# Safety, Pharmacology, and Subjective Effects of LSD, Psilocybin, MDMA and its Enantiomers

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Prof. Dr. med. Dipl. phys. Eva Scheurer
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“At the threshold of perception, the veil lifts and the extraordinary world behind ordinary reality shines through”

*Albert Hofmann*

—

# PREFACE

All research in this thesis is published in peer-reviewed journals and presented in form of scientific papers. References for each paper are presented within each publication. The general reference list at the end of the thesis is covering the introduction and discussion part. All presented research was performed at the University Hospital Basel and the University of Basel.

During the course of writing this thesis, I used ChatGPT, an artificial intelligence (AI) language model based on OpenAI's GPT-4 architecture, to help improve the readability and coherence of the introduction, discussion, conclusion & outlook. This tool assisted me in refining my language, ensuring that complex ideas were communicated effectively, and that the overall presentation was more accessible. The content and ideas presented in this thesis are my own and not generated by AI.

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# CONTRIBUTIONS

I contributed as lead author or shared lead author to the publications presented in this thesis. For the first and third project, I took part in the planning, analyzed the data, and performed the research together with other research group members, MD students and master students under my supervision. The second project consisted of three already completed clinical studies which I brought together in a safety analysis. All work was conducted under the supervision of Prof. Matthias Liechti and with the help of the Psychopharmacology Research Group.

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# SUMMARY

Classic psychedelics such as psilocybin and lysergic acid diethylamide (LSD) and the entactogen 3,4-Methylenedioxymethamphetamine (MDMA) are being investigated for their potential in substance-assisted therapy for various psychiatric and neurological disorders. While first results propose potential in treating these conditions, there is a lack of phase I studies examining the safety, pharmacology, and subjective effects of these compounds in healthy volunteers, as usually is the case in drug development. Previous research has shown that the acute positive effects of psychedelics are linked to their therapeutic benefits, making it essential to enhance these acute subjective effects. MDMA is a racemic substance that has already been investigated more extensively in phase I studies, yet preclinical research suggests that its enantiomers may have different effects, with one potentially being more suitable for substance-assisted therapy, regarding the safety. This thesis includes three projects aimed at expanding our knowledge of the safety, pharmacology and subjective effects of LSD, psilocybin, MDMA and the enantiomers *R*-MDMA and *S*-MDMA.

The first project involved a clinical study with healthy volunteers where MDMA (100 mg) was used as a pharmacological tool to enhance the psychedelic effects of LSD (100 µg). While the effects profile of the combined LSD + MDMA administration did not differ significantly from LSD alone, the duration of effects was extended by an average of 1.5 hours. This is likely due to MDMA's strong inhibition of the Cytochrome P450 2D6 (CYP2D6) enzyme, which slowed the metabolization of LSD, resulting in higher plasma concentration and a longer elimination half-life. This finding further supports a role for CYP2D6 in the LSD metabolism. The LSD + MDMA combination induced higher blood pressure and heart rate, with similar minimal increases in body temperature compared with LSD alone. Even though the combined administration is intriguing, it probably offers no additional benefit to LSD-assisted psychotherapy in patients.

The second project included three completed studies with 113 psilocybin administrations at doses from 15 to 30 mg in 85 healthy volunteers. Safety data of these studies were pooled and revealed comparable positive effects for 20, 25, and 30 mg psilocybin, while significant "anxiety" was only observed with the 25 and 30 mg doses. Increases in blood pressure (>140 mmHg), heart rate (>100 bpm), and body temperature (>38°C) were noted in 50%, 7%, and 16% of participants, respectively, after psilocybin administration. The autonomic effects of psilocybin were similar to those of LSD and less pronounced than those of MDMA. Acute adverse effects included fatigue, lack of concentration, lethargy, vertigo, feeling of weakness, and decreased appetite. Overall, single-dose administrations of psilocybin up to 30 mg were found to be safe regarding psychological and physical harm in healthy volunteers in a controlled setting. However, risk and benefits of using psilocybin in patients need further investigation.

The third project examined the acute and subacute effects of MDMA (125 mg) and its enantiomers *R*-MDMA (125 and 250 mg) and *S*-MDMA (125 mg). While small differences in subjective effects were observed with MDMA, *R*-MDMA and *S*-MDMA, dose equivalence was not achieved, leaving it unclear whether these differences are due to their distinct binding profiles or the dosing. The results suggest dose equivalence regarding subjective effects with 125 mg MDMA, 300 mg *R*-MDMA, and 100 mg *S*-MDMA. The elimination half-life of *R*-MDMA increased dose-dependently from 11 hours with 125 mg racemic MDMA, to 12 hours with 125 mg *R*-MDMA, to 14 hours with 250 mg *R*-MDMA. In contrast, the elimination half-life of *S*-MDMA decreased when administered without *R*-MDMA. Additionally, the formation of 4-Hydroxy-3-methoxymethamphetamine (HMMA), a metabolite produced via CYP2D6, did not increase with higher doses of *R*-MDMA, indicating that *R*-MDMA dose-dependently inhibits CYP2D6. The extent to which *S*-MDMA inhibits CYP2D6 remains to be determined.

All projects uncovered new findings about these compounds, providing valuable insights to inform and guide future clinical studies in both healthy volunteers and patients.

# INTRODUCTION

The present thesis focuses on three main compounds: LSD, psilocybin, and MDMA. All three are currently utilized within the Swiss limited use program and are being developed into medications. MDMA it at the forefront for treating post-traumatic stress disorder (PTSD), psilocybin for treatment-resistant depression (TRD), and LSD for generalized anxiety disorder. Investigating the clinical pharmacology of these compounds is crucial to their development and success which was the goal of this thesis.

## 1.1. LSD

Lysergic acid diethylamide (LSD), which is a classic psychedelic, was first synthesized by Swiss chemist Albert Hofmann in 1938 in Basel, Switzerland. After resynthesis in 1943 he accidentally absorbed a small amount through his skin and a few days later, when he intentionally ingested 250 micrograms, he experienced profound and intense psychedelic effects [1]. Between 1949 and 1966 Sandoz distributed LSD under the brand name Delysid® to physicians and psychiatrists globally for research purposes such as enhancing psychotherapy or exploring model psychosis [1, 2]. However, LSD moved beyond clinical research and was banned by the US government in 1968 [3]. In recent years, there has been a revival of interest in its therapeutic possibilities. The first modern study with LSD was conducted by Swiss psychiatrist Peter Gasser in 2008 and included 12 patients with anxiety associated with a life-threatening disease [4, 5].

LSD is chemically classified as a semisynthetic ergoline, a derivative of lysergic acid, which is a component of the ergot alkaloids produced by the ergot fungus. The main mechanism of LSD is a potent partial agonism on the serotonin $(5\text{-HT})_{2A}$ receptor. The $5\text{-HT}_{2A}$ receptor mediates the typical effects of classic psychedelics and can be blocked with a pre- or post-treatment with the antagonist ketanserin [6-9]. LSD additionally binds to $5\text{-HT}_{1A}$, $5\text{-HT}_{2C}$, adrenergic and dopaminergic receptors [10, 11].

The pharmacokinetics show dose-proportional increases in plasma concentration and first-order elimination kinetics [12]. Maximal concentration ($C_{max}$) values are reached after 1.4 – 1.6 hours, with an elimination half-life between 3.9 and 4.3 hours for doses of 100 – 200 µg LSD [13, 14]. LSD is metabolized to 2-Oxo-3-hydroxy-LSD (O-H-LSD) and N-demethylated LSD (nor-LSD) by cytochrome P450 (CYP) enzymes. In vitro studies showed involvement of CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 enzymes [15, 16]. A pooled analysis in healthy volunteers showed that poor metabolizers of CYP2D6 have an overall higher exposure to LSD (higher maximal plasma concentration and longer half-live) and show more anxiety compared to normally functional CYP2D6 metabolizers [17].

A pooled analysis of acute LSD effects in healthy volunteers showed that after oral administration, the onset of the acute subjective effects (mean ± SD) started after 0.5 ± 0.3 hours with a dose of 100 µg [18]. Peak effects were reached after 2.5 ± 1.1 hours and the effect duration was 8.5 ± 3.2 hours with 100 µg LSD [18]. LSD induces significant alterations in consciousness, affecting perception, cognition, thinking and emotional processing. These changes involve illusions, pseudo-hallucinations, intensified color perception, synesthesia, and changes in time perception [8, 13, 19]. LSD shows low toxicity with no documented human deaths from an LSD overdose [2]. Safety concerns include challenging experiences (i.e., "bad trips"), acute anxiety, flashbacks, and hallucinogen persisting perception disorder (HPPD) [2].

## 1.2. Psilocybin

Psilocybin is currently the most broadly investigated psychedelic compound. Psilocybin is the prodrug of psilocin, the active compound in psychedelic mushrooms [20]. The use of these mushrooms in religious and healing ceremonies dates back centuries [21]. In 1957, Swiss chemist Albert Hofmann, known for synthesizing LSD, isolated and identified psilocybin and psilocin as the active compounds in these mushrooms [22]. Psilocybin was subsequently marketed by Sandoz as Indocybin® in 1958 for research purposes and to support psychotherapeutic procedures [22]. However, like LSD, psilocybin was banned after getting attention outside of laboratories during the 1960s counterculture movement. Renewed interest in psilocybin appeared in the early 2000s when psychopharmacologist Roland Griffiths published a clinical study about mystical-type experiences induced by psilocybin in healthy volunteers [23]. The first modern study investigating psilocybin in patients was conducted and published in 2006 by psychiatrist Francisco Moreno, focusing on obsessive-compulsive disorder (OCD) [24].

Psilocybin is chemically classified as a naturally occurring tryptamine [22]. Psilocin is an agonist at the 5-$HT_{2A}$ receptor and inhibits the 5-HT transporter (SERT) [11]. Similar to LSD, the main mechanism of psilocin to induce psychedelic effects is the activation of the 5-$HT_{2A}$ receptor. Psilocin additionally interacts with 5-$HT_{1A}$, 5-$HT_{2B}$, and 5-$HT_{2C}$ receptors [25].

Effects of psilocybin are largely similar to those of LSD despite minor receptor differences. However, psilocybin is less potent, requiring a higher dosage to achieve comparable effects. Three studies with psilocybin have been conducted by the Psychopharmacology Research Group of the University Hospital Basel in Switzerland, covering a dose range from 15 – 30 mg. After oral administration of psilocybin, the onset of the acute subjective effects started between 0.5 and 0.8 hours [13, 26]. Peak effects were reached after 2.1 – 2.3 hours and the effect lasted for 4.9 – 6.5 hours [13, 26]. Psilocybin also induced moderate cardiovascular stimulation similar to that of LSD. Other than a shorter effect duration, the psychedelic effects of psilocybin do not differ significantly from those of LSD [13, 26]. As LSD, psilocybin exhibits low toxicity and minimal potential for abuse, as shown by lack of self-administration in animal studies [27]. The primary safety concerns are psychological and include the same as with LSD [27, 28].

## 1.3. MDMA and its enantiomers

3,4-Methylenedioxymethamphetamine (MDMA) was first synthesized in 1912 by the German pharmaceutical company Merck, initially as a precursor to a blood-clotting agent [29]. The psychoactive properties were only recognized later when American chemist Alexander Shulgin began studying the compound in the 1970s [30]. He introduced MDMA to psychotherapists, with the intent to use it as an adjunct to therapy due to its ability to enhance empathy and communication. In the 1980s, MDMA gained popularity as a recreational drug and in 1985 it was banned and classified as a Schedule I controlled substance [31, 32]. The first study investigating MDMA in patients was conducted by psychiatrist Michael Mithoefer of the Multidisciplinary Association for Psychedelic Studies (MAPS) in the early 2000s focusing on using MDMA-assisted psychotherapy to treat PTSD [33].

Chemically, MDMA is classified as a substituted amphetamine and represents the prototypical compound within the class of empathogens or entactogens [31]. MDMA primarily induces 5-HT release via the serotonin transporter by reversing SERT and to a lesser extent also induces norepinephrine (NE) and dopamine (DA) release [34, 35]. Additionally, it's potential to release oxytocin has been shown to be important for MDMA's effects [36].

After oral administration of 125 mg MDMA the onset of the acute subjective effects (mean ± SD) started after around 33 ± 24 minutes, reached its peak after 1.6 ± 0.8 hours and lasted 4.2 ± 1.3 hours [37]. MDMA induces feelings of well-being, positive mood, enhanced feelings of affection and connectedness to other people, increased openness, loss of anxiety and feeling at peace [38, 39]. Acute adverse effects of MDMA include increased blood pressure, heart rate, and body temperature, bruxism, reduced appetite, and impaired balance [33, 37]. Subacute adverse effects such as low mood and fatigue on the following days have been described [40]. MDMA has shown some reward-related effects in both animals and humans, yet the risk of developing dependence is considered low, especially in healthy volunteers with no history of drug dependence and compared with other drugs of abuse [41-43].

MDMA is a racemic substance containing equal amounts of the enantiomers *S*(+)-MDMA and *R*(-)-MDMA. Preclinical research indicates that *S*-MDMA mainly releases dopamine, norepinephrine, serotonin, and oxytocin while *R*-MDMA may act more directly on serotonin 5-$HT_{2A}$ receptors and release prolactin [44-46]. Animal studies suggest that the two enantiomers of MDMA act synergistically to produce the subjective effects. *S*-MDMA mainly contributes to psychostimulation, whereas *R*-MDMA potentially shows more prosocial effects and exhibits fewer adverse effects including less hyperthermia and neurotoxicity [47].

## 1.4. Therapeutic use of the compounds

All three main compounds discussed in the present thesis are now at the forefront of substance-assisted therapy and have received FDA breakthrough therapy designation [48-52]. LSD for generalized anxiety disorder, psilocybin for treatment resistant depression and MDMA for PTSD.

Switzerland holds a unique legal position regarding the therapeutic use of psychedelic substances. Since 2014, it has been possible again to treat patients with various treatment-resistant psychiatric disorders using LSD- and MDMA-assisted psychotherapy under the framework of compassionate use [53]. Since 2021, psilocybin has also been included in this compassionate use framework for such treatments [54]. Although, some countries have legalized selected psychoactive compounds for medical use, the experience and expertise in this area is likely not at the same level as in Switzerland. Over the past 9 years, more than 1000 individual case permits have been issued to around 60 therapists and an estimated 2000 to 3000 treatments using LSD, psilocybin, or MDMA have been carried out [54].

Between the 1950s and 1970s, LSD was extensively studied as a treatment for various psychiatric disorders. However, these early studies did not meet the methodological standards of today's clinical research. Consequently, while the findings were intriguing, the results of these studies were not robust enough to withstand contemporary scientific expectations. Between 1988 and 1993, a small group of therapists were able to conduct LSD- and MDMA-assisted therapies in Switzerland [55]. Research in healthy volunteers with psychedelics (psilocybin and N,N-Dimethyltryptamine; DMT) and MDMA started again in the 1990s [56-60].

LSD has been investigated in patients with anxiety associated with or without a life-threatening disease [4, 5, 61, 62], in patients with major depression (NCT03866252), in patients with attention deficit hyperactivity disorder (ADHD; NCT05200936) and is under investigation in patients with cluster headache (NCT03781128). LSD not only reduced anxiety symptoms, but also reduced concurrent depressive symptoms often associated with anxiety disorders [4, 5, 61]. These anxiolytic effects have led to further development of LSD into a medication that will soon enter phase III trials.

Various studies with psilocybin have been conducted and showed promising results for anxiety and depression in patients with life-threatening cancer [63-65]. Additionally, studies with psilocybin showed potential in treating patients with OCD [24], major depressive disorder [66-68], treatment-resistant depression [69, 70], and substance use disorder [71-74]. Psilocybin has also been investigated for neurological disorders like cluster headache [75, 76] and migraine [77]. Further investigations are exploring psilocybin for

additional conditions such as anorexia nervosa [78], PTSD (NCT05554094), post-treatment lyme disease (NCT05305105), chronic pain (NCT05068791), and autism spectrum disorder (NCT05651126). Psilocybin is currently the most prominent candidate in the class of classical psychedelics and is under investigation for TRD in phase III trials.

The first controlled clinical study in patients with PTSD was published in 2010 by psychiatrist Michael Mithoefer [33]. MDMA-assisted therapy seemed to be promising for PTSD, therefore more controlled studies were conducted in the following years [79, 80]. Subsequently, MAPS which conducted or financed most of these small phase II studies planned and conducted two following phase III studies, again with promising results [81, 82]. Results of these clinical studies also propose improvement of eating disorder symptoms [83], decrease of alcohol use [84], and reduction in chronic pain [85] among patients with PTSD. Further conditions which MDMA is being investigated for are social anxiety in autistic adults [86], anxiety in patients with life-threatening illnesses [87], and alcohol use disorder [88].

## 1.5. Significance

Clinical research to investigate substance-assisted therapy for various psychiatric disorders is accelerating. For these therapies to be successful it is crucial to investigate effectiveness and safety, as well as the underlying factors that contribute to their efficacy.

Findings from clinical studies with LSD and psilocybin implicate that the acute psychedelic experience is associated with the therapeutic outcome. A more positive experience seems to be linked with greater therapeutic long-term effects of psychedelics in patients [61, 64, 65, 89, 90] and prolonged positive mood effects in healthy participants [91, 92]. Given that the acute psychedelic experience is crucial for the therapeutic benefit, inducing an overall positive acute response with low ratings of anxiety is desirable. The first project describes results of a clinical study in healthy volunteers where we tried to ameliorate the LSD experience with MDMA as a pharmacological enhancer (NCT04516902).

Although numerous phase I studies have been conducted with LSD, there is a lack of clinical studies assessing the safety of psilocybin in healthy individuals. As psilocybin is currently one of the most researched psychedelics, conducting thorough phase I studies with it remains essential as is done with every medication in development. While adverse effects are often assessed in clinical studies with patients, these studies often involve a limited number of participants and primarily focus on the effectiveness of the psychoactive compound. The second project provides extensive and well-standardized data of acute subjective effects, vital signs, and physical and psychological adverse effects in healthy volunteers.

MDMA has been demonstrated to be safe in controlled settings with healthy individuals [37]. However, it induces stronger cardiovascular stimulation compared with psychedelics, which could make it less safe for certain patient groups with preexisting health conditions such as hypertension or heart issues. Various in vitro studies and animal research suggest that the enantiomer *R*-MDMA might be a safer alternative for substance-assisted therapy compared with racemic MDMA. Previous data indicates that *R*-MDMA produces less cardiovascular stimulation, less hyperthermia, and possibly less neurotoxicity while still producing typical MDMA effects. However, these findings have not been investigated in humans. Therefore, the third project includes a clinical study in healthy volunteers where we compared both enantiomers and racemic MDMA to see if there are significant differences between these substances (NCT05277636).

The outcomes of these three projects will deepen the understanding of the physiological and psychological effects of these compounds, while also providing essential

safety data relevant to psychiatry, psychology, and forensic toxicology. Furthermore, they will have significant public health implications by providing new data on LSD, psilocybin and MDMA.

## 1.6. Aims & Hypotheses

The main goal of this thesis was to contribute to the overall understanding of the subjective effects, pharmacology, and safety of LSD, psilocybin, and MDMA. These compounds are widely used recreationally but they have recently been reintroduced into psychiatric therapy as adjuncts to psychotherapy for various conditions. Both the studies conducted and those studies pooled for the safety analyses were phase I studies involving healthy volunteers and were carried out in a highly controlled environment at the University Hospital Basel in Switzerland.

The first aim was to explore whether MDMA could be used as a pharmacological tool to amplify the positive effects and reduce the negative effects induced by LSD. This drug combination is popular among recreational users and is commonly referred to as "candyflipping." It was hypothesized that combined LSD-MDMA administration would result in higher ratings of "good drug effect", "trust", "openness", and lower ratings of "bad drug effects" and "anxiety". Additionally, the goal was to describe subjective, autonomic, and pharmacokinetic effects of the combined LSD-MDMA administration for the first time in a controlled setting.

The second aim was to compile a dataset on the safety of psilocybin administration. The project used data from three completed clinical studies with healthy volunteers. Differences in subjective effects, blood pressure, heart rate, body temperature, acute and subacute adverse effects, reports of flashbacks, and liver and kidney function before and after the studies were investigated across various doses ranging from 15 to 30 mg of psilocybin. It was hypothesized that psilocybin would primarily induce positive subjective effects and cause tolerable, transient autonomic stimulation. A slight increase in negative effects, such as "bad drug effects" or "anxiety," was expected at higher doses compared to lower doses of psilocybin.

The third aim was to investigate the effects of both MDMA enantiomers *R*-MDMA and *S*-MDMA and compare them to racemic MDMA in humans for the first time. It was hypothesized that *R*-MDMA would induce more psychedelic-like effects and fewer stimulant effects compared with *S*-MDMA and racemic MDMA. Conversely, *S*-MDMA was expected to induce greater subjective and autonomic stimulation compared with *R*-MDMA. Additionally, the individual pharmacokinetic profiles of *R*-MDMA and *S*-MDMA were analyzed.

# PUBLICATIONS

## 2.1. Acute effects of MDMA and LSD co-administration in a double-blind placebo-controlled study in healthy participants

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# Acute effects of MDMA and LSD co-administration in a double-blind placebo-controlled study in healthy participants

Isabelle Straumann[1,2], Laura Ley[1,2], Friederike Holze[1,2], Anna M. Becker[1,2], Aaron Klaiber[1,2], Kathrin Wey[1,2], Urs Duthaler[1,2], Nimmy Varghese[3,4], Anne Eckert[3,4] and Matthias E. Liechti[1,2]✉



There is renewed interest in the use of lysergic acid diethylamide (LSD) in psychiatric research and practice. Although acute subjective effects of LSD are mostly positive, negative subjective effects, including anxiety, may occur. The induction of overall positive acute subjective effects is desired in psychedelic-assisted therapy because positive acute experiences are associated with greater therapeutic long-term benefits. 3,4-Methylenedioxymethamphetamine (MDMA) produces marked positive subjective effects and is used recreationally with LSD, known as "candyflipping." The present study investigated whether the co-administration of MDMA can be used to augment acute subjective effects of LSD. We used a double-blind, randomized, placebo-controlled, crossover design with 24 healthy subjects (12 women, 12 men) to compare the co-administration of MDMA (100 mg) and LSD (100 µg) with MDMA and LSD administration alone and placebo. Outcome measures included subjective, autonomic, and endocrine effects and pharmacokinetics. MDMA co-administration with LSD did not change the quality of acute subjective effects compared with LSD alone. However, acute subjective effects lasted longer after LSD + MDMA co-administration compared with LSD and MDMA alone, consistent with higher plasma concentrations of LSD ($C_{max}$ and area under the curve) and a longer plasma elimination half-life of LSD when MDMA was co-administered. The LSD + MDMA combination increased blood pressure, heart rate, and pupil size more than LSD alone. Both MDMA alone and the LSD + MDMA combination increased oxytocin levels more than LSD alone. Overall, the co-administration of MDMA (100 mg) did not improve acute effects or the safety profile of LSD (100 µg). The combined use of MDMA and LSD is unlikely to provide relevant benefits over LSD alone in psychedelic-assisted therapy. Trial registration: ClinicalTrials.gov identifier: NCT04516902.

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## INTRODUCTION

Lysergic acid diethylamide (LSD) is a classic serotonergic psychedelic that is widely used recreationally and increasingly investigated in patients who suffer from psychiatric conditions, such as anxiety and depression [1, 2]. LSD acutely produces mostly positive experiences of alterations of consciousness but may also produce negative subjective effects, including acute anxiety [3–8]. Acute negative psychological effects are also considered the main risk of psychedelic substance use in humans [9]. Clinical trials showed that positive psychedelic-induced experiences are associated with more positive long-term therapeutic improvements in patients in psychedelic-assisted therapy [1, 10–13]. Additionally, low ratings of acute anxiety induced by a psychedelic predicted positive long-term clinical outcomes in patients [10]. Thus, the induction of a positive acute psychedelic experience may be desirable to enhance treatment outcome, although challenging experiences may also have therapeutic potential [14, 15].

3,4-Methylenedioxymethamphetamine (MDMA) is investigated in MDMA-assisted therapy [16]. MDMA acutely induces mostly positive subjective effects, including increases in well-being, empathy, trust, and closeness to others [3, 17–19]. The combined administration of MDMA and LSD is known as "candyflipping" among recreational substance users [20–24] and reportedly induces synergistic acute positive mood effects [24]. However, no controlled study has investigated the combined administration of MDMA and LSD. Therefore, the present study investigated whether MDMA can be used to optimize the acute effects profile of LSD by inducing more positive mood and less anxiety compared with LSD alone.

The primary hypothesis was that the co-administration of MDMA and LSD results in higher acute "good drug effects," well-being, openness, and trust and lower "bad drug effects" and anxiety compared with LSD administration alone.

## METHODS AND MATERIALS

### Study design

The study used a double-blind, placebo-controlled, crossover design with four experimental test sessions to investigate responses to (*i*) placebo, (*ii*) 100 mg MDMA, (*iii*) 100 µg LSD, and (*iv*) 100 µg LSD + 100 mg MDMA. Block randomization was used with counter-balanced treatment order. The washout periods between sessions were at least 10 days. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines in Good Clinical Practice and approved by the Ethics Committee of Northwest Switzerland (EKNZ) and

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Swiss Federal Office for Public Health. The study was registered at ClinicalTrials.gov (NCT04516902).

### Participants

Twenty-four healthy participants (12 men and 12 women; mean age ± SD: 30 ± 7 years; range: 25–54 years) were recruited by word of mouth or from a pool of volunteers who had contacted our research group because they were interested in participating in a clinical trial on psychedelics. All of the subjects provided written informed consent and were paid for their participation. Exclusion criteria were age <25 years or >65 years, pregnancy (urine pregnancy test at screening and before each test session), personal or family (first-degree relative) history of major psychiatric disorders (assessed by the Semi-structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Axis I disorders by a trained psychologist), the use of medications (e.g., antidepressants, antipsychotics, and sedatives) that may interfere with the study medications, chronic or acute physical illness (e.g., abnormal physical exam, electrocardiogram, or hematological and chemical blood analyses), tobacco smoking (>10 cigarettes/day), lifetime prevalence of hallucinogens or MDMA use >20 times, illicit drug use within the last 2 months (except for $\Delta^9$-tetrahydrocannabinol), and illicit drug use during the study period (determined by urine drug tests). The participants were asked to consume no more than 20 standard alcoholic drinks/week and have no more than one drink on the day before the test sessions. Twelve participants had previously used a psychedelic, including LSD (6 participants, 1–3 times), psilocybin (9 participants, 1–2 times), *N,N*-dimethyltryptamine (DMT; one participant, one time), and mescaline (one participant, 1 time). Nine participants had used MDMA (1–13 times), 12 participants had used a stimulant, including methylphenidate (5 participants, 1–10 times), amphetamine (3 participants, 1–7 times), and cocaine (4 participants, 2–10 times), one participant had used 4-bromo-2,5-dimethoxyphenethylamine (2C-B; 1 time), and one participant had used ketamine (1 time). Four participants had never used any illicit drugs with the exception of cannabis.

### Study drugs

LSD base (Lipomed AG, Arlesheim, Switzerland) was administered as an oral solution that was produced according to good manufacturing practice in units that contained 100 µg LSD base in 1 ml of 96% ethanol [25]. The exact analytically confirmed LSD base content (mean ± SD) was 92.5 ± 1.89 µg ($n = 10$ samples). Placebo consisted of identical units that were filled with ethanol only. MDMA (ReseaChem, Burgdorf, Switzerland) was administered in opaque capsules that contained a 25 mg dose of MDMA hydrochloride and an exact analytically confirmed actual MDMA content of 25.40 ± 0.48 mg ($n = 9$ samples). Placebo consisted of identical opaque capsules that were filled with mannitol. A double-dummy method was used. The subjects received four capsules and one solution in each session: (*i*) four placebo capsules and one placebo solution, (*ii*) four 25 mg MDMA capsules and one placebo solution, (*iii*) four placebo capsules and one 100 µg LSD solution, and (*iv*) four 25 mg MDMA capsules and one 100 µg LSD solution. Then, 2.5 h after administration, at the end of each session, and at the end of the study, the participants guessed their treatment assignment to evaluate blinding.

### Study procedures

The study included a screening visit, four 13-h test sessions with follow-up measurements 24 h after drug intake, and an end-of-study visit which took place on average 31 days after the last test session. Test days were separated by at least 10 days. The sessions were conducted in a calm hospital room. Only one research subject and one investigator were present during each test session. The test sessions began at 8:00 AM. A urine sample was taken to verify abstinence from drugs of abuse, and a urine pregnancy test was performed in women. The subjects then underwent baseline measurements. A standardized breakfast (two croissants) was served. Substances were administered at 9:00 AM. The outcome measures were repeatedly assessed for 12 h. Standardized lunches and dinners were served at 1:30 PM and 6:00 PM, respectively. The subjects were never alone during the acute effect phase. The subjects were sent home at 9:15 PM and returned the next day for follow-up measurements at 9:00 AM.

### Subjective drug effects and effect durations

Subjective effects were assessed repeatedly using visual analog scales (VASs) [3, 6] 0.5 h before and 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 h after drug administration. The Adjective Mood Rating Scale (AMRS) [26] was used 0.5 h before and 3, 6, 9, 12, and 24 h after drug administration. The 5 Dimensions of Altered States of Consciousness (5D-ASC) scale [27, 28] was used as the primary outcome measure and was administered 12 h after drug administration to retrospectively rate peak drug effects. Mystical experiences were assessed 12 h after drug administration using the States of Consciousness Questionnaire (SOCQ) [29, 30] that includes the 43-item Mystical Effects Questionnaire (MEQ43) [29], 30-item Mystical Effects Questionnaire (MEQ30) [31], and subscales for "aesthetic experience," "connectedness," "distressing experience," and negative "nadir" effects. Subjective effect measurements are described in detail in the Supplementary Methods online.

The time to onset, time to maximal effect, time to offset, and effect duration were assessed in Phoenix WinNonlin 8.3 (Certara, Princeton, NJ, USA) using the "any drug effect" VAS effect-time plots and an onset/offset threshold of 10% of the maximum individual response as described previously in detail [7, 25].

### Autonomic and adverse effects

Blood pressure, heart rate, and tympanic body temperature were repeatedly measured at baseline and 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 h after drug administration [32]. Pupil size was assessed at baseline and 1, 2.5, 4, 7, 11, and 24 h after drug administration [6]. Adverse effects were assessed 0.5 h before and 12 and 24 h after drug administration using the List of Complaints [33].

### Circulating oxytocin and brain-derived neurotrophic factor

Plasma concentrations of oxytocin were measured before and 1.5, 3, and 6 h after drug administration and were determined as previously described [3, 6, 7, 34]. Serum BDNF levels were measured at baseline and 3, 6, 9, 12, and 24 h after drug administration (Supplementary Methods).

### Plasma LSD and MDMA concentrations

Plasma concentrations of LSD and MDMA and their metabolites were measured before and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 h after drug administration. Blood was collected into lithium heparin tubes. The blood samples were immediately centrifuged, and the plasma was subsequently stored at −80°C until analysis. Plasma concentrations of LSD and its metabolite 2-oxo-3-hydroxy-LSD (O-H-LSD) were determined by ultra-high-performance liquid chromatography tandem mass spectrometry with a lower limit of quantification of 10 pg/ml [25].

MDMA and its metabolites 3,4-methylenedioxyamphetamine (MDA) and 4-hydroxy-3-methoxymethamphetamine (HMMA) were analyzed in human plasma using high-performance liquid chromatography tandem mass spectrometry as previously described. HMMA concentration was determined after enzymatic deglucuronidation [35].

### Pharmacokinetic analyses

Pharmacokinetic parameters were estimated using non-compartmental methods as described previously [25]. Analyses were conducted using Phoenix WinNonlin 8.3 (Certara, Princeton, NJ, USA).

### Data analysis

Peak ($E_{max}$ and/or $E_{min}$) or peak change from baseline ($\Delta E_{max}$) values were determined for repeated measures. The values were then analyzed using repeated-measures analysis of variance (ANOVA), with drug as the within-subjects factor, followed by the Tukey *post hoc* tests using R 4.2.1 software (RStudio, PBC, Boston, MA, USA) and Statistica 12 software (StatSoft, Tulsa, OK, USA). The criterion for significance was $p < 0.05$.

## RESULTS

### Subjective drug effects

Subjective effects over time on the VAS are shown in Fig. 1 and Supplementary Fig. S1. Statistics are summarized in Table 1 and Supplementary Table S1. Alteration of mind and mystical-type effects are shown in Fig. 2 and Supplementary Fig. S2. Statistics are summarized in Supplementary Tables S2 and S3. Effects on mood over time on the AMRS are shown in Supplementary Fig. S3. The corresponding peak responses and statistics are presented in Supplementary Table S4. Characteristics of subjective responses are shown in Supplementary Table S5.

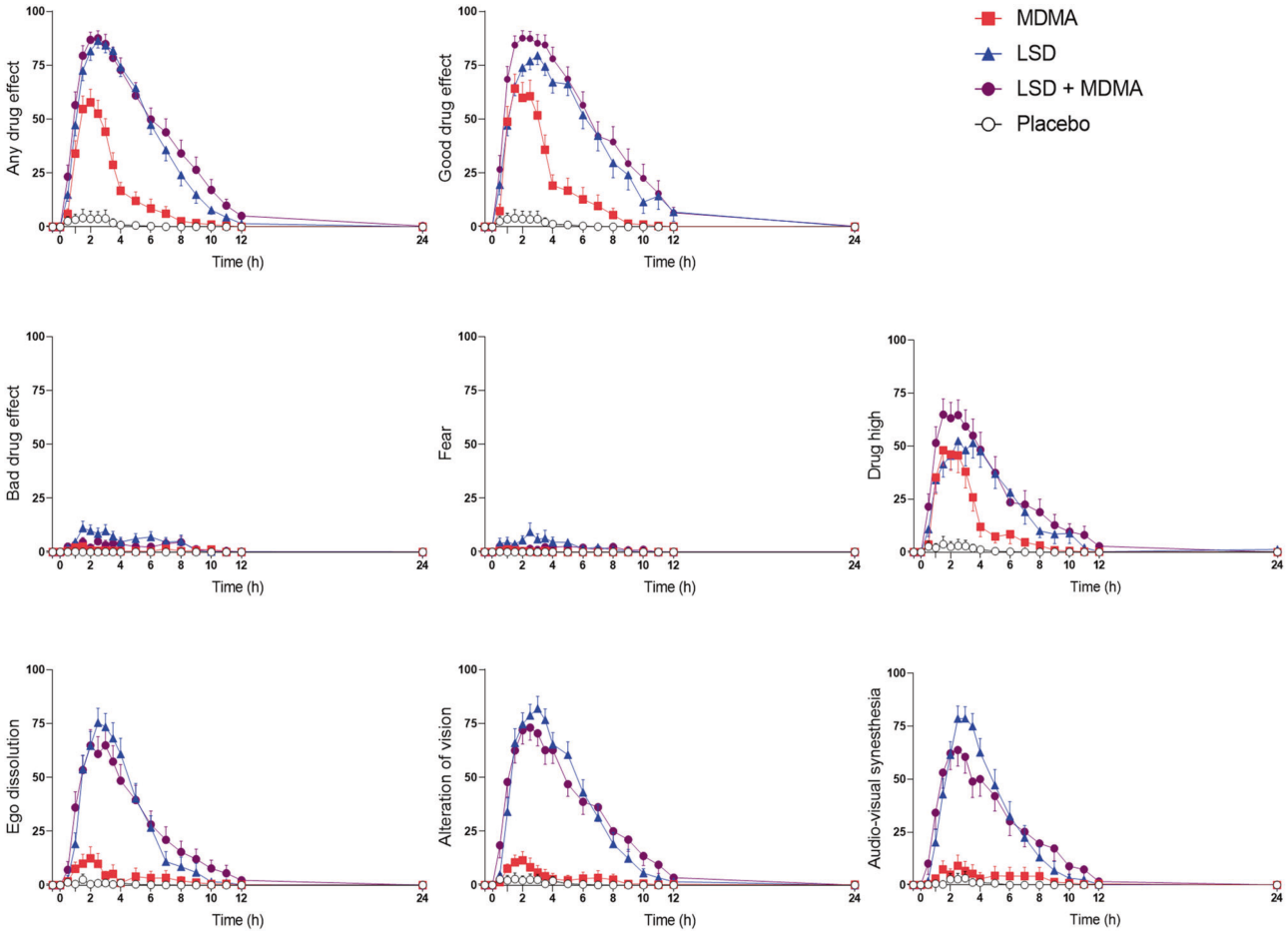


**Fig. 1 Acute subjective effects of 100 µg lysergic acid diethylamide (LSD), 100 mg 3,4-methylenedioxymethamphetamine (MDMA), and the LSD + MDMA combination over time on the Visual Analog Scale (VAS).** LSD and the LSD + MDMA combination produced comparable subjective effects with no significant differences in $E_{max}$ values (Table 1). However, the co-administration of MDMA and LSD prolonged the psychedelic experience compared with LSD alone (Supplementary Table S5). Overall, effects of LSD and LSD + MDMA were significantly stronger and longer compared with MDMA alone. There was no significant difference in peak "drug high" between the substances alone and the combination. The substances were administered at $t = 0$ h. The data are expressed as the mean ± SEM percentage of maximally possible scores in 24 subjects. The corresponding maximal responses and statistics are shown in Table 1.

The LSD + MDMA combination did not induce significantly different subjective responses on the VASs, 5D-ASC, MEQ, or AMRS compared with LSD alone (Figs. 1 and 2, Supplementary Figs. S1–3, Table 1, Supplementary Tables S1–4). LSD and the LSD + MDMA combination produced overall greater psychedelic effects compared with MDMA alone. LSD and the LSD + MDMA combination induced greater "any drug effects," "good drug effects," "ego dissolution," "alteration of vision," and "audio-visual synesthesia" compared with MDMA alone (Fig. 1). In contrast, ratings of "drug high" were comparable for MDMA, LSD, and the LSD + MDMA combination (Fig. 1). LSD and LSD + MDMA induced increased ratings in all main dimensions and subscales of the 5D-ASC with the exception of the subscale anxiety which only showed a trend wise increase with LSD ($p = 0.073$). MDMA only increased the subscale blissful state (Fig. 2.). LSD and the LSD + MDMA combination induced more emotional excitation, introversion, anxiety and depression compared to MDMA on the AMRS (Supplementary Fig. S3).

Subjective "any drug effects" lasted an average of 1.5 h longer after the LSD + MDMA combination (mean = 9.9 h) compared with LSD alone (mean = 8.4 h; $p < 0.05$; Fig. 1, Supplementary Table S5).

## Autonomic and adverse effects

Autonomic effects over time and respective peak effects are shown in Fig. 3 and Table 1, respectively. MDMA and the LSD + MDMA combination induced higher increases in blood pressure, heart rate, and pupil size compared with LSD alone (Fig. 3, Supplementary Fig. S4, Table 1). Body temperature increased similarly for LSD and the LSD + MDMA combination but less when MDMA was administered alone (Fig. 3). The LSD + MDMA combination and LSD alone produced similar total acute and subacute adverse effects scores on the List of Complaints, exceeding those of MDMA (Table 1). Frequently reported adverse effects on the List of Complaints are presented in Supplementary Table S6. Headache, lack of energy, loss of appetite, and dry mouth were similarly often reported with MDMA, LSD, and LSD + MDMA. Acute nausea was more frequent with MDMA than LSD. No severe adverse events were observed.

## Effects on circulating oxytocin and BDNF

Effects of MDMA, LSD, and the LSD + MDMA combination on plasma levels of oxytocin and BDNF are shown in Supplementary Fig. S5 and Table 1. MDMA alone and the LSD + MDMA combination robustly increased oxytocin, with greater peak increases compared with LSD alone. LSD alone produced only minimal increases in oxytocin. Effects of MDMA and LSD on oxytocin were additive when the two substances were combined. MDMA, LSD, and the LSD + MDMA combination had no significant effects on serum BDNF concentrations (Supplementary Fig. S5, Table 1).

## Plasma drug concentrations

The concentration-time curves for LSD, MDMA, and their metabolites are shown in Supplementary Figs. S6 and S7. Table 2 and Supplementary Table S7 show the corresponding

**Table 1.** Mean values and statistics for the acute effects of LSD, MDMA, LSD + MDMA and placebo, $N = 24$.

| | | Placebo Mean ± SEM | MDMA Mean ± SEM | LSD Mean ± SEM | LSD + MDMA Mean ± SEM | $F_{3, 69}$ | $P=$ | Pla − MDMA | Pla − LSD | Pla − LSD + MDMA | MDMA −LSD | MDMA − LSD + MDMA | LSD − LSD + MDMA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visual Analog Scale (VAS, % max) | | | | | | | | | | | | | |
| Unidirectional Scales (0–100) | | | | | | | | | | | | | |
| Any drug effect | $\Delta E_{max}$ | 5.3 ± 4.0 | 64 ± 5.6 | 90 ± 3.1 | 93 ± 2.6 | 145 | <0.001 | *** | *** | *** | *** | *** | NS |
| Good drug effect | $\Delta E_{max}$ | 5.1 ± 4.0 | 73 ± 5.7 | 87 ± 3.6 | 95 ± 1.9 | 138 | <0.001 | *** | *** | *** | * | *** | NS |
| Bad drug effect | $\Delta E_{max}$ | 0.2 ± 0.2 | 6.4 ± 2.1 | 18 ± 3.5 | 14 ± 4.1 | 7.9 | <0.001 | NS | *** | ** | * | NS | NS |
| Feeling high | $\Delta E_{max}$ | 3.7 ± 3.7 | 59 ± 7.4 | 70 ± 7.3 | 77 ± 6.7 | 36 | <0.001 | *** | *** | *** | NS | NS | NS |
| Fear | $\Delta E_{max}$ | 0.2 ± 0.1 | 2.3 ± 0.9 | 13 ± 4.1 | 8.2 ± 2.3 | 6.9 | <0.001 | NS | *** | NS | ** | NS | NS |
| Nausea | $\Delta E_{max}$ | 1.0 + 0.7 | 7.9 ± 2.6 | 25 ± 4.5 | 21 ± 4.8 | 15 | <0.001 | NS | *** | *** | *** | * | NS |
| Alteration of vision | $\Delta E_{max}$ | 2.9 ± 2.8 | 17 ± 4.8 | 89 ± 4.0 | 87 ± 4.1 | 197 | <0.001 | * | *** | *** | *** | *** | NS |
| Sounds influence vision | $\Delta E_{max}$ | 3.2 ± 3.2 | 11 ± 5.2 | 86 ± 4.4 | 79 ± 6.0 | 119 | <0.001 | NS | *** | *** | *** | *** | NS |
| Alteration of sense of time | $\Delta E_{max}$ | 4.4 ± 4.2 | 24 ± 5.9 | 86 ± 5.5 | 92 ± 2.8 | 121 | <0.001 | ** | *** | *** | *** | *** | NS |
| Ego dissolution | $\Delta E_{max}$ | 2.7 ± 2.5 | 15 ± 5.8 | 82 ± 6.2 | 79 ± 6.2 | 87 | <0.001 | NS | *** | *** | *** | *** | NS |
| Autonomic Effects | | | | | | | | | | | | | |
| Systolic blood pressure (mmHg) | $E_{max}$ | 124 ± 2.4 | 148 ± 2.9 | 137 ± 2.7 | 150 ± 2.9 | 81 | <0.001 | *** | *** | *** | *** | NS | *** |
| Diastolic blood pressure (mmHg) | $E_{max}$ | 77 ± 1.7 | 89 ± 1.4 | 85 ± 1.8 | 90 ± 1.4 | 33 | <0.001 | *** | *** | *** | NS | NS | * |
| Mean arterial pressure (mmHg) | $E_{max}$ | 92 ± 1.7 | 107 ± 1.6 | 102 ± 2.0 | 109 ± 1.6 | 60 | <0.001 | *** | *** | *** | ** | NS | *** |
| Heart rate (beats/min) | $E_{max}$ | 77 ± 2.6 | 95 ± 3.4 | 92 ± 4.5 | 100 ± 3.6 | 25 | <0.001 | *** | *** | *** | NS | NS | * |
| Rate pressure product (mmHg × bpm) | $E_{max}$ | 9290 ± 502 | 13698 ± 550 | 12385 ± 724 | 14678 ± 726 | 43 | <0.001 | *** | *** | *** | NS | NS | *** |
| Body temperature (°C) | $E_{max}$ | 37.0 ± 0.05 | 37.3 ± 0.07 | 37.4 ± 0.06 | 37.5 ± 0.08 | 27 | <0.001 | *** | *** | *** | NS | * | NS |
| Pupil size (mm)[a] | $E_{max}$ | 6.0 ± 0.2 | 7.1 ± 0.2 | 7.0 ± 0.2 | 7.2 ± 0.1 | 76 | <0.001 | *** | *** | *** | NS | NS | * |
| Pupil size after light (mm)[a] | $E_{max}$ | 4.3 ± 0.2 | 6.2 ± 0.2 | 5.7 ± 0.2 | 6.5 ± 0.2 | 4.2 | <0.001 | *** | *** | *** | *** | * | *** |
| Pupil contraction (mm)[a] | $E_{min}$ | 1.4 ± 0.1 | 0.8 ± 0.1 | 1.2 ± 0.1 | 0.6 ± 0.1 | 20 | <0.001 | *** | NS | *** | ** | NS | *** |
| List of Complaints (LC Score) | | | | | | | | | | | | | |
| Acute adverse effects | 0–12 h | 1.9 ± 1.1 | 8.6 ± 1.8 | 15 ± 1.9 | 15 ± 2.2 | 38 | <0.001 | *** | *** | *** | *** | *** | NS |
| Subacute adverse effects | 12–24 h | −0.2 ± 0.5 | 2.5 ± 0.9 | 3.1 ± 1.0 | 5.5 ± 1.4 | 11 | <0.001 | * | ** | *** | NS | * | NS |
| Hormones and Markers | | | | | | | | | | | | | |
| Oxytocin (pg/mL) | Δ1.5h | −1.6 ± 6.3 | 190 ± 44 | 30 ± 9.5 | 177 ± 33 | 14 | <0.001 | *** | NS | *** | *** | NS | ** |
| | Δ3h | −4.0 ± 5.7 | 212 ± 29 | 35 ± 8.1 | 246 ± 30 | 36 | <0.001 | *** | NS | *** | *** | NS | *** |
| | Δ6h | −12 ± 6.3 | 29 ± 14 | 36 ± 8.5 | 111 ± 15 | 22 | <0.001 | NS | * | *** | NS | *** | *** |
| | $\Delta C_{max}$ | 6.0 ± 5.3 | 289 ± 38 | 60 ± 9.0 | 286 ± 30 | 45 | <0.001 | *** | NS | *** | *** | NS | *** |
| BDNF (ng/mL) | $\Delta C_{max}$ | 9.6 ± 1.7 | 7.1 ± 2.1 | 7.4 ± 1.7 | 7.4 ± 1.3 | 0.5 | NS | – | – | – | – | – | – |

*NS* not significant, $\Delta E_{max}$ maximal effect difference from baseline, $\Delta E_{min}$ minimal effect difference from baseline.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
[a]$N = 23$.

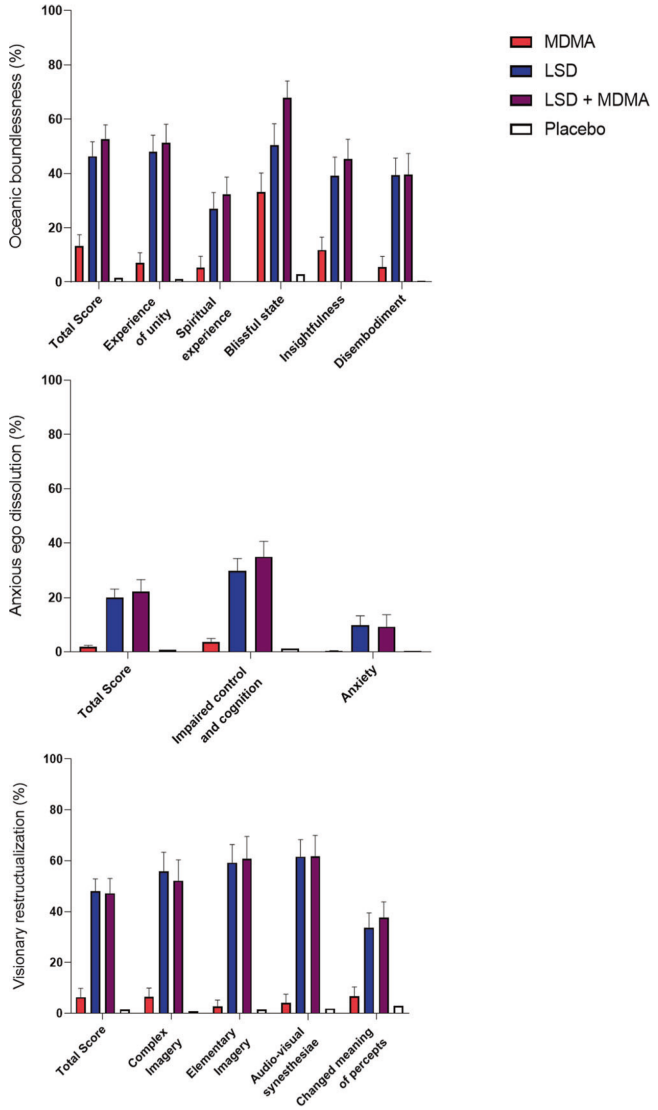


**Fig. 2 Acute mystical-type experiences on the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale.** The combination of LSD (100 µg) and MDMA (100 mg) induced comparable effects to LSD (100 µg) alone. MDMA (100 mg) alone only significantly induced mystical-type effects on the lower-order "blissful state" scale. The data are expressed as the mean ± SEM percentage of maximally possible scale scores in 24 subjects. Statistics are shown in Supplementary Table S2.

pharmacokinetic parameters. MDMA slightly altered the pharmacokinetics of LSD. Specifically, the peak plasma concentration of LSD was higher in the LSD + MDMA condition (2.1 ng/mL) compared with LSD alone (1.9 ng/ml; $T = 2.09$; $p < 0.05$). The plasma LSD elimination half-life was longer in the LSD + MDMA condition (5.2 h) compared with LSD alone (3.9 h; $T = 5.00$; $p < 0.001$). The area under the concentration time curve ($AUC_{\infty}$) also increased to 19 ng·h/ml in the LSD + MDMA condition compared with LSD alone (14 ng·h/mL; $T = 3.53$; $p < 0.01$; Table 2).

## Blinding

Data on the participants' retrospective identification of their substance condition after the session and after the study are shown in Supplementary Table S8. During and after receiving LSD + MDMA, 50% and 46% of the participants, respectively, thought they received LSD alone. During and after receiving LSD alone, 25% and 38% of the participants, respectively, thought they received LSD + MDMA. When asked at the end of the study, 25% of the participants mistook LSD for LSD + MDMA and vice versa.

## DISCUSSION

The main finding of the present study was that MDMA co-administration did not relevantly alter acute psychedelic effects of LSD while producing greater autonomic effects compared with LSD alone. However, LSD + MDMA co-administration prolonged acute subjective effects compared with LSD alone. The prolonged LSD response is consistent with a higher plasma concentration of LSD ($C_{max}$ and AUC) and a longer plasma elimination half-life of LSD when it was co-administered with MDMA and as determined in the present study. Acute effects of LSD and MDMA alone have previously been compared in healthy participants [3], but the present study was the first to investigate the combined use of MDMA and LSD in a controlled laboratory setting and using defined doses of both substances. Synergistic discriminative effects of LSD and MDMA were previously reported in rats [24]. However, the rats were trained to discriminate MDMA (1.5 mg/kg) alone from saline, and then the co-administration of a low MDMA dose (0.15 mg/kg) with LSD (0.04 mg/kg) produced a full MDMA-like response [24]. Acute subjective effects of LSD are primarily positive. However, there are also negative subjective effects (e.g., anxiety) of LSD, depending on the dose of LSD used, personality traits of the person using LSD, their life circumstances, and the setting [1, 3–7, 9, 36]. Acute negative psychological effects are the main adverse events that are associated with LSD when it is used in psychedelic-assisted therapy [1]. In contrast to LSD, MDMA induces fewer psychedelic effects with little anxious ego-dissolution [3]. MDMA typically produces robust positive subjective effects, including enhanced feelings of positive mood, well-being, empathy, trust, and closeness to others [3, 16–19].

Therefore, we hypothesized that adding MDMA to LSD would enhance positive mood effects and decrease anxiety that is associated with the LSD response. The same approach is also used by recreational substance users when combining MDMA and LSD in "candyflipping." Contrary to our expectation, the present controlled study showed that the co-administration of LSD and MDMA and administration of LSD alone produced overall very similar subjective effects on the VAS, 5D-ASC, and MEQ. However, although no significant differences were seen, the addition of MDMA tended to nonsignificantly increase ratings of "happy," "open," and "trust" on the VAS and "well-being" on the AMRS, especially in the beginning of the experience compared with LSD alone. Additionally, ratings of "well-being" on the AMRS increased at the beginning of the drug response but dropped at 6 h when the MDMA effect ended. This may indicate some enhanced MDMA-typical subjective effects with the combination compared with LSD alone. Furthermore, we only tested single dose levels of both LSD and MDMA and co-administration at the same time. An LSD base dose of 100 µg has previously been used in several studies in healthy participants [3, 8, 36, 37] and could be considered a moderately high dose. LSD at a dose of 100 µg mainly induces high acute positive effects and nominally less anxiety compared with a higher dose of 200 µg [7, 36]. Thus, we cannot exclude the possibility that MDMA may reduce negative mood effects, including anxiety, of higher LSD doses than the dose that was used in the present study. The MDMA dose of 100 mg was lower than the 120–125 mg doses that were mostly used in healthy research participants [19] and patients [16]. A 100 mg dose of MDMA that is administered in women is equivalent to 120–125 mg in men and can be considered a fully psychoactive dose in women when given alone [19, 38] and not co-administered with LSD. Nevertheless, we cannot exclude different interactive effects of MDMA and LSD at different dose levels and administration time-points than those that were used herein. The duration of the acute LSD response is longer than the MDMA response, as confirmed in the present study. Future studies may test the administration of MDMA 1–4 h after LSD or use a prolonged MDMA release formulation or pro-drug of MDMA to better align its effects with the time course of the LSD effect.

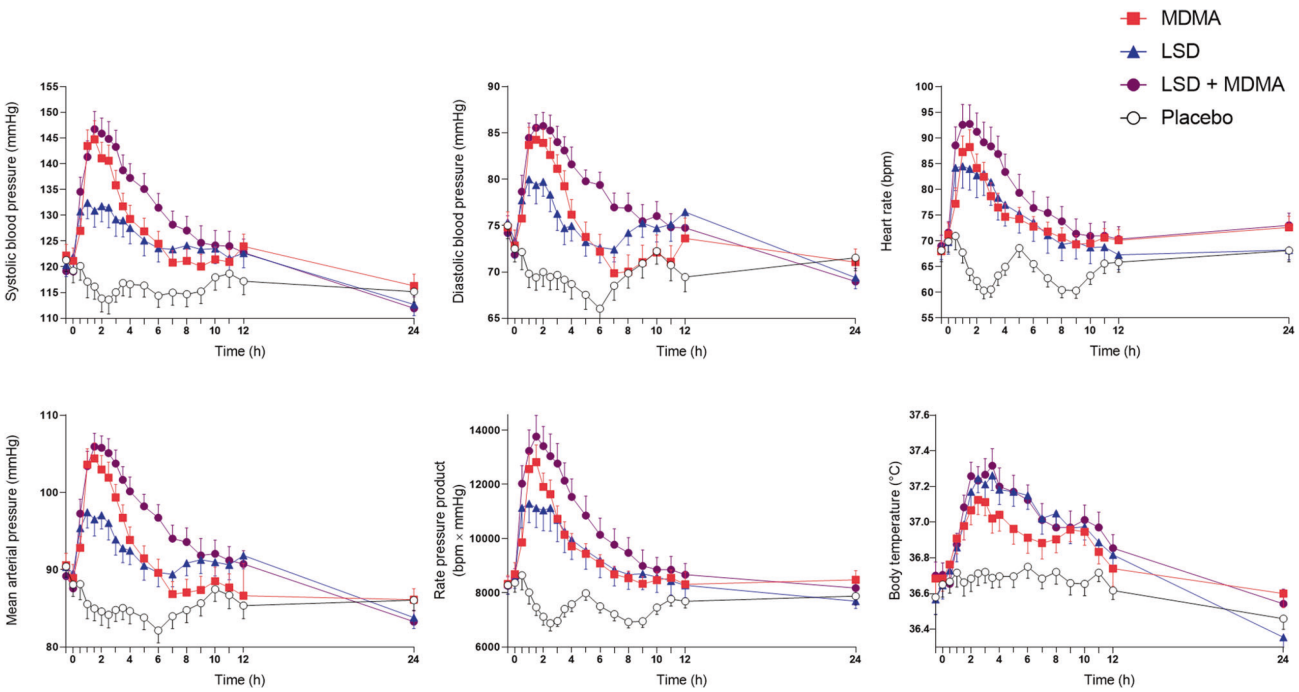


**Fig. 3 Acute autonomic effects of 100 µg lysergic acid diethylamide (LSD), 100 mg 3,4-methylenedioxymethamphetamine (MDMA), and the LSD + MDMA combination (100 µg+100 mg) over time.** LSD, MDMA, and the LSD + MDMA combination increased blood pressure, heart rate, and body temperature compared with placebo. MDMA alone and the LSD + MDMA combination increased blood pressure and heart rate more compared with LSD alone. The substances were administered at t = 0 h. The data are expressed as the mean ± SEM in 24 subjects. The corresponding maximal responses and statistics are shown in Table 1.

Moreover, the combination of MDMA and psilocybin may be interesting because of their similar durations of action [3, 36]. However, average peak effects of MDMA and LSD were reached at similar times in the present study, indicating a good match of the two subjective effect-time curves over the first 4 h. The potential drop in positive MDMA effects might have resulted in more negative mood states from 5 to 12 h in some participants, indicated by the trend-wise lower "well-being" ratings on the AMRS and higher "depression" ratings on the AMRS toward the end of the LSD response when it was co-administered with MDMA. Notably, recreational users reportedly often take MDMA after LSD when "candyflipping."

LSD, MDMA, and their combination produced significant autonomic stimulant effects as reported previously [3, 9, 39]. The LSD + MDMA combination induced greater increases in blood pressure and heart rate compared with LSD alone. Body temperature increased similarly after LSD + MDMA co-administration and LSD administration alone and more after LSD + MDMA co-administration compared with MDMA administration alone.

MDMA had no relevant effects on the quality of the acute response to LSD, whereas the LSD + MDMA combination resulted in a longer effect duration compared with LSD and MDMA alone. This can be explained by higher plasma concentrations (both $C_{max}$ and AUC) and a longer plasma elimination half-life of LSD when it was co-administered with MDMA. Thus, MDMA and LSD primarily interact pharmacokinetically and not pharmacodynamically. Additionally, the higher plasma exposure to LSD could be explained by metabolic P450 enzyme CYP2D6 inhibition by MDMA [38, 40]. MDMA is a strong inhibitor of CYP2D6, turning any CYP2D6 extensive or rapid metabolizer into a poor metabolizer within approximately 2 h [41]. Additionally, CYP2D6 poor metabolizers exhibited higher plasma concentrations and a longer elimination half-life of LSD compared with extensive metabolizers [42]. Thus, the present study further confirms a role for CYP2D6 in the metabolism of LSD. A similar or substantial increase in plasma LSD concentrations could be expected when patients who are on antidepressants that inhibit CYP2D6 (e.g., fluoxetine, paroxetine, duloxetine, and bupropion) and are treated with LSD-assisted therapy. This interaction warrants further study.

We also evaluated selected interactive endocrine effects of LSD and MDMA. The marked release of oxytocin may mediate some of subjective effects of MDMA [17, 43, 44]. LSD also increased circulating oxytocin, although not robustly and to a lower extent than MDMA [3, 6, 7]. In the present study, effects of MDMA and LSD on plasma oxytocin concentrations were additive. Neither MDMA nor LSD altered serum concentrations of BDNF, adding further data to several inconclusive studies [3, 7, 8, 45].

The present study also provided insights into the ways in which neurotransmitters mediate subjective effects of psychoactive substances. LSD directly activates the serotonin 5-hydroxytryptamine-2A (5-$HT_{2A}$) receptor [46], which primarily mediates its acute psychedelic effects [7, 8, 47]. MDMA induces the release of endogenous norepinephrine, serotonin, and oxytocin [44, 48, 49]. The present study indicates that stimulating serotonin and norepinephrine with the empathogen MDMA, in addition to the direct activation of 5-$HT_{2A}$ receptors by the psychedelic LSD, does not relevantly alter the subjective effects profile of a psychedelic alone. This finding is also consistent with the observation that LSD alone strongly exerts several MDMA-like empathogenic effects, including similar ratings of well-being, happiness, closeness to others, openness, and trust, as previously reported [3, 6] and confirmed in the present study. Interestingly, the additional release of serotonin and oxytocin by MDMA does not appear to result in relevant additional psychoactive effects of LSD. The additional release of norepinephrine by MDMA explains the greater cardiovascular stimulation after the co-administration of LSD and MDMA compared with LSD alone.

We found no indication of greater serotonin toxicity when MDMA and LSD were co-administered. MDMA did not increase thermogenic effects of LSD alone. Nausea was similarly frequent after the co-administration of LSD and MDMA and the administration of either substance alone.

**Table 2.** Pharmacokinetic parameters based on non-compartmental analyses [geometric mean (95% CI), range], $N = 24$.

| | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) | $AUC_{24}$ (ng·h/mL) | $AUC_{\infty}$ (ng·h/mL) | CL/F (L/h) | $V_z/F$ (L) |
|---|---|---|---|---|---|---|---|
| LSD | | | | | | | |
| LSD + Placebo administration | 1.9 (1.7–2.1) | 1.6 (1.4–1.9) | 3.9 (3.5–4.4) | 14 (12–16) | 14 (12–17) | 6.9 (5.8–8.3) | 39 (35–44) |
| | 1.2–3.6 | 1.0–3.0 | 2.5–6.3 | 8.7–34 | 8.9–39 | 2.5–11 | 19–61 |
| LSD+MDMA administration | 2.1 (1.9–2.3)* | 1.6 (1.4–1.9) | 5.2 (4.6–5.9)*** | 17 (15–21)** | 19 (16–22)** | 5.3 (4.5–6.4)** | 40 (36–45) |
| | 1.2–3.3 | 1.0–3.5 | 2.5–8.9 | 8.1–33 | 8.3–39 | 2.6–12 | 27–77 |
| MDMA | | | | | | | |
| MDMA + Placebo administration | 233 (215–252) | 2.8 (2.5–3.2) | 8.3 (7.5–9.1)[a] | 2596 (2333–2889)[a] | 3083 (2713–3505)[a] | 32 (29–37)[a] | 388 (357–422)[a] |
| | 167–306 | 1.5–5.0 | 5.0–12 | 1699–4143 | 1827–5251 | 19–55 | 274–515 |
| LSD+MDMA administration | 208 (189–228)*** | 3.5 (3.0–4.0)** | 8.2 (7.5–9.1) | 2568 (2319–2843) | 3068 (2712–3472) | 33 (29–37) | 386 (354–422) |
| | 130–318 | 2.0–6.0 | 5.6–16 | 1510–4202 | 1674–6540 | 15–60 | 237–574 |

*AUC* area under the plasma concentration-time curve, $AUC_{\infty}$ AUC from time zero to infinity, $AUC_{24}$ from time 0 to 24, *CL/F* apparent total clearance, $C_{max}$ maximum observed plasma concentration, $T_{1/2}$ plasma half-life, $T_{max}$ time to reach $C_{max}$, *95% CI* 95% confidence interval, $V_z/F$ apparent volume of distribution.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ compared with LSD or MDMA alone, respectively (paired T-test).
[a]$N = 23$.

The role of dopamine in subjective effects of LSD remains unclear [50, 51]. LSD binds to dopamine $D_1$ and $D_2$ receptors [46]. We consider direct dopamine receptor stimulation irrelevant for psychedelic properties of LSD because subjective effects of LSD can be fully antagonized by blocking 5-$HT_2$ receptors [7, 8] and are very comparable to subjective effects of psilocybin [36] (a psychedelic with no relevant effects on $D_1$ or $D_2$ receptors) [46]. MDMA also induces the release of dopamine [52], and this may explain the nominally greater well-being ratings after the co-administration of MDMA and LSD compared with LSD alone.

The present study has several strengths. We used a relatively large study sample ($n = 24$) and powerful within-subject comparisons in a randomized double-blind design. The LSD and MDMA doses were pharmacologically well characterized. We included equal numbers of male and female participants and used internationally established psychometric outcome measures. Plasma LSD and MDMA concentrations were determined at close intervals in all participants and analyzed with validated analytical methods.

Notwithstanding these strengths, the present study also has limitations. We used only one dose of LSD and MDMA. The study used a highly controlled hospital setting and included only healthy volunteers. Thus, people in different environments and patients with psychiatric disorders may respond differently to these substances. Finally, the outcome measures may not have been sufficiently sensitive to capture all aspects of a psychedelic experience and/or very subtle differences between acute effects of LSD + MDMA compared with LSD alone.

## CONCLUSION

MDMA co-administration did not alter acute psychedelic effects of LSD. However, MDMA acted as a blocker of the metabolism of LSD to prolong its presence in the body and acute effects. The LSD + MDMA combination produced more autonomic effects compared with LSD alone. There is likely little benefit in combining MDMA and LSD in psychedelic-assisted therapy.

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## AUTHOR CONTRIBUTIONS

IS, LL, and MEL designed the research. IS, AMB, AK, KW, NV, and AE performed the research. IS, FH, UD, and MEL analyzed the data. IS and MEL wrote the manuscript with input from all other authors. All authors gave final approval to the manuscript.

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## COMPETING INTERESTS

MEL is a consultant for Mind Medicine, Inc. The other authors declare no competing interests. Knowhow and data associated with this work and owned by the University

Hospital Basel were licensed by Mind Medicine, Inc. Mind Medicine, Inc., had no role in planning or conducting the present study or the present publication.

## ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1038/s41386-023-01609-0.

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## Supplement

## Methods

*Subjective drug effects measurements*
*Visual Analog Scales (VASs)*

Subjective effects were assessed repeatedly using visual analog scales (VASs) [1,2]. 0.5 h before and 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 h after drug administration. The VASs included “any drug effect”, “good drug effect”, “bad drug effect”, “feeling high”, “fear”, “nausea”, “alteration of vision”, “sounds seem to influence what I see”, “alteration of sense of time” and “ego dissolution,” that were presented as 100-mm horizontal lines (0-100%), marked from “not at all” on the left to “extremely” on the right [1,3]. Further VASs included “feeling emotional”, “happy”, “talkative”, “open”, “trust”, “I feel close to others” “I want to be alone”, “I want to be with others” and “my focus is directed inward/outward”. These VASs were bidirectional and marked with “normal” in the middle at 0 mm and “not at all” (-50 mm) on the left and “extremely” (50 mm) on the right. The primary VAS outcome measures were “good drug effect”, “trust”, “open”, “bad drug effects” and “fear”. These VASs have been repeatedly used and shown to be sensitive with MDMA and LSD [1-6]. The VAS can be completed relatively rapidly and easily by the participant even during the LSD/MDMA experience and allows for a valid prospective definition of the drug effects over time. They are sensitive and relatively simple measures. More complex assessments of the state of LSD and MDMA have to be performed primarily at the end of the session and include entire multi-item questionnaires. The VAS “any drug effect” is an overall effect measure to characterize the overall effect intensity and time course. The VAS “good drug effect” is an overall measure of effects subjectively considered positive and interrelated with other measures such as “drug liking”. The VAS “bad drug effect” is an overall measure of any negative effects and related to “fear”. Typically, “bad drug effects” of LSD tend to occur only at higher doses or plasma concentrations according to previous PK-PD analyses [4,5]. The VAS “ego dissolution” was marked with the sentence: “the boundaries between myself and my surroundings seemed to blur”. This is also an item of the 5D-ASC (no. 71) which has been used as a simple measure of “ego dissolution” previously [7,8] and can be used repeatedly as a single VAS [1,4]. VASs were assessed each time LSD and MDMA blood concentrations were measured.

*Adjective Mood Rating Scale (AMRS)*

The Adjective Mood Rating Scale (AMRS) [9] was used 0.5 h before and 3, 6, 9, 12, and 24 h after drug administration. The AMRS is a validated 60-item Likert mood rating scale mainly use in Europe and consists of subscales including ratings on “well-being”, “anxiety”, “inactivity”, “extraversion”, “introversion”, and “emotional excitation”. It is suitable for repeated measurements of mood states. The short German EWL60S version was used [9]. The completion of the ratings under the effects of psychedelics substances is possible but difficult because it lasts several minutes. The scale was used in paper and pencil version but it may be more suitable to use this measure verbally during states of markedly impaired concentration. The AMRS was included as a primary measure because it could be considered a better validated measure of mood states and producing more defined ratings than the VAS and to support findings on the VAS (AMRS well-being considered similar to VAS good drug effects; AMRS anxiety considered similar to VAS fear).

*5 Dimension of Altered States of Consciousness (5D-ASC) scale*

The 5 Dimensions of Altered States of Consciousness (5D-ASC) scale [10,11] was used as the primary outcome measure and was administered 12 h after drug administration to retrospectively rate peak drug effects. The 5D-ASC scale measures altered states of consciousness and contains 94 items (visual analog scales). The instrument consists of five subscales/dimensions [10] and 11 lower-order scales [11]. The 5D-ASC dimension “Oceanic

Boundlessness" (27 items) measures derealization and depersonalization associated with positive emotional states, ranging from heightened mood to euphoric exaltation. The corresponding lower-order scales include "experience of unity," "spiritual experience," "blissful state," "insightfulness," and "disembodiment." The dimension "Anxious Ego Dissolution" (21 items) summarizes ego-disintegration and loss of self-control phenomena associated with anxiety. The corresponding lower-order scales include "impaired control of cognition" and "anxiety." The dimension "Visionary Restructuralization" (18 items) consists of the lower-order scales "complex imagery," "elementary imagery," "audio-visual synesthesia," and "changed meaning of percepts." Two additional dimensions describe "Auditory Alterations" (15 items) and "Reduction of Vigilance" (12 items). The total 3D-ASC score is the total of the three main dimensions "Oceanic Boundlessness", "Anxious Ego-Dissolution", and "Visionary Restructuralization" and can be used as a measure of the overall intensity of the alteration of the mind [8]. The scale is well-validated in German [10] and many other languages and widely used to characterize the subjective effects of various psychedelic drugs. In particular, the scale has been used by most research groups to psychometrically assess LSD and MDMA effects [1,2,12-16]. Furthermore, acute ratings on the 5D-ASC after administration of psilocybin have been used to predict long-term effects of psychedelic treatments in patients [17,18]. Ratings on the 5D-ASC have been shown to closely correlate with ratings on the Mystical Effects Questionnaire (MEQ, see below) [8] which is primarily used by research groups in the US [18].

*Mystical Effects Questionnaire (MEQ30)*

Mystical experiences were assessed 12 h after drug administration using the 100-item States of Consciousness Questionnaire (SOCQ) [8,19] that includes the 43-item Mystical Effects Questionnaire (MEQ43) [19], 30-item Mystical Effects Questionnaire (MEQ30) [20], and subscales for "aesthetic experience" and negative "nadir" effects. The published German version was used [8]. The MEQ has been used in numerous experimental and therapeutic trials with psilocybin [18,19,21-27]. The MEQ items provide scale scores for each of seven domains of mystical experiences: internal unity, external unity, sacredness, noetic quality (as real as or more real than everyday reality), deeply felt positive mood, transcendence of time and space, and ineffability/paradoxicality (difficulty describing the experience in words). The total of all scale scores was used as an overall measure of the mystical-type experience. We also derived the four scale scores of the newly validated revised 30-item MEQ: mystical, positive mood, transcendence of time and space, and ineffability [20]. A complete mystical experience was defined as scores ≥ 60% on all MEQ30 factors [20]. While we prefer the German 5D-ASC scale, the German version of the MEQ was also included to facilitate comparison of our findings with those from research using the MEQ (mainly US). Additionally, some aspects of the LSD experience may be better captured with this scale. For the scale validation see [20]. For an analysis of the interrelation of the two measures with regards to responses to LSD see [8]. For the German translation of the MEQ30 see online supplement of [8].

*Brain-derived neurotropic factor measurements*

Serum concentrations of brain-derived neurotrophic factor (BDNF) were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Biosensis Mature BDNF Rapid ELISA Kit: Human, Mouse, Rat; Thebarton, SA, Australia). Blood samples were drawn using serum tubes. After 30 min at room temperature, the serum tubes were centrifuged at 14,100 × *g* for 10 min at 4°C. Samples were stored at -80°C before the analysis of BDNF levels. Serum samples were diluted (1:100), and BDNF was detected on a pre-coated mouse monoclonal anti-mature BDNF 96-well plate as described in the manufacturer's protocol. Absorbance was read at 450 nm within 5 min after adding the stop solution in a microplate reader. The correction wavelength was set to 690 nm to determine BDNF concentrations according to the standard curve that was calculated from a 4-parameter logistics curve fit.

## Results

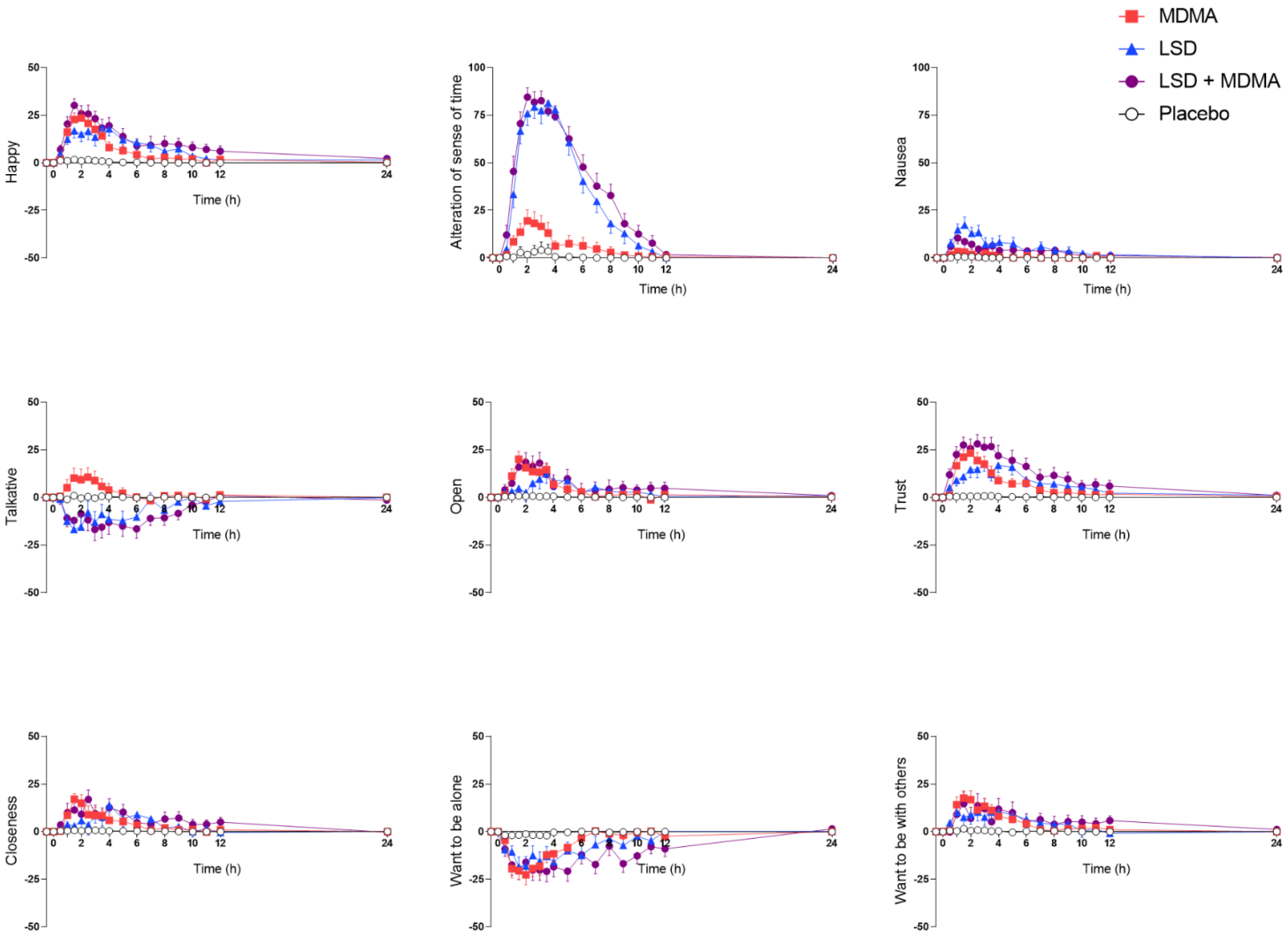
MDMA
LSD
LSD + MDMA
Placebo
Happy
Alteration of sense of time
Nausea
Talkative
Open
Trust
Closeness
Want to be alone
Want to be with others
Time (h)

**Figure S1.** Acute subjective effects induced by 3,4-Methylendioxymethamphetamin (MDMA), lysergic acid diethylamide (LSD) and the combination of LSD and MDMA over time on the Visual Analog Scale (VAS). MDMA (100 mg), LSD (100 µg), and LSD & MDMA (100 µg, 100 mg), or placebo was administered at t = 0 h. Generally, LSD and the co-administration of LSD and MDMA produced comparable subjective effects on all depicted VASs. MDMA alone also showed comparable subjective effects except on the VAS “alteration of sense of time” and “talkative”. The data are expressed as the mean ± SEM percentage of maximally possible scale scores in 24 subjects. The corresponding maximal responses and statistics are shown in Table 1 and in Supplementary Table S1.

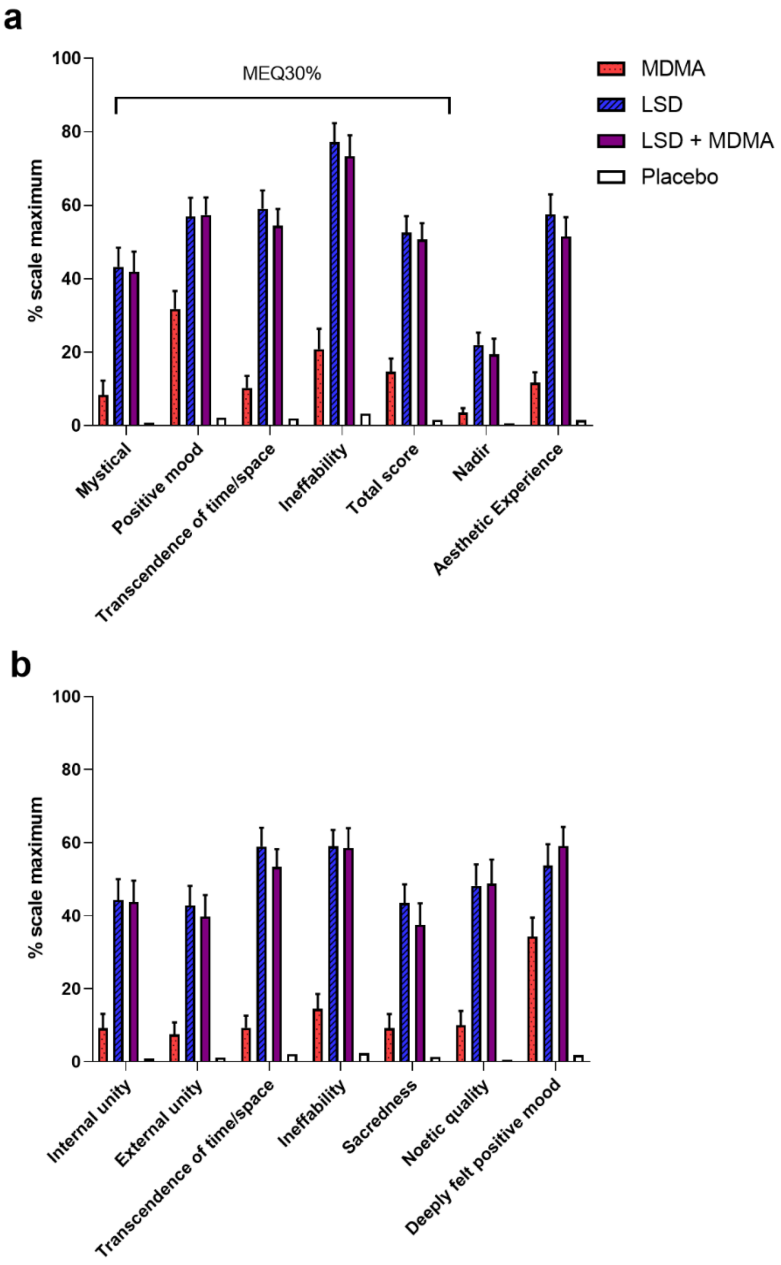


**Figure S2.** Acute mystical-type experiences on the Mystical Effects Questionnaire (MEQ). The combination of 100 µg LSD with 100 mg MDMA induced overall comparable effects to 100 µg of LSD alone on the MEQ30 (**a**) and the MEQ43 (**b**). 100 mg MDMA alone only showed significant mystical-type effects for the positive mood subscales on both the MEQ30 and MEQ45. Ineffability in the MEQ30 and the MEQ30 total score were significant as well for MDMA alone. The data are expressed as the mean ± SEM percentage of maximally possible scale scores in 24 subjects. Statistics are shown in Supplementary Table S3.

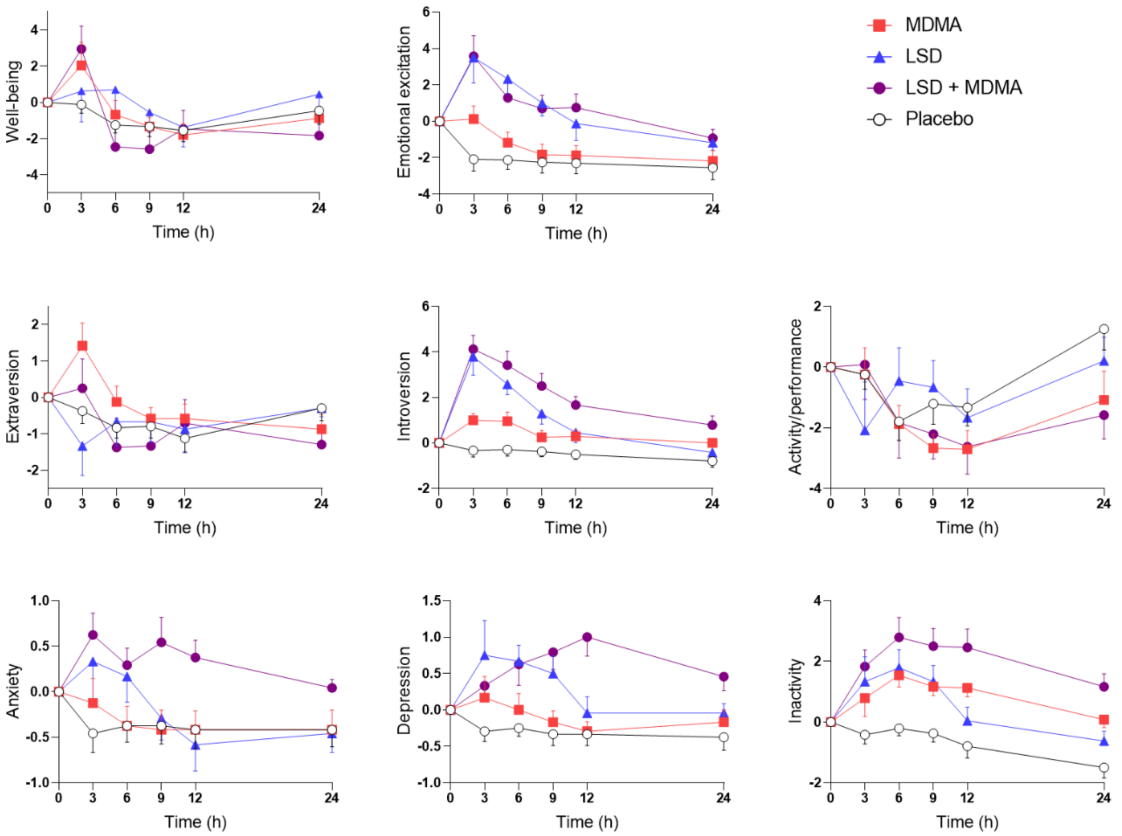


**Figure S3**. Subjective effects over time on the Adjective Mood Rating Scale (AMRS). The data are expressed as mean ± SEM changes from baseline. All conditions nominally reduced activity ratings on the AMRS with no difference between placebo and either active drug condition. All substance conditions significantly increased inactivity ratings compared with placebo. LSD and LSD with co-administered MDMA significantly altered peak well-being ratings compared with placebo. While all substance conditions increased introversion compared with Placebo, LSD and the combination of LSD and MDMA increased introversion compared to MDMA alone as well. Emotional excitation was enhanced with LSD and the co-administered LSD and MDMA compared to Placebo and MDMA alone. LSD as well as LSD with MDMA combined both significantly increased self-rated anxiety compared to Placebo and MDMA alone. The combined LSD and MDMA and LSD alone increased self-rating of depression compared to Placebo and MDMA alone. LSD (100 µg), LSD & MDMA (100 µg, 100 mg), MDMA (100 mg) or placebo was administered at t = 0 h. The data are expressed as the mean ± SEM percentage of maximally possible scale scores in 24 subjects. The corresponding maximal effects and statistics are shown in Supplementary Table S4.

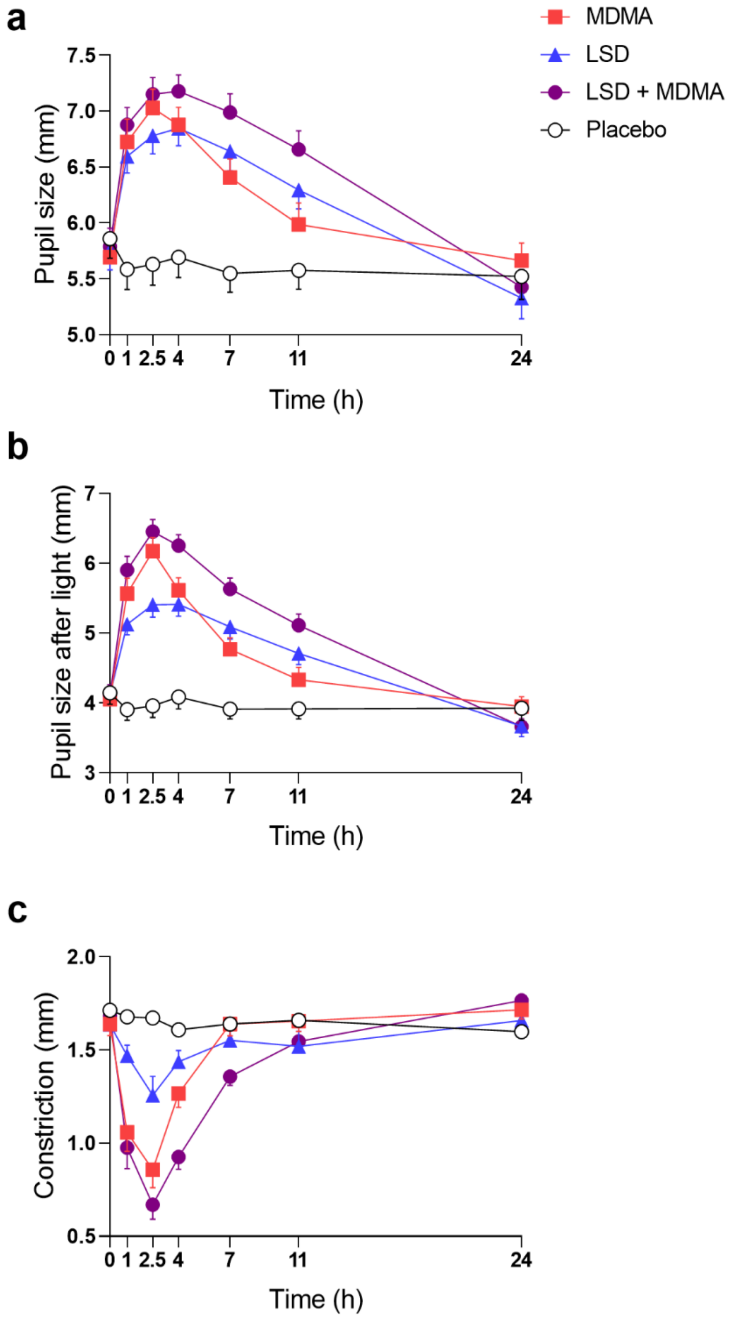


**Figure S4.** Effects of lysergic acid diethylamide (LSD), 3,4-Methylendioxymethamphetamin (MDMA), and the combination of LSD and MDMA over time on pupillary function. All conditions increased pupil size compared to placebo, additionally (**a-b**) at all doses and reduced the reaction to light (**c**). The reduction of the pupillary constriction in response to light was statistically significant more pronounced with LSD & MDMA and MDMA alone compared to LSD. LSD (100 µg), MDMA (100 mg), LSD & MDMA (100 µg, 100 mg) or placebo was administered at t = 0 h. The data are expressed as the mean ± SEM in 23 subjects. The corresponding maximal effects and statistics are shown in Table 1.

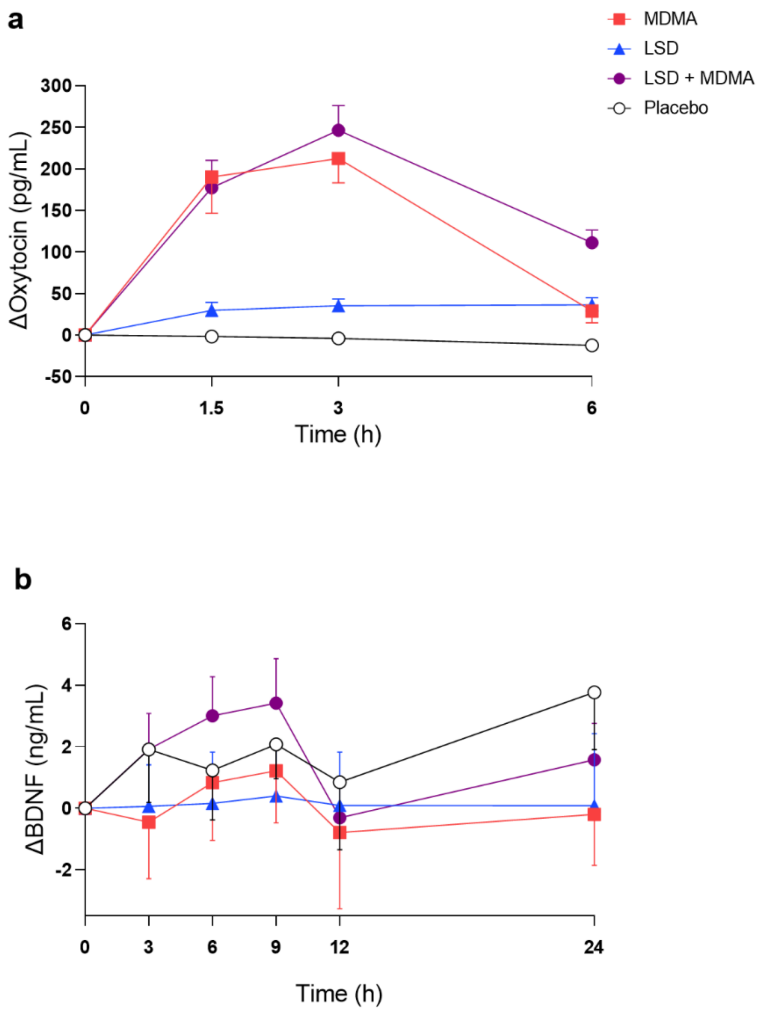


**Figure S5.** Plasma concentrations of oxytocin (**a**), and serum concentrations of Brain-Derived Neurotrophic Factor (**b**, BDNF). The data are expressed as mean ± SEM. LSD (100 µg), MDMA (100 mg), LSD & MDMA (100 µg, 100 mg) or placebo was administered at t = 0 h. The corresponding maximal effects and statistics are shown in Table 1.

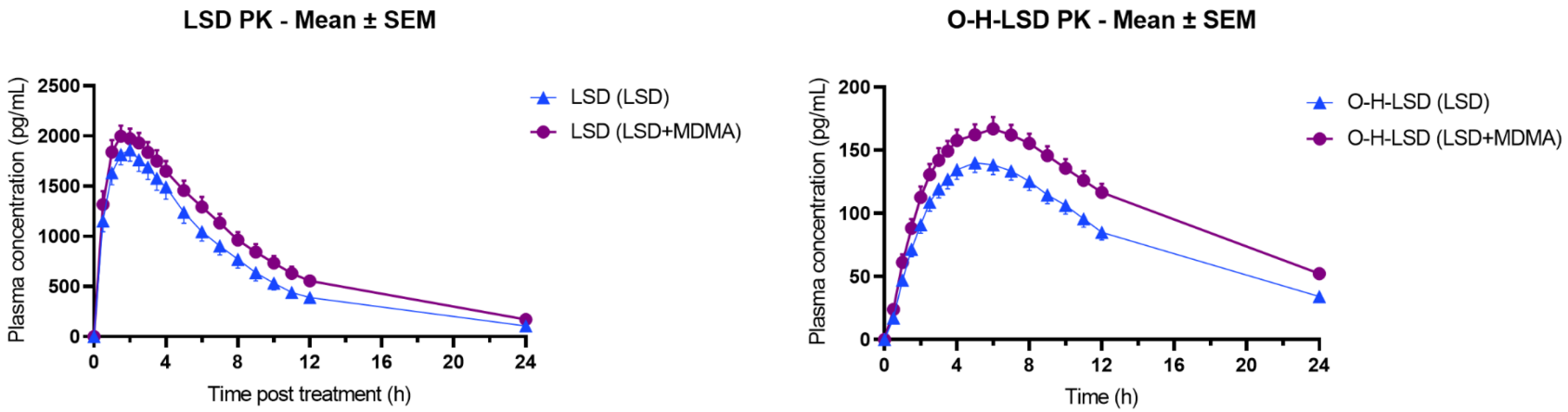


**Figure S6.** Plasma concentrations of LSD and its main metabolite 2-oxo-3-hydroxy-LSD (O-H-LSD) with and without MDMA. The data are expressed as mean ± SEM. LSD (100 µg) or LSD & MDMA (100 µg, 100 mg) was administered at t = 0 h. The corresponding pharmacokinetic parameters were determined by non-compartmental analysis and are shown in Table 2 and Table S7.

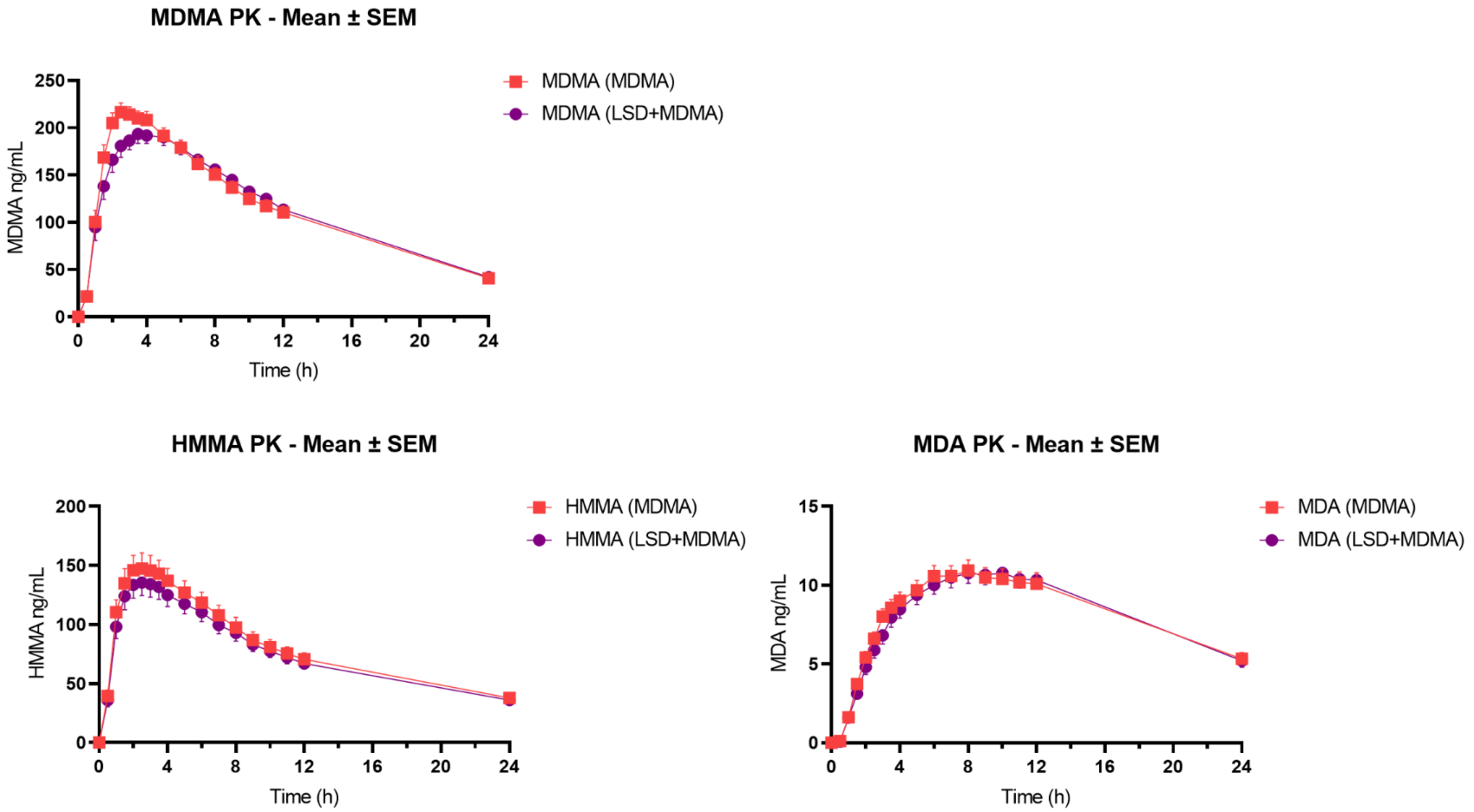


**Figure S7.** Plasma concentrations of MDMA and the metabolites 4-Hydroxy-3-methoxymethamphetamine (HMMA) and 3,4-methylenedioxyamphetamine (MDA) with and without LSD. HMMA concentrations were determined after enzymatic deglucuronidation. The data are expressed as mean ± SEM. MDMA (100 mg) or LSD & MDMA (100 µg, 100 mg) was administered at t = 0 h. The corresponding pharmacokinetic parameters were determined by non-compartmental analysis and are shown in Table 2 and Table S7.

**Table S1. Mean values and statistics for the acute subjective effects on the Visual Analog Scale (VAS)**

| | | Placebo mean±SEM | MDMA mean±SEM | LSD mean±SEM | LSD+MDMA mean±SEM | $F_{3, 69}$ | P= | Pla - MDMA | Pla - LSD | Pla - MDMA + LSD | MDMA - LSD | MDMA - MDMA + LSD | LSD - MDMA + LSD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visual Analog Scale (VAS, %max) | | | | | | | | | | | | | |
| Bidirectional Scales (-50 to 50) | | | | | | | | | | | | | |
| Emotional | $\Delta E_{max}$ | 1.5 ± 1.2 | 21 ± 3.4 | 28 ± 3.9 | 27 ± 4.0 | 22 | <0.001 | *** | *** | *** | NS | NS | NS |
| | $\Delta E_{min}$ | 0 ± 0 | -2.3 ± 1.1 | -5.3 ± 2.7 | -5.3 ± 2.7 | 1.7 | NS | - | - | - | - | - | - |
| Happy | $\Delta E_{min}$ | 2.0 ± 1.3 | 31 ± 3.3 | 31 ± 3.8 | 38 ± 3.2 | 37 | <0.001 | *** | *** | *** | NS | NS | NS |
| | $\Delta E_{min}$ | 0 ± 0 | -2.5 ± 1.4 | -5.9 ± 2.0 | -6.5 ± 2.5 | 3.2 | 0.029 | NS | NS | * | NS | NS | NS |
| Talkative | $\Delta E_{max}$ | 1.3 ± 1.3 | 24 ± 4.1 | 16 ± 3.5 | 22 ± 3.9 | 13 | <0.001 | *** | ** | *** | NS | NS | NS |
| | $\Delta E_{min}$ | -1.4 ± 0.8 | -14 ± 2.8 | -40 ± 2.7 | -40 ± 2.7 | 88 | <0.001 | *** | *** | *** | *** | *** | NS |
| Open | $\Delta E_{max}$ | 0.9 ± 0.9 | 27 ± 3.6 | 26 ± 3.7 | 32 ± 3.7 | 28 | <0.001 | *** | *** | *** | NS | NS | NS |
| | $\Delta E_{min}$ | 0 ± 0 | -8.0 ± 2.8 | -15 ± 3.6 | -19 ± 4.1 | 9.3 | <0.001 | NS | ** | *** | NS | * | NS |
| Trust | $\Delta E_{max}$ | 0.8 ± 0.8 | 29 ± 3.6 | 31 ± 3.8 | 38 ± 3.1 | 46 | <0.001 | *** | *** | *** | NS | NS | NS |
| | $\Delta E_{min}$ | 0 ± 0 | -1.1 ± 1.0 | -6.1 ± 2.7 | -5.6 ± 2.8 | 3.2 | NS | - | - | - | - | - | - |
| I feel close to others | $\Delta E_{max}$ | 0.8 ± 0.8 | 25 ± 3.4 | 24 ± 3.9 | 29 ± 3.5 | 27 | <0.001 | *** | *** | *** | NS | NS | NS |
| | $\Delta E_{min}$ | 0 ± 0 | -8.2 ± 3.1 | -14 ± 3.2 | -16 ± 3.4 | 7.4 | <0.001 | NS | ** | *** | NS | NS | NS |
| I want to be alone | $\Delta E_{max}$ | 0.2 ± 0.2 | 4.9 ± 1.7 | 10 ± 2.5 | 13 ± 3.2 | 8.0 | <0.001 | NS | ** | *** | NS | * | NS |
| | $\Delta E_{min}$ | -2.1 ± 2.1 | -33 ± 4.0 | -36 ± 3.8 | -36 ± 4.0 | 32 | <0.001 | *** | *** | *** | NS | NS | NS |
| I want to be with others | $\Delta E_{max}$ | 1.5 ± 1.5 | 28 ± 4.0 | 21 ± 4.1 | 30 ± 4.3 | 21 | <0.001 | *** | *** | *** | NS | NS | NS |
| | $\Delta E_{min}$ | -0.3 ± 0.3 | -3.8 ±1.5 | -16 ± 3.5 | -20 ± 4.2 | 13 | <0.001 | NS | *** | *** | ** | *** | NS |

*P<0.05, **P<0.01, ***P<0.001; NS, not significant; $\Delta E_{max}$, maximal effect difference from baseline; $\Delta E_{min}$, minimal effect difference from baseline; N=24

**Table S2. Mean values and statistics for the acute subjective effects on the 5 Dimensions of Altered States of Consciousness (5D-ASC) Scale**

| | | Placebo mean±SEM | MDMA mean±SEM | LSD mean±SEM | LSD+MDMA mean±SEM | $F_{3,69}$ | P= | Pla - MDMA | Pla - LSD | Pla - MDMA + LSD | MDMA - LSD | MDMA - MDMA + LSD | LSD - MDMA + LSD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 Dimensions of Altered States of Consciousness (5D-ASC) Scale | | | | | | | | | | | | | |
| 5D-ASC total Score | % score | 1.1 ± 1.1 | 7.3 ± 2.3 | 34 ± 3.4 | 37 ± 3.9 | 69 | <0.001 | NS | *** | *** | *** | *** | NS |
| 3D-ASC total Score | % score | 1.3 ± 1.3 | 7.8 ± 2.7 | 38 ± 4.0 | 41 ± 4.5 | 65 | <0.001 | NS | *** | *** | *** | *** | NS |
| Oceanic boundlessness | % score | 1.5 ± 1.5 | 13 ± 4.1 | 46 ± 5.4 | 53 ± 5.3 | 49 | <0.001 | NS | *** | *** | *** | *** | NS |
| Anxious ego-dissolution | % score | 0.6 ± 0.6 | 1.8 ± 0.6 | 20 ± 3.1 | 22 ± 4.4 | 21 | <0.001 | NS | *** | *** | *** | *** | NS |
| Visionary restructuralization | % score | 1.6 ± 1.6 | 6.4 ± 3.4 | 48 ± 5.0 | 47 ± 5.9 | 58 | <0.001 | NS | *** | *** | *** | *** | NS |
| Auditory alterations | % score | 0.4 ± 0.4 | 0.9 ± 0.6 | 11 ± 3.3 | 13 ± 3.6 | 8.0 | <0.001 | NS | * | ** | * | ** | NS |
| Reductions of vigilance | % score | 1.5 ± 1.5 | 14 ± 3.6 | 43 ± 5.0 | 46 ± 5.8 | 43 | <0.001 | NS | *** | *** | *** | *** | NS |
| Experience of unity | % score | 1.0 ± 1.0 | 7.0 ± 3.8 | 48 ± 6.1 | 51 ± 6.8 | 37 | <0.001 | NS | *** | *** | *** | *** | NS |
| Spiritual experience | % score | 0 ± 0 | 5.3 ± 4.2 | 27 ± 5.9 | 32 ± 6.4 | 14 | <0.001 | NS | *** | *** | ** | *** | NS |
| Blissful state | % score | 2.9 ± 2.9 | 33 ± 7.0 | 50 ± 7.9 | 68 ± 6.2 | 23 | <0.001 | ** | *** | *** | NS | *** | NS |
| Insightfulness | % score | 0 ± 0 | 12 ± 4.8 | 39 ± 6.8 | 45 ± 7.2 | 21 | <0.001 | NS | *** | *** | *** | *** | NS |
| Disembodiment | % score | 0.5 ± 0.5 | 5.6 ± 3.8 | 39 ± 6.2 | 40 ± 7.9 | 19 | <0.001 | NS | *** | *** | *** | *** | NS |
| Impaired control and cognition | % score | 1.3 ± 1.3 | 3.6 ± 1.3 | 30 ± 4.4 | 35 ± 5.6 | 29 | <0.001 | NS | *** | *** | *** | *** | NS |
| Anxiety | % score | 0.2 ± 0.2 | 0.3 ± 0.2 | 9.9 ± 3.4 | 9.3 ± 4.4 | 3.8 | 0.014 | NS | NS | NS | NS | NS | NS |
| Complex imagery | % score | 0.8 ± 0.8 | 6.5 ± 3.5 | 56 ± 7.5 | 52 ± 8.2 | 34 | <0.001 | NS | *** | *** | *** | *** | NS |
| Elementary imagery | % score | 1.5 ± 1.5 | 2.7 ± 2.5 | 59 ± 7.1 | 61 ± 8.8 | 43 | <0.001 | NS | *** | *** | *** | *** | NS |
| Audio-visual synesthesia | % score | 1.9 ± 1.9 | 4.2 ± 3.4 | 62 ± 6.7 | 62 ± 8.2 | 48 | <0.001 | NS | *** | *** | *** | *** | NS |
| Changed meaning of percepts | % score | 2.9 ± 2.9 | 6.7 ± 3.7 | 34 ± 5.9 | 38 ± 6.2 | 25 | <0.001 | NS | *** | *** | *** | *** | NS |

*P<0.05, **P<0.01, ***P<0.001; NS, not significant; N=24

**Table S3. Mean values and statistics for the acute subjective effects on the Mystical Experience Questionnaire (MEQ)**

| | | Placebo mean±SEM | MDMA mean±SEM | LSD mean±SEM | LSD+MDMA mean±SEM | $F_{3,69}$ | P= | Pla - MDMA | Pla - LSD | Pla - MDMA + LSD | MDMA - LSD | MDMA - MDMA + LSD | LSD - MDMA + LSD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mystical Experiences Questionnaire (MEQ30) | | | | | | | | | | | | | |
| Mystical | % score | 0.8 ± 0.8 | 8.3 ± 3.9 | 43 ± 5.2 | 42 ± 5.6 | 34 | <0.001 | NS | *** | *** | *** | *** | NS |
| Positive mood | % score | 2.2 ± 2.2 | 32 ± 4.9 | 57 ± 5.1 | 57 ± 4.8 | 47 | <0.001 | *** | *** | *** | *** | *** | NS |
| Transcendence of time/space | % score | 1.9 ± 1.9 | 10 ± 3.3 | 59 ± 5.0 | 54 ± 4.6 | 87 | <0.001 | NS | *** | *** | *** | *** | NS |
| Ineffability | % score | 3.3 ± 3.3 | 21 ± 5.5 | 77 ± 5.1 | 73 ± 5.7 | 76 | <0.001 | * | *** | *** | *** | *** | NS |
| MEQ30 total score | % score | 1.6 ± 1.6 | 15 ± 3.6 | 53 ± 4.5 | 51 ± 4.5 | 66 | <0.001 | * | *** | *** | *** | *** | NS |
| Nadir effects | % score | 0.6 ± 0.6 | 3.6 ± 1.2 | 22 ± 3.3 | 19 ± 4.3 | 20 | <0.001 | NS | *** | *** | *** | *** | NS |
| Aesthetic Experience | % score | 1.5 ± 1.5 | 12 ± 2.9 | 58 ± 5.5 | 52 ± 5.3 | 73 | <0.001 | NS | *** | *** | *** | *** | NS |
| Connectedness | % score | 2.2 ± 2.2 | 27 ± 5.2 | 55 ± 6.0 | 56 ± 5.1 | 40 | <0.001 | *** | *** | *** | *** | *** | NS |
| Closeness with guide | % score | 2.5 ± 2.5 | 33 ± 7.0 | 39 ± 7.3 | 43 ± 6.9 | 11 | <0.001 | *** | *** | *** | NS | NS | NS |
| Distressing Experience | % score | 0.3 ± 0.3 | 2.8 ± 1.2 | 21 ± 4.4 | 18 ± 5.1 | 13 | <0.001 | NS | *** | ** | *** | ** | NS |
| Mystical Experiences Questionnaire (MEQ43) | | | | | | | | | | | | | |
| Internal unity | % score | 0.8 ± 0.8 | 9.2 ± 3.9 | 44 ± 5.7 | 44 ± 5.8 | 32 | <0.001 | NS | *** | *** | *** | *** | NS |
| External unity | % score | 1.1 ± 1.1 | 7.5 ± 3.3 | 43 ± 5.3 | 40 ± 6.0 | 33 | <0.001 | NS | *** | *** | *** | *** | NS |
| Sacredness | % score | 1.3 ± 1.3 | 9.2 ± 3.9 | 43 ± 5.1 | 38 ± 5.9 | 29 | <0.001 | NS | *** | *** | *** | *** | NS |
| Noetic quality | % score | 0.6 ± 0.6 | 10 ± 3.9 | 48 ± 5.9 | 49 ± 6.6 | 35 | <0.001 | NS | *** | *** | *** | *** | NS |
| Deeply felt positive mood | % score | 1.8 ± 1.8 | 34 ± 5.2 | 54 ± 5.9 | 59 ± 5.2 | 41 | <0.001 | *** | *** | *** | ** | *** | NS |
| Transcendence of time/space | % score | 2.1 ± 2.1 | 9.3 ± 3.3 | 59 ± 5.1 | 53 ± 4.9 | 78 | <0.001 | NS | *** | *** | *** | *** | NS |
| Ineffability | % score | 2.3 ± 1.3 | 15 ± 4.1 | 59 ± 4.5 | 59 ± 5.5 | 78 | <0.001 | NS | *** | *** | *** | *** | NS |

*P<0.05, **P<0.01, ***P<0.001; NS, not significant; N=24

**Table S4. Mean values and statistics for the acute subjective effects on the Adjective Mood Rating Scale (AMRS)**

| | | Placebo mean±SEM | MDMA mean±SEM | LSD mean±SEM | LSD+MDMA mean±SEM | $F_{3,69}$ | P= | Pla - MDMA | Pla - LSD | Pla - MDMA + LSD | MDMA - LSD | MDMA - MDMA + LSD | LSD - MDMA + LSD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adjective Mood Rating Scale (AMRS, score) | | | | | | | | | | | | | |
| General well-being | $\Delta E_{max}$ | 1.1 ± 0.6 | 3.6 ± 1.1 | 4.9 ± 1.0 | 4.4 ± 0.9 | 3.8 | 0.014 | NS | * | * | NS | NS | NS |
| Emotional excitation | $\Delta E_{max}$ | -1.7 ± 0.6 | 0.3 ± 0.7 | 5.3 ± 1.0 | 4.5 ± 1.1 | 20 | <0.001 | NS | *** | *** | *** | ** | NS |
| Extraversion | $\Delta E_{max}$ | 0.5 ± 0.3 | 2.3 ± 0.5 | 1.4 ± 0.4 | 1.6 ± 0.6 | 2.5 | 0.071 | * | NS | NS | NS | NS | NS |
| Introversion | $\Delta E_{max}$ | 0.1 ± 0.3 | 1.9 ± 0.3 | 4.8 ± 0.6 | 5.1 ± 0.5 | 33 | <0.001 | * | *** | *** | *** | *** | NS |
| Anxiety | $\Delta E_{max}$ | -0.3 ± 0.2 | 0 ± 0.3 | 1.0 ± 0.3 | 1.1 ± 0.3 | 7.7 | <0.001 | NS | ** | ** | * | * | NS |
| Depression | $\Delta E_{max}$ | -0.3 ± 0.1 | 0.6 ± 0.3 | 1.6 ± 0.4 | 1.5 ± 0.3 | 13 | <0.001 | NS | *** | *** | * | * | NS |
| Activity/Performance | $\Delta E_{max}$ | 2.0 ± 0.7 | 1.9 ± 0.8 | 3.2 ± 1.1 | 2.0 ± 1.0 | 0.6 | NS | - | - | - | - | - | - |
| Inactivity | $\Delta E_{max}$ | 1.8 ± 0.9 | 6.7 ± 0.9 | 9.5 ± 1.2 | 9.8 ± 1.3 | 15 | <0.001 | ** | *** | *** | NS | * | NS |

*P<0.05, **P<0.01, ***P<0.001; NS, not significant; $\Delta E_{max}$, maximal effect difference from baseline; $\Delta E_{min}$, minimal effect difference from baseline; N=24

**Table S5. Parameters characterizing the subjective drug effect-time curves of LSD, MDMA and LSD+MDMA**

| | MDMA | LSD | LSD+MDMA | $F_{2,46}$ | P= |
|---|---|---|---|---|---|
| Time to onset (h) | 0.5 ± 0.1<br>(0.1 - 1.3) | 0.4 ± 0.1<br>(0.1 - 1.1) | 0.4 ± 0.1<br>(0.1 - 1.1) | 2.2 | 0.117 |
| Time to offset (h) | 4.9 ± 0.4<br>(1.0 - 11) | 8.9 ± 0.4***<br>(5.7 - 12) | 10 ± 0.8***<br>(5.7 - 21) | 46 | <0.001 |
| Time to maximal effect (h) | 1.9 ± 0.1<br>(1.0 - 3.0) | 2.2 ± 0.1<br>(1.0 - 3.5) | 2.3 ± 0.3<br>(0.5 - 7.0) | 1.4 | 0.264 |
| Effect duration (h) | 4.3 ± 0.4<br>(0.7 - 10) | 8.4 ± 0.4***<br>(5.1 - 11) | 9.9 ± 0.8***#<br>(5.1 - 21) | 49 | <0.001 |
| Maximal effect (%) | 64 ± 5.6<br>(16 - 100) | 90 ± 3.1***<br>(41 - 100) | 93 ± 2.6***<br>(47 - 100) | 24 | <0.001 |
| AUEC | 182 ± 28<br>(16 - 635) | 494 ± 33***<br>(115 - 786) | 575 ± 46***<br>(162 - 1121) | 74 | <0.001 |

Parameters are for "any drug effects". The threshold to determine times to onset and offset was set individually at 10% of the individual, maximal response. Values are mean ± SEM (range). *p<0.05, **p<0.01, ***p<0.001 compared with 100 mg of MDMA; #P<0.05 compared with 100 µg LSD ; AUEC, area under the effect curve; N=24

**Table S6. Acute and subacute adverse drug effects**

| | Placebo | | | MDMA | | | LSD | | | LSD+MDMA | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0h | 0-12h | 12-24h | 0h | 0-12h | 12-24h | 0h | 0-12h | 12-24h | 0h | 0-12h | 12-24h |
| Tiredness | 12 | 17 | 11 | 13 | 19 | 18 | 13 | 19 | 19 | 12 | 19 | 18 |
| Headache | 2 | 11 | 9 | 4 | 16 | 15 | 0 | 17 | 13 | 0 | 16 | 13 |
| Lack of energy | 3 | 3 | 4 | 1 | 12 | 7 | 1 | 12 | 10 | 1 | 15 | 9 |
| Loss of appetite | 1 | 1 | 0 | 2 | 13 | 3 | 1 | 12 | 4 | 0 | 16 | 12 |
| Dry mouth | 4 | 3 | 1 | 1 | 12 | 0 | 1 | 17 | 5 | 0 | 17 | 6 |
| Lack of concentration | 0 | 2 | 1 | 0 | 16 | 4 | 0 | 6 | 5 | 0 | 16 | 8 |
| Dullness | 1 | 2 | 2 | 1 | 7 | 7 | 1 | 9 | 8 | 2 | 12 | 8 |
| Nausea | 0 | 4 | 1 | 0 | 14 | 2 | 0 | 7 | 2 | 0 | 11 | 3 |
| Brooding | 2 | 1 | 1 | 1 | 11 | 5 | 3 | 4 | 3 | 1 | 11 | 7 |
| Rapid exhaustibility | 0 | 1 | 0 | 1 | 9 | 3 | 0 | 5 | 4 | 0 | 10 | 6 |
| Teeth grinding, jaw rigidity | 0 | 1 | 0 | 0 | 9 | 1 | 0 | 11 | 0 | 0 | 14 | 2 |
| Trembling | 0 | 1 | 0 | 0 | 15 | 1 | 0 | 5 | 0 | 0 | 14 | 1 |
| Inner restlessness | 2 | 2 | 0 | 1 | 12 | 2 | 1 | 5 | 0 | 2 | 11 | 2 |
| Feeling of weakness | 1 | 1 | 0 | 0 | 11 | 4 | 0 | 3 | 1 | 2 | 8 | 5 |
| Restlessness in legs | 0 | 2 | 0 | 0 | 9 | 1 | 0 | 6 | 1 | 0 | 12 | 2 |
| Inner tension | 1 | 2 | 0 | 1 | 14 | 2 | 3 | 2 | 0 | 1 | 10 | 2 |
| Excessive perspiration | 1 | 1 | 1 | 0 | 7 | 3 | 0 | 9 | 1 | 0 | 7 | 2 |
| Heart palpitations | 0 | 2 | 0 | 0 | 9 | 0 | 0 | 9 | 0 | 0 | 10 | 0 |
| Frequent urination | 1 | 5 | 0 | 0 | 9 | 2 | 1 | 4 | 1 | 0 | 7 | 1 |
| Hypersensitivity to certain odors | 0 | 0 | 0 | 0 | 9 | 2 | 0 | 2 | 1 | 0 | 6 | 7 |

Data indicate number of subjects reporting an effect among a total of 24 subjects.

**Table S7.** Pharmacokinetic parameters of the metabolites based on non-compartmental analyses [geometric mean (95% CI), range], N=24.

| | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) | $AUC_{24}$ (ng·h/mL) | $AUC_{\infty}$ (ng·h/mL) | CL/F (L/h) | $V_z$/F (L) |
|---|---|---|---|---|---|---|---|
| **O-H-LSD** | | | | | | | |
| LSD+Placebo administration | 0.1 (0.1-0.2)<br>0.01-0.2 | 5.3 (4.8-5.9)<br>3.5-8.0 | 8.7 (7.6-9.9)<br>5.6-29 | 1.8 (1.6-2.1)<br>0.8-3.5 | 2.4 (2.0-2.7)<br>0.9-5.1 | 43 (36-50)<br>20-106 | 533 (466-610)<br>341-1184 |
| LSD+MDMA administration | 0.2 (0.1-0.2)<br>0.1-0.3 | 5.4 (4.7-6.2)<br>3.0-10 | 10 (8.9-12)<br>5.2-28 | 2.5 (2.3-2.7)<br>1.6-4.1 | 3.3 (3.0-3.7)<br>1.9-6.5 | 30 (27-34)<br>15-52 | 450 (393-514)<br>246-796 |
| **MDA** | | | | | | | |
| MDMA+Placebo administration | *11 (9.8-13)<br>7.0-19 | *8.0 (7.3-8.8)<br>5.0-12 | **14 (12-16)<br>8.6-22 | *183 (160-208)<br>114-337 | **287 (248-333)<br>165-559 | **348 (301-403)<br>179-607 | **7057 (6090-8177)<br>3841-12670 |
| LSD+MDMA administration | 11 (9.8-13)<br>4.7-18 | 8.8 (7.9-9.7)<br>4.0-12 | *13 (11-14)<br>8.7-34 | 181 (159-206)<br>78-341 | *275 (232-324)<br>109-950 | *364 (308-430)<br>105-917 | *6700 (5841-7684)<br>4689-14599 |
| **HMMA** | | | | | | | |
| MDMA+Placebo administration | 142 (116-175)<br>33-282 | 2.8 (2.3-3.3)<br>1.5-6.0 | *14 (12-16)<br>10-35 | *1740 (1435-2110)<br>437-3038 | *2482 (2063-2985)<br>655-4293 | *40 (33-48)<br>23-153 | *805 (649-998)<br>404-3407 |
| LSD+MDMA administration | 132 (110-159)<br>39-252 | 2.6 (2.3-3.0)<br>1.5-5.0 | 14 (13-15)<br>7.8-25 | 1663 (1415-1955)<br>564-2810 | 2375 (2049-2753)<br>789-4006 | 42 (36-49)<br>25-127 | 839 (694-1014)<br>402-2377 |

AUC, area under the plasma concentration-time curve; $AUC_{\infty}$, AUC from time zero to infinity; $AUC_{24}$, from time 0-24; CL/F apparent total clearance; $C_{max}$, maximum observed plasma concentration; $T_{1/2}$, plasma half-life; $T_{max}$, time to reach $C_{max}$; 95%CI, 95% confidence interval; $V_z$/F, apparent volume of distribution; *N=23; **N=22

**Table S8. Drug dose identification during the session (2.5h after drug administration), after the session (24h), and after study completion**

| | Placebo | | | MDMA | | | LSD | | | LSD+MDMA | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | during Session | after Session | after Study | during Session | after Session | after Study | during Session | after Session | after Study | during Session | after Session | after Study |
| correctly identified | 96% | 96% | 100% | 83% | 96% | 100% | 71% | 58% | 75% | 37.5% | 46% | 75% |
| missclassified as placebo | | | | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% |
| missclassified as 100 mg MDMA | 4% | 4% | 0% | | | | 4% | 4% | 0% | 12.5% | 8% | 0% |
| missclassified as 100 µg LSD | 0% | 0% | 0% | 4% | 0% | 0% | | | | 50% | 46% | 25% |
| missclassified as 100 mg MDMA + 100 µg LSD | 0% | 0% | 0% | 13% | 4% | 0% | 25% | 38% | 25% | | | |

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## 2.2. Safety pharmacology of acute psilocybin administration in healthy participants

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ABSTRACT

Psilocybin is being studied for its therapeutic potential in various mental health disorders, such as depression, anxiety, and addiction. Initial studies suggested that psilocybin is generally safe when used under controlled conditions, but more research is needed to better understand its safety profile. We report safety pharmacology data from a pooled analysis of three randomized crossover studies that included 85 healthy participants and 113 single-dose administrations of psilocybin. Single oral doses included 15 mg, 20 mg, 25 mg, and 30 mg psilocybin dihydrate. We investigated subjective effects, blood pressure, heart rate, body temperature, acute and subacute adverse effects, reports of flashbacks, and liver and kidney function before and after the studies. The 20, 25, and 30 mg doses of psilocybin produced stronger effects than the 15 mg dose. Psilocybin at all doses induced higher "good drug effects" than "bad drug effects." Only the 25 and 30 mg doses increased anxiety. Psilocybin elevated autonomic effects only moderately. Tachycardia (>100 beats/min) was observed with 7% of all psilocybin administrations. Body temperature >38° was reached in 7%, 9%, 17%, and 32% of the participants with the 15, 20, 25, and 30 mg doses, respectively. Kidney and liver function parameters were unaltered at the end of the study. Five participants (6%) reported transient flashback phenomena. No serious adverse reactions occurred. These findings suggest that a single administration of psilocybin is safe with regard to acute psychological and physical harm in healthy participants in a controlled research setting.

## 1. Introduction

Psilocybin is a classic psychedelic that is used recreationally and has been investigated clinically as a medication for patients with depression (Carhart-Harris et al., 2021; Carhart-Harris et al., 2016; Davis et al., 2021; Goodwin et al., 2022; Griffiths et al., 2016; Raison et al., 2023; Ross et al., 2016; von Rotz et al., 2023), anxiety (Griffiths et al., 2016; Ross et al., 2016), addiction (Bogenschutz et al., 2022; Garcia-Romeu et al., 2014; Johnson et al., 2016), cluster headache (Davenport, 2016), and migraine (Schindler et al., 2021). Additional indications are under investigation.

The future medical use of psilocybin will depend on its safety and efficacy. Initial studies suggested that psilocybin is generally safe when used under controlled conditions. Although various recent Phase 2 clinical trials showed mostly mild and transient adverse effects, more information on clinical safety is needed (Dodd et al., 2022; Rossi et al., 2022). Safety concerns include challenging experiences (i.e., "bad trips"), acute anxiety, flashbacks, and hallucinogen perception disorder (HPPD). Cardiovascular stimulation has been reported in both healthy participants and patients (Davis et al., 2021; Griffiths et al., 2016; Griffiths et al., 2011; Griffiths et al., 2006; Hasler et al., 2004; Ross et al., 2016; von Rotz et al., 2023), but studies in patients do not typically allow frequent and well-standardized assessments of vital signs. The present analysis provided additional highly controlled data on the safety pharmacology of single-dose administrations of psilocybin.

The aim of the present study was to describe acute subjective, autonomic, and adverse effects during the acute and subacute psilocybin response and blood laboratory markers of kidney and liver function at both the start and end of the study. These data were collected from a series of clinical Phase 1 trials in healthy participants that were conducted in the same laboratory and used the same highly standardized data recording methods (Becker et al., 2022; Holze et al., 2022b; Ley

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et al., 2023). The studies used a representative dose range of psilocybin from moderate-low (15 mg) to moderate (20 mg) to moderate-high (25 mg) to high (30 mg) experiential doses as used in psilocybin-assisted psychotherapy (Bogenschutz et al., 2022; Carhart-Harris et al., 2021; Davis et al., 2021; Goodwin et al., 2022) and in people with no or minimal prior psilocybin use, which is also likely the case when psilocybin is used in patients.

## 2. Experimental procedures

### 2.1. Study design

This was a pooled analysis of three double-blind, placebo-controlled, random-order, crossover studies in healthy participants. All trials were previously published in detail (Becker et al., 2022; Holze et al., 2022b; Ley et al., 2023). All studies were conducted at the University Hospital Basel and included a total of 85 participants who were all psychiatrically and physically screened and healthy. The aim of the present analysis was to assess the safety pharmacology of single-dose administrations of psilocybin in healthy participants with no regular psychedelic use and no or minimal prior use. The first study (Study 1) (Becker et al., 2022) included 24 healthy participants who received two single administrations of 25 mg psilocybin with placebo or escitalopram pretreatment. Only the administration of placebo as a pretreatment was used in the present analysis. The second study (Study 2) (Holze et al., 2022b) included 28 healthy participants who received two administrations of psilocybin (15 and 30 mg), two administrations of LSD, and placebo. Study 3 (Ley et al., 2023) included 33 healthy participants who received a single dose each of LSD, mescaline, 20 mg psilocybin, and placebo. Only the psilocybin alone and placebo conditions were used for the present analysis. Overall, all three studies encompassed a total of 113 psilocybin administrations. In all studies, the washout periods between single-dose administrations were at least 10 days to reduce possible carryover effects. The studies were all registered at ClinicalTrials.gov (Study 1: NCT03912974; Study 2: NCT03604744; Study 3: NCT04227756) and approved by the local ethics committee. The studies were conducted in accordance with the Declaration of Helsinki. Psilocybin administration in healthy participants was authorized by the Swiss Federal Office for Public Health (BAG), Bern, Switzerland. Informed consent was obtained from all participants who were included in the studies. All participants were paid for their participation.

### 2.2. Participants

The characteristics of the study participants are shown in Table 1. A total of 85 healthy participants (43 men, 42 women), 25–55 years old (mean ± SD = 32 ± 8 years; range: 25–55 years), were mostly recruited from the University of Basel campus and included in the studies. The mean ± SD (range) ages were 34 ± 10 (25–55) years, 35 ± 9 (25–52) years, and 29 ± 4 (25–44) years for Study 1, Study 2, and Study 3, respectively. The mean ± SD body weight was 71 ± 11 kg (range: 50–112 kg). Thirty-three participants received a single dose of psilocybin only, and 52 participants received two single-dose administrations of psilocybin (28 at two different doses, 15 and 30 mg; 24 at the same dose, 25 mg; only the session with placebo as the pretreatment was used). Exclusion criteria were reported in detail elsewhere (Becker et al., 2022; Holze et al., 2022b; Ley et al., 2023) and included a history of psychiatric disorders, physical illness, a lifetime history of using illicit drugs more than 10 times (with the exception of past cannabis use) for Studies 1 and 2, a lifetime history of using psychedelic drugs more than 20 times for Study 3, illicit drug use within the last 2 months, and illicit drug use during the study, determined by urine tests that were conducted before the test sessions. Fifty-four participants (64%) had prior drug experience (1–100 times), of which 41 participants (48%) had previously used a psychedelic (1–10 times). Further substance experiences included methylenedioxymethamphetamine (MDMA; 42 participants [49%], 1–30 times), amphetamine (23 participants [27%], 1–50 times), cocaine (18 participants [21%], 1–100 times), methylphenidate (four participants [5%], 1–2 times), 4-Bromo-2,5-dimethoxyphenethylamine (2C–B; three participants [4%], 1–2 times), ketamine (five participants [6%], 1–5 times), and nitrous oxide (11 participants [13%], 1–20 times).

**Table 1**
Demographics of study participants.

| Condition | | 2. And 3. Study | 1. Study | 2. Study | 3. Study |
|---|---|---|---|---|---|
| | | Placebo | Psilocybin | Psilocybin | Psilocybin |
| Dose | mg | 0 | 25 | 15 and 30 | 20 |
| Administrations | N | 60 | 24 | 28 | 33 |
| Body weight | kg | 71 ± 11 | 70 ± 13 | 72 ± 12 | 71 ± 9.7 |
| Range body weight | kg | 52–104 | 50–112 | 55–104 | 52–90 |
| BMI | kg/m2 | 23 ± 2 | 24 ± 2 | 23 ± 3 | 23 ± 2 |
| Participant age | years | 32 ± 8 | 34 ± 10 | 35 ± 9 | 29 ± 4 |
| Range participant age | years | 25–52 | 25–55 | 25–52 | 25–44 |
| Previous psychedelic use | N (%) | 34 (57) | 7 (29) | 14 (50) | 20 (61) |
| Range previous psychedelic use | | 1–10 | 1–5 | 1–6 | 1–10 |

N, number of subjects; data are mean ± SD unless indicated otherwise.

### 2.3. Study drug

Psilocybin (99.7% purity, determined by high-performance liquid chromatography; ReseaChem GmbH, Burgdorf, Switzerland) was administered as opaque capsules that contained 5 mg psilocybin dihydrate and an exact analytically confirmed psilocybin content of 4.61 ± 0.09 mg (mean ± SD, $n$ = 10 samples). Placebo consisted of identical opaque capsules that were filled with mannitol. All drug products were produced according to good manufacturing practice (GMP) by a licensed GMP facility (Apotheke Dr. Hysek, Biel, Switzerland). Stability of the psilocybin formulation was confirmed for the study durations. In Study 1, the participants knew they would receive psilocybin. Studies 2 and 3 were double-blind and included inactive placebo and other psychoactive substances. At the end of the study, blinding was assessed.

### 2.4. Study procedures

All studies included a screening visit, two to five test sessions (each separated by at least 10 days), and an end-of-study visit. The sessions were conducted in a calm standard hospital room that was equipped with a hospital bed for the participant and a desk and chair for the investigator. The room had an adjoining balcony that participants were allowed to access after peak effects had subsided in company of the investigator. Only one research participant and one or two investigators were present during each test session. Participants were allowed to bring their own music and occupy their time for when effects had subsided or for days in which placebo was administered (e.g., book, laptop, games, etc.). Blindfolds were provided upon request. The test sessions began at approximately 8:00 a.m. Individual emotional states were assessed before drug administration to exclude risk factors for emotional disturbances. This procedure consisted of several questions, including "Did anything unusual happen lately?," "Do you feel stressed for any reason (personal or professional)?," "Did you have any sleep disturbances lately?," "Do you have any expectations or fear regarding today's session?," and "Are you feeling ready to participate today?" If any of these questions were answered with "yes" (or "no" for the last question), then the reason was discussed. If the investigator had any doubt, then the session was rescheduled to ensure that none of the participants were in an unfavorable state of mind when taking psilocybin. The participants then underwent baseline measurements, including vital signs.

Psilocybin or placebo was administered at approximately 9:00 a.m. The participants were never alone during the next 7–12 h after drug administration, and an investigator was in a room next to the participant for up to 24 h (except for Study 1, in which participants were sent home after 7 h, accompanied by a friend or family member).

### 2.5. Pharmacodynamic measures

Visual Analog Scales (VASs) were repeatedly used to assess subjective effects over time (Hysek et al., 2014). The VASs included "any drug effect," "good drug effect," "bad drug effect," "anxiety," and "ego dissolution". The VASs were presented as 100-mm horizontal lines (0–100%), marked from "not at all" on the left to "extremely" on the right. The VASs were applied before and 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, and 24 h after psilocybin or placebo administration. In Study 1, the 3.5 h time point and all time points after 7 h were not assessed. Severe anxiety was defined as > 75% on the "anxiety" VAS. The 5 Dimensions of Altered States of Consciousness (5D-ASC) scale (Dittrich, 1998; Studerus et al., 2010) was administered 24 h (or 7 h in Study 1) after drug administration to retrospectively rate peak drug effects. The "Oceanic Boundlessness" (OB) and "Anxious Ego-Dissolution" (AED) dimensions are reported herein and serve to describe overall rather positive and negative alterations of mind, respectively (Becker et al., 2022; Holze et al., 2022b; Ley et al., 2023).

Blood pressure, heart rate, and body temperature were assessed repeatedly at the same time points when the VASs were administered. Systolic and diastolic blood pressure and heart rate were measured using an automatic oscillometric device (OMRON Healthcare Europe NA, Hoofddorp, Netherlands). The measurements were performed in duplicate at an interval of 1 min and after a resting time of at least 10 min. Averages were used for further analysis. Core (tympanic) temperature was measured using a Braun ThermoScan ear thermometer (Welch Allyn, Skaneateles Falls, NY, USA). Criteria for grouping participants into proportions with a certain degree of autonomic stimulation were diastolic blood pressure > 90 and > 100 mmHg and systolic blood pressure > 140, > 160, and > 180 mmHg. Tachycardia was defined as > 100 beats/min. Hyperthermia and hyperpyrexia were defined as tympanic body temperature > 38°C and 40°C, respectively.

Acute and subacute adverse effects were assessed using the List of Complaints (Hysek et al., 2012a, 2012b; Zerssen, 1976). The scale consists of 66 items, yielding a total adverse effects score (non-weighted sum of all items) that reliably measures physical and general discomfort. The List of Complaints was administered before and 12 h (7 h for Study 1; acute adverse effects) and 24 h (subacute adverse effects) after psilocybin or placebo administration. Subacute adverse effects were not recorded in Study 1. Additionally, participants were asked at the beginning of each study session and at the end of study visit to report any adverse events from 24 h after drug administration until the next study visit. Adverse events were evaluated with a study physician. In Study 1 (Becker et al., 2022), QT times were measured, and QTc times were calculated and compared 1 h before and 2.5 h after the administration of 25 mg psilocybin.

### 2.6. Blood sampling and end-of-study visit

Blood chemistry and blood cell count tests were performed at the screening visit at the start of the study and at the end-of-study visit, which were separated by 161 ± 85 days (mean ± SD). The end-of-study visit, including blood sampling, occurred at variable time intervals (28 ± 18 days) after the last substance administration. The analyses were performed using standard assays according to Good Laboratory Practice by the Laboratory Medicine Department of the hospital. The glomerular filtration rate was determined by the Cockcroft-Gault Equation using plasma creatinine concentrations, age, and sex of the participant. At the end-of-study visit, the participants were asked to retrospectively rate whether the experience was positive or negative, whether earlier experiences with substances had an influence on the psilocybin experience, and whether they considered taking psilocybin again and in what setting. The participants were also asked whether they experienced "flashbacks" or any other change in perception (e.g., alterations of spatial perception, color vision, or patterns) and how long they lasted. "Flashbacks" were defined as temporary reoccurrence of the altered state of consciousness. Persistent changes in perception would have led to further assessments of possible hallucinogen perception disorder. This was assessed in a structured manner only at the end-of-study visit; therefore, we only report "flashback" phenomena that occurred until the end-of-study visit. "Flashbacks" that occurred outside this time period were not assessed.

### 2.7. Statistical analyses

The statistical analyses were performed using R 4.2.1 software (RStudio, PBC, Boston, MA, USA) and Statistica 12 software (StatSoft, Tulsa, OK, USA). We conducted analyses of variance (ANOVAs) with dose as a factor, followed by Tukey *post hoc* tests. Fisher's exact tests were used to compare proportions. To assess order effects of the substance administration, order (psilocybin-first vs. psilocybin-second) was incorporated as an additional factor in the ANOVAs. Differences in kidney and liver function and blood cell counts between the screening and end-of-study visit measures were analyzed using paired *t*-tests. The level of significance was set to $p < 0.05$.

## 3. Results

### 3.1. Acute subjective effects of psilocybin

Characteristics of the study participants are shown in Table 1.

*Positive subjective effects.* All doses from 15 to 30 mg psilocybin increased "any drug effect" and "good drug effect" on the VAS and OB ratings on the 5D-ASC compared with placebo (Table 2). The 20, 25, and 30 mg doses induced greater increases in "any drug effects" and "good drug effects" compared with the lower 15 mg dose (Table 2). Ratings of subjective "good drug effects" that were higher than 50% of the scale maximum occurred in 79%, 91%, 88%, and 96% of the participants at the 15, 20, 25, and 30 mg doses of psilocybin, respectively (Table 2). Mean ratings of OB were 24%, 31%, 41%, and 37% with 15, 20, 25, and 30 mg psilocybin, respectively. Ratings of OB that were higher than 50% of the scale maximum occurred in 14%, 27%, 42%, and 25% of the participants at the 15, 20, 25, and 30 mg doses of psilocybin, respectively (Table 2).

*Negative subjective effects.* "Bad drug effects" on the VAS and AED ratings on the 5D-ASC increased with all doses from 15 to 30 mg compared with placebo (Table 2). Subjective "bad drug effects" with a rating higher than 50% of the scale maximum were reported by 14%, 18%, 42%, and 32% of the participants at the 15, 20, 25, and 30 mg doses, respectively (Table 2). Ratings of "anxiety" on the VAS moderately increased at the 25 and 30 mg doses but not at 15 or 20 mg dose compared with placebo (Table 2). Ratings of "anxiety" that were higher than 50% of the scale maximum were reached in 7%, 6%, 17%, and 11% of the participants at the 15, 20, 25, and 30 mg doses, respectively (Table 2). Mean AED ratings were 9%, 10%, 25%, and 17% at the 15, 20, 25, and 30 mg doses, respectively. Ratings of AED that were higher than 50% of the scale maximum occurred in 4%, 0%, 13%, and 7% of the participants at the 15, 20, 25, and 30 mg doses of psilocybin, respectively (Table 2).

Mean ratings of "ego dissolution" on the VAS increased dose-dependently with higher doses (Table 2). Ratings of more than 50% of the scale maximum for the VAS "ego dissolution" were reached in 46%, 67%, 75%, and 89% of the participants at 15, 20, 25, and 30 mg psilocybin, respectively (Table 2). Effect onset and time to maximal effect of the subjective "any drug effect" (mean ± SD) were 0.6 ± 0.4 h and 2.1

**Table 2**
Subjective and adverse effects of psilocybin in healthy subjects.

| Psilocybin Dose | Placebo (N = 60) | 15 mg (N = 28) | 20 mg (N = 33) | 25 mg (N = 24) | 30 mg (N = 28) | *F4,168* | *P* = |
|---|---|---|---|---|---|---|---|
| **Visual Analog Scale (VAS)** | | | | | | | |
| Any drug effect | 2.4 ± 5.5 | 68 ± 26*** | 86 ± 17***### | 86 ± 26***## | 88 ± 17***### | 205.35 | <0.001*** |
| >25, N (%) | 1 (2) | 26 (93)*** | 33 (100)*** | 22 (92)*** | 28 (100)*** | | |
| >50, N (%) | 0 (0) | 20 (71)*** | 31 (94)***# | 22 (92)*** | 27 (96)***# | | |
| >75, N (%) | 0 (0) | 10 (36)*** | 26 (79)***### | 21 (88)***### | 21 (75)***## | | |
| 100, N (%) | 0 (0) | 6 (21)*** | 13 (39)*** | 10 (42)*** | 16 (57)***# | | |
| Good drug effect | 1.4 ± 3.9 | 68 ± 25*** | 86 ± 18***## | 80 ± 30*** | 84 ± 18***# | 177.31 | <0.001*** |
| >25, N (%) | 1 (2) | 26 (93)*** | 33 (100)*** | 21 (88)*** | 28 (100)*** | | |
| >50, N (%) | 0 (0) | 22 (79)*** | 30 (91)*** | 21 (88)*** | 27 (96)*** | | |
| >75, N (%) | 0 (0) | 10 (36)*** | 26 (79)***### | 18 (75)***## | 19 (68)***# | | |
| Bad drug effect | 0.0 ± 0.2 | 16 ± 27* | 22 ± 30*** | 37 ± 35***# | 27 ± 32*** | 12.37 | <0.001*** |
| >25, N (%) | 0 (0) | 4 (14)** | 10 (30)*** | 14 (58)***## | 10 (36)*** | | |
| >50, N (%) | 0 (0) | 4 (14)** | 6 (18)** | 10 (42)***# | 9 (32)*** | | |
| >75, N (%) | 0 (0) | 3 (11)* | 2 (6) | 4 (17)** | 2 (7) | | |
| Anxiety | 0.0 ± 0.0 | 6.4 ± 17 | 6.1 ± 16 | 19 ± 29*** | 17 ± 27*** | 6.94 | <0.001*** |
| >25, N (%) | 0 (0) | 2 (7) | 4 (12)* | 5 (21)** | 6 (21)*** | | |
| >50, N (%) | 0 (0) | 2 (7) | 2 (6) | 4 (17)** | 3 (11)* | | |
| >75, N (%) | 0 (0) | 1 (4) | 0 (0) | 2 (8) | 2 (7) | | |
| Ego Dissolution | 0.3 ± 1.4 | 47 ± 37*** | 59 ± 35*** | 65 ± 38*** | 78 ± 30***### | 50.25 | <0.001*** |
| >25, N (%) | 0 (0) | 17 (61)*** | 27 (82)*** | 19 (79)*** | 26 (93)***## | | |
| >50, N (%) | 0 (0) | 13 (46)*** | 22 (67)*** | 18 (75)***# | 25 (89)***## | | |
| >75, N (%) | 0 (0) | 8 (29)*** | 14 (42)*** | 15 (63)***# | 17 (61)***# | | |
| **5-Dimensions of Altered States of Consciousness (5D-ASC) scale** | | | | | | | |
| Oceanic Boundlessness (OB)(%) | 0.6 ± 2.4 | 24 ± 21*** | 31 ± 23*** | 41 ± 29***# | 37 ± 20*** | 32.58 | <0.001*** |
| >25, N (%) | 0 (0) | 10 (36)*** | 18 (55)*** | 14 (58)*** | 19 (68)***# | | |
| >50, N (%) | 0 (0) | 4 (14)** | 9 (27)*** | 10 (42)***# | 7 (25)*** | | |
| >75, N (%) | 0 (0) | 1 (4) | 1 (3) | 3 (13)* | 2 (7) | | |
| Anxious Ego-Dissolution (AED)(%) | 0.0 ± 0.0 | 9.3 ± 15** | 10 ± 11*** | 25 ± 20***###+++ | 17 ± 15*** | 21.29 | <0.001*** |
| >25, N (%) | 0 (0) | 2 (7) | 4 (12)* | 12 (50)***##++ | 7 (25)*** | | |
| >50, N (%) | 0 (0) | 1 (4) | 0 (0) | 3 (13)* | 2 (7) | | |
| >75, N (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | |
| **List of Complaints (LC) total score** | | | | | | | |
| Before, N | 0.8 ± 1.3 | 1.0 ± 1.7 | 1.1 ± 2.1 | 1.5 ± 2.2 | 0.5 ± 1.2 | 1.29 | NS |
| Acute adverse effects, up to 12 h, N | 1.8 ± 2.5 | 8.9 ± 7.6*** | 11 ± 8.2*** | 13 ± 10*** | 13 ± 8.6*** | 19.05 | <0.001*** |
| Subacute adverse effects, up to 24 h, N | 1.7 ± 3.1 | 2.4 ± 2.6 | 4.0 ± 5.3* | | 4.1 ± 4.2* | 3.96α | 0.010* |
| **Parameters describing the effect over time curve (VAS any drug effect)** | | | | | | | |
| time to effect onset | mean + SD | 0.8 ± 0.3+†† | 0.5 ± 0.3# | 0.4 ± 0.3## | 0.7 ± 0.4+†† | 7.27β | <0.001*** |
| time to maximal effect | mean + SD | 2.1 ± 0.5 | 2.1 ± 1.0 | 1.9 ± 0.8 | 2.1 ± 0.8 | 2.54β | 0.064 |
| time to effect offset | mean + SD | 6.3 ± 2.1 | 5.3 ± 1.7 | 5.0 ± 1.5 | 7.2 ± 2.2 | 0.52β | 0.672 |
| effect duration | mean + SD | 5.6 ± 2.2 | 4.9 ± 1.7 | 5.1 ± 1.8 | 6.4 ± 2.3 | 1.34β | 0.269 |
| range duration | hours | 2.5–10 | 2.6–10 | 2.4–8.0 | 3.7–12 | | |
| <6h | N (%) | 20 (71) | 28 (88) | 15 (65) | 16 (57) | | |
| 6–7h | N (%) | 0 (0) | 1 (3) | 4 (17) | 2 (7) | | |
| 7–8h | N (%) | 3 (11) | 1 (3) | 4 (17) | 3 (11) | | |
| >8h | N (%) | 5 (18) | 2 (6) | 0 (0) | 7 (25) | | |
| **Psilocin plasma concentration** | | | | | | | |
| Cmax ng/mL | | 14 ± 3.4 | 18 ± 5.4# | 20 ± 5.4### | 25 ± 8.1###+++† | 21.5γ | <0.001*** |
| AUC∞ ng*h/mL | | 61 ± 15 | 88 ± 22### | 90 ± 37### | 121 ± 30###+++††† | 35.2γ | <0.001*** |

Values are Emax (maximal effects) shown as mean ± SD or N, number of subjects (%) or count of adverse events; SD, standart deviation; *P < 0.05, **P < 0.01, ***P < 0.001 compared to placebo, #P < 0.05, ##P < 0.01, ###P < 0.001 compared to 15 mg; +P < 0.05, ++P < 0.01, +++P < 0.001 compared to 20 mg; †P < 0.05, ††P < 0.01, †††P < 0.001 compared to 25 mg; α, F(3,145); β, F(3,66); γ, F(3,108).

± 0.8 h for all doses, respectively. The effect duration was 5.5 ± 2.1 h for all doses. Respective values for each dose are shown in Table 2. Values did not differ relevantly across the dose range tested. Subjective effects of psilocybin did not differ if psilocybin was administered first or after another treatment.

### 3.2. Acute effects of psilocybin on vital signs

Psilocybin produced significant acute and transient increases in blood pressure and body temperature. Clear dose dependence was not observed. Systolic blood pressure values > 140, > 160, and > 180 mmHg were observed in 50%, 6%, and 0% of all psilocybin administrations, respectively (Table 3). No severe hypertension (systolic blood pressure > 180 mmHg) was observed. Maximal diastolic and systolic blood pressure values among the 113 psilocybin administrations were 115 and 180 mmHg, respectively. A peak heart rate > 100 beats/min was reached in 7%, 3%, 4%, and 11% of the administrations of 15, 20, 25, and 30 mg psilocybin, respectively. Over all 113 psilocybin administrations, tachycardia (> 100 beats/min) was observed in 7%. The highest heart rate of any participant was 140 beats/min. Body temperature increased dose-dependently with values > 38 °C reached in 7%, 9%, 17%, and 32% of administrations of 15, 20, 25, and 30 mg psilocybin. Overall, psilocybin increased body temperature to > 38°C in 16% of all psilocybin administrations. The highest body temperature was 39.0°C. No hyperpyrexia (> 40°C) occurred (Table 3). Vital sign changes did not differ if psilocybin was administered first or after another treatment. Over all participants in Study 1 (Becker et al., 2022), psilocybin did not increase the QTc time 2.5 h after administration compared with the QTc time that was measured 1 h prior. The longest QTc interval that was observed in any participant was 481 ms 2.5 h after psilocybin administration.

### 3.3. Adverse effects of psilocybin

Psilocybin produced significant acute and subacute adverse effects on the List of Complaints compared with placebo (Table 2). Adverse

**Table 3**
Maximal effects of psilocybin on vital signs.

| Psilocybin dose | Placebo (N = 60) | 15 mg (N = 28) | 20 mg (N = 33) | 25 mg (N = 24) | 30 mg (N = 28) | *F4,168* | *P* = |
|---|---|---|---|---|---|---|---|
| Diastolic blood pressure (mean ± SD, mmHg) | 81 ± 7 | 89 ± 8*** | 89 ± 7 *** | 88 ± 7*** | 93 ± 8*** | 16.296 | <0.001*** |
| >90, N (%) | 4 (7) | 10 (36)** | 11 (33)** | 8 (33)** | 13 (46)*** | | |
| >100, N (%) | 0 (0) | 4 (14)** | 3 (9)* | 0 (0) | 5 (18)** | | |
| Max, mmHg | 95 | 111 | 104 | 100 | 115 | | |
| Systolic blood pressure (mean ± SD, mmHg) | 131 ± 10 | 140 ± 11** | 141 ± 13*** | 136 ± 11 | 146 ± 14***$ | 9.405 | <0.001*** |
| >140, N (%) | 8 (13) | 13 (46)** | 17 (52)*** | 8 (33) | 19 (68)***$ | | |
| >160, N (%) | 0 (0) | 1 (4) | 2 (6) | 1 (4) | 3 (11)* | | |
| >180, N (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | |
| Max, mmHg | 156 | 163 | 170 | 161 | 180 | | |
| Heart rate (mean ± SD, beats/min) | 74 ± 10 | 78 ± 11 | 79 ± 10 | 78 ± 12 | 82 ± 17 | 2.387 | NS |
| >80, N (%) | 15 (25) | 12 (43) | 14 (42) | 10 (42) | 12 (43) | | |
| >100, N (%) | 1 (2) | 2 (7) | 1 (3) | 1 (4) | 3 (11) | | |
| >120, N (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (4) | | |
| Max, beats/min | 108 | 104 | 114 | 108 | 140 | | |
| Body temperature (mean ± SD, °C) | 37.1 ± 0.3 | 37.6 ± 0.4*** | 37.6 ± 0.4*** | 37.6 ± 0.4*** | 37.9 ± 0.5***# | 24.253 | <0.001*** |
| >38, N (%) | 0 (0) | 2 (7) | 3 (9)* | 4 (17)** | 9 (32)***#+ | | |
| Max, °C | 37.8 | 38.7 | 39.0 | 38.5 | 38.8 | | |

Values are mean ± SD or N, number of subjects (%); SD, standard deviation; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with placebo, #$P < 0.05$ compared with 15 mg, +$P < 0.05$ compared with 20 mg, $P $< 0.05 compared with 25 mg. Proportions were compared using Fisher's exact test.

effects were comparable at the 15, 20, 25, and 30 mg doses and greater than with placebo (Table 2). Specific acute and subacute complaints are listed in Table 4. The most frequent acute adverse effects included fatigue, lack of concentration, headache, lethargy, vertigo, feeling of physical or emotional weakness, decreased appetite, nausea, feeling dull, and being easily exhausted (Table 4). The most frequent subacute adverse effects included tiredness, headache, lack of energy, neck pain, and feeling dull (Table 4). Acute anxiety on the List of Complaints was reported by 7%, 6%, 38%, and 21% of the participants at 15, 20, 25, and 30 mg psilocybin, respectively, and in one participant after placebo administration (Table 4). The number of adverse effects was unchanged if psilocybin was administered first or after another treatment. Five participants (6%) reported flashbacks after psilocybin. In four of the participants, flashbacks reportedly occurred once 30 ± 29 h (mean ± SD; range: 10–72 h) after psilocybin administration. One participant reported reoccurring visual flashbacks that were not disruptive or

**Table 4**
Acute and subacute advere effects of psilocybin on the List of Complaints.

| Psilocybin Dose | Acute adverse effects (up to 12 h) | | | | | Subacute adverse effects (up to 24 h) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo (N = 60) | 15 mg (N = 28) | 20 mg (N = 33) | 25 mg (N = 24) | 30 mg (N = 28) | Placebo (N = 60) | 15 mg (N = 28) | 20 mg (N = 33) | 30 mg (N = 28) |
| **N (%)** | | | | | | | | | |
| Fatigue | 37 (62) | 23 (82) | 28 (85)* | 18 (75) | 25 (89)* | 31 (52) | 18 (64) | 28 (85)** | 17 (61)+ |
| Lack of concentration | 0 (0) | 17 (61)*** | 19 (58)*** | 13 (54)*** | 15 (54)*** | 1 (2) | 1 (4) | 4 (12) | 3 (11) |
| Headache | 18 (30) | 14 (50) | 17 (52)* | 13 (54)* | 18 (64)** | 15 (25) | 10 (36) | 13 (39) | 14 (50)* |
| Lethargy | 4 (7) | 11 (39)*** | 13 (39)*** | 11 (46)*** | 16 (57)*** | 4 (7) | 3 (11) | 8 (24)* | 10 (36)** |
| Vertigo | 0 (0) | 9 (32)*** | 13 (39)*** | 9 (38)*** | 16 (57)*** | 0 (0) | 0 (0) | 0 (0) | 1 (4) |
| Feeling of weakness | 3 (5) | 10 (36)*** | 13 (39)*** | 10 (42)*** | 14 (50)*** | 1 (2) | 2 (7) | 2 (6) | 6 (21)** |
| Decreased appetite | 1 (2) | 7 (25)** | 11 (33)*** | 9 (38)*** | 18 (64) ***##+ | 1 (2) | 0 (0) | 1 (3) | 4 (14)* |
| Nausea | 1 (2) | 7 (25)** | 17 (52)***# | 11 (46)*** | 9 (32)*** | 1 (2) | 0 (0) | 2 (6) | 2 (7) |
| Feeling dull | 6 (10) | 12 (43)** | 13 (39)** | 4 (17) | 12 (43)** | 2 (3) | 2 (7) | 7 (21)** | 7 (25)** |
| Easily exhausted | 1 (2) | 8 (29)*** | 7 (21)** | 9 (38)*** | 15 (54)***+ | 1 (2) | 0 (0) | 1 (3) | 5 (18)* |
| Crying | 0 (0) | 4 (14)** | 8 (24)*** | 10 (42)***# | 11 (39)*** | 0 (0) | 0 (0) | 1 (3) | 0 (0) |
| Dry mouth | 1 (2) | 9 (32)*** | 8 (24)*** | 6 (25)** | 9 (32)*** | 1 (2) | 1 (4) | 0 (0) | 3 (11) |
| Chills | 2 (3) | 7 (25)** | 12 (36)*** | 5 (21)* | 7 (25)** | 1 (2) | 0 (0) | 2 (6) | 0 (0) |
| Dizziness | 0 (0) | 7 (25)*** | 8 (24)*** | 7 (29)*** | 9 (32)*** | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Tension | 1 (2) | 8 (29)*** | 11 (33)*** | 4 (17)* | 8 (29)*** | 1 (2) | 1 (4) | 1 (3) | 1 (4) |
| Uneasiness | 1 (2) | 4 (14)* | 7 (21)** | 9 (38)*** | 9 (32)*** | 2 (3) | 0 (0) | 2 (6) | 1 (4) |
| Hypersomnia | 3 (5) | 8 (29)** | 7 (21)* | 6 (25)* | 7 (25)* | 2 (3) | 5 (18)* | 5 (15) | 5 (18)* |
| Memory impairment | 0 (0) | 5 (18)** | 8 (24)*** | 6 (25)*** | 8 (29)*** | 0 (0) | 0 (0) | 1 (3) | 0 (0) |
| Micturition urgency | 1 (2) | 6 (21)** | 6 (18)** | 8 (33)*** | 6 (21)** | 4 (7) | 4 (14) | 2 (6) | 1 (4) |
| Obsessive rumination | 1 (2) | 6 (21)** | 5 (15)* | 5 (21)** | 9 (32)*** | 2 (3) | 1 (4) | 4 (12) | 2 (7) |
| Sensory processing sensitivity | 0 (0) | 5 (18)** | 9 (27)*** | 2 (8) | 8 (29)*** | 0 (0) | 0 (0) | 0 (0) | 2 (7) |
| Restlessness | 0 (0) | 5 (18)** | 7 (21)*** | 8 (33)*** | 4 (14)** | 0 (0) | 1 (4) | 1 (3) | 1 (4) |
| Neck pain | 6 (10) | 3 (11) | 6 (18) | 5 (21) | 8 (29) | 6 (10) | 4 (14) | 8 (24) | 6 (21) |
| Discomfort | 0 (0) | 4 (14)** | 4 (12)* | 6 (25)*** | 6 (21)*** | 0 (0) | 2 (7) | 1 (3) | 1 (4) |
| Hyperhidrosis | 0 (0) | 4 (14)** | 3 (9)* | 6 (25)*** | 7 (25)*** | 0 (0) | 2 (7) | 3 (9)* | 2 (7) |
| Throat tightness | 2 (3) | 4 (14) | 5 (15) | 4 (17) | 6 (21)* | 1 (2) | 1 (4) | 0 (0) | 3 (11) |
| Anxiety | 1 (2) | 2 (7) | 2 (6) | 9 (38) ***#++ | 6 (21)** | 0 (0) | 1 (4) | 0 (0) | 1 (4) |
| Hot flush | 1 (2) | 3 (11) | 4 (12) | 4 (17)* | 6 (21)** | 2 (3) | 0 (0) | 1 (3) | 3 (11) |
| Negative thoughts | 0 (0) | 3 (11)* | 4 (21)* | 5 (21)** | 5 (18)** | 1 (2) | 0 (0) | 1 (3) | 0 (0) |
| Back pain | 5 (8) | 3 (11) | 2 (6) | 4 (17) | 5 (18) | 5 (8) | 2 (7) | 5 (15) | 3 (11) |

N, number of subjects (%); *P < 0.05, **P < 0.01, ***P < 0.001 compared with placebo, #P < 0.05, ##P < 0.01 compared with 15 mg, +P < 0.05, ++P < 0.01, +++P < 0.001 compared with 20 mg (Fisher's exact test).

frightening but were occurring over several months. Flashbacks of Study 1 and Study 2 are also described in detail elsewhere (Muller et al., 2022). No serious adverse reactions occurred. Additional possibly treatment-related adverse events that were spontaneously reported within the first 48 h after discharge from the study visits included headache (10% after psilocybin, 7% after placebo), depressive mood (4% after psilocybin, 0% after placebo), nausea (3% after psilocybin, 0% after placebo), restlessness (2% after psilocybin, 0% after placebo), insomnia/nightmares (2% after psilocybin, 0% after placebo), circulatory collapse (1% after psilocybin, 0% after placebo), paranoid thoughts (1% after psilocybin, 0% after placebo), tendency to cry (1% after psilocybin, 0% after placebo), nosebleed (1% after psilocybin, 0% after placebo), and muscle twitches (1% after psilocybin, 0% after placebo).

### 3.4. Plasma psilocin concentrations

Peak plasma psilocin (active metabolite of psilocybin) concentrations and areas under the plasma concentration curve for all dose groups are shown in Table 2. The full pharmacokinetics of psilocybin of the studies are reported in detail elsewhere (Holze et al., 2023a; Ley et al., 2023).

### 3.5. Effects of psilocybin on kidney and liver function and changes in blood cell counts

At the end of the study, 28 ± 18 days (mean ± SD) after the last substance administration, plasma creatinine levels and the estimated glomerular filtration rate were unchanged compared with the start of the study (Table 5). Similarly, plasma levels of alanine aminotransferase and γ-glutamyl transpeptidase were similar at the screening visit and end-of-study visit. Hemoglobin levels decreased during the study because of the blood sampling. Red and white blood cell counts remained unchanged.

**Table 5**
Kidney and liver function parameters and blood cell counts before and at study end.

| Screening | | End of Study | *t*-test | |
|---|---|---|---|---|
| Kidney and liver function | N = 85 | | t | P = |
| Creatinine (normal: <97 µM) | | | | |
| mean ± SD, µM (range) | 71 ± 13 (48–107) | 71 ± 14 (42–100) | 0.25 | NS |
| Glomerular filtration rate CCR (normal: >90 ml/min) | | | | |
| mean ± SD, ml/min (range) | 109 ± 12 (79–129) | 109 ± 13 (80–134) | 0.08 | NS |
| Alanine aminotransferase (normal: <59 U/l) | | | | |
| mean ± SD, U/l (range) | 23 ± 10 (7–64) | 22 ± 13 (6–99) | 0.24 | NS |
| **Blood cell counts** | **N = 85** | | | |
| White blood cells (normal: 3.5–10.0 x109/l) | | | | |
| mean ± SD, x109/l (range) | 6.1 ± 1.5 (2.3–10) | 6.2 ± 1.6 (2.5–11) | −0.60 | NS |
| Red blood cells (normal: 4.2–6.3 x1012/l) | | | | |
| mean ± SD, x1012/l (range) | 4.6 ± 0.4 (3.8–5.6) | 4.6 ± 0.4 (3.7–5.8) | 1.79 | NS |
| Hemoglobin (normal: 120–180 g/l) | | | | |
| mean ± SD, g/l (range) | 140 ± 13 (117–180) | 137 ± 14 (104–167) | 4.08 | <0.001*** |
| Thrombocytes (normal: 150-450 x109/l) | | | | |
| mean ± SD, x109/l (range) | 248 ± 51 (160–376) | 251 ± 56 (147–431) | −0.79 | NS |

Values are mean ± SD: standard deviation (range); N: number of subjects.

### 3.6. Participants' interest in using psilocybin again

Seventy-two percent of the participants were psilocybin-naive at the start of the study, and the other 28% had limited experience with psilocybin (i.e., maximum ≤5 exposures). Eighty-five participants were asked at the end of the study whether they would consider taking psilocybin again. Two participants (2%) reported that they would probably not take psilocybin again under any circumstances. Seventy participants (82%) reported that they would consider taking psilocybin again. Thirteen participants (15%) reported that they might consider taking psilocybin again. Thirty-eight participants (45%) would only take psilocybin in another clinical study or safe environment. Fifty-two participants (61%) indicated that they would take psilocybin together with friends in a recreational setting. Twenty-six participants (31%) indicated that they would take psilocybin in nature rather than in a hospital setting. Seventy-four participants (87%; 34 women, 41 men) reported a positive overall psilocybin experience, nine participants (11%; seven women, one man) reported a neutral experience, and two participants (2%; one woman and one man) reported a disappointing or bad experience. Forty-two participants (49%) reported that a past drug experience with a psychedelic compound had an influence on their experience during the study, whereas 24 participants (28%) reported that their earlier experiences did not have an impact.

## 4. Discussion

The present study analyzed pooled data from three randomized controlled Phase 1 studies of psilocybin and characterized acute subjective, autonomic, and adverse effects of different doses in healthy participants. In contrast to the primary reports of each study, the present pooled analysis focused on reporting proportions of participants who exhibited extreme values rather than population means.

Overall, positive subjective effects, including "good drug effect" and OB, were reached already at the lower doses and to a higher extent than negative subjective drug effects, including "bad drug effect," "anxiety," and AED. These data may help identify a therapeutic dose to be used in psilocybin-assisted psychotherapy that induces strong and primarily positive acute effects and no or only minimal negative subjective effects. Several clinical studies have shown that a positive acute psychedelic experience predicted long-term therapeutic outcomes in patients with depression, anxiety, or tobacco dependence (Garcia-Romeu et al., 2014; Griffiths et al., 2016; Holze et al., 2023b; Roseman et al., 2017; Ross et al., 2016) and long-term positive mood effects in healthy participants (McCulloch et al., 2022; Schmid and Liechti, 2018). Therefore, inducing mostly positive effects is desirable, although challenging experiences may also have therapeutic potential (Barrett et al., 2016; Carbonaro et al., 2016; Gashi et al., 2021). The 20, 25, and 30 mg doses of psilocybin appear to be comparable when considering the magnitude of their positive subjective effects and stronger than the 15 mg dose. All four doses induced greater negative subjective effects ("bad drug effect") compared with placebo, but significant "anxiety" occurred only with the 25 and 30 mg doses. The subjective "bad drug effect" was not defined exclusively as a psychological effect but could also mean that the participants were feeling physical discomfort, such as nausea or headache. "Oceanic Boundlessness" and AED ratings were comparable over all doses of psilocybin. "Ego dissolution" assessed over time increased with the dose and exhibited a stronger association with "good drug effect" than with "bad drug effect", suggesting a rather positive than negative valence.

The average onset time, time to peak effect, and effect duration (mean ± SD) over all doses of psilocybin were 0.6 ± 0.4 h, 2.1 ± 0.8 h, and 5.5 ± 2.1 h, respectively. Previously, the onset time of psilocybin was reported to be 20–40 min, and the duration was reported to be shorter than 6 h (Hasler et al., 2004), which was confirmed by our analysis. However, the time to peak effects in the present analysis was 2 h and longer than the previously reported 60–90 min (Hasler et al.,

2004).

With regard to cardiovascular risks, psilocybin induced mild sympathomimetic activation in most participants. Tachycardia (> 100 beats/min) was observed in 7% of psilocybin administrations, and hypertension (systolic blood pressure > 140 mmHg) was observed in 50% of psilocybin administrations. Tachycardia occurred in 3% and 20% of the participants, and hypertension occurred in 52% and 53% after the administration of equivalent doses of 20 mg psilocybin and 0.1 mg LSD, respectively (Holze et al., 2022a). In contrast, MDMA, which is also used in substance-assisted therapy, induced tachycardia in 33% of the participants and hypertension in 90% of the participants in a similar analysis of pooled studies (Vizeli and Liechti, 2017). Thus, MDMA produces overall clearly greater cardiovascular stimulation than the psychedelics psilocybin and LSD at commonly used doses. Psilocybin may thus be an alternative to MDMA in patients with cardiovascular risk factors.

The data confirmed the overall comparable cardiovascular stimulation of psilocybin and LSD at equivalent psychoactive doses (Holze et al., 2022b). In another previous study, psilocybin also produced comparable sympathomimetic activation at doses of 10, 20, and 30 mg/70 kg body weight (Carbonaro et al., 2018) as reported in the present study. The present analysis also showed that psilocybin increased body temperature dose-dependently. Psilocybin increased body temperature to > 38°C in 16% of all psilocybin administrations and comparably to LSD (Holze et al., 2022a). Only in one participant did body temperature increase above 38.8°C (to 39.0°C), which was presumably because of a beginning COVID-19 infection. No hyperpyrexia (> 40°C) occurred. We did not find significant QTc interval prolongation during the peak response to psilocybin compared with the QTc interval before psilocybin administration in Study 1 (Becker et al., 2022).

Acute negative psychological effects are considered the main risk of psychedelic substance use in humans (Holze et al., 2022a; Johnson et al., 2008). However, psilocybin also induces physical discomfort. Frequent acute adverse events were general exhaustion, including fatigue, lack of concentration, lethargy, vertigo, feeling of weakness, and decreased appetite. The reported subacute adverse effects up to 24 h suggest a state of "exhaustion" akin to fatigue that is experienced after intense mental or physical activity. In contrast, between-session adverse events were equally frequent after psilocybin and placebo administration, indicating no prolonged after-effects of psilocybin beyond 24 h. Notably, adverse effects, such as fatigue and headache, could also be seen in participants after placebo administration, so lying in a hospital bed for most of the day and not being able to consume caffeine could have exacerbated these symptoms.

Headache and nausea are two adverse events that have been typically described in other clinical studies after psilocybin administration (Dodd et al., 2022; Johnson et al., 2012; Rossi et al., 2022). In the present analysis, headache up to 12 h after psilocybin administration occurred in 55% of the participants and up to 24 h in 42% of the participants. Nausea up to 12 h after administration occurred in 39% of the participations and up to 24 h in 4% of the participations. There was no clear dose dependence for headache or nausea. Anxiety on the List of Complaints was indicated by 38% of the participants who ingested the 25 mg psilocybin. During the study sessions, anxiety could be reduced by verbal support in all participants, and benzodiazepines were not used. No cases of severe anxiety, panic attacks, or acute suicidality occurred. Overall acute adverse effects were quite common and mostly not dose-dependent within the 15–30 mg dose range. Adverse effects of psilocybin were transient and not sufficiently disabling or severe to require medical intervention. As subacute adverse events, flashbacks and hallucinogen persisting perception disorder have been previously described following the use of psychedelics. However, the frequency and nature of flashbacks and risk factors are still unidentified (Halpern et al., 2016; Martinotti et al., 2018). A pooled analysis of several studies was published in 2022 (Muller et al., 2022), which also included Studies 1 and 2 in the present pooled analysis. Together with the present analysis, the findings indicate that even in controlled studies, flashbacks are possible but mostly transient and not frightening. One participant reported reoccurring visual flashbacks after psilocybin and LSD administration, which were not disruptive or frightening but were occurring over several months as already described previously (Muller et al., 2022). Hallucinogen persisting perception disorder (Halpern et al., 2016) was not observed in the present pooled analysis. Similar to the present analysis, flashbacks were reported by 7% of the participants within 24–86 h after LSD administration (Holze et al., 2022a).

In the present study, psilocybin did not influence average levels of liver enzymes 1 month after psilocybin administration. An expected decrease in hemoglobin levels was observed at the end-of-study visit. These findings were attributable to the overall blood loss of 250–800 ml through blood sampling during the test sessions as observed previously in similar studies (Holze et al., 2022a; Vizeli and Liechti, 2017) or after blood donation.

Retrospectively, 87% of the participants in the present analysis reported an overall positive subjective experience, whereas only 2% reported a disappointing or bad psilocybin experience. The results of this study indicate that psilocybin appears to be safe in a controlled setting with transient adverse effects. The safety data can partially be applied to the use of psilocybin in patients. The study participants typically had no or very little previous psilocybin experience, similar to most patients. Furthermore, psilocybin-assisted therapy is typically used sporadically 2–3 times and spaced several weeks apart in addition to conventional non-substance-assisted psychotherapy (Schmid et al., 2021). Consistent with the present data, there are no reports of acute serious adverse reactions to psilocybin or other serotonergic psychedelics in modern clinical studies (Andersen et al., 2021; Breeksema et al., 2022). However, these data were collected from mostly young and physically and psychiatrically healthy people. The results may also differ in patients with psychiatric or cardiovascular disorders.

The present study has several strengths. We used data from three randomized controlled trials that were conducted within the same highly controlled laboratory setting. All studies included similar numbers of male and female participants and used psilocybin capsules from the same batch that was well-characterized pharmaceutically with a known exact drug content. The doses in this pooled analysis were in the typical range that is used in clinical research with psilocybin in patients. Additionally, the doses of psilocybin were well defined. Drug dose is the most important known predictor of the psilocybin experience (Studerus et al., 2012).

The present study also has limitations. We pooled three studies that included different people. Only the 15 and 30 mg doses in Study 2 were administered in the same participants. Study 1 that included the 25 mg dose was not a placebo-controlled study, and measures were only assessed up to 7 h after psilocybin administration. In Studies 2 and 3, participants also ingested other substances (LSD and mescaline), which might have partially affected the psilocybin experience or changed expectations when administered before psilocybin. However, no significant main effect of order of the substance sessions was detected, and there was no interaction with dose when order was incorporated as an additional factor in the ANOVAs. Additionally, previous substance use has not been shown to affect the acute subjective effects of LSD in a previous smaller study (Holze et al., 2021). Another important caveat poses that although the unpleasant effects in our study were modest and transient, we only included psychiatrically healthy participants. Therefore, the risks of psilocybin use might be different in a more heterogeneous population and in patients in a therapeutic setting and need to be further investigated. Moreover, the participants were mostly young and physically healthy, but older patients or patients with cardiovascular risk factors may also be treated with psilocybin. Furthermore, we included 85 participants who received psilocybin a total of 113 times. This sample size is too small to detect infrequent (0.1–1%) or rare (<0.1%) adverse events. Additionally, there was no long-term follow-up. Although doses of psilocybin were well defined, individual differences in the bioavailability or metabolism of psilocybin were not

included in this study. In this analysis we have outlined acute safety concerns related to psilocybin administration but have not examined potential risk factors for adverse events. Previous analyses indicated that "emotional excitability" prior to drug intake predicts unpleasant or anxious reactions to psilocybin, whereas factors such as drug use, sex, and body weight do not relevantly alter acute effects or safety of psilocybin (Holze et al., 2023a; Studerus et al., 2012).

## 5. Conclusion

Single-dose administrations of psilocybin up to 30 mg were safe with regard to acute psychological and physical harm in healthy participants in a controlled clinical setting. Psilocybin induced mild cardiovascular stimulation. Acute subjective effects were predominantly positive, but transient anxiety and "bad drug effects" occurred. These safety data do not raise any concerns about single-dose, infrequent psilocybin administration in a controlled clinical setting. However, risks and benefits of using psilocybin in patients need further study.

## Author contributions

IS analyzed the data. IS and FH wrote the manuscript. FH, AMB, LL, and NH conducted the research. MEL conceived the study, obtained funding, analyzed the data, and wrote the manuscript.

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## Declaration of competing interest

MEL is a consultant for Mind Medicine, Inc. The other authors declare no conflicts of interests. Knowhow and data associated with this work and owned by the University Hospital Basel were licensed by Mind Medicine, Inc. Mind Medicine, Inc., had no role in financing, planning, or conducting the present study or the present publication.

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## 2.3. Acute effects of R-MDMA, S-MDMA, and racemic MDMA in a randomized double-blind cross-over trial in healthy participants

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# Acute effects of *R*-MDMA, *S*-MDMA, and racemic MDMA in a randomized double-blind cross-over trial in healthy participants

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Racemic 3,4-methylenedioxymethamphetamine (MDMA) acutely increases mood, feelings of empathy, trust, and closeness to others and is investigated to assist psychotherapy. Preclinical research indicates that *S*-MDMA releases monoamines and oxytocin more potently than *R*-MDMA, whereas *R*-MDMA more potently stimulates serotonin 5-hydroxytryptamine-2A receptors. *S*-MDMA may have more stimulant properties, and *R*-MDMA may be more psychedelic-like. However, acute effects of *S*- and *R*-MDMA have not been examined in a controlled human study. We used a double-blind, randomized, placebo-controlled, crossover design to compare acute effects of MDMA (125 mg), *S*-MDMA (125 mg), *R*-MDMA (125 mg and 250 mg), and placebo in 24 healthy participants. Outcome measures included subjective, autonomic, and adverse effects, pharmacokinetics, and plasma oxytocin, prolactin, and cortisol concentrations. *S*-MDMA (125 mg) induced greater subjective effects ("stimulation," "drug high," "happy," "open") and higher increases in blood pressure than *R*-MDMA (both 125 and 250 mg) and MDMA (125 mg). Unexpectedly, *R*-MDMA did not produce more psychedelic-like effects than *S*-MDMA. *S*-MDMA increased plasma prolactin more than MDMA, and *S*-MDMA increased plasma cortisol and oxytocin more than MDMA and *R*-MDMA. The plasma elimination half-life of *S*-MDMA was 4.1 h after administration. The half-life of *R*-MDMA was 12 and 14 h after the administration of 125 and 250 mg, respectively. Half-lives for *S*-MDMA and *R*-MDMA were 5.1 h and 11 h, respectively, after racemic MDMA administration. Concentrations of the CYP2D6-formed MDMA-metabolite 4-hydroxy-3-methoxymethamphetamine were lower after *R*-MDMA administration compared with *S*-MDMA administration. The pharmacokinetic findings are consistent with the *R*-MDMA-mediated inhibition of CYP2D6. Stronger stimulant-like effects of *S*-MDMA in the present study may reflect the higher potency of *S*-MDMA rather than qualitative differences between *S*-MDMA and *R*-MDMA. Equivalent acute effects of *S*-MDMA, MDMA, and *R*-MDMA can be expected at doses of 100, 125, and 300 mg, respectively, and need to be investigated.

Trial registration: ClinicalTrials.gov identifier: NCT05277636

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## INTRODUCTION

3,4-Methylenedioxymethamphetamine (MDMA) releases serotonin (5-hydroxytryptamine [5-HT]), norepinephrine, dopamine, and oxytocin and induces feelings of well-being, empathy, trust, closeness, and connectedness [1, 2]. Acute subjective effects of MDMA are considered helpful to assist psychotherapy for posttraumatic stress disorder [3]. MDMA is a racemic substance that contains equal amounts of the enantiomers *S*(+)- and *R*(-)-MDMA. Preclinical research indicates that *S*-MDMA more potently releases monoamines and oxytocin than *R*-MDMA, whereas *R*-MDMA may act more potently on 5-$HT_{2A}$ receptors [4–10]. Behavioral animal studies indicate that *S*-MDMA is more stimulant-like than *R*-MDMA, and *R*-MDMA may be more psychedelic-like while still producing MDMA-typical effects [11–13]. For example, the stimulant d-amphetamine substituted for *S*-MDMA- but not *R*-MDMA-trained animals while the psychedelic 2,5-dimethoxy-4-propylthiophenethylamine substituted for *R*-MDMA- but not *S*-MDMA-trained animals in drug-discrimination studies in mice [11]. Additionally, preclinical research indicates that *R*-MDMA induces less hyperthermia and less neurotoxicity [14–16]. Research on abuse-related behavioral effects in Rhesus monkeys showed comparable [17] or little to no drug self-administration of *R*-MDMA compared with MDMA and *S*-MDMA [18]. Consistently, priming with MDMA or *S*-MDMA but not with *R*-MDMA reinstated extinguished amphetamine self-administration behavior [19]. Because of these preclinical results, *R*-MDMA has been discussed as a potentially safer tool for substance-assisted therapy than racemic MDMA [12]. However, acute effects of *S*- and *R*-MDMA have not been validly compared in a human study. Therefore, the present study compared acute responses to racemic MDMA, *S*-MDMA, *R*-MDMA, and placebo in a double-blind, crossover study in healthy participants.

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The primary study hypothesis was that *S*-MDMA would induce greater ratings of subjective stimulation on the Visual Analog Scale (VAS) than *R*-MDMA, and *R*-MDMA would induce more psychedelic-like effects on the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale than *S*-MDMA.

## METHODS AND MATERIALS

### Study design

The study used a double-blind, placebo-controlled, crossover design with five experimental test sessions to investigate responses to (*i*) placebo, (*ii*) 125 mg racemic MDMA, (*iii*) 125 mg *S*-MDMA, (*iv*) 125 mg *R*-MDMA, and (*v*) 250 mg *R*-MDMA. Participants were informed that they would get all treatments. Block randomization was used with counterbalanced treatment order. The washout periods between sessions were at least 10 days. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines in Good Clinical Practice and approved by the Ethics Committee of Northwest Switzerland (EKNZ) and Swiss Federal Office for Public Health. The study was registered at ClinicalTrials.gov (NCT05277636).

### Participants

Twenty-four healthy participants (12 men and 12 women; mean age ±SD: 29 ± 9 years; range: 18–47 years) were recruited by word of mouth or from a pool of volunteers who had contacted our research group because they were interested in participating in a clinical trial on psychedelics or entactogens. All of the subjects provided written informed consent and were paid for their participation. Exclusion criteria were <18 years or >65 years of age, pregnancy (urine pregnancy test at screening and before each test session), personal or family (first-degree relative) history of major psychiatric disorders (assessed by the Semi-structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, Axis I disorders), the use of medications (e.g., antidepressants, antipsychotics, and sedatives) that may interfere with the study medications, chronic or acute physical illness (e.g., abnormal physical exam, electrocardiogram, or hematological and chemical blood analyses), tobacco smoking (>10 cigarettes/day), lifetime prevalence of illicit substances >20 times or use within the last 2 months (except for $\Delta^9$-tetrahydrocannabinol; THC), and illicit drug use during the study period (including THC; urine drug test performed randomly prior to one study day). The participants were asked to consume no more than 15 standard alcoholic drinks/week and have no more than one drink on the day before the test sessions. Prior and current substance use is described in the Supplementary Methods and in Supplementary Table S1.

### Study drugs

We selected 125 mg racemic MDMA as a common and safe dose [20]. Based on animal data, 125 mg *S*-MDMA and 125 mg racemic MDMA were expected to be overall equipotent in inducing stimulant-type and adverse effects in humans. *R*-MDMA was administered at a dose of 125 mg and additionally at a higher dose of 250 mg based on its lower potency and to be able to assess its effect characteristics more fully. Preliminary data indicated that *S*-MDMA was active at 80–120 mg, and *R*-MDMA was expected to be active at doses near 300 mg in humans [21]. Fixed rather than weight-based doses were used for practical reasons and because MDMA has not been adjusted to body weight in phase 3 studies and in limited use outside clinical studies. MDMA (ReseaChem, Burgdorf, Switzerland) was administered in opaque capsules that contained 25 mg MDMA hydrochloride and an exact analytically confirmed actual MDMA content of 25.40 ± 0.48 mg ($n = 9$ samples). *S*-MDMA (ReseaChem, Burgdorf, Switzerland) was administered in opaque capsules that contained 25 mg *S*-MDMA hydrochloride and an exact analytically confirmed actual *S*-MDMA content of 25.56 ± 0.62 mg ($n = 10$). *R*-MDMA (ReseaChem, Burgdorf, Switzerland) was administered in opaque capsules that contained 25 mg *R*-MDMA hydrochloride and an exact analytically confirmed actual *R*-MDMA content of 25.50 ± 1.30 mg ($n = 10$). Placebo consisted of identical opaque capsules that were filled with mannitol. All capsules were produced according to Good Manufacturing Practice guidelines (Dr. Hysek AG, Biel, Switzerland). The subjects received 10 capsules in each session: (*i*) 10 placebo capsules, (*ii*) five 25 mg (±)-MDMA capsules and five placebo capsules, (*iii*) five *S*-MDMA capsules and five placebo capsules, (*iv*) five 25 mg *R*-MDMA capsules and five placebo capsules, and (*v*) ten 25 mg *R*-MDMA capsules. At the end of each session and at the end of the study, the participants guessed their treatment assignment to evaluate blinding.

### Study procedures

The study included a screening visit, five 10-h test sessions with follow-up measurements 24 h after drug intake, and an end-of-study visit that occurred an average of 14 days after the last test session. The sessions were conducted in a calm hospital room. Only one research participant and one investigator were present during each test session. The test sessions began at 8:00 AM. A urine pregnancy test was performed in women with childbearing potential. The participants underwent baseline measurements. A standardized breakfast (two croissants) was served. Substances were administered at 9:00 AM. The outcome measures were repeatedly assessed for 9 h. Standardized lunches were served at 1:30 PM. The participants were sent home at 6:15 PM and returned the next day for follow-up measurements at 9:00 AM.

### Subjective drug effects and effect durations

Subjective effects were assessed repeatedly using VASs 0.5 h before and 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, and 24 h after drug administration. The VAS "simulated" was the primary measure to assess stimulation. The Adjective Mood Rating Scale (AMRS) [22] was used 0.5 h before and 2.5, 5, and 9 h after drug administration. The 5D-ASC scale [23] and the 3D-ASC total score were used as the primary measure to assess psychedelic-like effects. It was administered 9 h after drug administration to retrospectively rate peak drug effects. Mystical experiences were assessed 9 h after drug administration using the Psychedelic Experience Scale (PES) [24], a revalidation of the 100-item States of Consciousness Questionnaire (SOCQ) [25], which includes the 30-item Mystical Experience Questionnaire (MEQ30) [24, 26]. Subjective effect measurements are described in detail in the Supplementary Methods online.

The time to onset, time to maximal effect, time to offset, effect duration, and area under the effect curve were assessed using Phoenix WinNonlin 8.3 (Certara, Princeton, NJ, USA) and "any drug effect" VAS effect-time plots and an onset/offset threshold of 10% of the maximum possible response. Participants with responses <10% on this scale were not used to determine the time to onset, time to offset, or effect duration.

### Autonomic and adverse effects

Blood pressure, heart rate, and tympanic body temperature were repeatedly measured at baseline and 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, and 24 h after drug administration. Adverse effects were assessed 0.5 h before and 9, 24 and 72 h after drug administration using the List of Complaints [27]. To assess adverse effects on mood 1–3 days after substance administration, the Beck Depression Inventory (BDI) [28] and Symptom-Check-List-90-R (SCL-90-R) [29] were used 72 h after administration.

### Endocrine effects

Plasma concentrations of oxytocin were measured before and 2, 3, and 6 h after drug administration and determined as previously described [30]. Plasma concentrations of cortisol and prolactin were measured at baseline and 2 and 3 h after drug administration using an electrochemiluminescence immunoassay as previously described [31].

### Plasma MDMA concentrations

Plasma concentrations of MDMA, *S*-MDMA, *R*-MDMA, and their metabolites were measured before and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, and 24 h after drug administration. Blood was collected into lithium heparin tubes. The blood samples were immediately centrifuged, and the plasma was subsequently stored at −80 °C until analysis.

MDMA, *S*-MDMA, *R*-MDMA, and their metabolites 3,4-methylenedioxyamphetamine (MDA) and 4-hydroxy-3-methoxymethamphetamine (HMMA) were analyzed in human plasma using an achiral high-performance liquid chromatography tandem mass spectrometry method and additionally an enantioselective method for racemic MDMA as previously described [32]. HMMA concentrations were determined after enzymatic deglucuronidation.

### Pharmacokinetic analyses

Pharmacokinetic parameters were estimated using non-compartmental methods. Analyses were conducted using Phoenix WinNonlin 8.3 (Certara, Princeton, NJ, USA).

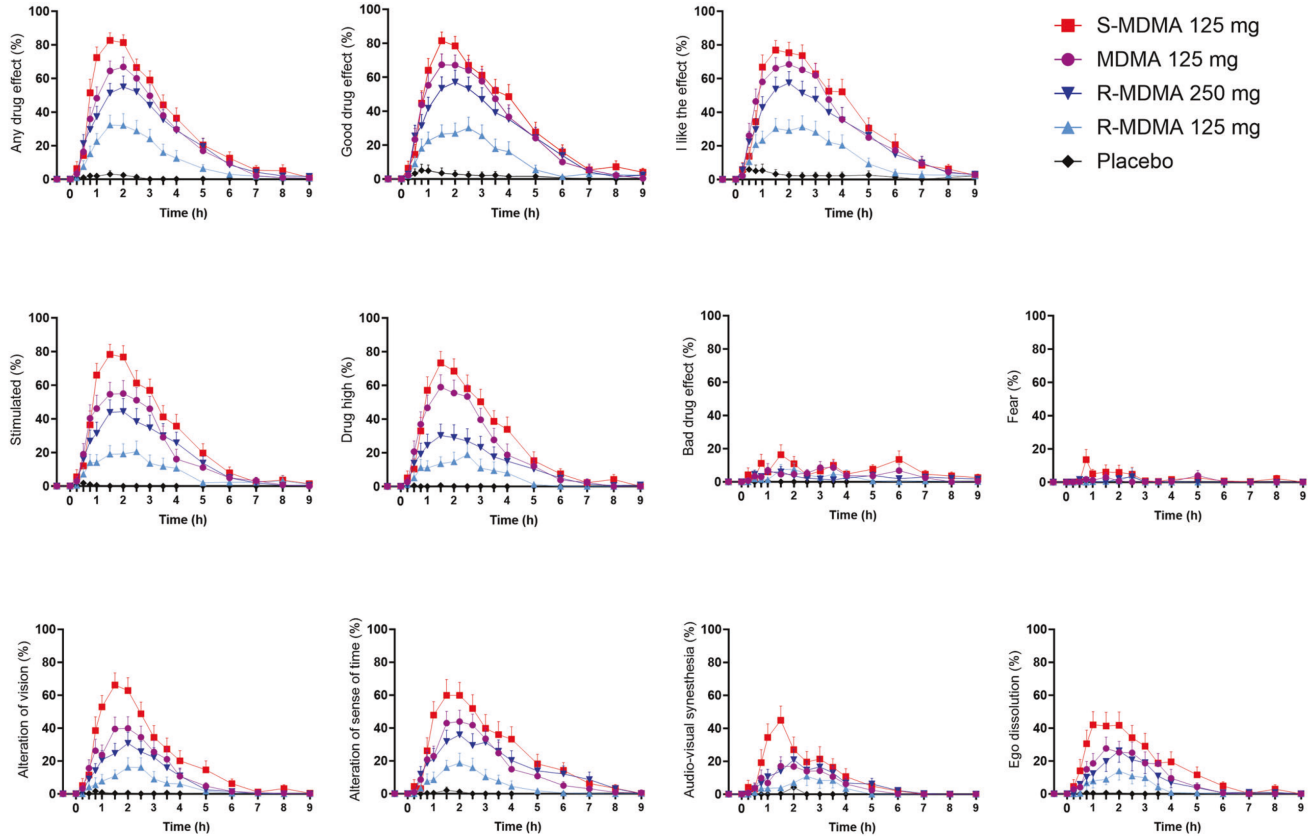


**Fig. 1 Acute subjective effects of 125 mg MDMA, 125 mg *S*-MDMA, 125 mg *R*-MDMA, and 250 mg *R*-MDMA on the Visual Analog Scale (VAS).** *S*-MDMA produced overall stronger subjective responses than MDMA, with significant differences in "bad drug effects," "alteration of vision," and "audio-visual synesthesia." *R*-MDMA at both doses produced overall lower subjective effects than MDMA, with significant differences in "drug high," "happy," "content," "talkative," "open," "trust," and "I feel close to others." The substances were administered at $t = 0$ h. The data are expressed as the mean ± SEM percentage of maximally possible scores in 24 participants. The corresponding maximal responses and statistics are shown in Table 1.

### Data analysis

Peak ($E_{max}$ and/or $E_{min}$) or peak change from baseline ($\Delta E_{max}$) values were determined for repeated measures. The values were then analyzed using repeated-measures analysis of variance (ANOVA), with drug as the within-subjects factor, followed by the Tukey *post hoc* tests using R 4.2.1 software (RStudio, PBC, Boston, MA, USA). The criterion for significance was $p < 0.05$.

## RESULTS

### Subjective drug effects

Subjective effects over time on the VAS are shown in Fig. 1 and Supplementary Fig. S1. Subjective peak responses and statistics are shown in Table 1. *S*-MDMA produced overall greater subjective effects than MDMA and *R*-MDMA at the doses used. Specifically, *S*-MDMA induced significantly stronger "bad drug effects," "alteration of vision," and "audio-visual synesthesia" than MDMA and significantly stronger effects than 250 mg *R*-MDMA on most VASs including "stimulation". Both *R*-MDMA doses induced lower effects on "drug high," "happy," "content," "talkative," "open," "trust," and "I feel close to others" than MDMA and *S*-MDMA (Fig. 1, Supplementary Fig. S1, Table 1). Responses in female participants were greater than in male participants due to lower body weights in women (Supplementary Fig. S2 and Supplementary Table S2). Responses in participants with and without previous MDMA experiences did not differ (Supplementary Fig. S3 and Supplementary Table S3). The mean effect duration was 3.5, 4.2, 4.7, and 5.2 h after the administration of 125 mg *R*-MDMA, MDMA, *S*-MDMA, and 250 mg *R*-MDMA, respectively (Supplementary Table S4). MDMA, *S*-MDMA, and 250 mg *R*-MDMA induced comparable alterations of mind and mystical-type effects on the 5D-ASC and PES48/MEQ, respectively (Fig. 2, Supplementary Fig. S4, statistics in Supplementary Tables S5 and S6). R-MDMA and S-MDMA also similarly increased the 3D-ASC total score reflecting comparable psychedelic effects (Supplementary Table S5). On the AMRS, 250 mg *R*-MDMA induced significantly higher "Introversion" than MDMA, and *S*-MDMA induced more "emotional excitation" than *R*-MDMA (Supplementary Fig. S5, Supplementary Table S7).

### Autonomic and adverse effects

Autonomic effects over time and related peak responses are shown in Fig. 3 and Table 1, respectively. *S*-MDMA induced higher increases in blood pressure than MDMA and *R*-MDMA. MDMA, *S*-MDMA, and 250 mg *R*-MDMA increased heart rate and body temperature comparably.

All substances produced similar acute and subacute adverse effects on the List of Complaints (Table 1). Frequently reported adverse effects included fatigue, headache, decreased appetite, feeling dull, lack of concentration, and dry mouth (Supplementary Table S8). All substances nominally increased self-ratings of depressive mood on the BDI 1–3 days after substance administration. Significantly higher ratings were seen for *S*-MDMA compared with placebo, with no significant differences between active drug substances (Table 1). No severe adverse events were observed.

### Endocrine effects

All substances increased plasma prolactin and cortisol compared with placebo. *S*-MDMA increased plasma prolactin more than

**Table 1.** Mean values and statistics for the acute subjective effects of MDMA, S-MDMA, R-MDMA and placebo.

| | | Placebo | 125 mg R-MDMA | 250 mg R-MDMA | 125 mg MDMA | 125 mg S-MDMA | $F_{4, 92}$ | $P=$ | Pla - R-MDMA (125 mg) | Pla - R-MDMA (250 mg) | Pla - MDMA | Pla - S-MDMA | R-MDMA (125 mg) -R-MDMA (250 mg) | R-MDMA (125 mg) - MDMA | R-MDMA (125 mg) - S-MDMA | R-MDMA (250 mg) - MDMA | R-MDMA (250 mg) - S-MDMA | MDMA - S-MDMA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | Mean ± SEM | Mean ± SEM | Mean ± SEM | Mean ± SEM | | | | | | | | | | | | |
| Visual Analog Scale (VAS, %max) | | | | | | | | | | | | | | | | | | |
| Unidirectional scales (0–100) | | | | | | | | | | | | | | | | | | |
| Any drug effect | $\Delta E_{max}$ | 4.8 ±2.1 | 42 ±7.3 | 66 ±6.1 | 77 ±5.3 | 90 ±3.1 | 68.92 | <0.001 | *** | *** | *** | *** | *** | *** | *** | NS | ** | NS |
| Good drug effect | $\Delta E_{max}$ | 7.9 ±4.1 | 43 ±7.1 | 68 ±6.6 | 78 ±5.1 | 90 ±3.8 | 54.97 | <0.001 | *** | *** | *** | *** | *** | *** | *** | NS | ** | NS |
| Bad drug effect | $\Delta E_{max}$ | 0.5 ±0.3 | 14 ±5.1 | 19 ±4.6 | 20 ±5.9 | 39 ±7.0 | 10.51 | <0.001 | NS | * | * | *** | NS | NS | *** | NS | * | * |
| I like the effect | $\Delta E_{max}$ | 7.7 ±3.8 | 47 ±7.1 | 68 ±6.6 | 81 ±5.0 | 91 ±3.6 | 60.12 | <0.001 | *** | *** | *** | *** | ** | *** | *** | NS | ** | NS |
| Stimulated | $\Delta E_{max}$ | 2.5 ±1.1 | 31 ±6.9 | 60 ±6.7 | 70 ±6.7 | 88 ±3.7 | 58.82 | <0.001 | *** | *** | *** | *** | *** | *** | *** | NS | *** | NS |
| Drug high | $\Delta E_{max}$ | 1.4 ±0.6 | 29 ±7.0 | 48 ±7.6 | 73 ±6.7 | 84 ±5.1 | 49.31 | <0.001 | *** | *** | *** | *** | * | *** | *** | ** | *** | NS |
| Fear | $\Delta E_{max}$ | 0.0 ±0.0 | 4.9 ±4.2 | 5.8 ±3.4 | 5.9 ±3.4 | 19 ±6.9 | 3.90 | 0.006 | NS | NS | NS | ** | NS | NS | * | NS | NS | NS |
| Alteration of vision | $\Delta E_{max}$ | 3.0 ±1.6 | 24 ±6.9 | 37 ±6.7 | 54 ±7.8 | 74 ±6.7 | 32.23 | <0.001 | * | *** | *** | *** | NS | *** | *** | NS | *** | * |
| Alteration of sense of time | $\Delta E_{max}$ | 2.2 ±2.0 | 28 ±7.2 | 46 ±7.7 | 60 ±6.8 | 73 ±6.6 | 34.55 | <0.001 | ** | *** | *** | *** | NS | *** | *** | NS | ** | NS |
| Audio-visual synesthesia | $\Delta E_{max}$ | 4.6 ±4.2 | 15 ±5.9 | 31 ±6.8 | 29 ±6.8 | 53 ±8.3 | 16.01 | <0.001 | NS | ** | ** | *** | NS | NS | *** | NS | ** | ** |
| Ego dissolution | $\Delta E_{max}$ | 1.5 ±0.8 | 22 ±7.4 | 32 ±7.4 | 41 ±7.7 | 58 ±8.2 | 17.83 | <0.001 | * | *** | *** | *** | NS | NS | *** | NS | ** | NS |
| Bidirectional scales (−50 to 50) | | | | | | | | | | | | | | | | | | |
| Happy | $\Delta E_{max}$ | 3.9 ±2.2 | 14 ±3.5 | 24 ±3.8 | 34 ±3.3 | 38 ±3.4 | 32.25 | <0.001 | * | *** | *** | *** | NS | *** | *** | * | *** | NS |
| Content | $\Delta E_{min}$ | 4.8 ±2.2 | 19 ±3.4 | 30 ±3.6 | 39 ±2.8 | 44 ±2.5 | 46.83 | <0.001 | *** | *** | *** | *** | * | *** | *** | * | *** | NS |
| Talkative | $\Delta E_{max}$ | 2.8 ±1.6 | 13 ±3.2 | 22 ±3.9 | 35 ±3.6 | 37 ±3.9 | 30.55 | <0.001 | NS | *** | *** | *** | NS | *** | *** | ** | ** | NS |
| Open | $\Delta E_{max}$ | 4.3 ±2.3 | 15 ±3.4 | 28 ±3.9 | 40 ±2.9 | 42 ±2.9 | 50.64 | <0.001 | * | *** | *** | *** | ** | *** | *** | ** | *** | NS |
| Trust | $\Delta E_{max}$ | 4.0 ±2.0 | 16 ±3.5 | 24 ±4.1 | 40 ±3.1 | 44 ±2.3 | 48.93 | <0.001 | ** | *** | *** | *** | NS | *** | *** | *** | *** | NS |
| I feel close to others | $\Delta E_{max}$ | 0.8 ±0.4 | 14 ±3.1 | 23 ±3.9 | 34 ±3.3 | 41 ±3.4 | 43.83 | <0.001 | ** | *** | *** | *** | NS | *** | *** | ** | *** | NS |
| I want to be alone | $\Delta E_{max}$ | 0.2 ±0.2 | 6.1 ±2.6 | 10 ±3.4 | 6.9 ±2.7 | 12 ±3.4 | 4.15 | 0.004 | NS | * | NS | ** | NS | NS | NS | NS | NS | NS |
| I want to be with others | $\Delta E_{max}$ | 1.8 ±1.1 | 17 ±3.4 | 24 ±4.0 | 31 ±3.5 | 40 ±3.5 | 32.15 | <0.001 | *** | *** | *** | *** | NS | ** | *** | NS | *** | NS |
| Autonomic effects | | | | | | | | | | | | | | | | | | |
| Systolic blood pressure (mmHg) | $E_{max}$ | 127 ±2.7 | 138 ±2.5 | 147 ±2.5 | 152 ±2.3 | 160 ±3.1 | 74.46 | <0.001 | *** | *** | *** | *** | *** | *** | *** | NS | *** | ** |
| Diastolic blood pressure (mmHg) | $E_{max}$ | 78 ±0.8 | 84 ±1.1 | 91 ±1.6 | 92 ±1.3 | 97 ±1.6 | 62.90 | <0.001 | *** | *** | *** | *** | *** | *** | *** | NS | *** | *** |
| Mean arterial pressure (mmHg) | $E_{max}$ | 94 ±1.0 | 101 ±1.4 | 108 ±1.8 | 111 ±1.3 | 117 ±1.9 | 93.43 | <0.001 | *** | *** | *** | *** | *** | *** | *** | NS | *** | *** |
| Heart rate (beats/min) | $E_{max}$ | 75 ±1.3 | 87 ±2.6 | 93 ±3.4 | 95 ±3.5 | 100 ±3.3 | 21.50 | <0.001 | *** | *** | *** | *** | NS | NS | *** | NS | NS | NS |
| Rate pressure product (mmHg x bpm) | $E_{max}$ | 9135 ±218 | 11565 ±476 | 12999 ±569 | 14018 ±662 | 15389 ±705 | 41.15 | <0.001 | *** | *** | *** | *** | NS | *** | *** | NS | *** | NS |
| Body temperature (°C) | $E_{max}$ | 37.1 ±0.06 | 37.4 ±0.09 | 37.5 ±0.09 | 37.6 ±0.08 | 37.7 ±0.10 | 10.25 | <0.001 | NS | *** | *** | *** | NS | NS | * | NS | NS | NS |
| List of complaints (LC score) | | | | | | | | | | | | | | | | | | |
| Acute adverse effects | 0–9 h | 0.5 ±0.5 | 9.4 ±1.8 | 14 ±1.9 | 10 ±1.7 | 13 ±1.5 | 21.58 | <0.001 | *** | *** | *** | *** | NS | NS | NS | NS | NS | NS |

**Table 1.** continued

| | | Placebo | 125 mg R-MDMA | 250 mg R-MDMA | 125 mg MDMA | 125 mg S-MDMA | $F_{4, 92}$ | $P=$ | Pla - R-MDMA (125 mg) | Pla - R-MDMA (250 mg) | Pla - MDMA | Pla - S-MDMA | R-MDMA (125 mg) -R-MDMA (250 mg) | R-MDMA (125 mg) - MDMA | R-MDMA (125 mg) - S-MDMA | R-MDMA (250 mg) - MDMA | R-MDMA (250 mg) - S-MDMA | MDMA - S-MDMA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean ± SEM | Mean ± SEM | Mean ± SEM | Mean ± SEM | Mean ± SEM | | | | | | | | | | | | |
| Subacute adverse effects | 9–24 h | 0.1 ±0.5 | 6.7 ±1.9 | 8.2 ±1.5 | 5.4 ±1.3 | 7.2 ±1.4 | 8.95 | <0.001 | *** | *** | ** | *** | NS | NS | NS | NS | NS | NS |
| Subacute adverse effects | 24–72 h | 1.3 ±0.7 | 6.9 ±1.8 | 6.0 ±1.7 | 5.1 ±1.6 | 10 ±2.2 | 6.05 | <0.001 | * | NS | NS | *** | NS | NS | NS | NS | NS | NS |
| Becks depression-inventar (BDI) | | | | | | | | | | | | | | | | | | |
| BDI Score | 24–72 h | 2.0 ±0.9 | 4.3 ±1.2 | 4.4 ±1.2 | 4.8 ±1.3 | 8.4 ±1.7 | 4.07 | 0.004 | NS | NS | NS | * | NS | NS | NS | NS | NS | NS |
| Symptom checklist 90 R (SCL-90-R) | | | | | | | | | | | | | | | | | | |
| GSI score | 24–72 h | 0.08 ±0.02 | 0.18 ±0.05 | 0.17 ±0.05 | 0.14 ±0.03 | 0.34 ±0.77 | 5.02 | 0.001 | NS | NS | NS | * | NS | NS | NS | NS | NS | NS |
| Hormones and markers | | | | | | | | | | | | | | | | | | |
| Oxytocin (pg/mL)[α] | $\Delta C_{max}$ | 2.9 ±1.9 | 48 ±13 | 178 ±22 | 296 ±33 | 436 ±40 | $66.2^{\beta}$ | <0.001 | NS | *** | *** | *** | *** | *** | *** | ** | *** | *** |
| Cortisol (nmol/L) | $\Delta C_{max}$ | −156 ±27 | 140 ±28 | 249 ±26 | 285 ±26 | 398 ±27 | 81.90 | <0.001 | *** | *** | *** | *** | ** | ** | *** | NS | *** | * |
| Prolactin (µg/L) | $\Delta C_{max}$ | −6.5 ±2.0 | 13 ±4.5 | 35 ±5.5 | 39 ±7.1 | 53 ±8.5 | 32.20 | <0.001 | *** | *** | *** | *** | *** | ** | *** | NS | NS | ** |

*NS* not significant, $\Delta E_{max}$ maximal effect difference from baseline, $\Delta C_{max}$ maximal plasma concentrationfrom baseline, $N = 24$, $\alpha N = 20$, $\beta = F_{4,81}$.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

MDMA and plasma oxytocin and cortisol more than MDMA and *R*-MDMA (Supplementary Fig. S6, Table 1).

### Plasma drug concentrations

Pharmacokinetic parameters are shown in Table 2. Concentration-time curves are shown in Supplementary Figs. S7–S9. Elimination half-lives ($t_{1/2}$) for *S*-MDMA and *R*-MDMA were 5.1 and 11 h, respectively, when racemic MDMA was administered. The half-life of *S*-MDMA was 4.1 h when it was administered alone. The half-life of *R*-MDMA was 12 and 14 h after administration of the 125 and 250 mg doses, respectively (Table 2).

### Correlations

Correlations between the drug plasma concentrations and subjective, cardiovascular, cortisol, and prolactin responses are shown in Supplementary Figs. S10–S13, respectively.

### Blinding

Participants could not distinguish effects of the active substances (Supplementary Table S9) after the treatment session or at the end-of-study visit. Placebo was correctly identified by 83% of participants after the study session.

## DISCUSSION

The present controlled study was the first to directly compare acute effects of MDMA, *S*-, and *R*-MDMA. As hypothesized, *S*-MDMA induced greater subjective stimulation than *R*-MDMA. However, at the doses used *S*-MDMA also had greater effects than *R*-MDMA on many other mood scales. Contrary to our hypothesis, *R*-MDMA did not produce greater psychedelic effects than *S*-MDMA. We observed overall comparable effects of MDMA, *S*-MDMA, and *R*-MDMA with regard to effect strength and quality of the responses with minor differences. Specifically, *S*-MDMA induced overall slightly stronger effects and significantly greater bad drug effects, visual alterations, and synesthesia on the VAS, comparable psychedelic- and mystical-type alterations of mind on the 5D-ASC and MEQ, and comparable mood effects on the AMRS compared with MDMA. *S*-MDMA produced greater increases in blood pressure, cortisol, and prolactin compared with MDMA and was the only substance to significantly induce depressive symptoms 1–3 days after administration. The higher 250 mg *R*-MDMA dose produced lower subjective effects on most VASs, comparable psychedelic-like alterations on the 5D-ASC and MEQ, and more introversion on the AMRS compared with MDMA and *S*-MDMA.

Evidence from animal studies and human reports indicates that both enantiomers of MDMA are active and produce differential effects or are even reportedly needed to synergistically produce the full MDMA experience [13, 16, 17]. Based on animal data, we expected that *S*-MDMA and racemic MDMA would be overall equipotent in inducing stimulant-type and adverse effects in humans [9, 13, 16, 33] and thus selected the same dose of 125 mg *S*-MDMA and MDMA for the present comparison. However, other self-administration data in humans indicated that a 100 mg dose of *S*-MDMA induced similar "intoxication" to 125 mg racemic MDMA [21]. The present findings confirm a slightly higher potency of *S*-MDMA compared with MDMA and indicate that a 100 mg dose of *S*-MDMA would be equivalent to a 125 mg dose of racemic MDMA. Thus, the overall slightly greater subjective and cardiostimulant effects of *S*-MDMA in the present study may mainly reflect the 25% greater potency of *S*-MDMA compared with MDMA rather than any qualitative differences between *S*-MDMA and MDMA.

Nevertheless, supporting our primary hypothesis, *S*-MDMA exhibited more cardio- and psychostimulant effects than MDMA and *R*-MDMA in the present study, consistent with animal data [11]. The stronger increase in blood pressure in response to *S*-

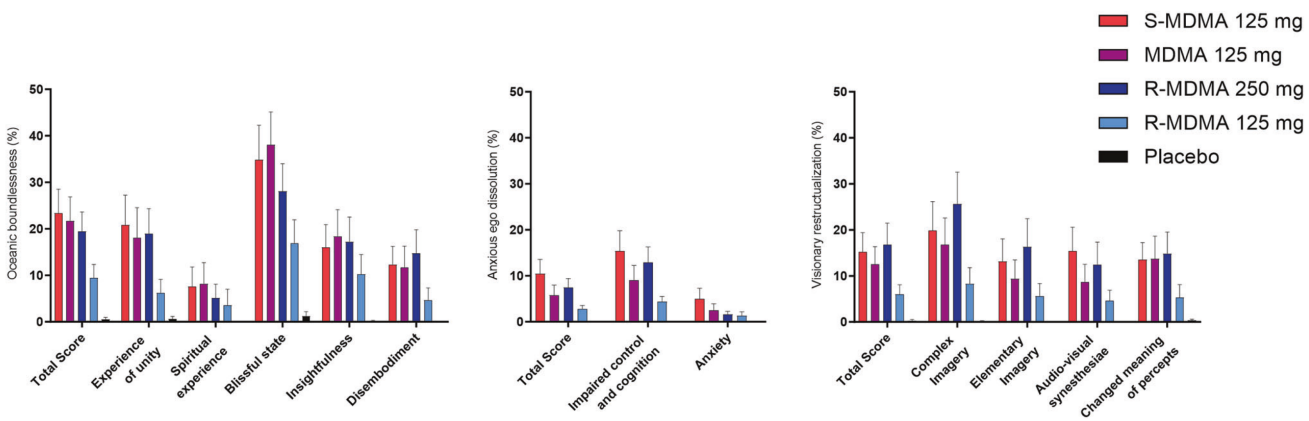


**Fig. 2 Acute mystical-type experiences on the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale.** MDMA, *S*-MDMA, and 250 mg *R*-MDMA induced comparable alterations of mind. The data are expressed as the mean ± SEM percentage of maximally possible scale scores in 24 participants. Statistics are shown in Supplementary Table S5.

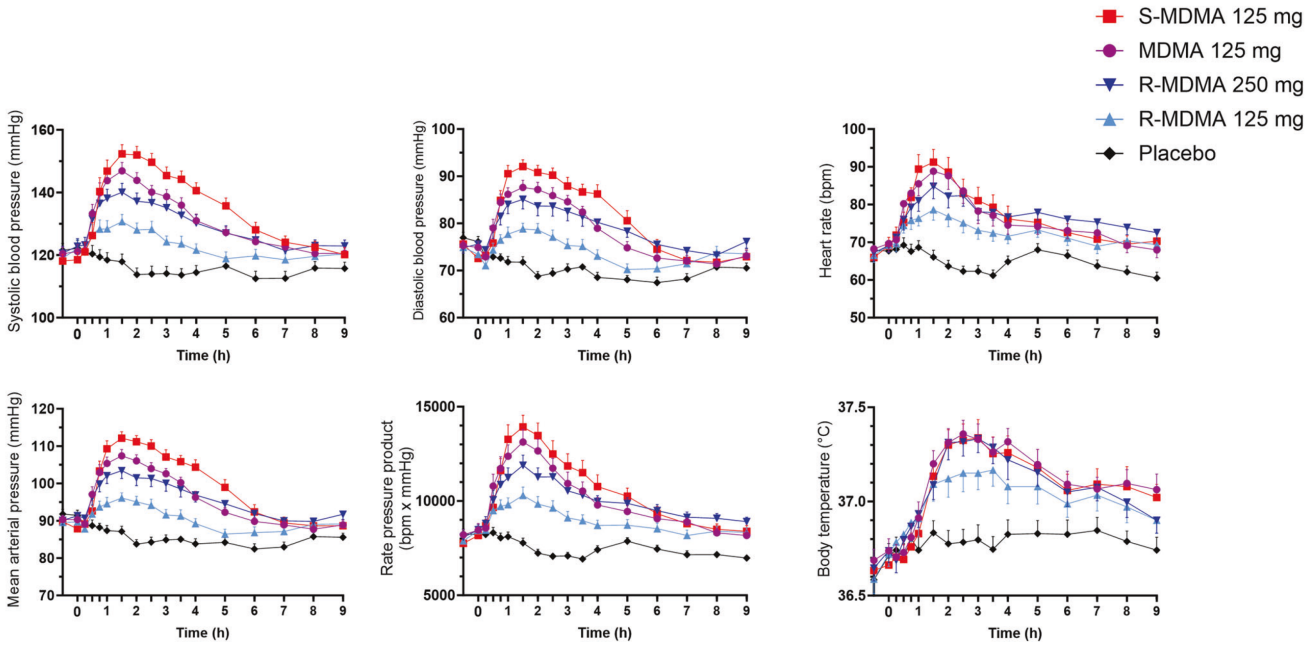


**Fig. 3 Acute autonomic effects.** *S*-MDMA induced greater increases in blood pressure compared with MDMA and both *R*-MDMA doses. MDMA, *S*-MDMA, and 250 mg *R*-MDMA increased heart rate and body temperature comparably. The substances were administered at $t = 0$ h. The data are expressed mean ± SEM in 24 participants. The corresponding maximal responses and statistics are shown in Table 1.

MDMA compared with *R*-MDMA may reflect the higher potency of *S*-MDMA to interact with the norepinephrine-transporter and release norepinephrine compared with *R*-MDMA [4, 34]. Additionally, *S*-MDMA was the only substance to significantly produce depressed mood ratings 1–3 days after drug administration, which could reflect greater transient serotonin depletion [35]. In the present study, we also observed significantly higher ratings of "drug high" after the administration of *S*-MDMA compared with *R*-MDMA. *S*-MDMA was found to be more potent than *R*-MDMA in maintaining self-administration in rhesus monkeys [17], and *S*-MDMA but not *R*-MDMA reinstated responding for amphetamine, indicative of greater abuse liability [12, 19]. *S*-MDMA may be more addictive in humans than *R*-MDMA, but we cannot exclude the possibility that the small differences between substances in the present study are dose-dependent rather than substance-dependent.

*R*-MDMA was expected to elicit more psychedelic-like effects compared with *S*-MDMA because of its higher potency to stimulate 5-$HT_{2A}$ receptors [8]. However, in the present study, *R*-MDMA did not produce more psychedelic-like effects on the 5D-ASC or PES48/MEQ than *S*-MDMA or MDMA. Thus, we could not confirm our hypothesis that *R*-MDMA induces more psychedelic-like effects than *S*-MDMA at the doses used, although a higher dose of R-MDMA would need to be investigated. On the other hand, on the VAS, *S*-MDMA produced greater alterations of vision and greater audio-visual synesthesia than MDMA and *R*-MDMA, effects that would both be considered characteristic of psychedelics [36].

The therapeutic efficacy of MDMA might be enhanced by its ability to promote prosocial behaviors, foster openness, and facilitate a stronger therapeutic bond between the patient and therapist [2, 37, 38]. Animal studies found increases in social interaction in response to MDMA and higher doses of *R*-MDMA but only weak or no prosocial effects of *S*-MDMA [15, 39]. In the present first study in humans, all substances increased VAS ratings of "talkative," "open," "trust," "I feel close to others," and "I want to be with others" compared with placebo, but *S*-MDMA induced higher ratings on all these scales compared with *R*-MDMA at both

**Table 2.** Pharmacokinetic parameters based on non-compartmental analyses [geometric mean (95% CI), range], $N = 24$.

| | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) | $AUC_{24}$ (ng·h/mL) | $AUC_{\infty}$ (ng·h/mL) | CL/F (L/h) | $V_z$/F (L) |
|---|---|---|---|---|---|---|---|
| 125 mg (±)-MDMA | | | | | | | |
| (±)-MDMA | 290 (263–320) | 2.9 (2.5–3.5) | 8.7 (7.6–10) | 3274 (2881–3722) | 4007 (3390–4738) | 31 (26–37) | 392 (364–422) |
| | 180–408 | 1.5–7.0 | 4.6–16 | 1659–5209 | 1735–7591 | 16–72 | 273–530 |
| (±)-MDA | 14 (12–17) | 6.8 (5.9–7.7) | 14 (11–18) | 231 (197–271) | 340 (231–500) | 368 (250–540) | 7492 (6114–9181) |
| | 6.8–28 | 3.0–9.0 | 8.0–29 | 95–455 | 112–1145 | 109–1115 | 4376–12,862 |
| (±)-HMMA | 141 (112–177) | 2.9 (2.5–3.4) | 12 (11–13) | 1666 (1332–2084) | 2274 (1814–2851) | 55 (44–69) | 943 (750–1186) |
| | 49–431 | 1.5–7.0 | 7.7–18 | 563–4876 | 648–6070 | 21–193 | 304–2456 |
| S-MDMA | 123 (111–137) | 2.8 (2.4–3.4) | 5.1 (4.7–5.5) | 1051 (933–1186) | 1111 (977–1263) | 56 (49–64) | 413 (379–450) |
| | 72–189 | 1.5–7.0 | 3.5–7.4 | 567–1571 | 574–1710 | 37–109 | 292–595 |
| S-MDA | 12 (10–14) | 6.3 (5.5–7.3) | 11 (9.3–13) | 158 (128–197) | 230 (187–283) | 272 (221–334) | 4311 (3632–5119) |
| | 5.8–24 | 3.0–9.0 | 7.0–17 | 37–315 | 144–449 | 139–433 | 2294–6726 |
| R-MDMA | 167 (151–184) | 3.3 (2.7–4.1) | 11 (9.1–13) | 2224 (1944–2544) | 2995 (2436–3681) | 21 (17–26) | 327 (301–356) |
| | 100–232 | 2.0–9.0 | 5.1–24 | 1092–3539 | 1166–6410 | 9.8–54 | 231–456 |
| R-MDA | 4.2 (3.6–5.0) | 14 (11–18) | | 72 (58–89) | | | |
| | 2.4–11 | 7.0–24 | | 13–171 | | | |
| 125 mg S-MDMA | | | | | | | |
| S-MDMA | 239 (215–265) | 2.8 (2.3–3.4) | 4.1 (3.6–4.6) | 1869 (1659–2106) | 1917 (1680–2187) | 65 (57–74) | 382 (349–418) |
| | 137–413 | 1.0–8.0 | 2.3–7.4 | 949–2862 | 954–3051 | 41–131 | 253–606 |
| S-MDA | 21 (18–25) | 5.6 (5.0–6.3) | 8.0 (6.9–9.2) | 261 (209–326) | 349 (296–411) | 358 (304–422) | 4126 (3443–4944) |
| | 9.0–46 | 3.0–9.0 | 4.0–12 | 62–608 | 196–761 | 164–637 | 2045–8142 |
| HMMA | 175 (145–211) | 3.6 (3.2–4.1) | 7.7 (6.8–8.8) | 1955 (1666–2294) | 2293 (1973–2665) | 55 (47–63) | 609 (491–754) |
| | 71–421 | 1.5–7.0 | 4.8–13 | 822–3581 | 989–3768 | 33–126 | 249–1564 |
| 125 mg R-MDMA | | | | | | | |
| R-MDMA | 335 (305–368) | 3.2 (2.7–3.8) | 12 (11–14) | 4775 (4249–5366) | 6869 (5803–8132) | 18 (15–22) | 328 (298–361) |
| | 209–463 | 2.0–7.0 | 6.6–32 | 2307–6916 | 2559–14771 | 8.5–49 | 199–550 |
| R-MDA | 8.2 (6.8–9.8) | 16 (13–20) | | 146 (121–175) | | | |
| | 3.4–18 | 7.0–24 | | 61–337 | | | |
| HMMA | 142 (105–191) | 2.3 (1.8–2.8) | 19 (17–22) | 1631 (1300–2045) | 2956 (2369–3688) | 42 (34–53) | 1181 (943–1479) |
| | 28–551 | 0.8–6.0 | 12–39 | 500–5026 | 730–7100 | 18–171 | 376–4297 |
| 250 mg R-MDMA | | | | | | | |
| R-MDMA | 694 (638–755) | 3.6 (2.9–4.3) | 14 (13–16) | 10,087 (9113–11,164) | 15754 (13,939–17,805) | 16 (14–18) | 329 (302–358) |
| | 501–975 | 1.5–8.0 | 10–28 | 5770–15,780 | 10,049–29,136 | 8.6–25 | 203–466 |
| R-MDA | 16 (13–19) | 22 (19–25) | | 273 (228–327) | | | |
| | 7.7–41 | 8.0–24 | | 120–725 | | | |
| HMMA | 162 (128–203) | 2.8 (2.3–3.4) | 18 (16–21) | 2020 (1672–2441) | 3559 (2929–4325) | 70 (58–85) | 1840 (1513–2239) |
| | 60–539 | 1.5–8.0 | 7.2–35 | 908–5211 | 1450–8484 | 29–172 | 807–3958 |

*AUC* area under the plasma concentration-time curve, $AUC_{\infty}$ AUC from time zero to infinity, $AUC_{24}$ from time 0 to 24, *CL/F* apparent total clearance, $C_{max}$ maximum observed plasma concentration, $T_{1/2}$ plasma half-life, $T_{max}$ time to reach $C_{max}$, *95%CI* 95% confidence interval, $V_z/F$ apparent volume of distribution.

doses. All substances produced comparable increases in ratings of feelings of "connectedness" on the PES48 compared with placebo. Thus, the present findings do not indicate greater prosocial effects of *R*-MDMA compared with MDMA or *S*-MDMA.

Oxytocin has overlapping social cognitive effects with MDMA [2, 40–42] and contributes to acute subjective effects of MDMA [1]. Cortisol and prolactin could be considered biomarkers of the serotonergic activity of MDMA [43]. In the present study, all substances increased circulating levels of oxytocin, cortisol, and prolactin. *S*-MDMA produced greater increases in oxytocin and cortisol compared with *R*-MDMA. *S*-MDMA also released prolactin at least as effectively as *R*-MDMA, in contrast to a study in rhesus monkeys [10]. The present findings align with stronger stimulation of the serotonin system by *S*-MDMA compared with *R*-MDMA at the doses used in the present study and are consistent with the greater serotonergic potency (but not selectivity) of *S*-MDMA compared with *R*-MDMA [4, 34].

Animal studies reported no hyperthermic effects of *R*-MDMA in mice or rats [14–16]. However, we found similar minimal increases in body temperature after *S*-MDMA and *R*-MDMA in the present human study.

Based on preliminary human data, the potency of *R*-MDMA was considered lower than MDMA and *S*-MDMA, with an effective dose "that might lie in the vicinity of 300 mg" [21]. Subjective effects of the *R*-MDMA doses that were used in the present study were lower than the 125 mg MDMA and 125 mg *S*-MDMA doses and indicate that a 300 mg dose may induce a comparable overall response to 125 mg MDMA or 100 mg *S*-MDMA. Thus, we would consider *S*-MDMA to be 1.25-fold more potent than MDMA and *R*-MDMA to be 2.4-fold less potent than MDMA. The in vitro potency of *S*-MDMA to release norepinephrine [34] or interact with the norepinephrine transporter was 4-fold higher compared with *R*-MDMA, predicting an approximately 4-fold higher potency in vivo [44].

Pharmacokinetics of *R*- and *S*-MDMA in humans have only been described after the administration of racemic MDMA [45–47]. After MDMA administration, *R*-MDMA had higher plasma concentrations ($C_{max}$ and area under the curve) and an extended half-life compared with *S*-MDMA [45–47]. The present study confirmed the greater plasma exposure and longer elimination half-life of *R*-MDMA compared with *S*-MDMA after the administration of racemic MDMA. Additionally, the present study characterized pharmacokinetics of *S*-MDMA and *R*-MDMA in the absence of interactions with the other enantiomer. The elimination half-life of *S*-MDMA was 4.1 h when it was administered alone but 5.1 h when it was administered with *R*-MDMA in the form of racemic MDMA. The elimination half-life of *R*-MDMA was 12 and 14 h for the 125 and 250 mg doses of pure *R*-MDMA, respectively, indicating an increase with dose. Additionally, the formation of *R*-MDA from *R*-MDMA was dose-proportional, whereas the formation of HMMA from *R*-MDMA decreased with higher doses of *R*-MDMA. Although the dose of *R*-MDMA was doubled from 125 mg to 250 mg, the HMMA concentration did not double as well. Altogether, the data confirm that *R*-MDMA inhibits CYP2D6, thereby inhibiting its own inactivation to HMMA [48] similar to MDMA [49]. The present findings that the half-life of *S*-MDMA becomes shorter when it is administered without the *R*-enantiomer and that the HMMA concentrations were elevated when *S*-MDMA was administered compared with when *R*-MDMA was administered, indicating potentially less inhibition of CYP2D6 by *S*-MDMA.

We also showed that MDMA and MDA in humans did not undergo chiral inversion [32]. Thus, although HMMA was not enatioselectively measured, it can be assumed that only *S*- and *R*-HMMA are formed after *S*- and *R*-MDMA administration, respectively.

The present study has several strengths. A relatively large study sample ($n = 24$) and powerful within-subjects comparisons were used in a randomized double-blind design. Excellent blinding between *S*-MDMA, *R*-MDMA, and MDMA was confirmed. Two doses of the main substance of interest, *R*-MDMA, were included. We also included equal numbers of male and female participants. We used a wide range of internationally established psychometric outcome measures. Plasma concentrations were determined at close intervals in all participants and analyzed with validated achiral and chiral methods [32].

Notwithstanding its strengths, the present study also has limitations. To avoid too many exposures to MDMA, we had to limit the use of doses for each substance. We used only one dose of *S*-MDMA and only two doses of *R*-MDMA and failed to use exactly equivalent doses of the different substances. Doses of 100 mg *S*-MDMA and 300 mg *R*-MDMA would have been more equivalent. Consequently, we cannot confirm whether the observed differences between substances were attributable to the use of non-equivalent doses or qualitative properties of the substances. The study used a highly controlled hospital setting and included only healthy volunteers. People in different environments and patients with psychiatric disorders may respond differently to these substances. The outcome measures might not have been sufficiently sensitive to capture all aspects of the substance experience and very subtle differences between acute effects of MDMA and its enantiomers.

## CONCLUSION

In conclusion, the present study found that racemic MDMA, *S*-MDMA, and *R*-MDMA induced overall similar qualitative subjective and adverse effects when dosed equivalently. *S*-MDMA may have slightly greater stimulant-like properties than MDMA and *R*-MDMA. The results indicate dose-equivalence with regard to overall acute effects of 125 mg MDMA, 100 mg *S*-MDMA, and 300 mg *R*-MDMA. The pharmacokinetic findings indicate that *R*-MDMA dose-dependently inhibits CYP2D6 and thus its own inactivation and the inactivation of *S*-MDMA when administered as racemic MDMA. Overall, the present findings do not presently indicate relevant beneficial effects of *R*-MDMA or *S*-MDMA over MDMA in substance-assisted therapy in patients.

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## AUTHOR CONTRIBUTIONS

IS and MEL designed the research. IA, IS, DL, DR, AK, NV, and AE performed the research. IS, DL, and MEL analyzed the data. IS and MEL wrote the manuscript with input from all other authors. All authors gave final approval to the manuscript.

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## COMPETING INTERESTS

MEL is a consultant for Mind Medicine, Inc. The other authors declare no conflicts of interest. Knowhow and data associated with this work are owned by the University

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## ADDITIONAL INFORMATION

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## Supplement

## Methods

*Sample size calculation*

Power analysis was performed with PASS®, Hintze J. Kaysville, Utah, US. A difference of 15% in the primary measures was considered clinically meaningful. A sample size of 16 achieves 80% power to detect a difference of 15% between the null hypothesis mean of 100% and the alternative hypothesis mean of 85% with an estimated standard deviation of 20% and with a significance level (alpha) of 0.05 using a two-sided one-sample t-test. The study would have been adequately powered for the primary endpoint with a sample size of 16. A minimal sample size of 20 accounted for additional endpoints although these analyses remain more exploratory and/or confirmatory of the primary endpoint findings but using alternative and additional measures. Based on our experience with a similar study we assume a screening-failure rate of 25% and we expect to screen 36 subjects to include 24 in the study.

*Prior and current substance use*

We aimed at including persons with no or limited previous drug experience as similar substance use experiences are mostly observed in patients treated with MDMA. Thus, persons with no prior experience were included as well as persons with a few prior experiences. However, we excluded persons with > 20 prior illicit substance uses. There was no restriction on prior use of $\Delta^9$-tetrahydrocannabinol (THC) as THC-use is prevalent. However, persons with any substance use disorder including THC were excluded.

Eleven participants had previously used MDMA (1–9 times), 11 participants had used a psychedelic (1–10 times), and nine participants had used a stimulant, including cocaine (eight participants, 1–5 times), amphetamine (six participants, 1–3 times), and methylphenidate (three participants, once). Five participants had used nitrous oxide (1–5 times), four participants had used ketamine (1–3 times), and one participant had used 4-bromo-2,5-dimethoxyphenethylamine (once). Six participants had never used any illicit drugs, with the exception of THC. One participant smoked two tobacco cigarettes daily and three participants smoked occasionally. Seven-teen participants drank alcohol. Mean+SD consumption of alcohol was 2.8+3.0 standard drinks per week (range: 1-10). Twenty-two participants had use cannabis (Table S1).

Table S1. Life-time prevalence of illicit drug use and current substance use

| Subject | MDMA | hallucinogens | sedatives | stimulants | opioids | THC | nicotine | alcohol | caffeine |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 5 | 5 | 3 | 3 | 1 | ~200 | 0 | 3 | 2 |
| 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 4 |
| 3 | 1 | 4 | 0 | 3 | 0 | ~180 | 0 | 10 | 3 |
| 4 | 1 | 0 | 0 | 0 | 0 | ~100 | 0 | 8 | 1 |
| 5 | 0 | 2 | 0 | 1 | 0 | ~100 | 0 | 2 | 2 |
| 6 | 0 | 0 | 0 | 0 | 0 | ~100 | 0 | 0 | 0 |
| 7 | 3 | 0 | 2 | 8 | 0 | ~69 | ~60 | 8 | 1 |
| 8 | 5 | 1 | 3 | 7 | 0 | ~500 | 0 | 5 | 2 |
| 9 | 0 | 0 | 2 | 0 | 1 | 5 | 0 | 3 | 2 |
| 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 11 | 0 | 1 | 0 | 0 | 0 | ~100 | 0 | 0 | 2 |
| 12 | 0 | 0 | 5 | 1 | 0 | 20 | 0 | 0 | 1 |
| 13 | 0 | 0 | 0 | 0 | 0 | 20 | 1 – 5 | 3 | 1 |
| 14 | 3 | 10 | 0 | 3 | 1 | ~1000 | 0 | 0 | 1 |
| 15 | 0 | 0 | 2 | 0 | 0 | 1 | 0 | 0 | 0 |
| 16 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 3 |
| 17 | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 1 |
| 18 | 3 | 10 | 0 | 0 | 0 | > 10.000 | 5 – 20 | 5 | 4 |
| 19 | 6 | 1 | 1 | 5 | 0 | ~1000 | ~80 | 5 | 10 |
| 20 | 9 | 9 | 1 | 0 | 0 | ~200 | 0 | 6 | 3 |
| 21 | 0 | 0 | 0 | 0 | 0 | 20 | 0 | 2 | 5 |
| 22 | 6 | 1 | 0 | 2 | 0 | ~50 | 0 | 2 | 0 |
| 23 | 0 | 7 | 0 | 0 | 0 | ~80 | 0 | 0 | 0 |
| 24 | 0 | 2 | 0 | 0 | 0 | 20 | 0 | 1 | 4 |

Values are times used in life, except nicotine (cigarettes per month), alcohol (units per week), and caffeine (cups per day)

*Subjective drug effects measurements*
*Visual Analog Scales (VASs)*

Subjective effects were assessed repeatedly using visual analog scales (VASs) [1,2]. 0.5 h before and 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, and 24 h after drug administration. The VASs included “any drug effect”, “good drug effect”, “bad drug effect”, “stimulated”, “liking”, “feeling high”, “fear”, “alteration of vision”, “sounds seem to influence what I see”, “alteration of sense of time” and “ego dissolution” that were presented as 100-mm horizontal lines (0-100%), marked from “not at all” on the left to “extremely” on the right [1,3]. Further VASs included “happy”, “content”, “talkative”, “open”, “trust”, “I feel close to others” “I want to be alone”, and “I want to be with others”. These VASs were bidirectional and marked with “normal” in the middle at 0 mm and “not at all” (-50 mm) on the left and “extremely” (50 mm) on the right. The primary VAS outcome measure was “stimulation”. The VASs included in the present study have been repeatedly used and shown to be sensitive with MDMA [1,3-5]. Additionally the VAS “alteration of vision”, “sounds seem to influence what I see”, “alteration of sense of time” and “ego dissolution” were included because they were shown to be increased in response to the administration of different psychedelics [5-7] and to better capture potentially psychedelic-like effects of R-MDMA. The VAS can be completed relatively rapidly and easily by the participant even during the MDMA experience and allows for a valid prospective definition of the drug effects over time. They are sensitive and relatively simple measures. More complex assessments of the state of MDMA have to be performed primarily at the end of the session and include entire multi-item questionnaires. The VAS “any drug effect” is an overall effect measure to characterize the overall effect intensity and time course. The VAS “good drug effect” is an overall measure of effects subjectively considered positive and interrelated with other measures such as “drug liking”. The VAS “bad drug effect” is an overall measure of any negative effects and related to “fear”. The VAS “ego dissolution” was marked with the sentence: “the boundaries between myself and my surroundings seemed to blur”. This is also an item of the 5D-ASC (no. 71) which has been used as a simple measure of “ego dissolution” previously [8,9] and can be used repeatedly as a single VAS [1,10]. VASs were assessed each time MDMA blood concentrations were measured.

*Adjective Mood Rating Scale (AMRS)*

The Adjective Mood Rating Scale (AMRS) [11] was used 0.5 h before and 2.5, 5, and 9 h after drug administration. The AMRS is a validated 60-item Likert mood rating scale mainly use in Europe and consists of subscales including ratings on “well-being”, “anxiety”, “inactivity”, “extraversion”, “introversion”, and “emotional excitation”. It is suitable for repeated measurements of mood states. The short German EWL60S version was used [11]. The completion of the ratings under the effects of psychedelic substances is possible but difficult because it lasts several minutes. The scale was used in paper and pencil version, but it may be more suitable to use this measure verbally during states of markedly impaired concentration. The AMRS was included as a secondary measure because it could be considered a better validated measure of mood states and producing more defined ratings than the VAS and to support findings on the VAS (AMRS well-being considered similar to VAS good drug effects; AMRS anxiety considered similar to VAS fear).

*5 Dimension of Altered States of Consciousness (5D-ASC) scale*

The 5 Dimensions of Altered States of Consciousness (5D-ASC) scale [12,13] was used as the primary outcome measure for psychedelic-like effects and was administered 9 h after drug administration to retrospectively rate peak drug effects. The 5D-ASC scale measures altered states of consciousness and contains 94 items (visual analog scales). The instrument consists of five subscales/dimensions [12] and 11 lower-order scales [13]. The 5D-ASC dimension “Oceanic Boundlessness” (27 items) measures derealization and depersonalization associated with positive emotional states, ranging from heightened mood to euphoric

exaltation. The corresponding lower-order scales include “experience of unity,” “spiritual experience,” “blissful state,” “insightfulness,” and “disembodiment.” The dimension “Anxious Ego Dissolution” (21 items) summarizes ego-disintegration and loss of self-control phenomena associated with anxiety. The corresponding lower-order scales include “impaired control of cognition” and “anxiety.” The dimension “Visionary Restructuralization” (18 items) consists of the lower-order scales “complex imagery,” “elementary imagery,” “audio-visual synesthesia,” and “changed meaning of percepts.” Two additional dimensions describe “Auditory Alterations” (15 items) and “Reduction of Vigilance” (12 items). The total 3D-ASC score is the total of the three main dimensions “Oceanic Boundlessness”, “Anxious Ego-Dissolution”, and “Visionary Restructuralization” and can be used as a measure of the overall intensity of the alteration of the mind [9]. The scale is well-validated in German [12] and many other languages and widely used to characterize the subjective effects of various psychedelic drugs. In particular, the scale has been used by most research groups to psychometrically assess LSD, psilocybin and MDMA effects [1,2,7,14-18]. Furthermore, acute ratings on the 5D-ASC after administration of psilocybin and LSD have been used to predict long-term effects of psychedelic treatments in patients [19-21]. Ratings on the 5D-ASC have been shown to closely correlate with ratings on the Mystical Effects Questionnaire (MEQ, see below) [9] which is primarily used by research groups in the US [20].

*Psychedelic Experience Scale (PES) and Mystical Effects Questionnaire (MEQ)*

Mystical experiences were assessed 9 h after drug administration using the Psychedelic Experience Questionnaire/Scale (PES) [22] that represents a revalidation of the original 100-item States of Consciousness Questionnaire (SOCQ) [9,23] and includes the 43-item Mystical Effects Questionnaire (MEQ43) [23], the 30-item Mystical Effects Questionnaire (MEQ30) [24], and the 40-item Mystical Effects Questionnaire (MEQ40) [22]. The MEQ30 subscales are “mystical”, “positive mood”, “transcendence of time/space”, and “ineffability” and their total provides the MEQ30 total score. Ten more items allow to derive the additional subscales “paradoxicality” and “connectedness” (40-item MEQ40). Eight more items allow to derive the additional “visual experience” and “distressing experience” subscales that together with all other subscales for the PES subscales (48 items from the 100-item SOCQ. Note that the full 100-item questionnaire was completed by the participants and only 48 items are needed to derive the validate subscales [22]. Future research could use the full 100-item scale (SOCQ) or just the 48-items needed for the PES analysis. The published German version was used [9,22]. The MEQ has been used in numerous experimental and therapeutic trials with psilocybin [20,23,25-31]. The MEQ has also been used in many experimental trials with LSD and MDMA [1,2,5,7,32,33] We derived the four scale scores of the newly validated revised 30-item MEQ: mystical, positive mood, transcendence of time and space, and ineffability [24].

## Results

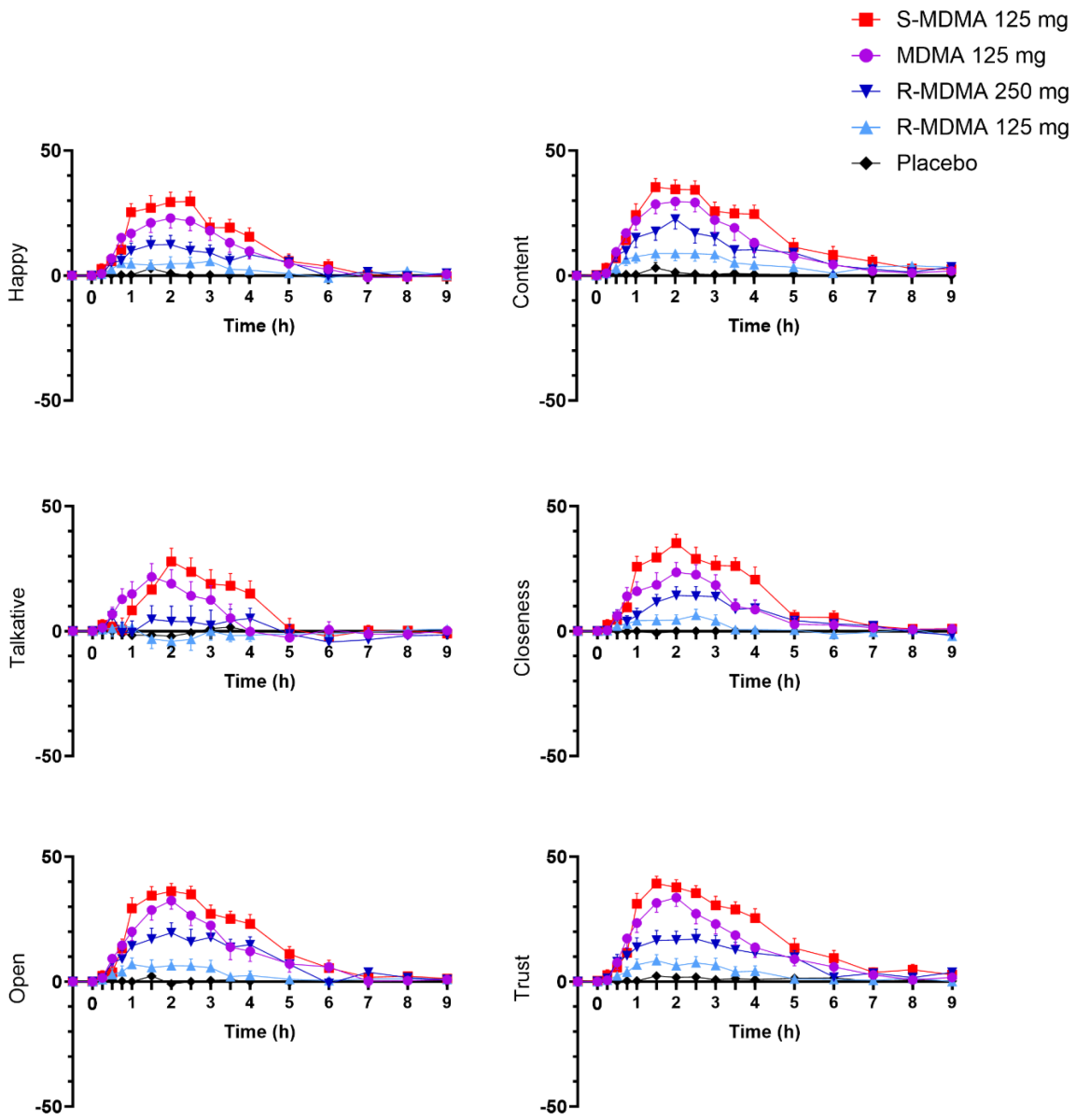



**Figure S1.** Acute subjective effects induced by 3,4-Methylendioxymethamphetamin (MDMA), *S*-MDMA, *R*-MDMA and placebo over time on the Visual Analog Scale (VAS). All substance conditions induced increases on the bidirectional VAS shown in this figure. *R*-MDMA at both doses induced weaker effects than *S*-MDMA and MDMA on all these VAS items. MDMA (125 mg), *S*-MDMA (125 mg), *R*-MDMA (125 mg), *R*-MDMA (250 mg) or placebo was administered at t = 0 h. The data are expressed as the mean ± SEM percentage of maximally possible scale scores in 24 subjects. The corresponding maximal responses and statistics are shown in Table 1.

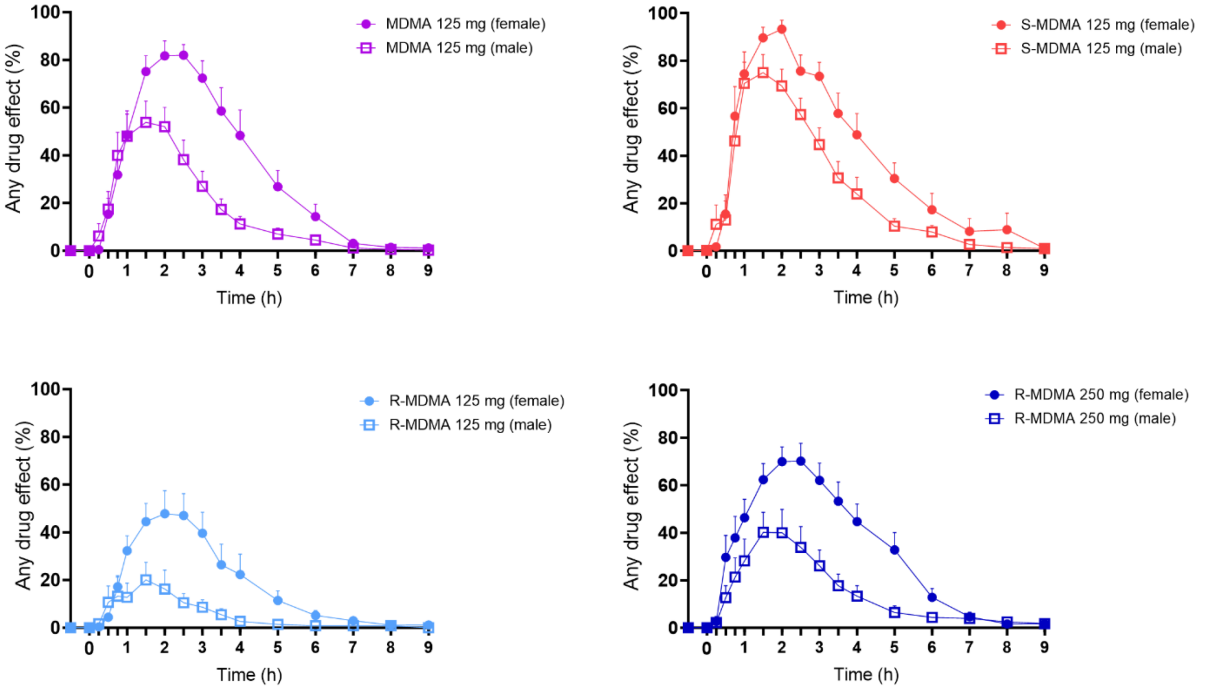



**Figure S2.** Sex differences in "any drug effects" of MDMA, *S*-MDMA, and *R*-MDMA on the VAS. Female participants reported stronger "any drug effects" than male participants across all substance conditions. However, when adjusting for weight, the difference in "any drug effects" between female and male became non-significant and is therefore driven by the lower body weight of women compared with men and the higher doses of the substances per kg body weight in women compared with men. The weight-dependent greater plasma levels were observed with all substances and indicate that lower doses could be used in humans with lower body weight. In the present study, the weight and sex-differences did not confound the results because treatments were compared within-subjects. MDMA (125 mg), *S*-MDMA (125 mg), *R*-MDMA (125 mg), *R*-MDMA (250 mg) or placebo was administered at t = 0 h. The data are expressed as the mean ± SEM percentage of maximally possible scale scores in 24 participants (12 female, 12 male). The corresponding maximal responses are shown in Table S2.

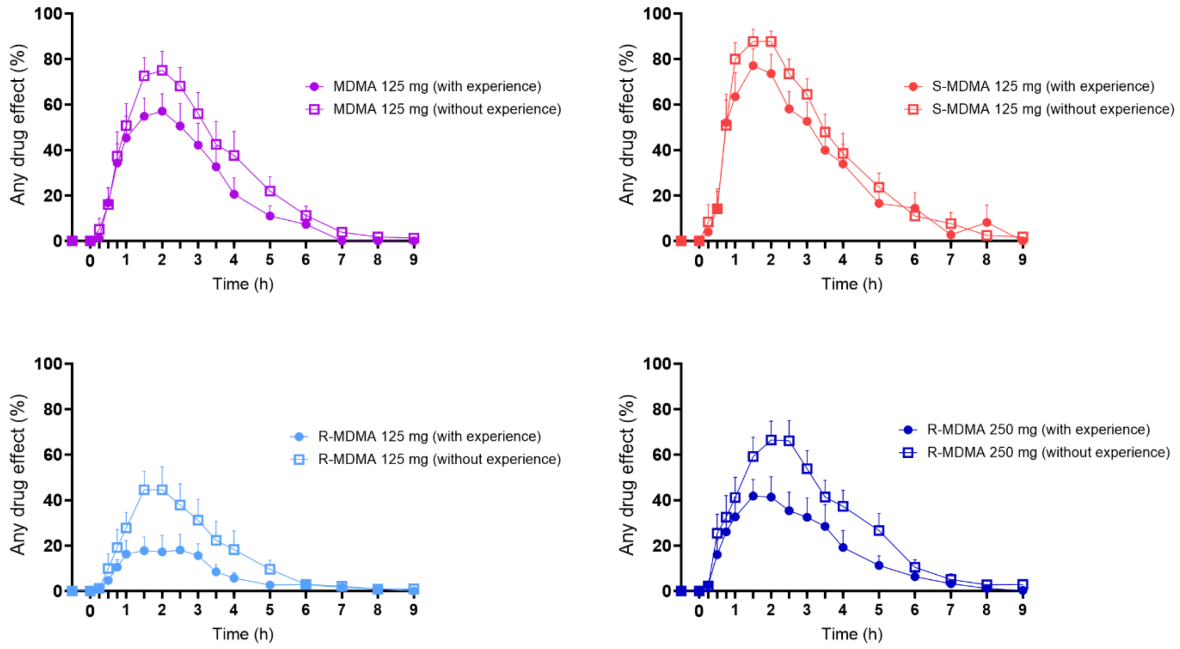



**Figure S3.** Differences in "any drug effects" of MDMA, *S*-MDMA, and *R*-MDMA between participants with and without previous MDMA experience on the VAS. Participants without prior MDMA experience indicated slightly higher "any drug effects" compared with participants with previous MDMA experience, although the differences were not statistically significant. MDMA (125 mg), *S*-MDMA (125 mg), *R*-MDMA (125 mg), *R*-MDMA (250 mg) or placebo was administered at t = 0 h. Prior drug experience did not confound the comparison between substances because there were no relevant order effects, and the order of the substance administration was balanced across the study. The data are expressed as the mean ± SEM percentage of maximally possible scale scores in 24 subjects, with 11 participants having prior MDMA experience and 13 participants having no previous experience with MDMA. The corresponding maximal responses are shown in Table S3.

We also compared the subjective effects in the 18 participants with prior illicit substance experience with those in 6 participants with no prior illicit substance experience (with the exception of THC). The findings were similar to those shown above in Figure S3 for the MDMA-experienced and MDMA-naïve participants with no statistical difference. Furthermore, there may be confounding by other differences besides prior drug experience such as sex.

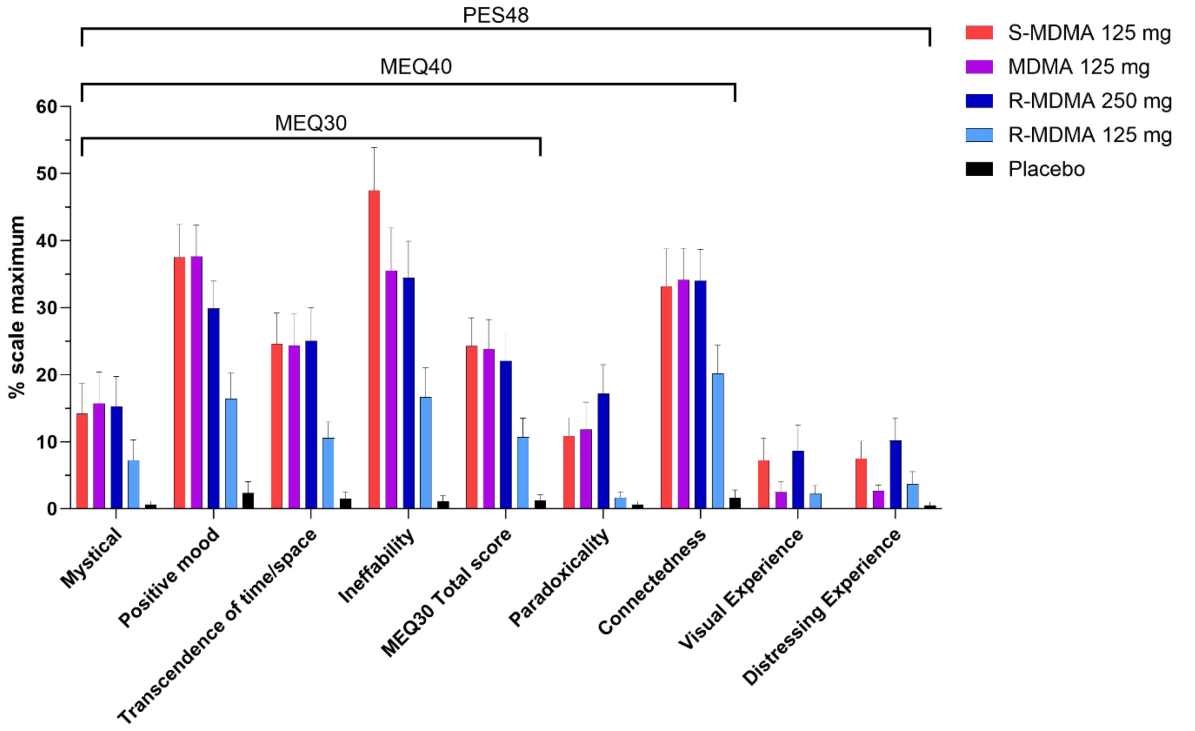



**Figure S4.** Acute mystical-type experiences on the Psychedelic Experience Scale (PES) and the 30- and 40-item Mystical Effects Questionnaire (MEQ30 and MEQ40, respectively). MDMA (125 mg), *S*-MDMA (125 mg) and *R*-MDMA (250 mg) induced overall comparable effects on the MEQ30, the MEQ40 and the 48-item PES48. 125 mg *R*-MDMA only induced effects on the subscales positive mood and ineffability on the MEQ30 and the ME30 total score. Additionally, 125 mg *R*-MDMA also induced effects on the connectedness subscale of the MEQ40 which were comparable to the other substances. The data are expressed as the mean ± SEM percentage of maximally possible scale scores in 24 subjects. Statistics are shown in Supplementary Table S6.

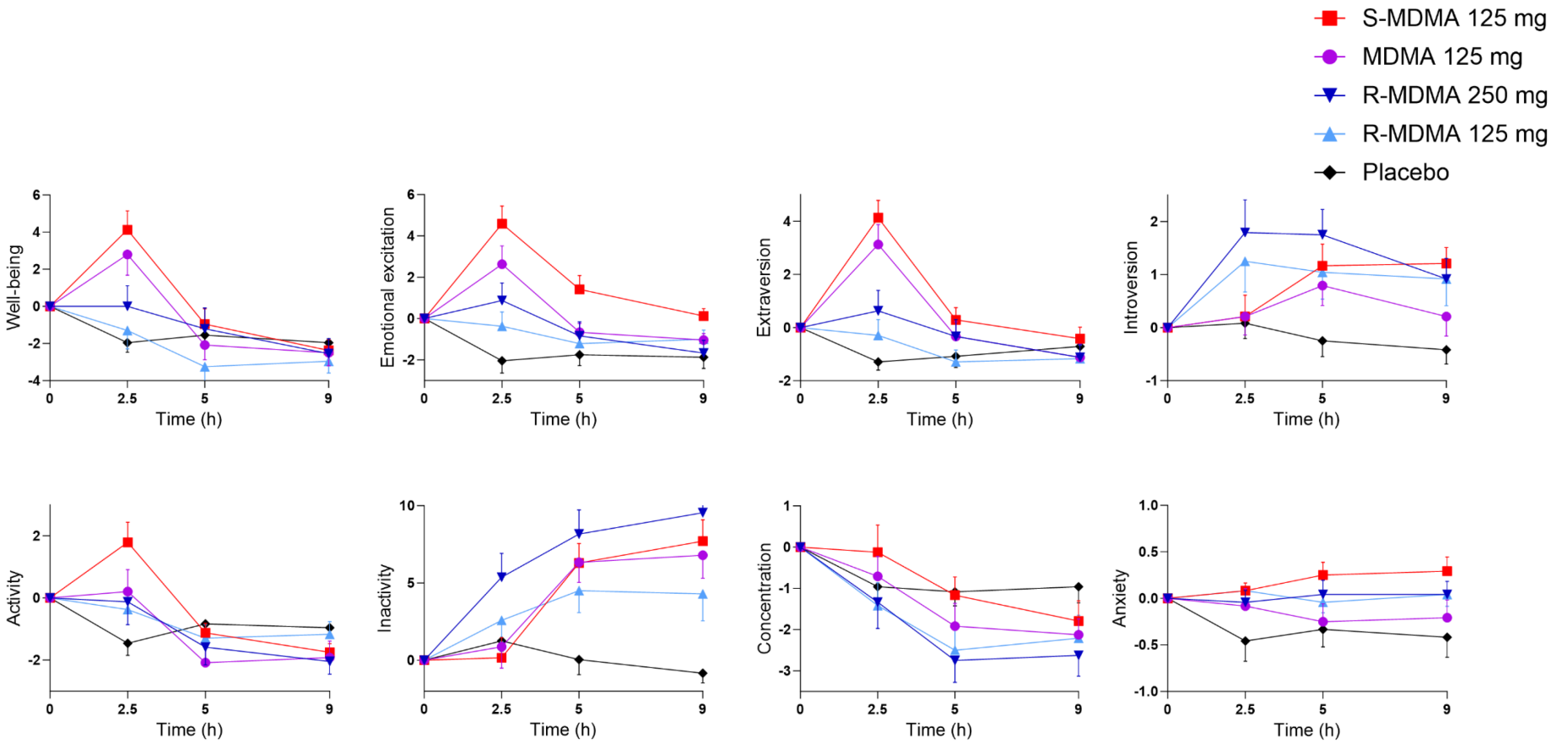



**Figure S5**. Subjective effects over time on the Adjective Mood Rating Scale (AMRS). MDMA and *S*-MDMA both increased well-being and emotional excitation and *S*-MDMA induced more emotional excitation than both doses of *R*-MDMA. MDMA, *S*-MDMA and 250 mg *R*-MDMA all significantly induced inactivity and extraversion. Introversion was induced by all enantiomer conditions but not with MDMA itself. 250 mg *R*-MDMA induced more "introversion" than MDMA. Only *S*-MDMA induced self-rated anxiety and none of the conditions changed values in activity and concentration. MDMA, *S*-MDMA, 125 mg *R*-MDMA, 250 mg *R*-MDMA or placebo was administered at t = 0 h. The data are expressed as mean ± SEM changes from baseline in 24 subjects. The corresponding maximal effects and statistics are shown in Supplementary Table S7.

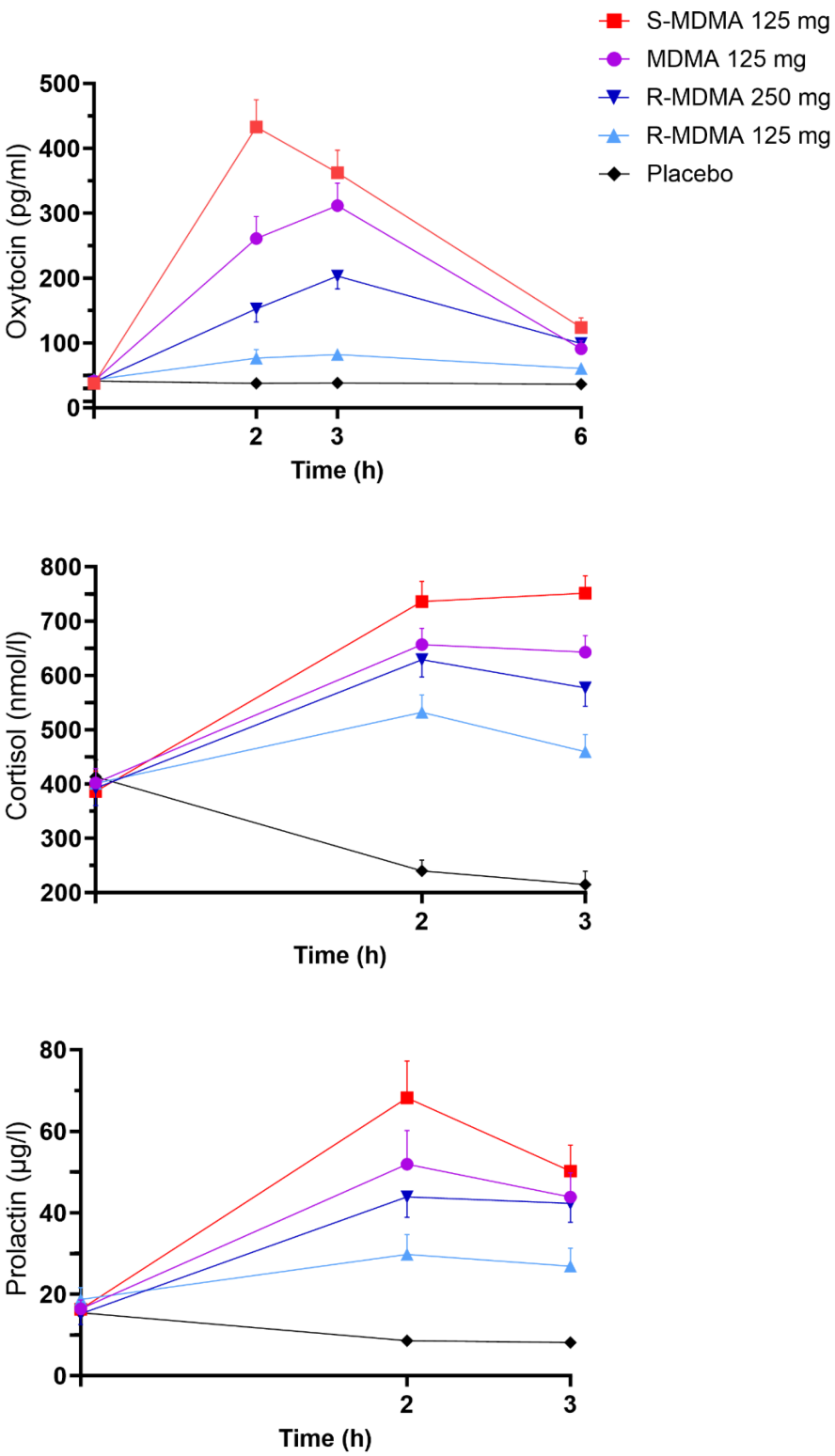



**Figure S6.** Plasma concentrations of oxytocin, cortisol, and prolactin with MDMA, *S*-MDMA. *R*-MDMA, and placebo. All substances increased oxytocin, cortisol, and prolactin compared with placebo. *S*-MDMA increased oxytocin and cortisol release more compared to MDMA and both doses of *R*-MDMA. Prolactin release was increased more with *S*-MDMA compared to MDMA and 125 mg *R*-MDMA. The data are expressed as mean ± SEM. 125 mg MDMA, 125 mg *S*-MDMA, 125 mg *R*-MDMA, 250 mg *R*-MDMA or placebo was administered at t = 0 h. The corresponding maximal effects and statistics are shown in Table 1.

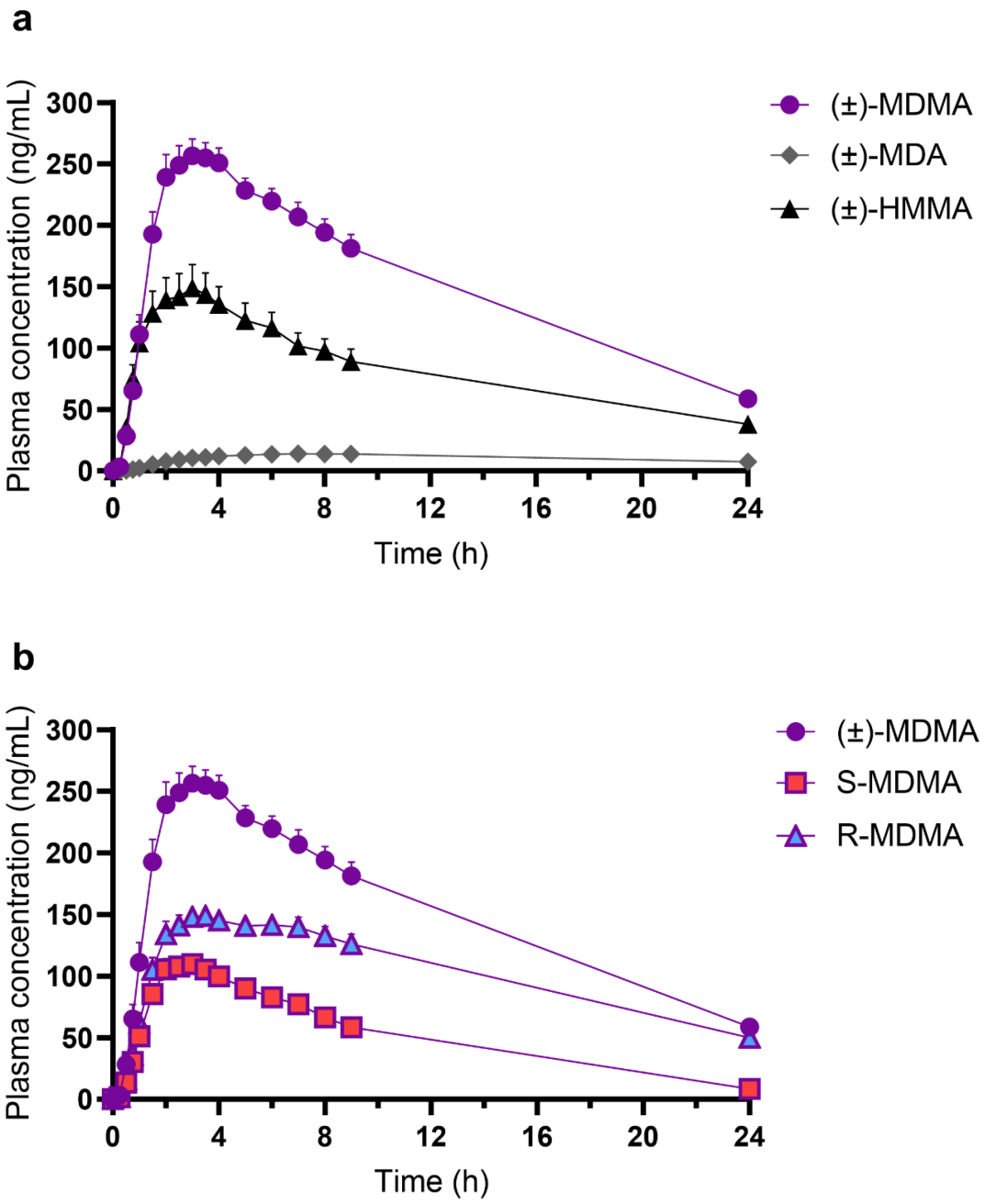



**Figure S7.** (**a**) Plasma concentrations of (±)-MDMA and its metabolites (±)-MDA and (±)-HMMA when 125 mg (±)-MDMA was administered. HMMA concentrations were determined after enzymatic deglucuronidation. (**b**) Plasma concentrations of the racemic (±)-MDMA and its enantiomers *S*- and *R*-MDMA were measured separately after the administration of 125 mg (±)-MDMA. Plasma concentration ($C_{max}$ and area under the curve (AUC)) was higher, and half-life ($t_{1/2}$) was longer for the *R*-enantiomer compared to the *S*-enantiomer. The data are expressed as mean ± SEM. (±)-MDMA was administered at t = 0 h. The corresponding pharmacokinetic parameters were determined by non-compartmental analysis and are shown in Table 2.

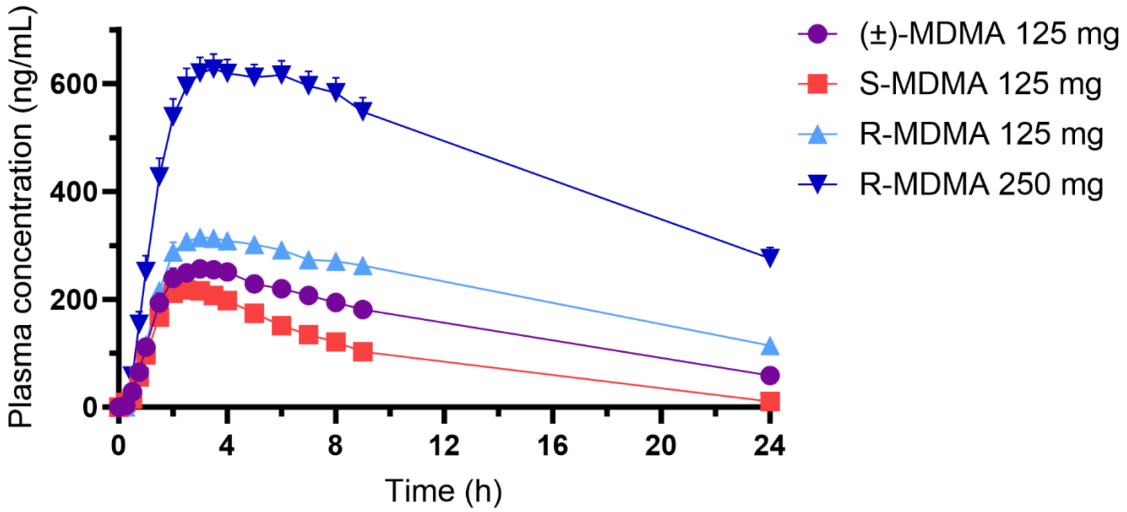



**Figure S8.** Plasma concentrations of (±)-MDMA, *S*-MDMA and *R*-MDMA after administration of the respective substance. The enantiomer *R*-MDMA reaches higher plasma concentrations and *S*-MDMA lower plasma concentrations compared with (±)-MDMA when administered at the same dose. The data are expressed as mean ± SEM. (±)-MDMA (125 mg), *S*-MDMA (125 mg), *R*-MDMA (125 mg), or *R*-MDMA (250 mg) was administered at t = 0 h. The corresponding pharmacokinetic parameters were determined by non-compartmental analysis and are shown in Table 2.

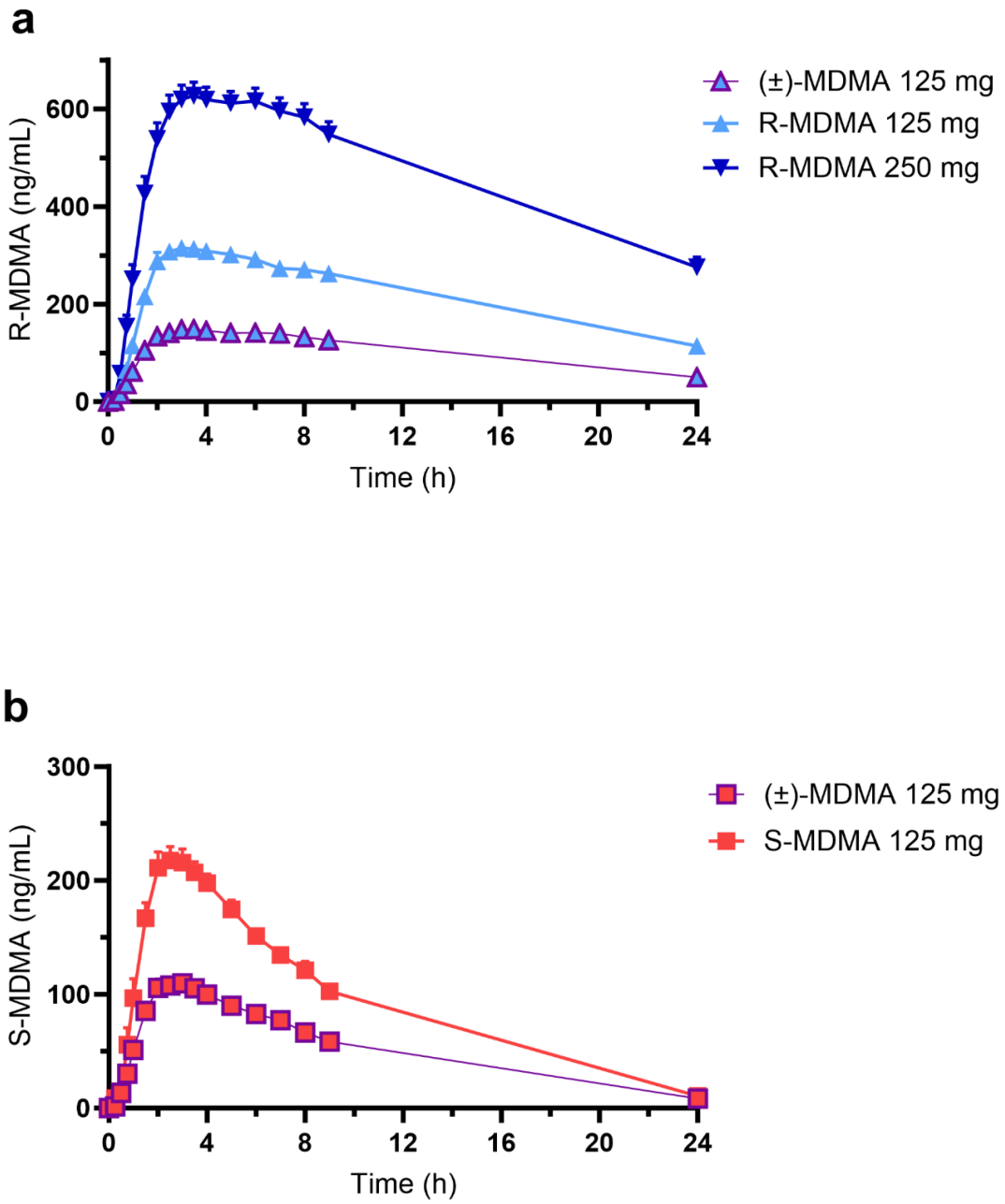



**Figure S9.** (**a**) Plasma concentration of *R*-MDMA when 125 mg (±)-MDMA, 125 mg *R*-MDMA and 250 mg *R*-MDMA was administered. The half-life of *R*-MDMA increases with higher doses of *R*-MDMA given. (**b**) Plasma concentration of *S*-MDMA when 125 mg (±)-MDMA and 125 mg *S*-MDMA were administered. Administration of only the *S*-enantiomer shortened the half-life by one hour compared to the administration as racemic (±)-MDMA. The data are expressed as mean ± SEM. (±)-MDMA (125 mg), *S*-MDMA (125 mg), *R*-MDMA (125 mg), or *R*-MDMA (250 mg) was administered at t = 0 h. The corresponding pharmacokinetic parameters were determined by non-compartmental analysis and are shown in Table 2.

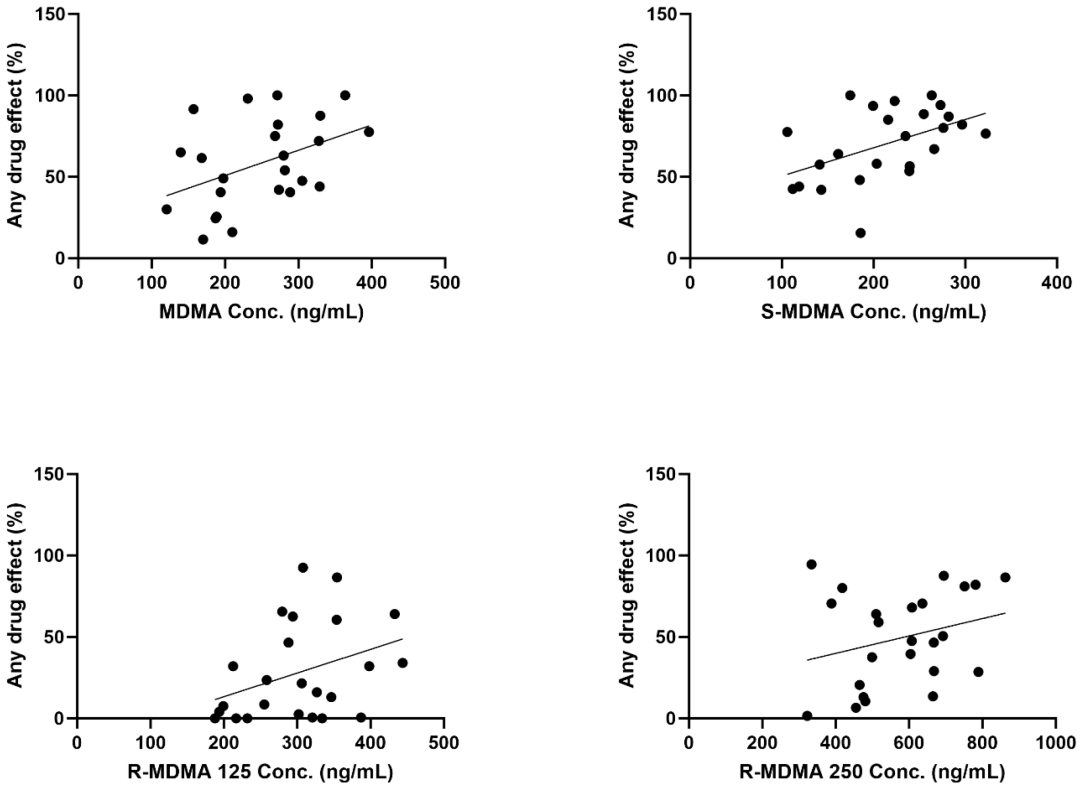



**Figure S10.** Correlations between substance plasma concentrations and the subjective "Any drug effect" rating. The data points represent the "any drug effect" on the VAS at time points 2 and 3 hours (expressed as the mean) as a measure of the subjective peak response and at the same time points where the cortisol and prolactin concentrations were measured, as well as the mean plasma substance concentrations at these time points. Pearson correlation analyses with a significance criterion of $p<0.05$ were conducted. Correlation coefficients and p-values for the substances were: MDMA (r=0.43, $p=0.04$), *S*-MDMA (r=0.48, $p=0.02$), R-MDMA 125 mg (r=0.36, $p=0.08$), and R-MDMA 250 mg (r=0.27, $r=0.2$).

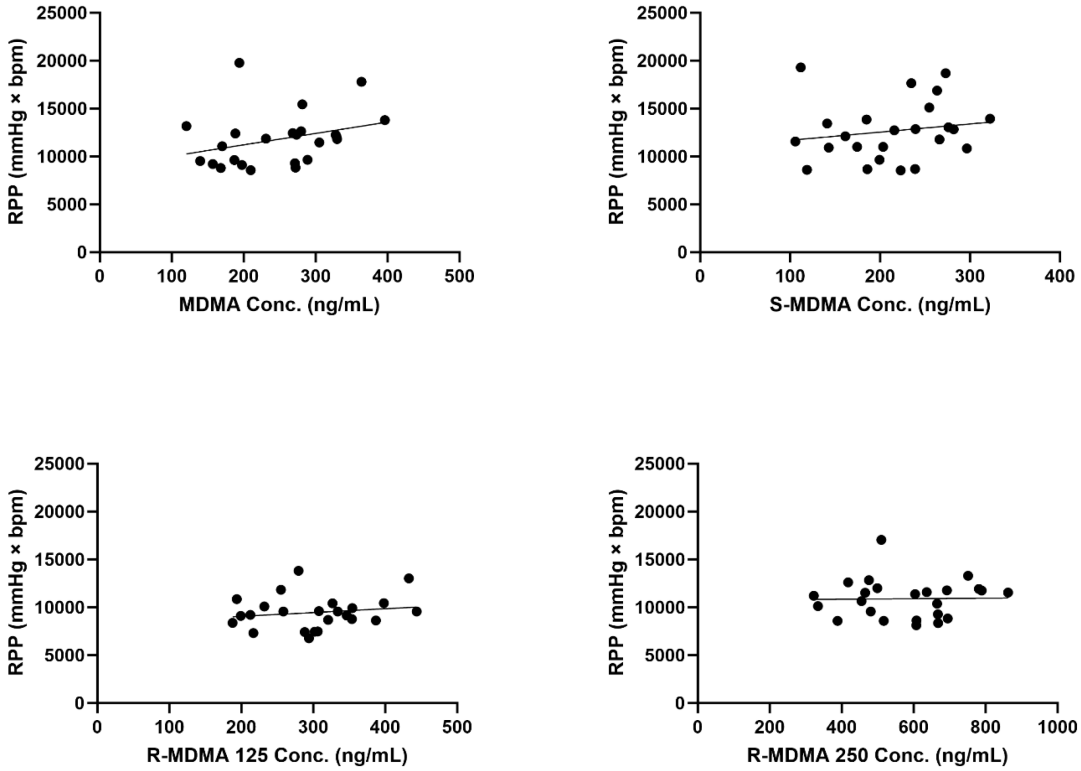



**Figure S11.** Correlations between substance plasma concentration and the cardiovacular response expressed by the rate pressure product (RPP). The data points represent the rate pressure product at time points 2 and 3 hours (expressed as the mean) as a measure of the autonomic peak response and at the same time points where the cortisol and prolactin concentrations were measured, as well as the mean plasma substance concentrations at these time points. Pearson correlation analyses with a significance criterion of $p<0.05$ were conducted. Correlation coefficients and p-values for the substances were: MDMA (r=0.31, $p=0.14$), *S*-MDMA (r=0.17, $p=0.43$), R-MDMA 125 mg (r=0.17, $p=0.43$), and R-MDMA 250 mg (r=0.02, $r=0.93$).

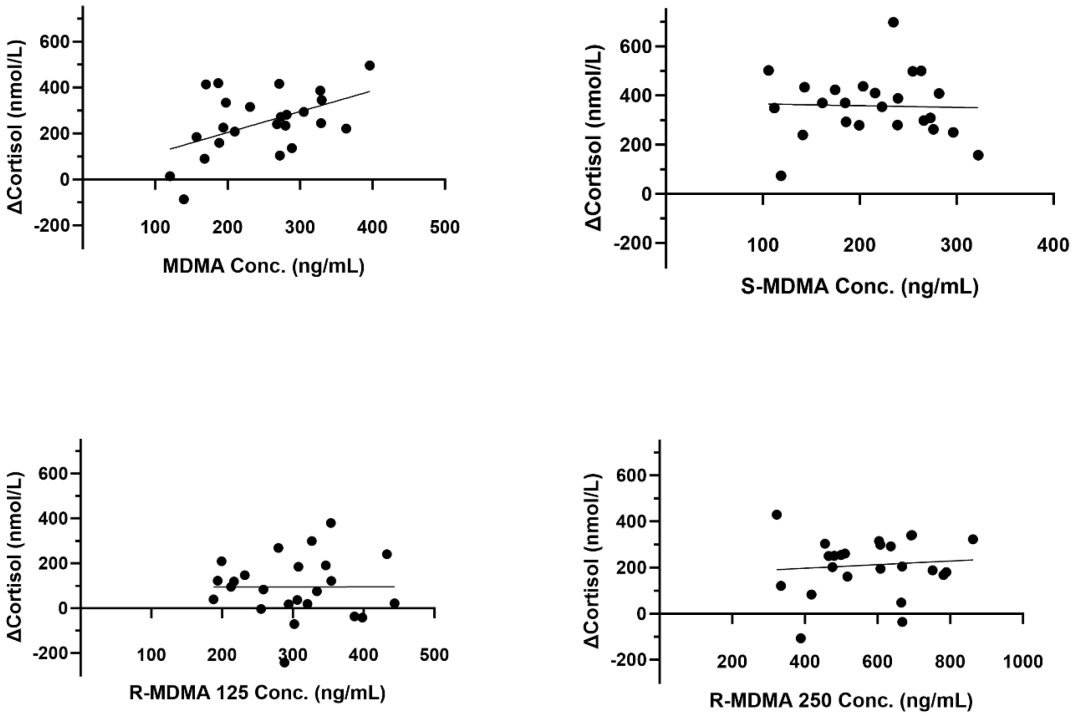



**Figure S12.** Correlations substance and cortisol plasma concentrations. The data points represent the change of cortisol levels from baseline to after 2 and 3 hours (expressed as the mean), as well as the mean plasma substance concentrations at these time points. Pearson correlation analyses with a significance criterion of $p<0.05$ were conducted. Correlation coefficients and p-values for the substances were: MDMA (r=0.50, $p=0.01$), *S*-MDMA (r=-0.03, $p=0.88$), *R*-MDMA 125 mg (r=0.001, $p=1.0$), and *R*-MDMA 250 mg (r=0.09, $p=0.66$), respectively.

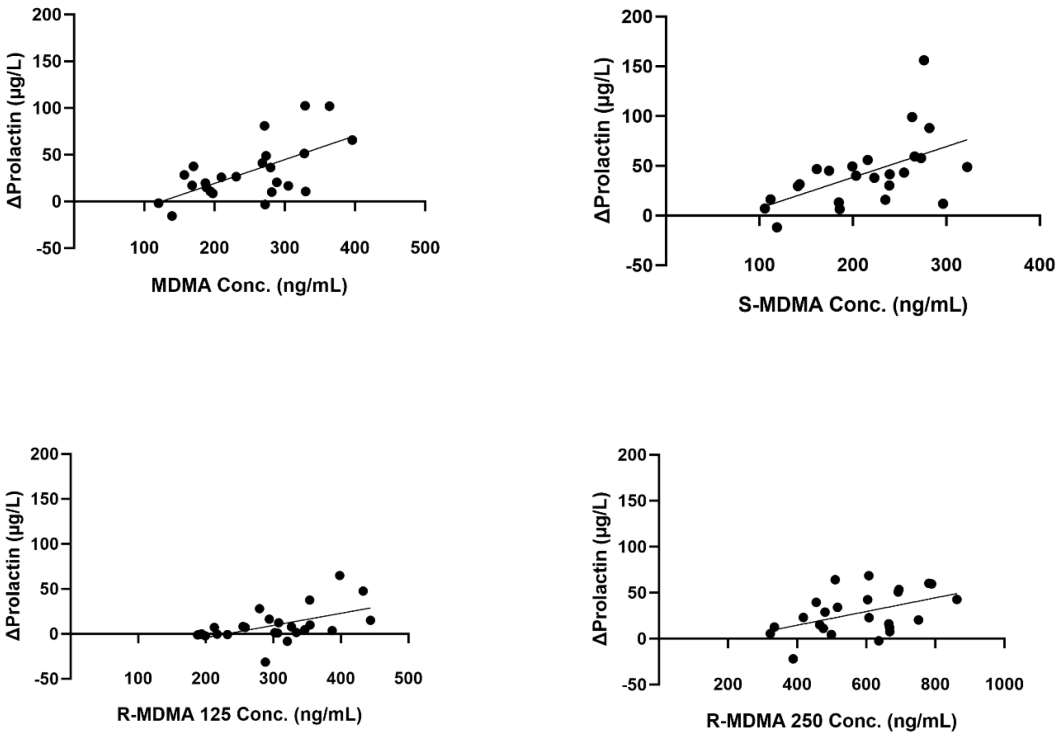



**Figure S13.** Correlations between substance and prolactin plasma concentrations. The data points represent the change of prolactin levels from baseline to after 2 and 3 hours (expressed as the mean), as well as the mean plasma substance concentrations at these time points. Pearson correlation analyses with a significance criterion of $p<0.05$ were conducted. Correlation coefficients and p-values for the substances were: MDMA (r=0.62, $p=0.001$), *S*-MDMA (r=0.54, $p=0.01$), *R*-MDMA 125 mg (r=0.51, $p=0.01$), and *R*-MDMA 250 mg (r=0.47, $p=0.02$), respectively.

**Table S2. Sex differences in mean acute subjective effects of MDMA, S-MDMA, R-MDMA and placebo on the Visual Analogue Scale (VAS)**

| | | Placebo | 125 mg R-MDMA | 250 mg R-MDMA | 125 mg MDMA | 125 mg S-MDMA |
|---|---|---|---|---|---|---|
| | | (mean ± SEM) | (mean ± SEM) | (mean ± SEM) | (mean ± SEM) | (mean ± SEM) |
| Visual Analog Scale (VAS, %max) | | | | | | |
| Unidirectional Scales (0-100) | | | | | | |
| **Any drug effect** | $\Delta E_{max}$ | 4.8 ± 2.1 | 42 ± 7.3 | 66 ± 6.1 | 77 ± 5.3 | 90 ± 3.1 |
| female | $\Delta E_{max}$ | 6.3 ± 4.1 | 57 ± 9.0 | 83 ± 4.5 | 91 ± 3.8 | 97 ± 2.3 |
| male | $\Delta E_{max}$ | 3.3 ± 1.1 | 27 ± 10 | 50 ± 9.2 | 63 ± 8.1 | 82 ± 5.0 |
| **Good drug effect** | $\Delta E_{max}$ | 7.9 ± 4.1 | 43 ± 7.1 | 68 ± 6.6 | 78 ± 5.1 | 90 ± 3.8 |
| female | $\Delta E_{max}$ | 7.7 ± 6.0 | 54 ± 10 | 82 ± 7.4 | 87 ± 5.6 | 93 ± 5.2 |
| male | $\Delta E_{max}$ | 8.1 ± 5.8 | 32 ± 9.4 | 55 ± 9.8 | 69 ± 8.0 | 87 ± 5.6 |
| **Bad drug effect** | $\Delta E_{max}$ | 0.5 ± 0.3 | 14 ± 5.1 | 19 ± 4.6 | 20 ± 5.9 | 39 ± 7.0 |
| female | $\Delta E_{max}$ | 0.8 ± 0.6 | 21 ± 7.5 | 29 ± 6.5 | 30 ± 8.0 | 40 ± 8.3 |
| male | $\Delta E_{max}$ | 0.3 ± 0.2 | 8.1 ± 6.7 | 9.9 ± 5.3 | 11 ± 8.2 | 39 ± 12 |
| **I like the effect** | $\Delta E_{max}$ | 7.7 ± 3.8 | 47 ± 7.1 | 68 ± 6.6 | 81 ± 5.0 | 91 ± 3.6 |
| female | $\Delta E_{max}$ | 8.1 ± 5.4 | 58 ± 9.6 | 86 ± 6.5 | 89 ± 5.5 | 94 ± 3.8 |
| male | $\Delta E_{max}$ | 7.3 ± 5.6 | 37 ± 9.7 | 50 ± 9.2 | 72 ± 7.8 | 88 ± 6.0 |
| **Stimulated** | $\Delta E_{max}$ | 2.5 ± 1.1 | 31 ± 6.9 | 60 ± 6.7 | 70 ± 6.7 | 88 ± 3.7 |
| female | $\Delta E_{max}$ | 1.8 ± 1.1 | 40 ± 10 | 74 ± 8.3 | 80 ± 6.7 | 91 ± 4.5 |
| male | $\Delta E_{max}$ | 3.3 ± 2.0 | 22 ± 9.1 | 46 ± 9.2 | 61 ± 11 | 84 ± 6.0 |
| **Drug high** | $\Delta E_{max}$ | 1.4 ± 0.6 | 29 ± 7.0 | 48 ± 7.6 | 73 ± 6.7 | 84 ± 5.1 |
| female | $\Delta E_{max}$ | 1.6 ± 1.0 | 37 ± 9.9 | 65 ± 9.7 | 85 ± 6.9 | 93 ± 4.5 |
| male | $\Delta E_{max}$ | 1.3 ± 0.9 | 20 ± 9.7 | 31 ± 9.7 | 61 ± 11 | 75 ± 8.7 |
| **Fear** | $\Delta E_{max}$ | 0.0 ± 0.0 | 4.9 ± 4.2 | 5.8 ± 3.4 | 5.9 ± 3.4 | 19 ± 6.9 |
| female | $\Delta E_{max}$ | 0.0 ± 0.0 | 9.0 ± 8.3 | 4.8 ± 2.8 | 6.2 ± 6.0 | 21 ± 11 |
| male | $\Delta E_{max}$ | 0.1 ± 0.1 | 0.8 ± 0.7 | 6.8 ± 6.3 | 5.6 ± 3.6 | 16 ± 8.6 |
| **Alteration of vision** | $\Delta E_{max}$ | 3.0 ± 1.6 | 24 ± 6.9 | 37 ± 6.7 | 54 ± 7.8 | 74 ± 6.7 |
| female | $\Delta E_{max}$ | 4.4 ± 3.1 | 28 ± 10 | 47 ± 9.5 | 60 ± 11 | 79 ± 9.1 |
| male | $\Delta E_{max}$ | 1.7 ± 1.0 | 20 ± 9.6 | 27 ± 8.8 | 48 ± 11 | 70 ± 10 |
| **Alteration of sense of time** | $\Delta E_{max}$ | 2.2 ± 2.0 | 28 ± 7.2 | 46 ± 7.7 | 60 ± 6.8 | 73 ± 6.6 |
| female | $\Delta E_{max}$ | 4.0 ± 4.0 | 37 ± 10 | 61 ± 10 | 73 ± 7.7 | 87 ± 7.5 |
| male | $\Delta E_{max}$ | 0.4 ± 0.3 | 19 ± 9.9 | 32 ± 10 | 47 ± 10 | 58 ± 9.5 |
| **Audio-visual synesthesia** | $\Delta E_{max}$ | 4.6 ± 4.2 | 15 ± 5.9 | 31 ± 6.8 | 29 ± 6.8 | 53 ± 8.3 |
| female | $\Delta E_{max}$ | 0.7 ± 0.7 | 17 ± 8.8 | 38 ± 9.2 | 30 ± 8.7 | 57 ± 12 |
| male | $\Delta E_{max}$ | 8.5 ± 8.3 | 13 ± 8.2 | 23 ± 10 | 29 ± 11 | 49 ± 12 |
| **Ego dissolution** | $\Delta E_{max}$ | 1.5 ± 0.8 | 22 ± 7.4 | 32 ± 7.4 | 41 ± 7.7 | 58 ± 8.2 |
| female | $\Delta E_{max}$ | 2.0 ± 1.4 | 28 ± 11 | 43 ± 10 | 48 ± 11 | 72 ± 11 |
| male | $\Delta E_{max}$ | 1.0 ± 1.0 | 16 ± 9.7 | 21 ± 10 | 33 ± 10 | 45 ± 12 |

$\Delta E_{max}$, maximal effect difference from baseline; N=24 (12 female, 12 male)

**Table S3. Differences in mean acute subjective effects of MDMA, S-MDMA, R-MDMA and placebo between participants with and without previous MDMA experience on the Visual Analogue Scale (VAS)**

| | | Placebo | 125 mg R-MDMA | 250 mg R-MDMA | 125 mg MDMA | 125 mg S-MDMA |
|---|---|---|---|---|---|---|
| | | (mean ± SEM) | (mean ± SEM) | (mean ± SEM) | (mean ± SEM) | (mean ± SEM) |
| Visual Analog Scale (VAS, %max) | | | | | | |
| Unidirectional Scales (0-100) | | | | | | |
| **Any drug effect** | $\Delta E_{max}$ | 4.8 ± 2.1 | 42 ± 7.3 | 66 ± 6.1 | 77 ± 5.3 | 90 ± 3.1 |
| with experience | $\Delta E_{max}$ | 3.6 ± 1.2 | 25 ± 7.7 | 54 ± 9.1 | 68 ± 7.2 | 88 ± 5.1 |
| without experience | $\Delta E_{max}$ | 6.0 ± 3.8 | 57 ± 10 | 77 ± 7.3 | 84 ± 7.2 | 91 ± 3.9 |
| **Good drug effect** | $\Delta E_{max}$ | 7.9 ± 4.1 | 43 ± 7.1 | 68 ± 6.6 | 78 ± 5.1 | 90 ± 3.8 |
| with experience | $\Delta E_{max}$ | 2.2 ± 1.1 | 30 ± 8.2 | 54 ± 11 | 73 ± 7.2 | 87 ± 6.4 |
| without experience | $\Delta E_{max}$ | 13 ± 7.4 | 54 ± 10 | 80 ± 6.4 | 82 ± 7.3 | 92 ± 4.6 |
| **Bad drug effect** | $\Delta E_{max}$ | 0.5 ± 0.3 | 14 ± 5.1 | 19 ± 4.6 | 20 ± 5.9 | 39 ± 7.0 |
| with experience | $\Delta E_{max}$ | 0.9 ± 0.7 | 5.8 ± 3.6 | 14 ± 6.1 | 16 ± 6.4 | 37 ± 8.9 |
| without experience | $\Delta E_{max}$ | 0.2 ± 0.2 | 22 ± 8.6 | 24 ± 6.6 | 24 ± 9.6 | 42 ± 11 |
| **I like the effect** | $\Delta E_{max}$ | 7.7 ± 3.8 | 47 ± 7.1 | 68 ± 6.6 | 81 ± 5.0 | 91 ± 3.6 |
| with experience | $\Delta E_{max}$ | 3.0 ± 1.5 | 35 ± 9.0 | 55 ± 10 | 75 ± 7.4 | 89 ± 5.6 |
| without experience | $\Delta E_{max}$ | 12 ± 6.8 | 57 ± 10 | 79 ± 7.6 | 85 ± 6.8 | 93 ± 4.7 |
| **Stimulated** | $\Delta E_{max}$ | 2.5 ± 1.1 | 31 ± 6.9 | 60 ± 6.7 | 70 ± 6.7 | 88 ± 3.7 |
| with experience | $\Delta E_{max}$ | 1.0 ± 0.8 | 18 ± 5.7 | 51 ± 11 | 61 ± 10 | 85 ± 7.1 |
| without experience | $\Delta E_{max}$ | 3.8 ± 1.9 | 42 ± 11 | 68 ± 7.9 | 79 ± 8.6 | 90 ± 3.4 |
| **Drug high** | $\Delta E_{max}$ | 1.4 ± 0.6 | 29 ± 7.0 | 48 ± 7.6 | 73 ± 6.7 | 84 ± 5.1 |
| with experience | $\Delta E_{max}$ | 0.3 ± 0.2 | 12 ± 5.0 | 40 ± 12 | 63 ± 10 | 78 ± 9.5 |
| without experience | $\Delta E_{max}$ | 2.4 ± 1.1 | 43 ± 11 | 55 ± 9.8 | 82 ± 8.6 | 89 ± 5.0 |
| **Fear** | $\Delta E_{max}$ | 0.0 ± 0.0 | 4.9 ± 4.2 | 5.8 ± 3.4 | 5.9 ± 3.4 | 19 ± 6.9 |
| with experience | $\Delta E_{max}$ | 0.0 ± 0.0 | 0.7 ± 0.7 | 1.7 ± 1.7 | 0.6 ± 0.5 | 22 ± 12 |
| without experience | $\Delta E_{max}$ | 0.1 ± 0.1 | 8.4 ± 7.7 | 9.2 ± 6.0 | 10 ± 6.1 | 16 ± 8.1 |
| **Alteration of vision** | $\Delta E_{max}$ | 3.0 ± 1.6 | 24 ± 6.9 | 37 ± 6.7 | 54 ± 7.8 | 74 ± 6.7 |
| with experience | $\Delta E_{max}$ | 1.4 ± 0.7 | 8.5 ± 3.8 | 28 ± 9.3 | 43 ± 11 | 63 ± 12 |
| without experience | $\Delta E_{max}$ | 4.5 ± 2.9 | 37 ± 11 | 45 ± 9.2 | 63 ± 11 | 84 ± 5.5 |
| **Alteration of sense of time** | $\Delta E_{max}$ | 2.2 ± 2.0 | 28 ± 7.2 | 46 ± 7.7 | 60 ± 6.8 | 73 ± 6.6 |
| with experience | $\Delta E_{max}$ | 0.0 ± 0.0 | 13 ± 7.3 | 26 ± 9.3 | 48 ± 11 | 62 ± 11 |
| without experience | $\Delta E_{max}$ | 4.1 ± 3.7 | 41 ± 11 | 63 ± 9.9 | 70 ± 8.2 | 81 ± 7.2 |
| **Audio-visual synesthesia** | $\Delta E_{max}$ | 4.6 ± 4.2 | 15 ± 5.9 | 31 ± 6.8 | 29 ± 6.8 | 53 ± 8.3 |
| with experience | $\Delta E_{max}$ | 0.0 ± 0.0 | 4.5 ± 2.9 | 14 ± 4.9 | 20 ± 7.6 | 42 ± 11 |
| without experience | $\Delta E_{max}$ | 8.5 ± 7.7 | 23 ± 10 | 45 ± 11 | 37 ± 10 | 62 ± 12 |
| **Ego dissolution** | $\Delta E_{max}$ | 1.5 ± 0.8 | 22 ± 7.4 | 32 ± 7.4 | 41 ± 7.7 | 58 ± 8.2 |
| with experience | $\Delta E_{max}$ | 0.7 ± 0.5 | 11 ± 8.2 | 21 ± 10 | 30 ± 9.9 | 50 ± 13 |
| without experience | $\Delta E_{max}$ | 2.2 ± 1.5 | 31 ± 11 | 40 ± 11 | 50 ± 11 | 66 ± 10 |

$\Delta E_{max}$, maximal effect difference from baseline; with experience, with previous MDMA experience before the study; without experience, without previous MDMA experience before the study; N=24, $N_{with\ experience}$ = 11, $N_{without\ experience}$ = 13

**Table S4. Parameters characterizing the subjective drug effect-time curves of MDMA, S-MDMA and R-MDMA**

| | R-MDMA 125 mg | R-MDMA 250 mg | MDMA 125 mg | S-MDMA 125 mg |
|---|---|---|---|---|
| Time to onset (h) | 0.8 ± 0.1[α]<br>(0.3 - 2.0) | 0.6 ± 0.1[γ]<br>(0.1 - 1.8) | 0.6 ± 0.1<br>(0.04 - 1.1) | 0.5 ± 0.01<br>(0.03 - 1.0) |
| Time to offset (h) | 3.9 ± 0.5[α]<br>(1.1 - 8.5) | 5.8 ± 0.8[γ]<br>(1.7 - 22) | 4.8 ± 0.3<br>(2.3 - 7.8) | 5.2 ± 0.3<br>(2.4 - 9.0) |
| Time to maximal effect (h) | 1.7 ± 0.1[β]<br>(0.5 - 3.5) | 1.8 ± 0.2<br>(0.8 - 5.0) | 1.9 ± 0.2<br>(0.8 - 4.0) | 1.4 ± 0.2<br>(0.3 - 4.0) |
| Effect duration (h) | 3.5 ± 0.5[α]<br>(0.7 - 8.0) | 5.2 ± 0.8[γ]<br>(1.0 - 21) | 4.2 ± 0.3<br>(1.5 - 7.0) | 4.7 ± 0.3<br>(1.8 - 8.5) |
| Maximal effect (%) | 46 ± 7.4[β]<br>(3 - 100) | 66 ± 6.1<br>(4 - 100) | 77 ± 5.3<br>(22 - 100) | 90 ± 3.1<br>(51 - 100) |
| AUEC (h*pg/mL) | 115 ± 22[β]<br>(1.9 - 336) | 216 ± 28<br>(6.2 - 553) | 225 ± 24<br>(37 - 455) | 293 ± 24<br>(71 ± 637) |

Parameters are for "any drug effects". The threshold to determine times to onset and offset was set at 10% of the maximal possible response. Values are mean ± SEM (range). N=24; [α]N=18; [β]N=22 ; [γ]N=23

**Table S5. Mean values and statistics for the acute subjective effects of MDMA, S-MDMA, R-MDMA and placebo on the 5 Dimensions of Altered States of Consciousness (5D-ASC) Scale**

| | | Placebo | 125 mg R-MDMA | 250 mg R-MDMA | 125 mg MDMA | 125 mg S-MDMA | $F_{4,92}$ | P= | Pla - R-MDMA (125 mg) | Pla - R-MDMA (250 mg) | Pla - MDMA | Pla - S-MDMA | R-MDMA (125 mg) - R-MDMA (250 mg) | R-MDMA (125 mg) - MDMA | R-MDMA (125 mg) - S-MDMA | R-MDMA (250 mg) - MDMA | R-MDMA (250 mg) - S-MDMA | MDMA - S-MDMA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | mean ± SEM | mean ± SEM | mean ± SEM | mean ± SEM | mean ± SEM | | | | | | | | | | | | |
| 5 Dimensions of Altered States of Consciousness (5D-ASC) Scale | | | | | | | | | | | | | | | | | | |
| 5D-ASC total Score | % score | 0.6 ± 0.4 | 7.3 ± 1.8 | 17 ± 3.2 | 14 ± 3.3 | 17 ± 3.2 | 17.32 | <0.001 | * | *** | *** | *** | ** | * | ** | NS | NS | NS |
| 3D-ASC total Score | % score | 0.3 ± 0.3 | 6.4 ± 1.8 | 15 ± 3.3 | 14 ± 3.6 | 17 ± 3.7 | 15.04 | <0.001 | NS | *** | *** | *** | * | * | *** | NS | NS | NS |
| Oceanic boundlessness | % score | 0.5 ± 0.4 | 9.4 ± 2.9 | 19 ± 4.2 | 22 ± 5.1 | 23 ± 5.1 | 14.89 | <0.001 | NS | *** | *** | *** | * | ** | ** | NS | NS | NS |
| Anxious ego-dissolution | % score | 0.1 ± 0.0 | 2.8 ± 0.8 | 7.5 ± 1.9 | 5.8 ± 2.2 | 10 ± 3.1 | 6.94 | <0.001 | NS | ** | NS | *** | NS | NS | ** | NS | NS | NS |
| Visionary restructuralization | % score | 0.3 ± 0.3 | 6.0 ± 2.1 | 17 ± 4.7 | 12 ± 3.9 | 15 ± 4.2 | 9.30 | <0.001 | NS | *** | ** | *** | ** | NS | * | NS | NS | NS |
| Auditory alterations | % score | 0.0 ± 0.0 | 1.5 ± 0.7 | 8.2 ± 2.8 | 5.0 ± 2.5 | 5.5 ± 2.1 | 4.64 | 0.002 | NS | ** | NS | NS | * | NS | NS | NS | NS | NS |
| Reductions of vigilance | % score | 3.1 ± 1.5 | 21 ± 4.8 | 38 ± 6.3 | 26 ± 4.8 | 29 ± 4.2 | 16.38 | <0.001 | ** | *** | *** | *** | ** | NS | NS | NS | NS | NS |
| Experience of unity | % score | 0.6 ± 0.6 | 6.2 ± 2.9 | 19 ± 6.3 | 18 ± 6.5 | 21 ± 6.4 | 7.33 | <0.001 | NS | ** | ** | *** | NS | NS | * | NS | NS | NS |
| Spiritual experience | % score | 0.0 ± 0.0 | 3.6 ± 3.4 | 5.1 ± 3.0 | 8.2 ± 4.5 | 7.6 ± 4.2 | 2.57 | 0.043 | NS | NS | * | NS | NS | NS | NS | NS | NS | NS |
| Blissful state | % score | 1.2 ± 1.0 | 17 ± 5.0 | 28 ± 5.9 | 38 ± 7.1 | 35 ± 7.4 | 12.04 | <0.001 | NS | *** | *** | *** | NS | ** | * | NS | NS | NS |
| Insightfulness | % score | 0.2 ± 0.2 | 10 ± 4.2 | 17 ± 5.3 | 18 ± 5.7 | 16 ± 4.9 | 5.41 | <0.001 | NS | ** | ** | ** | NS | NS | NS | NS | NS | NS |
| Disembodiment | % score | 0.1 ± 0.1 | 4.6 ± 2.7 | 15 ± 5.0 | 12 ± 4.5 | 12 ± 3.9 | 4.82 | 0.001 | NS | ** | * | * | NS | NS | NS | NS | NS | NS |
| Impaired control and cognition | % score | 0.1 ± 0.1 | 4.4 ±1.2 | 13 ± 3.4 | 9.1 ± 3.2 | 15 ± 4.4 | 7.56 | <0.001 | NS | ** | * | *** | NS | NS | ** | NS | NS | NS |
| Anxiety | % score | 0.0 ± 0.0 | 1.3 ± 0.9 | 1.6 ± 0.7 | 2.5 ± 1.4 | 4.9 ± 2.3 | 2.41 | NS | - | - | - | - | - | - | - | - | - | - |
| Complex imagery | % score | 0.2 ± 0.1 | 8.3 ± 3.5 | 26 ± 7.0 | 17 ± 5.8 | 20 ± 6.3 | 7.42 | <0.001 | NS | *** | * | ** | * | NS | NS | NS | NS | NS |
| Elementary imagery | % score | 0.0 ± 0.0 | 5.6 ± 2.7 | 16 ± 6.1 | 9.4 ± 4.1 | 13 ± 4.9 | 3.28 | 0.015 | NS | * | NS | NS | NS | NS | NS | NS | NS | NS |
| Audio-visual synesthesia | % score | 0.0 ± 0.0 | 4.6 ± 2.2 | 12 ± 4.9 | 8.7 ± 3.9 | 15 ± 5.2 | 4.83 | 0.001 | NS | * | NS | ** | NS | NS | NS | NS | NS | NS |
| Changed meaning of percepts | % score | 0.3 ± 0.3 | 5.3 ± 2.8 | 15 ± 4.7 | 14 ± 4.9 | 14 ± 3.7 | 5.77 | <0.001 | NS | ** | ** | ** | NS | NS | NS | NS | NS | NS |

(*)P<0.1, *P<0.05, **P<0.01, ***P<0.001; NS, not significant N=24

**Table S6. Mean values and statistics for the acute subjective effects of MDMA, S-MDMA, R-MDMA and placebo on the Psychedelic Experience Questionnaire (PES48)**

| | | Placebo | 125 mg R-MDMA | 250 mg R-MDMA | 125 mg MDMA | 125 mg S-MDMA | $F_{4,92}$ | P= | Pla - R-MDMA (125 mg) | Pla - R-MDMA (250 mg) | Pla - MDMA | Pla - S-MDMA | R-MDMA (125 mg) - R-MDMA (250 mg) | R-MDMA (125 mg) - MDMA | R-MDMA (125 mg) - S-MDMA | R-MDMA (250 mg) - MDMA | R-MDMA (250 mg) - S-MDMA | MDMA - S-MDMA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | mean ± SEM | mean ± SEM | mean ± SEM | mean ± SEM | mean ± SEM | | | | | | | | | | | | |
| Mystical Experiences Questionnaire (MEQ30) | | | | | | | | | | | | | | | | | | |
| Mystical | % score | 0.6 ± 0.5 | 7.2 ± 3.1 | 15 ± 4.5 | 16 ± 4.6 | 14 ± 4.5 | 7.91 | <0.001 | NS | *** | *** | *** | NS | NS | NS | NS | NS | NS |
| Positive mood | % score | 2.4 ± 1.7 | 16 ± 3.8 | 30 ± 4.1 | 38 ± 4.7 | 38 ± 4.9 | 23.71 | <0.001 | * | *** | *** | *** | * | *** | *** | NS | NS | NS |
| Transcendence of time/space | % score | 1.5 ± 1.0 | 11 ± 2.4 | 25 ± 5.0 | 24 ± 4.7 | 25 ± 4.6 | 16.23 | <0.001 | NS | *** | *** | *** | ** | ** | ** | NS | NS | NS |
| Ineffability | % score | 1.1 ± 0.9 | 17 ± 4.3 | 34 ± 5.5 | 36 ± 6.3 | 48 ± 6.4 | 23.19 | <0.001 | * | *** | *** | *** | * | ** | *** | NS | NS | NS |
| MEQ30 total score | % score | 1.2 ± 0.9 | 11 ± 4.3 | 22 ± 4.0 | 24 ± 4.4 | 24 ± 4.2 | 20.37 | <0.001 | * | *** | *** | *** | ** | *** | *** | NS | NS | NS |
| Additional subscales on the Mystical Experience Questionnaire (MEQ40) | | | | | | | | | | | | | | | | | | |
| Paradoxicality | % score | 0.7 ± 0.5 | 1.7 ± 0.9 | 17 ± 4.3 | 12 ± 4.1 | 11 ± 2.8 | 9.08 | <0.001 | NS | *** | ** | * | *** | * | NS | NS | NS | NS |
| Connectedness | % score | 1.7 ± 1.2 | 20 ± 4.2 | 34 ± 4.7 | 34 ± 4.7 | 33 ± 5.6 | 16.87 | <0.001 | ** | *** | *** | *** | * | * | NS | NS | NS | NS |
| Additional subscales on the Psychedelic Experience Questionnaire/Scale (PES48) | | | | | | | | | | | | | | | | | | |
| Visual Experience | % score | 0.0 ± 0.0 | 2.2 ± 1.2 | 8.6 ± 3.9 | 2.5 ± 1.6 | 7.2 ± 3.3 | 3.52 | 0.01 | NS | * | NS | NS | NS | NS | NS | NS | NS | NS |
| Distressing Experience | % score | 0.5 ± 0.5 | 3.7 ± 1.9 | 10 ± 3.4 | 2.7 ± 0.9 | 7.5 ± 2.6 | 3.66 | 0.008 | NS | ** | NS | NS | NS | NS | NS | NS | NS | NS |
| Mystical Experiences Questionnaire (MEQ43) | | | | | | | | | | | | | | | | | | |
| Internal unity | % score | 0.3 ± 0.2 | 6.9 ± 2.9 | 15 ± 4.5 | 16 ± 4.3 | 13 ± 4.2 | 8.08 | <0.001 | NS | *** | *** | ** | NS | * | NS | NS | NS | NS |
| External unity | % score | 0.6 ± 0.6 | 3.6 ± 1.5 | 14 ± 4.5 | 14 ± 4.4 | 16 ± 4.7 | 8.35 | <0.001 | NS | ** | ** | *** | * | * | ** | NS | NS | NS |
| Sacredness | % score | 0.4 ± 0.4 | 6.3 ± 3.0 | 15 ± 3.6 | 13 ± 4.0 | 16 ± 4.2 | 8.66 | <0.001 | NS | *** | ** | *** | NS | NS | * | NS | NS | NS |
| Noetic quality | % score | 1.5 ± 1.3 | 14 ± 4.9 | 20 ± 5.6 | 16 ± 4.8 | 17 ± 4.5 | 5.94 | <0.001 | * | *** | ** | ** | NS | NS | NS | NS | NS | NS |
| Deeply felt positive mood | % score | 2.0 ± 1.4 | 18 ± 4.1 | 29 ± 4.6 | 41 ± 5.2 | 40 ± 5.3 | 21.89 | <0.001 | * | *** | *** | *** | NS | *** | *** | NS | NS | NS |
| Transcendence of time/space | % score | 1.6 ± 1.2 | 8.6 ± 2.0 | 24 ± 5.0 | 22 ± 4.9 | 21 ± 4.5 | 14.58 | <0.001 | NS | *** | *** | *** | *** | ** | ** | NS | NS | NS |
| Ineffability | % score | 1.0 ± 0.7 | 11 ± 2.9 | 29 ± 4.7 | 26 ± 5.2 | 32 ± 4.3 | 18.68 | <0.001 | NS | *** | *** | *** | *** | ** | *** | NS | NS | NS |

*P<0.05, **P<0.01, ***P<0.001; NS, not significant N=24

**Table S7. Mean values and statistics for the acute subjective effects of MDMA, S-MDMA, R-MDMA, and placebo on the Adjective Mood Rating Scale (AMRS)**

| | | Placebo | 125 mg R-MDMA | 250 mg R-MDMA | 125 mg MDMA | 125 mg S-MDMA | $F_{4,92}$ | P= | Pla - R-MDMA (125 mg) | Pla - R-MDMA (250 mg) | Pla - MDMA | Pla - S-MDMA | R-MDMA (125 mg) - R-MDMA (250 mg) | R-MDMA (125 mg) - MDMA | R-MDMA (125 mg) - S-MDMA | R-MDMA (250 mg) - MDMA | R-MDMA (250 mg) - S-MDMA | MDMA - S-MDMA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | mean ± SEM | mean ± SEM | mean ± SEM | mean ± SEM | mean ± SEM | | | | | | | | | | | | |
| Adjective Mood Rating Scale (AMRS, score) | | | | | | | | | | | | | | | | | | |
| General well-being | $\Delta E_{max}$ | -0.0 ± 0.5 | 1.6 ± 1.0 | 2.9 ± 1.0 | 3.5 ± 1.1 | 4.7 ± 0.9 | 4.40 | 0.003 | NS | NS | * | ** | NS | NS | NS | NS | NS | NS |
| Emotional excitation | $\Delta E_{max}$ | -0.2 ± 0.7 | 1.4 ± 0.7 | 2.2 ± 0.8 | 3.3 ± 0.8 | 5.7 ± 0.7 | 10.56 | <0.001 | NS | NS | ** | *** | NS | NS | *** | NS | ** | NS |
| Extraversion | $\Delta E_{max}$ | 0.2 ± 0.4 | 1.3 ± 0.7 | 2.4 ± 0.6 | 4.0 ± 0.6 | 4.5 ± 0.6 | 11.52 | <0.001 | NS | * | *** | *** | NS | ** | *** | NS | NS | NS |
| Introversion | $\Delta E_{max}$ | 0.5 ± 0.3 | 2.2 ± 0.5 | 3.0 ± 0.6 | 1.4 ± 0.3 | 2.5 ± 0.4 | 7.11 | <0.001 | * | *** | NS | ** | NS | NS | NS | * | NS | NS |
| Activity | $\Delta E_{max}$ | 0.7 ± 0.4 | 1.6 ± 0.5 | 1.6 ± 0.7 | 1.8 ± 0.6 | 2.7 ± 0.6 | 2.28 | NS | - | - | - | - | - | - | - | - | - | - |
| Inactivity | $\Delta E_{max}$ | 3.4 ± 0.8 | 7.8 ± 1.8 | 12 ± 1.8 | 9.7 ± 1.4 | 11 ± 1.3 | 8.69 | <0.001 | NS | *** | ** | *** | NS | NS | NS | NS | NS | NS |
| Concentration | $\Delta E_{max}$ | 1.0 ± 0.3 | 1.0 ± 0.6 | 0.4 ± 0.4 | 0.9 ± 0.4 | 1.3 ± 0.7 | 0.50 | NS | - | - | - | - | - | - | - | - | - | - |
| Anxiety | $\Delta E_{max}$ | -0.3 ± 0.2 | 0.5 ± 0.3 | 0.4 ± 0.2 | 0.2 ± 0.2 | 0.9 ± 0.2 | 3.74 | 0.007 | NS | NS | NS | ** | NS | NS | NS | NS | NS | NS |

*P<0.05, **P<0.01, ***P<0.001; NS, not significant; $\Delta E_{max}$, maximal effect difference from baseline; $\Delta E_{min}$, minimal effect difference from baseline; N=24

**Table S8. Acute adverse drug effects after administration of MDMA, S-MDMA, R-MDMA and placebo**

| | Placebo | | | | 125 mg R-MDMA | | | | 250 mg R-MDMA | | | | 125 mg MDMA | | | | 125 mg S-MDMA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0h | 0-9h | 9-24h | 24-72h | 0h | 0-9h | 9-24h | 24-72h | 0h | 0-9h | 9-24h | 24-72h | 0h | 0-9h | 9-24h | 24-72h | 0h | 0-9h | 9-24h | 24-72h |
| Fatigue | 14 | 13 | 10 | 10 | 16 | 18 | 16 | 13 | 13 | 21 | 19 | 12 | 10 | 20 | 18 | 14 | 16 | 22 | 21 | 13 |
| Headache | 3 | 5 | 6 | 6 | 1 | 13 | 11 | 14 | 4 | 15 | 15 | 11 | 3 | 9 | 12 | 11 | 4 | 16 | 11 | 11 |
| Lethargy | 0 | 5 | 2 | 4 | 1 | 13 | 9 | 11 | 0 | 15 | 12 | 9 | 2 | 14 | 9 | 9 | 2 | 17 | 14 | 11 |
| Decreased appetite | 1 | 0 | 1 | 4 | 0 | 12 | 9 | 8 | 1 | 14 | 11 | 7 | 2 | 14 | 8 | 6 | 1 | 16 | 10 | 7 |
| Feeling dull | 1 | 1 | 2 | 2 | 0 | 11 | 10 | 9 | 1 | 11 | 12 | 7 | 1 | 10 | 7 | 5 | 2 | 12 | 13 | 10 |
| Lack of concentration | 2 | 1 | 1 | 4 | 0 | 10 | 5 | 6 | 0 | 14 | 10 | 6 | 1 | 9 | 7 | 5 | 2 | 17 | 9 | 12 |
| Easily exhausted | 0 | 2 | 2 | 2 | 0 | 10 | 8 | 8 | 0 | 12 | 12 | 8 | 0 | 10 | 4 | 7 | 0 | 11 | 12 | 10 |
| Bruxism | 0 | 1 | 0 | 2 | 0 | 8 | 4 | 2 | 0 | 12 | 6 | 2 | 1 | 16 | 11 | 5 | 0 | 18 | 10 | 10 |
| Feeling of weakness | 0 | 2 | 1 | 3 | 0 | 8 | 4 | 8 | 1 | 11 | 13 | 7 | 0 | 6 | 5 | 5 | 0 | 9 | 13 | 11 |
| Hypersomnia | 0 | 3 | 1 | 3 | 0 | 9 | 6 | 4 | 1 | 13 | 9 | 5 | 0 | 7 | 6 | 3 | 0 | 12 | 12 | 9 |
| Dry mouth | 0 | 1 | 1 | 1 | 0 | 11 | 7 | 3 | 0 | 10 | 7 | 3 | 0 | 13 | 6 | 4 | 0 | 13 | 8 | 6 |
| Uneasiness | 2 | 1 | 1 | 2 | 1 | 8 | 3 | 5 | 0 | 14 | 6 | 4 | 0 | 8 | 2 | 3 | 1 | 11 | 5 | 12 |
| Tension | 3 | 1 | 0 | 2 | 1 | 7 | 2 | 2 | 2 | 11 | 3 | 3 | 1 | 4 | 2 | 2 | 1 | 10 | 3 | 9 |
| Job-related or personal worries | 4 | 1 | 2 | 2 | 3 | 4 | 3 | 3 | 1 | 7 | 4 | 3 | 3 | 4 | 1 | 4 | 2 | 6 | 3 | 6 |
| Dizziness | 0 | 1 | 0 | 0 | 0 | 7 | 4 | 4 | 0 | 8 | 5 | 4 | 0 | 5 | 3 | 2 | 0 | 11 | 5 | 6 |
| Heavy legs | 0 | 0 | 1 | 1 | 0 | 5 | 5 | 5 | 1 | 8 | 4 | 5 | 1 | 6 | 2 | 2 | 2 | 6 | 4 | 5 |
| Memory impairment | 1 | 0 | 2 | 2 | 0 | 5 | 3 | 3 | 1 | 6 | 3 | 6 | 0 | 3 | 4 | 2 | 1 | 6 | 5 | 8 |
| Obsessive rumination | 2 | 0 | 1 | 2 | 1 | 5 | 4 | 2 | 1 | 9 | 4 | 5 | 0 | 5 | 1 | 5 | 0 | 3 | 4 | 7 |
| Hyperhidrosis | 0 | 0 | 0 | 0 | 0 | 6 | 2 | 2 | 0 | 9 | 5 | 3 | 0 | 7 | 4 | 3 | 0 | 13 | 4 | 2 |
| Nausea | 0 | 1 | 0 | 1 | 1 | 5 | 5 | 4 | 0 | 8 | 7 | 6 | 0 | 5 | 2 | 2 | 0 | 5 | 4 | 3 |
| Vertigo | 0 | 1 | 1 | 0 | 0 | 4 | 3 | 2 | 0 | 11 | 3 | 4 | 0 | 7 | 3 | 2 | 0 | 8 | 3 | 6 |
| Crying | 0 | 0 | 0 | 3 | 0 | 5 | 3 | 5 | 1 | 4 | 4 | 6 | 0 | 5 | 3 | 5 | 0 | 2 | 3 | 8 |
| Insomnia | 2 | 0 | 1 | 2 | 0 | 1 | 5 | 5 | 0 | 4 | 5 | 4 | 0 | 3 | 5 | 4 | 1 | 2 | 1 | 8 |
| Micturition urgency | 0 | 4 | 2 | 0 | 1 | 7 | 1 | 2 | 0 | 9 | 1 | 1 | 0 | 7 | 2 | 1 | 1 | 9 | 3 | 1 |
| Hypersensitiviy to cold | 0 | 0 | 0 | 1 | 0 | 6 | 5 | 1 | 0 | 6 | 6 | 2 | 0 | 8 | 2 | 2 | 0 | 4 | 1 | 3 |
| Heart palpitations | 0 | 2 | 0 | 0 | 0 | 5 | 2 | 2 | 0 | 9 | 2 | 1 | 0 | 4 | 2 | 0 | 1 | 8 | 1 | 7 |
| Chills | 0 | 1 | 0 | 0 | 0 | 4 | 4 | 2 | 0 | 8 | 4 | 1 | 0 | 9 | 1 | 1 | 1 | 5 | 1 | 2 |
| Restlessness | 0 | 1 | 0 | 0 | 0 | 3 | 3 | 2 | 1 | 8 | 3 | 2 | 0 | 6 | 0 | 1 | 0 | 9 | 1 | 3 |
| Neck pain | 1 | 0 | 1 | 0 | 2 | 3 | 3 | 4 | 3 | 2 | 3 | 4 | 0 | 1 | 2 | 1 | 1 | 2 | 1 | 6 |
| Abnormal dreams | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 4 | 2 | 1 | 1 | 3 | 0 | 2 | 2 | 4 | 1 | 3 | 2 | 7 |
| Hot flush | 0 | 0 | 0 | 0 | 0 | 4 | 1 | 1 | 0 | 10 | 2 | 1 | 0 | 6 | 1 | 1 | 0 | 8 | 1 | 1 |
| Peripheral coldness | 0 | 1 | 0 | 1 | 1 | 2 | 3 | 2 | 0 | 3 | 2 | 2 | 1 | 5 | 0 | 0 | 2 | 4 | 1 | 2 |
| Negative thoughts | 1 | 0 | 0 | 0 | 0 | 4 | 1 | 1 | 0 | 4 | 4 | 1 | 0 | 2 | 1 | 3 | 0 | 2 | 2 | 5 |
| Sensory processing sensitivity | 0 | 0 | 0 | 0 | 0 | 2 | 5 | 3 | 0 | 0 | 2 | 2 | 0 | 2 | 1 | 3 | 1 | 1 | 4 | 4 |
| Abdominal distension | 0 | 0 | 0 | 0 | 0 | 3 | 4 | 4 | 1 | 7 | 2 | 1 | 0 | 2 | 1 | 0 | 0 | 4 | 1 | 0 |
| Tremor | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 1 | 0 | 6 | 0 | 0 | 0 | 5 | 0 | 1 | 0 | 8 | 1 | 4 |
| Abdominal pain | 0 | 1 | 1 | 0 | 0 | 2 | 4 | 5 | 1 | 1 | 2 | 1 | 0 | 3 | 3 | 2 | 0 | 1 | 0 | 1 |
| Discomfort | 0 | 0 | 0 | 0 | 1 | 3 | 4 | 2 | 0 | 3 | 2 | 1 | 0 | 0 | 0 | 2 | 0 | 3 | 1 | 6 |
| Irritability | 0 | 0 | 0 | 1 | 0 | 1 | 2 | 3 | 0 | 1 | 1 | 2 | 0 | 2 | 0 | 4 | 0 | 0 | 3 | 6 |
| Dysphagia | 1 | 1 | 2 | 2 | 0 | 1 | 2 | 2 | 0 | 1 | 2 | 1 | 0 | 0 | 1 | 1 | 1 | 3 | 2 | 2 |

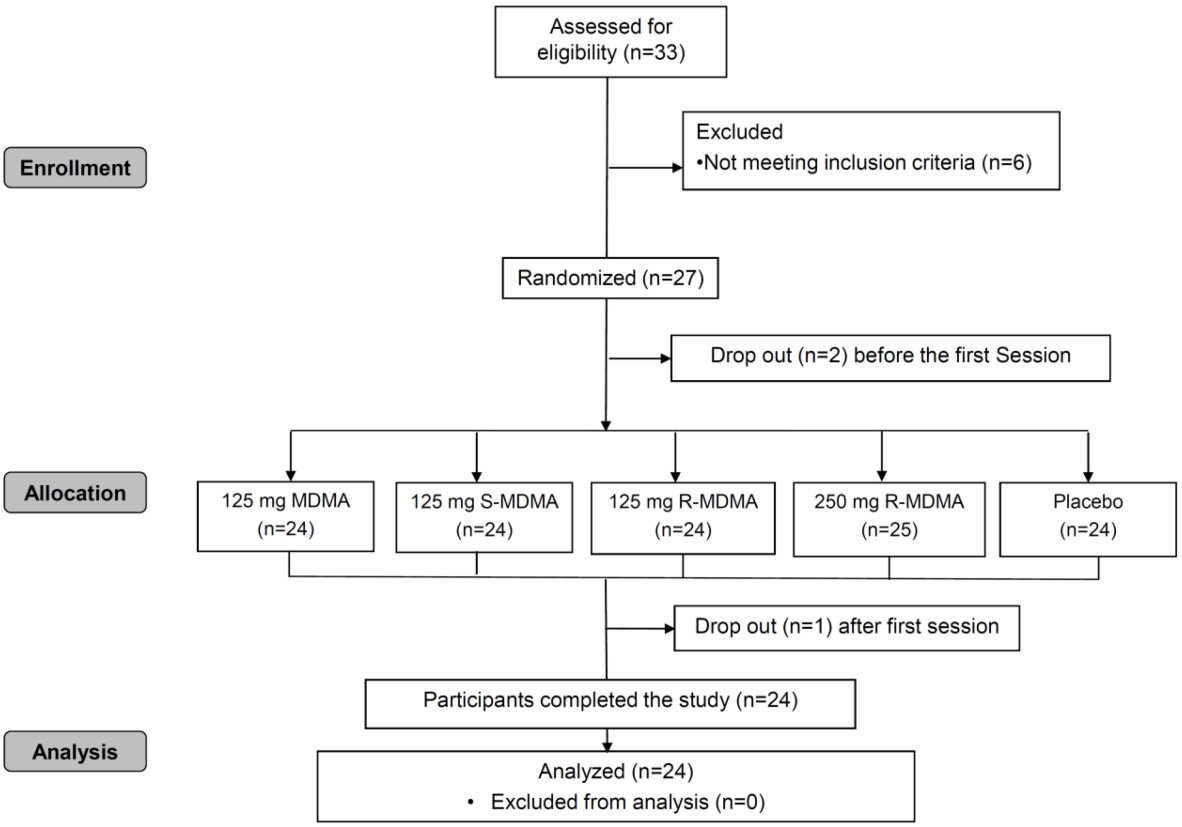
Data indicate number of subjects reporting an effect among a total of 24 subjects.

**Table S9. Drug dose identification after session and after the study**

| | Placebo | | R-MDMA 125 mg | | R-MDMA 250 mg | | MDMA 125 mg | | S-MDMA 125 mg | |
|---|---|---|---|---|---|---|---|---|---|---|
| | after Session | after Study | after Session | after Study | after Session | after Study | after Session | after Study | after Session | after Study |
| correctly identified | 83% | 92% | 58% | 71% | 42% | 33% | 25% | 29% | 21% | 25% |
| missclassified as placebo | | | 21% | 4% | 0% | 0% | 0% | 0% | 4% | 4% |
| missclassified as R-MDMA 125 mg | 17% | 8% | | | 33% | 4% | 21% | 8% | 29% | 8% |
| missclassified as R-MDMA 250 mg | 0% | 0% | 8% | 8% | | | 25% | 33% | 13% | 25% |
| missclassified as MDMA 125 mg | 0% | 0% | 8% | 8% | 12.5% | 25% | | | 33% | 38% |
| missclassified as S-MDMA 125 mg | 0% | 0% | 4% | 8% | 12.5% | 38% | 29% | 29% | | |

after session = 24h after substance administration; after study = at end of study visit

*Consort flow chart*



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# DISCUSSION, CONCLUSION & OUTLOOK

The present thesis describes the safety, pharmacology and subjective effects of LSD, psilocybin, MDMA and its enantiomers *R*-MDMA and *S*-MDMA in healthy volunteers. In detail it encompasses data from five clinical phase I studies. One study investigating the co-administration of LSD and MDMA compared to LSD alone, one pooled study including data from three separate studies compiling extensive safety pharmacology data for various doses of psilocybin, and one study investigating the differences between MDMA enantiomers *R*-MDMA and *S*-MDMA and the comparison to racemic MDMA. The findings are detailed in the published papers and the manuscript above. This section provides a brief discussion of the entire body of work, followed by a conclusion, and outlook.

The first project revealed that the subjective effects of a combined LSD-MDMA experience did not significantly differ from a pure LSD experience according to the assessed questionnaires. The LSD + MDMA combination tended to nonsignificantly increase ratings of "good drug effect," "drug high," "happy," "open," and "trust" on the Visual Analog Scale (VAS) compared with LSD alone, especially in the beginning. Additionally, ratings of "well-being" on the adjective mood rating scale (AMRS) showed an initial nonsignificant increase with the combined LSD + MDMA administration but dropped after 6 hours, indicating the end of the MDMA effect. Ratings of negative subjective effects, such as "bad drug effect," "fear," and "nausea" on the VAS were slightly higher with LSD alone, but overall remained low and did not significantly differ from the combined LSD + MDMA administration. In this clinical study, we only tested one dose of LSD (100 µg), and we cannot rule out the possibility that MDMA may reduce negative effects of higher LSD doses. Higher doses of LSD exceeding 100 µg, have been shown to induce significantly more "anxiety" [8]. Furthermore, we administered both substances at the same time, while recreational users reportedly often take MDMA after LSD when "candyflipping." This would ensure that MDMA effects do not drop while the subjective effects of LSD are still in the peak range. Another option would be to replace LSD with psilocybin, as psilocybin and MDMA have a similar duration of action [13, 37]. As expected, both LSD and MDMA produced moderate, transient increases in blood pressure, heart rate, and body temperature. The combined administration of LSD and MDMA resulted in higher blood pressure and heart rate compared to LSD alone, but not significantly higher than with MDMA alone. This additional increase is likely due to the release of norepinephrine triggered by MDMA, which plays a role in its cardiostimulant effects [93]. While this transient cardiovascular stimulation may not pose a problem for healthy individuals, it is important to consider when using this combination in patients with preexisting health conditions. The impact of a moderate dose of MDMA on systolic blood pressure is significantly higher than that of a moderate dose of LSD. However, diastolic blood pressure, heart rate, and rate pressure product do not seem to differ between the two

substances, even when MDMA is administered at a higher dose of 125 mg [94]. Body temperature increased similarly with the LSD + MDMA combination as with LSD alone, and more than with MDMA alone. A similar increase in body temperature for both substances has been shown previously when 125 mg MDMA and 100 µg of LSD were compared [94]. With no additional increase of body temperature, nausea or trembling, serotonin toxicity does not seem to increase when both substances were co-administered. MDMA strongly induces a release of oxytocin which has been shown to be important for the typical effects profile of MDMA [36, 95]. LSD also has been shown to release oxytocin but not as strongly as MDMA [13]. An interesting finding of this study was that the release of oxytocin seems to be additive when LSD and MDMA were combined. Although the subjective effects of the combined LSD and MDMA experience did not differ in quality from a pure LSD experience, the effects were prolonged by an average of 1.5 hours. This extended response correlated with higher plasma exposure ($C_{max}$ and AUC) and a longer elimination half-life of LSD. Pharmacokinetically, MDMA is a strong CYP2D6 inhibitor, effectively turning everyone into a CYP2D6 poor metabolizers 2 hours after administration [96]. LSD is suggested to be metabolized by CYP2D6 in vitro [15] and CYP2D6 poor metabolizer exhibited higher plasma concentrations and a longer elimination half-life of LSD compared with CYP2D6 extensive metabolizers [17]. Consequently, the interaction between LSD and MDMA is primarily pharmacokinetic rather than pharmacodynamic, with the study results further confirming a role for CYP2D6 in the metabolism of LSD. Overall, the combined use of LSD and MDMA is unlikely to provide relevant benefits over LSD alone in substance-assisted therapy.

The second project presented safety pharmacology data that could help determine an optimal dose for psilocybin-assisted therapy, aiming to induce strong, primarily positive acute effects with minimal negative subjective effects. The findings suggest that a dose of 20, 25, and 30 mg of psilocybin induce comparable positive effects while significant “anxiety” on the VAS was only observed with the 25 and 30 mg doses. Consequently, a 20 mg dose of psilocybin appears to be a prudent choice to enable a psychedelic experience that is primarily positive with minimal negative effects. This dose has also been shown to be equivalent in intensity to 100 µg of LSD [26], which is the dose currently used in most of the clinical studies with patients and healthy volunteers. The dose most often used in therapeutic studies with psilocybin is currently 25 mg, although smaller doses as well as higher doses up to 40 mg have been used [69, 70, 74, 97]. For the first time, data on average onset time, time to maximal effect, and effects duration for 113 psilocybin administrations dosed between 15 and 30 mg in healthy volunteers, have been presented. The average onset time of 0.6 hours and the time to peak effect at 2.1 hours were comparable to those observed with LSD [18]. However, as expected, the effect duration of psilocybin, at 5.5 hours, is notably shorter than

that of LSD. While the duration of LSD has been shown to be dose-dependent, there is not yet sufficient data on various psilocybin doses to establish a similar dose-response relationship. Whereas the impact of psilocybin on vital signs has been demonstrated in previous clinical studies, this pooled study focused on the proportions of participants exhibiting extreme values rather than population means. The autonomic effects of MDMA and LSD have been similarly described before [18, 37]. Overall, psilocybin induced mild sympathomimetic activation in most participants. Increases in blood pressure (>140 mmHg), heart rate (>100 bpm), and body temperature (>38°C) were noted in 50%, 7%, and 16% of participants, respectively, after psilocybin administration. When comparing psilocybin and LSD at likely equivalent doses of 20 mg and 100 µg, hypertension occurred in 52% and 53% of participants, respectively. In contrast, tachycardia occurred in only 3% of participants who ingested 20 mg of psilocybin compared to 20% of those who took 100 µg LSD, indicating a slightly greater potential for LSD to induce tachycardia. In a similar previous analysis, MDMA produced hypertension in 90% and tachycardia in 33% of participants. Consequently, MDMA clearly produces greater cardiovascular stimulation than both psilocybin and LSD at commonly used doses. Therefore, psilocybin may be a safer alternative to MDMA for patients with cardiovascular risk factors, assuming both compounds demonstrate therapeutic efficacy for a particular condition. Psilocybin caused a slight increase in body temperature, similar to the effect observed with LSD [18]. The project also compiled frequent adverse effects of various doses of psilocybin, which included general exhaustion, fatigue, lack of concentration, lethargy, vertigo, feeling of weakness, and decreased appetite. These adverse effects were similar to those observed with LSD [18]. As shown with the VAS, significant "anxiety" on the List of Complaints was only induced by the 25 and 30 mg doses of psilocybin. Acute anxiety could be alleviated with verbal support, and benzodiazepines were not used. There were no cases of severe anxiety, panic attacks, or acute suicidality. It is important to note that these participants were all healthy volunteers, and individuals with preexisting psychiatric conditions may react differently. Therefore, it seems wise to have emergency medications like ketanserin on hand, which has been shown to stop psychedelic effects induced by LSD within 2 hours of administration [9]. Overall, adverse effects of psilocybin were transient and not sufficiently disabling or severe to require medical intervention. Single-dose administrations of psilocybin up to 30 mg were safe regarding acute psychological and physical harm in healthy volunteers in a controlled setting. However, risks and benefits of using psilocybin in patients need further study.

The third project reported overall comparable effects of MDMA, *S*-MDMA and *R*-MDMA. *S*-MDMA induced slightly stronger effects and significant higher ratings of "bad drug effects," "visual alterations," and "synesthesia" on the VAS compared to MDMA and *R*-

MDMA. *S*-MDMA produced greater increases in blood pressure, cortisol, and prolactin. *S*-MDMA was the only substance that induced significant depressive symptoms 1 to 3 days after administration. *R*-MDMA produced lower subjective effects on most VASs, and increased introversion compared to MDMA and *S*-MDMA. MDMA, *S*-MDMA, and *R*-MDMA induced comparable psychedelic- and mystical-type effects. It is important to note that we did not achieve dose equivalence with MDMA and both its enantiomers, therefore it remains unclear whether the differences observed are due to their different binding profiles or the dosing. The results indicate dose equivalence regarding the overall acute effects of 125 mg MDMA, 100 mg *S*-MDMA, and 300 mg *R*-MDMA. The potential of *S*-MDMA to increase blood pressure more significantly may be due to dosing differences or its higher potency interacting with the norepinephrine transporter and releasing norepinephrine compared with *R*-MDMA [35]. The stronger depressed mood ratings observed 1 to 3 days after *S*-MDMA administration could reflect greater serotonin depletion [98] and could indicate more neurotoxic properties [99] compared with *R*-MDMA. Additionally, *S*-MDMA induced higher ratings of "drug high" on the VAS, suggesting it may be more addictive in humans, as shown in animal studies [47, 100], compared with *R*-MDMA. These effects were anticipated based on in vitro and animal data indicating the potential of *S*-MDMA to be a stronger releaser of monoamines and its more pronounced psychostimulant effects [35]. Contrary to our expectation, *R*-MDMA did not seem to induce more psychedelic-like effects. However, the fact that *R*-MDMA induced overall lower ratings on almost all subjective effects but the same amount of psychedelic- and mystical-type effects, suggest that if dosed equivalently, it might exhibit stronger psychedelic-like effects than *S*-MDMA or MDMA. Nevertheless, *S*-MDMA induced significantly higher ratings on the VAS items "alteration of vision" and "synesthesia," which are characteristic effects of psychedelics, compared with *R*-MDMA. Psychedelics typically induce lower ratings of social interaction, such as "talkative," "open," "trust," "I feel close to others," and "I want to be with others" compared with MDMA [94]. Therefore, if *R*-MDMA had more psychedelic-like effects it would align with the observation that these social interaction ratings were less pronounced with *R*-MDMA, contrary to the higher social interaction suggested by previous animal research [47, 101]. In contrast to previous research indicating no significant increase in body temperature with *R*-MDMA in animals and the assumption of fewer adverse effects [99, 101, 102], *R*-MDMA induced similar increases in body temperature and showed a comparable number of adverse effects on the List of Complaints as MDMA and *S*-MDMA. Regarding pharmacokinetics, the present study confirmed that *R*-MDMA has a greater exposure and a longer elimination half-life compared with *S*-MDMA after racemic MDMA administration. Additionally, we reported pharmacokinetic data of *S*-MDMA and *R*-MDMA without the influence of the other enantiomer. The elimination half-life of *R*-MDMA increases dose-dependently from 11 hours

with racemic MDMA to 12 hours with 125 mg *R*-MDMA to 14 hours with 250 mg *R*-MDMA. Conversely. the elimination half-life of *S*-MDMA decreased by 1 hour when administered without *R*-MDMA. Furthermore, we found that the formation of 4-Hydroxy-3-methoxymethamphetamine (HMMA), a metabolite produced via CYP2D6, did not increase with higher doses of *R*-MDMA. These findings confirm that *R*-MDMA dose-dependently inhibits CYP2D6, thereby inhibiting its own inactivation as well as that of *S*-MDMA in racemic MDMA. If and how much CYP2D6 is inhibited by *S*-MDMA has yet to be investigated.

The strengths of these studies include the use of relatively large samples sizes, with both conducted clinical studies including 24 healthy volunteers and equal numbers of male and female participants. The safety pharmacology analysis with 85 healthy individuals and 113 individual psilocybin session resulted in a comprehensive dataset. Four of the five studies in this thesis featured robust within-subject comparisons and randomized double-blind placebo-controlled designs. The substances were pharmacologically well characterized, and plasma concentrations were determined at close intervals using validated analytical methods. Additionally, all studies included internationally established psychometric outcome measurements, facilitating comparison and pooling of the data across different clinical studies.

Limitations of the studies included a restricted number of doses or one dose combination, leading to numerous alternative study designs that might have been better. All studies were conducted in a highly controlled hospital setting with only healthy volunteers. Individuals in different environments and patients with psychiatric disorders may respond differently to these substances. Furthermore, the second project pooled data from three different studies with different participants. These substances induce highly variable individual effects, and our outcome measurements may not have been sufficiently sensitive to capture all aspects of the psychedelic or MDMA experience, especially the very subtle differences in acute and subacute effects. There were also no long-term follow-ups after the end of study visit, to assess positive or negative long-term effects. Although all doses were well-defined, individual differences in the bioavailability or metabolism of the substances were not accounted for in these studies.

## Conclusion & Outlook

This thesis focused on the safety, pharmacology, and subjective effects of five psychoactive compounds: LSD, psilocybin, MDMA and its enantiomers *R*-MDMA and *S*-

MDMA. In summary, the projects revealed new findings about these compounds, which can be used to inform and guide future clinical studies in healthy volunteers and in patients.

First, the LSD-MDMA study reported the effects of the combined administration of LSD and MDMA, which did not result in different subjective effects compared with LSD alone but confirmed the role of CYP2D6 in LSD metabolism. It remains unclear whether enhancing psychedelic effects with MDMA is possible. Nevertheless, altering the doses or administration timings of both substances could potentially achieve different combination of effects. The idea of ameliorating the psychedelic effects warrants further investigation. We plan to conduct a clinical study in healthy volunteers, administering psilocybin and MDMA together. Based on the safety analysis of psilocybin, we anticipate the cardiovascular risks to be similar to those with the combination of LSD and MDMA, and the effect duration of psilocybin and MDMA are more closely aligned. This study will also investigate whether psilocybin is significantly metabolized by CYP2D6, although we currently do not believe this to be the case.

The safety analysis involving 113 administrations of psilocybin in the 15 to 30 mg dose range is already comprehensive. However, future additions to this dataset are anticipated. Another clinical study is currently underway using a 25 mg psilocybin dose, and our upcoming study combining psilocybin with MDMA will include additional administrations of pure 20 mg doses. Nevertheless, a dose-response study encompassing lower doses than 15 mg and higher than 30 mg would further enhance the completeness and value of our safety pharmacology analysis. This research is particularly relevant given that psilocybin is currently the most extensively studied psychedelic for substance-assisted therapy, and phase I data remains limited.

The third study indicated that the effects of MDMA and its enantiomers, *R*-MDMA and *S*-MDMA, may not differ as significantly as previously suggested by in vitro and animal data. Of particular interest was the finding that *R*-MDMA appears to inhibit CYP2D6 to a greater extent than *S*-MDMA. The impact of *R*-MDMA and *S*-MDMA on the inhibition of CYP2D6 will be further investigated through additional in vitro analyses by the Psychopharmacology Lab and in another clinical study involving healthy volunteers. This study will focus exclusively on the enantiomers administered at our proposed equivalent doses of 300 mg for *R*-MDMA and 100 mg for *S*-MDMA. Furthermore, we plan to include additional measures to explore changes in empathy induced by the substances using computer testing and tools for CYP2D6 phenotyping, to determine if there is any inhibition of CYP2D6 by *S*-MDMA.

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