Title

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Journal

ACS Chemical Neuroscience, 9(7)

ISSN

1948-7193

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Publication Date

2018-07-18

DOI

10.1021/acschemneuro.8b00134

Peer reviewed

HHS Public Access

Author manuscript

ACS Chem Neurosci. Author manuscript; available in PMC 2020 May 03.

Published in final edited form as:

ACS Chem Neurosci. 2018 July 18; 9(7): 1582–1590. doi:10.1021/acschemneuro.8b00134.

Effects of *N,N*-dimethyltryptamine (DMT) on rat behaviors relevant to anxiety and depression

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Abstract

Depression and anxiety disorders are debilitating diseases resulting in substantial economic costs to society. Traditional antidepressants often take weeks to months to positively affect mood and are ineffective for about 30% of the population. Alternatives, such as ketamine, a dissociative anesthetic capable of producing hallucinations, and the psychoactive tisane ayahuasca have shown great promise due to their fast-acting nature and effectiveness in treatment-resistant populations. Here, we investigate the effects of *N,N*-dimethyltryptamine (DMT), the principle hallucinogenic component of ayahuasca, in rodent behavioral assays relevant to anxiety and depression using adult, male, Sprague-Dawley rats. We find that while DMT elicits initial anxiogenic responses in several of these paradigms, its long-lasting effects tend to reduce anxiety by facilitating the extinction of cued fear memory. Furthermore, DMT reduces immobility in the forced swim test, which is a characteristic behavioral response induced by many antidepressants. Our results demonstrate that DMT produces antidepressant and anxiolytic behavioral effects in rodents, warranting further investigation of ayahuasca and classical psychedelics as treatments for depression and post-traumatic stress disorder.

Graphical Abstract

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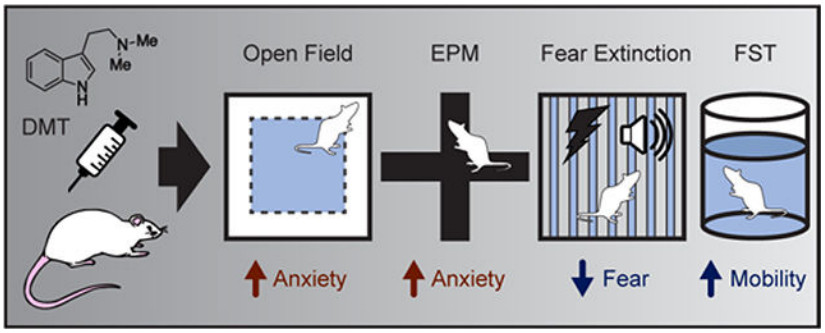
Author Contributions

D.E.O. was responsible for the overall experimental design. C.J.B. performed the behavioral experiments. L.P.C. performed the data analysis. L.E.D. synthesized and characterized DMT•fumarate (2:1). L.P.C. and D.E.O. wrote the manuscript with input from all authors.

The authors declare no conflict of interest.

Supporting Information

Figure S1; Figure S2; Table S1; Table S2; ^{1}H NMR spectrum, ^{13}C NMR spectrum, and LC-MS chromatogram for DMT.



Keywords

DMT; *N,N*-dimethyltryptamine; psychedelic; depression; post-traumatic stress disorder; ayahuasca

Introduction

Mood and anxiety disorders are among the leading causes of disability worldwide,[1,2] yet we still lack effective treatments. Current medications typically require 2–4 weeks before displaying efficacy, with approximately 1/3 of patients remaining unresponsive even after experimenting with several different medications.[3] This distinct lack of adequate treatments has led investigators to seek alternatives that are both fast-acting and effective in treatment-resistant populations. The archetype for this next-generation of neurotherapeutics has been the dissociative anesthetic ketamine, as it produces rapid clinical antidepressant effects[4,5,6] including in treatment-resistant populations.[7,8,9] Additionally, it has shown promise for treating post-traumatic stress disorder (PTSD).[10] There is a clear need to identify compounds that produce therapeutic effects comparable to ketamine in order to better understand the basic mechanisms of fast-acting antidepressants.

Perhaps some of the most promising compounds capable of eliciting beneficial clinical effects similar to ketamine are the classical serotonergic psychedelics such as psilocybin and LSD. In the past 30 years, there have been numerous clinical trials examining the therapeutic effects of these drugs,[11] with most reporting robust antidepressant and anxiolytic effects[12,13,14] even in treatment-resistant populations.[15,16,17] Though their notorious effects on perception have limited their therapeutic potential in mainstream medicine, these compounds have been used for centuries by people from a variety of cultures who consume psychedelic-rich plants and fungi during religious or healing ceremonies.[18] One such traditional botanical mixture, known as ayahuasca, has attracted considerable attention owing to its potent antidepressant and anxiolytic effects in humans.[11,19,20,21,22]

Ayahuasca is an Amazonian tisane, which can be prepared by boiling the *Banisteriopsis caapi* vine and the leaves of the shrub *Psychotria viridis*.[22] The latter plant contains substantial quantities of the classical hallucinogen *N,N*-dimethyltryptamine (DMT) while the former contains β-carboline alkaloids capable of inhibiting monoamine oxidase (MAO). As DMT is readily oxidized by MAO in the gut, the β-carbolines present in ayahuasca make DMT orally bioavailable.[23,24] Studies conducted on populations that regularly use

ayahuasca for religious purposes have demonstrated that it is relatively safe and could possibly promote mental well-being by reducing various measures of psychopathology and improving cognitive performance on tasks such as the Stroop and Wisconsin Card Sorting Tests.[25,26,27] In addition to having robust antidepressant and anxiolytic effects in humans,[11,19,20,21,22] ayahuasca has also been tested in several behavioral paradigms relevant to depression and anxiety. While the tisane reduces immobility time in the forced swim test, it also leads to anxiogenic responses in the open field and elevated plus maze.[28,29]

As ayahuasca is a complex mixture of psychoactive chemicals including tryptamine and β-carboline alkaloids (Figure 1),[21,30] delineating the exact roles of each of these compounds will be critical to understanding the behavioral effects of the concoction. Of the major alkaloids in ayahuasca, harmine and harmaline have received the most attention thus far. Both mice and rats treated with harmine display decreased immobility in the FST,[31,32] and harmine produces anxiolytic effects in rats as measured by behavior in the EPM.[33] Harmaline has been shown to have more complex effects on EPM behavior, as it produces anxiogenic or anxiolytic responses in mice depending on the dose.[34] In terms of exploratory behavior, neither acute nor chronic administration of harmine to rats had any effect on spontaneous locomotor activity in the open field.[35,36] In Table S1, we have summarized current literature assessing the effects of ayahuasca and its chemical constituents on rodent behaviors relevant to anxiety and depression.

While there have been a number of studies characterizing the effects of individual β-carboline alkaloids (e.g., harmine, harmaline, and tetrahydroharmine) in animal models of anxiety and depression, relatively little is known about the effects of *N,N*-dimethyltryptamine, the principle hallucinogenic component of ayahuasca. Here, we investigate the effects of a hallucinogenic dose of DMT in rodent behavioral tests relevant to anxiety, PTSD, and depression.

Results and Discussion

Because we were interested in assessing the effects of a hallucinogenic dose of DMT on rodent behaviors, we chose to use a 10 mg/kg dose of DMT for all of our studies. This dose, when converted to a human equivalent dose using allometric scaling,[37] is expected to be hallucinogenic based on the pioneering human studies conducted by Strassman and co-workers.[38] Furthermore, a preponderance of evidence from rodent drug discrimination studies using DMT and related compounds suggested that a 10 mg/kg dose would reliably produce effects characteristic of hallucinogens.[39,40,41,42,43,44,45,46,47]

Immediately following administration of an intraperitoneal dose of DMT (10 mg/kg), rats displayed flat body posture and hind limb abduction in their home cages (Figure S1), which is indicative of acute serotonin syndrome.[48,49,50,51] We did not observe any head-twitches or wet-dog shakes. After 30 minutes, DMT-treated rats began to engage in normal behaviors, and by one hour post-administration, they were qualitatively indistinguishable from vehicle-treated control animals. In order to specifically avoid any confounding effects from initial DMT-induced serotonin syndrome, all subsequent behavioral tests were conducted 1 h following DMT administration. DMT has a half-life of 5–15 min in rats following

intraperitoneal injection[52] and is rapidly metabolized and cleared from brain, liver, and plasma within 1 h.[53] This ensured that any behavioral effects observed would be due to persistent changes and not simply from the acute effects of the drug.

Animals were tested in both novelty-induced locomotion (NIL) and elevated plus maze (EPM) paradigms to assess the effects of compound on anxiety (Figure 2). When exposed to a novel open space, DMT-treated animals displayed reduced exploratory behavior and traveled a significantly shorter total distance (Figure 2b and 2c) than vehicle-treated controls, but the drug did not affect thigmotaxis (Figure 2d). Both the number of rearings and time spent rearing were significantly reduced by DMT (Figure 2e and 2f). Furthermore, the drug reduced the time spent engaging in stereotypies but not the total number, suggesting that each event occurred for a shorter period of time (Figure 2g and 2h). Taken together, an acute dose of DMT can have anxiogenic effects even after the drug has been cleared from the body.[52]

To corroborate these findings, we next assessed the effects of DMT on EPM behavior. DMT-treated animals spent a decreased percentage of time in the open arms of the maze (Figure 2i) and had a fewer number of open arm entries (Figure 2j). The total distance traveled in the maze (Figure 2k) and the average velocity of the rodents (Figure 2l) were not statistically different between DMT-treated and vehicle-treated groups. The number of closed arm entries was also not statistically different between the treatment groups (Mean ± SEM; VEH = 9.375 ± 1.179; DMT = 8.556 ± 1.642; P value = 0.6977, Student’s t test). These data indicate that DMT administration does not grossly impair locomotion 1 h after dosing, but does have anxiogenic affects.

We find that the behavioral effects in the NIL and EPM paradigms of a single hallucinogenic dose of DMT administered to rats are consistent with those of ayahuasca reported by Pic-Taylor and coworkers.[29] Specifically, both DMT and ayahuasca reduce exploratory behavior (e.g., total distance traveled and number of rearings) in the open field, but do not influence thigmotaxis, a more traditional measure of anxiety in the open field.[54] Furthermore, both DMT and ayahuasca tend to decrease the amount of time rats spend in the exposed areas of an elevated plus maze. These results contrast with the effects of harmine in these paradigms[33,35,36] and suggest that DMT is the component of ayahuasca that decreases exploratory behavior and promotes acute anxiety in rats. This conclusion is further supported by the seminal work of Geyer and coworkers, as they found that DMT decreased exploratory behaviors, decreased rearing, and promoted avoidance of the center of the arena in the behavioral pattern monitor.[55,56] Seeing as these behaviors did not occur in familiar environments, they concluded that DMT and related compounds potentiate neophobia.

The majority of studies regarding ayahuasca have focused on its ability to regulate mood and anxiety, and thus, very little is known about its effects on memory. Recently, Oliveira and co-workers discovered that chronic administration of ayahuasca did not impair spatial memory as measured by the Morris water maze, nor did it impact cued fear memory.[57] However, chronically administered ayahuasca did enhance both foreground and background contextual fear memory.[57] Therefore, we tested the effects of DMT on fear memory.

Rodents were subjected to a fear conditioning paradigm (Figure 3a and Figure S2) and both contextual and cued fear memory was assessed. Administration of DMT had no effect on initial freezing behavior prior to receiving foot shocks, however, it did significantly increase freezing immediately after the rodents received the training foot shocks (Figure 3b). This anxiogenic effect is consistent with our NIL and EPM experiments, however, DMT did not have a lasting impact on fear memory, as both contextual and cued fear memory, assessed in the days following conditioning, were indistinguishable between DMT- and vehicle-treated animals (Figure 3b).

There are several possible explanations for the differing results between our study and that of Oliveira and co-workers.[57] One possibility is that the effects of ayahuasca on fear conditioning are mediated by other compounds in the concoction, and not DMT. Alternatively, there could be differences between acute and chronic treatment paradigms.

While DMT did not significantly impact fear conditioning, it did promote cued fear extinction. Animals were fear conditioned as described previously in the absence of drug, and DMT was administered 1 h prior to cued fear extinction training (Figure 4a–e). The following day, cued extinction memory was assessed in the absence of drug. Tone presentations caused the DMT-treated group to freeze significantly less than the control group, indicating that DMT administered prior to extinction training resulted in a stronger extinction memory (Figure 4d and e).

Patients with PTSD exhibit deficits in cued extinction recall,[58] and thus, compounds capable of enhancing fear extinction learning/memory could prove to be effective therapeutics. Furthermore, our discovery that DMT promotes fear extinction in rats is consistent with previous reports demonstrating that psilocybin and MDMA promote cued fear extinction in mice,[59,60] and adds to the growing body of literature suggesting that classical psychedelics and entactogens might be useful for treating PTSD in the clinic.[16,17] In fact, MDMA was recently granted “breakthrough therapy” status by the Food and Drug Administration in order to expedite the approval process for this promising therapeutic.

In a second experiment, animals were subjected to foreground contextual conditioning using additional and more intense foot shocks in order to raise their baseline contextual freezing levels (Figure 4f–g). Contextual fear memory was extinguished on subsequent days 1 h following administration of DMT. Finally, contextual extinction memory was assessed on day 6 in the absence of drug. The DMT-treated animals were not statistically different from the vehicle control group (Figure 4h). Interestingly, the data from the contextual extinction experiment had a bimodal distribution, suggesting that there were responders and non-responders to contextual extinction training. Similar results in rat fear extinction experiments have been observed previously.[61]

Due to the known antidepressant properties of ayahuasca,[11,19,20,21,22] we next assessed the effects of DMT in the forced swim test (FST) (Figure 5a), a behavioral paradigm used to identify novel antidepressants, using ketamine as a positive control. We found that DMT significantly decreased the amount of time the rodents spent immobile and increased the amount of time they spent swimming (Figure 5b). There was no significant difference in

climbing behavior between DMT- and vehicle-treated animals. Notably, the effects of DMT in the FST were indistinguishable from those of the fast-acting antidepressant ketamine (Figure 5b). These results suggest that DMT has antidepressant properties in rodents.

While ayahuasca is known to produce anxiogenic effects in the open field and in the EPM, it also displays robust antidepressant properties in the FST.[28,29] Similarly, we find that DMT also decreases immobility and increases swimming behavior in this behavioral paradigm (Figure 5). Because DMT and ayahuasca actually reduce locomotor activity in the open field, the increased swimming behavior observed in the FST can be interpreted as a true antidepressant effect, and not simply due to a confounding effect from changes in general activity levels. Finally, as harmine alone has produced similar results in the FST,[31,32] it is likely that both DMT and the β-carboline alkaloids contribute to the antidepressant effects of ayahuasca. It will be interesting to see if DMT and harmine have any synergistic or additive effects that go beyond harmine's known capacity to increase DMT bioavailability through inhibition of monoamine oxidase.[24] DMT is known to inhibit the serotonin transporter,[62] which could possibly explain its antidepressant effects in the forced swim test. However, its K_i value is quite low (4 μM) as compared to common selective serotonin reuptake inhibitors such as fluoxetine (K_i value for fluoxetine = 7 nM).[63] Furthermore, ayahuasca produces rapid antidepressant effects in treatment-resistant populations, suggesting that it works through a different mechanism than traditional antidepressants.[19,20]

Perhaps the most intriguing aspect of the results presented here is the remarkable similarity between the effects of DMT in rats and those of the fast-acting antidepressant ketamine. In addition to having acute anxiogenic effects in the EPM,[64] ketamine facilitates fear extinction learning and reduces immobility in the FST.[65,66,67] These known effects of ketamine are the same as what we report here for DMT. In fact, when compared directly, we found that there was no statistical difference between DMT- and ketamine-treated animals in terms of the amount of time they spent immobile, swimming, or climbing in the FST. As the antidepressant effects of ketamine are known to be long-lasting, future studies should investigate if DMT produces similar persistent effects.

Ketamine is believed to exert its therapeutic effects by promoting structural and functional plasticity in the prefrontal cortex (PFC)—a key brain region involved in both extinction learning[68] and the top-down control of mood.[69] While the primary receptors targeted by ketamine and DMT are different (i.e., NMDA and 5-HT receptors, respectively), it is intriguing to speculate that they might produce similar downstream effects on neural plasticity ultimately underlying their behavioral effects. Two pieces of evidence suggest that this might be the case. First, DMT is rapidly metabolized,[52,53] however, its anxiolytic and antidepressant effects are observed long after the compound has been cleared from the body suggesting that plasticity might result in long-lasting changes contributing to its behavioral effects. Second, the related molecule 5-MeO-DMT was recently shown to promote the expression of proteins involved in the formation and maturation of dendritic spines in human cerebral organoids.[70] An important question that remains is whether or not DMT and/or ayahausca, like ketamine, is capable of promoting structural and functional plasticity in prefrontal cortical neurons.

Finally, our studies on the effects of DMT in rats raise important questions about the possible roles of endogenous DMT in regulating mood and anxiety. A preponderance of evidence suggests that DMT is a hallucinogenic compound produced by a variety of animals including humans.[71] Due to its rapid metabolism, exact in vivo quantification of DMT has proven challenging. Assuming that its endogenous production yields sufficient quantities, the results presented here suggest that it might play a natural role in the regulation of anxiety and mood.

In conclusion, we report the effects of DMT—the principle hallucinogenic component of ayahuasca—on rodent behaviors related to anxiety and depression. To the best of our knowledge, we describe the first example in rats of a classical serotonergic psychedelic facilitating fear extinction learning and producing antidepressant effects in the FST. Importantly, we find that like ketamine, DMT produces behavioral responses in several paradigms relevant to anxiety and depression. Our work coupled with the fast-acting clinical effects of ayahuasca, strengthens the growing evidence that classical serotonergic psychedelics might serve as fast-acting antidepressants and anxiolytics.

Methods

Animals

Sprague-Dawley rats were obtained from Charles River Laboratories (Wilmington, MA, USA), were housed two per cage, and were given *ad libitum* access to food and water. Lights in the vivarium were turned on at 07:00 hours and turned off at 19:00 hours. All experiments were performed on 8- to 14-week-old male rats. Studies were performed during the light-on phase, with experiments taking place between 08:00 and 18:00 hours. All experimental procedures involving animals were approved by the UC Davis Institutional Animal Care and Use Committee (IACUC) and adhered to principles described in the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The University of California, Davis is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC).

Drugs

The DMT utilized in these studies was synthesized in our laboratory using the following procedure. To an ice-cold solution of tryptamine (0.50 g, 3.1 mmol), and glacial acetic acid (0.89 mL, 15 mmol, 5.0 equiv) in MeOH (49 mL) was added sodium cyanoborohydride (0.39 g, 6.2 mmol, 2.0 eq.) followed by 37% formaldehyde$_{(aq)}$ (0.66 mL, 8.1 mmol, 2.6 equiv). The reaction was stirred at room temperature for 5 h before being concentrated under reduced pressure. The unpurified material was diluted with CH_2Cl_2 (50 mL) and 1M $NaOH_{(aq)}$ (100 mL). The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2 (50 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The unpurified material was dissolved in acetone (15 mL) and added to a boiling solution of fumaric acid (0.26 g, 2.2 mmol, 0.7 equiv) in acetone (50 mL). A precipitate formed immediately, and the solution was cooled to room temperature prior to being filtered. The resulting white solid was dried under reduced pressure to yield the pure compound as the fumarate salt (2:1 DMT:fumaric acid) (white

solid, 0.48 g, 62%): Melting Point = 140–142ºC; TLC R_f(DMT free base) = 0.35 (9:1 CH_2Cl_2:MeOH with 1% $NH_4OH_{(aq)}$); ^{1}H NMR (2:1 DMT:fumaric acid, 600 MHz, DMSO-d_6) δ 10.8 (brs, 1H), 7.5 (d, 1H, J = 7.9 Hz), 7.3 (d, 1H, J = 7.9 Hz), 7.1 (s, 1H), 7.0 (t, 1H, J = 7.9 Hz), 6.9 (t, 1H, J = 7.9 Hz), 6.5 (s, 1H), 2.9 (t, 2H, J = 8.6 Hz), 2.8 (t, 2H, J = 8.6 Hz), 2.4 (s, 6H) ppm; ^{13}C NMR (2:1 DMT:fumaric acid, 100 MHz, CD_3OD) δ 173.8, 138.2, 136.9, 128.1, 124.2, 122.7, 120.1, 119.0, 112.5, 110.0, 59.2, 43.4, 21.9 ppm; IR (2:1 DMT:fumaric acid, diamond, ATR) ν 3483, 3146, 3107, 3045, 2927, 2881, 1561, 1226, 749cm^{-1}. The compound was stored at −20ºC in the dark prior to use. The prepared DMT was judged to be analytically pure by both LC-MS and NMR spectroscopy. For each experiment, a solution of DMT•fumarate (2:1) in 0.9% sterile saline was freshly prepared and passed through a 0.2 μm syringe filter. For all experiments, DMT•fumarate (2:1) was administered at 10 mg/kg via intraperitoneal injection using an injection volume of 1 mL/kg. Ketamine•HCl was purchased from Fagron (St. Paul, MN; batch# 13B28-U03–010128) and administered at 10 mg/kg (in 0.9% sterile saline) via intraperitoneal injection using an injection volume of 1 mL/kg. We used this subanesthetic dose of ketamine as it has been shown previously to elicit robust effects in the forced swim test[72] (Browne and Lucki, 2013) without impairing motor function.[73,74,75] For our vehicle controls, 0.9% sterile saline solution was utilized.

Novelty-Induced Locomotion (NIL)

Drug-naïve rats were administered either DMT or vehicle 1 hr before behavioral testing. Animals were allowed to acclimate to the test room for 10 mins prior to being gently placed into the center of an AccuScan Instruments (Columbus, OH, USA) open field chamber (Digiscan Animal Activity Monitor Model #RXYZCM(16)CCD) and allowed to freely explore the chamber for 45 mins. At the conclusion of the test, animals were returned to their home cages and the test chambers cleaned with 10% Nolvasan. Horizontal motion, rotations, and stereotypies (repetitive beam breaks) were recorded in 1-min intervals for the duration of the test and analyzed using the program Integra. The margin of the arena was defined as being 10 cm from the wall. The open field chamber measured 41.9 cm L x 41.9 cm W x 28.6 cm H and was illuminated to between 25 and 30 lux.

Elevated Plus Maze (EPM)

The EPM apparatus consisted of a plus-shaped black plastic platform positioned 50 cm above the ground and was illuminated to between 20 and 25 lux. Two opposite arms of the maze were bordered by vertical walls measuring 31.75 cm high, with the other two arms possessing unprotected edges. The same animals were used in both the NIL and EPM tests. Two days following the NIL test, rats were administered DMT or vehicle (consistent with how they were dosed previously) 1 hr before being placed into the center of the maze facing an open arm and allowed to explore freely for 5 min. At the conclusion of the test, rats were returned to their home cages and the apparatus was cleaned with 10% Nolvasan. Animal movement was recorded and analyzed during the trial using EthoVision XT (version 9) software. The EPM is an established method for measuring anxiety in rodents.[76] (and Frye, 2007).

Fear Conditioning (FC)

On day 1, drug-naïve animals were administered either DMT or vehicle 1 hr prior to conditioning. They were placed in a fear conditioning apparatus (Med Associates model # MED-VFC2-SCT-R) for 3.5 min prior to three presentations of auditory cues (80 dB white noise, 30 s), each co-terminating with a foot shock (0.8 mA, 2 s.) and spaced 90 s apart. The fear conditioning apparatus consisted of a 30.5 cm x 24.1 cm x 21 cm internal soundproof chamber, with metal grated floors, an infrared camera, a sound generator, and a light source. After the last shock, the animals remained in the chambers for an additional 2 min before being returned to their home cages. During fear conditioning, the apparatus was illuminated to 100 lux and did not contain any additional odor cues. On day 2, contextual fear memory was assessed by exposing the animals to the conditioning context for 10 min before returning them to their home cages. On day 3, cued fear memory was assessed by exposing the animals to a novel context (lights off, A-frame insert, smooth plastic floor insert, additional vanilla odor) for 2 min prior to eight presentations of auditory cues (80 dB white noise, 30 s) spaced 30 s apart. Freezing responses for cue testing (day 3) are presented as the percentage of time spent freezing during the tone presentations. Fear conditioning experiments were performed between the hours of 08:00–11:00. Freezing behavior was scored using Med Associates Video Freeze software v2.25 (motion threshold = 18 au, detection method = linear, minimum freeze duration = 30 frames, which is equal to a 1 sec freeze). The apparatus was cleaned with 70% EtOH in between trials.

Cued Fear Extinction

On day 1, drug-naïve animals were fear conditioned as described above, but in the absence of drug, and allowed to rest on day 2. On day 3, the animals were administered either DMT or vehicle 1 hr prior to extinction training. Extinction training consisted of exposure to a novel context (lights off, A-frame insert, smooth plastic floor insert, additional vanilla odor) for 2 mins prior to 8 presentations of auditory cues (80 dB white noise, 30 s) spaced 30 s apart. After the extinction training, animals were returned to their home cages. The procedure was repeated on day 4 in the absence of drug. Fear extinction experiments were performed between the hours of 08:00–11:00. Freezing responses for cue testing (day 4) are presented as the percentage of time spent freezing during the tone presentations. Freezing behavior was scored using Med Associates Video Freeze software v2.25 (motion threshold = 18 au, detection method = linear, minimum freeze duration = 30 frames, which is equal to a 1 sec freeze). The apparatus was cleaned with 70% EtOH in between trials.

Contextual Fear Extinction

First, drug-naïve animals were subjected to an optimal foreground contextual fear conditioning protocol. Rats were placed into the fear conditioning apparatus for three mins before being subjected to six foot shocks (1.0 mA, 2 s) spaced 58 s apart. The use of this strong foot shock protocol was necessary to sufficiently increase baseline contextual freezing levels to ~60% so that extinction (i.e. reduction in freezing) could be effectively measured. After initiation of the last shock, the animals remained in the chambers for an additional 2 min before being returned to their home cages. The animals were allowed to rest on day 2. On day 3, they were administered either DMT or vehicle 1 hr prior being placed in

the fear conditioning context for 10 min. This procedure was repeated on days 4 and 5. On day 6, the animals were placed in the fear conditioning context without receiving any injections. Contextual fear conditioning experiments were performed between the hours of 08:00–11:00. Freezing behavior was scored using Med Associates Video Freeze software v2.25 (motion threshold = 18 au, detection method = linear, minimum freeze duration = 30 frames, which is equal to a 1 sec freeze) and reported as the percentage of time spent freezing over the entire 10 min session. The apparatus was cleaned with 70% EtOH in between trials.

Forced Swim Test

The FST apparatus consisted of a clear Plexiglas cylinder measuring 80 cm tall, 20 cm in diameter and filled with 30 cm of 24 ± 1ºC water. Fresh water was used for every rat. Drug-naïve animals were subjected to a pre-test phase in which they were placed in the cylinder for 15 mins before being dried and returned to their home cage. Twenty-four hours later, rats were again placed in the FST apparatus for 5 mins and their activity was video recorded. Each rat received three administrations of DMT, ketamine, or vehicle at 23.5, 6, and 1 hr before the test phase. This subchronic dosing paradigm has proven effective for a wide range of antidepressant compounds.[77] Each video was scored for immobility, swimming, and climbing behavior by a trained observer. The dominant behavior of the animal (i.e., immobility, swimming, or climbing) was determined every 5 sec and quantified as a “count.” As the experiment lasted for 5 mins, the sum of the counts for all four behaviors equals 60.

Data Analysis

Statistical analyses were performed using GraphPad Prism (version 7.0a). Data exhibiting a time dependency (e.g., 2b and S3) were analyzed using a two-way repeated measures analysis of variance (ANOVA). Comparisons of DMT- and vehicle-treated groups were accomplished using two-tailed Student’s t-tests or two-way ANOVAs with a Sidak Post-Hoc test. As data from the contextual extinction experiment (Figure 4h) displayed a bimodal distribution, a Mann-Whitney Test was used. To analyze data from the FST (Figure 5b), which involved multiple comparisons, a one-way ANOVA was utilized with Tukey’s post hoc test. Details of all statistical tests performed in this study are provided in Table S2. All data are represented as means ± SEM, NS = not significant, $*p < 0.05$, $**p < 0.01$

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would also like to acknowledge the Intellectual and Developmental Disabilities Research Center (U54 HD079125) Rat Behavioral Testing Core for equipment use and assistance. We would also like to thank Sina Soltanzadeh Zarandi for helpful discussions.

Funding

This work was supported by the UC Davis Medical Investigation of Neurodevelopmental Disorders (MIND) Institute, a National Science Foundation Predoctoral Fellowship (#1650042 to C.J.B.), and an NIH T32 grant (5T32MH082174-09 to L.P.C.).

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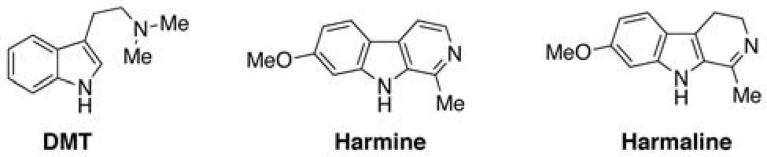

Figure 1.
Principle chemical components of ayahuasca.

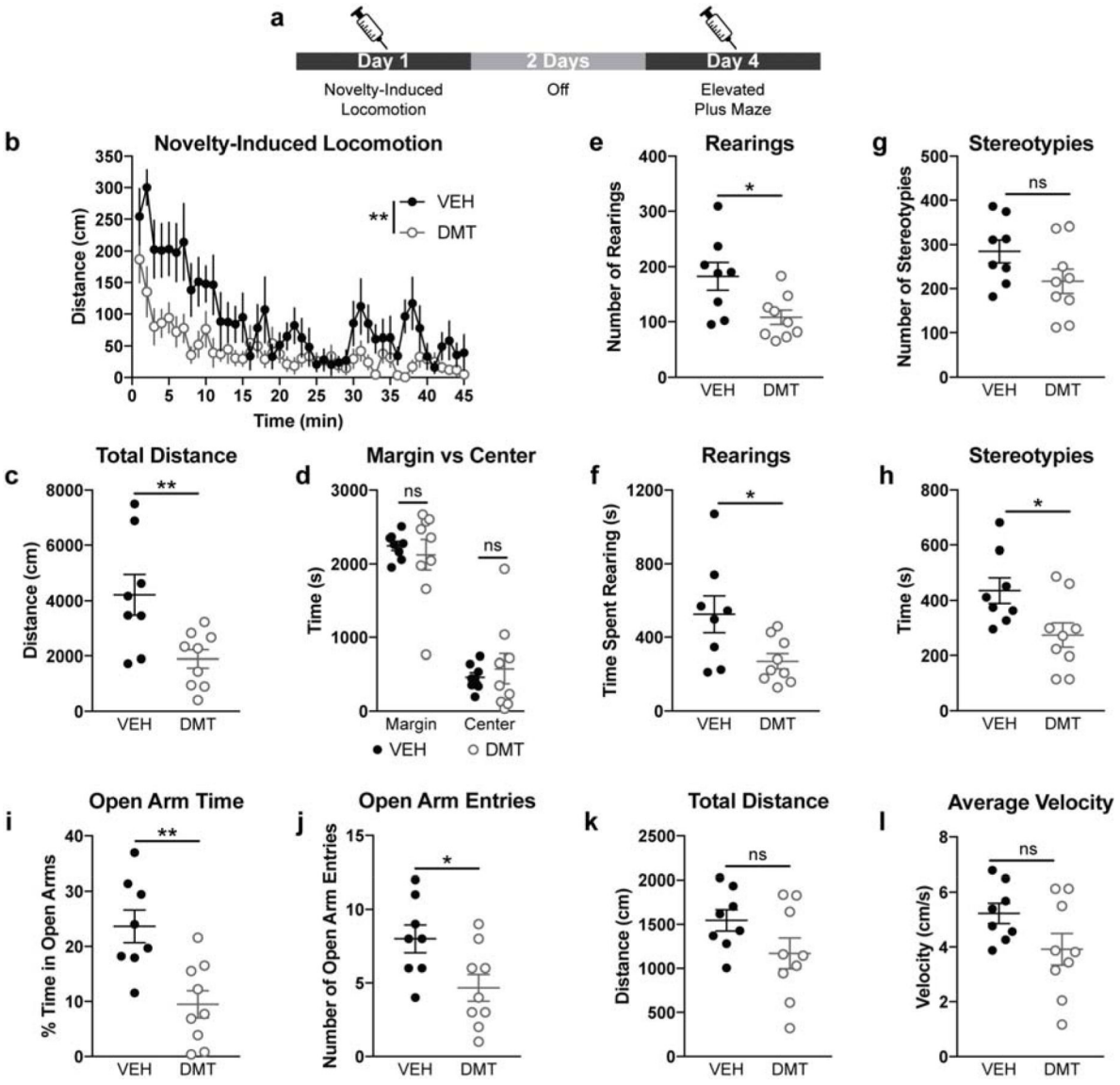

Figure 2.

Exploratory behavior and anxiety is impacted by an acute dose of DMT (10 mg/kg). (a) Timeline of behavioral tests. Drug-naïve animals were dosed 1 h prior to the novelty-induced locomotion test. After the completion of that experiment, these same animals were given two days of rest before being administered DMT 1 h prior to the elevated plus maze test. (b–c) Novelty-induced locomotion was quantified as total distance travelled in 1 min bins over time (b) and as the total distance travelled over the entire 45 min experiment (c). (d) The proportion of time spent on the margin of the arena versus the center was determined. (e–f) The number of vertical movements (e) (i.e., rearing) and total time spent rearing (f) were quantified. (g–h) The number of stereotypies (g) and total time spent engaged in stereotypies (h) were quantified. (i–l) Anxiety levels were measured using the elevated plus maze. The percentage of time spent in the open arms (i) as well as the number of open arm entries (j) was quantified. There was no difference between the treatment groups with respect to the total distance moved (k) or average velocity (l). Error bars

represent SEM, NS = not significant, *$P < 0.05$, **$P < 0.05$ as compared to vehicle control. N = 8 (VEH) N = 9 (DMT). VEH = vehicle, DMT = *N,N*-dimethyltryptamine

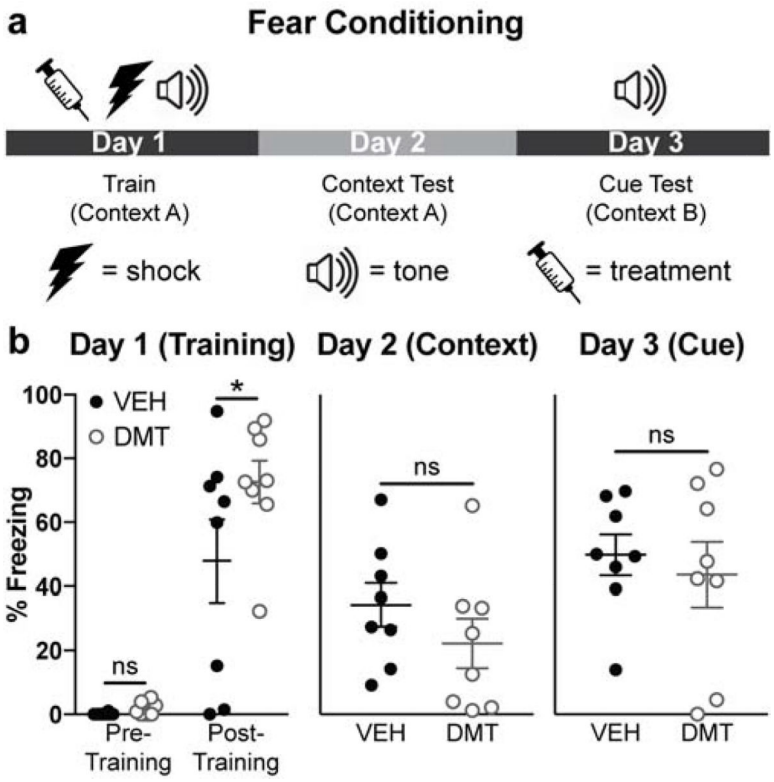

Figure 3.

An acute dose of DMT (10 mg/kg) prior to fear conditioning does not affect contextual or cued fear memory. (a) Experimental design for the fear conditioning experiment. (b) DMT increased immediate freezing following foot shocks, but had no effect on either contextual or cued fear memory. Pre-training and post-training represent the 2 mins immediately before and after the presentation of shocks, respectively. Contextual freezing was determined over the course of the entire 10 min session. Cued freezing was assessed as the percentage of time spent freezing during the 8 tone presentations. Error bars represent SEM, NS = not significant, $*P < 0.05$ as compared to vehicle control. N = 8 (VEH) N = 8 (DMT). VEH = vehicle, DMT = *N,N*-dimethyltryptamine

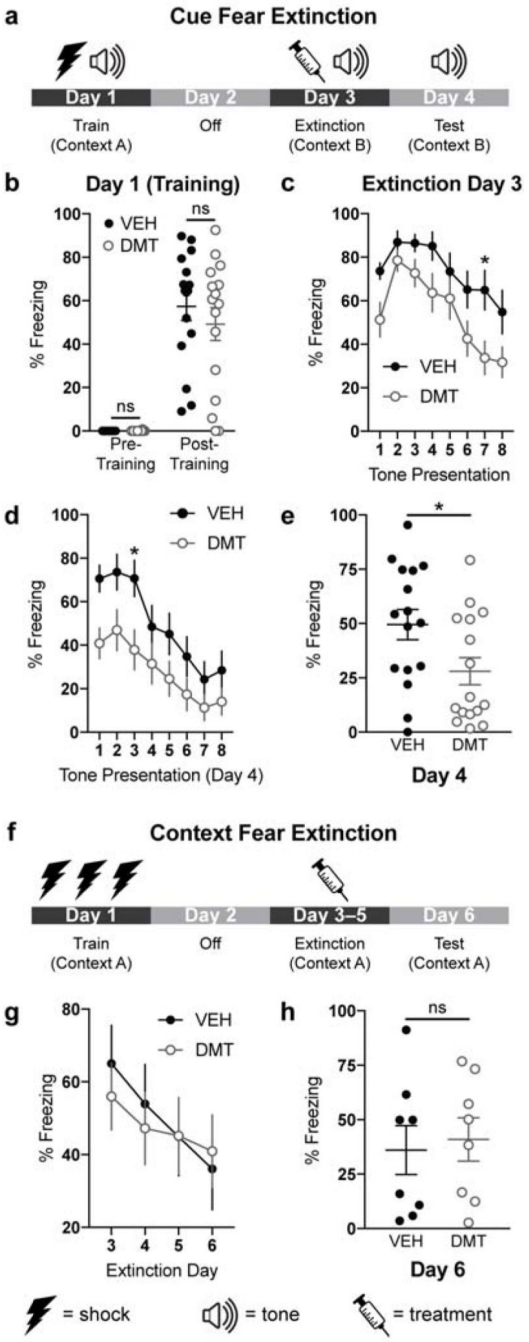

Figure 4.

An acute dose of DMT (10 mg/kg) facilitates cued, but not contextual, fear extinction. (a) Experimental design for the cued fear extinction experiment (N = 16 (VEH) N = 16 (DMT)). Following cued fear conditioning in context A, animals were dosed and subjected to one session of cued extinction training in context B on day 3. On day 4, the DMT-treated group demonstrated significantly lower freezing responses in the absence of drug. (b) Fear conditioning prior to drug treatment demonstrates that there is no difference between the two treatment groups. (c) Cued extinction during training day 3 demonstrates that administration

of DMT 1h prior to training does not impair the initial recall of the fear memory, but does enhance within session extinction. (d) Percentage of time spent freezing during each of the 8 auditory presentations on the test day (day 4). (e) Total percentage of time spent freezing during all 8 auditory presentations on the test day (day 4). (f) Experimental design for the context extinction experiment (N = 8 (VEH) N = 8 (DMT)). Animals were fear conditioned in context A, and dosed prior to contextual extinction training (days 3–5). On day 6, contextual fear memory was assessed in the absence of drug. (g) Percentage of time spent freezing during the entire 10 min session on each of the extinction days. Both treatment groups effectively extinguish contextual fear memories over time. The extinction day had a significant effect of freezing levels ($P = 0.0073$) as analyzed using a repeated measures two-way ANOVA. (h) Individual data points for the contextual extinction test in the absence of drug on day 6. Error bars represent SEM, NS = not significant, $*P < 0.05$, as compared to vehicle control. VEH = vehicle, DMT = *N,N*-dimethyltryptamine

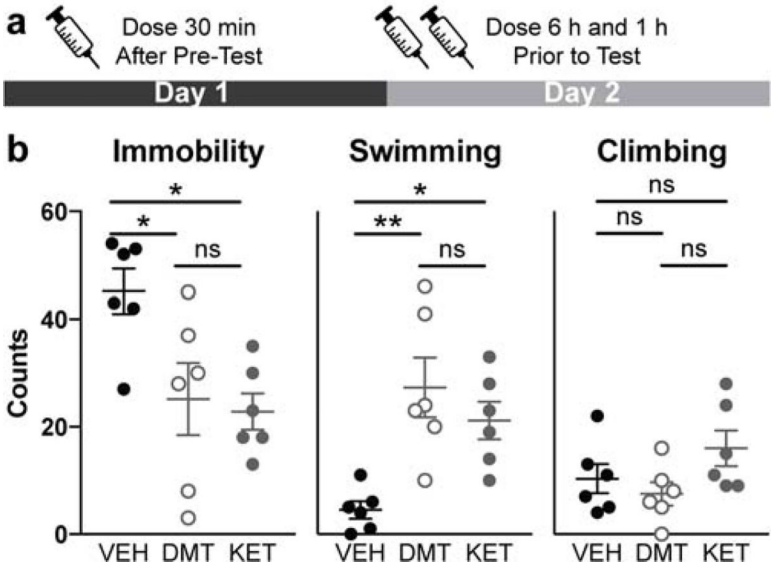

Figure 5.

An acute dose of DMT (10 mg/kg) elicits an antidepressant response in the forced swim test similar to ketamine (10 mg/kg). (a) Experimental design of the forced swim test. (b) Quantification of different forced swimming behaviors. Error bars represent SEM, NS = not significant, *$P < 0.05$, **$P < 0.01$. N = 6 (VEH) N = 6 (DMT) N = 6 (KET).VEH = vehicle, DMT = *N,N*-dimethyltryptamine, KET = ketamine