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Safety, Pharmacokinetics, and Pharmacodynamics of a 6-h *N*,*N*-Dimethyltryptamine (DMT) Infusion in Healthy Volunteers: A Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

The serotonergic psychedelic *N*,*N*-dimethyltryptamine (DMT) presumably stimulates neuroplasticity in vitro and in vivo, by which it may exert neuroprotective effects during acute ischemic stroke. Since neuroplasticity has been implicated in the mechanism of action of rehabilitative therapy in stroke recovery, a pharmacological augmentation strategy facilitating neuroplasticity could be beneficial. To optimize this treatment strategy, a detailed understanding of the safety, pharmacokinetics, and pharmacodynamics of prolonged DMT administration is required. This randomized, double-blind, placebo-controlled, single ascending dose study administered three intravenous doses of DMT as a 30-s bolus followed by a 6-h infusion: 1.5 mg + 0.105 mg/min, 7.5 mg + 0.525 mg/min, and 5.0 mg + 0.7875 mg/min. Twelve female and seventeen male psychedelic-experienced and naïve healthy participants, with a mean age of 27.3 (SD 10.2, range 19–57) years, were included. No serious adverse events occurred, and all adverse events were mild in intensity and self-limiting. No significant abnormalities in vital signs or 12-lead electrocardiography, and no suicidality or treatment-emergent psychopathology occurred. Moderate interindividual pharmacokinetic variability was observed. Mild psychedelic effects were accompanied by decreases in sustained attention, postural stability, and occipital alpha electroencephalographic power at the highest dose, which peaked rapidly after bolus administration and remained relatively stable or decreased over time. Together, DMT administered intravenously as a 30-s bolus followed by a 6-h infusion and reaching maximal exposures of approximately 35 ng/mL in healthy volunteers was safe and demonstrated rapidly occurring but mild psychedelic effects, providing the basis for future proof-of-mechanism studies in patient populations.

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Summary

- What is the current knowledge on the topic?
  - *N*,*N*-dimethyltryptamine (DMT) is a potent 5-HT_{2A} receptor-targeting psychedelic compound that is associated with a putative peak psychedelic exposure threshold in humans of approximately 35 ng/mL.
  - Prolonged intravenous DMT administration is currently being explored for its therapeutic potential in various neuropsychiatric and neurological disorders.
- What question did this study address?
  - This study characterized the safety, pharmacokinetics, and pharmacodynamics of a 6-h long DMT infusion in healthy volunteers at doses that are predicted to result in exposures below the putative psychedelic threshold.
- What does this study add to our knowledge?
  - DMT administered intravenously as a bolus over 30 s followed by an infusion over 6 h and reaching maximal exposures of approximately 35 ng/mL in healthy volunteers is safe.
  - Negligible psychedelic effects emerged at 25 ng/mL while robust, albeit still mild, psychedelic effects associated with EEG alpha power suppression occurred at 35 ng/mL.
  - Moderate pharmacokinetic variability was observed, consistent with previous DMT studies in humans.
- How might this change clinical pharmacology or translational science?
  - This study demonstrates that administering an intravenous 30-s DMT bolus followed by a 6-h DMT infusion is safe and induces relevant EEG effects as well as mild psychedelic and neurophysiological effects.
  - Together, these results provide the basis for future proof-of-mechanism studies in patient populations.

1 | Introduction

Stroke is the second most common cause of death and the third leading cause of acquired adult disability [1]. Approximately 80% of stroke survivors have upper limb motor impairments that gravely affect their ability to perform activities of daily living (ADL) and social participation [1]. Since the severity of upper limb paresis is an independent determinant of the outcome of ADL following stroke [2], rehabilitative therapy, or alternatively, pharmacological treatment, is considered crucial to achieve optimal functional recovery of the affected limb.

Cortical neuroplasticity has been put forward as the putative neurophysiological mechanism of rehabilitative therapy [3]. This is supported by reversal of decreased dendritic arborization in the injured motor cortex following stroke [3] and restoration of impaired motor skills following rehabilitative therapy in several rat stroke model studies [3, 4]. Similarly in human stroke patients, evidence of enhanced cortical neuroplasticity was observed with fMRI [5] and TMS targeting the motor cortex [6, 7] during rehabilitation. Moreover, the timing of rehabilitative therapy relative to the occurrence of stroke appears to moderate positive functional outcomes, as motor improvement was optimal within the first 3 months following stroke in humans [2]. Lastly, animal and human studies have demonstrated boosted neuroplasticity in the first weeks after stroke, as evidenced by increased synaptogenesis and alterations in cortical activity [8, 9]. Taken together, these results corroborate a "critical period" of neuroplasticity-related physiological changes following stroke resulting in stimulation of compensatory mechanisms promoting functional recovery [8–10].

Neuroplasticity-promoting pharmacological agents that exert sustained effects during the putative critical post-stroke period could theoretically benefit stroke patients. As such, serotonergic psychedelics are considered relevant candidates since they induce neurogenesis and increased dendritic complexity by 5-HT_{2A} (5-HT_{2A}R) and sigma-1 receptor (Sigma1R) agonism [11–13]. Facilitation of neuroplasticity was optimal at 24 h following 6 h of exposure to the psychedelic LSD in vitro, as rat cortical neurons demonstrated more sustained growth compared to exposure over 1 or 24 h [14]. However, in humans, potent 5-HT_{2A}R activation is associated with hallucinogenic effects involving alterations in ego boundaries, perception, mood, and cognition [15]. Since such effects are undesirable and might even prevent effective rehabilitative therapy in stroke patients, sub-psychedelic plasma exposures are indicated. Since sub-psychedelic doses of both LSD and DMT have demonstrated neuroplasticity-promoting effects in limbic circuits in humans [16] and increased functional plasticity in rat cortical slices [11], this is considered a viable strategy in stroke patients.

DMT is a potent agonist of both the 5-HT_{2A}R and Sigma1R, which exposures and possibly pharmacodynamic (PD) effects can be maintained at pseudo steady-state in humans by intravenous infusion [17–21]. In fact, continuous intravenous administration is preferable, as DMT is rapidly metabolized by the monoamine-oxidase A (MAO-A) enzyme, and potentially CYP2D6, in the gut and liver, rendering DMT inactive when administered orally as an isolated compound [22, 23]. In addition, DMT has demonstrated neuroplasticity-inducing effects up to 24 h following administration in in vitro and in *vivo* rat studies, as well as significantly lower ischemic lesion volumes at 24 h and better functional recovery compared with controls after 30 days in a rat stroke model [11, 24, 25]. Since Sigma1R stimulates cell survival by attenuating endoplasmic reticulum stress [26], and Sigma1R antagonists inhibit DMT protection on lesion volumes, this might present an additional relevant mechanism of action besides 5-HT_{2A}R agonism. Taken together, DMT represents a promising potential adjunctive treatment following stroke due to its specific pharmacokinetic (PK) and PD profiles [25].

As DMT administered intravenously over 6 h seems to optimally induce neuroplasticity in preclinical experiments relevant to stroke, this strategy merits further exploration in human stroke patients. However, the clinical pharmacology of prolonged DMT infusions at sub-psychedelic doses should first be characterized in healthy volunteers. Therefore, the current study aimed to investigate the safety, PK, and PD of a 30-s bolus followed by a 6-h DMT infusion in healthy volunteers at doses that are predicted to result in exposures below the putative psychedelic threshold. This infusion regimen was

selected to rapidly achieve target plasma exposures following the 30-s bolus, while the continuous infusion maintained these levels for 6 h. The continuous infusion is necessary to compensate for DMT's short half-life.

2 | Methods

2.1 | Study Design

A randomized, double-blind, placebo-controlled, single ascending dose study in healthy participants was performed at the Centre for Human Drug Research (Leiden, the Netherlands) according to the Dutch Act on Medical Research Involving Human Subjects and in compliance with all International Conference on Harmonization-Good Clinical Practice guidelines and the Declaration of Helsinki. It was approved on 06 September 2022 (CCMO code NL81883.056.22) by the BEBO Foundation for the Assessment of Ethics of Biomedical Research (Assen, the Netherlands).

2.2 | Participants

Three cohorts of 10 healthy psychedelic inexperienced and experienced participants (aged 18–60 years inclusive) were included between 15 November 2022 and 25 April 2023. All participants provided written informed consent prior to performing any study procedures. Exclusion criteria were: presence or history of hypertension or cardiovascular disease, a history of chronic migraines or seizure disorders, a positive pregnancy test at screening or admission, and use of > 5 cigarettes daily. To optimize safety, participants with a history of drug or alcohol abuse within the past year, a personal or first-degree family history of clinically relevant psychiatric disorders according to the DSM 5 (psychiatric history in second-degree relatives was discussed on a case-to-case basis), persistent psychological effects following previous use of psychedelics, and habitual use of psychedelics were excluded. Prior to dosing, participants were not allowed to use MAO inhibitors or psychoactive drugs for 30 days, cannabis or prescription drugs for 14 days, supplements for 7 days, and alcohol for 24 h. A detailed list of in- and exclusion criteria is present in the Supporting Information.

2.3 | Randomization

Eligible subjects were randomly assigned to either DMT or placebo using a computer-generated randomization schedule (ratio 8:2).

2.4 | Study Drug, Dose Selection and Escalation

DMT fumarate was administered as a 30-s bolus followed by a 6-h infusion. This dosing regimen was designed to rapidly increase plasma DMT levels to the target concentration and to maintain this exposure for 6 h. Planned dose levels were based on simulated DMT concentration-time profiles using an in-house developed population PK model based on observed data from a previous trial with DMT performed at CHDR [27, 28]. Since the aim of the current study was to investigate sub-psychedelic doses of DMT, dose levels were simulated to reach plasma exposures lower than those produced by a 0.2 mg/kg IV bolus (approximately 45 ng/mL), as at the time of designing this study this was demonstrated to be the threshold exposure for psychedelic effects in humans [29]. The starting dose in cohort 1, consisting of a 1.5 mg bolus followed by a 0.105 mg/min infusion, was expected to lead to mean exposures of 4.4 ng/mL, which is 10-fold below the psychedelic threshold. Subsequent dose levels were initially selected at 7.5 mg bolus followed by 0.525 mg/min infusion (anticipated exposure of 21.3 ng/mL) and 11.25 mg bolus followed by 0.7875 mg/min infusion (anticipated exposure of 33.3 ng/mL) and were re-evaluated based on blinded reviews of interim safety, PK, and PD data following each cohort (Table 1). For cohort 3, the planned bolus dose was decreased from 11.25 to 5.0 mg, but the infusion dose was maintained as initially anticipated, as mild psychedelic effects were reported following the 7.5 mg bolus administration in cohort 2.

2.5 | Study Procedures

All participants underwent a medical screening 28–2 days prior to dosing and were invited for an in-depth introduction and information session with their psychedelic guide. Upon admission (Day -1), a urine drug, pregnancy, and alcohol breath test were performed, and eligibility was reconfirmed. Participants were administered DMT or placebo in the morning on Day 1 and were released from the clinic before 1:00 PM on Day 2. Drug administration occurred in designated study rooms, which had been altered to make the environment comforting and calm, in line with safety guidelines [30, 31] for conducting clinical trials with psychedelic compounds. Participants remained in this room during drug administration in the presence of a psychedelic guide, a nurse, and a research assistant, but were served lunch in the general ward 3 h after the start of administration. Participants were fitted with an EEG cap and were made comfortable in a semi-supine position. A cannula was inserted in both arms. Prior to discharge on Day 2, a debriefing session took place by the psychedelic guide, and participants were examined by a physician.

2.5.1 | Safety Evaluations

Systolic (SBP) and diastolic blood pressure (DBP), pulse rate, temperature, respiratory rate, and 12-lead ECG were assessed

TABLE 1 | Infusion scheme and total dose per dose level.

Dose	Infusion scheme	Total dose administered (mg)
1	1.5 mg bolus + 0.105 mg/min infusion	39.3
2	7.5 mg bolus + 0.525 mg/min infusion	196.5
3	5.0 mg bolus + 0.7875 mg/min infusion	288.5

pre-dose and 60, 120, 180, 240, 300, 360, and 420 min and 24 h after the start of infusion. Following 5 min in a supine position, automated oscillometric blood pressures and pulse rate were measured using a Dash 4000, Dynamap 400, or ProCare 400, and ECGs were obtained using Marquette 2000/5500. Emergence of psychotic symptoms was assessed with the Brief Psychiatric Rating Scale pre-dose and 1 and 24 h after the start of infusion. Emergence of suicidality was assessed with the Columbia Suicide Severity Rating Scale pre-dose, on Day 2, and the follow-up visit. Emergence of serotonergic toxicity was assessed throughout Day 1 by the attending physician using the Hunters Criteria [32].

2.5.2 | Pharmacokinetic Assessments

Plasma DMT concentrations were collected in 4 mL K2-EDTA tubes at pre-dose and 2, 10, 30, 40, 60, 120, 180, 240, 300, 360, 365, 375, 390, 420, and 600 min after the start of infusion. Plasma samples were analyzed using a partially validated (unpublished, summary present in Supporting Information) API 6500+ LC–MS/MS bioanalytical method by Ardena Bioanalysis BV. The lower and upper limits of quantification for DMT were 0.100 and 100 ng/mL, respectively.

2.5.3 | Pharmacodynamic Assessments

2.5.3.1 | Real Time Intensity Scale (RTIS). The RTIS is a rater-based scale requiring participants to verbally rate the current psychological intensity of their experience from 0 to 10 (0 = not intense at all, representing the normal state; 10 = extremely intense) on three dimensions of visual, bodily, and emotional aspects of subjective drug experience. The RTIS was assessed at baseline and 10, 30, 45, 60, 120, 180, 240, 300, 360, 365, 375, 390, and 420 min after the start of infusion.

2.5.3.2 | Visual Analogue Scales (VAS). Three VAS were used: the VAS Bond and Lader (BL) (mm) to measure alertness, calmness, and changes in mood [33]; the VAS Bowdle (log mm+2) to evaluate psychomimetic drug effects [34] calculated as three main factors: feeling high, external perception, and internal perception; and the VAS drug rating (log mm+2) to measure feeling the drug, liking the drug, and disliking the drug. Participants indicated on a horizontal 100-mm VAS displayed on a laptop how they felt at baseline and 75, 195, 315, 435 min, and 24 h after the start of infusion.

2.5.3.3 | 11-Dimensions Altered States of Consciousness Rating Scale (11D-ASC) and the Hallucinogenic Rating Scale (HRS). The 11D-ASC scale is a 94-item self-report questionnaire that quantifies subjective alterations in mood, perception, and experience of self in relation to the environment on a scale from 0% to 100% (VAS). The HRS is a 99-item self-report questionnaire that quantifies the subjective effects experienced after the administration of DMT [29, 35]. Items were grouped in six empirically derived scales consisting of affect, cognition, intensity, perception, somaesthesia, and volition, with values ranging between minimally 0 and maximally 4. Both scales were performed 2 h after the end of infusion, using Dutch translations (translated using the back-translation method).

2.5.3.4 | NeuroCart Test Battery. Functional central nervous system (CNS) effects were measured using the NeuroCart (CHDR, Leiden, the Netherlands), an integrated battery of tests for a wide range of CNS domains, which was developed to assess CNS-active drugs [36]. Neurophysiologic functioning was measured with saccadic peak velocity (SPV) and smooth pursuit; postural stability with body sway; and attention and eye-hand coordination with adaptive tracking. Effects on brain activity were measured using EEG. Tests were performed twice predose at baseline and 120, 180, 300, 420 min, and 24 h after the start of the dosing. See Supporting Information for a detailed description of the NeuroCart.

2.5.3.5 | Neuroendocrine and Neurotrophic Biomarkers. Venous blood samples for prolactin, cortisol, serum, and plasma BDNF were collected predose and 2, 30, 120, 240, 360, 390, 420, 600, and 720 min and 24 h after the start of infusion. Prolactin and cortisol samples were collected in a 3.5 mL SST tube and analyzed by the Clinical Chemistry lab of Leiden University Medical Centre. Plasma and serum BDNF were collected in a 4 mL K2 EDTA tube and a 3.5 mL SST tube, respectively, and determined at the bioanalytical laboratory Ardena Bioanalysis BV using a fit-forfor-purpose qualified free BDNF Quantikine ELISA kit from R&D Systems (Minneapolis, USA, catalogue no. DBD00). Assay performance was monitored using Quantikine Immunoassay Control group 7 from R&D Systems (catalogue no. QC22) and endogenous serum and plasma Quality Checks (QCs).

2.5.3.6 | MAO-A Enzyme Activity. One MAO-A plasma sample was collected predose on the morning of dosing in a 4 mL K2-EDTA tube. MAO-A activity was determined at the bioanalytical laboratory Ardena Bioanalysis BV using the fit for purpose qualified Amplex Red Monoamine Oxidase Assay Kit (A12214) of ThermoFisher Scientific (Rockford, USA). *p*-Tyramine was used as a substrate for MAO-A and MAO-B. MAO-A was specifically inhibited using 1.00 μM of the selective inhibitor clorgyline. Samples were incubated according to the instruction provided with the kit. MAO-A specific activity in nmol/min/mL was calculated by subtracting the activity of the sample incubated with MAO-A inhibitor from the total Monoamine Oxidase activity. Assay performance was monitored using three QCs at the levels low (endogenous plasma pool), medium (endogenous human plasma pool spiked at 3.33 μg/mL recombinant human MAO-A; catalogue no. M7316, Sigma-Aldrich) and high (endogenous human plasma pool spiked at 33.3 μg/mL recombinant human MAO-A).

2.6 | Statistical Analysis

Safety parameters were not statistically analyzed.

Pharmacokinetic analysis was performed using a non-compartmental analysis with PK parameter calculations based on actual sampling time and dose corrected for fumarate salt content. The area under the curve (AUC) was calculated using the linear-up and log-down method. Half-life was derived by linear regression, based on a minimum of 3 points after maximum concentration and within the terminal phase of the PK profile, with a minimal r^2 of 0.85 and span ratio of > 1.5 times

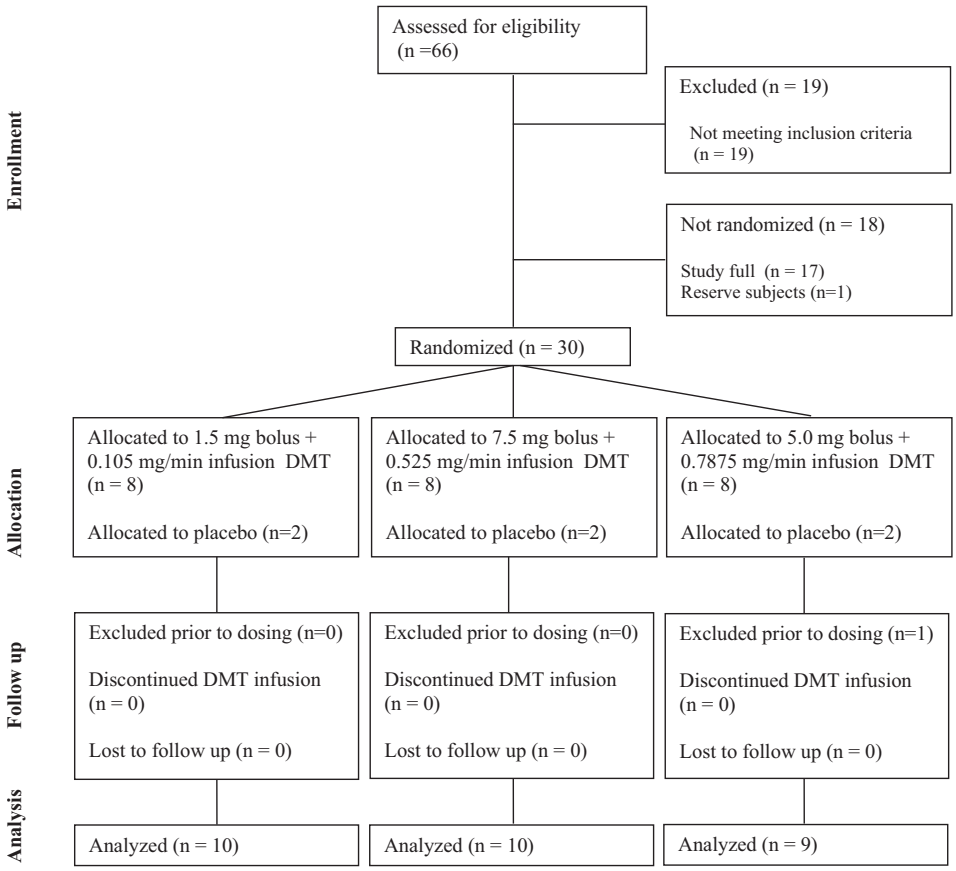

FIGURE 1 | Study flow chart.

the derived half-life. Additionally, the relationship between MAO-A enzyme activity and half-life, dose normalized AUC from time zero to infinity (AUC_{inf}), and dose normalized AUC from time zero to the last measurable concentration (AUC_{last}) was assessed by determination of the Pearson's correlation coefficient (*r*). Calculations were performed in R (V4.0.3) with the PKNCA package for determination of PK parameters [37, 38].

Repeatedly measured PD parameters (RTIS, VAS, NeuroCart, cortisol, prolactin and BDNF) were analyzed up to 24 h post-dose with a mixed effects model with treatment, time, and treatment by time as fixed factors, and participant as a random factor and the average of two pre-dose measurements as a covariate, using SAS9.4. Single measured PD parameters (HRS and 11D-ASC) were analyzed with a one-way analysis of covariance with treatment as a factor and the pre-dose measurement, if available, as a covariate. An exploratory post hoc analysis using descriptive statistics was used to determine differences in DMT plasma concentrations and RTIS values between males and females. Due to the nature of the data (non-normality and absence of variability under placebo) no formal statistical analysis for HRS and FDASC subscales was performed and results were reported with descriptive statistics. Additionally, due to a suspected error in data entry, the HRS subscale volition was not analyzed. Lastly, a *p*-value of < 0.05 was considered statistically significant in all analyses, without correction for multiple testing.

3 | Results

3.1 | Participant Characteristics

Twenty-nine participants, aged 19–57 years (12 females, 17 males), were randomized to receive DMT or placebo (Figure 1). One participant in dose level 3 was excluded from participation prior to administration of DMT, and, subsequently, the decision was made not to include a replacement.

No significant differences were observed for weight, height, or BMI between dose levels and between DMT and placebo (Table 2). The mean average age was variable between dose levels, ranging between 23.4 and 32.0 years, with the most considerable difference being 8.6 years between dose levels 1 and 3. Additionally, dose level 2 consisted of two participants of mixed race (25%), while all other dose levels solely contained white participants. Lastly, the placebo group contained the lowest number of females (17%) compared to other groups, with 38%, 50%, and 57% in dose levels 1, 2, and 3, respectively.

3.2 | Safety

All AEs were self-limiting and mild to moderate in intensity. The most commonly occurring AEs were headache, nausea, and fatigue for DMT and fatigue for placebo (Tables S1 and S2). The most commonly occurring AEs per dose were

TABLE 2 | Demographics per dose level.

Cohort		1	2	3	
Dose	All participants ($N=29$)	1.5 mg + 0.105 mg/min ($N=8$)	7.5 mg + 0.525 mg/min ($N=8$)	5.0 mg + 0.7875 mg/min ($N=7$)	Placebo ($N=6$)
Age (years)					
Mean (SD)	27.3 (10.2)	32.0 (10.2)	26.0 (12.7)	23.4 (3.6)	27.2 (11.8)
Min, Max	19, 57	21, 50	19, 57	19, 28	20, 51
Height (cm)					
Mean (SD)	179.1 (10.7)	178.4 (10.2)	175.9 (13.2)	176.9 (9.7)	186.8 (6.6)
Min, Max	160.8, 199.7	161.9, 189.2	160.8, 199.7	161.8, 192.0	178.4, 196.5
Weight (kg)					
Mean (SD)	72.2 (8.6)	71.6 (7.8)	70.5 (10.3)	70.7 (9.1)	76.7 (6.9)
Min, Max	56.1, 87.8	58.8, 84.5	56.1, 85.1	60.2, 83.4	67.8, 87.8
BMI (kg/m^2)					
Mean (SD)	22.5 (1.9)	22.5 (1.9)	22.9 (3.0)	22.5 (1.5)	22.0 (0.9)
Min, Max	18.5, 27.2	20.2, 25.7	18.5, 27.2	20.3, 25.0	21.0, 23.1
Sex					
Female	12 (41.4%)	3 (37.5%)	4 (50.0%)	4 (57.1%)	1 (16.7%)
Male	17 (58.6%)	5 (62.5%)	4 (50.0%)	3 (42.9%)	5 (83.3%)
Race					
Mixed	2 (6.9%)	0 (0%)	2 (25.0%)	0 (0%)	0 (0%)
White	27 (93.1%)	8 (100%)	6 (75.0%)	7 (100%)	6 (100%)

catheter site-related reactions for dose 1; headache, dizziness, fatigue, nausea, and feeling hot for dose 2; and injection site pain, headache, fatigue, nausea, and presyncope for dose 3. No dropouts occurred. One 18-year-old psychedelic-naïve female experienced anxiety and panic attacks the day after receiving a 7.5 mg bolus + 0.525 mg/min infusion. She reported that several life events had occurred the year prior and the DMT infusion triggered an emotional response to these events. Following a number of counseling sessions focused on integration of the psychedelic experience, these symptoms subsided within 6 months.

Dose-dependent increases in mean SBP of 10 and 20 mmHg were observed for DMT for doses 2 and 3, respectively, with maximum individual increases being 39 and 25 mmHg, respectively. Mean DBP increased by 9 mmHg for dose 3. All increases returned to baseline within 1 h after the DMT administration was discontinued (Figure S1). Lastly, no serotonergic toxicity was observed, and no clinically significant post-administration changes were demonstrated for temperature, respiratory rate, heart rate, CSSRS, BPRS, and ECG parameters.

3.3 | Pharmacokinetics

DMT plasma concentrations tended to increase dose proportionally, as mean AUC_{last} (±SD) values were 14.2 (6.8), 85.9 (21.6) and 157.6 (55.3) h*ng/mL for doses 1, 2, and 3, respectively, and mean C_{max} (±SD) was 4.6 (2.9), 25.3 (24.1) and 35.9 (34.0) ng/mL, respectively (Figure 2 and Table S3). Mean half-life was consistent across all dose levels, ranging from 0.2 to 0.3 h, and the volume of distribution during the terminal elimination phase was high, ranging from 431 to 616 L, with a steady-state volume of distribution ranging from 3834 to 6516 L. T_{max} demonstrated relatively high variability, as mean values were 0.9 [absolute range 0.0–5.9 h], 0.9 [0.0–5.0 h] and 1.9 h [0.8–5.1 h] for doses 1, 2, and 3, respectively. Coefficients of variation (%CV's) for C_{max}, AUC_{last}, and $t_{1/2}$ ranged from 34.8%–62.4%, 24.5%–47.7%, and 34.8%–62.4%, respectively. Lastly, no differences were observed in DMT plasma concentrations between sexes, except slightly higher values in females (~30 ng/mL) following dose 3 as compared to males (~20 ng/mL) (Figure S2).

3.4 | Pharmacodynamics

3.4.1 | Subjective Drug Effects

3.4.1.1 | RTIS. Compared with placebo, DMT statistically significantly increased mean RTIS "bodily intensity", "emotional and metacognitive intensity" and "visual intensity" for dose 3 (Figure 3 and Table 3). Increases appeared to be concentration-dependent for RTIS "bodily and visual

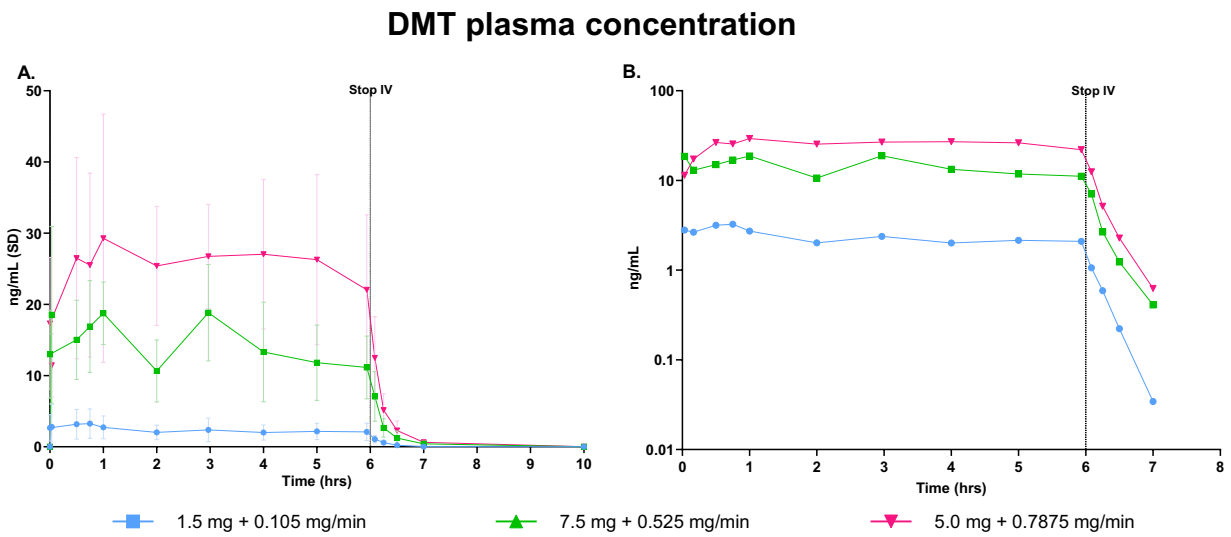

FIGURE 2 | Mean plasma concentration ± SD (ng/mL) of DMT up to 10 h after the start of infusion. (A) Linear scale and (B) logarithmic scale.

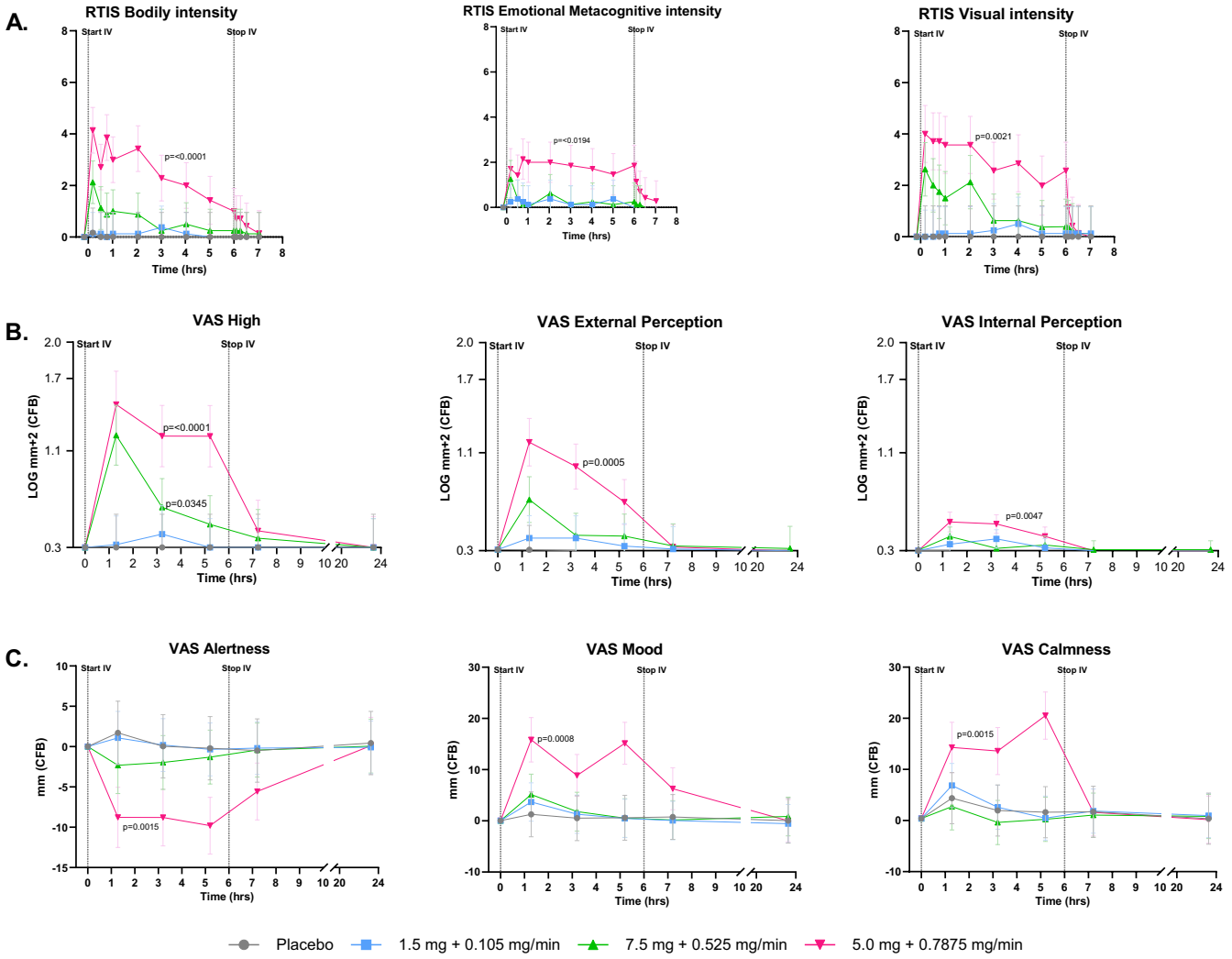

FIGURE 3 | Subjective drug effects of DMT on (A) RTIS bodily intensity, RTIS emotional and metacognitive intensity, and RTIS visual intensity, (B) VAS Bowdle Feeling high, External Perception, and Internal perception, and (C) VAS Bond and Lader Alertness, Mood, and Calmness. Values are represented as the least square mean change compared to baseline, with 95% CI error bars, up to 8 h (A) and 24 h (B, C) after start of infusion. *p*-values represent a statistically significant effect compared to placebo.

TABLE 3 | Subjective effects of DMT on VAS, Bowdle, Bond, and Lader, and Drug rating.

			Estimated difference (95% CI), *p*		
	Parameter	**Treatment, *p***	**Dose 1.5 mg + 0.105 mg/min vs. Placebo**	**Dose 7.5 mg + 0.525 mg/min vs. Placebo**	**Dose 5.0 mg + 0.7875 mg/min vs. Placebo**
Real time intensity scale	Bodily intensity	0.0010	0.1 (−0.9, 1.0) *p* = 0.8981	0.6 (−0.4, 1.5) *p* = 0.2221	1.8 (0.9, 2.8) *p* = 0.0005
	Visual intensity	0.0595	0.1 (−0.9, 1.2) *p* = 0.7912	0.2 (−0.8, 1.3) *p* = 0.6473	1.3 (0.2, 2.4) *p* = 0.0194
	Emotional intensity	0.0056	0.1 (−1.1, 1.4) *p* = 0.8315	0.9 (−0.3, 2.2) *p* = 0.1448	2.2 (0.9, 3.5) *p* = 0.0021
VAS Bond and Lader	Alertness (mm)	0.0020	−0.2 (−3.9, 3.5) *p* = 0.9251	−1.5 (−5.5, 2.5) *p* = 0.4474	−6.9 (−10.8, −2.9) *p* = 0.0015
	Calmness (mm)	0.0009	0.5 (−3.9, 5.0) *p* = 0.8031	−1.1 (−5.6, 3.4) *p* = 0.6139	8.0 (3.4, 12.7) *p* = 0.0015
	Mood (mm)	0.0011	0.4 (−3.9, 4.7) *p* = 0.8641	1.1 (−3.0, 5.2) *p* = 0.5972	8.6 (4.0, 13.2) *p* = 0.0008
VAS Bowdle	External perception (log mm + 2)	0.0020	0.053 (−0.153, 0.259) *p* = 0.5974	0.146 (−0.073, 0.365) *p* = 0.1810	0.402 (0.196, 0.608) *p* = 0.0005
	Internal perception (log mm + 2)	0.0302	0.036 (−0.040, 0.111) *p* = 0.3436	0.041 (−0.038, 0.120) *p* = 0.2929	0.115 (0.039, 0.191) *p* = 0.0047
	Feeling high (log mm + 2)	0.0002	0.026 (−0.254, 0.307) *p* = 0.8486	0.305 (0.024, 0.586) *p* = 0.0345	0.634 (0.345, 0.924) *p* = 0.0001
VAS drug effects	Feeling drug (log mm + 2)	< 0.0001	0.113 (−0.212, 0.438) *p* = 0.4795	0.555 (0.230, 0.881) *p* = 0.0017	0.936 (0.600, 1.271) *p* < 0.0001
	Liking drug (log mm + 2)	< 0.0001	0.182 (−0.164, 0.528) *p* = 0.2892	0.465 (0.129, 0.802) *p* = 0.0087	0.992 (0.646, 1.339) *p* < 0.0001
	Disliking drug (log mm + 2)	0.7188	0.166 (−0.175, 0.507) *p* = 0.3253	0.159 (−0.183, 0.500) *p* = 0.3471	0.165 (−0.186, 0.517) *p* = 0.3420

Note: Values are represented as estimated difference between DMT and placebo, with 95% CI, up to 24 h after start of infusion.

intensity", but not for "emotional intensity". No effects were observed on any RTIS for doses 1 or 2. For doses 2 and 3 all RTIS peaked rapidly after the bolus administration and gradually decreased from 2 h onwards. An exception was RTIS "emotional intensity" for dose 3, which remained elevated throughout the infusion. No differences were observed between sexes, except a slightly higher "visual," "emotional and metacognitive" and "bodily" intensity following dose 3 in females, which corresponds with the higher DMT plasma concentration attained by this subgroup (no statistical tests performed).

3.4.1.2 | VAS. Compared with placebo, DMT statistically significantly increased mean VAS BL "mood" and "calmness", and decreased "alertness" for dose 3, while these VAS's remained unaffected for doses 1 and 2 (Table 3). Furthermore, compared with placebo, DMT statistically significantly increased mean VAS Bowdle "feeling high", "external perception" and "internal perception", as well as VAS "drug liking" and "feeling drug" for dose 3. Additionally, for dose 2, DMT increased mean VAS Bowdle "feeling high", VAS "feeling drug" and VAS "liking drug" statistically significantly compared with placebo. These increases appeared to be concentration dependent solely for VAS "feeling high", "feeling drug" and "liking drug". DMT did not affect VAS "dislike drug" for any dose nor any other VAS scale for dose 1 (Table 3, Figure 3 and Figure S3).

3.4.1.3 | 11D-ASC. DMT demonstrated no effects for dose 1, while for dose 2 mean average scores ranged between 7.0% and 13.1% on all subscales, except "elementary imagery" (26.8% of maximum) (Figure 4). For dose 3, DMT demonstrated a distinct profile, as mean averages were highest for "complex imagery" (39.8%), "elementary imagery" (37.9%) and "blissful state" (31.9%) and lowest for "anxiety" (4.1%), "disembodiment" (3.4%) and "impaired control of cognition" (7.6%) (Figure 4). Lastly, for dose 2, participants reported a mean higher "anxiety" (12.4% vs. 4.1%), "disembodiment" (12.5% vs. 3.4%) and "impaired control of cognition" (12.1% vs. 7.6%) than dose 3.

3.4.1.4 | HRS. DMT demonstrated minimal effects on HRS subscales for dose 1, except for HRS "intensity", which reached a value of 0.9 (Figure 4). For dose 2, DMT increased HRS "affect" with 0.6, "cognition" with 0.5, "intensity" with 2.8, "perception" with 1.3, and "somaesthesia" with 1.1. Lastly, for dose 3, DMT

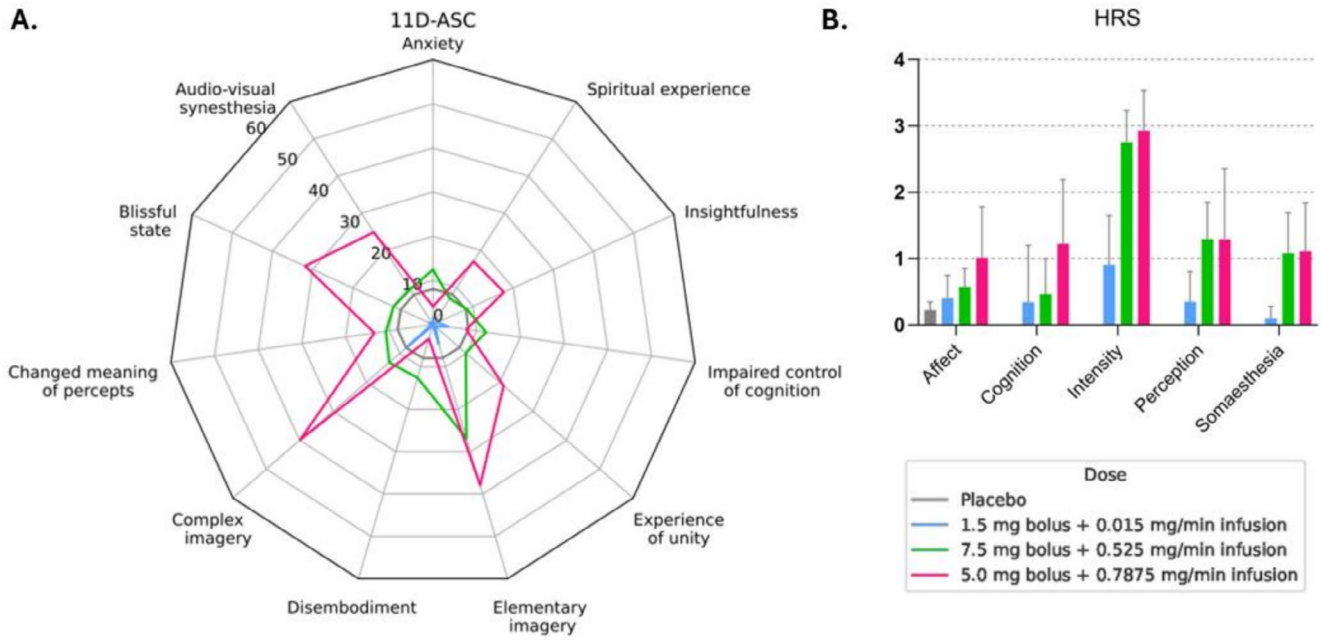

FIGURE 4 | Effects of DMT on the 11D-ASC and HRS. Values are represented as the mean (SD) value 2 h after dosing in (A) 11D-ASC and (B) HRS score. The 11D-ASC scale was adjusted from 0–100 to 0–60 to improve visualization of the data.

increased HRS "affect" with 1.1, "cognition" with 1.2, "intensity" with 2.9, "perception" with 1.3, and "somaesthesia" with 1.1. This increase appeared to be concentration dependent solely for HRS affect.

3.4.2 | Neurophysiological Assessments

3.4.2.1 | NeuroCart Test Battery. DMT did not affect SPV, saccadic inaccuracy, saccadic reaction time (SRT) or smooth pursuit eye movement compared with placebo for any dose (Figure 5 and Table S4). Compared with placebo, DMT statistically significantly decreased the mean performance percentage of adaptive tracking by −4.2% and −4.9%, while it increased the mean body sway by +59.9% and +56.6% sway over baseline, for dose 2 and 3, respectively, and the right and left pupil iris ratio by +0.07 for dose 3 only. Peak effects occurred approximately 1 and 6 h after the start of infusion for adaptive tracking and body sway, respectively, while the pupil iris ratio remained consistently elevated throughout the 6-h infusion.

3.4.2.2 | EEG. Compared with placebo, DMT statistically significantly decreased mean parieto-occipital alpha wave power for dose 3 and increased central gamma wave power for dose 2 (Figure 5 and Table S5).

3.4.2.3 | Neuro-Endocrine and Neurotrophic Biomarkers. DMT did not affect mean serum cortisol, prolactin, serum BDNF, and plasma BDNF compared with placebo for any dose (Figure S4).

3.4.2.4 | MAO-A Enzyme Activity. No statistically significant correlation between MAO-A activity and DMT half-life ($r = -0.098$; $p = 0.71$), dose-normalized AUC_{inf} ($r = 0.040$; $p = 0.88$) or dose-normalized AUC_{last} ($r = -0.076$; $p = 0.74$) was demonstrated (Figure S5).

4 | Discussion

The present study investigated the safety, PK, and PD of prolonged intravenous administration of DMT in healthy volunteers at doses predicted to result in exposures below the peak psychedelic exposure threshold assumed at the time of designing this study of approximately 45 ng/mL. DMT 39.3, 196.5, and 288.5 mg administered intravenously as a 30-s bolus followed by a 6-h infusion demonstrated an acceptable safety profile and reached average peak plasma exposures of ~5 to 36 ng/mL. Negligible psychedelic effects emerged at mean plasma concentrations of 25 ng/mL, while these were more robust, albeit still mild, at 36 ng/mL (Table S3).

All AEs were self-limiting and mild to moderate in intensity, with headache, nausea, and fatigue occurring most frequently. However, one participant experienced a moderate AE of anxiety following dose 2, necessitating counseling sessions. Interestingly, this participant's PK parameter values did not differ substantially from other participants, reaching, for instance, a C_{max} of 23.9 ng/mL versus the mean C_{max} of 25.3 ng/mL following dose 2. Elevations in SBP, DBP, and body temperature remained relatively stable during the infusion, indicating the absence of potential 5-HT mediated autonomic nervous system sensitization, and returned to baseline within an hour following its termination. Moreover, with average elevations of 10–20 mmHg in SBP and DBP at the highest exposure, cardiovascular effects were mild and in line with those observed previously at similar exposures [19, 29]. Furthermore, considering DMT's potent pro-serotonergic effects, no 5-HT mediated CNS toxicity emerged despite prolonged administration, which was consistent with such effects previously only reported at higher exposures [29]. DMT administered IV over 6 h up to exposures of 36 ng/mL therefore demonstrated an overall comparable safety profile to previous studies in which DMT was administered IV up to exposures

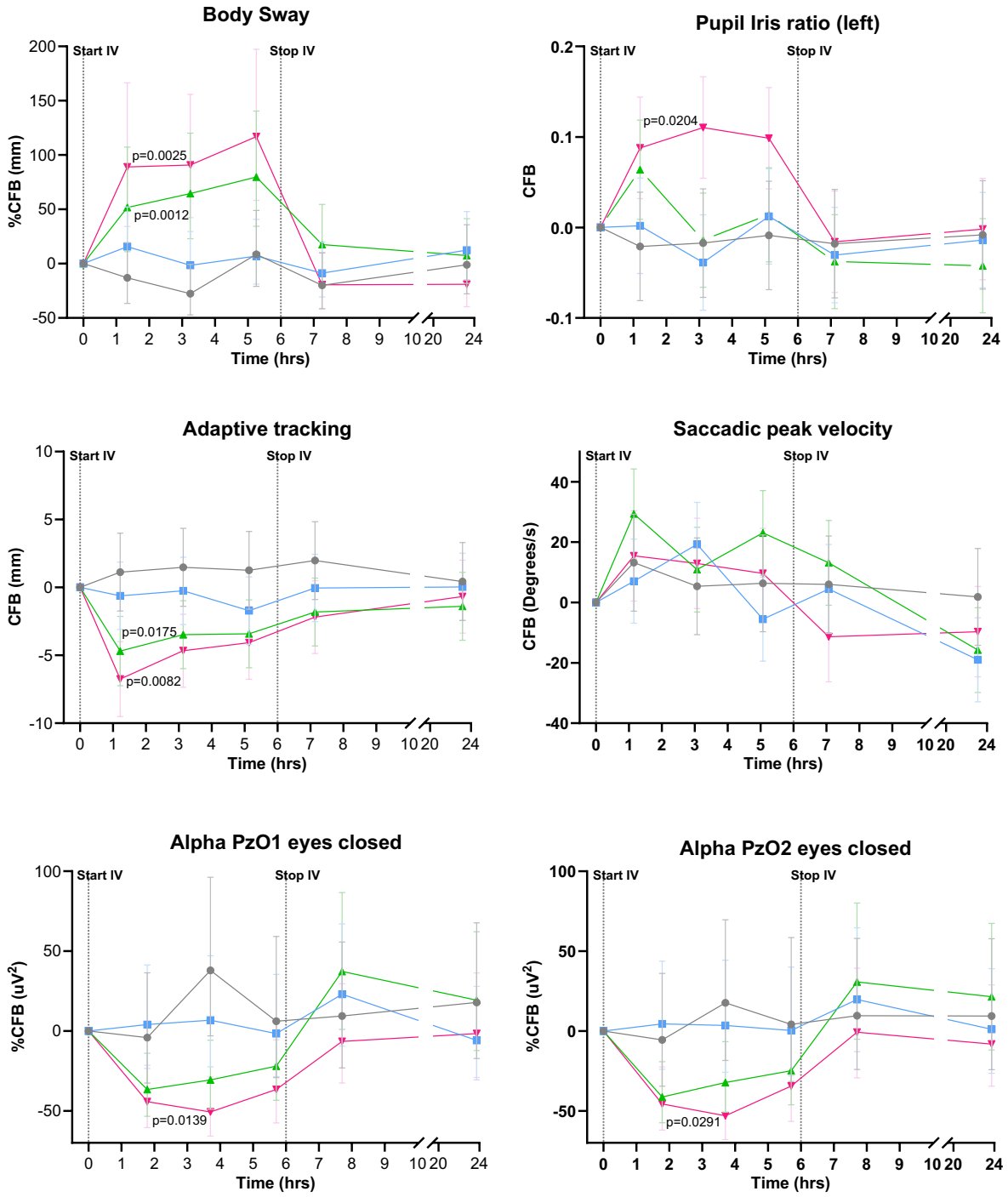

FIGURE 5 | Effects of DMT on the NeuroCart test battery for body sway, pupil-iris ratio, adaptive tracking, and saccadic peak velocity as well as occipital alpha wave power. Values are represented as the least square mean change compared to baseline, with 95% CI error bars, up to 24 h after start of infusion. *p*-values represent a statistically significant effect compared to placebo.

of 40 ng/mL over 1.5 h [18, 19, 29], supporting future proof-of-concept studies with prolonged DMT administration in relevant patient populations. However, even though management of BP in acute stroke remains controversial, DMT's cardiovascular effects should be considered when administering it to patients with ischemic stroke [39], and although no clinically significant serotonergic adverse effects were noted in these healthy unmedicated participants, (secondary) serotoninergic effects of concomitant medications should be carefully considered in future studies.

The applied DMT infusion scheme rapidly attained steady-state exposures and remained below the assumed psychedelic plasma concentration of approximately 45 ng/mL for the duration of the infusion. However, PK was variable with coefficients of variation (%CV's) ranging between ~20% and 60% for C_{max}, AUC and $t_{1/2}$, and although plasma concentrations remained relatively stable over the 6-h infusion period, fluctuations occurred resulting in interindividual variation in T_{max}. These findings can be considered specific to DMT, since moderate to high intersubject PK variability, as indicated by %CV's for C_{max} and/or AUC ranging

from 40% to 60%, was reported in most previous human studies [23]. Although potential study-specific sources of PK variability, including differences in bioavailability following oral administration, differences in body weight, and fat percentage (possibly due to sex differences) influencing DMT distribution and assay variability, are not expected to have had a major impact on variability in the current study, these might become relevant in future studies with more heterogeneous populations or different administration routes. In an exploratory post hoc analysis, no marked differences were observed in PK between sexes; however, due to the small sample size, no definitive conclusions can be drawn. Finally, DMT's rapid clearance by MAO-A, and to a lesser extent potentially CYP2D6 [23], presents another potential source of PK variability, as metabolic activity may vary between participants due to functional polymorphisms in the promotor region and epigenetic changes [40–42]. Although in the current study pre-dose MAO-A activity did not correlate with PK variability, the sample size is limited and, as MAO-A sampling was only performed once, dynamic changes in activity resulting from circadian rhythmicity cannot be excluded [43]. Additionally, DMT has previously demonstrated biphasic elimination, consisting of an initial rapid phase, likely driven by MAO-A metabolism, followed by a prolonged phase attributed to distribution processes [19, 20]. Due to a limited number of samples, in the current study, half-life was calculated across both phases, which may obscure a potential correlation between DMTs initial half-life and MAO-A activity. Lastly, no CYP450 genotyping was performed in the current study, precluding a correlation analysis of DMT's PK parameters with CYP2D6 metabolic phenotype. Nonetheless, since high intersubject PK variability is expected to result in increased PD variability, elucidating the contribution of individual differences in MAO-A and CYP2D6 activity resulting from genetic and/or environmental factors is considered prudent for DMT's further development.

Subjective drug effects comprised feeling high and alterations in visual perception and/or the experience of time, sound or bodily awareness. RTIS "bodily" and "visual intensity", HRS "affect", VAS "feeling high", VAS "feel drug" and "liking drug" increased exposure dependently at C_{max} of 25.3 and 35.9 ng/mL, respectively. These subjective effects were not associated with negative affective reactions, especially since increases in VAS "mood", VAS "calmness" and 11D-ASC "blissful state" indicating an agreeable experience were evident, while VAS "disliking drug" and 11D-ASC "anxiety", "disembodiment" and "anxious ego dissolution" remained largely unaffected across the exposure range. Lastly, although several subjective PD effects seemed to be consistent with DMT's time-concentration profile at the highest exposure, that was not the case for all effects. For instance, RTIS "emotional and cognitive intensity", VAS "alertness" and VAS "mood" seemed to track DMT exposures. Conversely, RTIS "visual" and "bodily intensity", VAS "feeling high" and VAS "external-" and "internal perception" demonstrated initial increases followed by gradual decreases from 3 h onwards, while VAS "calmness" tended to slightly increase between 3 and 6 h. Such changes over time despite a relatively stable plasma exposure might suggest some form of tachyphylaxis for the visual and sensory effects of DMT, but not for emotional and cognitive effects. This would support previous studies, where a similar effect was observed following a bolus plus a 30 or 90-min IV infusion [18, 19]. However, these findings remain observational and a definitive explanation remains uncertain pending additional PK-PD modeling.

The observed subjective drug effects were negligible at a mean C_{max} of 25.3 ng/mL for dose 2, while robust albeit mild effects were evident at a mean C_{max} of 35.9 ng/mL for dose 3 (Table S3). Thus, although the plasma concentrations attained in the current study were presumed to be below the psychedelic threshold of 45 ng/mL, they produced small but subjectively detectable effects compared to placebo. This observation leads us to hypothesize that the psychedelic threshold is lower than previously estimated, potentially below 35 or even 25 ng/mL. This revised threshold is further supported by a study demonstrating similar to somewhat higher subjective effect ratings of 5.1 and 7.6 on a 10-point scale following 90-min infusions of 0.6 and 1 mg/min, which resulted in DMT plasma concentrations of 24 and 39 ng/mL, respectively [19]. Furthermore, in the current study subjective effects peaked shortly following bolus administration, reaching intensities of 4/10 on the RTIS and 1.5/2.0 log mm+2 on VAS High, which can no longer be considered entirely sub-psychedelic. In contrast, during the infusion subjective effects were of lower intensity, averaging 2/10 on the RTIS and 1.2 log mm+2 on the VAS High. Therefore, to achieve a several hours long sustained sub-psychedelic state, an infusion-only regimen may be preferable to a bolus plus infusion approach. A slightly longer infusion period may facilitate effect optimisation in patients, while avoiding the risks of inducing unintended psychedelic effects with a loading dose.

DMT did not demonstrate effects indicative of CNS depression or sedation, as SPV and SRT remained unaffected. Nonetheless, it reduced psychomotor acuity and sustained attention for doses 2 and 3, as illustrated by increased body sway and reduced adaptive tracking performance, respectively. However, these CNS-depressant effects were limited, considering that they represent only 50%–60% of those previously demonstrated for the sedative-hypnotic GABA-A agonist lorazepam [44]. Increases in pupil iris ratio indicating mydriasis resulting from sympathetic nervous system activation were in line with elevated BP for dose 3, but serum cortisol and prolactin remained unaffected across dose levels. The absence of neuroendocrine activation is consistent with DMT exposures of 10 and 25 ng/mL, which have not caused significant neuroendocrine responses in previous studies [29]. Additionally, the occurrence of CNS effects, in the absence of neuroendocrine activation, indicates relatively higher central DMT exposures at relatively low plasma concentrations as a result of DMT's high lipophilicity [21]. Lastly, EEG gamma power was increased for dose 2, which was inconsistent and therefore probably spurious or confounded by muscular activity. Conversely, EEG alpha power suppression, which emerged for dose 3, has been shown to have a quantitative relationship with DMT plasma concentrations in recent studies [45].

BDNF remained unaffected across the investigated exposure range in the current study. Although BDNF plays a crucial role in neuroplasticity related to memory and learning [46], its potential as a peripheral pharmacological biomarker for central 5-HT2A agonism is impeded by several methodological issues. Most importantly, plasma BDNF probably predominantly comprises peripherally released ligand [46]; BDNF could be subject to circadian rhythmicity [47] and laboratory assays frequently

contend with poor reproducibility [48]. Moreover, recent studies have suggested that compounds with putative neuroplastic effects engage the BDNF tropomyosin receptor kinase B (TrkB)-receptor and not necessarily BDNF release induced by 5-HT2A interaction [49]. Therefore, relating human DMT plasma exposures in the current study to those associated with neuroplastic effects in preclinical experiments could indirectly support neuroplasticity in the absence of changes in peripheral BDNF. Since DMT plasma exposures have previously not been reported in in vivo studies, such an approach is impossible. Also, comparison of cerebrospinal fluid (CSF) DMT exposures between humans and preclinical species is equally untenable, as CSF DMT exposures have yet to be reported in any study. Alternatively, relating the doses in the current study to human equivalent dose (HED) [50] in preclinical studies is similarly problematic due to the differing administration regimens in rodent studies. Since these studies applied either 1 h femoral perfusions, repeated intraperitoneal bolus, or bolus followed by 24-h continuous infusions [24, 25], PK is not directly comparable to the 6-h IV infusion administered in the current study. Taken together, the absence of changes in plasma BDNF should not prematurely be interpreted as an apparent inability of DMT to induce neuroplastic changes below exposures of 36 ng/mL, as no unequivocal data currently support this. Future studies should therefore systematically explore peripheral and, where possible, CSF PK in both animals and humans, in an attempt to bridge the apparent gap in relating human exposures to in vivo experiments that confirm neuroplasticity.

Finally, a number of strengths and weaknesses deserve to be mentioned. The current study was performed in both psychedelic-experienced and inexperienced participants, creating a heterogeneous but representative clinical population, thereby providing a basis for extrapolation of findings to future patient populations. Validated subjective drug effect questionnaires and neurophysiological domains were repeatedly assessed, which guaranteed reliability and consistency of data, facilitating interstudy comparison with other 5-HT2A agonists. However, the study is limited by the relatively small sample size, which arguably limits definite conclusions being drawn. Finally, the study was conducted in a controlled research setting that required participants to interact with researchers and computerized assessments, while in previous studies participants were lying down with closed eyes. Since variations in setting are recognized to influence the psychedelic experience, it cannot be excluded that study-specific factors impacted the reported subjective effects in the current study.

In conclusion, the present study investigated the safety, PK, and PD of prolonged intravenous administration of DMT in healthy volunteers at doses predicted to result in exposures below the presumed putative peak psychedelic exposure threshold. DMT administered intravenously as a 30-s bolus followed by a 6-h infusion, reaching maximal exposures of approximately 36 ng/mL in healthy volunteers, was safe, with one notable exception regarding a subject who experienced anxiety for several months following DMT administration. The applied infusion scheme rapidly attained DMT steady-state exposures that remained below the putative psychedelic plasma concentration of approximately 25–35 ng/mL for the duration of the infusion and induced relevant EEG effects, consisting of alpha power suppression, in the presence of mild psychedelic effects and limited neurophysiological effects. Together, these results provide the basis for future proof-of-mechanism studies in patient populations. Nonetheless, the observed moderate PK variability necessitates the identification of potential sources of variability to support rational dose and infusion scheme selection. If this is insufficient to reduce PK variability, further individual control might be achieved with effect-based administration strategies like titration or clamping, but this would require additional investigations and PK/PD analyses.

Author Contributions

K.V.H., R.G.J.A.Z., C.S.B., N.S., C.S., J.M.A.G., and G.E.J. wrote the manuscript and designed the research; K.V.H., R.G.J.A.Z., and G.E.J. performed the research; K.V.H., G.E.J., M.E.O., M.B.L., and M.L.D.K. analyzed the data.

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Conflicts of Interest

C. S. Bryan and C. Stillwell are employees of Algernon Pharmaceuticals. All other authors declared no competing interests for this work.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.