/or low-stress social interaction [75]. Compared to animals living in standard conditions, those living in enriched environments show increased neuroplasticity, including enhanced BDNF signaling, increased synapse size and neurogenesis, and increased dendritic branching, length, and spine numbers [75–77]. Living environment could greatly impact the translational validity of neuroplasticity studies given the stark contrast between a standard laboratory animal environment and an average human environment, which might be duly described as "enriched." Neuroplasticity-enhancing drugs may encounter a ceiling effect, after which further enhancement is hardly possible [6]. If animals living in standard conditions have reduced neuroplasticity to begin with, they could be more responsive to drug-induced neuroplasticity than wild animals of the same species, or indeed, human beings.

How can we measure psychoplastogen-induced neuroplasticity in humans?

If BDNF may not be a reliable and valid marker of drug-induced neuroplasticity, other methods involving neuroimaging and electrophysiology might be better tools for examining potential effects of psychoplastogens in humans. These methods also have the advantage of being more specific to brain regions and neuroplastic processes than a general peripheral marker like BDNF.

Structural imaging with magnetic resonance imaging or positron emission tomography can assess structural neuroplastic changes after a drug intervention, though these may not always reflect enhanced capacity for neuroplasticity per se. Synaptic growth can also be assessed using positron emission tomography by targeting synaptic vesicle glycoprotein 2 A (SV2A) [78]. A few studies have already examined the effects of psychoplastogens on structural neuroplastic changes. Ketamine may cause neuronal growth in some brain regions of both healthy subjects and patients, particularly the hippocampus [79–82]. Like with BDNF, however, some studies also find no change or even volume decreases [83–85]. A recent systematic review suggested that ketamine's antidepressant effect may be associated with functional neuroplastic changes in the prefrontal cortex, frontoparietal regions, and striatum, which warrant further investigation [86]. Additionally, a study assessing SV2A density after ketamine treatment found no change in any healthy or patient group overall, though patients who began with lower SV2A density showed a significant increase in SV2A density in the dorsolateral prefrontal cortex and anterior cingulate cortex [87]. This would support the hypothesis that drug-induced neuroplasticity is most visible when a deficit is present at baseline.

Neuroplastic changes in functional connectivity can similarly be assessed using functional magnetic resonance imaging or magnetoencephalography, as well as electroencephalography

[88, 89]. Lasting changes in functional connectivity have been reported after treatment with psilocybin and ayahuasca in healthy subjects [90–92]. Additionally, ketamine appears to post-acutely increase functional connectivity in regions important for emotional regulation and reward processing in depressed patients, although findings are somewhat mixed and the literature is small [93].

Finally, stimulation-based methods involving electrophysiology, such as paired associative stimulation or sensory-induced long-term potentiation (LTP), can be used to assess neuroplasticity in humans [94, 95]. These methods induce short-lived functional changes resembling LTP or long-term depression, the amplitude of which is an index of the capacity for neuroplasticity, and are able to measure the brain's capacity for neuroplastic changes rather than simply the changes themselves. They are also sensitive to known correlates of neuroplasticity, including age, depression, physical activity, and short-term drug effects [96]. Sensory LTP in particular has been used in several studies of psychoplastogens, which have found increased visual LTP in depressed patients following ketamine treatment [97], as well as some evidence of complex neuroplastic effects in depressed patients receiving psilocybin [98] and healthy men microdosing LSD [99]. Overall, neuroimaging and electrophysiological methods likely offer more promising and specific avenues for exploring psychoplastogens' effects on neuroplasticity than a peripheral marker like BDNF.

Limitations

The results of this meta-analysis should be interpreted with certain limitations in mind. Firstly, handling and storage of BDNF samples can strongly impact results, and information on how this was controlled for was not always available. As discussed above, variations in the sensitivity and reliability of BDNF assays for mBDNF and its precursor proteins may introduce a great deal of noise, and most studies did not mention controlling for known covariates of BDNF. Additionally, one should consider the variation available in the potential moderator variables included. There was relatively little variation in dose, especially for ketamine. Studies of LSD and psilocybin in particular showed little variation in average participant age. Most studies also measured BDNF within a relatively short period of time after treatment (<48 h). This is the time frame in which preclinical studies observe rapid changes in brain BDNF [11]. However, a previous meta-analysis of ketamine treatments in depressed patients suggested that changes in peripheral BDNF in humans may only be visible on a larger time scale, e.g. several weeks, similar to BDNF changes following slower-acting antidepressant treatments. Relatedly, we did not have many studies with multiple ketamine infusions, and the ones we were able to include had a small (<7) number of infusions. Furthermore, this meta-analysis did not differentiate between treatment responders and non-responders in the studies of patients. It is possible that the effects of psychoplastogens on BDNF unfold over a longer timescale than analyzed here, and that they may be relatively specific to treatment responders who had been depressed. Similarly, psychoplastogens may act differently on different patient populations, but some patient groups (anxiety disorders, OCD) were too small to be analyzed here. Other moderator analyses that could not be conducted due to a lack of available data include the impact of smoking, medical comorbidity, and concurrent medication.

Additionally, we chose to analyze the effects of all known psychoplastogens together, given findings suggesting that they share downstream mechanisms of action involving glutamatergic signaling and remodeling of the extracellular matrix [20, 100, 101]. This is a similar approach to other meta-analyses analyzing multiple treatments expected to have similar effects on BDNF, for example antidepressant therapies [46–48]. However, it is possible that some psychoplastogens are more effective than others. We were only able to analyze ketamine, LSD, and psilocybin as

separate drugs, and the number of studies was still relatively small for LSD and psilocybin.

CONCLUSION AND OUTLOOK

Taken together, this analysis demonstrates that the rapid increase in neuroplasticity after psychoplastogens observed in preclinical studies was not found in human studies which used peripheral BDNF as a biomarker. Psychoplastogens as a whole, but also the subgroup of classic psychedelics and the individual substances ketamine, LSD, and psilocybin all showed no significant effect on peripheral BDNF. It is possible that peripheral BDNF is an unsuitable biomarker for rapid, psychoplastogen-induced neuroplasticity. Additionally, an increase in neuroplasticity may be most visible when neuroplastic deficits are present, which could cause some problems with translating findings from animals in standard laboratory environments to humans. These findings are important because peripheral BDNF is widely used as a marker of rapidly enhanced neuroplasticity in studies of psychoplastogens, and its usefulness in this regard appears extremely limited. If we are to determine whether psychoplastogens rapidly enhance neuroplasticity in humans like they appear to do in animals, neuroimaging and stimulation-based methods may be more informative than peripheral markers like BDNF. As it stands, peripheral BDNF gives us no discernible evidence of increased neuroplasticity in humans after psychedelics and other psychoplastogens.

DATA AVAILABILITY

The datasets analysed during the current study are available in the Open Science Framework (OSF) repository, <https://osf.io/t7d4c/>.

CODE AVAILABILITY

R code used for this analysis is available in the Open Science Framework (OSF) repository, <https://osf.io/t7d4c/>.

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ACKNOWLEDGEMENTS

We would like to thank Dr. Andrew Allen, Dr. Paul Glue, Dr. Michael Grunebaum, Dr. Rafael Guimarães dos Santos, Dr. Friederike Holze, Dr. Gustavo Medeiros, and Dr. Marie Woelfer for providing additional data from their publications for use in the meta-analysis.

AUTHOR CONTRIBUTIONS

AEC, AH and GH contributed to the conceptualization of this meta-analysis. AEC and AH carried out data collection and extraction. AC conducted the analysis and drafted the manuscript with support from AH and GH. GH reviewed and edited the manuscript and supervised the project.

FUNDING

This study was funded by the University of Fribourg, Switzerland. Open access funding provided by University of Fribourg.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41380-024-02830-z>.

Correspondence and requests for materials should be addressed to Gregor Hasler.

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Supplementary Information

Supplement to: Calder A, Hase A & Hasler G. (2024) Effects of Psychoplastogens on Blood Levels of Brain-Derived Neurotrophic Factor (BDNF) in Humans: A Systematic Review and Meta-Analysis.

ID	Authors	Overall	D1	D2	D3	D4	D5	D6	D7
Crossover Design									
1	Becker et al. (2022a)	+	+	+	+	+	!	+	
2	Becker et al. (2022b)	+	+	+	+	+	!	+	
3	Caliman-Fontes et al. (2023)	+	+	+	+	+	!	+	
4	Glue et al. (2020b)	+	+	+	+	+	!	+	
5	Holze et al. (2020)	+	+	+	+	+	!	+	
6	Holze et al. (2021)	+	+	+	+	+	!	+	
7	Holze et al. (2022)	+	+	+	+	+	!	+	
8	Hutten et al. (2021)	-	+	+	-	+	!	+	
9	Ley et al. (2023)	+	+	+	+	+	!	+	
10	Park et al. (2019)	+	+	+	+	+	!	+	
11	Straumann et al. (2023)	+	+	+	+	+	!	+	
12	Vogt et al. (2023)	+	+	+	+	+	!	+	
Parallel Design									
13	Allen et al. (2015)	!	!	!	+	+	!		
14	de Almeida et al. (2019)	-	!	-	-	+	-		
15	Glue et al. (2020a)	+	+	!	+	+	!		
16	Grunebaum et al. (2017)	+	+	!	+	+	+		
17	Grunebaum et al. (2018)	+	+	+	+	+	!		
18	Haile et al. (2014)	!	+	+	!	+	!		
19	Medeiros et al. (2021)	+	+	+	+	+	!		
20	Rocha et al. (2021)	-	+	+	-	+	!		
21	Woelfer et al. (2020)	!	+	+	!	+	!		
Nonrandomized Design									
22	Duncan et al. (2013)	-	-	+	+	+	+	+	-
23	Glue et al. (2020c)	-	-	+	+	+	+	+	!
24	Kang & Vasquez (2021)	-	-	+	+	+	!	+	!
25	Linkovski et al. (2018)	-	-	+	+	+	!	+	!
26	Machado-Vieira et al. (2009)	-	-	+	+	+	+	+	!
27	Rybakowski et al. (2013)	-	-	+	+	+	+	+	!
28	Wang et al. (2021)	-	-	+	+	+	!	+	-
29	Zheng et al. (2021)	-	-	+	+	+	!	+	!

Low risk
 Some concerns
 High risk

D1 Randomisation process
 D5 Bias arising from period and carryover effects
 D2 Deviations from the intended interventions
 D3 Missing outcome data
 D4 Measurement of the outcome
 D5 Selection of the reported result

D1 Bias due to confounding
 D2 Bias in selection of participants into the study
 D3 Bias in classification of interventions
 D4 Bias due to deviations from intended interventions
 D5 Bias due to missing data
 D6 Bias in measurement of outcomes
 D7 Bias in selection of the reported result

Figure S1. Results of the risk of bias assessment.

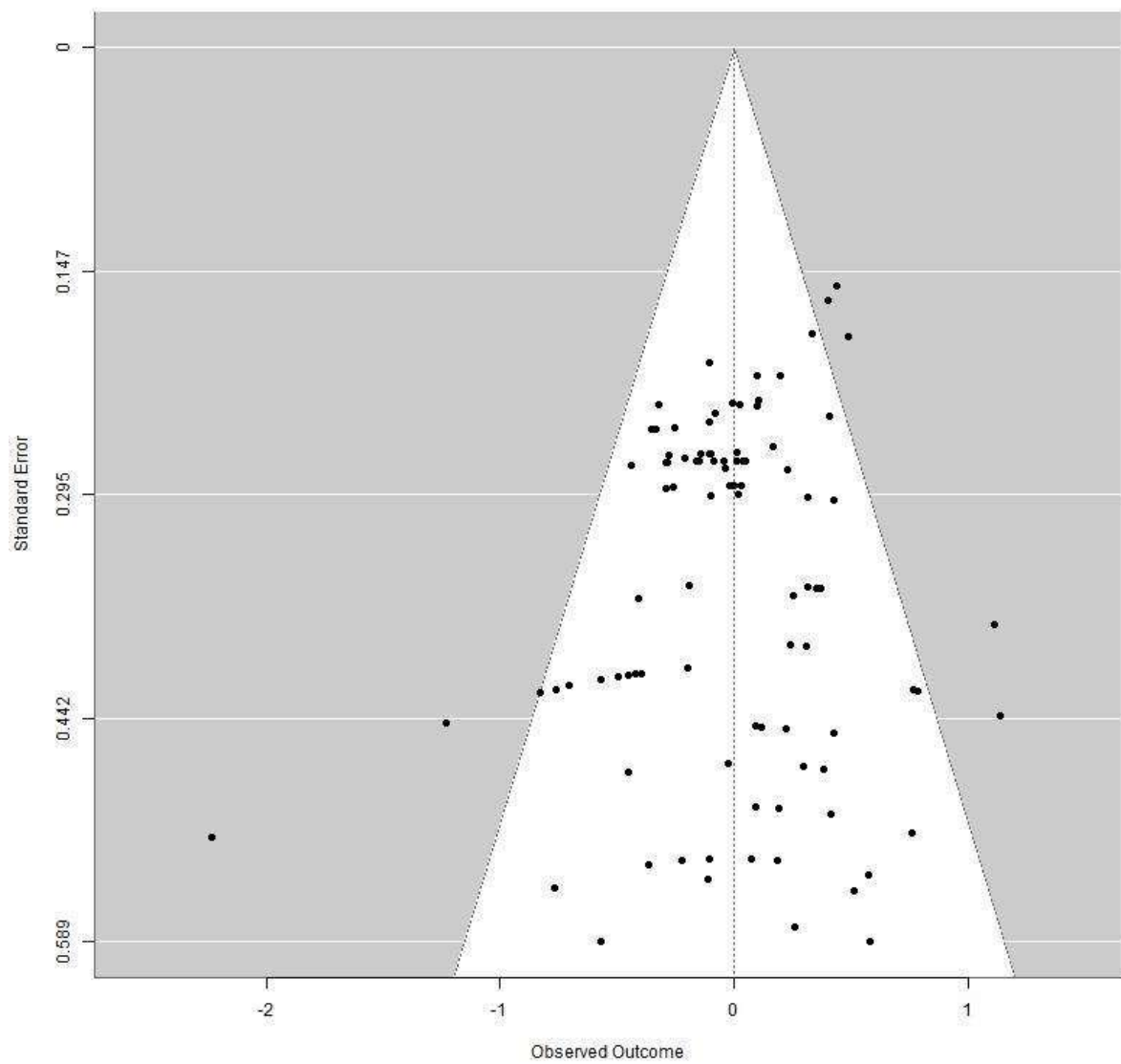


Figure S2. Funnel plot showing effect sizes and standard errors included in the meta-analysis of all psychoplastogens. Egger's test indicated no evidence of publication bias ($p = 0.15$).

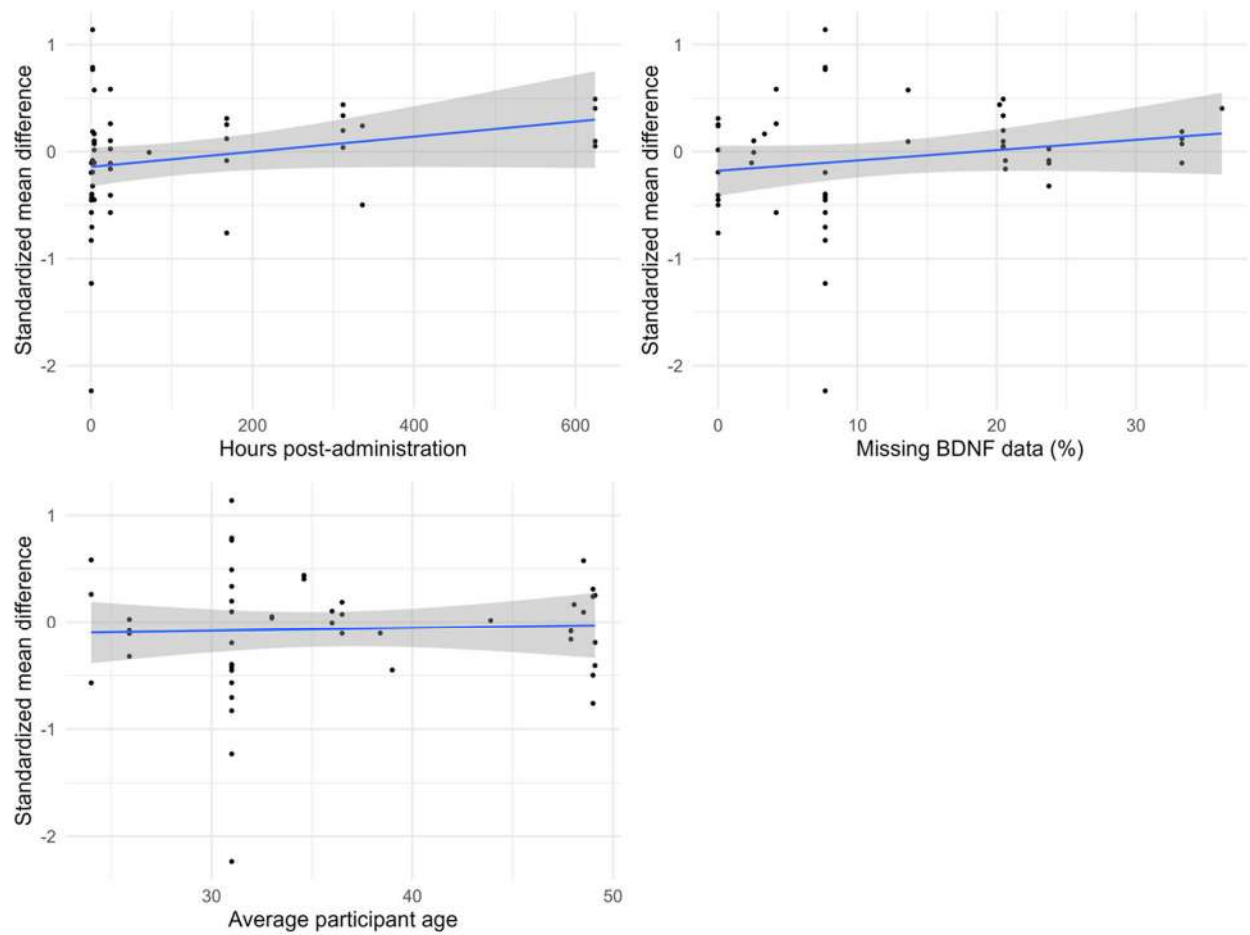


Figure S3. Relationship between effect sizes and the continuous variables of timing, percentage of missing values, and average participant age for studies administering ketamine. Shading shows 95% confidence intervals. The effect of hours post-administration was significant but extremely small ($SMD = 0.0007$, $p = 0.015$).

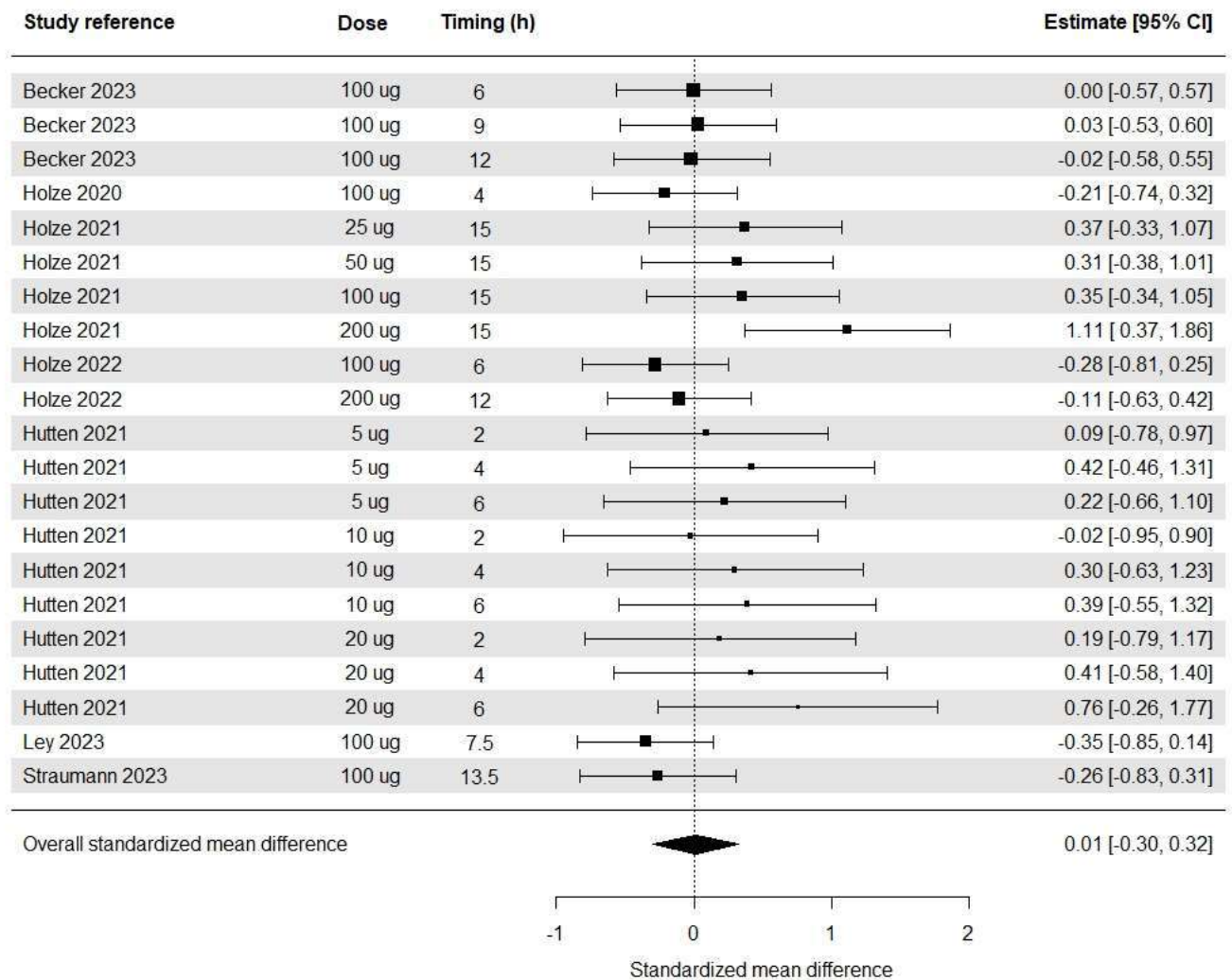


Figure S4. Forest plot showing overall effect size estimates of the change in BDNF after administration of LSD.

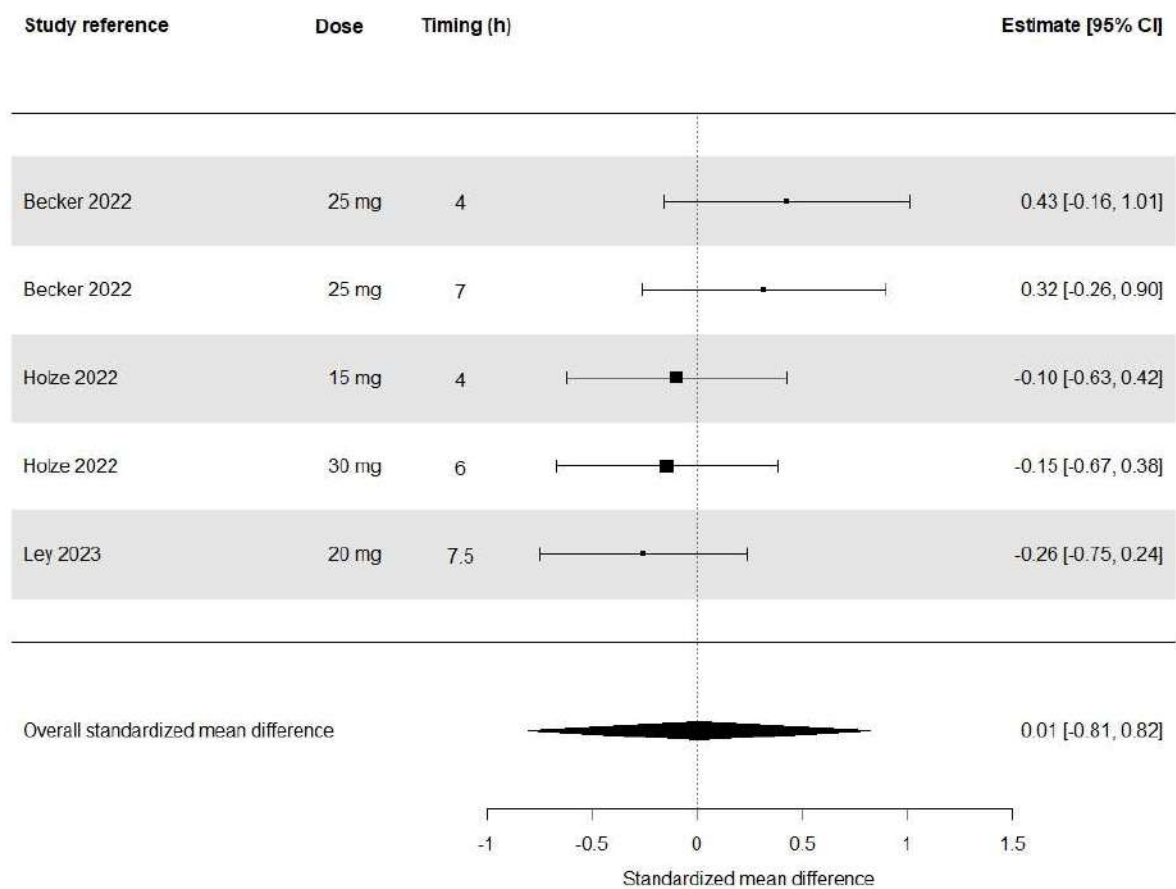


Figure S5. Forest plot showing overall effect size estimates of the change in BDNF after administration of psilocybin.

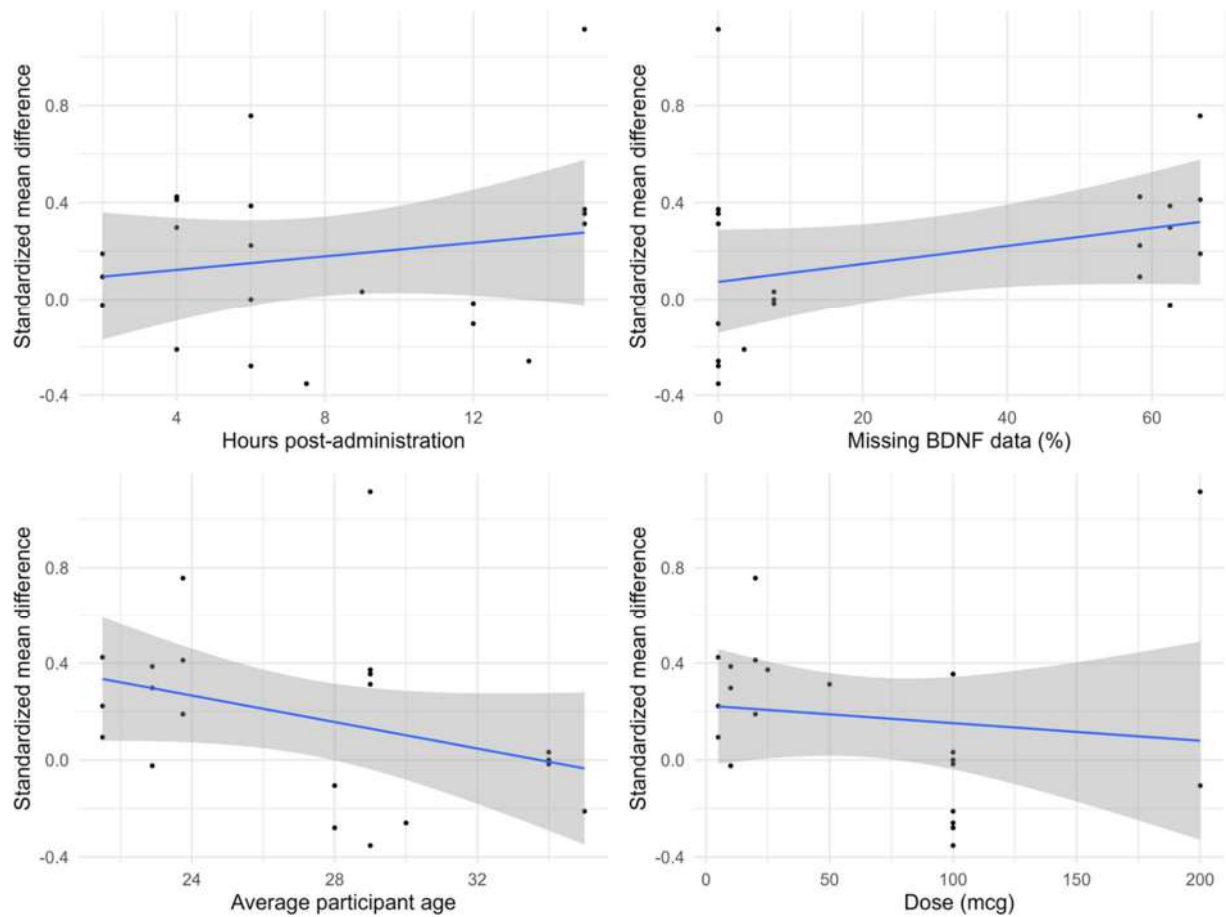


Figure S6. Relationship between effect sizes and the continuous variables of timing, percentage of missing values, average participant age, and dose for studies administering LSD. Shading shows 95% confidence intervals. No moderators showed a significant impact on effect sizes.

Supplementary information on BDNF Immunoassays

Table S1: Available information on sensitivity to mBDNF and proBDNF for immunoassays used in this meta-analysis. Information was taken from manufacturers' websites (accessed 15.07.2024) and from an independent validation study.

Manufacturer	Immunoassay	Sensitivity
Biosensis	Mature BDNF Rapid ELISA kit (no.BEK-2211-2P)	mBDNF with minimal cross-reactivity to proBDNF (Manufacturer's website)
Chemicon International	anti-BDNF sandwich ELISA kit	Not specified
Millipore	ChemiKine Sandwich ELISA (no. CYT306)	Total BDNF ¹ (Manufacturer's website)
MesoScale Discovery	custom assay	Not specified
Promega	BDNF ELISA kit (no. G7610)	Total BDNF ¹ (Manufacturer's website)
R&D Systems	DuoSet ELISA Development Kit (no. DY248)	Total BDNF (Manufacturer's website)
R&D Systems	Total BDNF Quantikine ELISA Kit (no. DBNT00)	Total BDNF (Manufacturer's website)

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Chapter IV Effects of lysergic acid diethylamide on markers of neuroplasticity and motor learning in healthy subjects: a randomized controlled study

Abigail E. Calder^{1,2}, Vincent J. Diehl^{1,3}, Morten P. Lietz^{1,2}, Parsa Yousefi^{1,2}, Nicole Friedli¹, Fabio Coviello¹, Antonin Rouaud¹, Kristian Beichmann¹, Anna Eckert⁴ & Gregor Hasler^{1,2,3}

¹ Molecular Psychiatry Lab, Faculty of Science and Medicine, University of Fribourg, Villars-sur-Glâne, Switzerland

² Fribourg Mental Health Network, Villars-sur-Glâne, Switzerland

³ Lake Lucerne Institute, Vitznau, Switzerland

⁴ Neurobiology Laboratory for Brain Aging and Mental Health, Psychiatric University Hospital, University of Basel, Basel, Switzerland

Submitted for publication October 10th, 2025

Abstract

Background. Preclinical studies suggest that LSD enhances neuroplasticity, but evidence in humans is uncertain. Learning ability is a key correlate of neuroplasticity. Motor learning, in particular, has clinical relevance but has not been investigated in human studies of psychedelics.

Methods. Forty-five healthy subjects (24 women) participated in this randomized crossover trial comparing 100µg LSD with a placebo. For up to one week after dosing, we investigated neurophysiological measures of perceptual and motor plasticity using auditory tetanization with electroencephalography (EEG), paired associative stimulation (PAS) with transcranial magnetic stimulation (TMS), and peripheral levels of brain-derived neurotrophic factor (BDNF). Online and offline motor learning were assessed with a sequence typing task. Questionnaires assessed perceived stress and cognitive flexibility.

Results. Offline motor learning significantly improved the day after LSD. One week after LSD, perceived stress was reduced, and aspects of cognitive flexibility were increased. EEG data showed that LSD acutely decreased amplitudes of auditory event-related potentials (ERPs) and modulated P2 ERPs one week later. Motor-evoked potentials measured with TMS showed increased amplitude and faster latency under LSD. LSD did not alter BDNF levels.

Conclusions. Improvements in motor learning, stress tolerance and cognitive flexibility support the hypothesis that LSD enhances neuroplasticity. These findings encourage future studies on LSD and learning and could have implications for the use of psychedelics in neurorehabilitation. Though tetanization and PAS may have limited usefulness as markers of neuroplasticity, the observed acute and lasting changes in neural signals provide insight into LSD's effects on the auditory and motor systems.

Introduction

The nervous system adapts its structure and function via a variety of interconnected processes occurring at every level from cell to behavior, together called neuroplasticity (1). Neuroplasticity is fundamental for learning in the broadest sense, including perceptual and motor learning (2). Though the brain always maintains some degree of plasticity, interventions which enhance neuroplasticity would have important clinical uses in psychiatry and neurorehabilitation (3, 4). Some targeted pharmacological interventions may rapidly and lastingly stimulate neuroplasticity, with the psychedelic lysergic acid diethylamide (LSD) appearing particularly potent (5, 6).

Preclinical studies suggest that LSD and other serotonergic psychedelics enhance synaptic plasticity, dendritogenesis, and neurotrophin signaling, particularly in cortical layer 5 pyramidal neurons expressing 5-HT_{2A} receptors (6-11). Psychedelics may also enhance the magnitude of long-term potentiation (LTP), a fundamental mechanism of synaptic plasticity and learning involving increases in synaptic strength after repeated activation (12, 13). At the behavioral level, this may constitute a re-opening of critical periods in which learning is more efficient for a short time, potentially providing a unique opportunity for psychological or neuro-rehabilitative interventions lasting for at least one week, and possibly up to three weeks (14, 15).

It has been theorized that LSD's enhancement of neuroplasticity partially underlies its lasting psychological effects (16). Combined with a supportive setting, a single dose of LSD can improve mood and well-being in healthy subjects (17), as well as symptoms of depression and anxiety (18-21) in patient populations, even a year or more later (22-24). These benefits may be mediated by circuit-specific neuroplastic growth which positively impacts emotional regulation, as well as cognitive and psychological flexibility (25, 26). Furthermore, facilitation of activity-dependent LTP at cortical synapses could be one mechanism by which psychedelics improve responsiveness to psychotherapy and other learning-related interventions, including therapeutic aspects of the LSD experience itself (13, 27, 28).

Methods developed to measure LTP-like plasticity in humans include sensory tetanization (ST) and paired associative stimulation (PAS), both of which combine brain stimulation with electrophysiology in a particular sensory or motor system (29, 30). Both were developed as translational measures of LTP mimicking the effects of rapid electrical stimulation (*tetanzation*) of neurons *in vitro* (31, 32). ST uses rapidly presented sensory stimulation (tones or images) to increase the amplitude of auditory or visual event-related potentials (ERPs) measured using electroencephalography (EEG) (33). PAS applies similar logic to the primary motor cortex by

combining transcranial magnetic stimulation (TMS) with peripheral nerve stimulation to alter the amplitude of motor-evoked potentials (MEPs) (32). In both paradigms, the difference in signal amplitude after stimulation, compared to before, is thought to reflect the brain's capacity for LTP (34). Additionally, ST and PAS have the advantage of capturing both neural excitability before stimulation and LTP-like change after stimulation. They have been used to assess LTP in a variety of populations (35-40) and in response to pharmacological interventions (41-43). Three recent studies have also used ST to measure LTP after low-dose LSD (44, 45) and psilocybin therapy for depression (46). Although none observed the expected effects, the doses of LSD may have been too small; no studies have yet attempted to measure neuroplasticity after the larger doses (ca. 100-200 μ g) which are typical of both psychedelic therapy and recreational use (47).

Enhancement of cortical LTP would be expected to facilitate learning (48). Motor learning, defined as improvement in performance of motor movements with practice, is of particular interest due to potential clinical relevance for neurorehabilitation (4, 49). LTP in the motor cortex underlies motor learning (50-52) and may be particularly crucial for memory consolidation during waking rest (offline learning), though it is also involved in the acquisition of a motor skill during practice (online learning) (53, 54). It has been proposed that psychedelics may improve motor learning via enhancement of synaptic plasticity (55-57). LSD has not yet been studied in the context of motor learning but improves performance on various other learning paradigms in animals (10, 12, 14, 58-60). In humans, a moderate dose of LSD (50 μ g) may improve visuospatial learning the next day (61), and a higher dose may acutely improve reward learning (62). Regarding motor learning, motor skills can be measured with simple sequence learning tasks which ask participants to perform a movement as quickly and accurately as possible (49).

The current study is the first to investigate the acute and post-acute effects of a moderately large dose of LSD on markers of LTP and motor learning in humans. We tested three neurophysiological markers of LTP at three timepoints chosen based on preclinical research: 6-8 hours, one day and one week after LSD. We also evaluated LSD's effects on motor learning performance, self-reported cognitive flexibility, and perceived stress. Our findings address important gaps in our understanding of psychedelic-induced neuroplasticity and offer rationale for future studies in clinical populations, particularly in neurorehabilitation.

Methods and Materials

Study design and participants

This study used a randomized, double-blind crossover design. Forty-five healthy participants (24 women) between the ages of 21 and 55 received one dose of 100µg LSD and one placebo (Apotheke Dr. Hysek AG, Biel, Switzerland). All participants provided written informed consent and were compensated. The study was conducted in accordance with the Declaration of Helsinki, approved by the Bern Cantonal Ethical Committee (BASEC-No. 2021-01322) and registered on ClinicalTrials.gov (NCT05177419). See supplement for details on inclusion criteria and drugs.

Study procedures

Participants completed a screening visit and seven experimental sessions including the two dosing days (Figure 1; see supplement for details). Dosing sessions were conducted in a quiet, comfortable room with one or two investigators present at all times (Figure 2). A washout period of > 4 weeks was required between the LSD and placebo appointments. Baseline measures of EEG and TMS were taken on the baseline visit and repeated during acute drug effects, as well as the next day and 6-8 days later (mean: 7.01). Motor learning was completed the day after dosing. Questionnaires were completed at baseline and one week after dosing. Because neuroplasticity is influenced by sleep, exercise, and time of day (63), experiments were always conducted in the afternoon in identical order. Additionally, participants reported on hours of sleep and exercise in the past 24 hours.

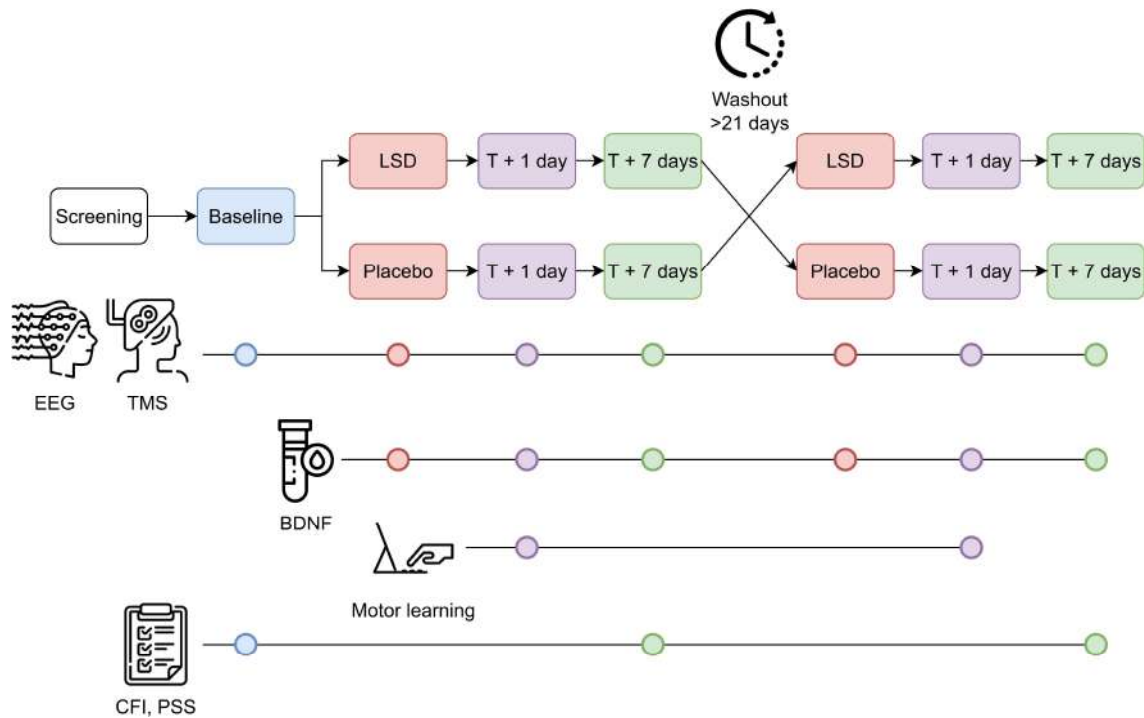


Figure 1. Study procedures at eight study appointments in a crossover design. White dots represent the experiments conducted at each appointment. BDNF = brain-derived neurotrophic factor; CFI = Cognitive Flexibility Inventory; EEG = electroencephalography; PSS = Perceived Stress Scale; T = time of dosing, TMS = transcranial magnetic stimulation.



Figure 2. The room used for dosing sessions in the study. Photo credit David Elmiger.

EEG procedures

EEG was recorded using 32 active electrodes in 10-20 system locations (see supplement). Auditory ST (Figure 3) was used to assess LTP-like plasticity over frontocentral electrodes as in previous studies (33, 64) (Figure S1). Participants were instructed to sit still and attend to a series of identical tones (1000Hz with Hanning window at edges, 50ms duration, 60dB) over in-ear headphones (ER-3C, Etymotic Research, IL, USA) with eyes open. In the first block, single tones were played at intervals of 1800-2600ms for 4.5 minutes. The ST block was played after a one-minute break and consisted of tones played at 13Hz for two minutes. Finally, after a two-minute break, the first block was repeated three more times at 15-minute intervals. LTP-like plasticity was operationalized as potentiation of auditory N1 and P2 ERP amplitudes after ST compared to before. Information on pre-processing and peak detection is in the supplement.

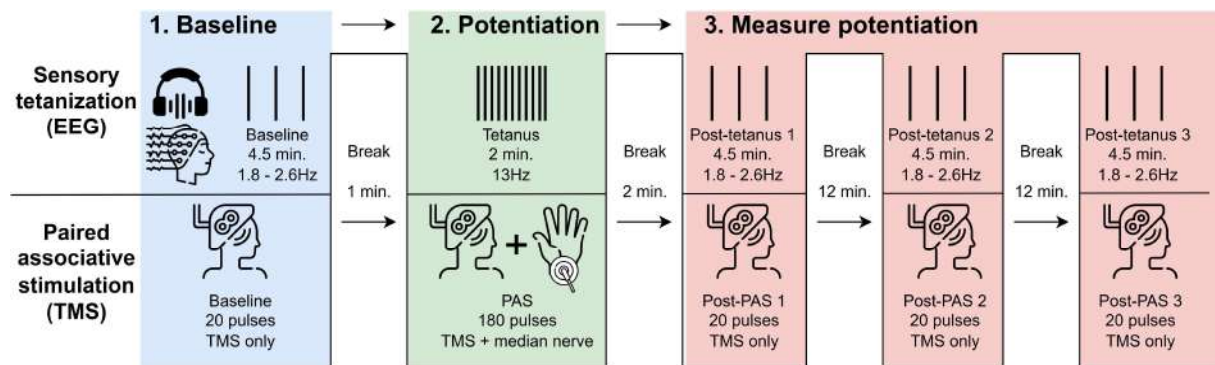


Figure 3. Procedures for assessing LTP-like plasticity using two stimulation-based methods. Sensory tetanization (ST, top) uses auditory tones played at 13Hz to potentiate auditory event-related potentials measured with electroencephalography (EEG). Paired associative stimulation (PAS, bottom) uses a combination of transcranial magnetic stimulation (TMS) and median nerve stimulation to potentiate motor-evoked potentials (MEPs) measured using electromyography. Both procedures first involve measuring baseline neural responses to the stimulus, namely auditory tones or single TMS pulses (1). Next, they aim to potentiate that response using brain stimulation (2). Finally, the effect of potentiation on neural signals is measured for approximately 30 minutes afterward (3). Potentiated signals are thought to reflect LTP-like neuroplasticity.

TMS procedures

TMS was conducted using a MagPro X100 (Tonica Elektronik A/S, Denmark) to measure motor cortical excitability and LTP-like plasticity. Participants were fitted with electrodes for measuring MEPs over the abductor pollicis brevis (APB) of the right hand using the belly-tendon configuration (35). The TMS coil was placed over the left motor cortex and calibrated so that a

single pulse produced an MEP with a peak-to-peak amplitude of approximately 1mV in the relaxed APB. Monophasic TMS pulses were delivered at a rate of 0.1Hz. Pulse strength was kept consistent for each participant throughout the study. See supplement and Figure 3 for detailed PAS procedures.

BDNF

BDNF was measured in blood plasma and serum before drug intake, as well as eight hours, one day and one week later (see supplement).

Motor learning

One day after drug administration, participants completed a sequence typing task developed based on previous studies (Figure 4). It assessed both online learning during active practice of a motor skill and offline learning improvements after rest (65-67). Participants were instructed to type a 9-digit number sequence (314211223 or 322112413, counterbalanced in random order) as quickly and accurately as possible using their left (non-dominant) hand. The task consisted of 10 practice blocks (online learning) and two test blocks after 10 and 80 minutes of rest (offline learning). Audiovisual feedback on performance was given after each trial and block and participants were encouraged to beat their high scores from the previous block. Learning in each block was operationalized as the change in average typing speed on correct trials since the previous practice block. During the 10-minute break before the first test block, participants rested while sitting with eyes closed. During the remaining 70 minutes before the final test block, participants completed other unrelated experiments (passive EEG recordings, questionnaires). Previous studies have shown that low-demand activities, like unrelated computer experiments or other normal daily activities, do not affect offline motor learning gains in adults (68, 69).

Questionnaires

Acute drug effects were assessed using hourly ratings (18, 70), as well as the 5-Dimensional Altered State of Consciousness Questionnaire (5D-ASC) and the Mystical Experience Questionnaire (MEQ) (71-73). Side effects were assessed using the Swiss Psychedelic Side Effects Inventory (SPSI) (74). Cognitive flexibility was assessed with the Cognitive Flexibility Inventory (CFI) and perceived psychological stress was measured using the Perceived Stress Scale (PSS) (75, 76). See supplement for details.

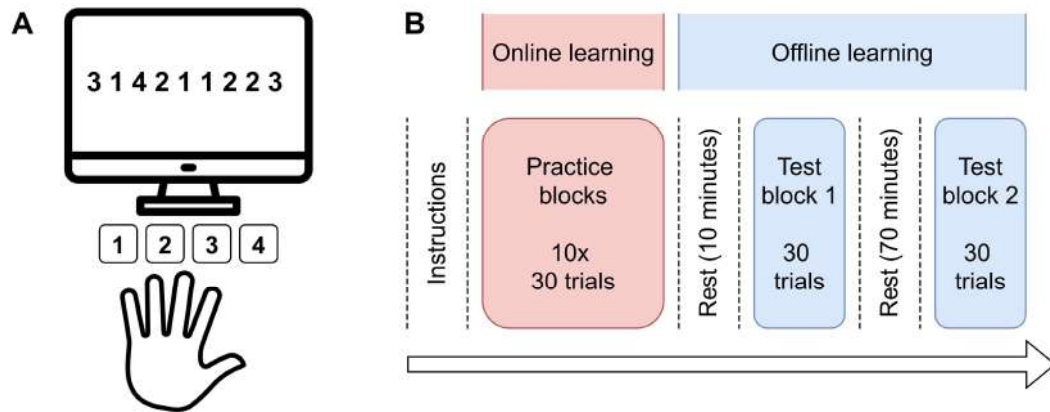


Figure 4. Procedures of the sequence typing task used to assess online and offline motor learning. Participants placed their left hand on a standard computer keyboard and were instructed to type a 9-digit key sequence as quickly and accurately as possible (A). They practiced the sequence repeatedly during ten practice blocks consisting of 30 trials each, as well as in two test blocks after resting (B).

Data analysis

Statistical analyses were conducted using R (Version 4.5.0)(77). Effects of LSD were analyzed using linear mixed effects models with fixed effects for drug, timepoint, and treatment order, with participant as the random effect (see supplement for further details). Post-hoc contrasts were conducted using estimated marginal means and the multivariate t-distribution method to control the familywise error rate. Because there were no significant order effects, all LSD and placebo visits were analyzed together.

Results

Sample Characteristics

Forty-five volunteers were included in the study, and data from 43 were analyzed (CONSORT (78) diagram in Figure 5). Demographics are shown in Table 1.

Table 1. Participant demographics (N = 43). Data on previous psychedelic experiences reflects answers regarding serotonergic psychedelics, excluding microdosing.

Characteristic	Mean (SD)
Age (years)	30.4 (8.4)
Body mass index	22.1 (2.3)
Education (years)	18.2 (2.6)
	N (%)
Sex	
Female	24 (55.8%)
Male	19 (44.2%)
Any previous psychedelic experiences	15 (35%)
If yes: how many?	2.4 (range 1-6)

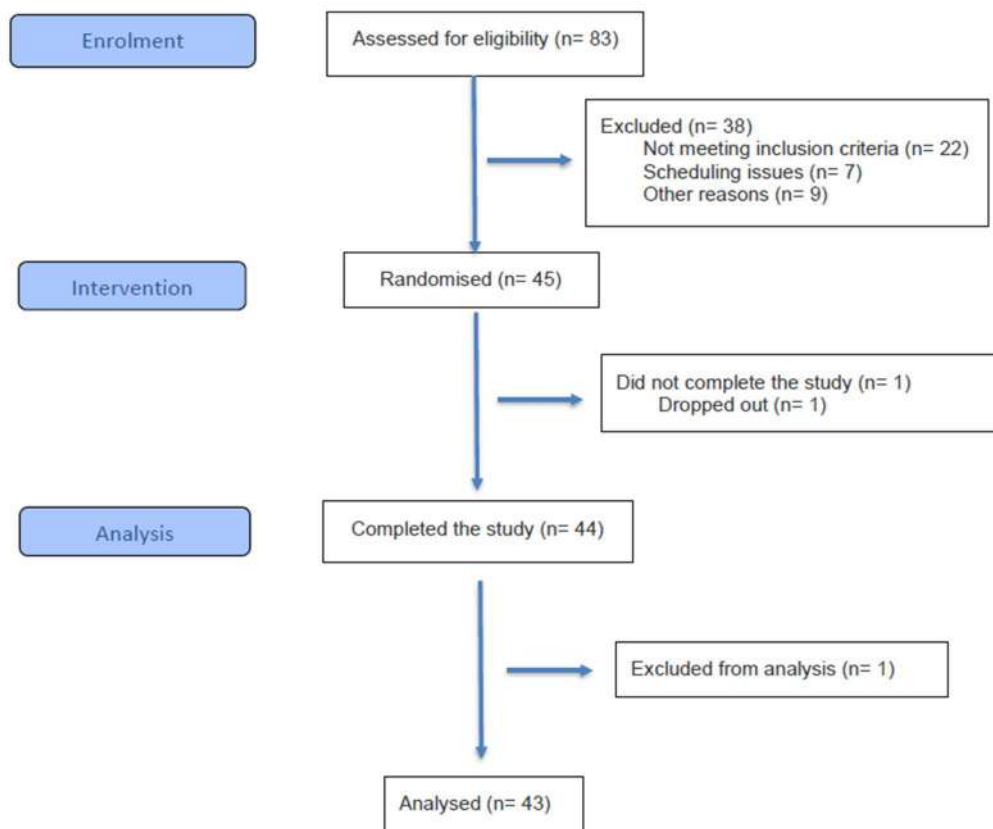


Figure 5. CONSORT flow diagram showing movement of participants through the trial. See supplement for details regarding excluded participants.

Subjective drug effects and side effects

LSD significantly increased hourly ratings of most drug effects, as well as scores on the 5D-ASC and MEQ (Figure 6, Table S1). Most participants reported positive effects of LSD on well-being (Table S2). Regarding blinding, all participants correctly identified the 100µg LSD dose. Blinding of the placebo as low-dose LSD was successful in 79% of participants (mean guess = 14µg, SD = 11.3). LSD increased the number of acute and post-acute side effects for up to 24 hours, though they were generally mild and transient (Tables S3-S4, Figure S2). There was one possibly treatment-related serious adverse event which resolved within the study timeframe (see supplement for a detailed discussion of this and other side effects).

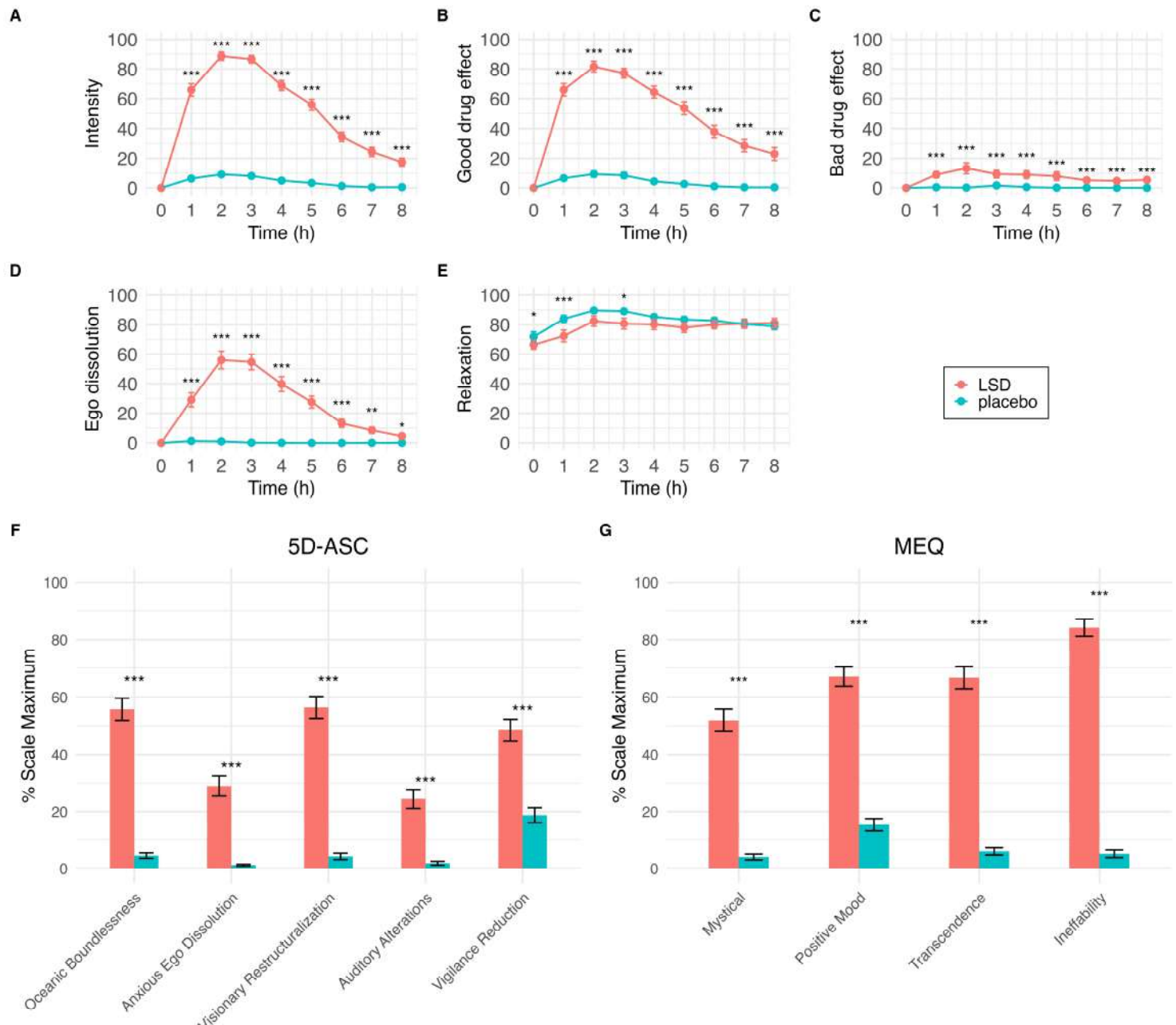


Figure 6. Acute subjective effects of 100µg LSD and placebo. LSD significantly increased hourly ratings of effect intensity (A), good drug effect (B), bad drug effect (C), and ego dissolution (D). LSD significantly but weakly decreased subjective feelings of relaxation (E). LSD also significantly increased scores on all subscales of the 5-Dimensional Altered States of Consciousness Questionnaire (5D-ASC) (F) and Mystical Experience Questionnaire (MEQ) (G). 5D-ASC and MEQ values are shown as the percentage of the maximum possible score. See Table S1 for summary statistics and results of mixed models. Error bars show SEM. $N = 43$. *** $p < .001$. ** $p < .01$, * $p < .05$.

EEG outcomes

We first investigated whether ST caused an LTP-like potentiation of ERPs. Contrary to expectations, there was no main effect of ST on amplitude of N1 ($\beta = 0.05$, $SE = 0.13$, $p = 0.70$) or P2 ($\beta = 0.15$, $SE = 0.18$, $p = 0.41$) (Table S5, Figure S3). The ST responder rate was 43% for N1 and

53% for P2. Planned contrasts by visit revealed that one week after treatment, P2 amplitude significantly decreased after ST in the LSD group only ($\beta = -0.47$, $SE = 0.17$, $p < 0.05$). The corresponding drug $\times$ ST interaction was initially significant ($\beta = -0.51$, $SE = 0.25$, unadjusted $p = 0.04$) but did not survive correction (adjusted $p = 0.14$). There were no other significant drug $\times$ ST or visit $\times$ ST interactions. To further investigate the post-tetanus reduction in P2 at one week, we analyzed change in P2 amplitudes over all four recording timepoints within that EEG session (one pre-ST, three post-ST). P2 amplitude significantly decreased in the LSD group compared to the placebo group ($\beta = -0.22$, $SE = 0.10$, $p < 0.05$) with a steady linear trend across all four timepoints (Figure 7A); this is not consistent with the expected effects of ST.

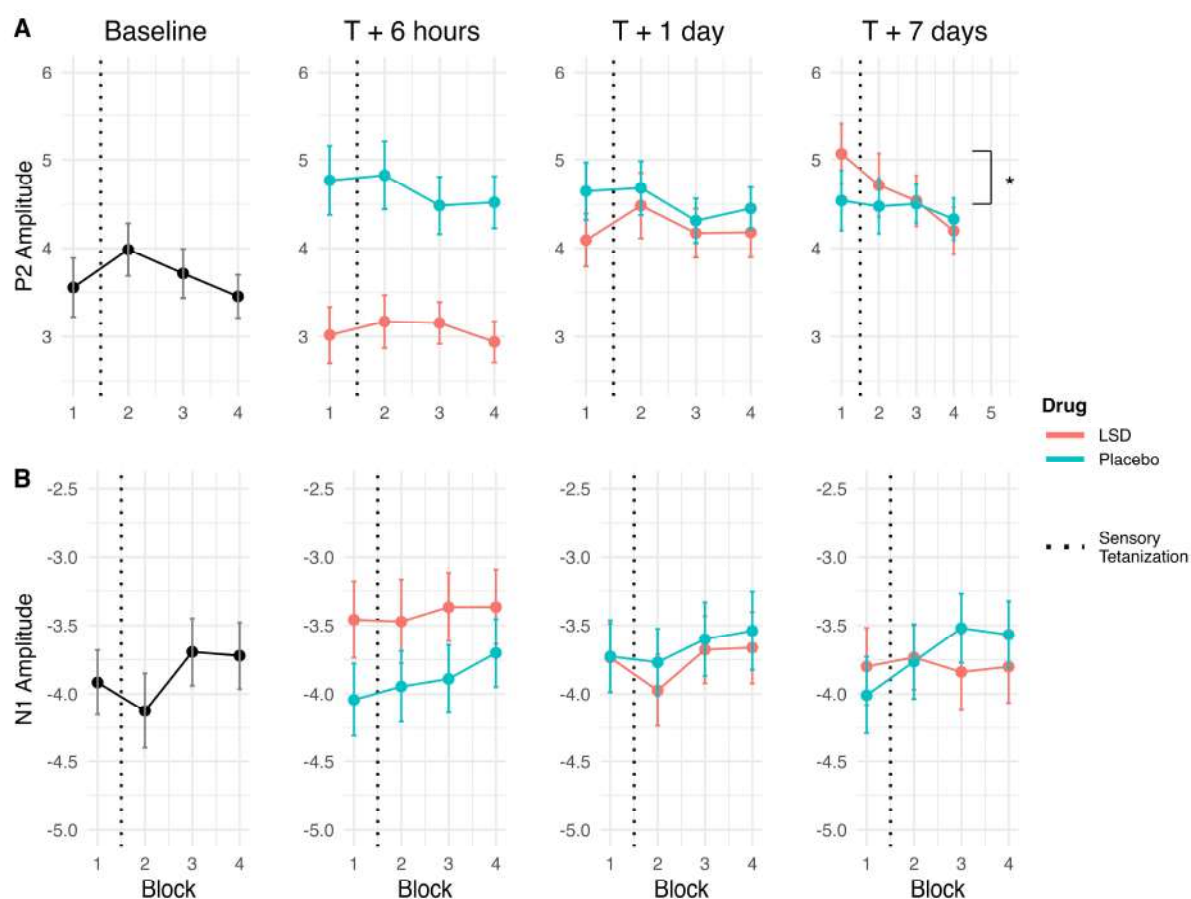


Figure 7. Auditory ERP amplitudes at all four EEG recording timepoints (one pre-tetanus, three post-tetanus) for each drug and visit. Analysis of linear trends showed that decreases in P2 amplitude one week after dosing were significantly greater after LSD than placebo. This effect was analyzed in post-hoc tests following the significant tetanus effect observed for P2 in the LSD group at one week; no rationale existed for statistical analysis of other linear trends in ERP amplitudes, which are shown for visual comparison only. See Figure 8 and Table S6 for main effects of LSD on auditory ERP amplitudes. Error bars show SEM. T = time of drug intake. Error bars show SEM. $N = 43$. $*p < .05$.

Regardless of ST, LSD showed main effects on ERP amplitudes (Figure 8, Table S6). Models analyzing all N1 and P2 ERPs together for each visit showed that LSD acutely and significantly reduced N1 ($\beta = 0.5$, $SE = 0.08$, $p < 0.001$) and P2 ($\beta = -1.33$, $SE = 0.11$, $p < 0.001$) amplitudes. P2 amplitude was still significantly reduced one day after LSD ($\beta = -0.32$, $SE = 0.11$, $p < 0.01$), which was the only significant post-acute effect.

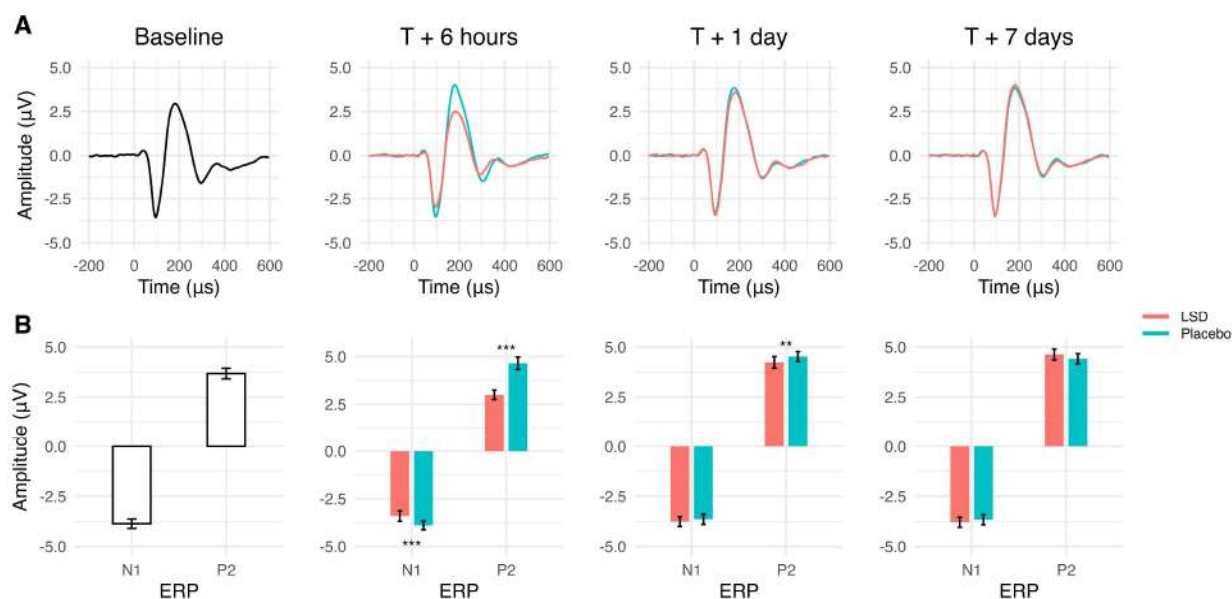


Figure 8. Waveforms (A) and amplitudes (B) of auditory N1 and P2 event-related potentials at baseline and at three timepoints after LSD and placebo administration. On dosing days, N1 and P2 amplitudes were significantly decreased in the LSD group. P2 was still decreased in the LSD group the following day. ERP = event-related potential, T = time of drug intake. Error bars show SEM. $N = 43$. *** $p < .001$, ** $p < .01$.

TMS outcomes

We first analyzed whether PAS induced LTP-like effects. There was neither a main effect of PAS on MEP amplitude ($\beta = 7.4$, $SE = 43.9$, $p = 0.87$) nor any significant PAS x drug interaction for any visit (Table S8). The responder rate for PAS was 53.4%. We therefore analyzed all MEPs for each visit together to assess LSD's impact on corticospinal excitability only.

MEP waveforms are shown in Figure 9A. There was a significant LSD effect on MEP amplitude ($\beta = 64.4$, $SE = 43.9$, $p < 0.01$). Post-hoc tests revealed that MEP amplitude was significantly increased in the LSD group on dosing days ($\beta = 64.4$, $SE = 26.6$, $p < 0.05$) and significantly decreased in the LSD group one day after dosing ($\beta = -80.8$, $SE = 26.1$, $p < 0.01$), compared to placebo (Figure 9B; Table S9). Additionally, there was a main effect of LSD on MEP latency

($\beta = -775.2$, $SE = 119.8$, $p < .001$). Post-hoc tests showed that this effect was driven by dosing days, on which the LSD group showed significantly decreased MEP latency ($\beta = -775.2$, $SE = 119.8$, $p < .001$) (Figure 9C, Figure S4).

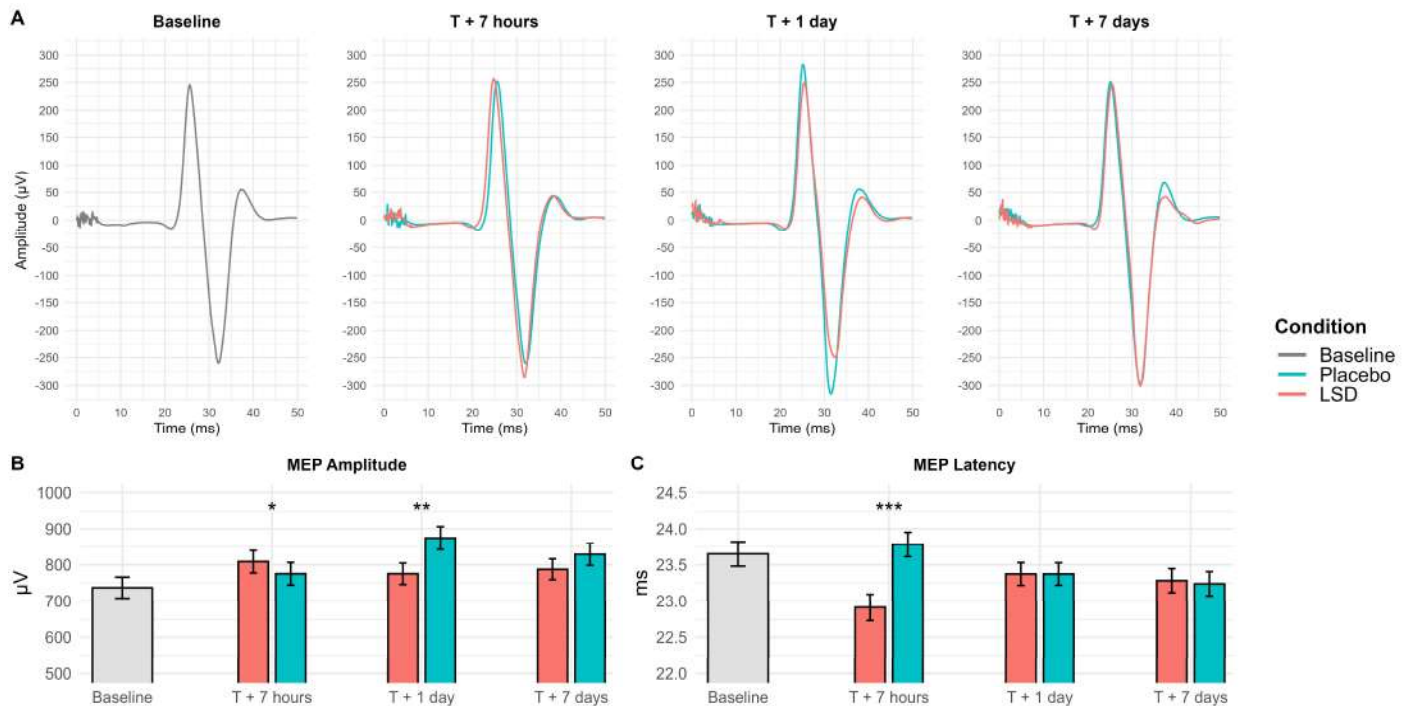


Figure 9. Waveforms (A), amplitudes (B) and latencies (C) of motor-evoked potentials (MEPs) at baseline and three timepoints after LSD and placebo administration. On dosing days, MEP amplitudes were significantly larger in the LSD group and latencies were significantly shorter. The next day, MEP amplitudes were significantly decreased in the LSD group, compared to placebo. T = time of drug intake. Error bars show SEM. N = 42. *** $p < .001$, ** $p < .01$, * $p < .05$.

BDNF

There was no effect of LSD on either serum or plasma BDNF at any timepoint (Table S10).

Motor Learning

On the motor learning task, mixed effects models showed a significant main effect of condition ($\beta = -216.2$, $SE = 7.4$, $p < .001$), indicating that participants' typing speed improved in the test blocks (offline learning) relative to practice blocks (online learning). There was also a significant drug x condition interaction ($\beta = 24.4$, $SE = 10.5$, $p < 0.05$). Post-hoc tests showed that the LSD group showed greater offline speed improvements than the placebo group ($\beta = -22.32$, $SE = 9.7$, $p < 0.05$; Figure 10, Table S11). This was primarily driven by the second test block completed 80 minutes after the end of practice ($\beta = -37.0$, $SE = 12.6$, $p < 0.01$). In the second test block, the LSD group was 348ms faster and the placebo group was 262ms faster than in the final practice

block, corresponding to a 32.8% greater improvement in the LSD group. LSD did not affect speed improvement during practice ($\beta = -2.1$, $SE = 4.8$, $p = .66$), initial speed in the first practice block ($\beta = 38.2$, $SE = 81.0$, $p = 0.64$) or accuracy during online ($\beta = 0.8$, $SE = 0.6$, $p = 0.16$) or offline learning ($\beta = 1.1$, $SE = 1.2$, $p = 0.36$). Finally, neither motor learning nor questionnaire scores correlated with neurophysiological outcomes (Table S12).

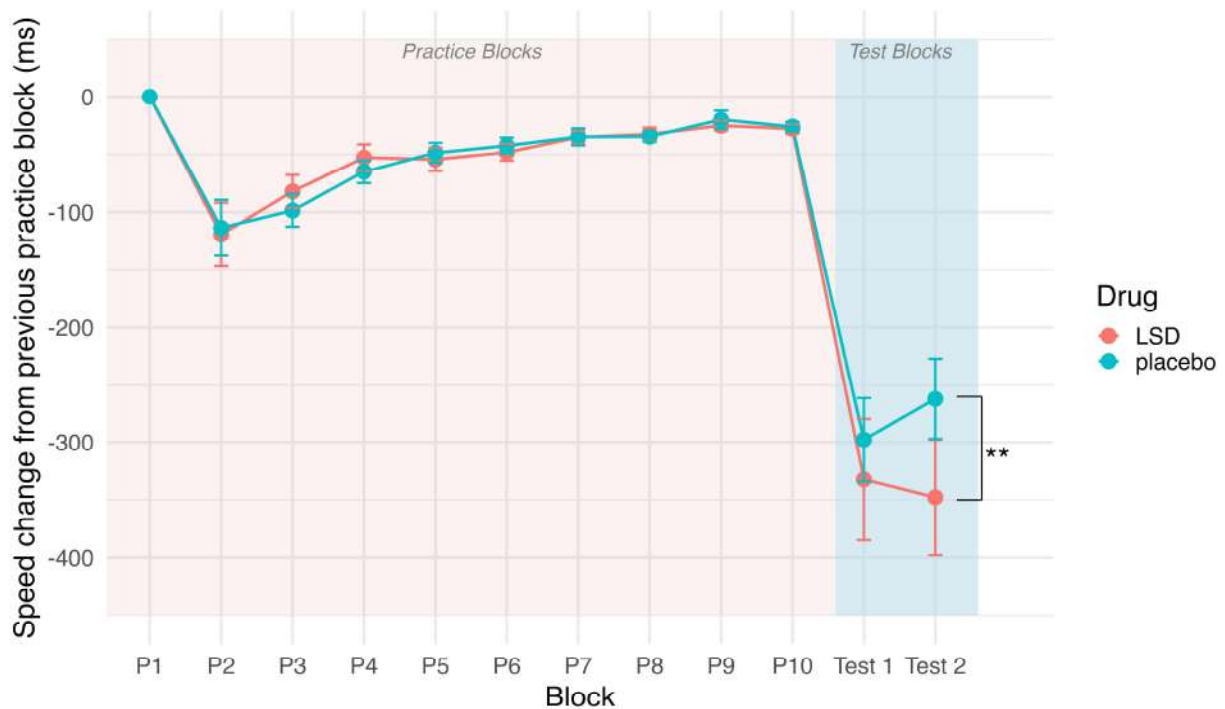


Figure 10. Improvement in typing speed in the motor learning task across ten consecutive practice blocks (P1 – P10; online learning) and two test blocks (offline learning) completed after resting for 10 and 80 minutes. Participants showed significantly more speed improvement in the test blocks after LSD than placebo, particularly after 80 minutes of rest. Error bars show SEM. $N = 42$. ** $p < .01$.

Cognitive Flexibility and Perceived Stress

One week after dosing, LSD significantly increased ratings on the *Alternatives* subscale of the CFI ($\beta = 1.92$, $SE = 0.63$, $p < 0.01$; Figure 11, Table S13), but not *Control* ($\beta = -0.53$, $SE = 0.67$, $p = 0.42$). LSD also significantly reduced PSS scores ($\beta = -1.94$, $SE = 0.91$, $p < 0.05$; Figure 11, Table S13).

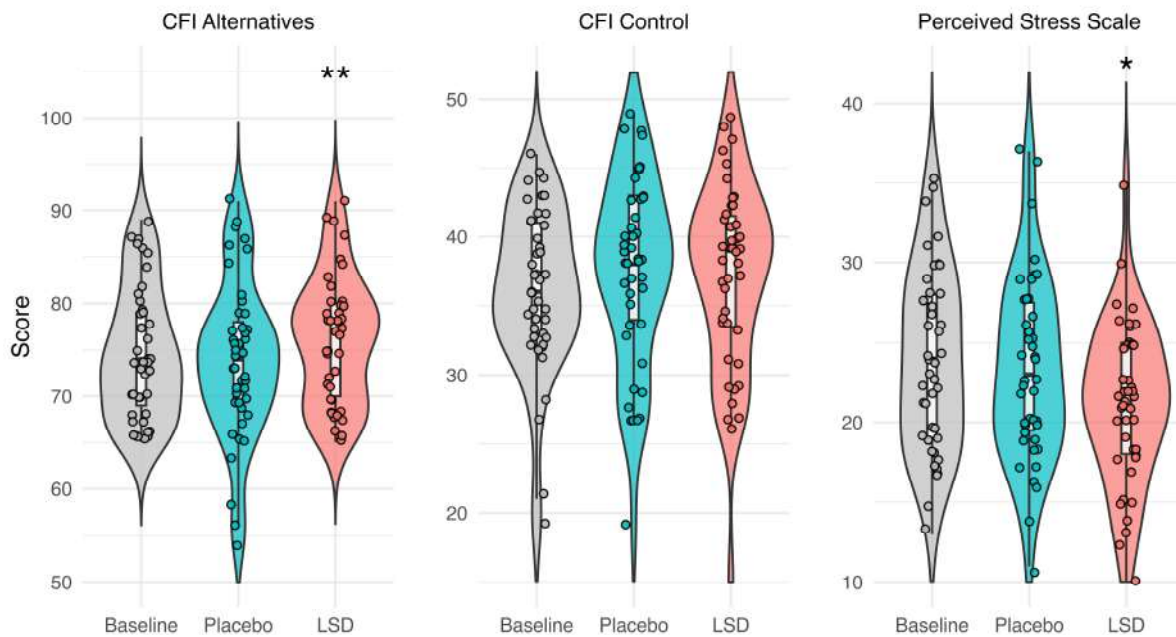


Figure 11. Scores on the two subscales of the Cognitive Flexibility Inventory (CFI), as well as the Perceived Stress Scale, at baseline and one week after drug administration. On the CFI, possible scores range from 13-91 for Alternatives and 7-49 for Control. Possible PSS scores range from 10-50. Statistical tests reflect contrasts between LSD and placebo with baseline scores as a covariate. Error bars show SEM. $N = 43$. * $p < 0.05$, ** $p < 0.01$.

Discussion

This randomized controlled crossover trial in healthy subjects is the first to demonstrate improvements in motor learning after a psychedelic drug, and LSD also led to improvements in perceived stress and aspects of cognitive flexibility. Additionally, we observed acute effects of LSD on neurophysiological markers of auditory processing and motor cortical excitability, with some effects lingering for up to one week. Like previous studies, LSD induced mostly positive acute and lasting subjective effects, as well as transient and tolerable side effects (18, 70, 73, 79, 80).

Though our EEG data do not allow for strong inferences about neuroplasticity, they provide some insights into LSD's effects on auditory processing. Acutely, LSD reduced the amplitude of the N1 and P2 components of auditory ERPs, and reduction in P2 linger somewhat one day later. N1 reflects early, bottom-up auditory processing and properties of the sensory stimulus (e.g. volume) (81). P2 is thought to reflect early attentional orientation and is sensitive to changes in stimulus familiarity and novelty (82, 83). Our findings align with previous reports that serotonergic psychedelics acutely reduce the amplitude of sensory ERPs (84-87). This may

reflect LSD's effects on early sensory processing and attentional allocation, as well as desynchronization of neural signals (84).

Three other recent studies have also used ST to measure neuroplasticity after psychedelics. Like the current study, all reported post-acute changes in electrophysiological signals but without the expected potentiation of ERP amplitudes (44-46). A study of high dose psilocybin reported a trend-level increase in evoked theta power during auditory ST, which we did not observe in this sample (see supplementary results) (46). A study of low dose LSD (14 x 10 μ g over 6 weeks) reported changes in laminar connectivity in the primary visual cortex two days after the final dose (45). Interestingly, a second low-dose LSD study (4x 15 μ g over two weeks) reported greater amplitude the auditory P3a component during a mismatch negativity paradigm one week after the final dose (44). This was interpreted as an effect of LSD on pre-attentive processing and novelty detection. In the current study, the LSD group showed a specific, linear decrease in P2 amplitude over the 45-minute recording session one week after dosing which we cannot easily attribute to ST. P2 amplitude is typically stable within a recording session but can decrease when a stimulus is presented repeatedly, a process called habituation (88). A gradual reduction in P2 amplitude could reflect a delayed effect of LSD on attention or habituation to a decreasingly novel stimulus. However, this result is difficult to interpret, and its timing does not align with the expected timing of LSD-induced neuroplasticity. Overall, the lasting effects on electrophysiological signals seen in this and other studies may reflect functional neuroplastic changes, but not necessarily LTP, and they require replication.

Though our TMS data also did not allow inferences about neuroplasticity, it offered novel insights into LSD's effects on the motor system. During TMS, LSD acutely increased peak-to-peak MEP amplitude and decreased latency, compared to placebo. Ketamine, SSRIs, and psychostimulants also acutely enhance MEP amplitude (89). The latency of MEP peaks reflects the conduction time for the neural signals triggered by TMS to reach the target muscle, and latency is sensitive to changes in corticospinal excitability (90). Fewer studies have investigated MEP latency after pharmacological manipulations than amplitude, and the effects of various pharmacological manipulations on MEP latency are relatively unknown (89, 91). However, faster, larger MEPs are consistent with increased corticospinal excitability, which could arise from enhanced glutamatergic neurotransmission in motor cortical neurons expressing 5-HT_{2A}Rs (90, 92, 93). Relatedly, LSD commonly causes muscle tightness and shaking, including in this sample (74). Decreased MEP amplitude the day after LSD compared to placebo could conceivably be related to fatigue, which was greater in the LSD group (94). In general, increased corticospinal excitability can underlie motor cortical plasticity and enhancing it in a targeted

manner could have clinical potential for improving motor function (95, 96). For example, it may be worth exploring whether LSD can acutely enhance motor function and learning at particular doses, including in clinical populations.

There is a need for reliable translational measures of psychedelic-induced neuroplasticity (97), and the fact that neither ST nor PAS potentiated electrophysiological signals is worth critical consideration. Unlike early studies of ST (34, 64, 98), a recent meta-analysis has suggested that ST does not reliably modulate ERP amplitude in either the auditory or visual domain (99).

Response rates for both auditory ST and PAS may hover around chance levels (50-60%), with high variability between subjects and only some studies observing significant potentiation (33, 100). A case has even been made that potentiation effects could be a statistical artefact driven by positively skewed and highly variable data which is sensitive to outliers (100). Though there is considerable interest in using LTP as a measure of psychedelic-induced neuroplasticity in humans, other translatable markers may be more promising (e.g. PET imaging of synaptic proteins) (97, 101). Relatedly, we found no LSD effect on BDNF, consistent with a recent meta-analysis (102).

One day after dosing, LSD selectively improved motor learning gains after rest (offline learning), though not during active practice (online learning). Periods of waking rest after learning facilitate memory consolidation, leading to performance improvements without additional practice (65, 67, 103). Offline learning gains are associated with LTP and changes in brain microstructure thought to reflect early synaptic consolidation and stabilization (53, 103-106), making the effect on offline learning consistent with studies showing enhanced synaptic plasticity after LSD. One previous study of 50µg LSD in healthy humans also found improvements in visuospatial learning and memory consolidation the day after dosing (61). Motor memory consolidation during waking rest is specifically associated with activation in the motor cortex, striatum, and hippocampus, as well as functional connectivity in frontoparietal networks (103, 105, 107). In preclinical studies, psychedelic-induced neuroplasticity has been shown to most strongly affect the neocortex and hippocampus (15). In humans, psilocybin was shown to lastingly increase functional connectivity between prefrontal and parietal regions, among others (108). Our findings indicate that LSD may influence offline motor learning in ways consistent with neuroplastic mechanisms underlying memory consolidation.

Improvements in motor speed can sometimes reflect speed-accuracy tradeoffs or increased motivation (109, 110). The lack of LSD effects on accuracy does not suggest a speed-accuracy tradeoff, and the lack of effects on online learning and initial typing speed do not suggest a

general effect on motivation; participants also reported greater fatigue the day after LSD compared to placebo. Nevertheless, future studies could measure motivation as a possible confounder. It will also be important to determine whether learning gains reflect greater capacity for retaining new skills or simply altered temporal dynamics of learning processes, and whether they generalize to other tasks and populations. Facilitation of motor learning could have potential uses in neurorehabilitation for acquired neural injury, in which (re-)learning of motor skills is imperative for patients to regain quality of life (56).

LSD significantly reduced perceived stress one week after dosing, consistent with other studies reporting positive changes in mood and well-being after psychedelic use (111). This is consistent with animal studies suggesting that psychedelics reduce behavioral and neural signs of stress and promote neuroplasticity in the mood-regulating prefrontal cortex (PFC) (5, 112, 113). Additionally, LSD increased scores on the *Alternatives* subscale of the CFI one week after dosing, and cognitive flexibility is also associated with PFC function and plasticity (114, 115). Notably, baseline CFI and PSS scores were close to maximum and minimum values, respectively. People with lower baseline cognitive flexibility or higher subjective stress may have more room to benefit, as implied by previous studies of psychedelics in both clinical and naturalistic contexts which found positive effects on cognitive flexibility and stress-related outcomes (26, 116, 117).

Limitations

This study had several important limitations. Because tests using auditory ST and PAS did not potential neural signals, we could not evaluate LSD's effects on functional plasticity in the intended manner. The effect of LSD on P2 ERPs one week after dosing should be considered exploratory. Additionally, the sample size of 43 may have been underpowered for detecting some interaction effects. The motor learning task was only given one day after dosing due to time constraints, but future studies would benefit from investigating the effects of LSD on learning at later timepoints, as well as whether learning gains are stable over time. Additionally, because LTP-like plasticity saturates, it is possible that young healthy participants show smaller effects than clinical or older populations (118). Finally, we attempted to reduce placebo effects by presenting the placebo as a low dose of LSD, but all participants still identified the real LSD dose and placebo effects could still have occurred.

Conclusions

A single dose of LSD improved motor learning performance the next day, as well as perceived stress and aspects of cognitive flexibility one week later, consistent with the theory that LSD

enhances cortical plasticity. LSD also acutely increased corticospinal excitability and modulated responses to auditory stimuli measured with EEG. Effects on P2 lingered for up to one week and need replication but could reflect more efficient habituation to stimuli. This and other studies show that stimulation-based markers of neuroplasticity are methodologically challenging. This encourages future studies using alternative markers, for example PET imaging. LSD's effects on motor learning deserve more detailed study.

Acknowledgements

This study was funded by the University of Fribourg, Switzerland, as well as a grant from the Source Research Foundation (2022 Student Grant to AEC). We are also grateful for a generous private philanthropic donation from Mr. Joel Richard. The study funders had no role in the design of the study, the collection, analysis, and interpretation of data, the writing of the report, or the decision to submit the manuscript for publication.

We would like to thank David Elmiger for providing photographs of the LSD session room. Additionally, some images were designed using resources by Freepik from Flaticon.com which are licensed as free with attribution.

Finally, we would like to thank all of the students and staff who assisted with experiments, including Pablo de Chambrier, David Elmiger, Cindy Fux, Svenja Liebschner, Pascal Pompetzki, Benjamin Rausch, Emiliano Schiatti, and Quentin Ulveling. We also thank Fides Meier for technical assistance with BDNF assays. Finally, we are grateful to Jonathan Dierks, Bernd Hinney, Simon Jost, and Ella Spillmann for technical assistance and for helping provide interpersonal support during and after LSD sessions.

Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

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SUPPLEMENT

Effects of lysergic acid diethylamide on markers of neuroplasticity and motor learning in healthy subjects: a randomized controlled study

Calder et al.

Supplemental Methods

Participants and inclusion criteria

Participants were recruited via study advertisements and word of mouth. Inclusion criteria were fluency in German, healthy weight range (BMI > 18 and < 29), right-handedness (Edinburgh Handedness Inventory > 60), and normal or corrected to normal hearing and vision. Sexually active women of childbearing age were required to be using effective birth control. Participants were excluded for the following reasons: any history of psychosis, mania, suicidality, or neurological or cardiovascular disease; a first-degree relative with any psychotic symptoms; any psychiatric illness within the past three years; pregnancy and nursing; current use of psychoactive medications; implanted metal or electronic devices; daily or near-daily consumption of alcohol, nicotine, or illicit substances; use of serotonergic psychedelics on more than 10 previous occasions or within the prior 3 months. Participants were required to refrain from illicit substances for the duration of the study, as well as from consuming alcohol and nicotine in the 24 hours before any study appointment.

Study drugs and randomization

The use of LSD was approved by the Swiss Federal Office of Public Health. Units of 100µg LSD base (Bözinger Apotheke, Biel, Switzerland) were produced according to good manufacturing practice and administered orally in 1mL ethanol. Placebo solutions were visually identical and contained 1mL ethanol. The manufacturer randomly allocated participants to receive LSD or placebo first and study staff administering doses were blind to the randomization.

Detailed experimental procedures

Screening. Screening consisted of an interview assessing inclusion criteria, including the SCID-5-CV diagnostic interview (119). It also included preparation for the effects of LSD (see “Preparation and setting for LSD sessions” in the final section of the supplementary materials below).

Blinding. At the screening visit, participants were told that they would receive one moderately high dose of 100µg LSD and one lower, unknown dose of LSD (actually the placebo; participants were debriefed at the final visit). This was done in order to make the impact of placebo effects between the two drug conditions as comparable as possible. We chose to use an inactive placebo rather than a small dose of LSD because we could not rule out the possibility that even small doses of LSD have neuroplastic effects (120).

Baseline visit. Baseline measurements were taken in the afternoon of the second study visit. Participants arrived in the early afternoon and first underwent sensory tetanization (ST). Questionnaires were filled out in the breaks and after the EEG recording. Participants then underwent paired associative stimulation (PAS) and, finally, a second preparatory session for the LSD day (see below).

Measurements on dosing days. Participants arrived between 8:00 and 9:00 in the morning and were advised to eat a light breakfast and consume no more caffeine than usual. Urine tests confirmed abstinence from illicit drugs and absence of pregnancy. A blood draw was done shortly after arrival to assess baseline BDNF levels prior to drug administration. LSD or placebo was administered orally in a double-blind manner one hour after participants’ arrival. Once per hour for the first eight hours after drug administration, participants verbally rated the intensity of overall drug effects, pleasant effects, unpleasant effects, ego dissolution, and relaxation on a scale from 0-100, as has been done in previous studies (18).

Approximately five hours after drug administration, we began preparing participants for EEG measurements. ST was conducted six hours after drug administration. PAS was conducted approximately seven hours after drug administration. A second blood draw for analyzing BDNF was taken eight hours after drug administration. Participants were picked up by a friend or family member once experiments had concluded and drug effects had adequately subsided. They were instructed to complete the 5D-ASC and MEQ before the next appointment, but only after drug effects had completely subsided.

Follow-up visits. Participants attended follow-up visits the next day and 6-8 days after drug administration (mean: 7.01). Both visits took place in the afternoon and consisted of ST with questionnaires during the breaks as necessary, followed by the SPSI, PAS, and finally a blood draw for assessing BDNF. Additionally, the motor learning task was completed before all other tests at the visit one day after dosing.

EEG recording and preprocessing

EEG recordings were conducted using 32 actively shielded wet electrodes (actiCAP slim EEG system) in 10-20 system locations with an electrode cap and a LiveAmp amplifier (Brain Products GmbH, Germany). Signals were recorded at 1000Hz and impedances were kept below 25k Ω as recommended by the manufacturer for actively shielded electrodes.

Pre-processing was conducted offline using EEGLAB (Version 2024.2)(121). Data were downsampled to 250Hz and bandpass filtered between 1 and 30Hz. Epochs began 200ms before stimulus onset and ended 600ms after onset. A baseline correction was applied using the 200ms before stimulus onset. Bad channels were interpolated and large artefacts were removed, then independent component analysis was used to remove eye movement artefacts. Smaller artefacts were flagged using a custom script and approved for removal by manual inspection. Similar to previous auditory ST studies (33), we analyzed the amplitude of auditory N1 (greatest negative peak 50-150ms after stimulus) and P2 (greatest positive peak 150-250ms after stimulus) ERP components averaged over frontocentral electrodes (Cz, Fz, FC1, and FC2). This choice of electrodes is consistent with previous studies (33, 64), and it also reflects the region at which both components showed the strongest signal in our data (Figure S1).

Participants who showed any increase in ERP amplitude after ST were classified as “responders” in calculations of responder rates, consistent with previous studies (33).

Additionally, we attempted to replicate a previous exploratory analysis from a study using ST after psilocybin therapy which demonstrated a trend-level increase in evoked theta power two weeks after psilocybin treatment (46). To this end, we performed a Morlet wavelet transform over the same data used to analyze N1 and P2 ERPs. For each epoch, EEG signals over frontocentral electrodes were decomposed into steps of 0.5Hz for frequencies between 4 and 30 Hz. Raw power estimates (event-related spectral perturbations) were converted into decibels using $\log_{10}$ transformation. For each subject and timepoint, we then calculated average power in the theta range (4-8Hz) between 50 and 250 ms after each auditory stimuli to yield a measure of evoked theta power in the relevant time range for N1 and P2 ERPs.

Software

Computer-based experiments (motor learning, ST) were run using E-Prime (Version 3.03.219, Psychology Software Tools Inc., USA).

Paired associative stimulation

PAS was conducted using a MagPro X100 (Tonica Elektronik A/S, Denmark) coupled to a Dantec Keypoint electrical stimulator (Alpine Biomed ApS, Skovlunde, Denmark) and electrodes for electromyography of the right abductor pollicis brevis (APB). We used a prototypical PAS procedure as described in previous studies (122) (see also Figure 3 of the main text).

First, baseline MEP amplitude in the right APB was determined using a train of 20 monophasic TMS pulses delivered at 0.1Hz. Next, paired stimulation was applied using both TMS pulses and peripheral electrical stimulation of the right median nerve at 300% of the perceptual threshold. This stimulation strength is calibrated to be noticeable without being painful. Median nerve stimulation was delivered 25ms before the TMS pulse so that both arrived at motor cortical synapses simultaneously, as required for induction of Hebbian LTP. Over 30 minutes, 180 paired pulses were delivered at a rate of 0.1Hz. Participants were asked to silently count the number of pulses in order to keep their attention on the stimuli, which is important for successful PAS. Finally, the baseline train of TMS pulses was repeated three times at intervals of 15 minutes (2, 17 and 32 minutes after the end of the paired pulses) in order to measure changes in MEP amplitude.

Prior to analysis, peak and latency detection were performed with custom R scripts and confirmed by manual inspection. MEPs with a peak-to-peak amplitude of $<50\mu\text{V}$ were rejected (123).

Latency was defined as the earliest timepoint at which an MEP deviated from baseline motor activity by at least $25\mu\text{V}$. Participants who showed any increase in MEP amplitude after PAS were classified as “responders” in calculations of responder rates, consistent with previous studies (37). When displaying grand average MEP waveforms, positive MEP peaks were aligned to the median peak latency of the given condition and visit. This ensured that grand averages preserved true peak amplitudes without flattening due to latency variability.

BDNF

Plasma samples were collected with EDTA tubes and serum samples were collected using rapid serum tubes. Serum samples were allowed to clot for five minutes according to manufacturer instructions. Samples were immediately centrifuged for 10 minutes at 3000 RPM, after which serum and plasma were extracted and frozen at -80° until analysis. BDNF levels were measured using the Biosensis Mature BDNF Rapid ELISA Kit (Thebarton, Australia).

Questionnaires

Side effects were assessed using a preliminary version of the Swiss Psychedelic Side Effects Inventory (SPSI) (74). The SPSI records information on 32 side effects relevant to psychedelics and includes information on severity, positive or negative impact, timing, and duration. It also includes a standardized rating of the possibility that a side effect is treatment-related (causality) which is applicable to both placebo and drug conditions even if blinding has been broken. One investigator (AEC or VJD) who had been present on the dosing day conducted the SPSI in interview format both one day and seven days after dosing. One day after dosing, participants reported on side effects they experienced both acutely (within 12 hours of dosing) and post-acutely up until the time of the interview. One week after dosing, participants reported on post-acute side effects occurring since the previous appointment. If any potentially drug-related negative side effects persisted at the final study appointment, investigators followed up with participants until they resolved.

The Cognitive Flexibility Inventory (CFI) and Perceived Stress Scale (PSS) were included as possible subjective correlates of LSD-induced neuroplasticity. The CFI consists of two factors: *Alternatives*, or the ability to perceive multiple possible explanations for an event and generate multiple possible solutions to a problem, and *Control*, or one's perceived ability to control difficult situations. The Perceived Stress Scale (PSS) is used to assess subjective psychological stress and participants always answered in relation to the past week.

Data analysis

Effects of LSD were analyzed using linear mixed effects models with fixed effects for drug, visit, and treatment order and random effects for individual participants (*lme4 package*, version 1.1.37 (124)). Additionally, models assessing hourly ratings of acute drug effects included drug x hour interactions as fixed effects. Models assessing effects of PAS, ST, BDNF, and motor

learning included exercise and sleep as covariates because these can strongly impact neuroplasticity. When applicable, baseline values were included as covariates in the models. Furthermore, the two models assessing N1 and P2 auditory ERP amplitudes included fixed effects for tetanus condition (pre- or post-tetanus), and all post-tetanus timepoints were included individually without averaging or other transformations. These models also included three-way interaction effects between drug, visit and tetanus condition. The two models assessing TMS amplitude and latency included fixed effects for PAS condition (pre- or post-PAS) and interaction effects in the same manner, and additionally included a fixed effect for number of stimuli counted during PAS. Models assessing motor learning included fixed and effects for learning condition (online or offline) with each block included individually, as well as an interaction effect between drug and learning condition.

Robust estimators were used when assumptions of linear mixed effects models were violated (*robustlmm* package, version 3.3-3 (125)). Post-hoc contrasts at each timepoint (on dosing days, one day later, and one week later) were conducted using estimated marginal means using either pairwise comparisons or linear trends (*emmeans* package, version 1.11.1 (126)). *P* values were adjusted using the multivariate *t* method to control the familywise error rate. Correlations were calculated using Spearman's correlation coefficient with FDR correction for multiple comparisons.

Supplemental Results

Information on missing data

A total of 45 participants were enrolled in the study (Figure 5). One participant was excluded from analysis because of vomiting shortly after LSD ingestion, after which no LSD effects occurred. A second participant was excluded due to dropping out and retrospectively clarifying that inclusion criteria for the study were not met (see also “side effects” below). Additionally, one participant was excluded from TMS analyses because no clear MEPs could be recorded. One participant was excluded from BDNF analyses due to lack of viable blood samples. Additionally, several other participants had missing BDNF data due to difficulties performing blood draws, affecting 1.8% of analyzed samples. Finally, one participant was excluded from motor learning analyses because of a logistic issue with laboratory access at one of the relevant study appointments.

Evoked theta power

There was no effect of LSD on evoked theta power at any timepoint (Table S7).

Side effects

Side effects were analyzed for all 45 participants. LSD increased the number of possibly drug-related side effects reported acutely ($\beta = 6.58$, $SE = 0.49$, $p < 0.001$) and post-acutely within 36 hours after administration ($\beta = 1.40$, $SE = 0.49$, $p < 0.01$), with a trend-level increase during the week after administration ($\beta = 0.88$, $SE = 0.49$, $p = 0.07$) (Table S3, S4). There were no differences in subjective impact scores at any timepoint, and most side effects were rated as having a neutral impact (Figure S2). We followed up with five participants who reported mild but ongoing negative side effects possibly related to LSD at the final study appointment (anxiety ($n = 2$), reduced stress resilience ($n = 1$), concentration problems ($n = 1$), confusion about the meaning of the experience ($n = 1$). All resolved within 1-3 weeks without professional intervention and none were reported to have lasting negative effects on participants' well-being. We are not aware of any post-trial adverse events.

Participants could report other side effects than the 32 specified on the SPSI. Other reported acute side effects after LSD were mild and rated as having a neutral impact, including brief shortness of breath ($n = 2$, presumably related to anxiety); back pain, difficulty moving, nosebleed, metal taste in the mouth, buzzing sounds in the ears, increased need to urinate, increased hair shedding (all $n = 1$). Other reported post-acute side effects were also mild and included altered perception of other people ($n = 3$); changes in the menstrual cycle ($n = 2$); reduced stress resilience, reduced insecurity, nosebleed (same participant as above), pale complexion, increased thoughts about what is important in life (all $n = 1$). All but one (reduced stress resilience) were described as having neutral impact.

Finally, one participant dropped out and was excluded from analysis after a serious adverse event (SAE) which was deemed to have a possible relationship to LSD. The participant in question received LSD on his first dosing day and reported mostly positive effects. Two investigators were present (AEC and a psychiatrist) who noted no unusual or concerning LSD effects. At follow-ups, the participant reported no notable adverse effects apart from mild fatigue. However, two weeks after receiving LSD, he informed the study team that he could not complete his remaining three study appointments due to voluntary in-patient hospitalization for a depressive episode. He clarified that he had been experiencing depressive symptoms since

before entering the study and that some of the statements about his current mental health given during screening had not been entirely accurate, for which he expressed remorse. He further explained the hospitalization by stating that the LSD session had motivated him to face his condition and seek treatment, and he emphasized that the LSD session had neither improved nor worsened his symptoms. The participant was entirely cooperative with all required reporting procedures and was discharged after two weeks of inpatient care. The study team followed up again after an additional month, at which time he reported that he was receiving outpatient treatment and showing overall improvement.

Supplemental Tables and Figures

Table S1. Hourly ratings of subjective drug effects after drug intake, as well as questionnaire scores for the 5-Dimensional Altered State of Consciousness Questionnaire (5D-ASC) and Mystical Experience Questionnaire (MEQ). Statistics indicate contrasts between placebo (reference level) and LSD. N = 43.

Rating	Hour	Placebo mean (SD)	LSD mean (SD)	Estimate	SE	z	p
Intensity	0	0.00 (0.00)	0.00 (0.00)	0	2.06	0	1
	1	6.33 (7.46)	65.88 (27.62)	62.45	2.06	30.3	<.001
	2	9.14 (9.55)	88.70 (18.67)	83.61	2.06	40.56	<.001
	3	8.09 (11.21)	86.56 (16.99)	81.84	2.06	39.7	<.001
	4	4.95 (7.21)	68.84 (22.03)	66.31	2.06	32.17	<.001
	5	3.35 (5.37)	55.81 (24.49)	52.12	2.06	25.28	<.001
	6	1.30 (2.65)	34.52 (20.74)	30.77	2.07	14.83	<.001
	7	0.44 (1.72)	24.38 (20.03)	19.94	2.07	9.61	<.001
	8	0.51 (2.14)	17.43 (17.68)	13.41	2.07	6.47	<.001
Good drug effect	0	0.00 (0.00)	0.00 (0.00)	0	2.32	0	1
	1	6.56 (10.29)	65.98 (27.38)	64.62	2.32	27.82	<.001
	2	9.35 (13.71)	81.58 (23.56)	78.88	2.32	33.96	<.001
	3	8.49 (13.76)	77.14 (20.94)	73.43	2.34	31.42	<.001
	4	4.42 (6.53)	64.44 (26.62)	63.04	2.32	27.14	<.001
	5	2.67 (4.77)	53.57 (27.78)	52.93	2.34	22.64	<.001
	6	1.12 (2.46)	37.98 (27.47)	33.35	2.34	14.27	<.001
	7	0.42 (1.67)	28.57 (26.65)	21.01	2.34	8.99	<.001
	8	0.40 (1.71)	22.98 (28.20)	14.52	2.34	6.21	<.001
Bad drug effect	0	0.00 (0.00)	0.00 (0.00)	0	0.36	0	1
	1	0.44 (1.20)	8.95 (14.08)	2.92	0.36	8.16	<.001
	2	0.19 (0.63)	13.28 (24.40)	2.24	0.36	6.27	<.001
	3	1.67 (9.90)	9.33 (16.60)	1.73	0.36	4.8	<.001
	4	0.56 (2.13)	8.98 (17.23)	1.41	0.36	3.93	1e-04
	5	0.14 (0.52)	7.95 (19.09)	1.32	0.36	3.68	2e-04
	6	0.16 (0.65)	5.17 (10.02)	1.64	0.36	4.55	<.001
	7	0.05 (0.21)	4.71 (8.65)	1.52	0.36	4.22	<.001
	8	0.05 (0.30)	5.43 (11.24)	1.49	0.36	4.13	<.001
Ego dissolution	0	0.00 (0.00)	0.00 (0.00)	0	1.95	0	1
	1	1.33 (3.94)	29.07 (31.27)	17.5	1.95	8.99	<.001
	2	1.05 (2.74)	56.07 (39.37)	67.88	1.95	34.86	<.001
	3	0.23 (1.07)	54.67 (34.27)	57.14	1.96	29.17	<.001
	4	0.12 (0.76)	39.77 (32.95)	33.26	1.95	17.08	<.001
	5	0.00 (0.00)	27.57 (26.40)	21.05	1.96	10.75	<.001
	6	0.00 (0.00)	13.17 (17.84)	9.72	1.96	4.96	<.001
	7	0.12 (0.76)	8.50 (13.92)	5.97	1.96	3.05	0.0023
	8	0.12 (0.76)	4.55 (7.96)	4.34	1.96	2.22	0.0266
Relaxation	0	71.86 (21.99)	66.40 (19.64)	6.36	2.95	2.16	0.031
	1	83.95 (15.68)	72.40 (26.07)	10.26	2.95	3.48	5e-04
	2	89.63 (10.63)	82.44 (23.03)	5.16	2.95	1.75	0.0801
	3	89.14 (11.50)	80.71 (23.70)	6.23	2.97	2.1	0.0358
	4	85.23 (13.76)	80.21 (23.12)	1.29	2.95	0.44	0.6604
	5	83.49 (13.69)	78.00 (21.26)	1.77	2.97	0.6	0.5498
	6	82.77 (14.04)	80.00 (17.91)	1.69	2.97	0.57	0.5689
	7	80.37 (16.08)	80.71 (20.11)	1.95	2.97	0.66	0.5109
	8	78.93 (15.15)	81.12 (20.35)	3.77	2.97	1.27	0.2034

5D-ASC							
Oceanic Boundlessness	4.48 (6.33)	55.80 (25.43)	52.78	3.8	13.89	<.001	
Anxious Ego Dissolution	1.13 (2.16)	28.96 (23.17)	25.92	3.8	6.82	<.001	
Visionary Restructuralization	4.21 (7.29)	56.43 (25.16)	53.21	3.8	14	<.001	
Auditory Alterations	1.81 (4.32)	24.45 (21.80)	21.01	3.8	5.53	<.001	
Vigilance Reduction	18.75 (17.17)	48.47 (25.03)	30.61	3.8	8.06	<.001	
MEQ-30							
Mystical	4.00 (6.63)	51.94 (25.78)	50.25	3.03	16.61	<.001	
Positive Mood	15.43 (14.11)	67.05 (21.80)	53.4	3.03	17.64	<.001	
Transcendence	5.97 (8.25)	66.67 (24.83)	63.72	3.03	21.05	<.001	
Ineffability	5.12 (8.71)	84.19 (19.68)	81.09	3.03	26.8	<.001	

Table S2. Percentage of participants who gave each possible rating of lasting LSD effects on subjective well-being at the final study visit, divided by order (LSD or placebo first). Participants most commonly reported mildly or moderately positive lasting effects on well-being, and no one reported negative lasting effects. *N* = 43.

“Do you have the feeling that the LSD experience led to changes in your personal well-being or life satisfaction?”		
	LSD first (<i>n</i> = 21)	Placebo first (<i>n</i> = 22)
Strong increase	14.29%	22.73%
Moderate increase	23.81%	22.73%
Slight increase	38.1%	36.36%
No change	23.81%	18.18%
Slight decrease	0%	0%
Moderate decrease	0%	0%
Strong decrease	0%	0%
<i>Time since LSD experience (days)</i>	<i>72.57 (62.41)</i>	<i>6.95 (0.56)</i>

Table S3. Impact of LSD on side effects recorded with the Swiss Psychedelic Side Effects Inventory (SPSI). Data show the number of possibly treatment-related side effects and ratings of their subjective impact at three timepoints after drug administration. Impact ratings range from - 2 (very negative) to +2 (very positive). Statistics indicate results of linear mixed effects models with placebo as the reference level. *N* = 45.

Timepoint	Placebo mean (SD)	LSD mean (SD)	Estimate	SE	z	p
Number of side effects						
Acute (<12h)	2.64 (2.20)	9.38 (4.22)	6.58	0.49	13.36	<.001
Post-acute (12-36h)	3.96 (3.01)	5.76 (3.80)	1.4	0.49	2.85	0.004
Prolonged (36h - 1 week)	1.40 (1.89)	2.29 (2.20)	0.88	0.49	1.78	0.075
Subjective impact of side effects						
Acute (<12h)	0.00 (0.37)	0.33 (1.43)	0	0	1.2	0.231
Post-acute (12-36h)	-0.56 (1.42)	-0.31 (1.08)	0	0	1.07	0.286
Prolonged (36h - 1 week)	-0.27 (1.12)	-0.31 (0.79)	0	0	-1.13	0.258

Table S4. Percentage of participants reporting each side effect from the Swiss Psychedelic Side Effects Inventory (SPSI) arranged in the order of most frequent acute effects after LSD. Only side effects rated as at least possibly drug-related are shown. See also Figure S2 for visualization of impact ratings from the SPSI. N = 45.

Side effect	LSD acute (<12h)	LSD post- acute (12-36h)	LSD prolonged (36h-7d)	Placebo acute (<12h)	Placebo post-acute (12-36h)	Placebo prolonged (36h-7d)
Vision changes	95.56	15.56	11.11	33.33	4.44	0
Difficulty concentrating	71.11	35.56	17.78	20	26.67	4.44
Appetite changes	66.67	28.89	15.56	6.67	8.89	2.22
Muscle shaking, tightness	64.44	11.11	8.89	6.67	20	8.89
Hot, cold, sweaty	60	15.56	2.22	17.78	4.44	0
Nausea, vomiting	60	11.11	0	4.44	15.56	2.22
Anxious, fearful, panicked	44.44	40	17.78	11.11	13.33	6.67
Fatigue, tiredness	44.44	77.78	60	57.78	64.44	42.22
Headache	42.22	60	17.78	28.89	55.56	11.11
Confusion, disorientation	40	11.11	4.44	0	4.44	2.22
Depersonalization	40	0	0	0	2.22	0
Derealization	37.78	2.22	0	0	0	0
Bloating, diarrhea	33.33	26.67	0	6.67	28.89	4.44
Dizziness, faintness	33.33	8.89	0	17.78	8.89	2.22
Memory problems	33.33	6.67	6.67	11.11	6.67	2.22
Heart racing, chest pressure	31.11	13.33	0	15.56	11.11	2.22
Restless, irritable	28.89	24.44	8.89	6.67	24.44	15.56
Hearing changes	22.22	8.89	2.22	6.67	2.22	0
Fear of going insane	20	8.89	0	0	0	0
Lonely, isolated	17.78	13.33	11.11	4.44	4.44	2.22
Negative thoughts about self	15.56	0	2.22	0	4.44	0
Sad, mournful, depressed	11.11	17.78	8.89	6.67	8.89	2.22
Apathetic, empty	8.89	6.67	2.22	2.22	13.33	2.22
Distressing memories	4.44	6.67	4.44	0	0	0
Paranoia	4.44	0	0	0	0	0
Sleep difficulties	4.44	91.11	17.78	0	51.11	24.44
Existential distress	2.22	0	0	0	0	0
Desire to take again	0	0	0	0	0	0
Elated, excitable, impulsive	0	0	0	0	0	0
Psychedelic flashbacks	0	33.33	8.89	0	11.11	2.22
Suicidality	0	0	0	0	0	0
Thought disorder	0	0	0	0	0	0

Table S5. Main effects from mixed effects models demonstrating that there was no effect of sensory tetanization (ST; in bold) on amplitude of N1 (top) or P2 (bottom) event-related potentials (ERPs). Post-hoc contrasts confirmed that ST did not potentiate ERPs at any visit. T = time of drug intake. N = 43.

Fixed effect	Coefficient	SE	CI low	CI high	t	df	p
N1 model							
drug	-0.57	0.15	-0.87	-0.27	-3.72	987	<0.001
visit T+1	-0.30	0.16	-0.60	0.01	-1.92	987	0.055
visit T+7	-0.40	0.15	-0.71	-0.10	-2.62	987	0.009
ST	0.05	0.13	-0.20	0.30	0.39	987	0.700
baseline amplitude	0.92	0.06	0.80	1.04	14.51	987	<0.001
order	0.10	0.19	-0.29	0.48	0.49	987	0.625
exercise	0.03	0.03	-0.03	0.10	1.03	987	0.302
sleep	0.03	0.02	-0.01	0.07	1.42	987	0.156
P2 model							
drug	1.55	0.22	1.12	1.98	7.05	987	<0.001
visit T+1	0.97	0.22	0.53	1.41	4.34	987	<0.001
visit T+7	1.75	0.22	1.31	2.18	7.86	987	<0.001
ST	0.15	0.18	-0.21	0.51	0.82	987	0.414
baseline amplitude	0.63	0.07	0.49	0.78	8.85	987	<0.001
order	0.03	0.31	-0.58	0.63	0.09	987	0.929
exercise	-0.03	0.05	-0.12	0.06	-0.62	987	0.533
sleep	-0.01	0.03	-0.07	0.05	-0.32	987	0.746

Table S6. Effects of LSD on amplitude of N1 and P2 auditory event-related potentials (ERPs) after auditory stimuli during each recording session. Statistics show contrasts between placebo (reference) and LSD at each timepoint. T = time of drug intake. N = 43.

ERP	Timepoint	Placebo mean (SD)	LSD mean (SD)	Estimate	SE	z	p
N1	T + 6h	-3.90 (1.66)	-3.42 (1.70)	0.5	0.08	6.45	<.001
N1	T + 1d	-3.66 (1.71)	-3.76 (1.64)	-0.01	0.08	-0.17	0.869
N1	T + 7d	-3.72 (1.69)	-3.79 (1.72)	-0.04	0.08	-0.56	0.579
P2	T + 6h	4.65 (2.28)	3.07 (1.69)	-1.33	0.11	-12.07	<.001
P2	T + 1d	4.52 (1.83)	4.23 (1.99)	-0.32	0.11	-2.92	0.004
P2	T + 7d	4.46 (1.80)	4.63 (2.07)	-0.02	0.11	-0.22	0.825

Table S7. Results of contrasts from linear mixed effects models assessing the effects of LSD on evoked theta power at each visit. We found no effect of LSD on evoked theta power. T = time of drug intake. N = 43.

Timepoint	Placebo	LSD	Estimate	SE	z	p
	mean (SD)	mean (SD)				
T + 6h	2.85 (2.48)	3.14 (2.67)	0.33	0.23	1.44	0.151
T + 1d	2.98 (2.37)	2.94 (2.27)	-0.11	0.23	-0.46	0.647
T + 7d	2.90 (2.49)	3.08 (2.69)	0.07	0.23	0.32	0.751

Table S8. Results from mixed effects models demonstrating that there was no overall effect of paired associative stimulation (PAS, in bold) on amplitude of motor-evoked potentials (MEPs). Post-hoc contrasts confirmed that there was no potentiation effect on MEPs at any visit. T = time of drug intake. N = 42.

Fixed effect	Coefficient	SE	CI low	CI high	t	df	p
drug	-76.21	52.21	-178.68	26.27	-1.46	923	0.145
visit T+1	-107.19	53.10	-211.40	-2.99	-2.02	923	0.044
visit T+7	-54.91	53.04	-159.00	49.18	-1.04	923	0.301
PAS	7.44	43.87	-78.65	93.53	0.17	923	0.865
order	-67.04	62.33	-189.37	55.29	-1.08	923	0.282
exercise	6.10	11.86	-17.18	29.38	0.51	923	0.607
sleep	7.71	6.93	-5.89	21.32	1.11	923	0.266
TMS count	1.23	0.30	0.63	1.82	4.04	923	<0.001
baseline amplitude	0.76	0.09	0.59	0.93	8.79	923	<0.001
drug x PAS	16.12	60.08	-101.79	134.02	0.27	923	0.789

Table S9. Effects of LSD on amplitudes and latencies of motor-evoked potentials (MEPs). MEP amplitude was acutely increased under LSD and decreased one day after LSD. Latency was acutely decreased under LSD. Statistics show contrasts between placebo (reference) and LSD at each timepoint. T = time of drug intake. N = 42.

MEP Parameter	Timepoint	Placebo mean (SD)	LSD mean (SD)	Estimate	SE	z	p
amplitude	T + 7h	775.16 (403.29)	808.60 (375.73)	64.4	26.63	2.42	0.016
amplitude	T + 1d	874.35 (397.24)	775.24 (375.80)	-80.76	26.11	-3.09	0.002
amplitude	T + 7d	829.02 (394.67)	787.45 (370.08)	-40.71	25.4	-1.6	0.109
latency	T + 7h	23781.99 (2190.11)	22913.53 (2149.46)	-775.19	119.75	-6.47	<.001
latency	T + 1d	23372.61 (1941.89)	23372.69 (2004.43)	-104.7	117.58	-0.89	0.373
latency	T + 7d	23238.02 (2169.24)	23281.63 (2142.94)	42.69	114.4	0.37	0.709

Table S10. Effects of LSD on plasma and serum brain-derived neurotrophic factor (BDNF) at four timepoints before and after dosing. Statistics show contrasts between placebo (reference) and LSD at each timepoint. T = time of drug intake. N = 42.

Timepoint	Blood fraction	Placebo mean (SD)	LSD mean (SD)	Estimate	SE	z	p
T - 0.5h	serum	22.97 (5.68)	23.55 (7.48)	0.49	1.21	0.41	0.685
T + 8h	serum	22.73 (5.85)	23.92 (7.57)	1.06	1.23	0.86	0.389
T + 1d	serum	23.93 (8.03)	23.93 (7.65)	-0.63	1.22	-0.52	0.605
T + 7d	serum	25.97 (7.43)	26.36 (8.81)	-0.37	1.19	-0.31	0.757
T - 0.5h	plasma	1.93 (1.87)	1.97 (1.35)	0.26	0.16	1.61	0.107
T + 8h	plasma	1.55 (1.07)	1.77 (1.75)	0.07	0.17	0.39	0.698
T + 1d	plasma	2.06 (1.92)	1.75 (1.34)	-0.19	0.17	-1.11	0.267
T + 7d	plasma	1.75 (1.41)	1.98 (1.69)	0.03	0.16	0.2	0.844

Table S11. Effects of LSD on typing speed improvement during a motor learning task one day after drug administration. P2-P10 indicate practice blocks assessing online learning; T1 and T2 indicate blocks after 10 and 80 minutes of rest assessing offline learning. Data show improvement in each block compared to the previous practice block. More negative values indicate greater improvement. Note that the first practice block (P1) is not shown because it has no difference to a previous block. Statistics show results of linear mixed effects models with contrasts between placebo (reference level) and LSD. N = 42.

Block	Placebo mean (SD)	LSD mean (SD)	Estimate	SE	z	p
P2	-123.83 (144.59)	-119.35 (177.95)	11.85	12.56	0.94	0.346
P3	-98.30 (93.60)	-82.05 (92.43)	20.03	12.56	1.59	0.111
P4	-66.44 (63.99)	-52.76 (74.30)	15.42	12.56	1.23	0.220
P5	-50.79 (55.10)	-54.36 (64.97)	-2.57	12.56	-0.2	0.838
P6	-40.89 (44.59)	-48.15 (46.73)	-8.03	12.56	-0.64	0.523
P7	-38.66 (41.18)	-35.18 (35.35)	2.52	12.56	0.2	0.841
P8	-34.65 (29.75)	-32.50 (36.01)	1.76	12.56	0.14	0.889
P9	-26.91 (26.07)	-25.15 (26.76)	0.37	12.56	0.03	0.977
P10	-24.46 (24.57)	-27.87 (27.07)	-3.57	12.56	-0.28	0.776
T1	-283.54 (222.94)	-332.33 (341.63)	-5.71	12.56	-0.45	0.650
T2	-254.40 (227.08)	-347.86 (324.61)	-36.98	12.56	-2.94	0.003

Table S12. Results of Spearman correlations assessing relationships between behavioral and neurophysiological outcomes, with correction for false discovery rate. No significant correlations were found. Correlations with offline motor learning used improvement in the test block after 80 minutes of rest. BDNF = brain-derived neurotrophic factor, CFI = Cognitive Flexibility Inventory, MEP = motor-evoked potential, PSS = Perceived Stress Scale, T = time of drug intake. N = 43.

Outcome 1	Outcome 2	Timepoint	Spearman's ρ	p	p (corrected)
Motor learning	MEP amplitude	T+7h	0.06	0.59	0.77
Motor learning	MEP latency	T+7h	0.18	0.12	0.56
Motor learning	MEP amplitude	T+1d	0.09	0.44	0.77
Motor learning	P2 amplitude	T+1d	-0.08	0.47	0.77
Motor learning	Serum BDNF	T+1d	-0.06	0.62	0.77
Motor learning	Plasma BDNF	T+1d	-0.02	0.83	0.92
PSS	Serum BDNF	T+7d	0.00	0.97	0.97
PSS	Plasma BDNF	T+7d	0.10	0.39	0.77
CFI Alternatives	Serum BDNF	T+7d	-0.15	0.17	0.56
CFI Alternatives	Plasma BDNF	T+7d	0.19	0.09	0.56

Table S13. Scores on two subscales of the Cognitive Flexibility Inventory (CFI) and Perceived Stress Scale (PSS) one week after LSD and placebo. LSD significantly increased scores on the Alternatives subscale of the CFI and significantly decreased scores on the PSS. Statistics show contrasts between placebo (reference) and LSD one week after dosing from mixed effects models including baseline scores as covariates. N = 43.

Questionnaire	Placebo	LSD	Estimate	SE	z	p
	mean (SD)	mean (SD)				
CFI Alternatives	73.93 (8.46)	76.00 (6.85)	1.92	0.63	3.04	0.002
CFI Control	37.56 (6.80)	37.07 (6.90)	-0.53	0.67	-0.8	0.424
Perceived Stress Scale	23.23 (5.69)	21.21 (4.96)	-1.94	0.91	-2.14	0.032

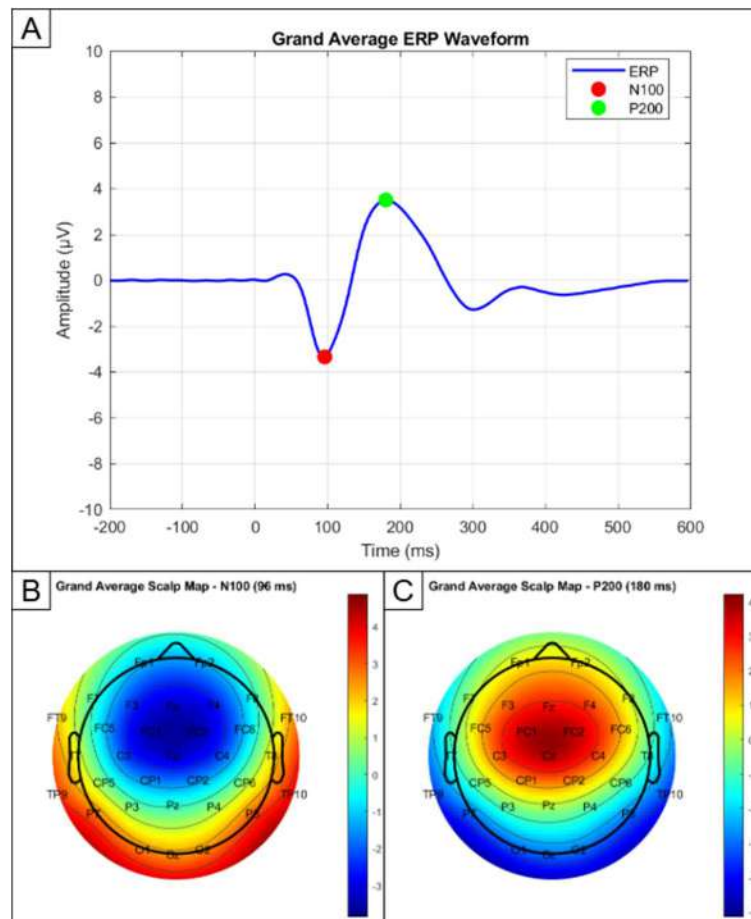


Figure S1. Grand average ERP waveforms (A) and scalp signals for auditory N1 (B) and P2 (C) event-related potentials across all participants and visits.

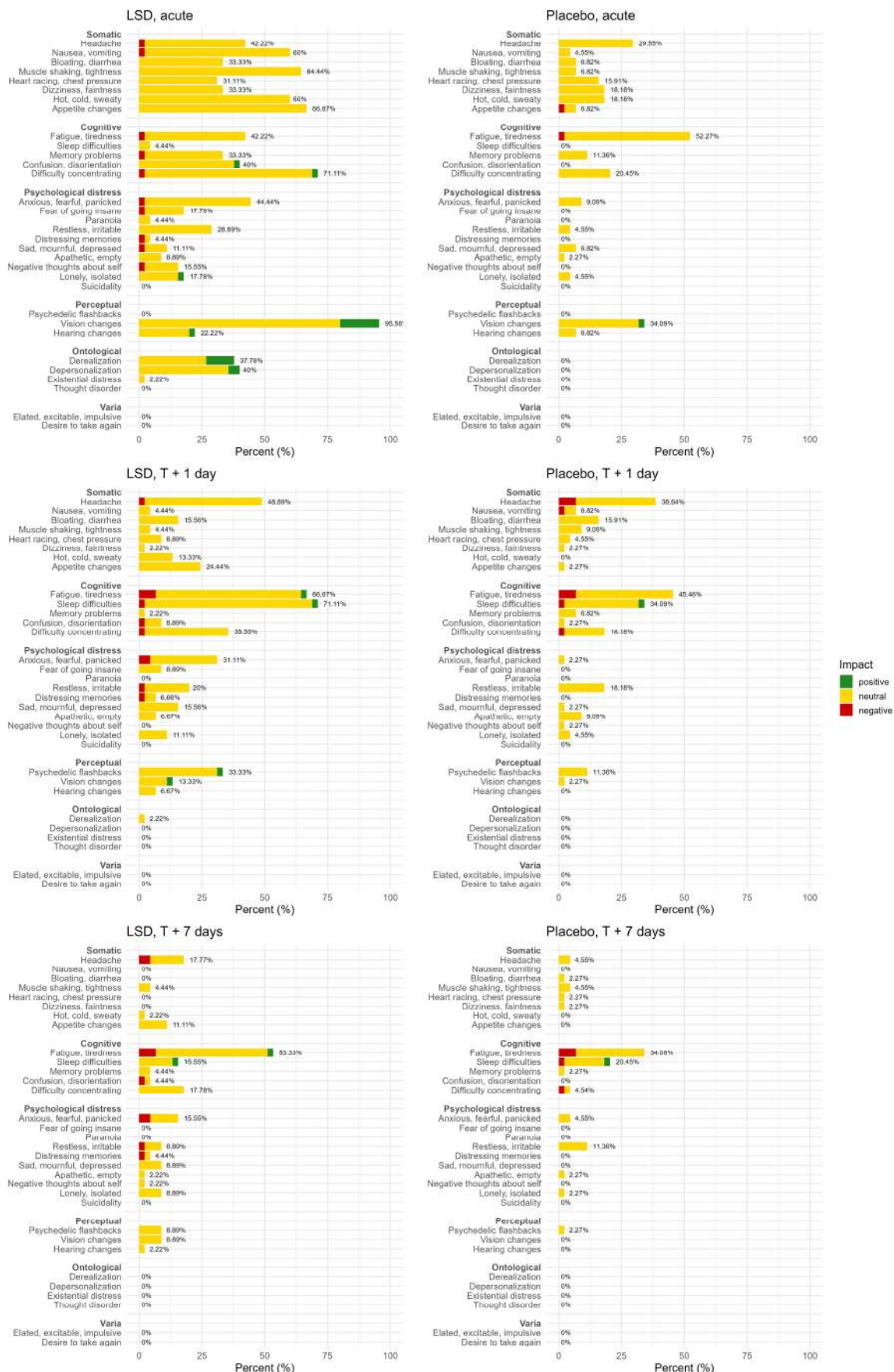


Figure S2. Descriptive graph of subjective impact ratings for possibly drug-related side effects reported on the Swiss Psychedelic Side Effects Inventory (SPSI) for three time periods after administration of LSD and placebo. Impact ratings range from -2 (very negative) to +2 (very positive). Side effects were considered acute if they occurred within 12 hours of drug administration. N = 45.

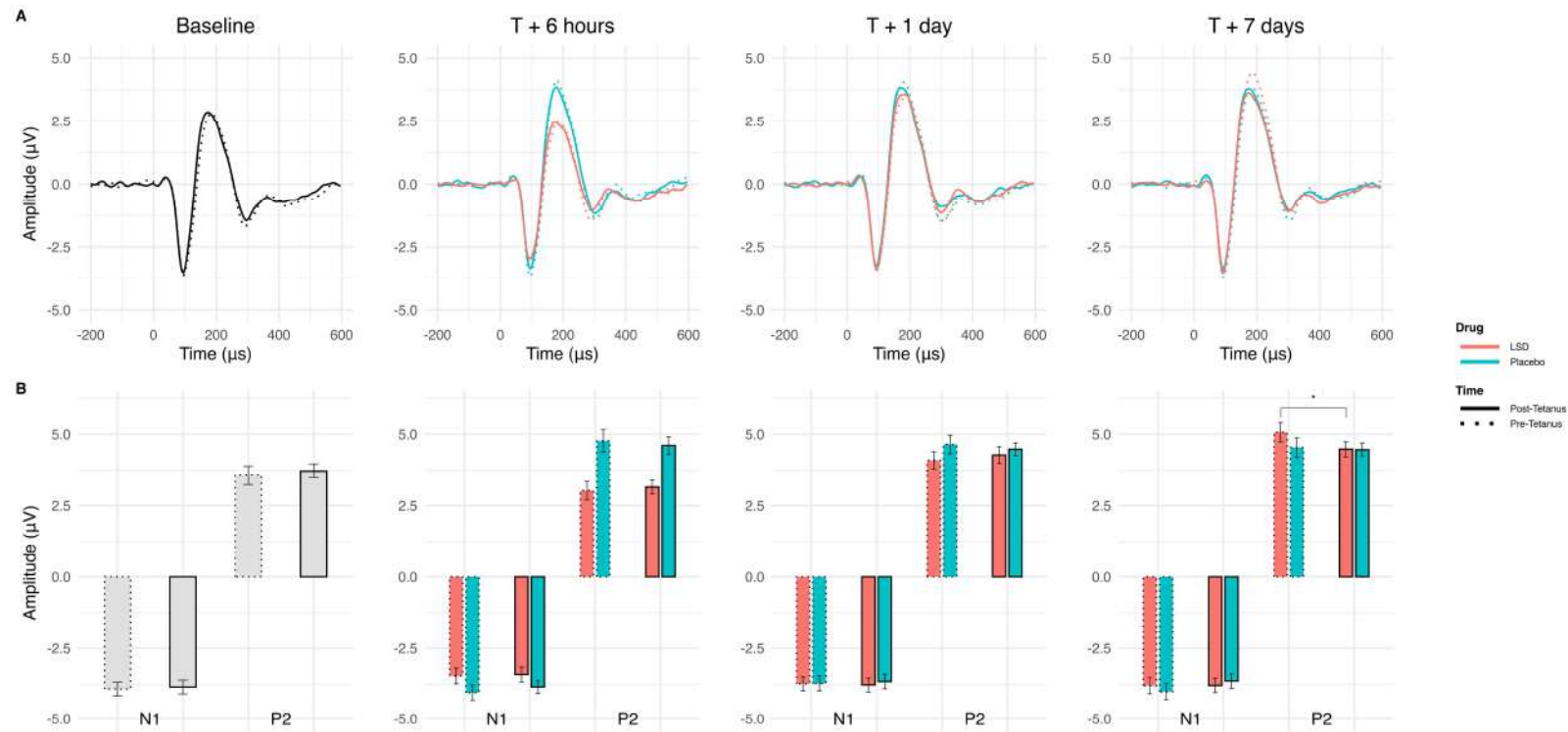


Figure S3. Effects of LSD on auditory event-related potentials (ERPs) before and after sensory tetanization (ST). $N = 43$. Waveforms (A) show average ERPs before and after ST for each drug and visit. Bar graphs show mean amplitude of N1 and P2 components before and after ST for each drug and visit. P2 amplitude significantly decreased after tetanus in the LSD group one week after dosing. Only statistical tests related to ST are shown here; see main text for main effects of LSD on auditory ERPs. Error bars show SEM. T = time of drug intake. $N = 43$. *** $p < .001$. ** $p < .01$, * $p < .05$.

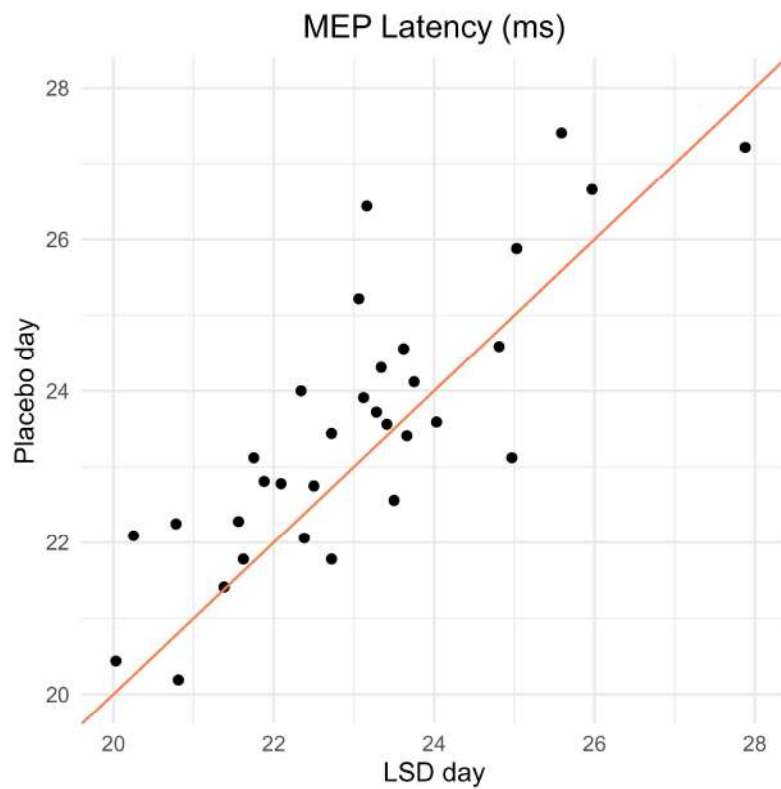


Figure S4. Latency of motor-evoked potentials (MEPs) in the LSD and placebo conditions on dosing days at seven hours after drug administration. Each point represents one participant. The orange line ($y = x$) represents equal latency in both conditions. Points above the line represent those participants who had faster latency under LSD than placebo. $N = 35$. The smaller sample on dosing days, compared to other timepoints, was due to the acute effects of LSD occasionally interfering with the tolerability of TMS experiments.

ReSPCT reporting of preparation and setting for LSD sessions

The following information on the setting surrounding LSD sessions has been prepared with reference to the ReSPCT Guidelines for Reporting of Setting in Psychedelic Clinical Trials (1).

Physical environment of LSD sessions

Dosing sessions took place indoors in the research wing of a mental health clinic located on the outskirts of Fribourg, Switzerland in a suburban area with views of meadows, trees, apartment buildings, a flower garden, and mountains. Participants had free access to the study room, a balcony, and a single stall bathroom directly across the hall. We aimed to create a comfortable living room-like atmosphere in the study room. In addition to necessary computers and supplies required for tests, the study room contained comfortable furniture (armchair, meditation cushions, bed with adjustable bedframe), wall art featuring natural landscapes, house plants, a rug, other small decorations (e.g. origami, decorative rocks), and a bookshelf with titles related to neuroscience and psychedelics (see Figure 2 of the main text). We avoided objects with overt religious or spiritual connotations and participants were encouraged to bring their own objects if desired.

Several lighting options were available and participants were allowed to adjust them at will (outside of experiments). There was one white fluorescent light on the ceiling with adjustable brightness. There were also two strips of colored lights on the ceiling which could be turned on or off and made to be nearly any color. Participants were given the color remote at the beginning of dosing sessions. Blinds and/or curtains could be closed to darken the room. Participants were given a comfortable blindfold and could bring their own headphones if desired; otherwise music was played over loudspeakers. Participants were encouraged to use blindfolds and listen to music if they desired an intense introspective experience, but this was not required.

Participants could sometimes hear noise from outside or from neighboring clinic rooms, e.g. people talking, cars, or music. The possibility of hearing these noises was discussed beforehand to set expectations, and participants were encouraged to shut windows or wear headphones if noises were bothersome. There were no disturbances which compromised participants' privacy, though participants were advised that they might see other (friendly) researchers if they stepped into the hallway (e.g. to go to the balcony or bathroom). Participants on LSD were never unaccompanied except when in the bathroom, in which case a facilitator waited outside.

Study team

At least one member of the facilitator team (AEC) was kept consistent throughout all preparation, dosing and integration sessions, and participants had the same facilitators at all appointments whenever scheduling permitted. All study personnel had a background in (clinical) psychology or psychiatry and several were members of the Swiss Medical Society of Psycholytic Therapy (SÄPT). Facilitators underwent in-house training for the study and were expected to regularly visit external training seminars (e.g. via the SÄPT) and participate in supervision and intervision.

Dosing session procedures

At least one, and most often two facilitators were always present with a single participant during dosing sessions. Before LSD was administered, facilitators reviewed the plan for the day with participants and asked about any recent stressors that could impact the experience. They then revisited discussions about participants' readiness to take LSD, strategies for navigating the experience, intentions or wishes, and any remaining questions. A 10-minute guided meditation was offered immediately after drug ingestion with a focus on using the breath as an anchor during the experience, as well as slow breathing to induce relaxation and brief reminders for what to expect from an LSD experience. For the first five hours after dosing, no experiments or activities were planned and participants could freely choose to sit, lie down, or move about the room. They were encouraged to introspect and listen to music, but they could also request silence, talk with the investigators, and do other calm activities (e.g. drawing, reading, light movement). Facilitators usually sat in chairs 1-2 meters away from the participant but asked for participants' preferences on this and adjusted as needed. No other study staff were present in the room or interacted with participants. Facilitators played music from a pre-programmed playlist chosen to facilitate relaxation and positive mood, unless participants requested otherwise. Participants were asked to bring their own food and drink and were allowed to eat or drink at any time outside of experiments. Facilitators offered light snacks (e.g. fruits), water, and caffeine-free herbal or fruit tea throughout the day.

We used a non-directive guiding approach unless participants requested direction or intervention was needed to ensure safety. Facilitators used various techniques to reduce anxiety or other unwanted effects. The goal of interventions was to increase comfort and prevent an overwhelmingly negative experience, particularly one dominated by feelings of strong fear and helplessness (2). Support methods included, but were not limited to:

- Verbal reassurance
- Reminders of important information from preparatory sessions, e.g. that participants had taken a drug in a safe setting, they will not be left alone, effects will subside by the evening, etc.
- Suggestions for controlling attention, e.g. observing and slowing the breath, focusing directly on intimidating aspects of the experience to facilitate resolution of unpleasant feelings, or “letting go” and relaxing attention as broadly as possible
- Simple guided meditations (e.g. body scan) or breathing exercises (e.g. square breaths) to facilitate mental and physical relaxation
- Hand-holding or a light hand on the shoulder, only with prior and continuous consent
- Addressing potential external sources of discomfort in the individual (e.g. hunger, thirst, temperature) or environment (lights, sounds)
- Any other strategies deemed to be potentially helpful in the moment

Five hours after dosing, participants were asked to participate in experiments, all of which had been previously encountered in a sober state. It was important to balance experimental rigor with ethical treatment of participants in a strongly altered state of consciousness. Participants were advised that if any experiment was too uncomfortable due to LSD effects, it could be delayed or skipped. Additionally, the schedule was planned with 30-minute time buffers between experiments so that a delay beginning one would not necessarily delay the others. The vast majority of participants were comfortable with the experiments and deviations from protocol were rare. Experiments ended 8-9 hours after dosing. Before sending participants home, the study team briefly discussed the LSD experience with them and issued some practical reminders about what to expect that evening and the next morning. Once LSD effects had sufficiently subsided, participants returned home with a friend or relative, typically 9-10 hours after dosing. There were never any time constraints that caused dosing sessions to end prematurely before a participant wished to return home.

Preparation for LSD effects

Participants attended two semi-structured preparatory sessions during the first two study visits, each lasting 1-2 hours. The study lead (AEC) was always present and the second facilitator for that participant was present for at least one preparatory session. Because the study was conducted in healthy subjects, we had no therapeutic goals or orientation.

In general, the LSD experience was framed as a journey through an altered state of consciousness in which aspects of one's mind and environment become strongly amplified or altered. We emphasized that LSD experiences could be interesting or insightful, but sometimes also unpredictable or random. Participants were informed about possible effects on perception, thoughts, emotions, memories, and self-perception, as well as possible adverse effects, using language that strove to be neutral but informative and reflected the most recent scientific understanding. Participants were also advised that LSD sometimes (but not always) has long-term effects on well-being, mood, and outlook on life, which are usually positive but could include rare adverse effects like perceptual changes, mood disturbances, and others (3); participants were guaranteed ongoing support from the study team should they experience prolonged adverse effects. Additionally, we asked participants about motivations for taking LSD and previous knowledge of LSD. When necessary, we addressed any unrealistic expectations. Participants were encouraged to be as open as possible about questions, concerns, and previous experiences with altered states of consciousness.

The second preparatory session was used to clarify practical aspects (e.g. schedule, what to bring). The role of the facilitators and what to expect from the laboratory setting were discussed in detail, and we asked participants for their preferences about activities, music, interpersonal support, and related topics during the dosing session. Participants were advised that some people like to set a goal or intention before taking LSD to direct the experience, but this was not required. We discussed personal topics which might arise spontaneously during the LSD session, as well as how participants might choose to respond to these. Additionally, we discussed the possibility of experiencing unpleasant or overwhelming effects, particularly fear of losing control. Facilitators explained how strong emotions can sometimes become amplified and how to manage overwhelming feelings (see support methods above), as well as the importance of asking us for help when needed. We emphasized cultivating participants' trust in their own ability to navigate the experience, but also in the readiness of the study team to assist and accept any reaction to LSD that might manifest.

Integration protocol

At each of the two follow-up appointments, facilitators conducted a semi-structured integration session lasting 30-90 minutes, depending on participants' desire to discuss the experience. We discussed the events of the dosing day in roughly chronological order and encouraged participants to freely tell their narrative of the experience while listening in a non-judgmental

manner. We inquired about how the evening had gone after returning home, how much participants had slept, and how they were currently feeling the day after LSD. We also specifically asked whether any drug effects that had been particularly surprising, challenging, or positive. We revisited any intentions and discussed possible takeaways from the experience, as well as anything participants wanted support with managing or understanding. Participants were advised that activities like journaling, making art, and discussing the experience with supportive others could help them further process and understand what to make of the experience. They were also reminded that they could request additional support from the study team if they had difficulty processing the experience.

Supplemental References

1. Pronovost-Morgan C, Greenway KT, Roseman L, Re SE. An international Delphi consensus for reporting of setting in psychedelic clinical trials. *Nat Med.* 2025;31(7):2186-95.
2. Calder AE, Diehl VJ, Hasler G. Traumatic Psychedelic Experiences. *Curr Top Behav Neurosci.* 2025:1-26.
3. Calder AE, Hasler G. Validation of the Swiss Psychedelic Side Effects Inventory: Standardized assessment of adverse effects in studies of psychedelics and MDMA. *J Affect Disord.* 2024;365:258-64.

Chapter V General Discussion

This thesis was an examination of a highly influential theory in the study of psychedelics: that they enhance neuroplasticity, and that this has meaningful effects on human behavior. Three research projects investigated what we really know (and do not know) about psychedelic-induced neuroplasticity, then attempted to find evidence of it in human subjects. This final chapter contains a summary of the findings, as well as a general discussion of their nuances, strengths, limitations, and implications for future research.

1. Summary of findings

Chapter II consisted of a review of current evidence for psychedelic-induced neuroplasticity, focusing on serotonergic psychedelics. Neuroplasticity is an umbrella term summarizing various related, but distinct processes of neural reorganization in response to its environment. We differentiated between them and found that psychedelics may not affect all of these equally. The evidence was strongest for increases in synaptic plasticity and brain neurotrophin signaling, including the expression of plasticity-promoting genes. By contrast, studies of neurogenesis (in animals) and peripheral BDNF (in humans) showed mixed results or even decreases in response to psychedelics. We also examined the evidence that psychedelic-induced neuroplasticity depends on 5-HT_{2A}R activation, concluding that this is probably the case and that some studies which seemed to find otherwise may have used doses of 5-HT_{2A}R antagonists which were too low to fully block neuroplastic effects.

With the relative specificity for 5-HT_{2A}R in mind, we emphasized that psychedelic-induced neuroplasticity does not affect every brain region equally, and that this is important for understanding its impact. The neocortex has a high level of 5-HT_{2A}R expression, and the strongest evidence for psychedelic-induced neuroplasticity is found in studies of the neocortex, particularly the PFC, which is also a clinically important area for mood regulation. We summarized the evidence for other regions as well, particularly the hippocampus, and contrasted psychedelics with addictive substances which also enhance neuroplasticity but primarily do so in dopaminergic neurons of the mesolimbic pathway.

An important emphasis of the paper was a detailed examination of the temporal dynamics of enhanced neuroplasticity. We found that certain changes in gene expression had been observed after only a few hours, followed by synaptic and dendritic growth beginning within 4-6 hours; these changes may be expected to last for at least 3-7 days. Even after this period of

growth subsides, the newly formed synapses and dendritic spines may survive long-term, suggesting a mechanism for enduring neuroplastic changes after psychedelic exposure.

We noted that the vast majority of evidence for enhanced neuroplasticity was from animal studies. The human studies which did exist most commonly used BDNF as a biomarker of neuroplasticity. The fact that most evidence came from animal studies raised an important question: does psychedelic-induced neuroplasticity relate to any important outcomes in humans? We reviewed previous studies that had found correlations between elevated neuroplasticity and changes in depression and anxiety (or animal models of the same) after psychedelic exposure. We also found theoretical reasons to hypothesize that enhanced cortical neuroplasticity, if it occurs, could be related to psychedelics' lasting effects on mood regulation, cognition (including cognitive flexibility), and possibly improvements in learning – though data relating these outcomes to neuroplasticity was sparse in animals and nearly non-existent in humans. We concluded that there is moderately strong evidence that psychedelics enhance several facets of neuroplasticity in laboratory animals, but that whether these findings translate to humans remains an open question, in addition to other open questions about optimal dosing, differences between specific substances, and whether neuroplastic effects are related to clinical or behavioral outcomes.

Chapter III was a pre-registered meta-analysis assessing the effects of psychedelics and other available psychoplastogens (mostly serotonergic psychedelics and ketamine) on peripheral BDNF in humans. As we had previously established, BDNF is the most common marker of neuroplasticity in studies of psychedelics in humans. However, existing studies had reported mixed results and it remained unclear whether peripheral BDNF can accurately reflect short-term changes in brain BDNF, or indeed brain BDNF at all. Furthermore, researching for the review in Chapter II had made me aware that existing papers summarizing findings on BDNF did not always identify all relevant papers using typical literature search strategies. Specifically, many seemed to miss studies in which BDNF was not a key outcome and not mentioned in the abstract, which meant they may be disproportionately missing null results. We thus used an unusually thorough search strategy for the meta-analysis to ensure we identified all of the relevant papers, even non-significant results in the supplementary files of a publication. We analyzed all possible timepoints and doses reported in each paper, as well as several possible moderators.

We included 29 studies delivering 104 effect sizes and found no overall significant effect of psychoplastogens on BDNF, even when considering available covariates. There was also no

effect for ketamine or serotonergic psychedelics individually. This did not change based on blood fraction (plasma or serum) or patient group. There was a significant, but extremely tiny increase in effect size at later measurement timepoints (up to 26 days after the intervention), though only a few studies measured BDNF > 24h after the intervention at all. The most impactful moderators related to study design so that greater effects were seen for less rigorous study designs, higher percentages of missing data, and higher risk of bias, all of which pointed to reduced differences in BDNF levels with greater study rigor. We therefore concluded that psychoplastogens do not impact peripheral BDNF in humans.

Though it was clear that no effect on BDNF could be found, the reasons for this were less clear. We proposed two possible explanations: that peripheral BDNF does not reliably reflect brain BDNF, particularly not short-term changes in brain BDNF, or that psychoplastogens do not have the same effects on neuroplasticity in humans as in animals. To the first, assays measuring peripheral BDNF are known to be somewhat unreliable and are sensitive to variations in handling and storage. Even with reliable assays, the percentage of peripheral BDNF that originates in the brain may be minimal, as BDNF is also stored and excreted by platelets and many other organs. Additionally, a study of ketamine treatment in rats suggested that peripheral BDNF can change after psychoplastogen treatment even if brain BDNF does not. Finally, even if changes in peripheral BDNF reliably reflect changes in brain BDNF, we discussed the possibility that it may be much easier to enhance neuroplasticity in laboratory animals than in humans. Lab animals living in typical cages are known to show reduced neuroplasticity compared to animals living in more stimulating environments, possibly giving them a neuroplastic deficit that healthy human subjects would not have.

Chapter IV was a randomized, placebo-controlled crossover trial investigating the effects of 100 µg LSD on neuroplasticity in 45 healthy subjects. We measured BDNF and LTP-like plasticity using ST and PAS at three timepoints after dosing, namely 6-8 hours, one day, and one week. We also included measures of motor learning, cognitive flexibility, and perceived stress.

The primary finding from this study was a positive effect of LSD on motor learning one day after dosing. LSD selectively enhanced offline learning improvements after rest, though not online learning during active practice. We could also show that this effect was unlikely to be due to a speed/accuracy trade-off, general increase in motor speed, or increased motivation the day after LSD intake. As was expected after the results of the meta-analysis described in Chapter III, LSD had no effect on peripheral BDNF at any timepoint. Additionally, like the BDNF meta-

analysis, this study led us to critically discuss the validity of some translational markers of psychedelic-induced neuroplasticity in humans, in this case ST and PAS.

Despite their limitations, ST and PAS still allowed insights into LSD's effects on auditory processing and the motor system. LSD acutely dampened auditory N1 and P2 ERP amplitudes, consistent with previous studies, and some of this effect lingered for P2 one day later. One week after dosing, the LSD group also showed a significant decrease in P2 amplitude during the EEG recording session, likely not due to ST. This decrease was difficult to interpret, though we tentatively guessed that it might reflect a habituation process to the auditory stimulus. Additionally, LSD acutely increased MEP amplitude and decreased MEP latency during TMS, an effect which has not been reported before. Post-acute effects of LSD on MEPs were limited to decreased amplitude one day later compared to the placebo group. We concluded that these effects likely reflected increased corticospinal excitability during LSD sessions, perhaps followed by fatigue the next day.

Finally, LSD decreased ratings of perceived stress and increased ratings on the *Alternatives* subscale of the CFI one week after dosing. Together with the findings on motor learning, this meant that the three behavioral indicators of LTP-like plasticity in this study supported the theory that LSD could enhance neuroplasticity in human subjects. The physiological measures, by contrast, could not offer conclusive evidence for or against our hypotheses, and the study generally concluded that better neurophysiological measures of neuroplasticity in human subjects are needed to complement the positive behavioral results.

2. Discussion of findings

2.1 Motor learning

The key finding from the study of LSD and neuroplasticity was that LSD significantly improved offline motor learning one day after LSD treatment. I regard this finding as exciting on the one hand, because we are the first to demonstrate that LSD could positively affect motor learning. On the other hand, it requires replication and there are many nuances of LSD's effect on motor learning that still need to be explored. Our findings justify further studies designed to elucidate how exactly LSD impacts motor learning and whether this has practical or clinical meaning.

Motor learning is a complex process influenced not only by learning ability and neuroplasticity, but also attention, motivation, the timing of practice sessions, and other factors (1, 2). I see great potential to explore exactly how LSD affects motor learning through experimental

manipulation of these parameters in future studies. For example, experimental designs using more than two offline learning timepoints could elucidate whether offline learning gains are larger after LSD, simply more stable over time, or both, informing theories about LSD's impact on motor memory consolidation. An additional possibility could be that participants are more sensitive to manipulations of motivation or reward after LSD, given LSD's possible effects on reward processing (3, 4). On the other hand, participants in the LSD group reported greater tiredness on the day after dosing, which could also affect learning performance (5, 6).

Measuring motor learning 2-3 days after LSD exposure rather than just one may be interesting for future studies because preclinical studies suggest that this is within the peak of enhanced neuroplasticity (7, 8), but perhaps without the confounder of tiredness that is often present the day after an LSD experience. Finally, it is worth exploring how different doses of LSD and other psychoplastogens might affect other types of learning in the days after exposure, for example associative learning, fear conditioning, language learning, or even recovery of neural function after a stroke (9).

We did not see correlations between motor learning and MEP amplitude or BDNF, and we were not able to test for correlations with participants' responses to ST or PAS. However, this may not be unusual. Other studies have also failed to find correlations between motor learning and purported neurophysiological measures of plasticity, including peripheral BDNF and PAS (10-12). Though PAS and motor learning interact with each other in some studies (see above), they do not necessarily correlate, suggesting that PAS response is not necessarily a biomarker of motor learning capability.

Neuroplasticity is subject to strong homeostatic regulation and thus cannot be increased above a certain level (13). The young, healthy participants used in this study likely had relatively high levels of neuroplasticity to begin with (14, 15). This means that if the learning effects in this study were indeed due to increased neuroplasticity, they may be relatively weak compared to effects seen in other populations with reduced neuroplasticity, such as older adults or clinical populations (e.g. people with depression). Future research of LSD and learning in these populations would thus be illuminating. Along these lines, our lab is already conducting a follow-up study of LSD in healthy older adults which measures performance on the same learning task one day and one week after dosing (BASEC 2023-01272).

2.2 Perceived stress and cognitive flexibility

We showed that LSD reduced perceived stress and increased specific aspects of cognitive flexibility one week after dosing. These effects were consistent with previous reports of psychedelics' lasting effects in humans, including both healthy subjects and patients with depression, anxiety, and substance abuse disorders (16). Though we were not able to assess the relationship between neuroplasticity and stress or cognitive flexibility, our findings add to the body of literature showing lasting positive effects of LSD and other psychedelics when taken in a safe setting.

With questionnaires in particular, we must be cautious about placebo effects related to participants' expectations of LSD (17). We attempted to control for at least some of the impact of placebo effects by convincing participants that the placebo was a low dose of LSD, and this deception was successful in most participants. Our data therefore show that this blinding method can be successfully used and may be one viable strategy to address blinding problems in studies of psychedelics, particularly when participants are led to believe that microdoses may have positive effects (18). Nevertheless, we cannot rule out the possibility that placebo effects may have impacted our findings because participants may have expected greater effects from the large dose of LSD, which all correctly identified. On the other hand, examination of our self-report data made it clear that our healthy sample showed relatively high cognitive flexibility and relatively low perceived stress even at baseline. This means that we may have encountered a ceiling effect and that the difference could be relatively small compared to what one may see in other populations with greater room for improvement, for example patients with depression (19, 20).

It was interesting that LSD increased scores on the *Alternatives* subscales of the CFI, but not the *Control* subscale. This adds nuance to previous literature demonstrating effects of psychedelics on cognitive flexibility (19, 21, 22). It suggests that while LSD may increase people's ability to perceive many alternative courses of action or solutions to a problem, it does not necessarily make events in one's life feel more controllable. Interestingly, other studies have suggested that psychedelics may enhance people's acceptance of the difficulties in life which are not controllable, possibly explaining some of their therapeutic benefits (23).

If LSD lastingly reduces feelings of stress and increases cognitive flexibility even in healthy people, this strengthens the theory that psychedelics have some potential prophylactic effects against stress-related psychiatric disorders (24). High levels of stress and reduced cognitive flexibility are thought to be risk factors for depression, anxiety, substance abuse, and other

psychiatric disorders (25-27). Addressing these risk factors before disease onset could be an important step toward reducing the global burden of psychiatric disease. Importantly, however, these and other positive psychological effects are most likely when LSD is taken in safe and supportive settings, and a frightening psychedelic experience in an unsafe setting can sometimes increase anxiety and stress sensitivity (28).

2.3 BDNF

Another major finding of this thesis was the lack of evidence for any effects of psychoplastogens, including LSD, ketamine, and others, on peripheral BDNF. Our meta-analysis considered data for every available drug, timepoint, dose, and blood fraction taken from human subjects receiving psychoplastogens, and our thorough search strategy ensured that we also included null results which may not feature prominently in the given articles. We found no effect of any psychoplastogen on BDNF in the meta-analysis. Furthermore, the crossover trial showed no effect of LSD on BDNF eight hours, one day, or one week after dosing, as well as no correlation between BDNF and motor learning, perceived stress, or cognitive flexibility.

Based on our findings, we recommend that studies of psychedelics do not rely on peripheral BDNF in the search for psychedelic-induced neuroplasticity. However, I would also note that this does not mean that BDNF is useless as a marker of neuroplasticity in other contexts. Our data suggest that it may not be a useful marker for rapid changes in brain BDNF developing over the course of hours or days, such as those expected after psychedelic interventions. However, BDNF is widely used as a marker in studies of depression, neurodegenerative diseases, and other conditions related to neuroplasticity which develop over many months or years (29, 30). Assessing its usefulness across longer timescales is beyond the scope of this thesis.

2.4 Stimulation-based measurements of LTP-like plasticity

LTP is one of the best-studied aspects of neuroplasticity in *in vitro* and animal studies, but it has proven difficult to measure in humans (31). In the current work, the stimulation-based methods we used offered interesting insights into LSD's effects on neural signals (see below). However, the fact that they did not induce LTP-like signal potentiation as expected is worth a critical discussion with implications for the study of neuroplasticity in humans. Since the current work

was begun, new publications have shed light on some of the shortcomings of stimulation-based methods and potential strategies for improving them.

ST and PAS suffer from some of the same limitations. Perhaps the largest shortcoming of both is response variability: many studies have a high number of non-responders who show no LTP-like potentiation of neural signals (32). After both ST and PAS, some participants show increased signal amplitude, some decreased amplitude, and others barely any change (33-36). Some scholars have criticized PAS for its low response rates in many studies, and the sources of this variability are not well understood (35, 37). Effects can also vary across test sessions even in the same individual (38). Overall responder rates are estimated at around 50-60% for both auditory ST and PAS (39-41). This is in contrast to electrical induction of LTP *in vivo*, which is much more consistent (33). Attempts to elucidate the sources of variation between responders and non-responders have had limited success (42).

Apart from variability in individual participants' responses, not all studies find a statistically significant effect of ST or PAS on signal amplitudes in their samples. While some studies do find the originally reported increases in ERP amplitudes after auditory ST, others report no change or even significant decreases (40, 43-45). Furthermore, a recent meta-analysis found no overall effect of either auditory or visual ST (40). A large quantitative review reported overall significant PAS effects on MEP amplitude, with the results suggesting that precisely the parameters we used should produce robust effects (46). On the other hand, a different pooled analysis of PAS studies found no significant effect of PAS and suggested that the overall 53% responder rate was not above chance levels (41).

What explains the conflicting results, and can we make these methods more reliable? Several scholars have put forth plausible theories. Firstly, it is possible that successful ST and PAS studies are more likely to be published (40, 41). Some previous studies have also mitigated the problem of non-responders by only selecting participants who were responsive to PAS in an initial experiment (47). On the other hand, it is also possible that ST and PAS effects are so subtle that many studies are underpowered to find them; one relatively large study analyzing auditory ST had some success in inducing LTP-like changes and noted that their sample (N = 93) was larger than in most previous studies (39).

Different analysis techniques may also explain contradictory findings. For example, one study which found potentiation defined it as the percentage of post-tetanus N1 ERPs which exceeded the pre-tetanus amplitude, which differs from our use of a linear mixed effects model without any data transformation (48). Statistical choices may also strongly affect whether PAS effects

are observed, and it has been suggested that some previous findings showing potentiation of MEPs after PAS could be a statistical artefact resulting from the fact that MEPs 1) can never be negative and 2) have a skewed positive distribution (41). This problem would also affect the ERPs analyzed in ST.

Another perhaps obvious consideration is the possibility that we may have implemented the methods incorrectly, particularly for PAS because its evidence base appears stronger. Though we followed the prototypical methods from previous ST and PAS studies as closely as possible, we may not be able to rule this out. However, it is noteworthy that well-powered studies from groups with substantial experience in neurophysiology have also reported low responder rates and unreliable PAS effects (35, 41, 49). Additionally, interstimulus intervals of between 18.7 and 35ms have been able to induce LTP-like changes in previous PAS studies, suggesting that some margin of error is acceptable; we used 25ms (34). To the best of our knowledge, there were no methodological errors explaining our results.

Researchers hoping to use ST and PAS in future studies with psychedelics could consider several improvements to these methods gleaned from previous studies. Though ST typically uses pure tones as stimuli, one study found that short bursts of noise within a relatively narrow bandwidth induced greater potentiation (48). The same study showed that white noise induced the most stable LTP-like changes, possibly because it stimulates more auditory fibers. Additionally, classic ERP peak analyses may not be sensitive enough to detect neuroplastic effects, though whether more sophisticated analysis techniques detect LTP-like plasticity or something else is not clear (50). Some scholars have concluded that visual ST more reliably induces LTP-like changes than auditory ST, though it also shows high individual response variability (39). On the other hand, a recent meta-analysis suggested that neither auditory nor visual ST is particularly reliable (40). In general, it is still unclear exactly which variations in experimental protocols are most likely to yield successful LTP-like changes, and the few studies demonstrating improvements to the original ST method need replication.

Regarding PAS, some scholars have proposed calculating custom interstimulus intervals for PAS based on the speed of nerve conduction in each individual participant, rather than relying on one value (typically 25ms) for all participants (34). Shorter versions of the PAS protocol, while not used as often as the version from this study, may also produce more MEP facilitation (47). Additionally, it may be possible to screen participants for response to PAS before including them in studies (37, 47). One study found significant PAS responses in skilled athletes, but not

non-athlete controls, suggesting that baseline motor cortical excitability may positively predict response (51).

One could also attempt to maximize attention and alertness. Attention is considered a requirement for successful PAS, which is why we instruct participants to count the number of stimuli during the procedure. Auditory ST can induce LTP even when participants are not attentive to task stimuli (52), but greater attention could still enhance the effectiveness of ST at inducing LTP (33). During ST, we instructed participants to attentively listen to the tones with their eyes open, an instruction that was also displayed on the computer screen while tones were playing. However, it is possible that this was not sufficient, and participants may also have limited alertness during experimental sessions lasting 2-4 hours. This may be a reason to keep experimental sessions shorter in future studies.

To conclude this discussion, we chose three neurophysiological methods for measuring neuroplasticity after LSD: peripheral BDNF, ST, and PAS. One might say that all three carried some risk. The literature showed a believable theoretical basis justifying why each of these might reflect neuroplasticity, yet also controversy about whether they really measure what some scholars hope they do. As it turned out, a large part of this thesis was devoted to critically evaluating these methods as biomarkers of neuroplasticity. Though their limitations meant that we could not test our hypotheses about LSD-induced neuroplasticity in the way we hoped, the data from our ST and PAS experiments offer pertinent information to other scientists hoping to measure neuroplasticity after psychedelics in humans. ST in particular has been hailed as a new frontier for measuring neuroplasticity in studies of psychedelics (53), and the number of studies using has greatly increased since I began work on this thesis (45, 50, 54). The experiences of our research group, as well as others, suggest that future research on psychedelic and neuroplasticity may benefit from turning to other methods. For example, PET imaging of post-synaptic proteins has emerged as a worthy avenue of exploration in research on psychedelics and neuroplasticity, and it has clear translational value (55).

Despite the lack of LTP-like potentiation, our EEG and TMS paradigms both offered interesting insights into LSD's acute and post-acute effects on neural signals. We discuss these next.

2.5 Modulation of event-related potentials

LSD acutely decreased the amplitude of N1 and P2 ERPs in response to auditory stimuli, and the decrease in P2 was still weakly but significantly observable the next day. This was consistent with previous research investigating the effects of psychedelics on sensory ERPs of various

kinds, which generally find reduced amplitudes (56-59). ERP suppression may arise from LSD's effects on early sensory processing (reflected especially in N1 (60)), as well as attentional allocation to stimuli (reflected especially in P2 (61, 62)). Unlike MEPs, ERPs do not necessarily reflect the excitability of a sensory system. LSD acutely induces a broadband reduction in EEG oscillatory power and a desynchronization of neural signals, which can make ERPs appear smaller (57).

The effect of LSD on P2 one week after dosing is somewhat puzzling. Our initial analysis showed a significant, negative effect of ST on P2 amplitude in the LSD group only. However, we noted that other studies using ST had also observed changes in ERP amplitudes after ST which were not attributable to tetanus itself, sometimes also specific to certain timepoints (40, 54). We thus hypothesized that this effect was not due to ST at all, but rather another change in ERP amplitude over time independent of ST. To explore this possibility, we analyzed the amplitude of P2 over the four consecutive measurement timepoints of the 45-minute EEG session at one week, and we observed a gradual and linear decrease that was significantly greater after LSD than placebo. We guessed that this was unlikely to be an effect of ST because it was a decrease in amplitude, rather than the expected increase, and it was specific to one timepoint and group.

Why would P2 amplitude decrease over the recording session one week after LSD? One possible explanation is that it reflects more efficient habituation to the auditory stimulus. Habituation effects could likely affect P2 more greatly than N1, and they are form of short-term neuroplastic changes which would fit our theory that LSD enhances neuroplasticity (63). However, this finding is highly exploratory, and I hesitate to interpret it without replication. Firstly, the magnitude of the effect was small and I would not exclude the possibility that it could be due to chance, despite statistical significance after correcting for multiple comparisons. Secondly, if it does reflect more efficient neuroplastic adaptation to stimuli, it is unclear why the effect appeared so late. The abovementioned follow-up study of LSD in healthy older adults also includes ST at the same timepoints and will attempt to replicate this finding.

2.6 Modulation of motor-evoked potentials

LSD acutely increased peak-to-peak MEP amplitude and decreased latency seven hours after dosing. The next day, by contrast, the LSD group showed decreased MEP amplitude compared to the placebo group, and latency had normalized. MEPs in response to TMS over the primary motor cortex occur when cortical pyramidal neurons depolarize and catalyze a signal cascade spreading through the spinal cord, ending in the relevant motor neurons (64). Greater amplitude

is generally thought to reflect excitability of the primary motor cortex, while latency reflects the speed of neural conduction (65).

The most obvious explanation for larger and faster MEPs during acute drug effects would be that LSD increases corticospinal excitability (65). LSD is known to have some stimulant effects, and other stimulant drugs (e.g. amphetamines) have similar effects on MEPs (66). SSRIs and ketamine can also enhance MEP amplitude, potentially via serotonergic effects or indirect excitation of the motor system via NMDA receptor antagonism, respectively (66). The reduction in MEP amplitude the next day could have been a compensatory effect or an effect of fatigue, which was greater in participants who had received LSD according to our side effects data.

On that note, increased muscular excitability is consistent with some of LSD's known side effects. LSD relatively frequently causes muscle tightness and shaking (67), not only in humans but also in many other mammal species (68). These effects are strongest in the first 4-5 hours after dosing. Notably, participants were still able to relax the right hand to reduce baseline muscular activity during TMS eight hours after dosing, which was necessary for our procedures. However, self-reported muscular side effects and our TMS results may both reflect a general effect of LSD on corticospinal excitability. Interestingly, increased corticospinal excitability can sometimes indicate greater motor cortical plasticity, but whether that is the case with LSD and whether this has any clinical or practical significance remains to be seen (69, 70).

3. Strengths and limitations

Together, the combination of a thorough literature review, meta-analysis, and randomized controlled trial including neurophysiological, behavioral, and self-report outcomes makes this doctoral thesis a well-rounded examination of the effects of psychedelics, and particularly LSD, on neuroplasticity. It has several important strengths, but also limitations.

A strength of the literature review (Chapter II) is its organized and nuanced examination of different facets of psychedelic-induced neuroplasticity which had not been present in literature before. It considered the fact that different psychedelic drugs (and doses) may not affect the various molecular, cellular and network processes falling under the umbrella term of "neuroplasticity" in the same way. It also emphasized the importance of neural location, timing, and the inalienable impact of experience for understanding psychedelics' complex effects on neuroplasticity. Regarding limitations, the literature review could have been more rigorous if it had been a formal systematic review.

Strengths of the meta-analysis examining BDNF (Chapter III) included an unusually comprehensive search strategy which allowed us to identify all relevant data, even null results from supplementary files which did not feature prominently in a given article. We included a substantial number of articles (N = 29) and effect sizes (N = 104). Our integrative approach was very thorough, analyzing all available psychoplastogens, doses, timepoints, patient groups, and blood fractions. The meta-analysis was limited by the fact that BDNF assays are sensitive to variation in handling and storage, the impact of which we could not assess for most studies. Studies also had limited variation in many of the moderator variables, including patient groups, age, timing of measurements, drug, and dose; for example, LSD only had seven studies available.

Strengths of the randomized controlled crossover trial with LSD (Chapter IV) include the multimodal approach combining neurophysiological measures, well-established behavioral outcomes (motor learning), and self-report measures (cognitive flexibility, stress) with possible relationships to neuroplasticity. The inclusion of three timepoints up to one week after dosing allowed for an assessment of the temporal dynamics of LSD's effects. The study also contained several novel findings: it was the first study to assess the effects of any psychedelic on motor learning and MEPs, as well as the first to report lasting effects of LSD on perceived stress and self-reported cognitive flexibility in healthy subjects. Additionally, the study had a good gender balance (53% women) and was relatively well-powered with 45 subjects in a crossover design. The inclusion of both a baseline and a placebo control allowed for statistical analyses of appropriate rigor. Convincing participants that the placebo was a small dose of LSD was largely successful and may have minimized some of the placebo effects inherent in psychedelic studies.

The main limitation of the LSD study was the shortcomings of the neurophysiological methods used, which prohibited us from analyzing effects on neuroplasticity as planned. Motor learning was performed only one day after LSD due to time constraints, but investigating effects on motor learning one week after LSD would have been valuable for estimating when the window of neuroplasticity might close. Additionally, though we assessed some potential confounders of motor learning performance, we did not assess motivation. We also did not assess participants' expectations for the effects of LSD on our outcomes, which could have allowed us to analyze how strongly placebo effects may have affected our findings. Though the study was well-powered for detecting main effects, it may have been underpowered for detecting complex interactions. Finally, though animal studies show neuroplastic effects even in healthy animals,

the use of healthy participants means that some of our measures may have been subject to ceiling effects.

4. Conclusions and outlook

The findings of this thesis are an important step towards understanding the effects of LSD and other psychedelics on neuroplasticity. It shows that the evidence in preclinical studies is moderately strong and summarizes information on the temporal dynamics of psychedelic-induced neuroplasticity, namely that it may last for 3-7 days after drug administration.

Behavioral measures, most notably the motor learning task, produced results consistent with the hypothesis that LSD enhances neuroplasticity, and LSD's specific effects on offline learning offer an important insight into how LSD may affect neuroplastic processes during and after learning. The data on BDNF and stimulation-based markers of neuroplasticity highlight the continuing challenges of translating findings from animal studies to humans, and our critical appraisal of these methods offers valuable information to other scholars seeking to measure neuroplasticity after psychedelic interventions. Finally, the finding that LSD enhances corticomotor excitability is an important contribution to basic research on its effects.

LSD's positive effects on offline motor learning suggest an exciting avenue for future research. Though the theory that psychedelics enhance neuroplasticity is highly influential in the literature, there are few studies testing learning performance – the clearest correlate of neuroplasticity – after psychedelics. Our findings justify future studies on motor learning, and I would be particularly interested in studies with multiple measurement timepoints designed to assess how long improvements in learning performance (and possibly retention) might last. This could allow for important insights into how long the brain may be more sensitive to its environment after taking psychedelics, possibly optimizing the timing of clinical interventions involving these drugs. Additionally, studies in clinical populations may also be valuable to determine whether LSD or other psychoplastogens (including those without hallucinogenic effects) could enhance recovery of motor function after neural injury or stroke. Finally, it would be interesting to see whether LSD also enhances learning in other domains in humans, particularly on learning measures with high ecological validity.

LTP is the most well-studied neuroplastic process in animals, yet one of the most difficult to measure in humans. Innovations allowing for reliable measurement of LTP-like plasticity in humans are a worthy area of future research, and data on what does not work well is just as valuable as data on what does. It may yet be possible to improve the reliability of stimulation-

based measures of LTP using approaches suggested by previous studies. Beyond LTP, however, neuroimaging methods can assess structural and functional neuroplastic changes over time and relatively new PET tracers marking synaptic proteins (e.g. SV2A) could be particularly promising for translating findings on synaptogenesis from animals to humans. Reliable measures of neuroplasticity would allow us to investigate whether changes in neuroplasticity underlie psychedelics' lasting effects on learning, well-being, and psychiatric symptoms. Furthermore, progress toward measuring neuroplasticity in humans is valuable not only for research on psychoplastogens, but also for basic science on the fundamental property of the brain that is neuroplasticity.

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Acknowledgements

From the beginning to the end of this PhD, I've been privileged to know and learn from more people than I can name. Sometimes I can hardly believe I have so many kind, supportive, and knowledgeable people in my life, and I am grateful for you all from the bottom of my heart.

First and foremost, a special thanks goes to my advisor Professor Gregor Hasler for his mentorship and support throughout my PhD. I really valued the perspective of a mentor who shared my academic interests with enthusiasm, but had also built a long career outside of our small psychedelic research bubble. Thank you for helping me grow into an increasingly independent researcher, supporting my many side quests, and always being available when I needed advice.

I would also like to thank Professor Rick Strassman and Dr. Clifford Qualls for their kind and supportive mentorship from afar on one of those rewarding side projects. Thank you for welcoming me into a mountain of fascinating data – it was a pleasure to build something together.

I am also grateful to all of the more experienced researchers, doctors, and therapists who offered their generous time and advice, particularly in my early days in Switzerland. Thank you to Eva Schindowski, Helena Aicher, Friederike Holze, Andrea Jungaberle, and many other members of the Swiss Medical Society for Psycholytic Therapy (SÄPT) – sometimes just one short conversation made a big difference. You are what makes Switzerland such a wonderful place to do psychedelic research. I was and am touched by your willingness to share your vast experience with someone new, and I hope someday to pass it on.

The past five years have given me the privilege of seeing our research group in Fribourg grow, and I'm grateful to all my colleagues for their support, discourse, and friendship. Thank you to Max Nietscke and Adrian Hase for putting me at ease when everything was new and helping me navigate the beginning of the PhD. Thank you to Nicole Friedli, Morten Lietz, Parsa Yousefi, and again to Adrian for your enthusiastic collaboration, kindness, integrity, and fantastic senses of humor. A special thanks goes to Vincent Diehl for being part of the LSD study for so long – we were a great team and I was lucky to have a co-sitter who complemented me so well.

I also want to thank the many students, research interns, and others who generously offered their time and resources to support this research. Thank you to Fabio Coviello, Kristian Beichmann and Quentin Ulveling for building our first study team at the very beginning, and to the many students and research interns who were part of the LSD study: Pablo de Chambrier, Jonathan Dierks, David Elmiger, Cindy Fux, Bernd Hinney, Simon Jost, Svenja Liebschner, Pascal Pompetzki, Antonin Rouaud, Emiliano Schiatti, and Ella Spillman. I hope I could teach you all something, and thank you for helping our studies go so much more smoothly.

My heartfelt thanks goes out to all of the volunteers who gave their time and energy to participate in our LSD research. Yes, we were all there for science. But studies with psychedelics always have another side to them. There are moments from the LSD sessions I will always remember, and many of you taught me something new. Thank you for letting some nerdy scientists sit with you on LSD, whether your day was joyful, weird, insightful, difficult, or all of the above.

I may never get used to how lucky I am to have such good friends who have accompanied me throughout this process. The warmest thanks go to my friends Jason Day and Meriem Hatime. Thank you for keeping your doors and hearts open for tales of success or struggle, sincere discussion or absolute nonsense, long-promised leisure or inevitable new ideas. Science should have heart, and the heart is people like you.

I am also deeply grateful to my friends at the ALPS Foundation, present and former, for their warmth and rare drive to create something amazing just because we can. I truly don't think my PhD years would have been as successful if it weren't for that conference invitation in 2023. To Polina Catzeflis, Federico Seragnoli, Philipp Hampel, Cyril Petignat, Bianca Borsarini, many others already mentioned, and the entire ALPS team: Thank you for believing in me before I really did, and let's continue to build things together.

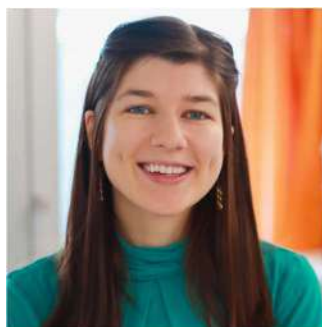
I also want to thank my family, especially my parents Kathy and Lendol, Anne Calder, and my brother Andy for their unconditional support. Thank you all for not batting an eye at my strange and faraway dreams, and for letting me ramble about psychedelics in respectable company. Dad, you once taught a six-year-old to ask, "What's the evidence for that?" I think we can say that got out of hand.

Last but certainly not least, I am grateful beyond words to my partner Felix Völker. Thank you for supporting my dream through the good, the bad, and the strange in every way that you could. I struck gold when I met you, and you prove it to me all the time.

Curriculum vitae

Personal Information

Name: Abigail Calder
Date of birth: 06. Sep 1993
Phone : +41 799556404
E-Mail: abigail.calder@unifr.ch
Address: Sonnhaldeweg 11,
3174 Thörishaus, CH



Education

Institute, Degree	Dates
University of Fribourg , Fribourg, CH Degree: Ph.D. (intended) Thesis supervisor: Prof. Dr. Gregor Hasler	01 Jan 2021 – present
University of Bonn , Bonn, DE Degree: M.Sc. Neuroscience Thesis Title: <i>Molecular Effects of Chronic, Low-dose THC and CBD Treatment on the Hippocampus in Old Mice</i> Thesis supervisor: Dr. Andras Bilkei-Gorzo	Oct 2017 – Jun 2020
Technische Universität Dresden , Dresden, DE Degree: B.Sc. Psychology Thesis Title: <i>Long-term effects of antenatal glucocorticoid treatment on hypothalamic-pituitary-adrenal axis activity and anxiety in late adolescence</i> Thesis supervisor: Prof. Dr. Shu-Chen Li	Oct 2014 – Sep 2017

Employment history

Doctoral researcher University of Fribourg, Fribourg, CH Thesis supervisor: Prof. Dr. Gregor Hasler	01 Jan 2021 - present
Scientific Associate MIND Foundation for Psychedelic Science, Berlin, DE	Jul 2020 – Oct 2021
Contributing Writer Psychedelic Science Review, Seattle, USA	Jul 2020 – Jan 2022
Laboratory assistant Laboratory for Experimental Neurophysiology, University of Bonn, DE	Jul 2019 – May 2020
Tutor – Block Seminar Neurophysiology University of Bonn, M.Sc. Neuroscience Program, DE	Oct 2018 – Dec 2018
Research Intern Clinic for Child and Adolescent Psychiatry, University Hospital Dresden, DE	Nov 2016 – Feb 2017
Laboratory assistant Department of Developmental Neuroscience, TU Dresden, DE	Jun 2015 – Aug 2017
Research Intern Multiple Sclerosis Center, University Hospital Dresden, DE	Feb 2014 – Jul 2014

Volunteer work, scientific societies

ALPS Foundation <i>Geneva, Switzerland</i> Research coordinator	March 2023 - present
Swiss Medical Society for Psycholytic Therapy <i>(Schweizer Ärztegesellschaft für Psycholytische Therapie)</i> Member	Oct 2021 – present
Psychedelic Research Organization of Fribourg (PROOF) <i>Fribourg, Switzerland</i> Journal Club Coordinator, Member	Mar 2021 – present

List of publications

***Calder, A.E.**, Diehl, V.J., Lietz, M.P., Yousefi, P., Friedli, N., Coviello, F., Rouaud, A., Beichmann, K., Eckert, A. & Hasler, G. (2025). Effects of lysergic acid diethylamide on markers of neuroplasticity and motor learning in healthy subjects: a randomized controlled study. *Submitted for publication*.

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**Publication forms part of the current thesis.*