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ARTICLE

Effects of the Psychedelic Amphetamine MDA (3,4-Methylenedioxyamphetamine) in Healthy Volunteers

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ABSTRACT

Entactogens such as 3,4-Methylenedioxymethamphetamine (MDMA, "molly", "ecstasy") appear to have unusual, potentially therapeutic, emotional effects. Understanding their mechanisms can benefit from clinical experiments with related drugs. Yet the first known drug with such properties, 3,4-Methylenedioxyamphetamine (MDA), remains poorly studied and its pharmacokinetics in humans are unknown. We conducted a within-subjects, double-blind, placebo-controlled study of 1.4 mg/kg oral racemic MDA and compared results to those from our prior similar studies with 1.5 mg/kg oral racemic MDMA. MDA was well-tolerated by participants. MDA induced robust increases in heart rate and blood pressure and increased cortisol and prolactin to a similar degree as MDMA. MDA self-report effects shared features with MDMA as well as with classical psychedelics. MDA self-report effects lasted longer than those of MDMA, with MDA effects remaining elevated at 8 h while MDMA effects resolved by 6 h. Cmax and $AUC_{0-\infty}$ for MDA were 229 ± 39 (mean ± SD) and 3636 ± 958 µg/L for MDA and 92 ± 61 and 1544 ± 741 µg/L for the metabolite 4-hydroxy-3-methoxyamphetamine (HMA). There was considerable between-subject variation in MDA/HMA ratios. The similarity of MDA and MDMA pharmacokinetics suggests that the greater duration of MDA effects is due to pharmacodynamics rather than pharmacokinetics.

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Psychedelic; entactogen; MDMA; amphetamine

Introduction

MDA (3,4-methylenedioxyamphetamine, "tenamfetamine," "Love Drug") is an illicit drug with a long history of experimental medical and nonmedical use (Pentney 2001). Like the structurally similar drug MDMA (3,4-methylenedioxymethamphetamine), MDA was explored as an adjunct to psychotherapy (Naranjo 1974; Yensen et al. 1976), but was scheduled as a controlled substance in the United States in 1970. MDA continues to appear in illegal drug preparations and is often sold as "ecstasy" in place of MDMA (Baggott et al. 2000; Brunt and Niesink 2011).

While it is sometimes described as an amphetamine or hallucinogen, reports suggest that MDA also shares the unusual social-emotional effects of MDMA, such as feeling emotionally close to others (Jackson and Reed 1970). These effects were proposed to represent a novel pharmacological category, termed entactogen (Nichols 1986). Yet MDA also has complex pharmacological mechanisms that overlap with classical psychedelics, such as LSD, and psychostimulants. Specifically, it acts as a serotonergic 5-HT_{2A} receptor agonist (as does the prototypical psychedelic LSD) and releases monoamines by interacting with monoamine plasmalemmal transporters (as do psychostimulants and MDMA) (Lyon, Glennon, and Titeler 1986; Paton et al. 1975). Consistent with early reports, rodent drug discrimination studies (Baker and Taylor 1997; Young and Glennon 1996) and rodent behavioral research (Quinteros-Munoz et al. 2010) confirm that MDA has classical psychedelic effects as well as some unusual effects of MDMA. This has not yet been shown in humans, as controlled studies of MDA in humans predate the widespread use of MDMA (Turek, Soskin, and Kurland 1974; Yensen et al. 1976). As a result, formal comparisons of the drugs in humans are lacking.

The pharmacokinetics of orally administered MDA in humans are also unknown. Some data were collected on MDA formation after MDMA administration (de la Torre et al. 2004; Kolbrich et al. 2008a). However, the metabolism of MDA may be altered by the presence of higher concentrations of MDMA and its other

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metabolites. Additionally, the self-report and physiological effects of MDA are reported to have a similar time course to that of MDMA (Shulgin and Shulgin 1991). This suggests that orally administered MDA will probably have similar kinetics to that of orally administered MDMA. To address these issues, we conducted a placebo-controlled study administering MDA to healthy volunteers in a laboratory setting. We compared MDA results to those of prior similar studies conducted using MDMA.

Material and methods

This double-blind, placebo-controlled, within-subjects crossover study was carried out at the UCSF Clinical Research Center at San Francisco General Hospital with participants admitted to the hospital for a single three-evening stay. Extensive safety monitoring was carried out from before drug administration until after drug effects resolved. Participants returned to the laboratory two weeks after discharge to ensure that residual toxicity was not present. The research was approved by the UCSF IRB and permitted by state and federal regulators (including California Research Advisory Panel, DEA, and FDA).

Source of MDMA comparison data

For drug comparisons, we include data from two placebo-controlled studies of the effects of 1.5 mg/kg oral racemic MDMA in healthy volunteers (Baggott et al. 2016a, 2016b). This dose is isomolar to the MDA dose we used. Methods are comparable to those described here and are fully detailed elsewhere (Baggott et al. 2016a, 2016b).

Participants

Participants were 12 healthy individuals with self-report experience with either MDA alone or experience with both MDMA and a classical serotonergic psychedelic, such as LSD. None had any DSM-IV drug dependence diagnoses (other than nicotine or caffeine). Safety screening procedures included history and physical, self-report drug history, 12-lead EKG, liver panel, and blood chemistry. Participants were asked to practice effective contraception during the study. Pregnancy and drug toxicology tests were performed before drug administration. Nicotine was forbidden during the hospital stay and caffeine was forbidden starting 10 hours before dosing.

Drugs and dosing

Racemic MDA was synthesized by the researchers with identity and purity confirmed using melting point, proton nuclear magnetic resonance (300 MHz), and elemental analysis under an FDA Investigational New Drug exemption.

Experimental drug administration occurred after a two-hour fast to minimize individual variance in drug absorption. Lactose in a gelatin capsule was used for the placebo. MDA was administered in a dose of 1.4 mg/kg body weight in a gelatin capsule identical to the placebo. Drug and placebo dosing occurred on consecutive days.

Measures

Timed measurements included blood samples for pharmacokinetic purposes, physiological measures of heart rate and blood pressure, self-report measures of drug effects, and computerized tasks. Measures relevant to visual changes and global psychedelic effects were described in a previous article (Baggott et al. 2010). With the exception of this subset of visual analog items, we present previously unreported measures here.

Self-report drug effects

We used the 66-item Altered States of Consciousness (ASC) visual analog scale (Studerus, Gamma, and Vollenweider 2010) to measure psychedelic-like self-report effects. This instrument has been previously used with classical psychedelics and MDMA (e.g., Schmid et al. 2014; Studerus, Gamma, and Vollenweider 2010). We report the original three main scales (Oceanic Boundlessness, Dread of Ego Dissolution, and Visionary Changes) and the 11 lower-order factors identified by Studerus, Gamma, and Vollenweider (2010). Because there was no validated English translation of the scale, we engaged a professional translator (who was familiar with psychedelic effects) to translate the instrument from the original German and then had it retranslated to German by a separate translator, confirming with the first translator that the meaning was unchanged. We gave the ASC 8 h after drug administration and asked participants to retrospectively rate the peak drug effects.

We used visual analog scales (VAS) to measure three main areas: *general drug effects* (Any drug effect, Good drug effect, Bad drug effect, High, Drug liking); *stimulant or entactogen (MDMA-like) effects* (Anxious; Stimulated; Relaxed; Clear-headed; Closeness to others; Insightful; Some events, objects, or other people have new meanings for me); and *psychedelic-like (LSD-like) effects* (The passing of time seems changed; Feelings of unreality; My body or body parts seem changed; Size, depth, or shape of surroundings seems changed; Difficulty controlling thoughts; Familiar things seem unfamiliar; When I close my eyes I see complex abstract patterns; When I close my eyes I see animals, people, or beings; When I close my eyes I see objects or non-living thing; When I close my eyes I see places or landscapes; Suspicious feelings that others may be against me). Questions about time distortions and

closed-eye imagery were asked immediately after the participants closed their eyes for a computer-timed 30-sec. VAS items were given repeatedly for up to 8 h to track changing drug effects.

We measured self-report affect with items from the Affect Valuation Index (AVI) (Tsai, Knutson, and Fung 2006). We measured social feelings with the Interpersonal Adjectives Scale-Revised (IASR) (Wiggins, Trapnell, and Phillips 1988). Both instruments use a circumplex approach in which a two-dimensional space is evenly sampled by octant subscales radiating like spokes on a wheel. In the case of the AVI, the two dimensions reflect Arousal (calm to excited/agitated) and Valence (positive to negative). In the case of the IASR, the two dimensions can be labeled as Dominance (concern for mastery and power that enhance and protect the individual) on the vertical axis and Affiliation (a concern for intimacy and solidarity with others) on the horizontal axis. Average locations of subscales in these two dimensions form summary scales (Kiesler 1991; Wiggins and Broughton 1991). We administered the AVI and IASR before and 2.5 h after drug administration.

Physiological, endocrine, and pharmacokinetic effects

Heart rate and blood pressure were measured before drug administration and then hourly until 8 h (6 h for comparison MDMA data) using a Philips C3 CO_2 Vital Signs Monitor (Philips Healthcare, Andover, MA). We collected blood samples via intravenous catheter before and 2 and 3 h after drug administration and assayed them for prolactin and cortisol (Nichols Institute, San Juan Capistrano, CA). We collected blood before and at 1, 2, 4, 6, 8, 12, 26, and 30 h after drug administration for pharmacokinetics measures. We measured concentrations of MDA and its major metabolite 4-hydroxy-3-methoxyamphetamine (HMA) using two-dimensional GC/MS, modifying the method of Kolbrich, Lowe, and Huestis (2008b) by using a single "cut" for all analytes, adding a 1 mL hexane wash step, and obtaining an expanded linear dynamic range for both substances (MDA: 1–400 μg/L and HMA: 2.5–400 μg/L).

Statistical analysis

We analyzed data using mixed-effects models in R (R Core Team 2014) with drug condition as a fixed effect and participant as a random effect using a two-tailed 0.05 level of significance. When analyses identified a main effect of drug condition, we made pairwise comparisons correcting for multiple comparisons using the method of Westfall (1997). Contrasts between placebo and active drug conditions were limited to within-study comparisons (i.e., MDA was only compared to placebo from the MDA study, while MDMA was only compared to placebo from the MDMA study). Repeated measures were baseline corrected and transformed to maximum effects (Emax) or area under the effects curve (AUC) (Eisenberg et al. 2007) summary measures before analysis. We estimated pharmacokinetic parameters in NONMEM (version 7; NONMEM Project Group, University of California, San Francisco) using a noncompartmental model using linear trapezoidal calculations and linear weighing of lambdas. Half-life was estimated using the method of Lee, Poon, and Kingdon (1990).

Results

Participants

Twelve participants were enrolled and completed the study. They were 27.8 ± 8 (mean ± SD) years of age, had completed 14.8 ± 2 years of education. Two were Hispanic or Latino (one Caucasian and one of African American ancestry) and 10 were not Hispanic or Latino (Caucasian ethnicity). Participants weighed 74.1 ± 9.2 kg and the absolute MDA doses administered were 83 to 128 mg.

Checking for sequence effects

We used a compact study design in which MDA and placebo occurred on consecutive days. Accordingly, half of the participants received placebo after MDA, raising the question of whether their placebo session reflected residual effects of MDA. To address this, we fit models for physiological, endocrine, and self-report VAS measures that included only placebo sessions and checked for differences between the placebo-MDA sequence, MDA-placebo sequence, and MDMA placebo sessions. This did not suggest any significant effects of sequence. There was an expected sequence effect for MDA and metabolite kinetics, which remained detectable on the second day. We handled this by excluding second-session placebo sessions from the kinetics analysis with the exception of 2 and 6 h samples, which were used as the scheduled 26 and 30 h samples from the previous session.

Self-report measures

Altered states measurement (ASC)

The drugs increased most scales of the ASC. MDA and MDMA had largely overlapping self-report effects, with MDA having more hallucinogen-like perceptual effects and MDMA having greater dysphoric effects (Figure 1).

Affect and social functioning (AVI and IASR)

MDA and MDMA similarly affected self-report affect and social functioning (Figure 2). Both the Arousal and Valence affect dimensions showed a significant effect of

drug condition (Arousal: $F_{3,68} = 5.30$, $p = 0.002$; Valence: $F_{3,68} = 2.35$, $p = 0.08$), with both drugs having similar effects. In contrast, only MDMA increased Affiliation.

VAS

MDA and MDMA again showed partly overlapping profiles (Table 1, Figure 3). The two drugs largely did not differ from each other when maximum effects (Emax) were examined (not shown). However, MDA effects had longer duration, so that when AUCs were examined, MDA showed greater scores in VAS measures of general drug effects, feelings of stimulation, and in psychedelic-like effects, such as time distortion and perception of closed eye patterns (as shown in Table 1). To confirm the greater duration of MDA effects, we examined baseline corrected scores at 6 h and 8 h for the five general drug effects items. While no MDMA effects were significantly elevated at 6 h, MDA continued to produce significant elevations in all five measures at 6 and in all except bad drug effect at 8 h. For example, at 6 h, any drug effect was 41.6 ± 7 higher for MDA compared to MDMA ($z = 6.3$, $p < 0.001$) and 46.4 ± 7 ($z = 6.7$, $p < 0.001$) higher for MDA compared to placebo. Similarly, at 8 h, any drug effect was 35.6 ± 10 higher for MDA than placebo ($t = 3.7$, $p = 0.001$).

Physiological and endocrine measures

Physiological changes

MDA and MDMA both increased heart rate and blood pressure. There were main effects of condition on baseline corrected maximum heart rate ($F_{3,22} = 17.1$, $p < 0.0001$), diastolic blood pressure ($F_{3,22} = 32.4$, $p < 0.0001$), and systolic blood pressure ($F_{3,22} = 61.7$, $p < 0.0001$). Heart rate increased 20 ± 3 bpm after MDA, which was significantly less than the 30.6 ± 4.5 bpm increase after MDMA ($p = 0.03$). Peak systolic blood pressure was comparably elevated after MDA (33 ± 2 mmHg) and MDMA (31 ± 3 mmHg) and there was a nonsignificant trend ($p = 0.06$) for diastolic blood pressure to increase more after MDA (24 ± 2 mmHg, vs. 19 ± 2 mmHg after MDMA).

Endocrine changes

Both MDA and MDMA elevated circulating serum prolactin and cortisol, with a non-significant trend for MDMA to produce higher peak prolactin than MDA ($p = 0.07$). Prolactin concentrations increased 16 ± 6 ng/mL after MDA and 29 ± 6 ng/mL after MDMA compared to placebo ($F_{3,25} = 13.0$, $p < 0.0001$), while cortisol rose 16 ± 1 µg/dL after MDA and 13 ± 2 µg/dL after MDMA compared to placebo ($F_{3,24} = 43.1$, $p < 0.0001$).

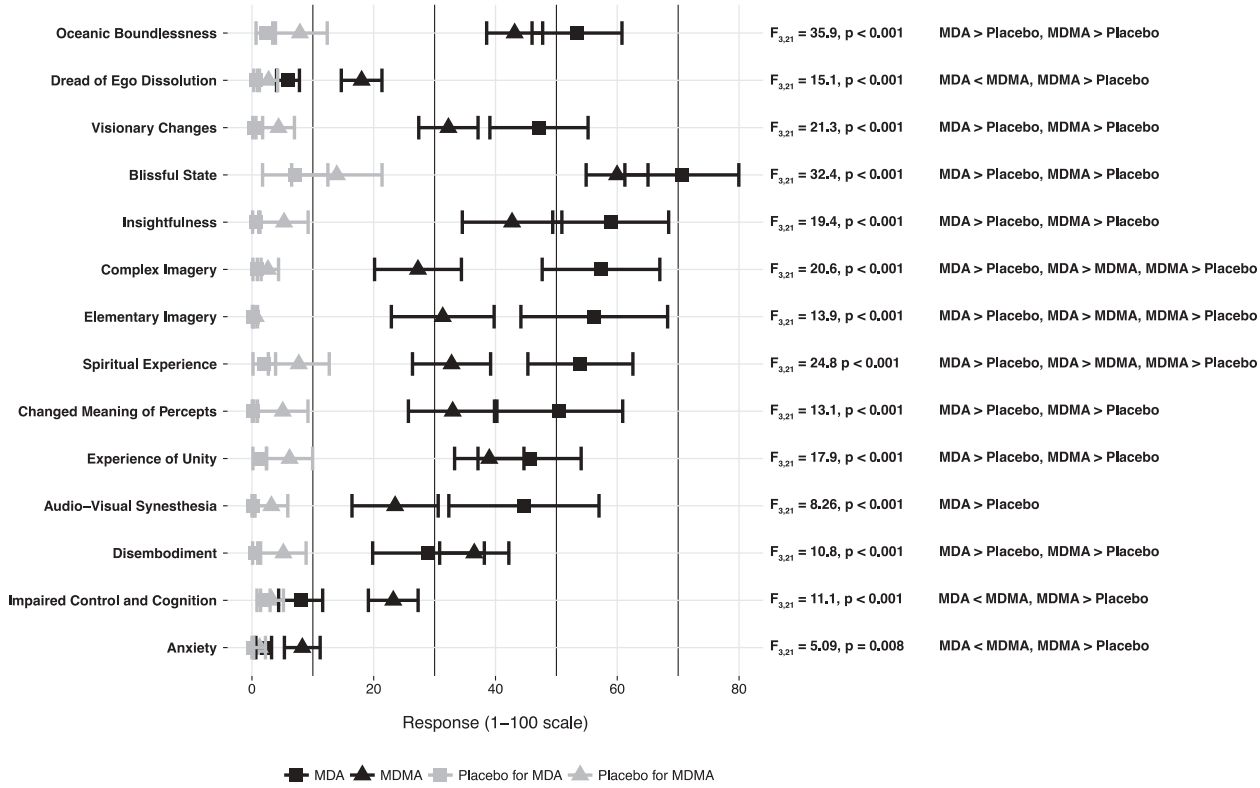

Figure 1. Comparison of MDA and MDMA effects on the Altered States of Consciousness (ASC). *N*= 12 for both MDA and MDMA data. Error bars indicate SEM.

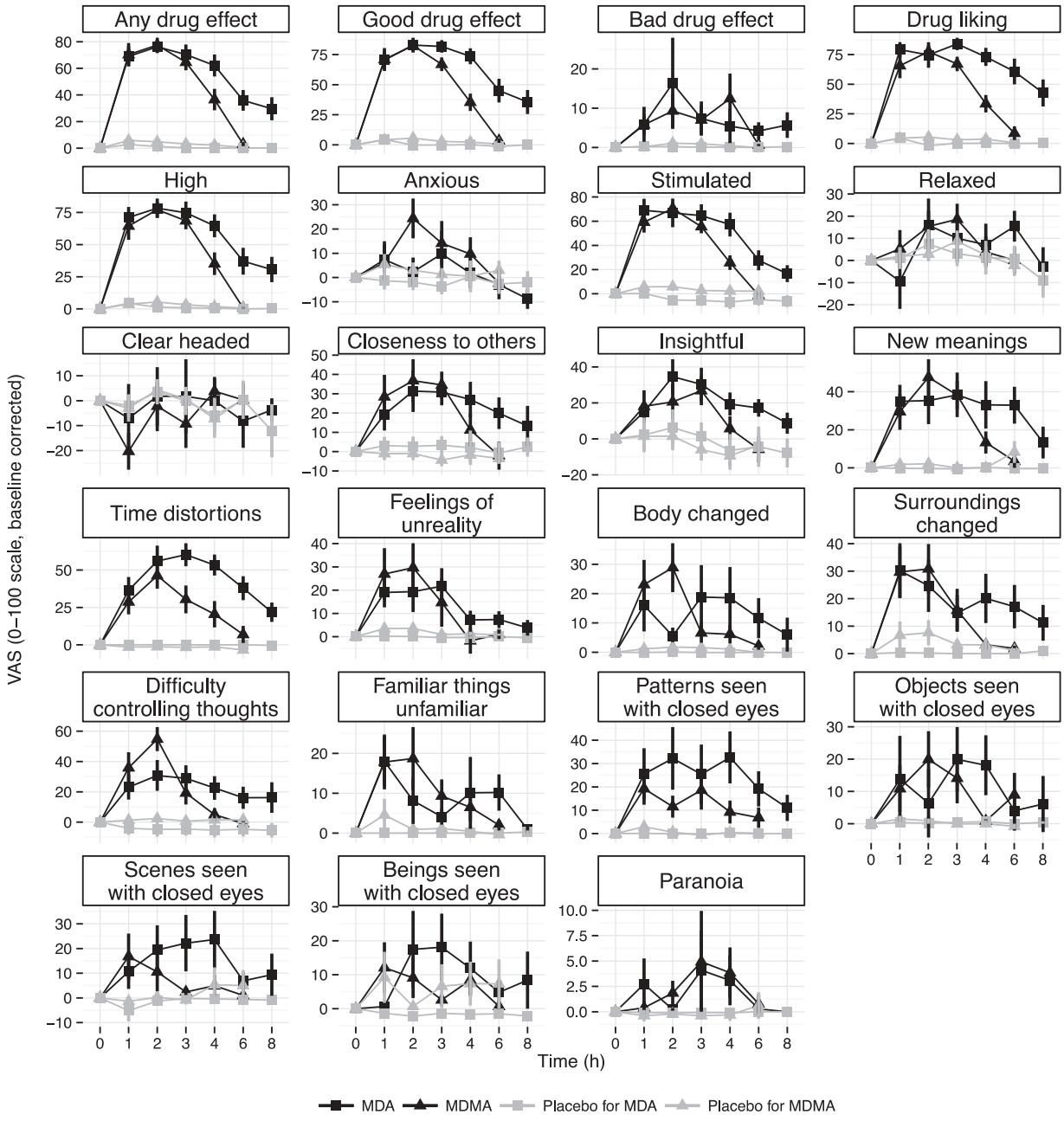

Figure 2. Time course of MDA and MDMA effects, as measured with visual analog items. $N = 12$ for MDA and $N = 16$ for MDMA data. Error bars indicate SEM.

Pharmacokinetics

Cmax and $AUC_{0-\infty}$ were 229 ± 39 µg/L (mean ± SD) and 3,636 ± 958 for MDA and 92 ± 61 µg/L and 1,544 ± 741 for the metabolite HMA. Elimination half-life was 10.9 ± 4 h for MDA and 14.1 ± 3 h for HMA. Total MDA clearance/F was 30,267 ± 8,214 mL/min. There was noticeable between-subject variation in HMA formation; HMA Cmax and $AUC_{0-\infty}$ varied over seven-fold and four-fold, respectively, between individuals.

Discussion

We conducted the first controlled study of MDA in humans in over 35 years and measured its pharmacokinetics in humans for the first time. MDA displayed a mixture of MDMA-like and psychedelic-like self-report effects, while also producing a robust sympathomimetic syndrome of increased heart rate and blood pressure.

MDA self-report effects shared features with classical psychedelics as well as with MDMA. Psychedelic-like effects often seen after LSD or psilocybin (Carhart-Harris

Table 1. Comparison of MDA and MDMA effects on visual analog scale items measuring general drug effects, MDMA-like (entactogen-like) and stimulant effects, and hallucinogen-like effects.

	Placebo for MDA		MDA		MDMA		Placebo for MDMA	Effect of Condition on Emax
Any drug effect AUC	4.7 ± 3	<	402.5 ± 46	>	270.3 ± 21	>	17.8 ± 11	F(3,21) = 62.9, p < 0.001
Good drug effect AUC	2.2 ± 4	<	461.1 ± 43	>	276.9 ± 20	>	16.8 ± 10	F(3,21) = 88.2, p < 0.001
Bad drug effect AUC	1.0 ± 1	≈	47.9 ± 26	≈	41.4 ± 16	≈	2.8 ± 2	F(3,21) = 3.1, p = 0.0487
High AUC	7.9 ± 4	<	416.9 ± 52	>	263.4 ± 25	>	15.9 ± 10	F(3,21) = 50.7, p < 0.001
Drug liking AUC	3.8 ± 4	<	502.5 ± 50	>	269.1 ± 29	>	18.9 ± 12	F(3,21) = 68.1, p < 0.001
Anxious AUC	−14.4 ± 28	x	10.4 ± 40	x	56.9 ± 29	x	13.5 ± 13	F(3,21) = 1.26, p = 0.3116
Stimulated AUC	−36.7 ± 32	<	350.4 ± 53	>	222.5 ± 20	>	19.7 ± 16	F(3,21) = 37.1, p < 0.001
Relaxed AUC	8.8 ± 37	x	49.7 ± 61	x	45.1 ± 30	x	14.7 ± 17	F(3,21) = 0.433, p = 0.7317
Clear headed AUC	−19.8 ± 40	x	−28.6 ± 72	x	−25.9 ± 29	x	−8.2 ± 21	F(3,21) = 0.051, p = 0.9842
Closeness to others AUC	11.5 ± 38	<	168.0 ± 53	≈	114.4 ± 44	>	−12.5 ± 16	F(3,21) = 5.26, p = 0.0073
Insightful AUC	−12.9 ± 60	<	143.2 ± 36	≈	68.1 ± 31	≈	−20.9 ± 37	F(3,21) = 3.19, p = 0.0446
New meanings AUC	−2.1 ± 2	<	235.8 ± 69	≈	138.7 ± 28	>	12.2 ± 6	F(3,21) = 10.8, p < 0.001
Time distortions AUC	−0.5 ± 1	<	321.6 ± 46	>	143.0 ± 31	>	−10.1 ± 9	F(3,21) = 32.3, p < 0.001
Feelings of unreality AUC	−2.0 ± 3	≈	87.1 ± 26	≈	69.6 ± 35	≈	10.6 ± 7	F(3,21) = 3.95, p = 0.022
Body changed AUC	−0.4 ± 1	≈	105.3 ± 60	≈	69.9 ± 18	≈	6.1 ± 4	F(3,21) = 3.17, p = 0.046
Surroundings changed AUC	1.6 ± 1	<	139.5 ± 54	≈	83.0 ± 24	≈	23.4 ± 12	F(3,21) = 5.04, p = 0.009
Difficulty controlling thoughts AUC	−34.9 ± 32	<	163.6 ± 51	≈	116.4 ± 25	>	8.2 ± 4	F(3,21) = 9.26, p < 0.001
Familiar things unfamiliar AUC	0.2 ± 1	<	66.6 ± 26	≈	57.5 ± 15	>	6.9 ± 4	F(3,21) = 6.24, p = 0.003
Patterns seen with closed eyes AUC	−0.1 ± 1	<	174.3 ± 58	>	70.1 ± 24	≈	3.8 ± 7	F(3,21) = 7.51, p = 0.001
Objects seen with closed eyes AUC	2.8 ± 2	x	86.6 ± 57	x	55.1 ± 23	x	1.5 ± 1	F(3,21) = 2.10, p = 0.131
Beings seen with closed eyes AUC	−13.0 ± 9	x	70.9 ± 38	x	37.2 ± 16	x	34.9 ± 31	F(3,21) = 1.71, p = 0.196
Scenes seen with closed eyes AUC	−10.9 ± 8	<	108.6 ± 49	≈	38.1 ± 17	≈	11.0 ± 19	F(3,21) = 3.68, p = 0.028
Paranoia AUC	−0.5 ± 1	x	13.8 ± 10	x	13.7 ± 9	x	−0.9 ± 3	F(3,21) = 1.71, p = 0.196

N = 12 for MDA and *N* = 16 for MDMA data. Values are given as mean ± SEM. The symbols >, <, and ≈ indicate greater than, less than, and not significantly different, while x indicates that there was no significant effect of condition and pairwise comparisons were accordingly not made.

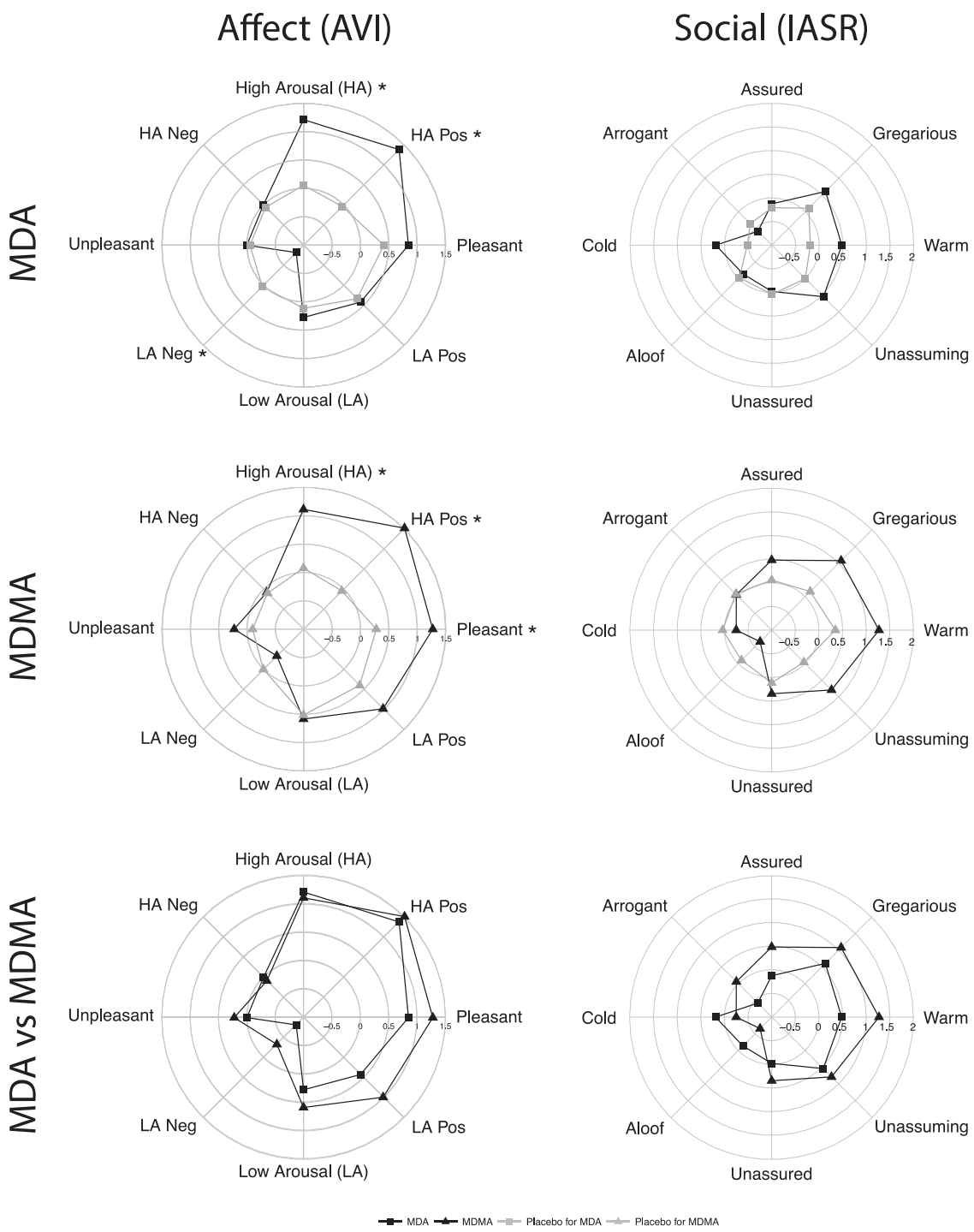

Figure 3. Comparison of MDA and MDMA effects on Affect (left) and Social feelings (right). $N = 12$ for both MDA and MDMA data. Affect was measured with subscales of the Affect Value Index (AVI), while social feelings were measured with the Interpersonal Adjective Scale Revised (IASR).

et al. 2016; Schmid et al. 2014; Studerus, Gamma, and Vollenweider 2010) and detected here after MDA included increased complex illusory imagery, synesthesia, and spiritual experiences. The greater psychedelic-like effects of MDA compared to MDMA may be attributed to its comparatively greater efficacy at stimulating 5-HT_{2A} receptors (Nash et al. 1994). Overall, MDA was similar to MDMA (e.g., increasing Closeness to other VAS), although it induced fewer dysphoric effects than MDMA, with lower scores being recorded on measures of anxiety and impaired control and cognition. Qualitatively, MDA appeared to produce a more introverted and emotionally intense prosocial state than MDMA, which seemed to encourage a more extraverted, gregarious prosocial state. These

similarities with psychedelics and MDMA are consistent with the rodent drug discrimination literature (Baker and Taylor 1997; Young and Glennon 1996) and illicit user reports (Jackson and Reed 1970; Weil 1976), although the current results provide specificity that can only be achieved with formal measures in controlled human research.

MDA induced robust acute increases in heart rate and blood pressure that were similar to those of MDMA as well as psychostimulants such as methamphetamine (Kirkpatrick et al. 2012). This is consistent with animal studies (Bexis and Docherty 2006; Quinteros-Munoz et al. 2010), as well as with assays indicating MDA nonselectively binds to α2- and α1- adrenoceptors (Bexis and Docherty 2006) and is a potent releaser of norepinephine (Setola et al. 2003). The pressor effects we measured were well-tolerated in our healthy participants, although these effects could be of concern in individuals with cardiovascular disease.

Our results provide insights into how to understand the pharmacological relationships between MDMA-like drugs, stimulants, and classical psychedelics. Early discussion of MDMA emphasized its unusual socioemotional effects, while noting that the "psychedelic amphetamine" MDA shared some of these qualities. Work by Nichols and colleagues established that these socioemotional effects were separable from the amphetamine-like euphoric properties of MDMA (Nichols and Oberlender 1990). In the intervening decades, additional substances have appeared in drug markets that have MDMA-like and stimulant-like effects to different degrees (Miliano et al. 2016; Simmler et al. 2013). Our results confirm early indications that MDA has entactogen, stimulant, and psychedelic effects (Jackson and Reed 1970; Weil 1976; Yensen et al. 1976). Thus, it may be useful to think about these and related drugs as having potential effects within three main dimensions: entactogen, stimulant, and classical psychedelic. The current results point to MDMA having strong entactogen effects, modest stimulant effects, and weak psychedelic effects, and MDA having significant effects in all three dimensions.

This is consistent with hypothesized mechanisms of entactogens, stimulants, and classical psychedelics. Noradrenergic effects appear important for the euphoric effects of stimulants (Rothman et al. 2001), while Simmler and Liechti (2018) note that the balance of dopaminergic and serotonergic effects distinguishes MDMA-like drugs from amphetamine-like stimulants. Indeed, MDMA has a DAT/SERT inhibition ratio of 0.08, while d-amphetamine and d-methamphetamine have values greater than 10 and MDA has an intermediate ratio of 0.24 (Simmler et al. 2013). In addition, ability to stimulate 5-HT_{2A} receptors appears important for psychedelic effects (Vollenweider et al. 1998) and distinguishes MDA from MDMA (Nash et al. 1994).

The kinetics of MDA were similar to that of MDMA, with the exception of a possibly longer half-life for MDA at this dose level. For example, Kolbrich et al. (2008a) reported a Cmax of 292 ± 76 μg/L, AUC of 3,485 ± 760 h·μg/L, and elimination half-life of 8.1 ± 2 h for 1.6 mg/kg oral MDMA, while we saw Cmax of 229 ± 39 μg/L, AUC of 3,636 ± 958 h·μg/L, and elimination half-life of 10.9 ± 4 h for 1.4 mg/kg MDA. The difference in duration of effects between these drugs may be due to the difference in half-life, although it may also reflect the partly different pharmacological mechanisms of the two drugs. MDMA effects appear to depend crucially on a limited pool of releasable monoamines, particularly 5-HT, while MDA effects appear to depend to a greater extent on direct 5-HT_{2A} agonism.

The pharmacokinetics of HMA in humans were previously estimated after administration of MDMA. However, HMA is a minor metabolite of MDMA, and past investigators cautioned that the half-life was uncertain due to the low concentrations and likely overestimated (de la Torre et al. 2000; Kolbrich et al. 2008a). We confirm this and find that the elimination half-life of HMA in the current study, 14.1 ± 3.5 h, is lower and has less variance than these past estimates (122.3 ± 158 h in Kolbrich et al. (2008a) and 34.7 ± 18 h in de la Torre et al. (2000)). In addition to difficulties estimating kinetic parameters from low concentrations, it is possible that HMA kinetics after MDMA could partly reflect greater metabolic competition from comparatively higher concentrations of MDMA and HMMA.

This report has several limitations. We administered MDA and placebo on consecutive days, which may have allowed residual next-day MDA effects to alter placebo measures in half of the MDA participants, decreasing sensitivity for detecting drug effects. In order to better interpret MDA effects, we made comparisons with MDMA data from separate studies. This reduced our statistical power compared to within-subjects designs, although comparisons with placebo were still made within-subjects. We administered racemic MDA and MDMA because these are the forms that are used nonmedically and are thus relevant to public health. However, administering the individual enantiomers would allow better understanding of pharmacological mechanisms. Finally, our modest sample size, low number of female participants, and single dose levels prevent us from fully characterizing the pharmacokinetics of MDA.

The present study is the first modern human experiment with MDA and the first characterization of MDA pharmacokinetics. Greater research with compounds related to MDMA has been suggested for understanding the pharmacological mechanisms of that drug's unusual and possibly therapeutically useful social-emotional effects (Sáez-Briones and Hernández 2013).

We confirm earlier reports that MDA has significant MDMA-like effects as well as LSD-like effects. This suggests that mechanistic studies with MDA may be useful for understanding entactogen effects. Research characterizing the individual enantiomers of both drugs would be particularly valuable to better separate potentially therapeutic effects from other effects.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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References

Baggott, M., B. Heifets, R. T. Jones, J. Mendelson, E. Sferios, and J. Zehnder. 2000. Chemical analysis of ecstasy pills. *JAMA* 284 (17):2190–2190.

Baggott, M. J., J. D. Siegrist, G. P. Galloway, L. C. Robertson, J. R. Coyle, and J. E. Mendelson. 2010. Investigating the mechanisms of hallucinogen-induced visions using 3, 4-methylenedioxyamphetamine (MDA): A randomized controlled trial in humans. *PLoS One* 5 (12):1–13. doi:10.1371/journal.pone.0014074.

Baggott, M. J., J. R. Coyle, J. D. Siegrist, K. J. Garrison, G. P. Galloway, and J. E. Mendelson. 2016a. Effects of MDMA on socioemotional feelings, authenticity, and autobiographical disclosure in healthy volunteers in a controlled setting. *Journal of Psychopharmacology (Oxford, England)* 30:378–87. doi:10.1177/0269881115626348.

Baggott, M. J., K. J. Garrison, J. R. Coyle, G. P. Galloway, A. J. Barnes, M. A. Huestis, and J. E. Mendelson. 2016b. Mdma impairs response to water intake in healthy volunteers. *Advances in Pharmacological Sciences* 2016. doi: 10.1155/2016/2175896.

Baker, L., and M. Taylor. 1997. Assessment of the MDA and MDMA optical isomers in a stimulant-hallucinogen discrimination. *Pharmacology Biochemistry and Behavior* 57 (4):737–48. doi:10.1016/S0091-3057(96)00334-6.

Bexis, S., and J. R. Docherty. 2006. Effects of MDMA, MDA and MDEA on blood pressure, heart rate, locomotor activity and body temperature in the rat involve α-adrenoceptors. *British Journal of Pharmacology* 147 (8):926–34. doi:10.1038/sj.bjp.0706688.

Brunt, T. M., and R. J. Niesink. 2011. The Drug Information and Monitoring System (DIMS) in the Netherlands: Implementation, results, and international comparison. *Drug Testing and Analysis* 3 (9):621–34. doi:10.1002/dta.323.

Carhart-Harris, R. L., S. Muthukumaraswamy, L. Roseman, M. Kaelen, W. Droog, K. Murphy, E. Tagliazucchi, E. E. Schenberg, T. Nest, C. Orban, et al. 2016. Neural correlates of the LSD experience revealed by multimodal neuroimaging. *Proceedings of the National Academy of Sciences* 113 (17):4853–58. doi:10.1073/pnas.1518377113.

de la Torre, R., M. Farre, P. Roset, C. H. López, M. Mas, J. Ortuno, E. Menoyo, N. Pizarro, J. Segura, and J. Cami. 2000. Pharmacology of MDMA in humans. *Annals of the New York Academy of Sciences* 914 (1):225–37.

de la Torre, R., M. Farre, P. N. Roset, N. Pizarro, S. Abanades, M. Segura, J. Segura, and J. Camí. 2004. Human pharmacology of MDMA: Pharmacokinetics, metabolism, and disposition. *Therapeutic Drug Monitoring* 26 (2):137–44.

Eisenberg, D., J. MacKillop, M. Modi, J. Beauchemin, D. Dang, S. A. Lisman, J. K. Lum, and D. S. Wilson. 2007. Examining impulsivity as an endophenotype using a behavioral approach: A DRD2 TaqI A and DRD4 48-bp VNTR association study. *Behavioral and Brain Functions : BBF* 3 (2):2. doi:10.1186/1744-9081-3-2.

Jackson, B., and A. Reed. 1970. Another abusable amphetamine. *JAMA* 211 (5):830–830.

Kiesler, D. J. 1991. Interpersonal methods of assessment and diagnosis. In *Handbook of social and clinical psychology: The health perspective*, ed. C. R. Snyder and D. R. Forsyth, 438–68. Elmsford, NY: Pergamo.

Kirkpatrick, M. G., E. W. Gunderson, A. Y. Perez, M. Haney, R. W. Foltin, and C. L. Hart. 2012. A direct comparison of the behavioral and physiological effects of methamphetamine and 3, 4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology* 219 (1):109–22. doi:10.1007/s00213-011-2383-4.

Kolbrich, E. A., R. H. Lowe, and M. A. Huestis. 2008b. Two-dimensional gas chromatography/electron-impact mass spectrometry with cryofocusing for simultaneous quantification of MDMA, MDA, HMMA, HMA, and MDEA in human plasma. *Clinical Chemistry* 54 (2):379–87. doi:10.1373/clinchem.2007.096800.

Kolbrich, E. A., R. S. Goodwin, D. A. Gorelick, R. J. Hayes, E. A. Stein, and M. A. Huestis. 2008a. Plasma pharmacokinetics of 3,4-methylenedioxymethamphetamine after controlled oral administration to young adults. *Therapeutic Drug Monitoring* 30 (3):320–32. doi:10.1097/FTD.0b013e3181684fa0.

Lee, M., W.-Y. Poon, and H. Kingdon. 1990. A two-phase linear regression model for biologic half-life data. *The Journal of Laboratory and Clinical Medicine* 115 (6):745–48.

Lyon, R. A., R. A. Glennon, and M. Titeler. 1986. 3, 4-Methylenedioxymethamphetamine (MDMA): Stereoselective interactions at brain 5-HT1 and 5-HT2 receptors. *Psychopharmacology* 88 (4):525–26.

Miliano, C., G. Serpelloni, C. Rimondo, M. Mereu, M. Marti, and M. A. De Luca. 2016. Neuropharmacology of new psychoactive substances (NPS): Focus on the rewarding and reinforcing properties of cannabimimetics and amphetamine-like stimulants. *Frontiers in Neuroscience* 10:153. doi:10.3389/fnins.2016.00153.

Naranjo, C. 1974. *The healing journey*. New York, NY: Pantheon Books.

Nash, J. F., B. L. Roth, J. D. Brodkin, D. E. Nichols, and G. A. Gudelsky. 1994. Effect of the R (−) and S (+) isomers of MDA and MDMA on phosphotidyl inositol turnover in cultured cells expressing 5-HT 2A or 5-HT 2C receptors. *Neuroscience Letters* 177 (1):111–15.

Nichols, D. E. 1986. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: Entactogens. *Journal of Psychoactive Drugs* 18 (4):305–13. doi:10.1080/02791072.1986.10472362.

Nichols, D. E., and R. Oberlender. 1990. Structure-activity relationships of MDMA and related compounds: A new class of psychoactive drugs? *Annals of the New York Academy of Sciences* 600 (1):613–23.

Paton, D., J. Bell, R. Yee, and D. Cook (eds) (1975). Pharmacology and toxicity of 3, 4-methylenedio xyamphetamine, para-methoxyamphetamine and related dimethoxyamphetamines. *Proceedings of the Western Pharmacology Society*. Lake Tahoe, California.

Pentney, A. R. 2001. An exploration of the history and controversies surrounding MDMA and MDA. *Journal of Psychoactive Drugs* 33 (3):213–21. doi:10.1080/02791072.2001.10400568.

Quinteros-Munoz, D., P. Sáez-Briones, G. Díaz-Véliz, S. Mora-Gutiérrez, M. Rebolledo-Fuentes, and B. K. Cassels. 2010. Behavioral profiles in rats distinguish among "ecstasy," methamphetamine and 2, 5-dimethoxy-4-iodoamphetamine: Mixed effects for "ecstasy" analogues. *Behavioral Neuroscience* 124 (5):662. doi:10.1037/a0020827.

R Core Team. 2014. *R: A language and environment for statistical computing, R foundation for statistical computing*. ISBN 3-900051-07-0: Vienna, Austria: R Foundation for Statistical Computing.

Rothman, R. B., M. H. Baumann, C. M. Dersch, D. V. Romero, K. C. Rice, F. I. Carroll, and J. S. Partilla. 2001. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse* 39 (1):32–41. doi:10.1002/1098-2396(20010101)39:1<32::AID-SYN5>3.0.CO;2-3.

Sáez-Briones, P., and A. Hernández. 2013. MDMA (3, 4-Methylenedioxymethamphetamine) analogues as tools to characterize MDMA-like effects: An approach to understand entactogen pharmacology. *Current Neuropharmacology* 11 (5):521. doi:10.2174/1570159X11311050007.

Schmid Y, Enzler F, Gasser P, Grouzmann E, Preller KH, Vollenweider FX, Brenneisen, R., Müller, F., Borgwardt, S. and Liechti, M.E. 2014. Acute effects of lysergic acid diethylamide in healthy subjects. *Biological Psychiatry* 78 (8):544–553.

Setola, V., S. J. Hufeisen, K. J. Grande-Allen, I. Vesely, R. A. Glennon, B. Blough, R. B. Rothman, and B. L. Roth. 2003. 3, 4-Methylenedioxymethamphetamine (MDMA,"Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro. *Molecular Pharmacology* 63 (6):1223–29. doi:10.1124/mol.63.6.1223.

Shulgin, A., and A. T. Shulgin. 1991. *Pihkal: A chemical love story*. Berkeley, CA: Transform Press. 978 plus introductory pagespp.

Simmler, L., T. Buser, M. Donzelli, Y. Schramm, L. H. Dieu, J. Huwyler, S. Chaboz, M. C. Hoener, and M. E. Liechti. 2013. Pharmacological characterization of designer cathinones in vitro. *British Journal of Pharmacology* 168 (2):458–70. doi:10.1111/j.1476-5381.2012.02145.x.

Simmler, L. D., and M. E. Liechti. 2018. Pharmacology of MDMA- and Amphetamine-Like New Psychoactive Substances. In: *New PsychoactiveSubstances. Handbook of ExperimentalPharmacology*, Eds. Maurer H., Brandt S., vol 252. Cham: Springer.

Studerus, E., A. Gamma, and F. X. Vollenweider. 2010. Psychometric evaluation of the altered states of consciousness rating scale (OAV). *PLoS One* 5 (8):e12412–e12412. doi:10.1371/journal.pone.0012412.

Tsai, J. L., B. Knutson, and H. H. Fung. 2006. Cultural variation in affect valuation. *Journal of Personality and Social Psychology* 90 (2):288. doi:10.1037/0022-3514.90.2.288.

Turek, I. S., R. A. Soskin, and A. A. Kurland. 1974. Methylenedioxyamphetamine (MDA)–subjective effects. *Journal of Psychoactive Drugs* 6 (1):7–14.

Vollenweider, F. X., M. F. Vollenweider-Scherpenhuyzen, A. Bäbler, H. Vogel, and D. Hell. 1998. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport* 9 (17):3897–902.

Weil, A. T. 1976. The love drug. *Journal of Psychoactive Drugs* 8 (4):335–37.

Westfall, P. H. 1997. Multiple testing of general contrasts using logical constraints and correlations. *Journal of the American Statistical Association* 92 (437):299–306. doi:10.1080/01621459.1997.10473627.

Wiggins, J. S., P. Trapnell, and N. Phillips. 1988. Psychometric and geometric characteristics of the revised Interpersonal Adjective Scales (IAS-R). *Multivariate Behavioral Research* 23 (4):517–30. doi:10.1207/s15327906mbr2304_8.

Wiggins, J. S., and R. Broughton. 1991. A geometric taxonomy of personality scales. *European Journal of Personality* 5 (5):343–65. doi:10.1002/(ISSN)1099-0984.

Yensen, R., F. B. Di Leo, J. C. Rhead, W. A. Richards, R. A. Soskin, B. Turek, and A. A. Kurland. 1976. MDA-assisted psychotherapy with neurotic outpatients: A pilot study. *The Journal of Nervous and Mental Disease* 163 (4):233–45.

Young, R., and R. A. Glennon. 1996. A three-lever operant procedure differentiates the stimulus effects of R (-)-MDA from S (+)-MDA. *Journal of Pharmacology and Experimental Therapeutics* 276 (2):594–601.