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ARTICLE

N,N-dimethyltryptamine affects electroencephalography response in a concentration-dependent manner—A pharmacokinetic/pharmacodynamic analysis

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Abstract

N,N-dimethyltryptamine (DMT) is a psychedelic substance and is being used as a research tool in investigations of the neurobiology behind the human consciousness using different brain imaging techniques. The effects of psychedelics have commonly been studied using electroencephalography (EEG) and have been shown to produce suppression of alpha power and increase in signal diversity. However, the relationship between DMT exposure and its EEG effects has never been quantified. In this work, a population pharmacokinetic/pharmacodynamic analysis was performed investigating the relationship between DMT plasma concentrations and its EEG effects. Data were obtained from a clinical study where DMT was administered by intravenous bolus dose to 13 healthy subjects. The effects on alpha power, beta power, and Lempel-Ziv complexity were evaluated. DMT was shown to fully suppress alpha power. Beta power was only partially suppressed, whereas an increase in Lempel-Ziv complexity was observed. The relationship between plasma concentrations and effects were described using effect compartment models with sigmoidal maximum inhibitory response or maximum stimulatory response models. Values of the concentration needed to reach half of the maximum response ($EC_{50,e}$) were estimated at 71, 137, and 54 nM for alpha, beta, and Lempel-Ziv complexity, respectively. A large amount of between-subject variability was associated with both beta power and Lempel-Ziv complexity with coefficients of variability of 75% and 77% for the corresponding $EC_{50,e}$ values, respectively. Alpha power appeared to be the most robust response, with a between-subject variability in $EC_{50,e}$ of 29%. Having a deeper understanding of these processes might prove beneficial in choosing appropriate doses and response biomarkers in the future clinical development of DMT.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The effects of the psychedelic compound N,N-dimethyltryptamine (DMT) has previously been studied with electroencephalography (EEG). However, any relationship between DMT exposure and its effects on the EEG spectrum has not been investigated.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study aimed to answer whether there is a relationship between DMT exposure and its effects on alpha power, beta power, and signal diversity.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The results indicate that there is a quantitative relationship between DMT concentrations and the observed effects on the EEG spectrum. The most robust relationship appears to be that between DMT and suppression in alpha power.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The results of this study are a step forward in understanding how DMT affects the brain. This new knowledge might prove important in increasing the chances for choosing appropriate dose levels and end points in the future clinical development of DMT.

INTRODUCTION

N,N-dimethyltryptamine (DMT) is a naturally occurring, endogenous, psychedelic compound that can produce intense alterations in perceptual, cognitive, and affective functions when administered exogenously.[1] Together with psilocybin and lysergic acid diethylamide, DMT belongs to the classic serotonergic psychedelics, a group of compounds that has recently received increased attention as potential treatment options in psychiatric disorders such as depression and substance abuse.[2–5] DMT is not orally active when administered alone,[6] and most research on DMT has been performed via administration of ayahuasca, a plant tea where DMT is the main psychoactive ingredient. Ayahuasca also contains harmala alkaloids, which act as monoamine oxidase inhibitors, thereby preventing degradation of DMT before it reaches the systemic circulation.[7] Ayahuasca has been shown to reduce depression rates in patients with recurrent and treatment-resistant depression.[8,9]

With its distinct subjective effects, DMT is also a potent research tool in studying the underlying neurobiological mechanisms behind the human consciousness. Several studies using different brain imaging techniques have been performed with DMT/ayahuasca, as well as other classic psychedelics, to examine its effects on the brain. Specifically, electroencephalography (EEG) or magnetoencephalography (MEG) have been used repeatedly to investigate the effects on spontaneous electrophysiological activity. Classic psychedelics have been found to reliably decrease power in the alpha frequency band and increase signal diversity.[10–18] Some studies have reported correlations between the observed EEG/MEG effects and the nature of the subjective experience.[12–14] However, these results are somewhat inconsistent. Research indicates that, to some extent, there is a relationship between different frequency bands and cognitive states. For example, alpha power has been linked to semantic orientation and short-term memory retention[19] and beta power to cognitive control of sensorimotor activity.[19,20] However, the correlation between different frequency bands and neuropsychiatric disorders is less conclusive. Consequently, more research is needed to understand if a link exists between the observed effects of psychedelics on the EEG spectrum and its potential therapeutic benefits.

Furthermore, it is not clear whether a relationship between the level of drug exposure and the size of the effects exist. In 2015, Schenberg et al.[16] aimed to investigate this by a combination of EEG recordings and quantification of ayahuasca constituents in plasma. Moreover, Timmermann et al.[13] performed a direct analysis of the relationship between EEG measures and DMT plasma levels. However, these studies relied on either generalized or mixed linear effects models to demonstrate correlations

between the two variables without attempting to estimate any pharmacokinetic (PK)/pharmacodynamic (PD) parameters describing the relationship. Although this might be sufficient to identify a relationship between exposure and effect, there are more powerful and appropriate tools available.

A better understanding of any potential relationship between DMT concentrations and its effects on the EEG spectrum would be beneficial in strengthening our understanding of how these compounds affect the activity of the human brain. This is an important aspect in the clinical development of DMT as a potential therapeutic option, as research has shown that having a good understanding of the target mechanism is essential in assuring that the right response is measured and the right exposure is achieved to obtain that response.[21]

In this work, a population PKPD analysis was performed to investigate the relationship between DMT plasma concentrations and its longitudinal effects on alpha power, beta power, and signal diversity as measured with EEG. Data were obtained from a placebo-controlled pilot study where DMT was administered intravenously, which allows analysis of DMT effects without the interference from other ayahuasca components.[13]

METHODS

Clinical study

A placebo-controlled clinical study was performed at the National Institute of Health Research Imperial Clinical Research Facility using a single-blind, fixed-sequence design. A total of 13 healthy subjects (seven men, median age 33 years [range, 22–48 years]) received a placebo administration at their first visit and DMT during their second visit 1 week later. DMT was administered as an intravenous bolus dose, and each subject received one of the following four DMT fumarate doses: 7 mg ($n = 3$), 14 mg ($n = 4$), 18 mg ($n = 1$), or 20 mg ($n = 5$). Doses were gradually increased to find a dose that would produce the desired level of psychedelic intensity without causing unexpected adverse effects. Nine blood samples per subject and occasion were collected at staggered timepoints for PK analysis up to 60 min after administration. Plasma was harvested and stored at −80°C before being shipped to Gothenburg on dry ice for bioanalysis. DMT in plasma was quantified using a previously described method of liquid chromatography with tandem mass spectrometry.[22]

The study was conducted in accordance with the revised Declaration of Helsinki (2000), the International Conference on Harmonization Good Clinical Practices guidelines, and the UK National Health Service Research Governance Framework and was approved by the National Research Ethics (NRES) Committee London–Brent and the Health Research Authority. All subjects provided written informed consent to participate in the study. The study has been described in more detail elsewhere.[13]

EEG recordings

A 32-channel Brainproducts EEG system (EasycapMR 32) was used for EEG measurements at a sampling rate of 1000 Hz. A 0.1-Hz high-pass filter and a 450-Hz anti-aliasing filter were applied. EEG data were preprocessed using a Fieldtrip toolbox. Data were band-pass filtered at 1–45 Hz and were visually inspected. Data containing gross artifacts, as well as segments in which ratings of intensity were collected, were removed from further analysis. The data were divided into the following frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and low gamma (30–45 Hz). Spontaneous signal diversity was computed to obtain a score of Lempel-Ziv complexity (LZc). Data were summarized as mean values per minute for modeling purposes (see Timmermann et al.[13] for EEG analysis details). Data were averaged across channels for this analysis.

Modeling approach

Data from all frequency bands as well as the LZc scores were visually explored to examine its potential for population PKPD modeling. Data that were deemed to exhibit an apparent exposure–response relationship were analyzed using nonlinear mixed-effects modeling in NONMEM version 7.4.3 (ICON Development Solutions).[23] Models were fitted using the first-order conditional estimation with interaction method. Pirana version 3.0.0 and Perl-speaks-NONMEM version 5.2.6[24] were used for model automation and diagnostics. Packages mrgsolve and nonmem2R in R version 4.1.1 were used for simulations and model diagnostics, respectively.

The analysis was performed using a previously developed population PK model describing DMT plasma concentrations in the study analyzed.[25] The same plasma concentration data that were used to develop the original PK model were used as input in this work. Briefly, DMT disposition was described by a two-compartment model with first-order elimination from the central compartment. Between-subject variability (BSV) was incorporated on clearance. The final PK parameters are summarized in Table S1. This model was now extended to develop PKPD models describing the relationship

between DMT plasma concentration and EEG effects of DMT. This was done using a "population PK parameters and data" approach, where population PK parameters are fixed but individual PK parameters are estimated simultaneously with PD parameters.[26] BSV and between-occasion variability (BOV) for EEG effects were described by exponential random effects following a log-normal distribution with a mean of zero and a variance of ω^2. Where BSV or BOV appeared to not follow a log-normal distribution, a Box–Cox transformation was performed to evaluate skewedness of the distribution. Residual variability (RUV) was assessed as additive, proportional, or combined additive and proportional errors.

PKPD model development

After graphical exploration of the data, the effects of DMT on alpha power, beta power, and LZc score were evaluated using effect compartment models, assuming that the response is mediated through DMT levels in a compartment corresponding to a theoretical biophase. The change in concentration in the effect compartment over time (dC_e/dt) is described as follows:

$$\frac{dC_e}{dt} = k_{e0} * (C_p - C_e), \quad (1)$$

where, k_{e0} is the effect compartment equilibrium rate constant, C_p is the plasma concentration of DMT, and C_e represents the concentration in the effect compartment.

The drug effect on alpha and beta power was assessed using inhibitory maximum inhibitory response (I_{max}) or sigmoid I_{max} models as described by

$$\text{Response} = R_0 * \left(1 - \frac{I_{max} * C_e^{\gamma}}{IC_{50,e}^{\gamma} + C_e^{\gamma}}\right), \quad (2)$$

where R_0 is the baseline response, that is, the alpha or beta power in the absence of drug, I_{max} is the maximum decrease in alpha or beta power, $IC_{50,e}$ is the concentration of DMT in the effect compartment required to produce half of the maximum response, and γ is a slope factor describing the sigmoidicity of the relationship. The effect on LZc was assessed using a linear maximum stimulatory response (E_{max}) or sigmoid E_{max} models, with the latter described by

$$\text{Response} = R_0 * \left(1 + \frac{E_{max} * C_e^{\gamma}}{EC_{50,e}^{\gamma} + C_e^{\gamma}}\right), \quad (3)$$

where R_0 is the LZc score in the absence of drug, E_{max} is the maximum increase in LZc score, and $EC_{50,e}$ is the concentration of DMT in the effect compartment required to produce half of the maximum response with γ as defined previously.

The placebo data were included to obtain an improved estimate of the baseline response. BSV was evaluated on all PD parameters. BOV was evaluated on baseline response.

Model evaluation

Model discrimination between nested models was based on the objective function value (OFV) where a change in OFV of −3.84 was considered a significant model improvement at $p = 0.05$ under the assumption that ΔOFV is approximately χ^2 distributed. Model performance was also assessed by assessing plausibility of parameter estimates, parameter precision, goodness-of-fit plots, individual prediction plots, and visual predictive checks (VPCs). Sampling importance resampling (samples/resamples = 5000/1000) was performed to determine precision of the parameter estimates and to calculate 95% confidence intervals.[27] The covariance output was used as the proposal distribution without an inflation factor. Parameter precision was considered acceptable if relative standard error was ≤30% for fixed effects and ≤50% for BSV parameters.

Simulations

Simulations were performed using the final models to evaluate the expected effects at five different dose levels (1, 4, 7, 14, and 20 mg) in 100 subjects. Dose levels were set to demonstrate a range of doses that would likely cause nonexistent (1 mg) to significant (20 mg) psychedelic experiences. Simulations were performed with BSV.

RESULTS

A total number of 238 observations after placebo administration and 252 observations after DMT administration (84, 63, 21, and 84 observations for the 7, 14, 18, and 20 mg doses, respectively) from 12 participants were recorded for alpha, beta, delta, and theta power and LZc score. In addition, the PK model was based on a total of 93 (19, 29, 6, and 39 for the 7, 14, 18, and 20 mg doses, respectively) DMT plasma concentration observations from 13 participants. EEG recordings were excluded from one of the participants who received a dose of 20 mg because of excessive movement artifacts after DMT administration.

After visual inspection, only the effects of DMT on alpha power, beta power, and LZc score were deemed appropriate for population PKPD modeling. No apparent placebo effect was observed in any of the cases. No apparent trend for a dose–response relationship was observed for delta or theta power. These data are shown in Figure 1.

The relationship between DMT concentrations and the observed effects were described using effect compartment models for all three response measurements to account for a delay in response compared with DMT concentrations. K_{e0} values were estimated between 0.59 and 1.2 min^{-1} for the different responses, indicating a short delay in response.

The effect of DMT on alpha power was described using a sigmoidal I_{max} response. Here, I_{max} was fixed to one in the final model because values close to one were

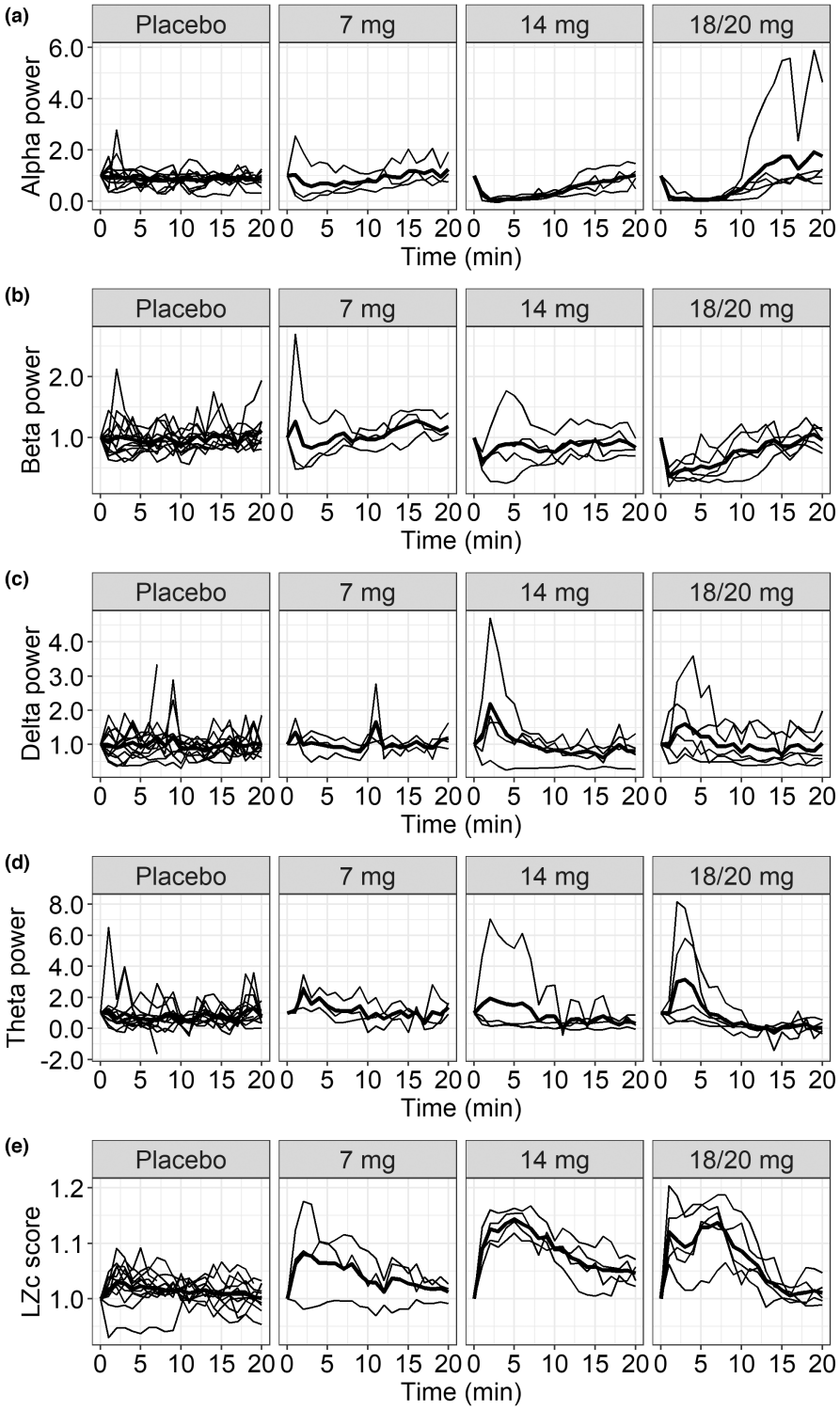

FIGURE 1 Observed effects as relative change from baseline in alpha power (a), beta power (b), delta power (c), theta power (d), and LZc (e) over time after intravenous bolus dose administration of placebo or DMT fumarate at four different dose levels in a total of 12 healthy subjects. Thick lines represent the average response at each timepoint. LZc, Lempel-Ziv complexity.

obtained when estimated. BSV was included on R_0 and $IC_{50,e}$. A Box–Cox transformation of the BSV for baseline response was included, showing that the distribution was negatively skewed. Inclusion of the Box–Cox transformation improved the precision of the estimated baseline response. BOV was incorporated on baseline and led to a significant improvement in model fit (ΔOFV = −168). RUV was described by a proportional error model. Model parameters for alpha power are summarized in Table 1.

The effect of DMT on beta power was also described using a sigmoidal I_{max} response. BSV was incorporated on R_0 and $IC_{50,e}$, and BOV was estimated for R_0. BSV on additional parameters could not be estimated with acceptable precision. A correlation was observed between BSV in R_0 and $IC_{50,e}$, and an omega block was incorporated to estimate the covariance between the two. RUV was described by a proportional error. Using a combined proportional and additive error model led to a significant improvement in model fit (ΔOFV = −21). However, the additive error was small and led to poor precision in several parameter estimates and was therefore not used in the final model. Model parameters for beta power are summarized in Table 2.

The relationship between DMT plasma concentration and LZc score was best described using a sigmoidal E_{max} response. The inclusion of a Hill coefficient (γ) significantly improved model fit (ΔOFV = −100). BSV was estimated for R_0, $EC_{50,e}$ and E_{max}. BOV was included on baseline and led to a significant improvement in model fit even though the estimated variability was small. A correlation was observed between the BSV for R_0 and E_{max} (92%). However, this was not estimated in the final model as it led to poor precision and ill conditioning of the model (condition number = 9603). RUV was described by an additive error. Model parameters for LZc score are summarized in Table 3.

The fit of the final models to the observed data are illustrated by VPCs in Figure 2 as well as through individual goodness-of-fit plots in Figure 3. The model code is provided in Appendix S1.

The results of the simulations using the final models are depicted as the expected effect over time (Figure 4) and the relationships between the observed effects and plasma concentration as well as effect compartment concentration (Figure 5).

TABLE 1 Final PKPD parameters describing the relationship between DMT plasma concentration and alpha power.

Parameter	Estimate (95% CI)	%RSE
R_0	0.83 (0.71; 0.94)	9
I_{max}	1 FIX	
$IC_{50,e}$ (nM)	71 (58; 84)	12
K_{e0} (min^{-1})	0.59 (0.51; 0.70)	10
γ	3.7 (3.0; 4.5)	12
Box–Cox shape parameter for random effects of baseline response	−0.35 (−0.54; −0.14)	35
BSV R_0 (%CV)	125 (94; 154)	30
BSV $IC_{50,e}$ (%CV)	29 (21; 37)	33
BOV R_0 (%CV)	32 (23; 46)	48
Proportional error (%CV)	40 (36; 44)	11

Abbreviations: γ, Hill coefficient describing the steepness of the relationship; BOV, between-occasion variability; BSV, between-subject variability; CI, confidence interval; CV, coefficient of variation; DMT, N,N-dimethyltryptamine; $IC_{50,e}$, concentration needed to reach half of the maximum response; I_{max}, maximum inhibitory response; K_{e0}, effect compartment equilibrium rate constant; PKPD, pharmacokinetic/pharmacodynamic; R_0, baseline alpha power; RSE, relative standard error.

TABLE 2 Final PKPD parameters describing the relationship between DMT plasma concentration and beta power.

Parameter	Estimate (95% CI)	%RSE
R_0	0.064 (0.052; 0.079)	13
I_{max}	0.70 (0.66; 0.72)	2.4
$IC_{50,e}$ (nM)	137 (104; 186)	18
K_{e0} (min^{-1})	1.2 (0.95; 1.7)	19
γ	5.2 (4.1; 6.7)	15
BSV R_0 (%CV)	63 (50; 85)	36
BSV $IC_{50,e}$ (%CV)	75 (56; 96)	34
Correlation BSV on R_0 and $IC_{50,e}$ (%)	−46 (−57; −33)	32
BOV R_0 (%CV)	21 (15; 27)	33
Proportional error (%CV)	18 (17; 19)	4.3

Abbreviations: γ, Hill coefficient describing the steepness of the relationship; BOV, between-occasion variability; BSV, between-subject variability; CI, confidence interval; CV, coefficient of variation; DMT, N,N-dimethyltryptamine; $IC_{50,e}$, concentration needed to reach half of the maximum response; I_{max}, maximum inhibitory response; K_{e0}, effect compartment equilibrium rate constant; PKPD, pharmacokinetic/pharmacodynamic; R_0, baseline beta power; RSE, relative standard error.

DISCUSSION

The effects of serotonergic psychedelics have been extensively studied using EEG in healthy human subjects. These studies have shown the most robust effects of psychedelics on EEG response to be suppression of alpha power and increase in signal diversity.[10–18] However, the relationship between drug exposure and the observed effects have not been fully evaluated. In this work, data from a previously published study were used to investigate any such relationship. A dataset including observed alpha,

TABLE 3 Final PKPD parameters describing the relationship between DMT plasma concentrations and Lempel-Ziv complexity score.

Parameter	Estimate (95% CI)	%RSE
R_0	0.321 (0.315; 0.332)	1.6
E_{max}	0.10 (0.091; 0.11)	4.8
$EC_{50,e}$ (nM)	54 (38; 72)	19
K_{e0} (min^{-1})	0.76 (0.65; 0.96)	12
γ	4.8 (3.9; 5.9)	13
BSV R_0 (%CV)	5.2 (3.9; 7.7)	53
BSV $EC_{50,e}$ (%CV)	77 (56; 110)	46
BSV E_{max} (%CV)	42 (31; 56)	38
BOV R_0 (%CV)	1.7 (1.3; 2.3)	39
Additive error (SD)	0.0061 (0.0058; 0.0066)	4.1

Abbreviations: γ, Hill coefficient describing the steepness of the relationship; BOV, between-occasion variability; BSV, between-subject variability; CI, confidence interval; CV, coefficient of variation; DMT, N,N-dimethyltryptamine; $EC_{50,e}$, concentration needed to reach half of the maximum response; E_{max}, maximum stimulatory response; K_{e0}, effect compartment equilibrium rate constant; PKPD, pharmacokinetic/pharmacodynamic; R_0, baseline Lempel-Ziv complexity score; RSE, relative standard error.

beta, delta, and theta power as well as LZc score after DMT and placebo administration was explored to evaluate any indications of an existing exposure–response relationship and appropriateness of each measurement for further, more detailed evaluation using population modeling. It was concluded that only alpha power, beta power, and LZc score showed a clear enough indication of such a relationship to make them suitable for further evaluation. As has been previously established,[13] effects in delta and theta power were also observed. However, no clear exposure–response relationship was observed in these data. Because the effects of DMT on the EEG spectrum is still at an exploratory stage,[13] we cannot say whether this was attributed to the small sample size or if there is indeed no such relationship. Consequently, with the limited number of participants and the seemingly small and variable response, it was concluded that more data would be needed to be able to draw any valuable conclusions in terms of potential PKPD relationships.

Hence, this study focused on the relationships between DMT plasma concentrations and its effects on alpha power, beta power, and LZc score. The PK model has been previously described elsewhere.[25] In this work, it was extended to include the aforementioned PD end points. A small delay in response compared with DMT plasma concentrations was observed. This was described by effect compartment models, which accounts for this delay by assuming that the drug needs to be distributed into an effect compartment before any response is generated. Effect compartment models were chosen over indirect response models to describe the data due to the nature of the response. EEG measures electrical signals in the brain that occur close to instantly as a response to a stimulus. The short delay observed in the effects is therefore more likely to be the consequence of a delay in distribution to the biophase. The obtained k_{e0} values of 0.59–1.2 min^{-1} are indicative of the short delay observed in this study. Furthermore, indirect response models may cause a shift in the time to maximum response across difference dose levels. No such shift was observed in these data. Indirect response models were indeed investigated for alpha power early in the modeling process but resulted in problems with minimization and poor estimate precision. However, the study is limited by the small sample size, and with more data it is possible that a shift in time to peak effect will become evident. It should also be pointed out that, in this study, EEG response was averaged in windows of 1 min. Slightly different k_{e0} values might be obtained if higher resolution data are applied.

DMT was shown to be capable of fully suppressing alpha power. This relationship was described by a sigmoidal I_{max} model, where I_{max} was fixed to 1 in the final model. An $IC_{50,e}$ value of 71 nM was estimated with a BSV of 29% coefficient of variation (CV). Baseline response in alpha power was shown to vary substantially both between individuals (125% CV) and occasions (32% CV). In addition, a large proportion of the participants receiving the highest dose also had a higher baseline response. However, the results of this work indicate that there is a clear relationship between DMT plasma concentrations and alpha power. As can be seen in Figures 4 and 5, according to the final model, doses above 10 mg are needed to achieve full suppression of alpha power.

The observed suppression in beta power was also described by a sigmoid I_{max} model. However, full suppression was not achieved with an I_{max} estimated at 0.7. Although an $IC_{50,e}$ value of 137 nM was estimated, a large variability was associated, and therefore the results should be interpreted with caution. As can be seen in Figure 1, only the highest dose was associated with a clear effect in beta power. The data also indicate that I_{max} has not been reached in this study, making it difficult to get reliable parameter estimates. More data, preferably including higher dose levels, are needed to get a better understanding of this relationship. In addition, a correlation between baseline values (R_0) and $IC_{50,e}$ was observed, where higher baseline values were associated with lower $IC_{50,e}$ values. Whether there is a physiological explanation for this or if it is a random artifact of the data cannot be concluded with the data available. However, it does not seem unreasonable that less drug may be needed to lower the power by 50% if the baseline value is higher to begin with.

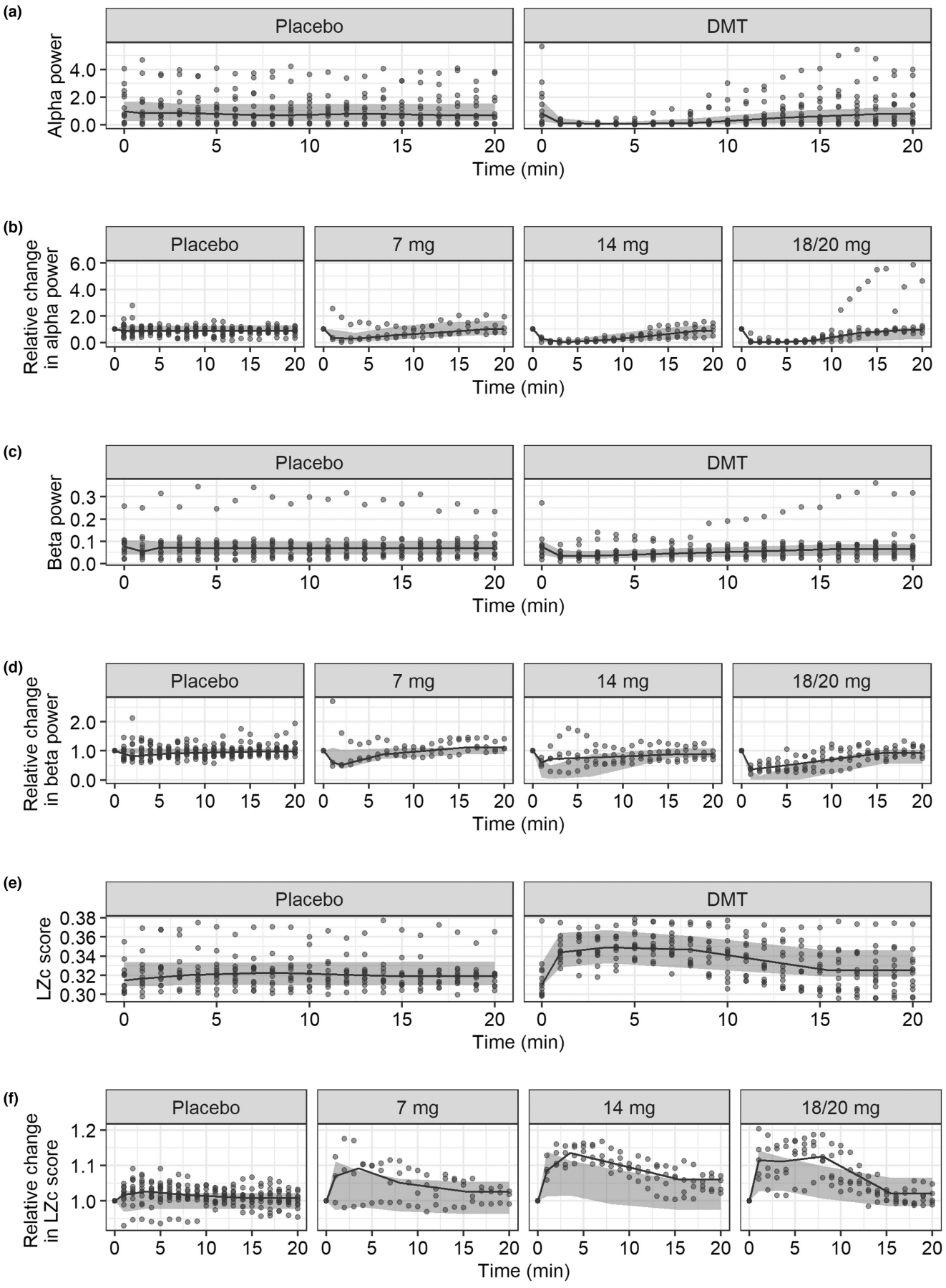
(a)
Placebo
DMT
Alpha power
Time (min)
(b)
Placebo
7 mg
14 mg
18/20 mg
Relative change in alpha power
Time (min)
(c)
Placebo
DMT
Beta power
Time (min)
(d)
Placebo
7 mg
14 mg
18/20 mg
Relative change in beta power
Time (min)
(e)
Placebo
DMT
LZc score
Time (min)
(f)
Placebo
7 mg
14 mg
18/20 mg
Relative change in LZc score
Time (min)

FIGURE 2 Visual predictive checks of the final models describing the (a) alpha power after intravenous bolus doses of placebo or DMT, (b) relative change in alpha power stratified by dose, (c) beta power after intravenous bolus doses of placebo or DMT, (d) relative change in beta power stratified by dose, (e) LZc score after intravenous bolus doses of placebo or DMT, and (f) relative change in LZc score stratified by dose in 12 healthy participants. Circles are observations, solid lines are medians of the observations, and gray areas are the 95% confidence intervals of the median of the simulated data. DMT, N,N-dimethyltryptamine; LZc, Lempel-Ziv complexity.

DMT produced an increase in signal diversity as measured by LZc score with a maximum relative increase of 10% compared with baseline and an $EC_{50,e}$ of 54 nM, with BSVs estimated at 77%, 42%, and 5.2% CVs for $EC_{50,e}$, E_{max}, and R_0, respectively. However, we cannot be certain that the true maximum response was achieved in this study. To confirm this, higher doses than what was administered in this study would need to be investigated.

As can be seen from the simulations, all three measurements of DMT effect are predicted to increase with increasing doses. The strongest relationship seems to be that between DMT concentrations and the decrease in alpha power, as it was associated with the least amount of variability between individuals. This strengthens the idea that suppression of alpha power is one of the most robust responses of DMT. The observed effect in LZc score is associated with some variability; however, it should be pointed out that the estimated parameter values describing the effects in LZc score are similar to those describing alpha power. Hence, the effects in LZc score will likely follow the effects in alpha power in a large part of the population. A large amount of variability was associated with the observations in beta power, making it close to impossible to predict what effect to expect on an individual level. This indicates that beta power might not be useful as an end point for measuring DMT effects. It should also be pointed out that the estimated Hill coefficients associated with all three models are high (about 4–5), implying that a small increase in concentration could lead to a substantial increase in effect, especially at the mid ranges of the observed effects.

To the best of our knowledge, this is the first time any relationship between the exposure of a psychedelic compound and its effects on EEG response has been analyzed using a population PKPD approach. Although there are limitations to this study, mainly in terms of the size of the population, the data indicate that there is a relationship between DMT concentrations and the observed suppression of alpha power and increase in signal diversity. It should be noted that a large variability was observed between individuals in this study. Due to the small sample size, no potential covariate effects were explored to explain this variability. This is something that could be evaluated in the future. In particular, large fluctuations in baseline values were observed. Baseline values were obtained during 1 min before DMT administration. It is possible that less variability might be observed if the baseline had been observed for a longer period of time. Furthermore, the accuracy of the PKPD model is impacted by the performance of the PK model. With the limited PK data available, no variability in volume distribution could be estimated. On an individual level, this means that the initial concentrations might in some case be over- or underpredicted. With the short delay in effect, this could affect the estimated $EC_{50,e}$ values for these individuals, leading to an inflated variability in $EC_{50,e}$. However, on a population level, we believe this to have only a minor impact.

Classic psychedelics have shown potential as treatment options in disorders with depressive symptomatology. However, clinical efficacy in terms of reduction of depression score cannot be reliably evaluated until a certain time has passed and also has the disadvantage of being a subjective measure. Hence, a biomarker that could aid in guiding dose levels would be beneficial in a clinical trial setting. Interestingly, increased alpha power has been observed in populations suffering from depression.[28] In addition, associations between signal diversity and depression have been observed, although it appears that signal diversity is increased in patients suffering from depression.[29,30] However, an acute increase of signal diversity in combination with alpha power suppression may be indicative of improved mental health subacute outcomes.[31,32] Nevertheless, the fact that these markers have shown potential in the diagnosis of depression indicates that the effects of DMT on the EEG/MEG spectrum may also be useful in understanding its potential therapeutic effects. If the EEG responses observed in this study are indeed connected to the therapeutic outcome, the results of this analysis indicate that they might be able to serve as useful clinical biomarkers in guiding therapeutic dose levels. Furthermore, it has been suggested that DMT does not produce tolerance in humans.[33] This opens the possibility for DMT to be administered as a continuous infusion, which could potentially be modulated according to the online response of biological markers. Our results may provide significant insights on which biological markers to use in this context, with alpha power proving to be a powerful measure to guide such an application. However, it is clear, both from this study and from the varying results in clinical studies with psychedelic compounds, that a better understanding of the exposure–response relationships as well as the relationship between immediate effects and

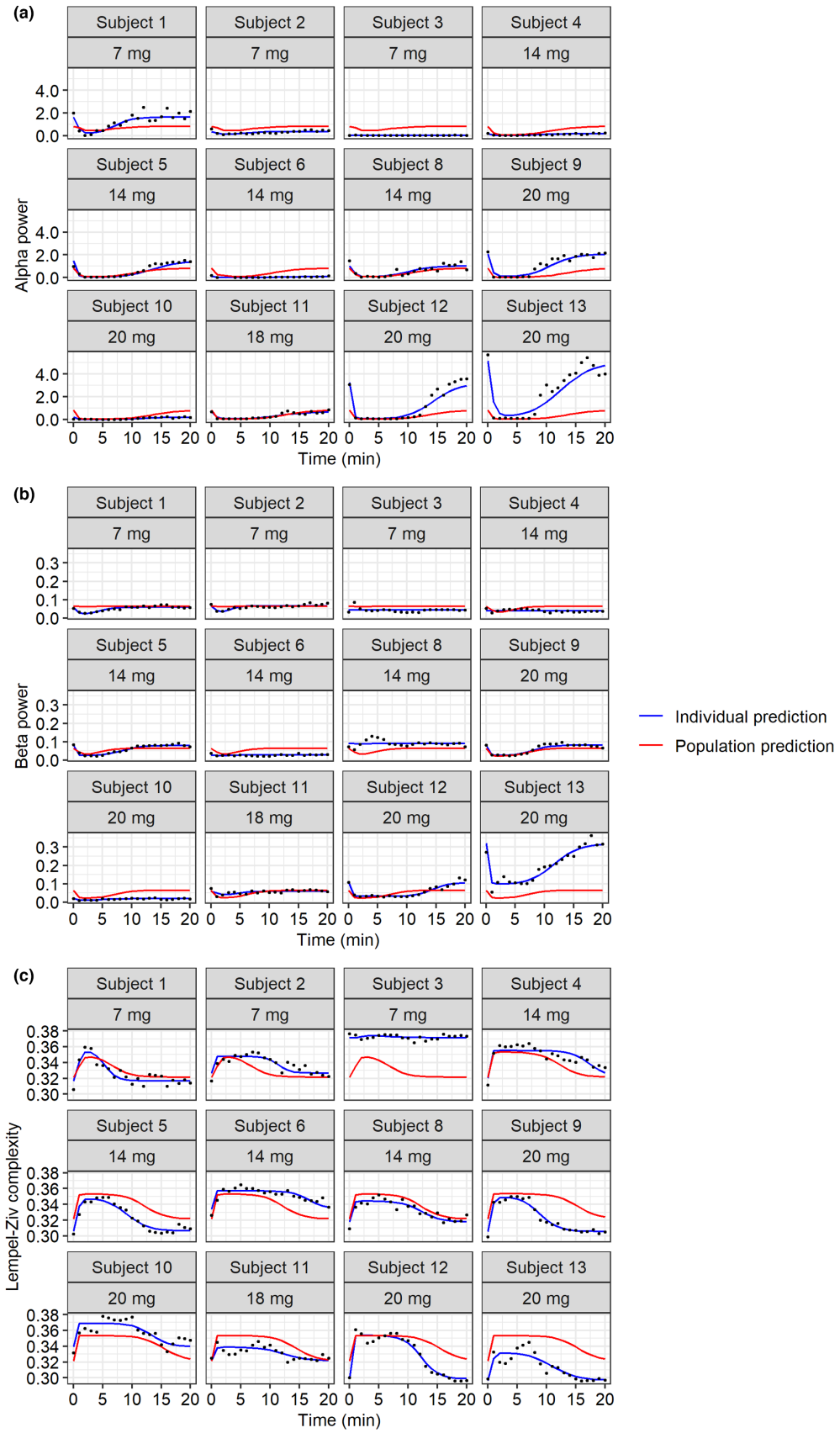

FIGURE 3 Plots illustrating the fit of the typical and individual predictions of alpha power (a), beta power (b), and Lempel-Ziv complexity score (c) across each individual. Circles represent the observed data, red lines are the typical predictions in the population, and blue lines are the individual predictions.

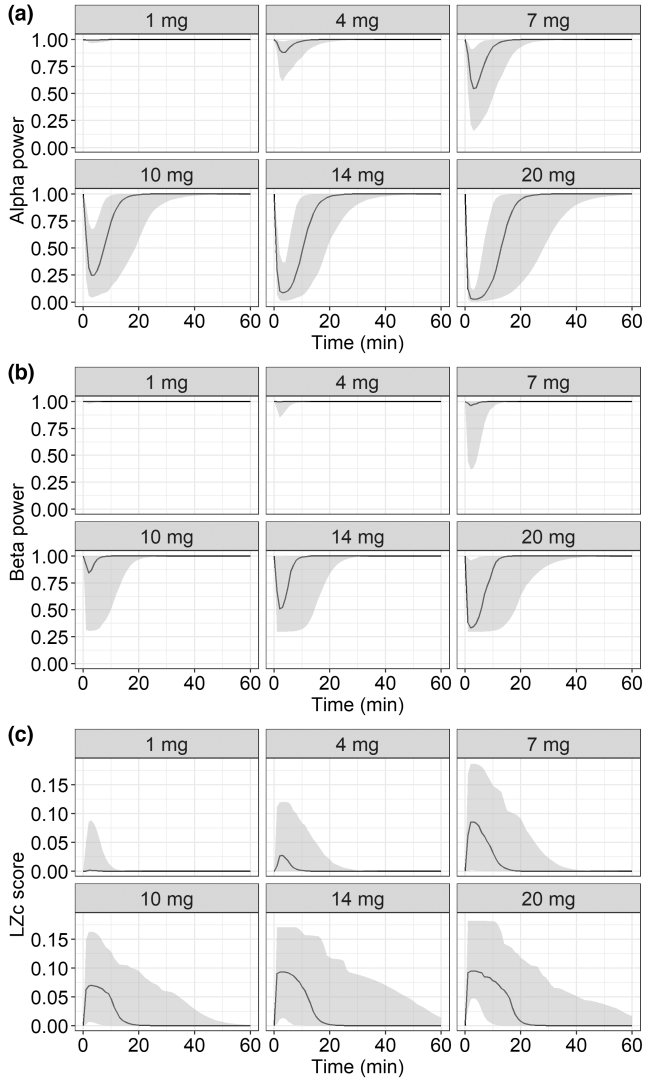

FIGURE 4 Simulations of relative decrease in alpha power (a), relative decrease in beta power (b), and relative increase in LZc score (c) over time after intravenous bolus administration of DMT fumarate at six different dose levels (1, 4, 7, 10, 14, and 20 mg) in 100 individuals. The effects are expressed as relative change compared with baseline. The solid line is the median prediction and the shaded area is the 90% prediction interval. LZc, Lempel-Ziv complexity.

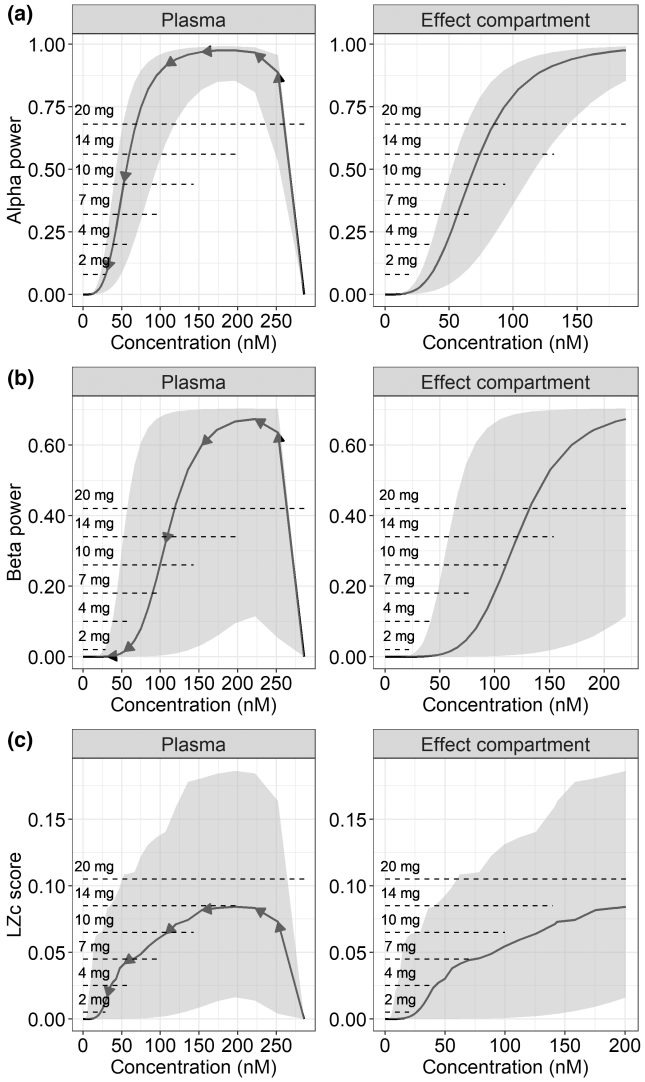

FIGURE 5 Simulated relationship between effect and plasma concentration (left) and effect compartment concentration (right) after intravenous bolus administration of a 20-mg DMT fumarate dose in 100 individuals. The effects are illustrated as relative change in alpha power (a), beta power (b), or LZc score (c) compared with baseline. The solid line is the median prediction, and the shaded area is the 90% prediction interval. The horizontal lines indicate the typical predicted concentration range associated with each respective dose level. Hysteresis in the relationship between effect and plasma concentration is indicated by the arrows showing the direction of effect/concentration over time.

therapeutic outcome would be beneficial in ensuring optimal dose regimens in future clinical studies.

In conclusion, this study applied nonlinear mixed-effects modeling to describe the relationship between DMT plasma concentrations and its effects on alpha power, beta power, and LZc score. The results indicate that there is a systemic concentration–response relationship between DMT and these effect measures. The most robust relationship seems to exist between DMT concentrations and a decrease in alpha power. This study adds new information to the current understanding of how DMT affects the brain. An understanding that is essential in the future clinical development of DMT. However, more research is needed to confirm these results and investigate whether these measurements can be useful in predicting any clinically relevant outcome.

AUTHOR CONTRIBUTIONS

E.E., C.T., R.C.-H., D.R., and M.A. wrote the manuscript. E.E., C.T., R.C.-H., and M.A. designed the research. E.E., C.T., R.C.-H., and M.A. performed the research. E.E., C.T., R.C.-H., D.R., and M.A. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

C.T. provides consultation work for Entheon Biomedical. R.C.-H. is an advisor for Entheon Biomedical and has previously been an advisor for Small Pharma. 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 at the end of this article.

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