

Electroencephalographic and Convulsive Effects of Binge Doses of (+)-Methamphetamine, 5-methoxydiisopropyltryptamine, and (±)-3,4-Methylenedioxymethamphetamine in Rats

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Abstract: The abuse of drugs such as methamphetamine (MA), 3,4-methylenedioxymethamphetamine (Ecstasy, MDMA), and 5-methoxydiisopropyltryptamine (5-MeO-DIPT; Foxy) is global. Symptoms from taking these drugs include tachycardia, agitation, hyperpyrexia, and sometimes seizures. We compared the EEG effects of these drugs in male Sprague-Dawley rats (~300 g) implanted with cortical electroencephalographic (EEG) electrodes prior to testing. Animals received four subcutaneous injections of MA, MDMA, or Foxy (10 mg/kg each as freebase, administered every 2 h), or saline as these doses produce lasting effects on learning, memory, and monoamines. EEG tracings were recorded before, during, and after treatment. Animals receiving MDMA showed no significant EEG abnormalities or myoclonus. MA treatment resulted in myoclonic activity and in brief (<10 s) EEG epileptiform activity in ~50% of the rats. Longer seizure activity (10 s to 5 min) was recorded in some MA-treated rats following the third and fourth doses. The onset of myoclonic activity following Foxy treatment occurred shortly after the first dose. All rats receiving Foxy showed seizures by the second dose and this continued throughout the treatment regimen. EEG abnormalities are observed after MA but not after MDMA binge dosing, which mimic the neurochemical changes seen in chronic users. While the neurochemical effects of Foxy are not known in humans, this drug causes severe EEG abnormalities and overt seizures in 100% of animals tested.

Keywords: Electroencephalographic activity, Foxy, MDMA, Methamphetamine, myoclonus.

INTRODUCTION

Among the symptoms associated with illicit drug use are seizures and/or abnormal electroencephalograms (EEG) [1-6] after use of methamphetamine (MA) and 3,4-methylenedioxymethamphetamine (MDMA). Studies have shown that abstinent MA users exhibit abnormal EEGs as well as higher power delta and theta wave (slow wave) activity [7] with psychomotor slowing. The increased theta quantitative EEG power was correlated with decreased reaction times in complex tasks and diminished accuracy on the N-back working memory task [8]. Others have shown that increased theta power (slow wave) in abstinent MA users is correlated with deficits in performance on verbal and

nonverbal learning and memory tests [9] and other symptoms (hypertension, elevated heart and respiratory rates, and hallucinations) [1, 10]. While MA-induced seizures are typically transient, there are cases showing status epilepticus [1]. High doses of MA and amphetamine elicit status epilepticus and myoclonus in mice [11] and rats [12]. In mice, seizure onset following intraventricular MA treatment is prolonged and MA-induced seizures are treatment-resistant [13].

MDMA use results in decreased EEG synchrony (coherence) [14-16]. Increases in alpha and beta power among MDMA users are also seen [14]. Increases in alpha waves are inversely correlated with mental activity [17, 18], while elevated beta wave activity is associated with depression [19] and stress/anxiety [20]. Abnormal EEGs following MDMA use have been reported [6, 21], including seizures [22-24]. While many of the cases suggest that drug-induced seizures are transient [1, 25], they are associated with long-term neurocognitive abnormalities [8, 26]. Fornai and colleagues found that exposing mice to MDMA resulted in EEG slowing [27, 28], increased susceptibility to seizure onset following kainic acid [28], and latent limbic hyperexcitability ([28]; however, see [27]). There was no evidence of spontaneous seizures resulting from MDMA.

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While abnormal EEG activity and seizures are known to occur following MA and MDMA abuse in humans, little is known about seizure risk from 5-methoxy-n,n-diisopropyltryptamine (Foxy). Foxy is a newer club drug with hallucinogenic properties. There are reports of users having seizures [29, 30], but it is not clear if these are attributable to interactions with other factors. We found that approximately half of Foxy-treated animals displayed seizure-like behavior [31]. The purpose of the present experiment was to compare the EEG profile of these three psychostimulants using a dose we have used in previous experiments that induced long-term learning and memory deficits and/or neurochemical changes. Specifically, the dose of MA has been shown to induce monoamine deficits [32-43], elevated glial fibrillary acidic protein [44, 45], and deficits in learning and memory [46, 47]. Using interspecies scaling [48], a 10 mg/kg administration of MA in rats is equivalent to that used by a MA user taking approximately 1 mg/kg [49], which is within the range of what drug users are known to take [50]. This same dose of MDMA has been shown to be both well-tolerated in rodents as well as causing reductions and other alterations in the serotonergic system [51-54], elevated anxiety [54, 55], changes in locomotor activity [54, 56, 57], and deficits in learning [56, 58] and memory [56]. Few studies have investigated the effects of Foxy. We have shown that a single dose of 20 mg/kg induces alterations in glucose and an elevated stress response during development and adulthood [59], while multiple doses of 10 or 20 mg/kg elicits elevated corticosterone and spatial learning deficits in adults [31]. In other studies where Foxy is administered to adolescent rats (P35-48, 6 × 5-20 mg/kg/48 h), spatial learning and serotonergic deficits were demonstrated [60, 61]. Furthermore, daily doses (4 × 10 mg/kg/2 h) during development results in long-term deficits in learning and increased anxiety [62]. We hypothesized that all three drugs would induce EEG abnormalities similar to those described in humans.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley CD (IGS) rats (225-250 g, Charles River Laboratories, Raleigh, NC) were habituated for at least 1 week and doubly housed in a vivarium controlled for temperature ($19 \pm 1^\circ\text{C}$) and humidity ($50\% \pm 10\%$). Animals were maintained on a 14 h light: 10 h dark cycle, and food and water were available *ad libitum*. Temperature transponders were implanted 3 days prior to surgery. All animal procedures were approved by the Institutional Animal Care and Use Committee of Cincinnati Children's Research Foundation.

Surgical Procedures

All procedures were performed under sterile conditions using isoflurane anesthesia (IsoThesia; Butler Animal Health Supply, Dublin OH). Rats were initially anesthetized by placing them in an airtight chamber and isoflurane (4-5%) vapor was infused into the chamber until the animal was unresponsive. The rat was then removed and anesthesia maintained using a gas anesthesia mask adaptor (Harvard Apparatus, Holliston, MA) connected to a Datex Ohmeda

Excel 210 SE (Soma Technology, Inc., Bloomfield, CT) for continuous flow of isoflurane (2-2.5%) for a duration of less than 1 h. Depth of anesthesia was assured by the absence of corneal and pedal reflexes. An insulated wire electrode (0.125 mm diameter) was implanted stereotaxically into the left posterior hippocampus (-3.6 mm AP, 4.9 mm; lateral, -5.0 mm deep with incisor bar at + 5.0) as described previously [63], with three additional screw electrodes implanted into the parietal cortex and two in the frontal cortex to serve as cortical, ground, and reference electrodes. Surgical adhesive and dental cement secured the electrodes in place and were used to stabilize the electrode housing unit implanted on top of the head. All animals received an injection of the analgesic Buprenex during recovery. The hippocampal electrode was a polyimide-insulated stainless steel wire (0.2 mm diameter, cut to 2 cm length (Plastics One Inc., Roanoke, VA)) and the end inserted into the brain was sanded to expose the wire, while the cortical electrodes were Teflon-coated stainless steel electrodes without sockets [20 mm length electrode with a screw size of 0-80 × 1/8, 3.2 mm length (Plastics One)]. All electrodes were soldered to a tinned brass Molex connector (Jameco Electronics, Belmont, CA), and conductance was tested prior to the experiment using a multimeter. Electrodes with the connectors were inserted following implantation into a 4-position Molex female connector housing unit (Jameco Electronics).

EEG Recordings and Drug Administration

The following day, animals were briefly exposed to isoflurane (2.5%) in order to attach the electrodes to the EEG machine (see below) using commercially available cables (Plastics One). Animals were placed in plastic bins (28 cm × 18 cm × 37 cm) such that the recording device could be secured above them. The rats were allowed to move freely throughout the recording phase. EEG was recorded in awake and unrestrained rats for 475 min. A 30 min baseline EEG was recorded from each rat prior to drug injection, and recordings continued for ~2 h after the final injection. Foxy, MA, or MDMA (4 × 10 mg/kg/2 h interval), or an equivalent volume of saline (SAL), was administered (s.c.) after the initial baseline reading (N = 4-8/treatment group).

Seizures were defined as a sudden onset of high amplitude (> 2x background) synchronized activity with signal progression (a change in amplitude and frequency over the course of the event) and a duration greater than 10 s. Myoclonic activity was identified by visual observation of an isolated brief sudden jerk of the body which was accompanied by a polyspike and wave discharge on the EEG.

Temperatures were taken every 30 min to monitor hyperthermia. No animals had body temperatures over 40°C at any time point. EEG data were recorded and saved digitally using a commercially available 32-channel EEG machine and Easy EEG II software V. 1.5 (Cadwell Laboratories, Kennewick, WA) and later analyzed with filters at 1 Hz and 70 Hz; 7 - 15 μV per mm. Up to three animals were injected sequentially and EEG recorded simultaneously and continuously. After each recording session, the entire EEG record was inspected for interictal epileptiform activity seizures by a clinically-qualified

electroencephalographer (KDH) blinded to treatment group. The EEG recordings were scored every 5 min as follows: 0 = normal; 1 = isolated interictal epileptiform discharges; 2 = rhythmic bursts of epileptiform discharge lasting < 10 s; 3 = electrographic seizures (between 10 s and 5 min in duration); 4 = continuous electrographic seizures (> 5 min) or discrete electrographic seizures separated by continuous paroxysmal epileptiform discharges; 5 = status epilepticus and death. Only intervals that were available or clear and decipherable (i.e., did not have high background, missing data due to a briefly disconnected cable, etc.) were included in the analysis. Representative EEGs of the seizures observed are shown in Fig. (1). The presence of myoclonic activity was recorded, and this activity could co-occur with EEG epileptiform activity.

Statistical Analysis

Data were analyzed using SAS Software (SAS Institute, v9.2, Cary, NC). One-way analysis of variance (ANOVA) using Proc Mixed procedure was utilized for the latency to first seizure. In cases where no seizure activity occurred, a maximum latency of 475 min was assigned. Fisher's test for uncorrelated proportions was used to determine the frequency of seizure types (i.e., the number of incidences of each seizure type/number of analyzed time intervals per treatment). Significance was set at $p \leq 0.05$, and data are presented as means \pm SEM.

RESULTS

Proportion of Animals Affected

The number of animals exhibiting EEG abnormalities or

myoclonic seizures were as follows: 0/4 SAL (0%); 1/7 MDMA (14.3%), 3/8 MA (37.5%), and 9/9 Foxy (100%).

Frequency of Seizure Activity

The frequency of each seizure type was calculated for each subject by determining the number of incidences of each type over the total number of intervals (Table 1). SAL- and MDMA-treated rats did not exhibit evidence of myoclonus, while MA had significantly greater occurrences of myoclonus than SAL or MDMA (Table 1). Foxy resulted in the greatest number of incidences of myoclonus, significantly greater than all other treatments. Both Foxy and MA treatments resulted in significantly more occurrences of Type 1 (isolated spikes), 2 (epileptiform discharges < 10 s), 3 (seizures between 10 s-5 min), and 4 (continuous seizures > 5 min) seizures than MDMA or SAL. Although MDMA administration resulted in a single Type 3 seizure, this did not result in a significant change in frequency relative to SAL treatment.

Latency to First Seizure Event

There was a significant main effect of Treatment for latency to first myoclonic event ($F(3,24)=3.01$, $p \leq 0.05$), such that Foxy-treated rats exhibited evidence of myoclonus whereas no evidence of myoclonus was noted for SAL- or MDMA-treated rats, (Fig. 2a). There was a trend ($p < 0.10$) for latency to be significant between MA and MDMA as well since some MA-treated animals showed a myoclonic episode. In terms of non-myoclonic seizure activity, there was a Treatment main effect [$F(3,24)=23.85$, $p < 0.0001$], (Fig. 2b). Foxy-treated rats developed epileptiform activity significantly sooner than MA-, or MDMA-treated rats, and

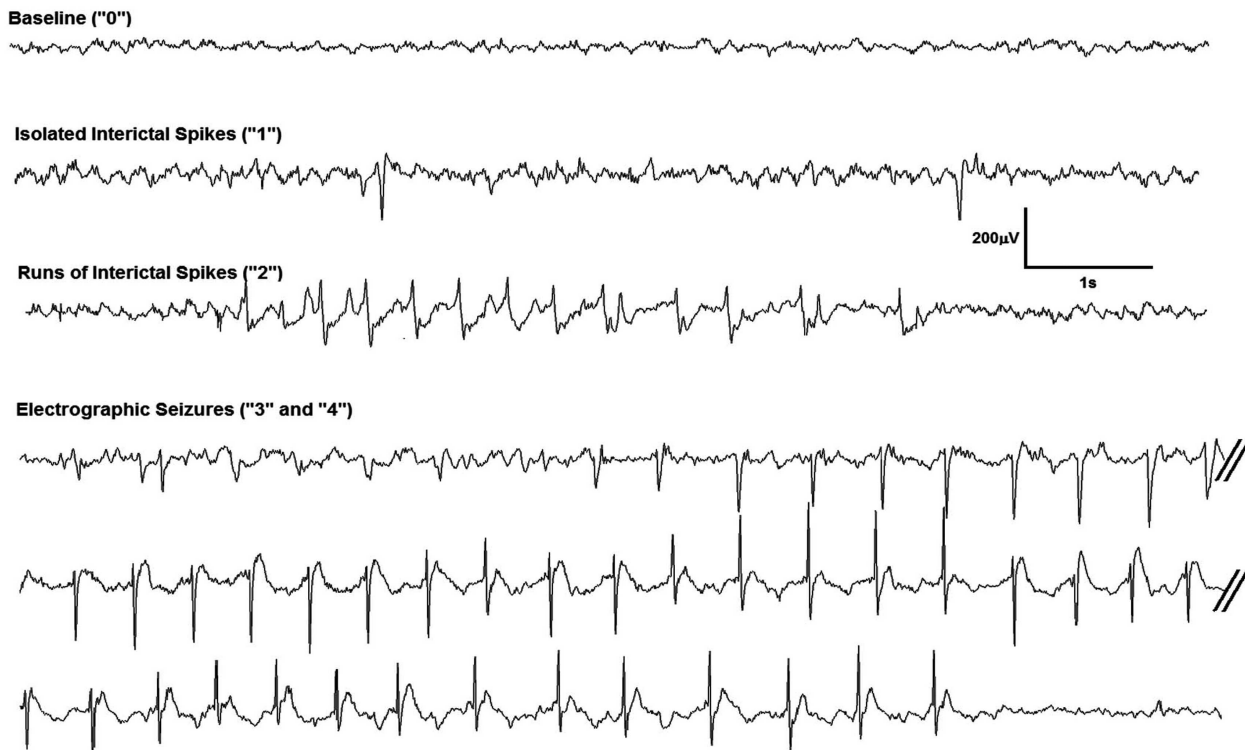


Fig. (1). Representative electrographs of EEG activity. The designations are as follows: normal activity (Type 0), isolated spikes (Type 1), runs of spikes < 10 s (Type 2), and continuous runs of spikes (10 s-5 min, Type 3; >5 min, Type 4).

Table 1. Frequency of Seizure Type Following Drug Treatment. Values are Expressed as Total Percent of Time Spent in the Respective Seizure State: The Raw Values (Total Number of Intervals in State/Total Number of Intervals Analyzed) are Expressed Below in Parentheses. *p < 0.05, **p < 0.01 vs. SAL; #p < 0.05, ###p < 0.01 vs MDMA; +p < 0.05, ++p < 0.01 vs MA

	Seizure Type				
	Myoclonus	Type 1	Type 2	Type 3	Type 4
SAL	0% (0/328)	0% (0/328)	0% (0/328)	0% (0/328)	0% (0/328)
MDMA	0% (0/565)	0% (0/565)	0% (0/565)	0.2% (1/565)	0% (0/565)
MA	4.3% (29/681) **,#	4.1% (28/681) **,#	4.4% (30/681) **,#	1.5% (10/681) *,#	1.0% (7/681) #
Foxy	13.8% (90/650) **,,##, ++	7.8% (51/650) **,,##, ++	38.6% (251/650) **,,##, ++	18.0% (117/650) **,,##, ++	9.4% (61/650) **,,##, ++

SAL-treated rats displayed no change. Additionally, MA treatment resulted in a shorter latency to electrographic seizures compared to the MDMA-treated rats.

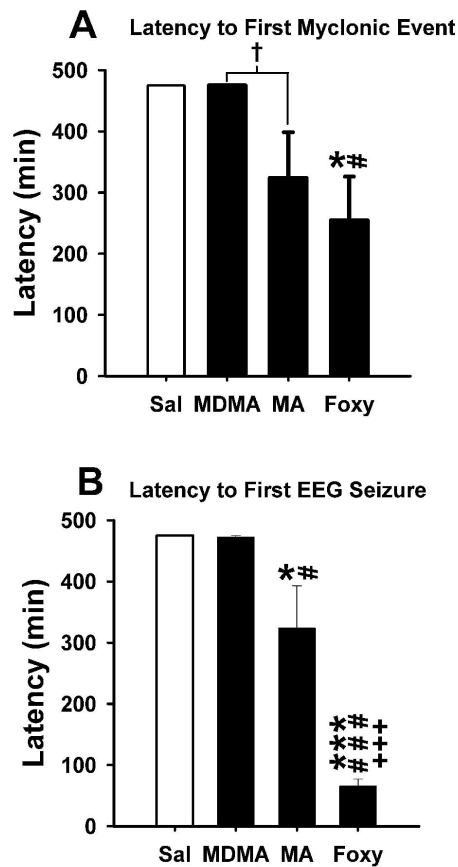


Fig. (2). Latency to First Seizure Activity. The time to onset of myoclonus (A) or abnormal electrographic activity (B) following treatment, averaged across all rats within each treatment group. *p < 0.05, ***p < 0.001 vs. SAL; #p < 0.05, ###p < 0.001 vs. MDMA; +p < 0.05, ++p < 0.001 vs. MA; †p < 0.10 as indicated by bars.

DISCUSSION

Seizures and abnormal EEG activity have been shown to be effects of high dose psychostimulant exposure [1-5], although it is not clear if this is the result of the drug or is secondary to confounders such as polydrug use, poor hydration, strenuous activity, inadequate nutrition, and/or genetic predisposition. This experiment determined the EEG profile in rats of three popular drugs of abuse using the exact dosing regimen shown to induce learning and memory deficits [46, 47, 56, 62] and neurochemical changes consistent with those seen in chronic users upon post mortem examination [33, 35, 51, 53, 60, 61]. Both Foxy and MA resulted in altered EEG activity, with Foxy producing more severe effects. This is the first study to characterize the EEG activity produced by Foxy and to include all three drugs within a single experiment where direct comparisons can be made. In addition to the severe effects of Foxy, the data also show the seizure-inducing effects of MA and supports the previous findings for MA in rats [12, 13]. Contrary to prediction, MDMA did not produce significant epileptiform activity.

MA affects dopamine (DA) [64, 65] as well as serotonin (5-HT) [66-68] and norepinephrine (NE) [64, 69]. Foxy affects the serotonergic system and most predominately the 5-HT_{2A} receptor [70], the 5-HT transporter [71], and 5-HT turnover [31] but does not appear to alter 5-HT, DA, or NE levels in adult rats [31]. In mice, Foxy reduces 5-HT levels in the hippocampus and prefrontal cortex [60]. MDMA affects the 5-HT system in rats [72, 73], non-human primates [74], and humans [75-77] with some effects upon DA [73, 78-81] and NE [82, 83]; however, it is primarily a dopaminergic agent in mice [84-86]. Given the EEG differences between drugs, i.e., lack of effects in MDMA-treated animals with inter-individual variation in susceptibility in MA-treated animals and consistent seizure activity in Foxy-treated animals, the serotonergic commonality among these drugs is unlikely to account for the EEG abnormalities observed.

The lack of abnormal EEG activity following MDMA was surprising given the clinical literature [6, 14, 21, 23, 24]. However, human seizures could be related to drug impurities, the combination of drugs abused simultaneously, hyperthermia, dehydration, or combinations of these [1, 21]. In addition, seizures may be secondary to toxicity resulting from excessive fluid intake that occurs when partiers overcompensate for the dehydration known to be associated with MDMA use. Excess fluid can produce hyponatremia which has been associated with seizure activity [3, 22, 24]. Interestingly, while we and others (in a mouse model) [28] did not observe significant spontaneous seizures, another group noted seizure activity following a single MDMA dose in mice [13]. In the latter experiment, MDMA was administered into the ventricles (i.c.v.) instead of peripherally (i.p. or s.c.). Intraventricular administration minimizes metabolism [87, 88] and provides a more potent route of administration. Furthermore, only one dose level of MDMA was used in the current study. While a higher dose might have induced seizure activity, we conducted the current study to determine the EEG profile following a dosing regimen of MDMA that does not increase mortality but induces long-term neurochemical and behavioral changes.

The data confirm previous findings that MA induces seizure activity as has been reported in humans [1, 2, 10, 89] and rodents [11, 13, 90]. In humans, seizures are typically transient [1, 2, 25], although status epilepticus is reported on rare occasions [1]. MA-induced seizures are independent of route of administration or prior exposure in humans [1, 3]. Our data are in accordance with the clinical features of MA-induced seizures, such that the EEG activity was brief (Types 1-2, isolated ictal spikes or runs < 10 s). While mouse studies using MA or amphetamine note that these drugs produce prolonged seizures [11, 13], our data show intermittent abnormalities with 1-1.5% of the intervals showing Type 3 or 4 seizures. Bowyer and colleagues, using a single dose of amphetamine (40 mg/kg) in rats, noted that while prolonged seizure activity did not appear as it did in mice, many of the treated rats became hyperthermic (> 41.4°C) and required cooling to prevent death [12]. No rat in the present study went above 40°C and no cooling was required. MA is known to induce hyperthermia, and the resulting thermic dysregulation has been shown to play a role in the resultant neurotoxicity [32, 33, 91]. However, experimental manipulations can spare the MA-induced thermic response while still causing deleterious effects [92-95]. Thus, we cannot discount the potentially protective effect that exposure to isoflurane, administered both during the surgery as well as prior to EEG recordings, might have had upon thermal regulation, as volatile anesthetics such as isoflurane inhibit thermoregulatory control and can induce hypothermia [96, 97]. Despite the fact that hyperthermia was not present, the literature indicates that a dose of 40 mg/kg of MA induces neurotoxicity [33, 35, 38, 40, 44, 45, 98]. However, hyperthermia may be a prerequisite to prolonged seizure activity, at least in rats, although a lack of status epilepticus does not necessarily indicate a lack of

neurotoxicity, as the aforementioned group reported blood brain barrier disruption and neurodegeneration [12]. Thus,

even the brief seizures noted here could be associated with MA-induced neurotoxicity.

Limitations of the current experiment include testing only one dose and dosing regimen of each drug, testing doses of each drug that are not equimolar to one another nor equal in internal area-under-the-curve exposure levels, testing a limited range of EEG parameters, testing during a limited range of times post-treatment (including not testing for long-term recovery and/or long-term residual adverse effects). However, there was a sound basis for the dose and dose schedule used. For example, all three drugs with the exact same dose and dosing regimen used here have been shown by us and others to induce clear-cut evidence of neurotoxicity and/or behavioral and cognitive effects (see above). Further, these doses, when extrapolated to humans using allometric scaling, are similar to those found in humans among psychostimulant abusers, and are therefore, relevant. Moreover, this is the first experiment to directly compare these stimulants for epileptiform effects and therefore make a novel contribution to what is known about the drugs. Future experiments should test a range of doses and times after treatment in order to develop a more complete profile of the epileptogenic action of each drug. We acknowledge that the present data represent only the first step in such understanding but a significant step nonetheless.

CONCLUSION

This experiment compared the seizure-inducing properties of three common psychostimulants of abuse at doses known to induce neurotoxicity and cognitive deficits. The principal finding was the rapid onset and enduring seizures produced by Foxy. Little is known about the mechanism of action or pharmacodynamics of this drug, but it is clear from the present data that this drug carries significant risk of adverse effects; effects that are far more severe than from MA or MDMA in terms of seizure liability. Seizures and EEG abnormalities are associated with cognitive impairments [99-101]. Consistent with this, we and others have shown that rats given Foxy (30-80 mg/kg total) resulted in egocentric and spatial learning deficits following treatment [31, 60, 61]. Further research into how Foxy induces seizures is warranted given the present findings.

AUTHORS' CONTRIBUTIONS

DLG performed the surgery, monitored and dosed the rats, analyzed data, and wrote the manuscript. NRH and TLS monitored and dosed the rats. KDH was responsible for training in the proper surgical techniques and for analyzing the raw EEG data. MTW and CVV assisted in experimental design, analysis, and manuscript preparation.

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CONFLICT OF INTEREST

None declared.

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