

Local field potential power spectra and locomotor activity following treatment with pseudoephedrine in mice

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The efficacy of pseudoephedrine (PSE) as a nasal decongestant has been well-demonstrated; however, PSE is strictly prescribed as a control substance due to its controversial psychostimulant effects. Although standard stimulatory drugs increase exploratory behavior and stimulate the dopamine system, the exact effects of PSE on locomotion and electrical activity in the striatum have not been determined. This study aimed to examine and compare the locomotor activities, local field potential (LFP) and sleep-wake patterns produced by PSE and morphine, which is a standard drug used to promote psychomotor activity. Male Swiss albino mice were anesthetized and implanted with an intracranial electrode into the striatum. Animals were divided into four groups, which received either saline, PSE or morphine. Locomotor activity and LFP signals were continuously monitored following pseudoephedrine or morphine treatment. One-way ANOVA revealed that locomotor count was significantly increased by morphine, but not PSE. Frequency analyses of LFP signals using fast Fourier transform also revealed significant increases in spectral powers of low- and high-gamma waves following treatment with morphine, but not PSE. Sleep-wake analysis also confirmed significant increases in waking and decreases in both non-rapid eye movement and rapid eye movement sleep following morphine treatment. Sleep-wakefulness did not appear to be disturbed by PSE treatment. These findings indicate that acute PSE administration, even at high doses, does not have psychostimulatory effects and may be relatively safe for the treatment of non-chronic nasal congestion.

Key words: morphine, pseudoephedrine, striatum, local field potential, psychostimulant, locomotion

INTRODUCTION

Pseudoephedrine (PSE) is an effective decongestant for the treatment of a stuffy nose and has been shown to reduce nasal resistance, as a sympathomimetic drug (Hendele, 1993). Efficacy for oral PSE against nasal congestion during the common cold has been consistently demonstrated by several studies (Loose and Winkel, 2004; Mizoguchi et al., 2007). However, there were warnings that PSE might have health risks and that over-the-counter sales should be banned re-

petitive administration of PSE was found to produce tolerance similar to that of amphetamine, a standard psychostimulant (Ruksee et al., 2008). The risk/benefit ratio of PSE use in patients with allergic rhinitis must be carefully weighed based on the occurrence of neurological adverse events (for review see Laccourreye et al., 2015). Physicians should be aware of the potential for complications, including stroke and neurological effects (N'Sondé and Wallaert, 2014).

However, PSE is safe and effective for the treatment of nasal congestion associated with acute upper respiratory tract infections (Eccles et al., 2005).

The efficacy of PSE against nasal congestion, without associated side effects, has been reported by a prospective, randomized, double-blind trial compared with placebo treatment (Eccles et al., 2005). Moreover, PSE combined with H1 antihistamine was found to be effective compared with placebo for four weeks (Nathan et al., 2006). In addition, 15-day treatment with oral PSE was more effective against nasal congestion than treatment with an oral leukotriene receptor antagonist (Mucha et al., 2006). However, PSE was demonstrated to produce CNS effects resembling those produced by amphetamine, with the potential to act as a drug of addiction (Tongjaroenbuangam et al., 1998). In general, the use of psychostimulants, such as amphetamine, methamphetamine, cocaine, or cathinone, has been associated with movement disorders. Psychostimulants may disrupt movement control and produce hypokinetic or hyperkinetic disorders, including parkinsonism, tremor, dyskinesias, and myoclonus (for review see Asser and Taba, 2015). Amphetamine has been used to induce locomotor activity in an animal model (Schmidt et al., 2010). The underlying mechanism of amphetamine involves pre-synaptic release of multiple monoamines, including noradrenaline, dopamine, and serotonin, and the inhibition of their reuptake from the synaptic cleft, which results in overall CNS activation and enhanced alertness (Iversen and Iversen, 1981). In contrast, morphine causes somnolence-like depressive activity (Wiffen et al., 2014) but also exhibits locomotor activity, as an excitatory effect (Babbini and Davis, 1972), indicating that morphine activates relatively direct CNS mechanisms, rather than enhancing cortical hyperexcitability or alertness, to increase locomotor activity. Moreover, morphine is an opioid that affects the electrical activities of the nucleus accumbens and striatum and increases movement in mice (Reakkamnuan et al., 2017), indicating that drugs of abuse or addiction modulate movement control, either directly or indirectly through the activation of the basal ganglia. PSE also increases Fos-like activity, both in the nucleus accumbens and the striatum, which are the brain areas that are essential for reinforcing effects and locomotor functions, respectively (Kumarnsit et al., 1999), indicating that PSE has CNS effects on the basal ganglia at the cellular level. Therefore, it is important to determine whether PSE acts as a psychostimulant affecting electrical activity of the striatum and increasing locomotor level.

The purpose of the present study was to detect changes in local field potential oscillatory patterns following PSE treatment in male Swiss ICR mice. Additionally, locomotor activity was monitored to determine the psychostimulant effects of PSE at the be-

havioral level. These studies will determine whether PSE stimulates the striatum, a psychomotor-associated brain region, and enhances exploratory behaviors. Morphine was used as a standard drug. Animals were implanted with an intracranial electrode in the striatum, for LFP signal recording. Animal movement was monitored by a web-based camera. The tested hypothesis was that a 15 mg/kg morphine dose would clearly alter LFP oscillations, whereas PSE (at doses of 50 and 100 mg/kg oral) would not.

METHODS

Animal models

Male Swiss albino ICR mice (25–45g) were supplied by the Southern Laboratory Animal Facility of Prince of Songkla University (Songkhla, Thailand). Animals were housed under standard environmental conditions ($22\pm 2^{\circ}\text{C}$, $55\pm 10\%$ humidity, and a 12/12-h light/dark cycle), and fed with standard commercial food pellets and water, ad libitum. Animals were used repeatedly, to reduce variability among individual animals and across different groups, to minimize the numbers of animals used and to reduce animal suffering, according to the guiding principles underpinning the humane use of animals in scientific research, referred to as the Three Rs - Replacement, Reduction, Refinement. The experimental protocols for the care and use of animals that are described in the present study were approved and guided by the Animal Ethical Committee of the Prince of Songkla University, under project license number MOE 0521.11/1560 Ref.70/2018.

Intracranial electrode implantation

A surgical procedure was performed for stereotaxic implantation of intracranial electrodes into the striatum. Animals were anesthetized, using a mixture of xylazine and zoletil, at 15 mg/kg and 50 mg/kg i.p., respectively. After animals were deeply anesthetized, their head was fixed with a stereotaxic apparatus. Stainless-steel electrodes ($279.4\ \mu\text{m}$ in diameter, coated) were stereotaxically implanted into the striatum (AP: +0.5 mm, ML: 2 mm to bregma, and DV: 3 mm). The reference electrode was fixed on the skull, at the midline over the cerebellum. All electrodes were secured in place using dental acrylic (Unifasttrad, Japan). A stereotaxic coordinate atlas was used to define the flat-skull positions (Paxinos and Franklin, 2004). After surgery, animals were housed individually, in single cages, and left for 10 days to recover from sur-

gery fully. The antibiotic ampicillin (General Drug House Co., Ltd., Thailand) was given intramuscularly, once per day, for three consecutive days, to prevent infection. At the end of the experiment, the accuracy of the electrode implantation was verified using histology. The animal brains were perfused and fixed in paraformaldehyde, embedded in paraffin, and coronally cut into 10-mm brain slices. Finally, the location of the electrode tip was confirmed within the striatum (Fig. 1).

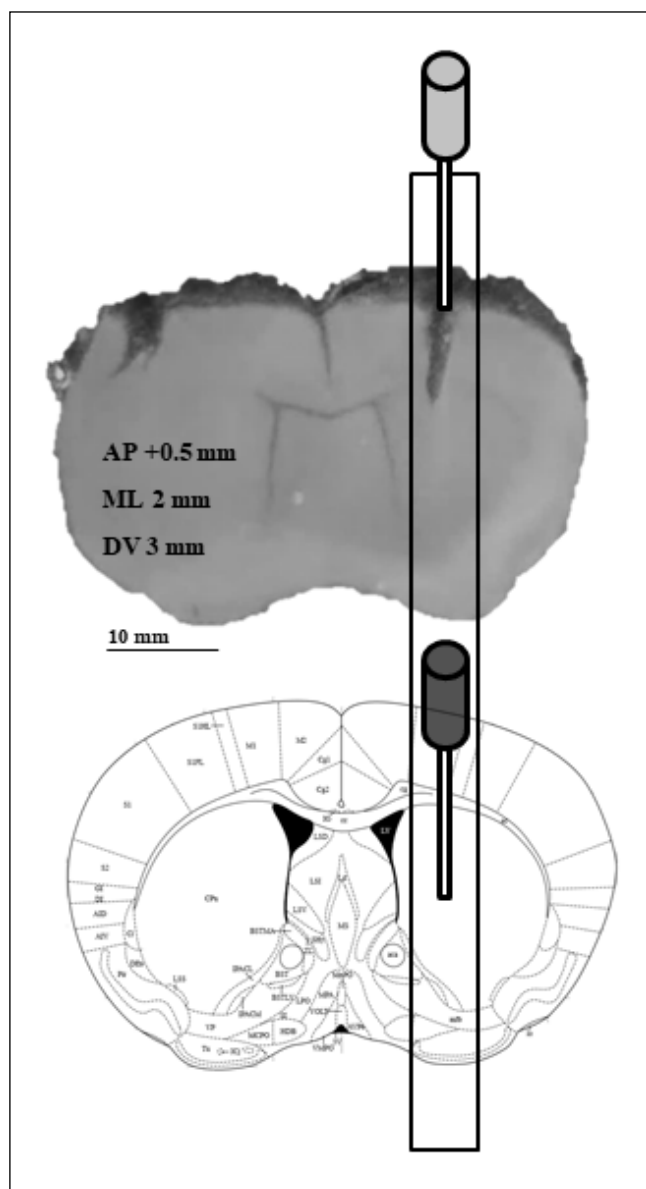


Fig. 1. Implantation and histological confirmation of an intracranial electrode in the striatum. The wire electrode was stereotaxically introduced into the striatum. At the end of the experiment, the mouse whole brain was collected, and a coronal brain slice was made through the striatum. A mouse brain atlas was used to confirm the electrode location within the striatum.

Recording and monitoring LFP patterns and locomotor activity

Animals were habituated to the recording conditions in a chamber for 180 min each day, for three consecutive days. On the experimental day, animals were randomly treated with either 0.9% NaCl (p.o), 50 mg/kg PSE, 100 mg/kg PSE (p.o), or 15 mg/kg morphine (i.p.) and individually placed into the recording chamber for LFP and locomotor recording ($n=9$ per group). A ball-tipped, stainless-steel, gavage pipette was used for the intragastric administration of PSE. Post-drug recording was performed for 3 h after drug administration (Fig. 2). Altogether, each animal was given all 4 treatments, with a 7-day washout period between treatments.

LFP signals were filtered through low-pass, at 200 Hz, high-pass, at 1 Hz, and digitized, at 2 kHz, by a PowerLab 16/35 system (AD Instruments, Castle Hill, NSW, Australia), with a 16-bit A/D. Data were stored in a PC, through the LabChart 7 software. Notch filtering, at 50 Hz, was applied to remove noises from power line artifacts. All LFP signals were processed through a 1–200 Hz band-pass digital filter (raw filtered signal). Fast Fourier transform (FFT) was used to analyze the spectral power of 6 discrete frequency bands: delta, 1–4 Hz; theta, 5–8 Hz; alpha, 9–12 Hz; beta, 13–34 Hz; low-gamma, 35–45 Hz; and high-gamma, 46–100 Hz. The spectral powers of discrete frequency bands under each treatment condition were averaged and expressed, either in time or frequency domains. The locomotor activities of the animals were recorded by using a video camera mounted on the top of the recording chamber. For the analysis, raw LFP signals and the video of moving animals were continuously transferred to a computer for data processing by LabChart software. The FFT algorithm was used to perform frequency power analyses.

Locomotor counts were analyzed, as described previously (Cheaha et al., 2014). A video camera was vertically mounted over the recording chamber to capture the animal images. For the analysis, the images of moving animals were continuously transferred to a computer for data processing. A tracking system was used to analyze the movement details of each animal. In brief, the videos in this study were processed proficiently by MATLAB software, including Autotyping 15.04. By using software, the floor space of the recording chamber was defined as the area that the animal could explore. Analyses of animal movements were based on the detection of contrasts between the animal body (white) and the chamber background (black). The animal body was tracked with a red (in the web version) spot. The software was programmed to count the

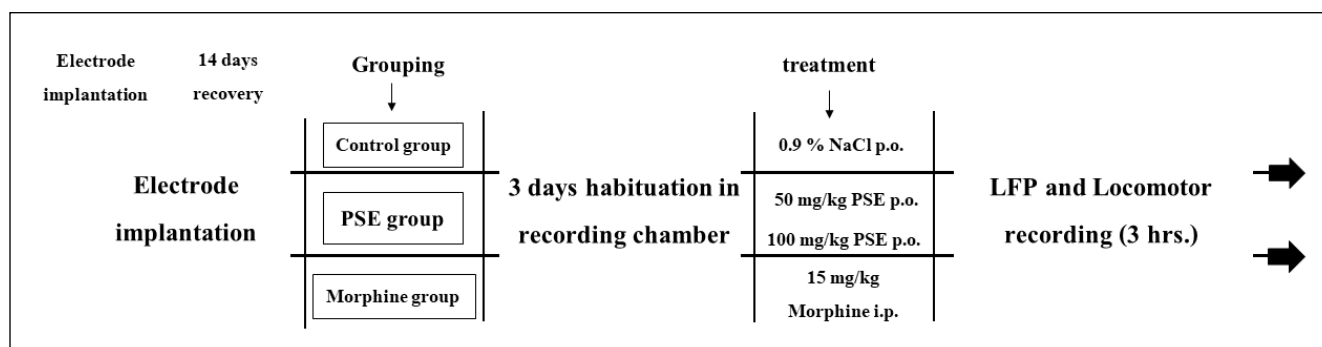


Fig. 2. Experimental procedure for testing the effects of pseudoephedrine and morphine administrations on spontaneous local field potential (LFP) signals and locomotor activity. Animals were anesthetized for intracranial electrode implantation, habituated with testing conditions, and repeatedly administered different treatments for the recording of LFP raw signals and locomotor activity.

number of movements. One count was determined as a period of continuous translocation until the animal stopped.

Sleep-wake parameters were analyzed from video records and LFP signals, following each treatment (Fig. 3). Video records of individual animals were used to identify periods of mobility and immobility. Then, LFP signals were converted into spectrograms to visualize changes in oscillations. Sleep spindles were identified by filtering the activity in the 12–16 Hz range. Previously, sleep spindles have been found during non-rapid eye movement (NREM) sleep, in both cortical

and subcortical brain regions, including the striatum (Boutin et al., 2018). Sleep spindles do not appear during rapid eye movement (REM) sleep or waking periods. The waking brain states were identified by intermittent locomotor activities and the appearance of extra gamma activity.

Statistical analysis

All data were averaged and expressed as the mean $\pm$ standard error of the mean (S.E.M.). The effects of PSE

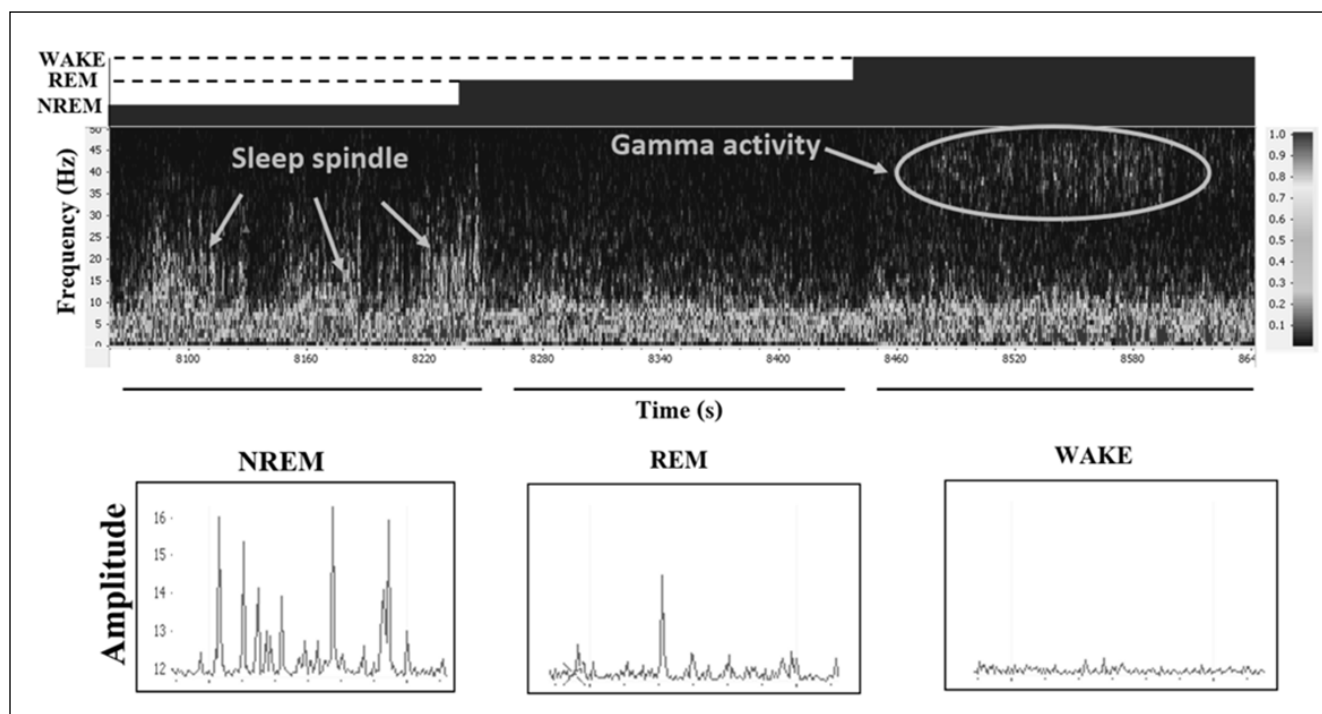


Fig. 3. The determination and scoring of sleep-wake parameters following pseudoephedrine and morphine treatments. Video records of locomotor activity and local field potential (LFP) signals were used. Animal movement, LFP sleep spindles, and gamma brain activity were used to determine periods of non-rapid eye movement (NREM) and REM sleep and waking states.

and morphine administrations on LFP power, frequency, and time and locomotor activity levels were analyzed by a repeated measure one-way ANOVA followed by multi-

ple comparisons using the Student-Newman-Keuls *post hoc* test, to indicate specific points of significance. Differences were considered to be significant at $p < 0.05$.

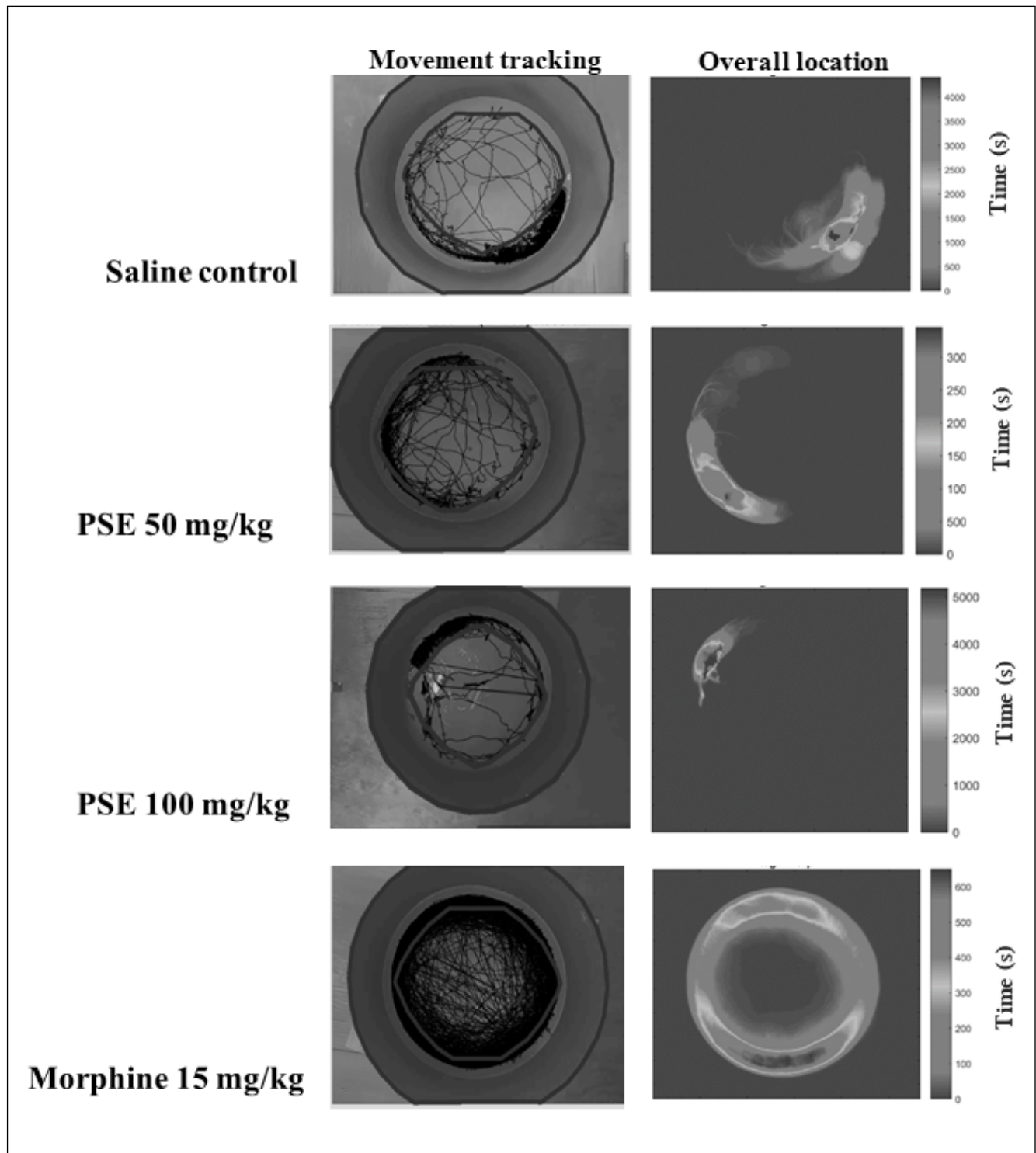


Fig. 4. Monitoring locomotor activity following saline, 50 and 100 mg/kg pseudoephedrine, and 15 mg/kg morphine treatments. A web-based camera was used to record animal movement. The levels of animal movements were detected by a tracking system. Movements within a specific area of the recording chamber are represented by grayscale code.

RESULTS

Locomotor activity levels following pseudoephedrine and morphine treatments

The exploratory movements of animals were monitored by using a web-based camera. Patterns of ambulatory behavior were computed by using a tracking system (Fig. 4). The movement patterns of 4 representative animals, during a 60–90 min period, are shown. The effects of treatments were compared to the levels in mice treated with saline control. The results showed that morphine increased animal movements, whereas PSE did not appear to affect animal movements, at either 50 or 100 mg/kg body weight (BW). A one-way ANOVA also confirmed a significant increase in locomotor counts induced by morphine ($F_{(3,35)}=31.350$, $p<0.05$) (Fig. 5). No significant difference in locomotor counts was observed following PSE treatments.

Local field potential oscillations in the striatum following pseudoephedrine and morphine treatments

Following morphine or PSE treatments, the raw signals of local field potential oscillations were subjected to visual inspection. Brain waves from rep-

resentative animals, under the four different treatment conditions, were compared (Fig. 6). The results showed that the brain waves from all animals contained both slow and fast activities within the raw signals. PSE treatment, at both 50 and 100 mg/kg BW, appeared to produce similar local field potential patterns as saline treatment. In contrast, differential signaling patterns were observed following 15 mg/kg BW morphine treatment, including additional fast activities, with gamma activity superimposed on basic slow-wave signals.

Raw signals were also expressed as spectrograms for inspection of frequency activities in time domain. Spectrograms of representative animals that received four different treatments were shown (Fig. 7). In comparison with the spectrogram for control animals, PSE-treated animals (both 50 and 100 mg/kg BW) appeared to show baseline levels of local field potentials. Relatively similar activities were observed for frequencies below 50 Hz. In contrast, dominant gamma frequency activity was observed following morphine treatment. Gamma activity clearly increased and ebbed within 3 h following morphine treatment.

Finally, frequency analyses of local field potentials during a 60–90 min period were focused to reveal the spectral powers in the frequency and time domains. Local field potentials were analyzed and expressed as percent total power every 30 mins (Fig. 8A–F). The results

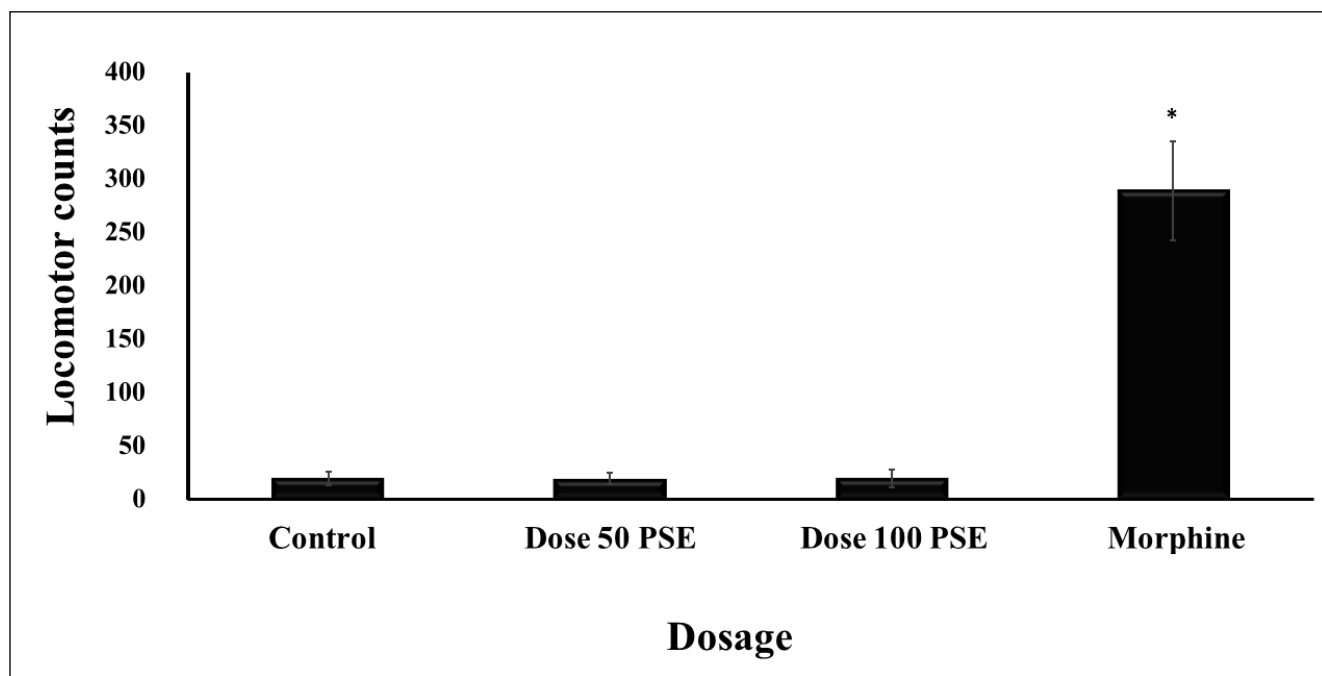


Fig. 5. Effects of morphine and pseudoephedrine treatments on locomotor activity levels. Locomotor counts were averaged and expressed as the mean $\pm$ S.E.M. The effects of treatment were determined using a one-way ANOVA, followed by multiple comparisons with the Student-Newman-Keuls *post hoc* test. $n=9$. * $P\leq 0.05$ compared with the control group.

showed increases in the frequency ranges for low-gamma and high-gamma bands, starting from 0–30 min until 150–180 min. Therefore, data from all time periods were collected for statistical analyses. Significant differences in low-gamma and high-gamma powers were found during all examined periods, including 0–30 min [low-gamma ($F_{(3,35)}=7.487$, $p<0.05$), high-gamma ($F_{(3,35)}=4.261$, $p<0.05$)], 30–60 min [low-gamma ($F_{(3,35)}=11.662$, $p<0.05$), high-gamma ($F_{(3,35)}=6.262$, $p<0.05$)], 60–90 min [low-gamma ($F_{(3,35)}=6.401$, $p<0.05$), high-gamma ($F_{(3,35)}=11.755$, $p<0.05$)], 90–120 min [low-gamma ($F_{(3,35)}=4.670$, $p<0.05$), high-gamma ($F_{(3,35)}=5.292$, $p<0.05$)], 120–150 min [low-gamma ($F_{(3,35)}=7.979$, $p<0.05$), high-gamma ($F_{(3,35)}=10.503$, $p<0.05$)], and 150–180 min [low-gamma ($F_{(3,35)}=5.709$, $p<0.05$), high-gamma ($F_{(3,35)}=7.731$, $p<0.05$)] (Fig. 9). Multiple comparisons also indicated that significant increases in low-gamma and high-gamma powers were only produced by morphine treatment. Neither the 50 nor 100 mg/kg BW PSE dose produced significant differences in power for these frequency bands. Moreover, the gamma powers of a wide frequency range of (35–100 Hz) were analyzed and expressed in the time domain. Gamma power was clearly increased by morphine but not by PSE treatment (Fig. 10A). Both the 50 and 100 mg/kg BW PSE treatment doses produced only baseline levels of gamma activity. Therefore, the averaged gamma powers during the 60–180 min period were statistically analyzed (Fig. 10B). A one-way ANOVA revealed that gamma ac-

tivity was significantly increased only by the morphine treatment ($F_{(3,35)}=9.975$, $p<0.05$). No significant effects on gamma activity were produced by PSE treatments.

Sleep-wakefulness following pseudoephedrine and morphine treatments

The effects of PSE and morphine treatments on sleep-wake patterns were analyzed. Data were scored and expressed as the total times of wake, NREM, and REM sleep (Fig. 11). One-way ANOVA revealed significant differences in the wake ($F_{(2,17)}=19.263$, $p<0.05$), NREM ($F_{(2,17)}=16.478$, $p<0.05$), and REM ($F_{(2,17)}=7.369$, $p<0.05$) sleep periods. Multiple comparisons also indicated that significant increases in the total time spent in all brain states were induced by morphine but not PSE.

DISCUSSION

Taken together, the present study clearly demonstrated increased locomotor activity and altered local field potential oscillations in the striatum of mice induced by morphine. No changes in these two parameters were observed following treatment with PSE. These findings suggest that PSE, even at high doses, is not potent enough to act as a stimulant. Movement behavior in animals has been shown to increase following

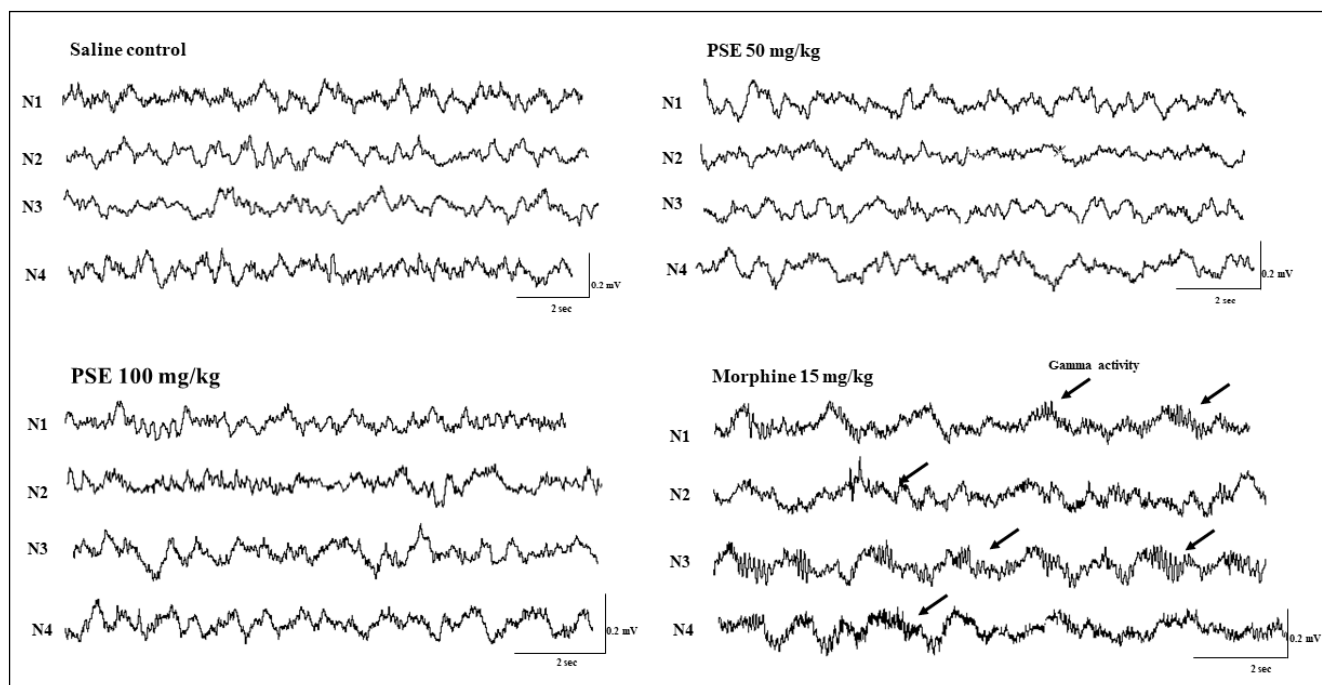


Fig. 6. Raw LFP signals in the striatum, following saline, 50 and 100 mg/kg pseudoephedrine, and 15 mg/kg morphine treatments. Representative LFPs of 4 mice per treatment are displayed in the time-domain.

treatment with standard drugs, such as amphetamine (McKinzie et al., 2002), cocaine (Yeh and Haertzen, 1991), modafinil (Simon et al., 1996), ethanol (Kliethermes, 2015), and morphine (Reakkamnuan et al., 2017). Enhancement of locomotion appears to be one of the most common effects of stimulant drugs. PSE, at a high dose (40 mg/kg), was once reported to significantly replicate amphetamine effects in rats, according to drug discrimination analysis (Tongjaroenbuangam et al., 1998). Ideally, drug discrimination analysis is used to determine whether a CNS chemical agent alters brain functions, leading to changes in mood, feelings, perceptions, and/or behaviors similar to those induced by a standard psychoactive drug, or results in neutral effects, similar to saline. As a sympathomimetic, PSE could potentially induce internal changes different

from those induced by saline. In particular, PSE increases systolic blood pressure (Hollander-Rodriguez et al., 2017) and causes other neurological effects (Lacourreye et al., 2015), which may be the properties that allowed PSE to mimic amphetamine activity. However, PSE is unlikely to act as a stimulant, based on the locomotor activity test and LFP pattern in the striatum. These two studies are relatively more direct methods that measure stimulant effects in comparison to drug discrimination analysis.

Previously, hypokinesia during parkinsonism has been reported, following the death of dopaminergic neurons in the substantia nigra pars compacta and reduced dopamine release in the striatum (Ehringer and Hornykiewicz, 1960; 1998), which results in motor dysregulation by the striatum. Lesions in the dorsal

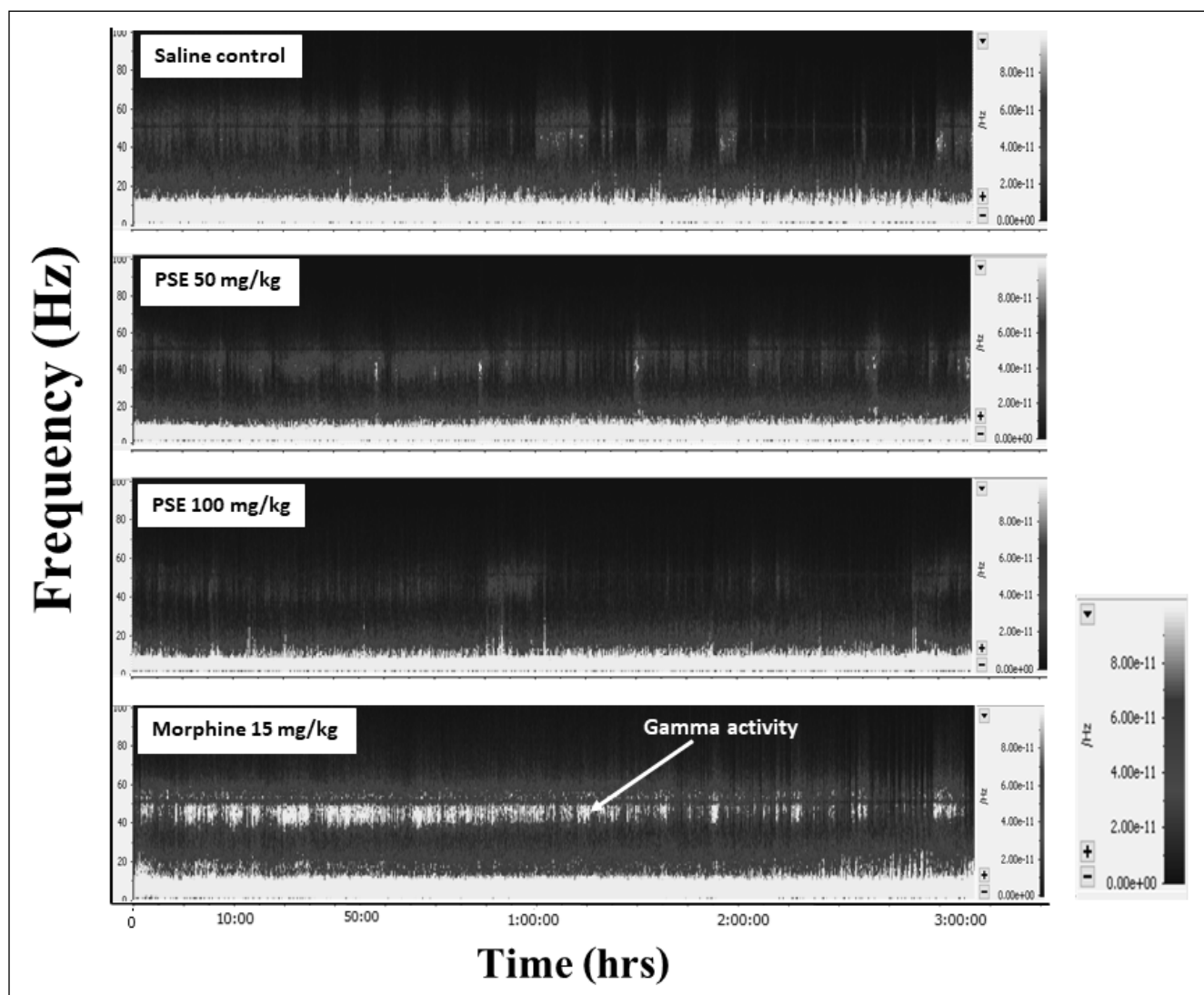


Fig. 7. Representative LFP spectrograms, displaying the dynamics of brain wave frequencies, for saline, 50 and 100 mg/kg pseudoephedrine, and morphine treatments. In spectrograms, the values of EEG powers are expressed as a grayscale of frequency against time.

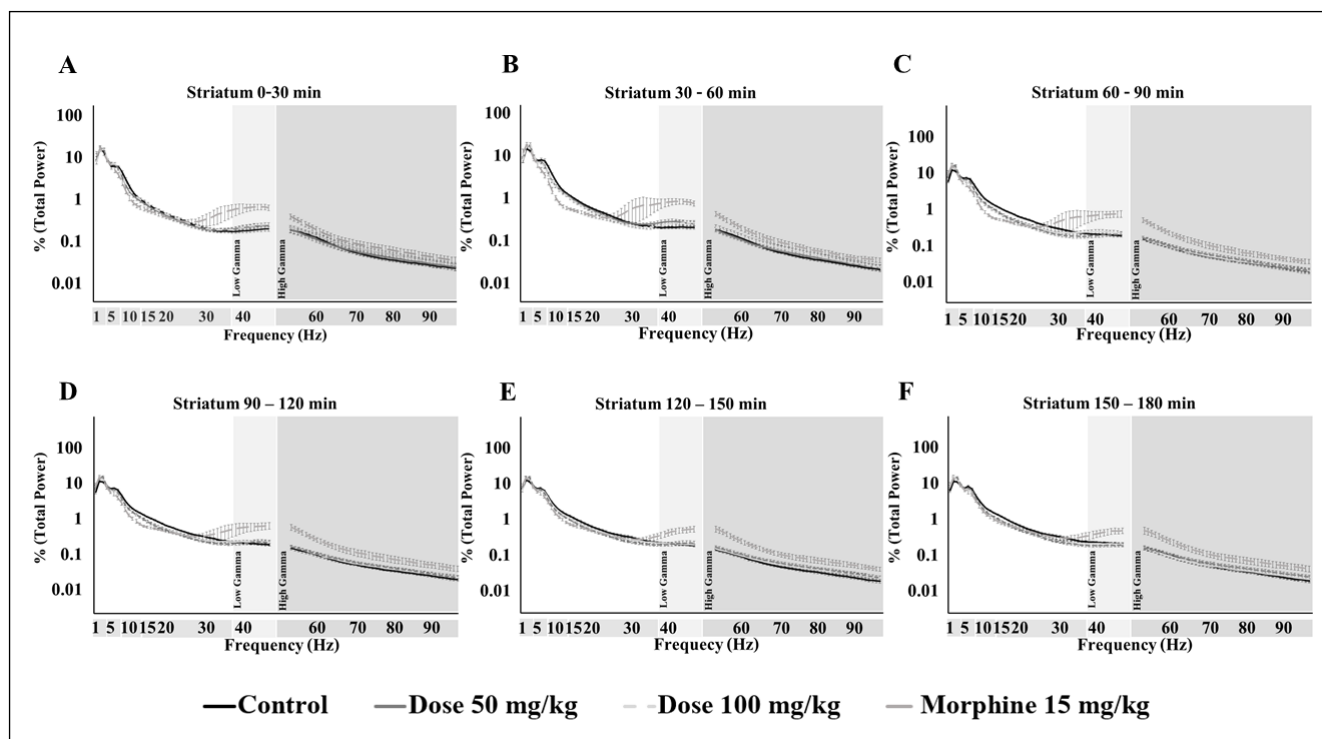


Fig. 8. Frequency analyses of striatal LFP oscillations. Spectral powers following saline, 50 and 100 mg/kg pseudoephedrine, and morphine treatments were analyzed every 30 mins and expressed as a percentage of total power in the frequency domain (A-F).

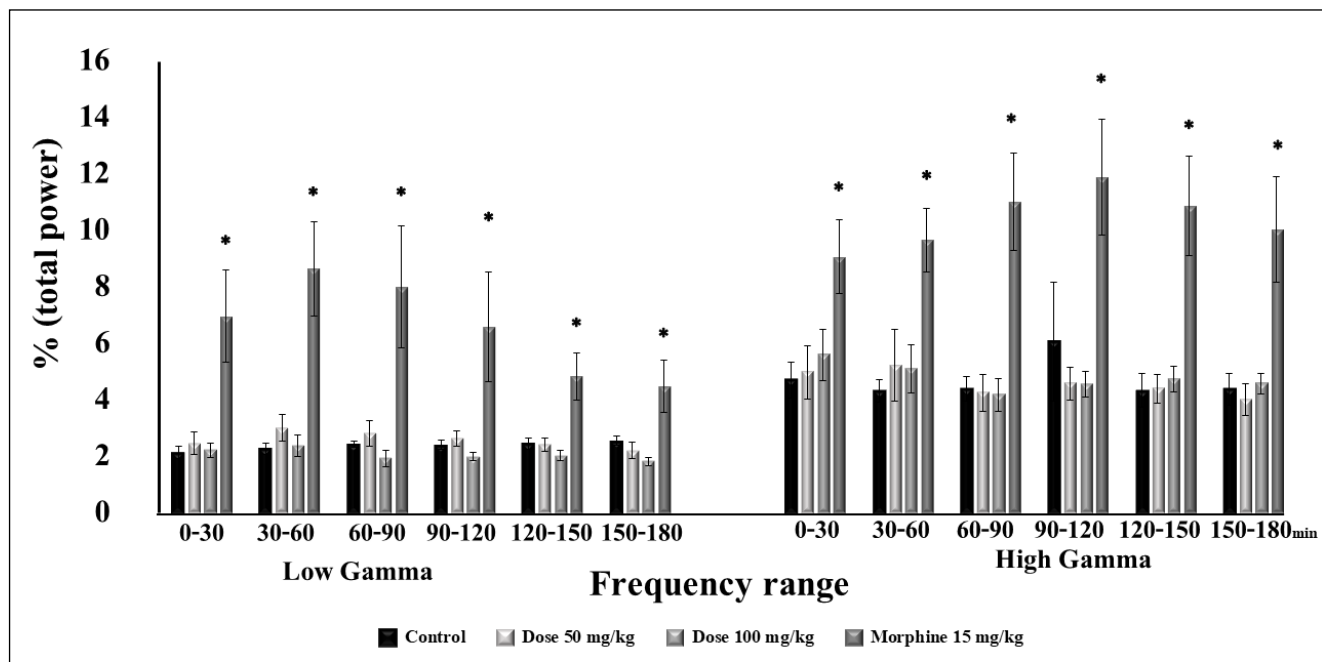


Fig. 9. Effects of saline, 50 and 100 mg/kg pseudoephedrine, and 15 mg/kg morphine treatments on low- and high-gamma frequency waves. Data are expressed as the mean $\pm$ S.E.M. The effects of treatments were determined using a one-way ANOVA, followed by multiple comparisons (Student-Newman-Keuls *post hoc* test). $n=10$. * $P \leq 0.05$ compared with control levels.

portion of the anterior striatum increased locomotor activity, whereas lesions in the ventral striatum decreased locomotor activity (Neill et al., 1974). Additionally, the striatum was found to mediate several non-motor functions and is a component of the neural circuits associated with the behavioral development of drug addiction (Ferguson et al., 2011). Direct and indirect striatal pathways specifically contribute to associative reward mechanisms and the learning behaviors necessary to avoid aversive stimuli, respectively (Hikida et al., 2010). Increased activity in the direct pathway promotes resilience against compulsive cocaine-seeking behavior (Bock et al., 2013). These findings suggested the involvement of the striatum in movement, reward, learning and addiction. Differential temporal patterns of locomotor activity were also observed following acute or chronic subcutaneous and intraperitoneal injections of cocaine in rats (Yeh and Haertzen, 1991). However, cocaine was demonstrated to produce both conditioned place preference and increased locomotor activity; however, no significant correlation between conditioned place preference, acute locomotor activation, and locomotor sensitization was observed among multiple mouse strains (Eisener-Dorman et al.,

2011). These findings indicated that the psychomotor and rewarding effects of cocaine are produced by separate mechanisms.

Local field potentials induced by standard stimulants in major brain areas, including the striatum of rats, have been analyzed and expressed as electroencephalograms to predict the efficacy and possible mechanisms of action of bioactive substances (Dimpfel, 2009). Changes in the EEG frequency patterns in rats were detected in response to the administration of multicomponent drugs (Dimpfel et al., 2012). Presentation of EEG frequencies following CNS drug administration is sometimes called EEG finger print. In human, it has been useful as a quantitative electroencephalography (qEEG) for investigating the cerebral bioavailability of new bioactive compounds (Dimpfel et al., 2015). Moreover, striatal activities in response to alcohol have been associated with the positive, stimulant-like effects of the drug and the differential effects of alcohol among individuals (Weafer et al., 2018). A consequence of stimulant-like action was also detected in human with attention deficit hyperactivity disorder when nicotine consuming reduced primarily elevated striatal DAT density (Krause et al., 2002), indi-

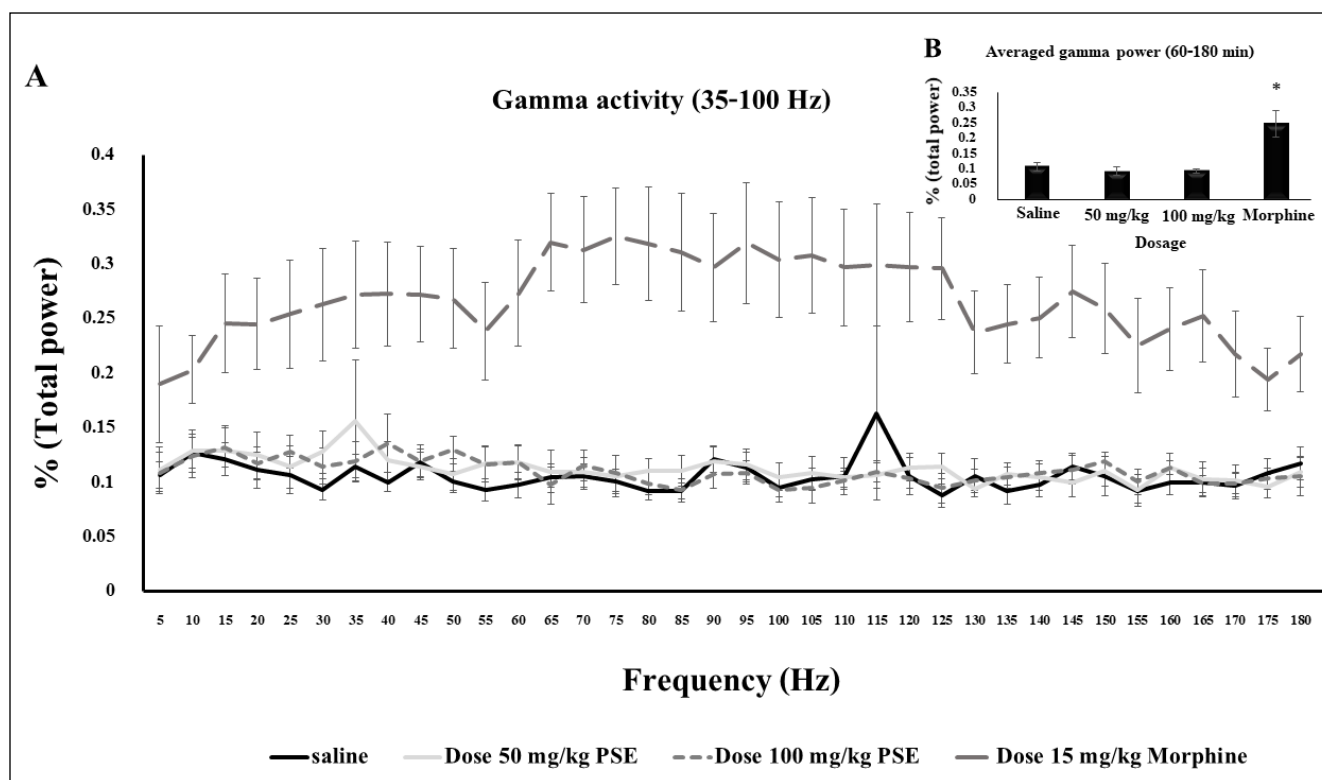


Fig. 10. Time-course analysis of the effects of 50 and 100 mg/kg pseudoephedrine and 15 mg/kg morphine treatments on gamma oscillations (35–100 Hz) in the striatum during a 3 h period. Values were normalized and expressed as a percent of total power (A). The inset values were calculated from the period of 60–180 min (B). Data are expressed as the mean $\pm$ S.E.M. The effects of treatments were determined by using a one-way ANOVA, followed by multiple comparisons (Student-Newman-Keuls *post hoc* test). $n=9$. * $P \leq 0.05$ compared with control levels.

cating that the striatum plays a critical role during the stimulatory effects of many drugs of addiction.

In terms of mechanism, the striatum appears to mediate several actions of psychostimulants. *In vivo* mouse model, (+) amphetamine activates D1 and D2 dopamine receptors to enhance locomotor activity (Simon et al., 1995). Significant decreases in striatal dopamine release, DAT availability, and D2/D3 receptor availability have been reported among stimulant users compared with healthy controls (Ashok et al., 2017). These data suggest that the dopamine system in the striatum may be downregulated in stimulant users. Apart from stimulation of striatal activity, a major character of stimulants is the activation of locomotor activity. Ambulation counts were clearly enhanced in an animal model, following treatment with 3,4-methylenedioxypyrovalerone (MDPV) or methamphetamine (Gatch et al., 2013). Previously, standard stimulants, such as methamphetamine, MDPV, and mephedrone, were found to have both stimulatory and rewarding effects following the inhalation of vaporized psychostimulants (Nguyen et al., 2016). The data may indicate a close link between emotionally driven movement and reward functions. These findings also suggest that the locomotor activity or reinforcement induced by stimulant drugs may be health risks associated with substances of abuse.

A major concern associated with PSE use is illicit drug production. Several chemical methods have been developed to extract and convert PSE into amphetamine (Bogun et al., 2017; Presley et al., 2018). Moreover, additional concerns have been raised based on research findings showing that PSE acts as a sympathomimetic. At the level of gene expression, PSE has been shown to exhibit stimulatory effects in the nucleus accumbens and striatum, two major brain regions that are generally sensitive to drugs of addiction (Kumarnsit et al., 1999). PSE produced cross-tolerance with amphetamine, as measured by c-Fos protein expression, in the brains of chronically treated rats (Ruksee et al., 2008). These studies demonstrated the CNS effects of i.p. PSE injections, indicating that PSE effectively crosses the blood-brain barrier. However, the present study did not show any consistent data at the levels of electrical brain and locomotor activities, indicating a lack of behavioral phenotype. No change of gamma power in the striatum was produced by PSE. It means that change in c-Fos protein expression does not lead to the level of LFP activity. The influence of immediate early gene expression was inadequate to alter gamma oscillation. Previously, an i.p. injection of morphine was found to induce gamma power in the nucleus accumbens, a brain region associated with the dopamine pathway (Reakkamnu-

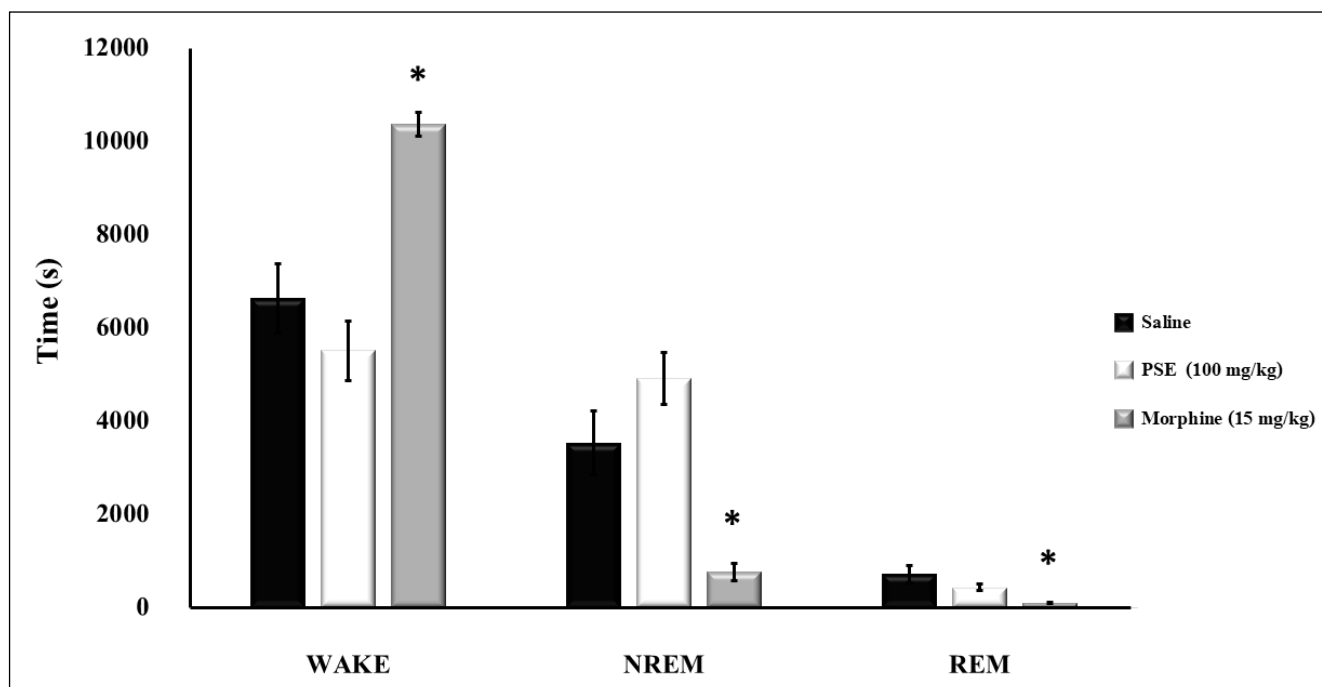


Fig. 11. Effects of 50 and 100 mg/kg pseudoephedrine and 15 mg/kg morphine treatments on sleep-wake cycles. The mean time spent in each brain state is shown. Sleep-wake data were analyzed from EEG signals recorded for 3 h following treatment. Data are expressed as the mean $\pm$ S.E.M. The effects of treatment were determined by using a one-way ANOVA, followed by multiple comparisons (Student-Newman-Keuls *post hoc* test). $n=9$. * $P \leq 0.05$ compared with control levels.

an et al., 2017), as rapidly as a few minutes following injection. Electrical brain activity plays many roles, particularly in neural network circuitries. Hence, PSE is likely to trigger effects within the striatum, rather than enhancing neural network connections between the striatum and other brain regions through gamma oscillations. Moreover, acute treatment with PSE did not affect the sleep-wake pattern, one of the most sensitive parameters for examining the effects of drugs on the CNS.

CONCLUSION

Altogether, the present findings demonstrated clear evidence of the psychostimulatory effects produced by morphine but found no similar effects for PSE. Previous studies have reported that cellular activity in the striatum was induced by PSE treatment. However, the present study confirmed that CNS activities induced by PSE have no detectable output at the levels of locomotor activity and local field potential oscillations in the striatum following acute treatment. Further studies might be necessary to examine the chronic effects of PSE on oscillations in the basal ganglia and locomotion compared with the levels produced by standard stimulant drugs. At this stage, these data support the use of PSE for the acute treatment of occasional nasal congestion. The continuous use of PSE for chronic diseases, such as allergic rhinitis or allergic with asthma, may not be recommended.

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