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Research paper

Dose response of acute cocaine on sleep/waking behavior in mice

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ABSTRACT

Chronic cocaine use has been associated with sleep disturbances, both during active use periods and during withdrawal and abstinence. Acute cocaine also increases waking at the expense of slow wave sleep and Rapid Eye Movement in non-human subjects. However, the effects of acute cocaine on sleep/waking activity in mice, a rodent model commonly used in both sleep and addiction research due to its high genetic tractability, has yet to be investigated. Sleep/waking activity was measured via polysomnography following IP administration of three doses of cocaine (3.6, 9.6, 18 mg/kg) and vehicle control in male C57BL/6 mice. Cocaine dose-dependently increased sleep latency, increased waking time and increased fast EEG activity within waking. Increases in waking occurred primarily during the first hour following injection, followed by rebound SWS sleep. Sleep/waking activity normalized within a 24-hour period. As with humans and other rodents, cocaine dose dependently reduces sleep in a wildtype strain of mice commonly used in reward and addiction research.

1. Introduction

Cocaine is a psychomotor stimulant which induces arousal and locomotor activity/hyperactivity following administration. As a drug with high abuse potential, there has been a substantial amount of research, both in human users and in preclinical models, into the consequences of cocaine use and potential therapeutic avenues (for review, Johanson and Fischman, 1989; Hanlon et al., 2013; Czoty et al., 2016), including research into sleep behavior. Sleep disruption has been observed under both binge taking and abstinence conditions in humans (Coffey et al., 2000; Pace-Schott et al., 2005; Angarita et al., 2016). In addition to changes in overall sleep time, during abstinence cocaine use has been reported to increase stage 2 slow wave sleep (SWS) at the expense of stage 3 and 4 SWS (Irwin et al., 2016), decrease Rapid Eye Movement (REM) latency (Johanson et al., 1999; Pace-Schott et al., 2005; Irwin et al., 2016), and increase REM time (Valladares and Irwin, 2007; Irwin et al., 2016).

Similar to the effects of binge cocaine and abstinence in humans, cocaine reduces sleep/waking activity in rats (Dugovic et al., 1992; Knapp et al., 2007; Chen et al., 2015) with some rebound sleep following acute administration (Dugovic et al., 1992; Knapp et al., 2007). However, the effect of acute or sub chronic cocaine on sleep/waking behavior in mice, a species often used in addiction and behavior research due to relative ease of genetic manipulations, has not been measured. Here, we show that cocaine dose-dependently increases sleep latency and REM latency, increases waking time by increasing the duration of waking episodes, alters EEG spectral density and induces a sleep rebound response.

2. Materials and methods

2.1. Animals

Adult male C57BL/6 mice (n = 7) were single housed following implantation of electrodes in a 12:12 light/dark cycle with food and water available ad libitum. All experiments were approved by the VA North Texas Health Care System IACUC. All efforts were made to minimize animal suffering and to reduce the number of animals used.

2.2. Surgical procedures

EEG and EMG electrodes were implanted as previously described (Bjorness et al., 2016). Briefly, mice were anesthetized with isoflurane and placed into a stereotaxic frame. Holes were drilled over the frontal cortex, over the right parietal cortex, and over the left occipital cortex after which custom EEG electrodes (Plastics One electrodes, Small Parts

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screws) were threaded into the holes. EMG electrodes (Plastics One) were placed under the dorsal nuchal muscle, the EEG and EMG electrodes were gathered into a six hole pedestal (Plastics One), and affixed to the skull via dental cement. The implant was coated with triple antibiotic ointment and the mice were given one administration of 0.03 mg buprenorphine for pain relief. Mice were given two weeks to recover from surgical procedures prior to acclimation to recording tethers.

2.3. Polysomnography and experimental design

Following recovery from implantation of electrodes, mice were habituated to recording tethers as previously described (Bjorness et al., 2016). Mice were housed in cages set above a treadmill belt throughout the recording period with a room temperature of 22.0 + /-1 ∘C. First, baseline, undisturbed EEG/EMG activity was measured for one day, after which mice were given saline, 3.6 mg/kg cocaine, 9.6 mg/kg cocaine, and 18 mg/kg cocaine with one injection (IP) per day on successive days. Injections were administered between zeitgeber time (ZT) 4.5–5.5 (i.e. 4.5–5.5 h following the start of the light period); this period was chosen since most behavioral testing in rodents occurs during the light phase, including addiction-related reward testing such as conditioned place preference and locomotor sensitization and occurs following the peak of SWS SWA early in the light phase (Bjorness et al., 2016). Saline was always the first injection to provide the experience of being removed from the cage while connected to the recording tether and injected, while 18 mg/kg cocaine was always the final injection (order of 3.6 mg/kg and 9.6 mg/kg cocaine counterbalanced between two sets of mice, first set n = 4, second set n = 3) since this dose carried the highest risk of inducing sensitization such that subsequent cocaine exposures would be followed by greater locomotor activity or stereotypy. These doses were chosen to represent low (subthreshold for conditioned place preference with this strain, Zachariou et al., 2001) moderate (typically induces conditioned place preference), and high (induces locomotor sensitization with this strain, Mongi-Bragato et al., 2016). Signals were scored offline using a custom Matlab (Mathworks) sleepscorer program by a scorer blinded to the condition (baseline/saline/cocaine) and epochs containing artifact were flagged and removed from power analysis. Waking, SWS, and REM sleep were defined using standard criteria as described previously (Bjorness et al., 2009; Bjorness et al., 2016), while power spectrum values were calculated as described previously (Bjorness et al., 2016).

2.4. Outcome measures

Three sets of outcome measures were used. First, objective measures of sleep time were calculated, including: latency to enter SWS, latency to enter prolonged SWS, latency to enter REM, percent time in state, average episode duration, and number of episodes. Episodes were defined as previously described (Bjorness et al., 2016). Briefly, an episode was initiated with three consecutive 10 second epochs of the same state and ended by three consecutive 10 second epochs of a different state. Second, homeostatic sleep drive, the increased drive in sleep that builds progressively during waking (Borbely, 1982), was assessed via slow wave activity (SWA, 0.5–4.5 Hz) normalized to average 24 h gamma (30–50 Hz, as described previously, Bjorness et al., 2016). Third, changes in spectral density were calculated using relative SWA, theta (6–10 Hz), spindle (8–16 Hz), sigma (16–30 Hz), and gamma normalized to total EEG power and compared to power at the same circadian time during baseline (percent change from baseline). These values were calculated in 1 h bins with the exception of relative band power across 24 h which was averaged across the entire 24 h period.

2.5. Drugs

Cocaine hydrochloride (Sigma Aldrich) was dissolved in sterile saline. Buprenoprhine (VANTXHS Pharmacy) was diluted in sterile saline.

3. Statistical analysis

For all outcome measures except sleep latency and spectral power, values were compared in three time frames; first, values within the first hour following injection were compared using a one-way ANOVA with repeated measures, second, values within the first 6 h following injection were compared using a two-way ANOVA with repeated measures (condition x time), and third, percent change from baseline across 24 h was calculated in 2 (waking and SWS) or 4 (REM) hour bins and compared via one way ANOVA with repeated measures. Longer bins were necessary for REM sleep averages since some animals did not show REM sleep for prolonged periods following injection. For sleep latency measures, one-way ANOVAs were used to compare latency to enter sleep (defined as the first episode of sleep with a minimum duration of 30 s), latency to enter prolonged SWS (defined as the first episode of SWS with a minimum duration of 5 min), and latency to enter REM sleep (defined as the first episode of REM sleep with a minimum duration of 30 s) following cocaine injection to sleep latency following saline injection. A one way ANOVA with repeated measures was used to compare the change in relative band power from baseline between injection conditions. A one sample t test was used to compare change in relative band power to baseline using a hypothetical value of 0. GraphPad Prism (GraphPad) was used for statistical analysis with statistical significance set at $p < 0.05$. One animal was excluded due to a bad injection for the 9.6 mg/kg dose. Exclusion was necessary for all analyses due to the use of repeated measures. Statistical comparisons and significance levels for each outcome measure is provided in the Supporting Information.

4. Results

4.1. Cocaine dose dependently increased sleep latency

Compared with saline injection, cocaine increased the latency to enter sleep (Fig. 1a, $F(2.148,10.74) = 18.66$, $p = 0.0003$) by 16.4 to 55.3 min (lowest and highest doses, respectively), to enter prolonged SWS (as defined as an episode of at least 5 min in duration (Fig. 1b, $F(1.612,8.058) = 33.64$, $p = 0.0002$)), and to enter REM sleep (Fig. 1c, $F(1.438,7.191) = 38.86$, $p = 0.0002$). Furthermore, there was a significant increase in latency to enter sleep, to enter prolonged sleep, and to enter REM between the lowest (3.6 mg/kg) and highest (18 mg/kg) doses of cocaine with additional differences between the middle (9.6 mg/kg) and highest dose of cocaine for the latency to enter sleep and enter prolonged SWS but not to enter REM sleep.

4.2. Increases in waking time occur primarily within the first 2 h post injection

Injection of saline or any of the three doses of cocaine increased time in waking ($F(1.682,8.409) = 48.11$, $p = 0.001$) and decreased time in SWS and REM in the first hour post injection compared to undisturbed baseline conditions (Fig. 2a, $F(1.576,7.878) = 39.93$, $p = 0.001$ and $F(1.582,7.909) = 16.88$, $p = 0.002$, respectively). Additionally, waking was increased and SWS decreased between saline and the highest dose of cocaine within this same period. Futhermore, increased waking between saline and the highest dose of cocaine was also apparent in the second hour following injection, while REM was decreased with all three cocaine doses in the second hour following injection compared to both baseline and saline conditions (Fig. 2b). When comparing waking/sleep time to change from baseline at the same circadian time, there was a significant effect of time ($F(11,55) = 3.993$, $p = 0.0003$), condition (substance/dose injected, $F(3,15) = 5.095$, $p = 0.0125$), and time x condition interaction for waking time (F

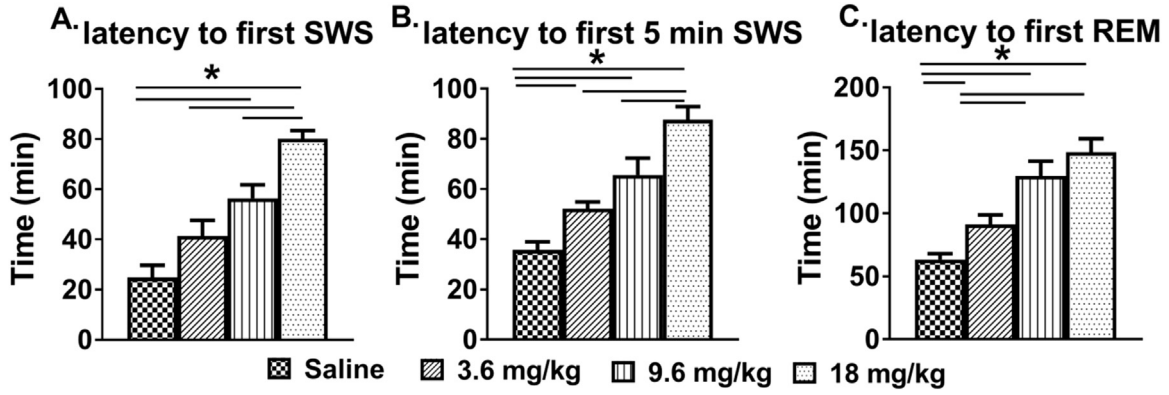

Fig. 1. Acute cocaine administration increased sleep latency following IP injection. Cocaine dose dependently increased the latency to initiate an episode of SWS (A), to initiate a prolonged episode of SWS (B), and to initiate an episode of REM sleep (C). Significant differences between conditions are indicated by solid horizontal lines. A complete summary of p values is provided in the Supporting Information.

(33,165) = 3.871, $p < 0.0001$) with significant differences between conditions in the first (all except low and medium dose), second (between saline, lowest dose compared to the highest dose), and the tenth (between saline, lowest dose compared to medium dose) 2 h bins (Fig. 2c). For SWS there was a significant time x condition interaction (F (33,165) = 2.42, $p = 0.0001$) with significant differences in the first (saline, lowest dose compared to the highest dose) and tenth (between saline, lowest, highest dose compared to the medium dose). For REM sleep there was no significant effect of time (4 h bins), condition, or time x condition interaction between groups.

4.3. Changes in waking time were primarily due to episode duration, while changes in SWS and REM were due to both episode duration and number of episodes

Injection of the medium and high dose of cocaine increased the duration of waking during the first hour following injection (F (1.916,9.58) = 8.93, $p = 0.007$), while the highest dose of cocaine decreased the duration of SWS to zero and all three doses of cocaine decreased REM sleep duration during this time period (Fig. 3a, F (1.932,9.66) = 10.56, $p = 0.004$). Additionally, REM sleep duration was decreased in the second hour following injection with the highest dose of cocaine (Fig. 3b). When comparing the change in episode duration from the same circadian time, there was a significant effect of time (F(11,55) = 6.42, $p < 0.0001$) and time x condition for waking (F (33,165) = 2.581, $p < 0.0001$) between saline, lowest cocaine compared to the highest cocaine in the first 2 h bin (Fig. 3c).

Conversely, there was no significant difference in the number of waking episodes between groups in the first hour following injection, while the number of SWS episodes was reduced following the highest dose of cocaine compared to baseline and saline injection and following the medium dose of cocaine compared to baseline (Fig. 4a, F (2.042,10.21) = 12.49, $p = 0.0017$); for the number of REM sleep episodes there was a significant difference between groups with non-significant trends between baseline and all injections (F(1.357,6.786) = 12.44, $p = 0.0077$). The number of waking episodes was significantly increased in the sixth hour following saline injection compared to all other groups (Fig. 4b), while the number of SWS episodes was decreased in the second hour following the highest dose of cocaine compared to saline and the lowest dose of cocaine and in the fifth hour following saline injection compared to baseline, lowest, and highest dose of cocaine. For REM sleep, the number of episodes in the second hour following injection for all cocaine doses was decreased compared to baseline and saline. When comparing the change in the number of episodes with the same time during baseline, there were no time x condition interactions in REM sleep between groups, while waking (F (33,165) = 1.924, $p = 0.004$) and SWS (F(33,165) = 2.111, $p = 0.0012$) showed similar patterns with significant differences between saline and the lowest dose (third and tenth bins), saline and the middle dose (tenth), saline and the highest dose (first and tenth both, third waking only), between the lowest and highest doses (first waking only), and between the middle and highest dose (tenth).

4.4. Cocaine reduced, then enhanced slow wave activity during slow wave sleep

Slow wave activity (SWA, 0.5–4.5 Hz, also called delta power) during SWS rather than sleep time is considered the best indicator of homeostatic sleep drive (Borbely, 1982; Tobler and Borbely, 1986; Greene, et al., 2017) and thus was used to assess changes in homeostatic sleep need following saline and cocaine injection. SWA across states (i.e. SWA during waking, SWS, and REM together) was decreased from baseline levels in the first hour following cocaine injection of any of the doses (Fig. 5a, F(1.953,9.767) = 16.75, $p = 0.0007$) and from saline levels compared to the highest dose. During the first hour following the highest dose of cocaine, the animals showed no SWS and there was no difference in SWA during waking. This suggests that the decrease in SWA across states was due to an increased time in waking (both increased total time and episode duration; an increase of 75.1 ± 2.5%, 55.3 ± 1.1 min, respectively) in the first hour following injection. In the subsequent 5 h following injection, SWA across states was increased relative to baseline in the second hour following the medium dose and the third and fourth hours following the highest dose, while SWS SWA was increased relative to baseline in the second hour following all doses and the third hour following all doses and saline (Fig. 5b, for SWS SWA the first 1 h bin was excluded from statistical analysis). For waking SWA, SWA was unchanged across groups in the first hour following injection after which SWA decreased following the highest dose in the second hour (relative to saline) and then increased in the fourth and sixth hours (relative to baseline, lowest dose and baseline, respectively). Additionally, waking SWA was increased following saline (relative to baseline) in the fifth and sixth hours. Compared to the same circadian time as baseline, there was a significant time x condition interaction (F(33,165) = 2.499, $p < 0.0001$) in SWA across states with % change SWA from baseline decreased following the highest dose (relative to saline) in the first bin (first 2 h) followed by a rebound increase (relative to saline and the lowest dose) in the second bin. During the later portion, % change SWA from baseline was increased in the medium and highest doses (relative to the lowest dose) and in the highest dose and saline (relative to the lowest dose) in the ninth and tenth bins, respectively, (Fig. 5c). Overall, for the highest dose of cocaine there was a pattern of decreased SWA followed by a rebound increase in SWA, which is consistent with stimulant-induced waking and subsequent recovery.

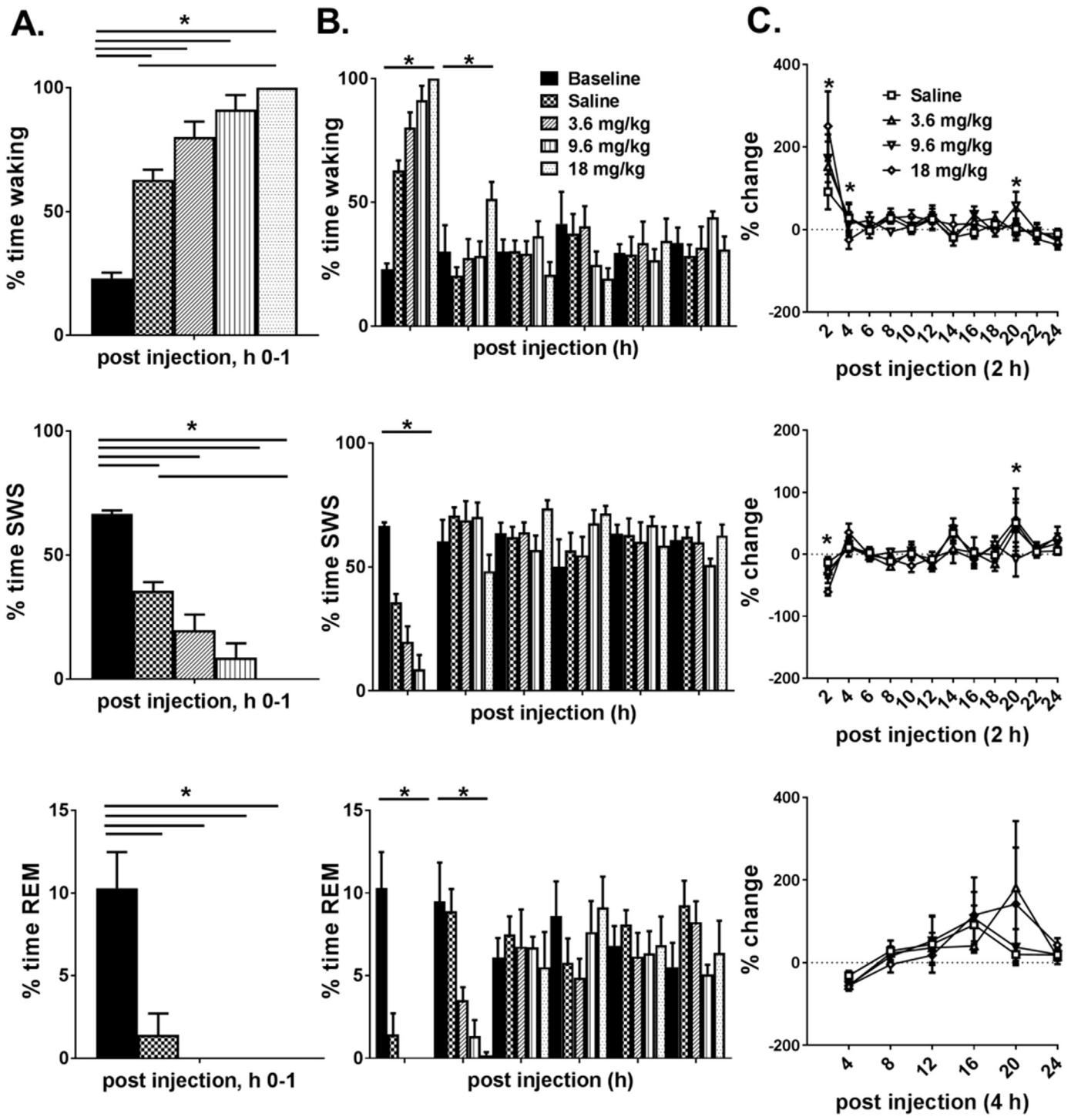

Fig. 2. Acute cocaine altered time in waking, SWS, and REM sleep. A) Acute cocaine increased waking and decreased SWS and REM sleep within the first hour following injection. Significant differences between conditions are indicated by solid horizontal lines. B) Waking and REM sleep alterations were still present in the second hour following injection with significant differences in waking between saline and the highest dose of cocaine and in REM between baseline and all cocaine doses and between saline and all cocaine doses. Time bins in which differences between conditions occur are marked with a horizontal solid line. C) Percent change in waking and SWS time relative to the same circadian time under baseline conditions was increased compared to saline injection during the first and tenth 2 h time bin (waking) and decreased first (SWS), second (waking) and tenth 2 h time bin (waking, SWS) as indicated by asterisks. A complete summary of p values is provided in the Supporting Information.

4.5. Cocaine increases fast activity within waking

In order to assess the relative contribution of slow and fast EEG power bands, power in each band was normalized to total EEG power and the percent change from baseline at the same circadian time was calculated. In the first hour following injection, there was a significant decrease in relative (band power normalized to total power) SWA power ($F(1.657,8.287) = 5.3$, $p = 0.037$) and a significant increase in relative sigma ($F(1.67,8.35) = 8.207$, $p = 0.013$) and gamma power ($F(1.863,9.313) = 12.52$, $p = 0.0025$) between saline injection and the highest dose of cocaine (Fig. 6a, d, e), while relative theta and spindle power was unchanged (Fig. 6b, c). Additionally, following all injections relative sigma and gamma power was increased compared to baseline (significant difference from 0) and following the highest dose of cocaine

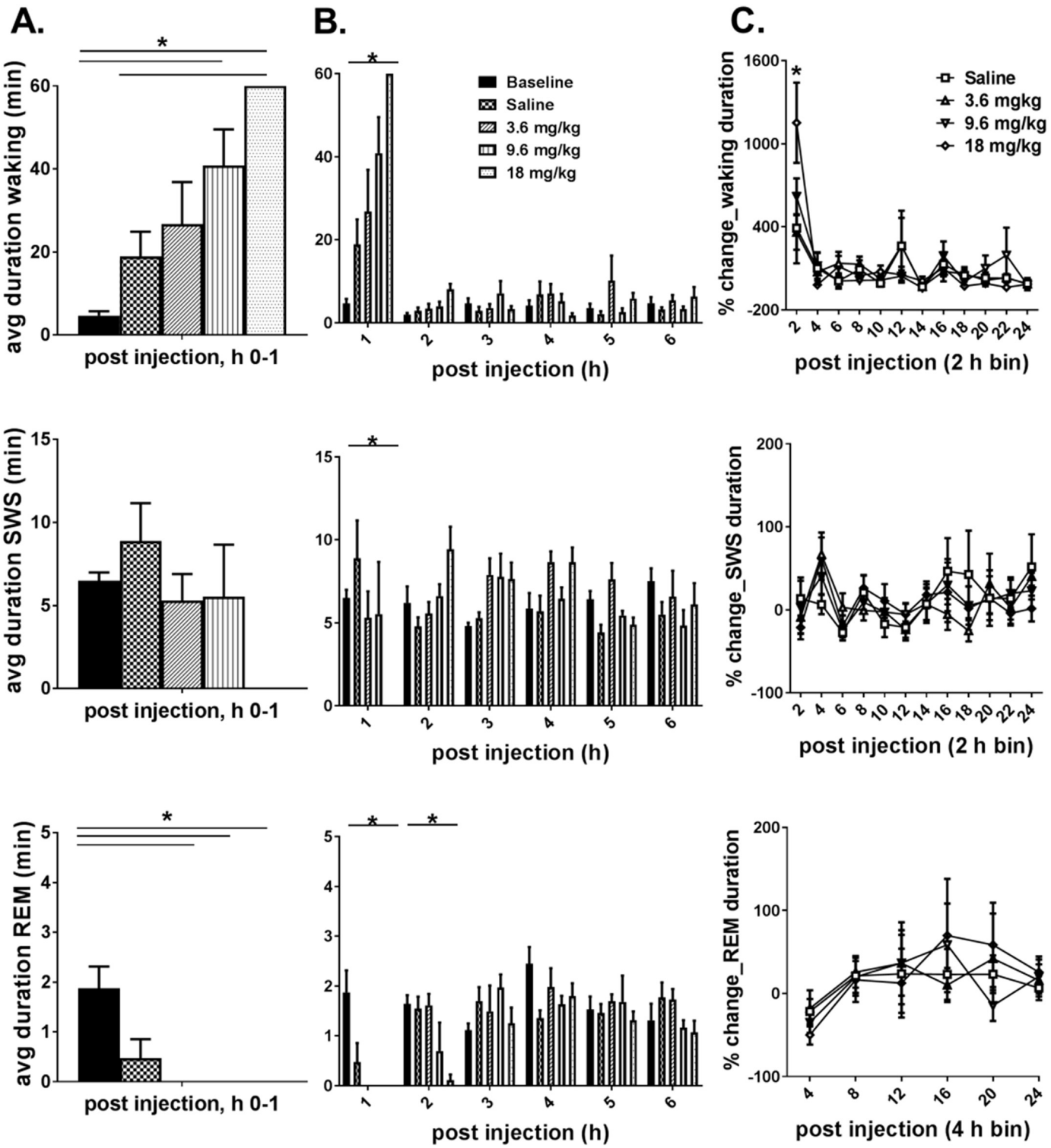

Fig. 3. Acute cocaine prolonged waking episodes and shortened SWS and REM episodes. A, B) In the first hour following cocaine administration, waking duration was increased, while SWS and REM duration was decreased. B) REM episodes remain shortened during the second hour following cocaine administration. Significant differences between conditions are indicated by solid horizontal lines. C) Percent change in waking duration compared to the same circadian time was increased in the first 2 h bin following injection as indicated by the asterisk. A complete summary of p values is provided in the Supporting Information.

relative SWA was decreased compared to baseline. Furthermore, total power was decreased from baseline to all injections and from saline to the highest dose of cocaine, likely due to the increased contribution of waking during this period following injections (Fig. 6f, F(2.218,11.09) = 18.4, $p = 0.0002$). Next, when comparing relative power within waking in the first hour following injection, there was a significant decrease in relative spindle power (F(1.249,6.245) = 17.32, $p = 0.0044$) between saline and the middle and highest doses of cocaine (Fig. 7c) and a significant increase in relative gamma power (F(2.038,10.19) = 18.66, $p = 0.0004$) following the highest dose of cocaine compared to all other injections (Fig. 7e). Additionally, following saline and the middle dose of cocaine, power was increased in

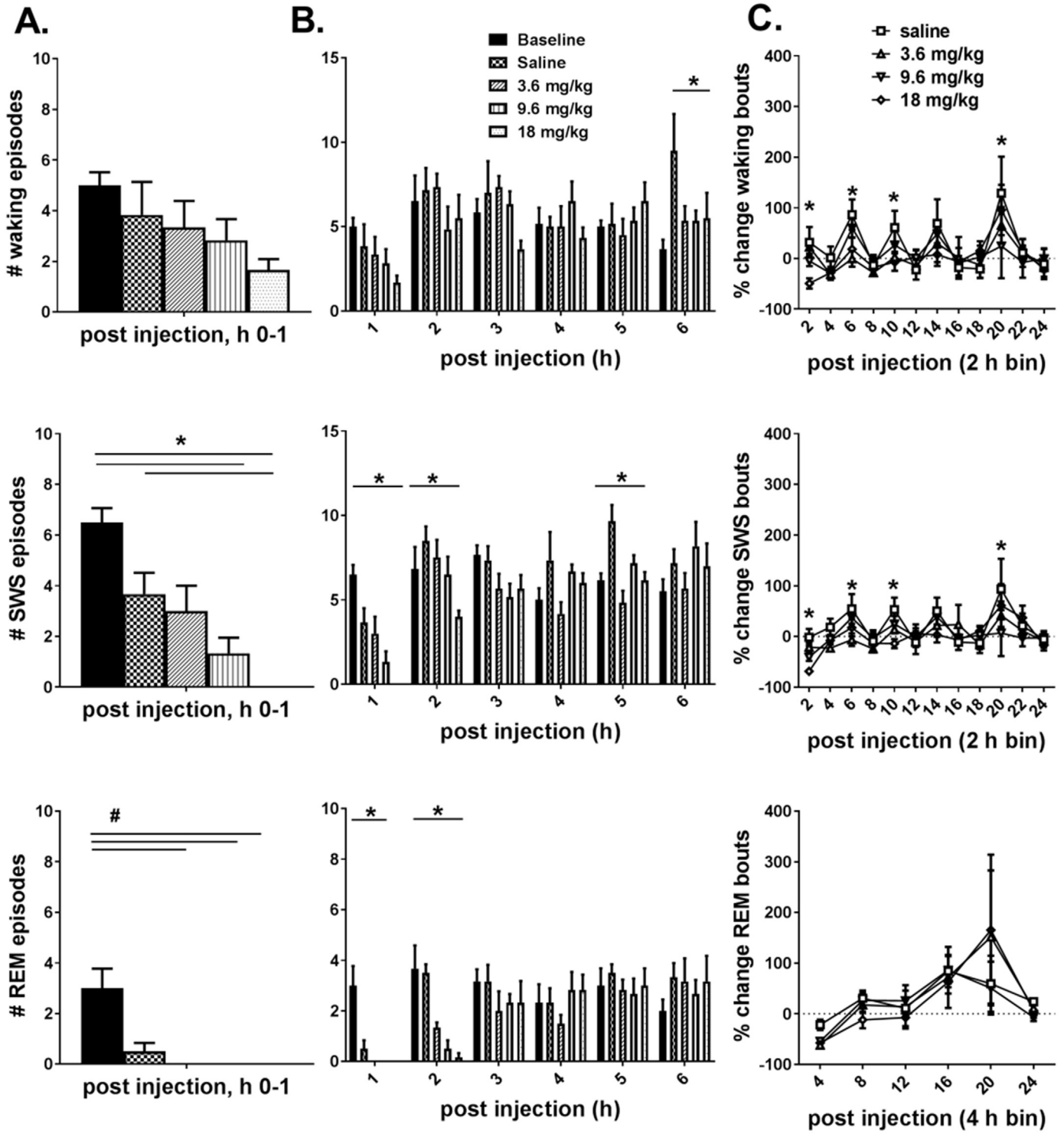

Fig. 4. Acute cocaine decreased the number of sleep episodes. A, B) The number of SWS and REM sleep episodes was decreased in the first, second, and in the case of SWS, fifth hour following cocaine, while the number of waking episodes was decreased in the sixth bin. Significant differences between conditions are indicated by solid horizontal lines. C) Compared to the same circadian time during baseline conditions, the number of waking and SWS bouts were altered (both increases and decreases by dose) in the first, third, fifth, and tenth 2 h bins as indicated by asterisks. A complete summary of p values is provided in the Supporting Information.

sigma compared to baseline (Fig. 7e), while following the highest dose of cocaine, power was increased in the sigma and gamma bands compared to baseline (Fig. 7d, e). There was no significant change in relative SWA, theta, or total power following any injection (Fig. 7a, b, f), indicating that the increase in gamma following the highest dose of cocaine represents greater desynchrony independent of the increase in waking time with this dose of cocaine. However, there was no change in relative power for any of the bands, nor total power across the average 24 h period following injection across all states or within waking specifically (data not shown).

5. Discussion

Here we show that acute cocaine in mice dose dependently: 1)

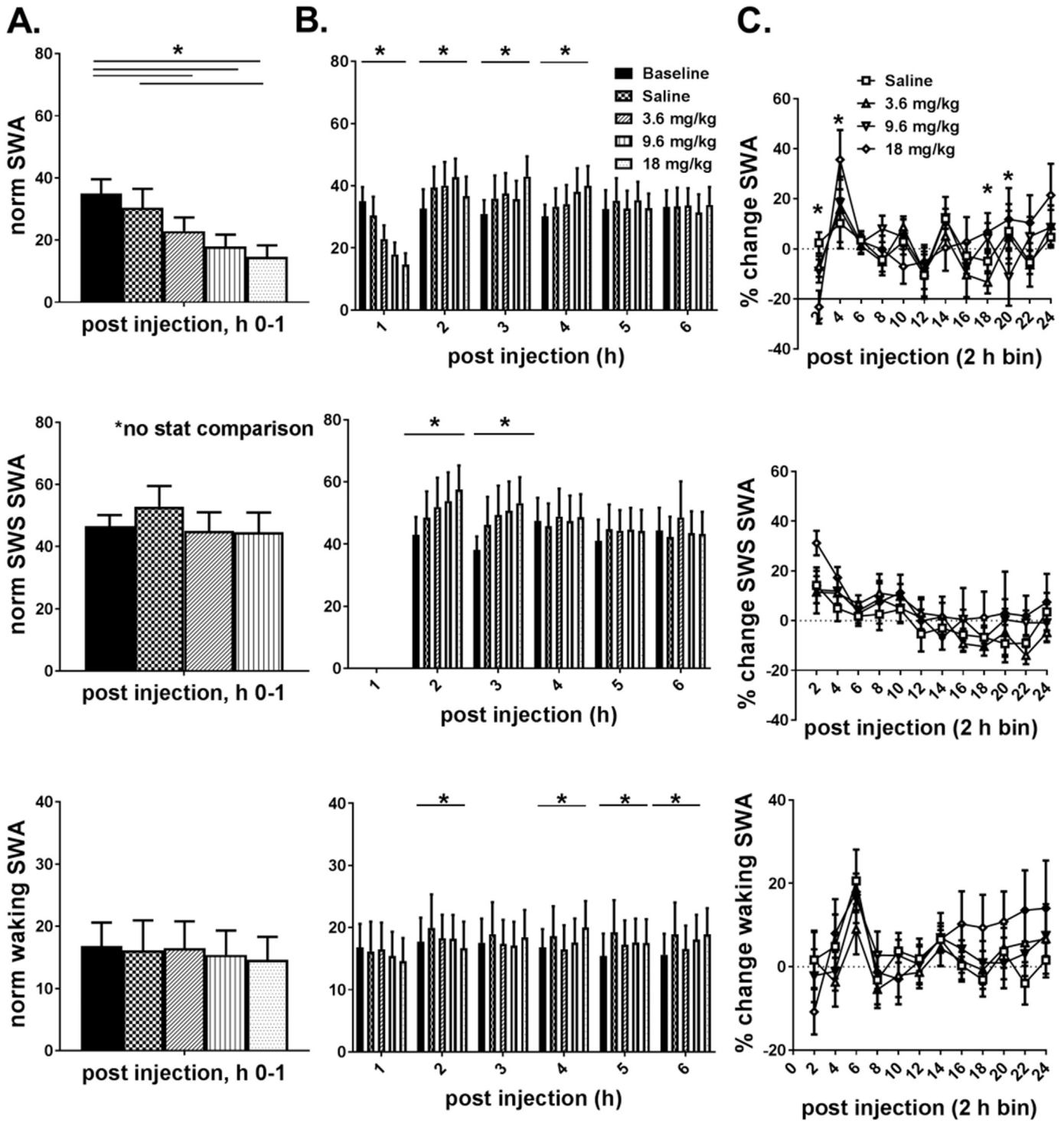

Fig. 5. SWA decreased following acute cocaine, due to increased proportion of waking. A,B) Acute cocaine decreased SWA power across states in the first hour following injection, while rebound SWA, SWS SWA, waking SWA was evident in the second, third, fourth and sixth hours following injection. Significant differences between conditions are indicated by solid horizontal lines. C) Compared to the same circadian time as baseline conditions, SWA power across states was reduced in the first 2 h bin and rebounds in the second 2 h bin with additional differences towards the end of the dark phase as indicated by asterisks. A complete summary of p values is provided in the Supporting Information.

increased waking and reduced sleep primarily in the first hour following injection due to increased duration of waking episodes and reduced frequency of sleep episodes, 2) reduced SWA followed by a subsequent rebound, and 3) increased fast EEG activity within waking with no affect on theta activity. Sleep/waking activity recovered within the 24 h period suggesting that there were no residual effects that carried over to the next injection period or that effects were too subtle to be captured by the analysis of averaging across 2 h (waking and SWS) or 4 h (REM) bins. Additionally, this also suggests that the mice were likely not anticipating the subsequent cocaine injections which would have resulted in anticipatory awakening prior to the subsequent injections.

The time frame of the peak sleep/waking effects matches the previous pharmacokinetic and pharmacodynamic effects of cocaine described with C57BL/6 mice following IP injections. Specifically, peak cocaine concentration in the brain occurs within the first 15 min

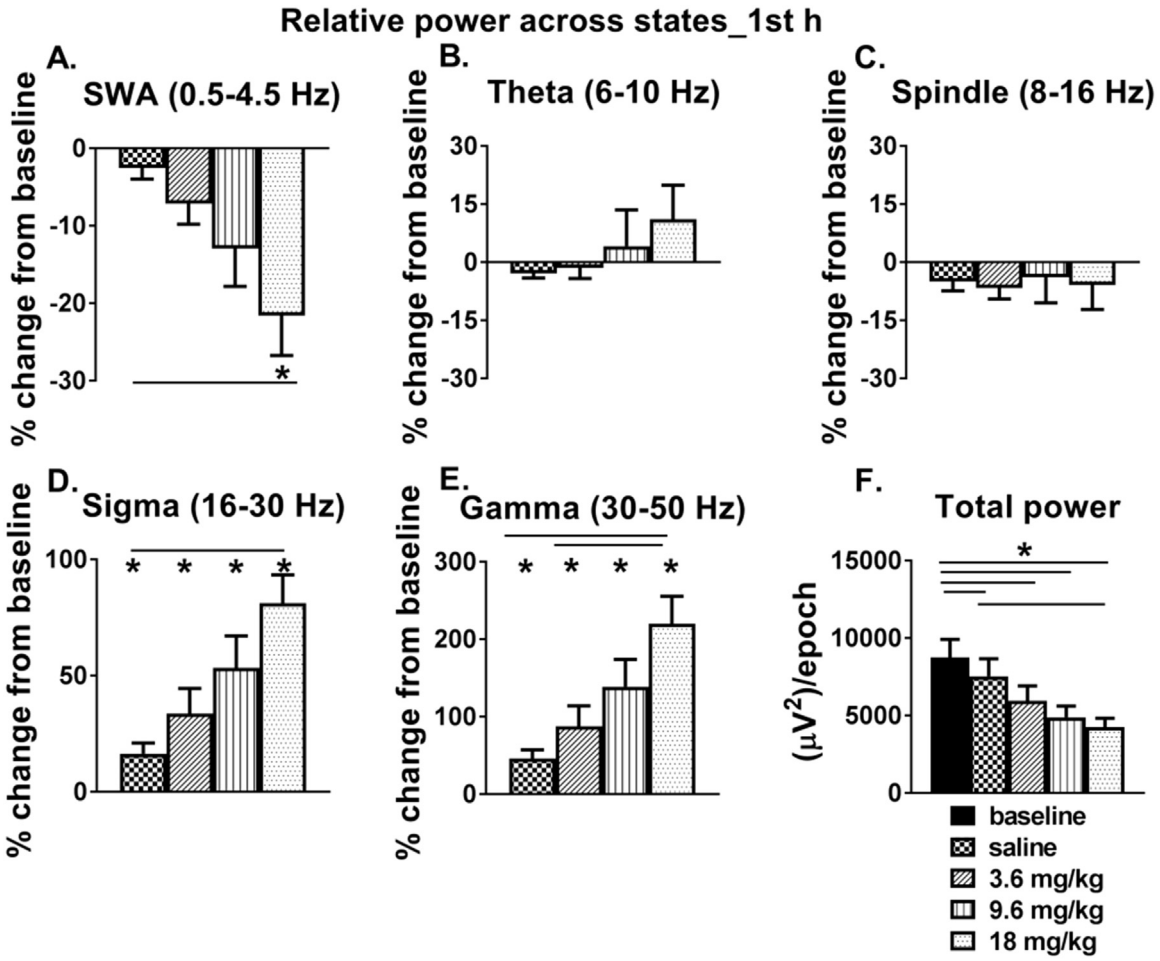

Fig. 6. Acute cocaine reduced the relative contributions of slow and increased the contributions of fast frequencies in the first hour following injection. Compared to the same circadian time under baseline conditions, cocaine A) reduced SWA, while faster sigma (D) and gamma (E) power were increased. Intermediate frequency bands, theta (B) and spindle (C) were unchanged. F) Furthermore, total power was reduced from baseline to all injections and from saline to the highest cocaine dose. Significant differences between conditions are indicated by solid horizontal lines, while significant differences from baseline are indicated by asterisks. A complete summary of p values is provided in the Supporting Information.

following injection and the estimated half life for clearance from the brain is 22.3 min (Azar et al., 1998). There is some evidence that the pharmacokinetics of cocaine changes with chronic use in that peak brain and plasma concentration is increased with 7–10 daily cocaine administrations in rats (Pettit et al., 1990; Cass and Zahniser, 1993); however, one study in mice showed an increase in brain concentration of cocaine between acute and 7 day chronic cocaine in young adult C67BL/6 mice, but not adult C57BL/6 mice (Mccarthy et al., 2004).

EEG desychrony following cocaine has previously been demonstrated in cocaine-experienced humans (Herning et al., 1985) and drug naïve rats (Chang et al., 1994; Smirnov and Kiyatkin, 2010) using IV administration. Conversely, Urbano and colleagues found that binge cocaine (3 administrations of 15 mg/kg cocaine across 3 h) in mice resulted in an increase in slow EEG power (1–12 Hz) with no changes in gamma (defined as 25–50 Hz, Urbano et al., 2009). It is possible that the source of the discrepancy between the current study and the previous finding of increased slow EEG activity and decreased fast EEG activity with cocaine administration in mice is due to acute versus "binge" administration. Binge cocaine in drug naïve rats results in tolerance of dopamine response (extracellular dopamine measured via microdialysis) within the nucleus accumbens and striatum, while drug-experienced animals do not show this same tolerance (Maisonneuve et al., 1995). Together, this indicates that both the pattern (binge versus single administration) and previous experience (drug naïve versus experienced) influences the response to cocaine in a manner that could differentially affect sleep/waking activity.

Gamma power was increased in the first hour following cocaine injection indicative of increased arousal (Maloney et al., 1997), while SWA was initially decreased followed by a subsequent recovery suggesting an increase in sleep need following stimulant-induced prolonged waking. Theta power has also been shown to increase with prolonged waking (Vyazovskiy and Tobler, 2005); the lack of increased theta in the current experiment may be due to the relatively short increased waking following cocaine (< 2 h) compared to enforced waking via sleep deprivation (significant increases seen after 4 h, Vyazovskiy and Tobler, 2005).

Cocaine blocks the dopamine, serotonin, and norepinephrine transporters (DAT, SERT, NET) with affinity for the DAT between that of SERT and NET; however, the behavioral effects of cocaine are highly correlated with inhibition of DAT as opposed to SERT or NET (Ritz et al., 1987). Blockade of DAT increases extracellular dopamine in association with increased arousal. There are several lines of evidence that dopamine is a wake-promoting neurotransmitter (for review Monti and Monti, 2007) including a recent demonstration that optogenetically stimulating dopamine neurons within the ventral tegmental area rapidly induced arousal from SWS (Eban-Rothschild et al., 2016). Furthermore, this wake-promoting feature of dopamine is in line with the prominent role of the mesocorticolimbic dopamine system in reward seeking and motivational behavior (for review, Koob and Volkow, 2010; Salamone and Correa, 2012; Feltenstein and See, 2013), given that these reward seeking and motivational behaviors occur during waking. Finally, DAT expression itself is modulated by cocaine

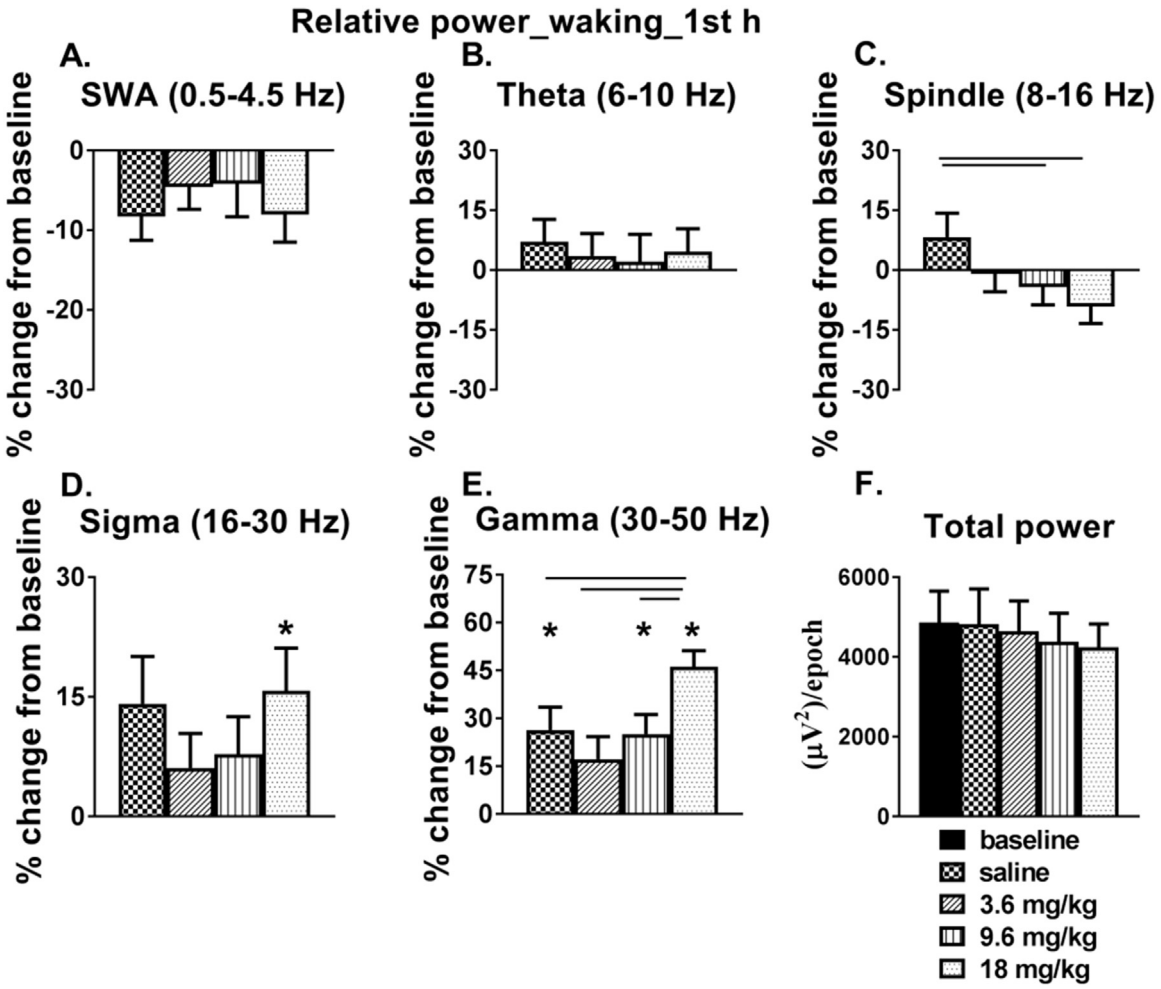

Fig. 7. Acute cocaine increased the contributions of fast frequencies within waking during the first hour following injection. Compared to the same circadian time under baseline conditions, cocaine reduced spindle power (C), while sigma (D) and gamma (E) power were increased. Slow and intermediate frequency bands, SWA (A) and theta (B) were unchanged. F) Total power was unchanged across conditions. Significant differences between conditions are indicated by solid horizontal lines, while significant differences from baseline are indicated by asterisks. A complete summary of p values is provided in the Supporting Information.

exposure with short access (5 day) resulting in decreased expression and long access (3–18 months) resulting in increased expression (Letchworth et al., 2001) which may account for differences in dopamine response to cocaine following different pattern and experience conditions.

In the current experiment there was a clear dose response effect with the largest sleep/waking effects following the highest dose of cocaine, intermediated effects with the middle dose, and subtle effects with the lowest dose. However, U shaped sleep/waking responses to cocaine have also been demonstrated. Rhesus monkeys with extensive cocaine self administration experience showed reduced sleep efficiency across a night of sleep that followed early morning administration with a preferred dose of cocaine, but not with lower or higher doses (Brutcher and Nader, 2013). Linear sleep/waking responses may be indicative of direct pharmacological effects of cocaine, while the non-linear sleep/waking responses may reflect the actions of more complex processes yet to be determined. Intriguingly, chronic cocaine reduces adenosine-mediated neuronal inhibition (Manzoni et al., 1998; Fiorillo and Williams, 2000) and activity of the adenosine transporter (Kubrusly and Bhide, 2010) which may have widespread sleep/waking effects given that adenosine is a key mediator of the homeostatic sleep response (Bjorness et al., 2016).

There are several limitations in the current experiment. First, order of saline and three cocaine doses were not fully randomized. Saline was chosen as the first injection to familiarize the mice to the injection process (removed from cage and IP injection while connected to the recording tether) while the highest cocaine dose was chosen as the last injection since it was the most likely to induce behavioral sensitization. Due to a within-subjects design it is possible that previous administrations of cocaine could influence arousal activity to subsequent administration via sensitization; however, sleep latency following 3.6 mg/kg as the first or second administration was similar as was 9.6 mg/kg (supplemental fig. 1). Second, cocaine was administered during a single circadian time point making possible circadian contributions unclear. Cocaine can induce a shift of the activity phase (Glass et al., 2012) and circadian genes influence reward seeking (Mcclung et al., 2005); however, there was no evidence of anticipatory waking prior to the last two cocaine administrations. Third, mice experienced one administration of cocaine per day for three days which is much different than the human experience and far short of an addiction model. The effect of binge administration (once per hour for three hours) on sleep/waking activity is currently being explored in C57BL/6 mice; however, sleep/waking measurements in humans occur after extensive experience such that truly chronic administration would be necessary to translate fully to the human condition as would the use of a self-administration as opposed to the experimenter-administered cocaine used here. Finally, there was no measure of reward seeking in the current experiment so the consequences of sleep loss on future drug seeking would be speculative.

Sleep disruption following cocaine use may have implications for

future drug use. Specifically, it has been hypothesized that sleep disruption during cocaine abstinence may influence the risk of relapse to cocaine similarly to the demonstrated sleep disruption-relapse risk for alcohol use (Brower et al., 2001). For cocaine relapse, the sleep disruption-relapse hypothesis is based on changes in SWS across abstinence and REM time in late abstinence that were correlated with negative urine samples in a set of people undergoing an 8 week treatment program (Angarita et al., 2014). Thus, treating sleep disruption may be an important tool in treating substance use disorders. Accordingly, Morgan and colleagues recently demonstrated that alongside cognitive behavioral therapy, morning-dosed modafinil increased SWS and cocaine abstinence (determined by drug-free urine samples) in men but not women undergoing treatment for cocaine dependence (Morgan et al., 2016).

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Conflicts of interest

TE Bjorness 'Conflicts of interest: none'.
RW Greene 'Conflicts of interest: none'.

Author contributions

T.E. Bjorness designed the experiment, collected and analyzed the data, and co-wrote the manuscript. R.W. Greene designed the experiment and co-wrote the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.nbscr.2018.02.001.

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