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Correlates of Polysomnographic Sleep Changes in Cocaine Dependence: Self-administration and Clinical Outcomes*

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Abstract

Background—Abstinence from chronic cocaine use is associated with abnormal sleep architecture. As sleep abnormalities are associated with clinical outcome in alcohol dependence, we hypothesized a similar relationship in cocaine dependence.

Methods—We report data from a cocaine self-administration study (N=12) and the placebo arm of a randomized clinical trial (N=20). Self-administration participants underwent three cocaine self-administration sessions during a three-week inpatient stay. Treatment participants underwent two weeks of inpatient followed by six weeks of outpatient treatment including once-weekly cognitive behavioral therapy. Measurements included polysomnography from early and late in abstinence during the inpatient stays. Clinical outcomes included amount of cocaine self-administered, urine tests, and self-reported use and withdrawal symptoms.

Results—Change in slow-wave sleep from early to late abstinence (SWS; $p=0.05$), late abstinence rapid eye movement sleep (REM; $p=0.002$), and late abstinence total sleep time ($p=0.02$) were negatively correlated with the amount of cocaine self-administered. Early

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Contributors

P.T. Morgan designed the study and wrote the protocol. G. A. Angarita and S. V. Canavan contributed equally to this work and are co-first authors. G. A. Angarita, S. V. Canavan, E. Forselius, A. Bessette, and P.T. Morgan recruited and screened participants, collected the data, and participated in clinical care and follow up. G. A. Angarita, S. V. Canavan, and P.T. Morgan performed statistical analyses and wrote the manuscript.

Conflict of Interest

No conflict declared.

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abstinence REM was positively correlated with withdrawal symptoms ($p=0.02$). Late abstinence REM was positively correlated with percent negative urines and maximum consecutive number of days abstinent (both $p<0.001$). SWS was positively correlated with percent negative urines ($p=0.03$) and participants with increased SWS had greater percent negative urines ($p=0.008$) and maximum consecutive number of days abstinent ($p=0.009$).

Conclusions—Correlations between sleep deficits and amount of cocaine self-administered, clinical outcomes, and severity of withdrawal symptoms underscore the relevance of sleep in clinical outcomes in the treatment of cocaine dependence.

Keywords

cocaine; sleep; polysomnography; clinical outcomes; self-administration; abstinence

1. INTRODUCTION

Cocaine use disorders exert a global impact. Not only has cocaine use increased in Europe and in some West African countries within the past decade (Degenhardt et al., 2011), but evidence-based ranking of addictive substances, using categories such as physical harm, dependence, and social stigma, has also listed cocaine as the second most harmful drug, after heroin (Nutt et al., 2007). North America has the world's highest prevalence rates for cocaine dependence, estimated at 1.6 million cases (Degenhardt et al., 2013). Despite reductions from peak use in the 1980s and 1990s, cocaine use remains a significant problem in the United States. In 2012, there were more current and more new users of cocaine than of heroin and methamphetamine combined (National Survey on Drug Use and Health, 2013). Despite decades of research into potential pharmacological treatment of cocaine dependence, no medication has been approved by the FDA to treat this condition.

In order to identify an effective pharmacotherapy that could be added to current psychosocial interventions (Simpson et al., 1999), one of the targets considered has been the disruption in sleep associated with chronic use of cocaine and withdrawal therefrom. This interest stems both from previous findings in cocaine users by our group and others, and from multiple findings on alcohol use disorders dating back to the 1970s (Allen et al., 1971; Allen and Wagman, 1975; Allen et al., 1977). One of the earliest studies on sleep in alcoholics found that rapid eye movement sleep, measured as a percentage of total sleep (REM%) decreased after 2–3 days of withdrawal but rebounded after 5–6 days (Allen et al., 1971). Later, this group demonstrated the potential clinical value of objectively measured sleep abnormalities: low REM% was positively correlated with response rate in a button-press task to obtain an alcoholic drink faster (Allen and Wagman, 1975). While some of the above findings on REM have been difficult to replicate, new findings have emerged. For instance, one study showed that persons with alcohol dependence who relapsed within 3 months of an inpatient admission had increased REM%, rather than decreased, and had shorter REM latency upon admission and upon discharge, in comparison with persons who remained abstinent (Gillin et al., 1994).

Other work has examined changes in the slow wave sleep (SWS) of alcohol users. This work ranges from documenting the potential ability of acute alcohol use to increase SWS

(Gross and Hasty, 1975) to several reports of abnormally low SWS among alcohol users, an effect that may remain for months (Brower, 2003). When it comes to the potential clinical relevance of SWS, Allen and colleagues examined SWS% in nine inpatients and found that subjects with poor outcomes had lower levels of SWS% at baseline, in comparison with the subjects who had good outcomes (Allen et al., 1977). Nevertheless, similar to the literature on REM, some findings on SWS have not been strongly replicated. For instance, study by Gillin et al (1994) showed no differences in Stage 3 or Stage 4 NREM sleep between abstainers and relapsers. In another study, subjects who relapsed had lower percentages of Stage 4 NREM sleep, but not SWS overall (Brower et al., 1998).

Intriguingly, deficits in SWS have been observed in chronic users of other addictive substances including central nervous system depressants such as heroin (Schierenbeck et al., 2008), stimulants such as amphetamines and cocaine (Thompson et al., 1995), and cannabis (Barratt et al., 1974; Bolla et al., 2008). Decreased SWS has been found early in abstinence and during sub-acute withdrawal from cocaine use (Angarita et al., 2014; Morgan et al., 2010; Schierenbeck et al., 2008) in addition to other polysomnographic changes present during the first weeks of abstinence from cocaine (Matuskey et al., 2011; Morgan et al., 2006, 2008, 2010). These changes include early REM rebound (Pace-Schott et al., 2005), prolongation of REM latency (Angarita et al., 2014), and decreases in REM, SWS, and total sleep time (TST) during the first 3 weeks of abstinence (Angarita et al., 2014; Morgan et al., 2006, 2008, 2010; Pace-Schott et al., 2005; Thompson et al., 1995).

Lastly, subjective self-reports of sleep may impact clinical outcomes in chronic substance users. For example, answering yes to the statement, “it takes me a long time to fall asleep” on the Nottingham Health Profile (NHP) questionnaire differentiated those who relapsed from those who abstained from alcohol (Foster et al., 1998). Another study, also among alcohol dependent subjects, demonstrated that the presence of subjective sleep disruption increased the likelihood of relapse (Brower et al., 2001). However, cocaine users exhibit the opposite trend of alcoholics when it comes to the clinical utility of subjective sleep measurements. Early work on inpatient cocaine dependent subjects studied for 28 days found conflicting subjective reports such as improvement on several sleep measurements (e.g., sleep quality) on one hand, and difficulties falling asleep, on the other (Weddington et al., 1990). Our group has shown that cocaine users report experiencing better sleep as abstinence progresses, despite the objective deterioration of multiple sleep measures along with worsening sleep-related cognitive function (Morgan et al., 2006). This discrepancy between subjective self-report and objective polysomnographic measurements has been replicated (Angarita et al., 2014).

However; in spite of the prior research on subjective and objective sleep abnormalities in chronic cocaine users, no work to date has associated sleep parameters during the initial abstinence period with later cocaine use or relapse.

The purpose of this work was to test for such an association by measuring sleep during confirmed abstinence in an inpatient setting as a predictor of two clinical phenotypes: laboratory cocaine self-administration (number of doses delivered) and use-related clinical outcome during treatment (i.e., percentage of urine tests negative for cocaine and maximum

consecutive number of days abstinent). To that end, we performed secondary analyses from two cohorts of participants: the first was a group of non-treatment seeking, cocaine dependent participants who self-administered cocaine during a period of inpatient abstinence; the second was a group participating in a combined inpatient-outpatient treatment protocol. Given that baseline sleep measures such as TST, SWS, and REM are perturbed in abstinent cocaine users relative to age matched controls, and considering that normalization of sleep measures have shown to be related to clinical outcomes in alcohol dependent patients, we hypothesized that decreased TST, SWS, and REM sleep measurements during abstinence, and the lack of normalization in those measurements in response to further abstinence, would positively correlate with worse clinical outcomes (e.g., more cocaine self-administration and lower percentage of negative urines/maximum number of consecutive days abstinent).

2. METHODS

2.1. Participants

Data is presented from two groups: 1) a “self-administration group” consisting of non-treatment seeking cocaine dependent individuals (N = 12) who participated in a laboratory study of intravenous cocaine self-administration (Morgan et al., 2008) and 2) a “treatment group” consisting of treatment-seeking cocaine dependent individuals enrolled in an ongoing clinical trial on modafinil who were randomized to receive placebo (N=20).

All participants met DSM-IV criteria for cocaine dependence, had been using cocaine for at least two years, were not taking any psychiatric medication, and were not dependent on any other drugs (except nicotine).

Potential participants were excluded if they had a medical condition that would render study participation unsafe, a chronic primary sleep disorder, a current non-substance/alcohol related axis I psychiatric disorder, or if taking either psychiatric medications or medications known to affect sleep. Female of childbearing potential were excluded if pregnant, lactating, or unwilling to use effective forms of contraception.

All participants reviewed and signed a consent form, approved by the local institutional review board, and understanding was assessed with a quiz.

2.1.1. Self-administration group—Detailed methods and outline of the self-administration study design were published previously (Morgan et al., 2006) and are summarized here in Figure 1. Briefly, 12 participants stayed inpatient for 23 days and were randomized to either an “early binge” group (N = 6) or a “late binge” group (N = 6) in a placebo-controlled manner to control for potential confounding effects of both inpatient hospitalization and potential subclinical withdrawal from other substances (e.g., alcohol, benzodiazepine, or cannabis). Both subgroups underwent an initial cocaine self-administration session on day 0 to assess safety and eligibility. The early binge subgroup completed 3 days of laboratory cocaine self-administration on study days 4–6 and 3 days of placebo (saline) self-administration on study days 18–20. The late binge subgroup completed the 3 days of placebo self-administration on study days 4–6 and the 3 days of

cocaine self-administration on study days 18–20. Participants were not aware of the early binge/late binge design, were not exposed to any medications during study days 1–3, 7–17, and 21–23, and were blinded as to whether they were receiving placebo or cocaine during any given session.

During each experimental self-administration day, participants were allowed to administer, ad libitum, up to 12 cocaine doses of 32 mg/70 kg over a 2-h binge period from 12 P.M. to 2 P.M. A 5-min lockout period following each bolus dose and a 384 mg/70 kg total daily limit were imposed. Safety cut-offs, based on heart rate and blood pressure, were also imposed.

Both subgroups underwent polysomnography (PSG) to measure their sleep on sixteen nights out of the 22-day protocol. Participants were allowed to sleep ad libitum between 9:30 P.M. and 7:45 A.M. every night while on the unit.

2.1.2. Treatment group—Participants in this randomized clinical trial first completed an initial 2-week inpatient phase, followed by a 6-week outpatient phase with thrice-weekly appointments. Inpatient treatment included both individual and group therapy, while outpatient treatment consisted of once-weekly, manual-guided cognitive behavioral therapy (Kadden et al., 1992). Contingency management (Budney and Higgins, 1998; Petry, 2000) rewarded attendance and completion of study related duties, but not abstinence. In weeks 3 and 6 of the outpatient phase, participants returned to the inpatient unit for additional inpatient stays of 2 nights each. While inpatient, scheduled bedtime was between 11:00 P.M. and 7:00 A.M., during which participants were required to be in bed with the lights off. Study procedures are outlined in Figure 1.

Data from overnight polysomnographic sleep studies (PSG) are reported from the inpatient portion of the study. Inpatient portion PSG studies were conducted on nights 3 and 4 (study week 1), and 10 and 11 (study week 2). The first night of each set was used as an accommodation night to acclimate the participant to wearing the polysomnographic equipment, while data from the second night was used for analyses. However, two PSG data points used night 3 and two PSG data points used night 10 because the second night data could not be scored.

To measure cocaine use during the study, urines were collected at the screen, at each inpatient admission, on initial inpatient days 1, 4, 8 and 11, and at each of the thrice-weekly outpatient appointments. Urines were tested for cocaine (benzoylecgonine) as well as opiates, benzodiazepines, methadone, amphetamines, barbiturates, cannabis, PCP, and propoxyphene.

Participants reported any substance use by filling out a timeline follow back calendar at each of their appointments (Miller and Del Boca, 1994; Sobell and Sobell, 1980). At the time of each inpatient admission they were also queried as to the day of their last cocaine use.

At screen and inpatient days 1, 4, 8 and 11, the Cocaine Selective Severity Assessment (CSSA) (Kampman et al., 1998) was administered to assess cocaine withdrawal symptoms.

2.2. Inpatient environment

Participants were admitted to a full-service locked inpatient psychiatric unit, where they slept in a single room every night with no napping allowed outside of bedtime hours. The unit provided all meals and snacks as part of a caffeine free diet. Participants could leave the unit for fresh air breaks three times per day, escorted by staff members.

2.3. Polysomnography

PSG was performed on the treatment group using a TEMEC 8 Channel Universal system (TEMEC Instrument B.V., Kerkrade, the Netherlands) and consisted of two electrographic (EEG) leads (C3-A2 and C4-A1), left and right electro-oculogram (EOG) referenced to the opposite mastoid, a two-lead chin electromyogram (EMG), and a two-lead electrocardiogram (ECG).

In the self-administration group, PSG was performed (Grass Instruments, Colleague System) using two additional EEG leads (O1-A2 and O2-A1).

On the first night of recording (night 3) for the treatment group, a more extensive clinical sleep study was carried out (Siesta; Compumedics, Abbotsford, Australia) to screen for sleep disorders. In addition to the above leads, this setup included four more EEG leads (F3-A2, F4-A1, O1-A2, and O2-A1), right and left leg EMGs, finger pulse oximeter, plethysmographic thoracic and abdominal belts, airflow sensor, and snore microphone.

All PSG records were scored according to American Academy of Sleep Medicine guidelines (Iber et al., 2007) by an experienced sleep scorer who was blind to treatment group and study night. Times spent in rapid eye movement (REM) sleep and non-REM (NREM) sleep stages 1, 2, and 3 were determined. Sleep onset latency was defined as time from “lights out” until the first epoch of sleep and REM latency was defined as time from sleep onset to the first epoch of REM sleep. Total sleep time (TST) was calculated by taking the time from sleep onset to the final awakening, minus time awake after sleep onset.

2.4. Definition of Outcomes

In order to be congruent with previous literature reporting sleep changes during abstinence from cocaine (e.g., abstinence days 1–3, 7–9, and 14–16; Morgan et al., 2010) and to incorporate the maximum number of PSG data points obtained, PSG outcomes in the self-administration group were averaged over “early abstinence” (abstinence days 1 to 6) and “late abstinence” (abstinence days 14 to 17). In the treatment group, early abstinence data is from study week 1 (median number of days abstinent: 5.5 ± 1 [semi-interquartile range]) and late abstinence data is from study week 2 (median number of days abstinent: 13 ± 1). Absolute times for sleep latency, total sleep time, REM sleep time, and N2 sleep time were analyzed. As slow-wave sleep (SWS; equivalent to non-REM stage 3) and REM latency times were not normally distributed and were very low in some participants at some points (Ansseau et al., 1985; Morgan et al., 2006; Moses et al., 1972;), relative rather than absolute changes in these measures from early to late in abstinence (percent SWS, percent REM latency) were used for these analyses. Individuals were also split into groups based on the

direction of change in these measures from early to late abstinence (SWS increased/not increased and REM latency prolonged/not prolonged) for further analyses.

For the self-administration group, the main outcome measure was the fraction of cocaine administered out of the total available doses.

For the treatment group, two types of clinical outcomes measures were used: percent of urines negative for cocaine metabolite (for which missed appointments are counted as positive), and maximum consecutive days abstinent, which was calculated using a combination of urine toxicology data and timeline follow back self-report to determine the number of days of abstinence at each study time point. A single, missed urine in this case was considered negative if the previous and subsequent urines were negative and the self-report from the subsequent session was negative for the intervening period.

Given previous finding on the discrepancies between subjective sleep self-reports and objective sleep findings in cocaine users (Morgan et al, 2006), we limited this analysis to objective sleep measurements.

As a preliminary analysis of subjective clinical correlates of objective sleep changes, withdrawal symptoms measured by the CSSA at early abstinence and late abstinence were compared to PSG measures in the complete sample, and in those participants who had a positive urine test for cocaine metabolite on admission (N = 12).

2.5. Statistical Analyses

Spearman correlations were performed to determine associations between PSG sleep measures and fraction of cocaine available administered, clinical cocaine use outcomes, and CSSA.

Unpaired, two-tailed t-tests were performed to compare self-administration or clinical outcome measures between SWS increased and not increased, and between REM latency prolonged and not prolonged subgroups.

All analyses were performed using an IBM SPSS Statistics processor, version 19.

3. RESULTS

3.1. Demographics

Demographic and baseline information is provided in Table 1. Subjects in the treatment group were older (44.6 vs. 38.6 years old; $t = 2.4$; $p = 0.02$) and had been using cocaine for longer than subjects on the self-administration group (25.2 vs. 17.4 years; $t = 2.8$; $p = 0.008$). In the treatment group, 3 individuals out of the initial 20 did not begin the outpatient period and therefore provided no cocaine use data, but were included in the CSSA analysis.

3.2. REM and TST

Absolute numbers for REM and TST from the self-administration and the treatment group, as well as similar information from previously published cohorts on alcohol dependent individuals (Brower and Hall, 2001; Colrain et al., 2009) and two reference groups of

insomnia patients (Huang et al., 2013; Voderholzer et al., 2003), are available in table 2. In the self-administration group (N = 12), REM time and TST late in abstinence were negatively correlated with fraction of cocaine self-administered.

In the treatment group (N = 17), REM time late in abstinence was positively correlated with percentage of negative urines and maximum consecutive number of days abstinent (Table 3).

3.3. SWS

Absolute numbers for SWS from the self-administration and treatment groups and similar data from the comparison cohorts on alcohol and insomnia, are available in Table 2.

Baseline slow wave sleep (SWS) data, normalized to healthy controls, is shown for the self-administration and treatment group (Figure 2), along with the reference groups of alcohol dependent individuals and the reference groups of insomnia patients (Huang et al., 2013; Voderholzer et al., 2003); each group is shown normalized to their own set of healthy controls and is of a comparable age range.

In the self-administration group (N = 12), percent change in SWS (percent SWS) showed a trend toward negative correlation with fraction of cocaine self-administered ($r = -0.57$; $p = 0.05$) and participants whose SWS time increased from early to late abstinence (N = 5) showed a trend toward less cocaine self-administered ($t = 2.12$; $p = 0.06$).

In the treatment group (N = 17), percent SWS was positively correlated with percentage of negative urines (Table 3) and participants whose SWS time increased from early to late abstinence (N = 10) had a higher percentage of negative urines and higher maximum consecutive number of days abstinent than the ones whose SWS did not increase (N = 7) (Figure 3).

3.4. REM Latency

Absolute numbers for REM Latency and similar data from the comparison cohorts on alcohol and insomnia are also available in table 2.

In the self-administration group (N = 12), there were no differences in the fraction of cocaine self-administered associated with changes in REM latency.

In the treatment group, participants without prolonged REM latency (N = 7) had a higher percentage of negative urines ($t = -2.8$; $p = 0.01$) than participants who exhibited prolonged REM latency (N = 10).

3.5. N2 and Sleep Latency

No statistically significant correlations between N2 sleep time or sleep latency and clinical outcomes were observed (all $r < 0.2$, $p > 0.1$).

3.6. Cocaine Withdrawal Symptoms

Among all participants in the treatment group ($N = 20$), there were no significant correlations between CSSA and REM sleep. Within the subgroup of participants with a positive urine test for cocaine metabolite upon admission ($N = 12$), there was a strong positive correlation between CSSA and REM sleep at early abstinence ($r = 0.67$; $p = 0.02$).

4. DISCUSSION

Although a growing body of literature has demonstrated the emergence of sleep disturbances during withdrawal from cocaine (Kowatch et al., 1992; Morgan et al., 2006, 2008, 2010; Pace-Schott et al., 2005; Schierenbeck et al., 2008) to our knowledge, no previous work has shown the potential impact of these sleep disturbances on human laboratory measures of cocaine self-administration or on treatment outcomes. Among individuals in the self-administration group ($N = 12$), total sleep time (TST) and rapid eye movement (REM) sleep late in abstinence were associated with lower cocaine self-administration. Among individuals in the treatment group ($N = 17$), REM sleep late in abstinence, and increased slow wave sleep (SWS) from early to late abstinence, were associated with better clinically relevant outcomes. Within the treatment group ($N = 20$), preliminary evidence also suggested that during early abstinence only ($N = 12$), REM sleep was positively correlated with severity of cocaine withdrawal symptoms, as measured by the Cocaine Selective Severity Assessment (CSSA). This work provides the first evidence of a relationship between abstinence-induced objective sleep related changes and clinically relevant measures of cocaine use.

The polysomnographic findings associated with less cocaine use and better clinical outcome appear to reflect a lesser degree of impairment in sleep architecture during the first two to three weeks of abstinence. In chronic cocaine users, REM time typically decreases from early to late abstinence (Morgan et al., 2008) and is less than REM in age-matched controls in late abstinence (Morgan et al., 2010). However, we found that REM time in late abstinence was positively correlated with better clinical outcomes and negatively correlated with amount of cocaine self-administered. Furthermore, SWS time appears to be persistently reduced in abstinence from chronic cocaine use (Morgan et al., 2010) yet was positively correlated with clinical outcome. Hence, chronic cocaine users who exhibited less severe REM and SWS time deficits in response to abstinence had better clinical outcomes. The finding regarding REM latency among treatment seeking participants is consistent with the pattern seen in SWS and REM time. REM latency is typically short in early abstinence but increases with continued abstinence (Morgan et al., 2008, 2010). Consequently, the correlation between the lack of such an increase and better clinical outcome is compatible with the idea that sleep changes opposite to the ones previously attributed to cocaine abstinence are associated with better clinical outcomes. We did not find, however, a correlation between REM latency time and outcomes, such as that observed in alcohol dependent persons (Gillin et al., 1994). Although this may indicate a difference in the importance of REM latency to clinical outcome in alcohol and cocaine dependence, it may simply reflect the large and non-continuous intra-individual variations in REM latency (i.e.,

REM latency times within an individual are often bimodal, as many participants vacillate between having or not having an early REM period; Ansseau et al., 1985).

Although the present work does not establish a causal relationship between sleep measures and cocaine use outcomes, substantial evidence points to the likelihood of this possibility. Indeed, sleep plays a fundamental role in regulating several neuropsychological processes that influence relapse, suggesting multiple concurrent mechanisms whereby disruption of sleep could potentially worsen clinical outcomes.

One potential mediating factor is cognitive performance. Several studies have not only shown that cocaine dependent persons have a wide variety of cognitive difficulties (Bauer, 1994; Di Sclafani et al., 2002; Hoff et al., 1996; Horner, 1999; Morgan et al., 2006, 2008; O'Malley et al., 1992), but have also demonstrated a connection between poor sleep and poor cognition in this population (Pace-Schott et al., 2005). Examples of this connection include the relationship between TST and sleep dependent procedural learning (Morgan et al., 2006), and the impact of early night SWS with late night REM on performance on a visual discrimination task. This has been documented in both healthy controls (Stickgold et al., 2000) and in cocaine users (Morgan et al., 2008), and illustrates the importance of sleep architecture for learning. The practical value of the sleep-cognition association is heightened by the relationship between cognitive performance and treatment retention (Aharonovich et al., 2006) as well as the relationship between cognitive performance and treatment outcomes (Teichner et al., 2001).

Another potential mediating factor is affect regulation. Negative affect, including irritability, depression, and stress, emerges during abstinence from cocaine and has been linked to subsequent cocaine use (Newton et al., 2003; Stulz et al., 2011). Cocaine dependent persons exhibit increased subjective and physiological reactivity to stressful situations (Fox et al., 2008) and experience cocaine craving in response to stress (Sinha et al., 1999) a reaction that has been linked to increased propensity for relapse (Sinha et al., 2006). Sleep, particularly REM sleep, is a crucial regulator of emotion (Perogamvros et al., 2013; Walker and van der Helm, 2009), as evidenced by the strong negative effects of sleep deprivation (Franzen et al., 2008; Pilcher and Huffcutt, 1996) and restriction (Dinges et al., 1997; Haack and Mullington, 2005) on mood, and on next-day ability to respond to stressors (Motomura et al., 2013; Yoo et al., 2007). Enhanced impulsivity in behavioral responses to negative stimuli is also observed in sleep-deprived individuals (Anderson and Platten, 2011). Negative affect and lack of appropriate response to stressors during abstinence, precipitated and maintained by sleep dysregulation, could therefore be a substantial contributor to the link between sleep deficits and treatment outcomes observed here.

In addition to the main associations between sleep deterioration and cocaine use outcomes, we also found preliminary evidence that REM sleep time early in abstinence correlates positively with withdrawal symptoms as evaluated by the CSSA, a measure that has been shown to predict treatment outcome (Kampman et al., 2001). As this correlation was only observed in the sub-sample ($N = 12$) with positive urine tests for cocaine metabolite at admission (i.e., in those participants who were less than 1 week abstinent at the time of measurement), it suggests a relationship specifically between the REM rebound that occurs

after cessation of cocaine use (Morgan et al., 2008; Yang et al., 2011) and other withdrawal symptoms. One potential limitation of this work is the demographic differences between the self-administration and the treatment group, including differences in age, years of cocaine use, and amount of alcohol use. However, it is also true that notwithstanding differences between these two groups, they are a fair representation of current cocaine users in the community (e.g., mean age in the mid 40s, lifetime years of cocaine use of 16 or more, average number of alcohol use close to 15 drinks per week, etc.; Johnson et al., 2013; Kampman et al., 2013; Matuskey et al., 2014). Furthermore, similar findings in both groups suggest that the observed correlations may generalize to chronic cocaine users more broadly.

A key limitation of the present study is its correlational design, which may not fully account for other factors affecting clinical outcomes. For instance, our group previously reported negative correlations between lifetime number of years of cocaine use and TST and SWS, as well as between age and SWS (Matuskey et al., 2012). This analysis also found a positive correlation between current alcohol use and TST (Matuskey et al., 2012). However, a more recent analysis of the participants in the current treatment group found no correlation between baseline alcohol use and PSG sleep outcomes (Angarita et al., 2014). In addition, post-hoc comparisons between the increased SWS and not increased SWS subgroups (from both the self-administration and the treatment group) and between the prolonged and not prolonged REM latency subgroups (from the treatment group) did not show differences by lifetime number of years of cocaine use, current alcohol use, and age (Supplementary Table 1¹).

Although we found associations between sleep measurements and clinically relevant outcomes, a causal link is not yet established. However, the similarity of the findings between the two studies – a laboratory-controlled self-administration study and a treatment study – as well as prior studies showing a potential role of sleepiness in the reinforcing and subjective effects of stimulants (Roehrs et al., 2004) and previously demonstrated effects of poor sleep on factors such as cognition, mood, and impulsivity, support the likelihood that there is a causal relationship between sleep and cocaine use in chronic cocaine users. This interpretation of the data is also supported by similar findings relating sleep to alcohol use (Allen et al., 1975, 1977; Benca et al., 1992; Brower and Hall, 2001; Brower, 2003; Colrain et al., 2009), and by longitudinal studies that suggest a “bi-directionality” in the relationship between sleep and substance use (Pasch et al., 2012; Shibley et al., 2008). To determine whether sleep architectural changes contribute causally to treatment outcome, present and future studies will examine the effect of normalization of sleep (e.g., with modafinil; Morgan et al., 2010) on clinical outcomes. As part of this future work, it will also be important to further investigate the discrepancy between objective sleep measurements and subjective self-reports of sleep, and to further examine whether cocaine users specifically associate sleep problems with relapse, given the strength of this association in alcohol users. Overall, the current findings not only suggest the importance of targeting sleep, but also identify possible polysomnographic goals such as increasing the amount of SWS and normalizing other abstinence induced changes in REM, TST, and REM latency. Further

¹Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

research is needed to establish a detailed understanding of specific mediating factors in the relationship between sleep and cocaine use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Outline of design for the self-administration and treatment studies. A) The self-administration study was a 23-day inpatient study with two blinded groups (early binge and late binge). To maintain blinding, all study protocols were the same between groups, including nights of polysomnography (PSG). Study days 1–3 were used to acclimate participants to sleeping in the inpatient environment, and to allow washout of any other substances used prior to admission, which might have had an immediate effect on sleep. “Early abstinence sleep” in the self-administration study included post-cocaine days 1–6 (broken up in 2 periods in the late-binge group). “Late abstinence sleep” included post-cocaine days 14–17. B) The treatment study consisted of 2 weeks inpatient followed by 6 weeks outpatient. “Early abstinence sleep” was measured on day 4 (median days post-cocaine use in these participants was 5.5), while “late abstinence sleep” was measured on day 11 (median days post-cocaine use was 13). In the event that sleep on night 4 could not be scored (2 nights of data), night 3 was used as the marker of “early abstinence sleep”; in the event that sleep on night 11 could not be scored (2 nights of data), night 10 was used.

Figure 2.

Baseline Slow Wave Sleep (SWS) data, normalized to healthy controls, is shown for the current groups of cocaine dependent participants, two reference groups of alcohol dependent individuals, and two reference groups of insomnia patients. SWS data from each group was normalized to data from healthy controls reported in the same study in order to correct for systematic differences in sleep data collection and scoring. Cocaine dependent data were normalized to a group of healthy controls reported in Morgan et al, 2010. Error bars are standard deviations.

Figure 3.

Clinical outcomes related to prolongation in slow-wave sleep time. Participants in the treatment study were separated into those who exhibited any prolongation in slow-wave sleep (SWS) time between early abstinence and late abstinence (“SWS prolonged” $n = 10$), and those who exhibited either no change or a decrease from early to late abstinence (“SWS non-prolonged,” $n = 7$). Clinical outcomes data during the following 6-week outpatient period, as measured by urinalysis and timeline follow back report, was then compared between the groups. SWS prolonged showed increases in abstinence in terms of both percentage of cocaine-negative urines and maximum consecutive days of abstinence. **, $p < 0.01$

Table 1

Demographic and baseline information.

	"Self-administration group"	"Treatment group"
N =	12	20
Years of age (Mean $\pm$ SD)	38.7 $\pm$ 7.1	44.7 $\pm$ 6.6
Sex (% male)	83.3	80.0
Years of education (Mean $\pm$ SD)	13.4 $\pm$ 2.3	12.0 $\pm$ 1.3
Race		
African	9	14
American:	3	4
Caucasian:	0	1
Hispanic:	0	1
Multiracial:		
Alcohol use (# of drinks/week)	6.1 $\pm$ 9.2	16.2 $\pm$ 15.8
Cigarette Smokers (%)	92	70
Years of cocaine use	17.4 $\pm$ 7.2	25.2 $\pm$ 7.7
Current cocaine use (grams/week)	9.4 $\pm$ 5.6	5.8 $\pm$ 6.6

Table 2

Absolute numbers (in minutes) for TST, SWS, REM, and REM latency from the current self-administration treatment groups, two reference groups of alcohol dependent individuals, and two reference groups of insomnia patients.

	Cocaine Dependent Subjects				Historical data published on other conditions			
	Self-Administration		Treatment		Alcohol (Brower)	Alcohol (Colrain)	Insomnia (Huang)	Insomnia (Voderholzer)
	Early Abstinence	Late Abstinence	Early Abstinence	Late Abstinence ^a		Males		
N	12		20		123	27	141	86
Mean age	38.7		44.7		37.7	50.5	42.17	41.7
TST	367.1 ± 31.3	336.9 ± 36.0	388.5 ± 46.8	341.5 ± 58.2	313.9 ± 48.4	398.2 ± 68.0	392.50 ± 89.16	405.9 ± 50.8
SWS	34.1 ± 28.2	34.7 ± 25.2	38.8 ± 34.9	38.9 ± 37.4	26.7 ± 27.6	26.3 ± 20.7	62.82 ± 35.58	28.1 ± 30.8
REM	98.7 ± 27.1	84.4 ± 27.5	97.0 ± 32.5	82.1 ± 24.8	62.8 ± 19.5	96.8 ± 30.3	61.68 ± 29.95	87.1 ± 21.8
REM latency	44.5 ± 18.8	61.1 ± 26.1	42.0 ± 37.6	60.9 ± 41.8	79.7 ± 52.7	95 ± 80.5		75.8 ± 36.8

All values reported as mean ± standard deviation, measured in minutes

^aTwo participants withdrew from the treatment study early and did not provide late abstinence data.

Table 3

Significant Correlation Coefficients between PSG measures and use outcomes.

PSG Measure	%Negative Urines (N = 17)	Maximum Consecutive Days Abstinent (N = 17)	Fraction of Cocaine Self Administered (N = 12)
REM ^a	0.75 ***	0.80 ***	-0.79 **
TST ^a			-0.65 *
SWS ^b	0.48 *		

*
p<0.05;**
p<0.005;***
p< 0.001^aREM and TST measured in late abstinence.^b SWS indicates percent of change from early abstinence to late abstinence.