Published in final edited form as:

Drug Alcohol Depend. 2012 September 1; 125(1-2): 132–139. doi:10.1016/j.drugalcdep.2012.04.004.

Response inhibition and psychomotor speed during methadone maintenance: impact of treatment duration, dose, and sleep deprivation

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Abstract

Background—In opiate-dependent individuals, abstinence results in deficits in cognitive functioning, which may be exacerbated by medication-associated sleep disruption.

Method—To assess cognitive function and the influence of sleep deprivation (SD), 14 healthy control (HC) and 22 methadone maintained (MM) participants completed the Continuous Performance Task (CPT) after a baseline night, a night of total SD, and two recovery sleep nights. The Digit Symbol Substitution Task (DSST) was administered at bedtime and in the morning. Secondary analyses separated MM participants into short- (<12 months; n=8) and long-term (12 months; n=14) treatment duration groups, and into low- (< 80 mg; n=9) and high-dose (≥ 80 mg; n=13) groups.

Results—Linear mixed model ANOVAs revealed that there was no effect of SD. Across all days MM participants had more errors of omission, fewer correct responses, and slower reaction times (RTs) on the CPT, and fewer accurate substitutions on the evening and morning DSST. Short-term MM participants exhibited slower RTs on the CPT, and fewer correct substitutions on the evening DSST compared to long-term MM participants. Low-dose MM participants had slower RTs on the CPT than HCs and high-dose MM participants.

Conclusion—These data demonstrate that methadone-maintained individuals exhibit poorer performance on tasks of psychomotor speed and selective attention/impulsivity, but with longer-

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CONTRIBUTORS Authors CM Dorsey and SE Lukas designed the study and wrote the protocol. Authors GH Trksak, DM Penetar, WL Tartarini, and MA Maywalt conducted the study and managed the data. Author BK Bracken undertook the statistical analysis, and wrote the first draft of the manuscript. All authors have contributed to and approved the final manuscript.

CONFLICT OF INTEREST No conflict declared.

term treatment, performance appears to return toward control levels. Furthermore, while one day of SD was enough to alter subjective reports of sleep quality, cognitive function may be more resilient.

Keywords

methadone maintained; sleep deprivation; psychomotor performance; impulsivity

1. INTRODUCTION

Worldwide, 21.9 million people used opiates in 2008 (United Nations Office of Drugs and Crimes, 2010). In the US, 1.9 million people are dependent on or abused prescription pain medications; 399,000 people meet these criteria for heroin (Substance Abuse and Mental Health Administration, 2010). Per year, there are 739,000 treatment admissions for prescription pain medication and 507,000 treatment admissions for heroin (Substance Abuse and Mental Health Administration, 2010). In the UK, there are 330,000 people who used heroin or cocaine; three quarters of adults seeking drug treatment are heroin addicts; and deaths from heroin are rising (National Treatment for Substance Misuse, 2009).

Methadone maintenance (MM) has been a standard opiate-dependence treatment for over 30 years. Once daily oral methadone is safe and efficacious at suppressing withdrawal symptoms and blocking euphoric effects associated with heroin administration (Committee of Methadone Program Administrators, 1997). MM positively impacts general health of opiate abusers, increasing treatment retention (Mattick et al., 2009), decreasing heroin use, improving health outcomes, and decreasing risky sexual behavior, HIV/AIDS, hepatitis and STDs (Committee of Methadone Program Administrators, 1997). MM increases productivity, decreases criminal activity (Hubbard et al., 1997; Gossop et al., 2005), and lowers mortality (Soyka et al., 2006; 2011).

In healthy volunteers, i.v. morphine increases subjective ratings of drug effect, but does not effect psychomotor speed (Hill and Zacny, 2000). Current heroin abusers perform worse on intra- and extra-dimensional set shifting and working memory tasks when compared to healthy controls (HCs; Ornstein et al., 2000). Memory and response inhibition decrements persist in initial (~2 weeks) MM therapy (Rapeli et al., 2007), but improvements on a subset of tasks including verbal learning and memory, visuospatial memory, psychomotor speed (Gruber et al., 2006), executive functioning (Soyka et al., 2008), and response inhibition (Soyka et al., 2010) are seen after several months of MM stabilization. However, reduced use of other drugs and alcohol, less harmful lifestyles, and learning effects may also contribute to improvements (Soyka et al., 2008). Even after stabilization on methadone, MM participants perform worse than HCs (Pirastu et al., 2006). In fact, higher methadone doses (Loeber et al., 2008) and more recent methadone administration (Curran et al., 2001) are associated with poorer performance. Even MM participants stably medicated for years perform worse than HCs and successfully abstinent heroin dependent individuals (Mintzer et al., 2005; Verdejo et al., 2005; Prosser et al., 2006).

Impaired sleep may contribute to reduced cognitive function (Schmutte et al., 2007). Methadone and heroin similarly disturb sleep, although methadone is about half as potent as heroin (Kay et al., 1981; Wang and Teichtahl, 2007). Disturbances to sleep architecture occur during all phases of opiate use (Wang and Teichtahl, 2007) with subjective sleep most disturbed at the end of opiate detoxification, and slowly normalizing by two weeks of abstinence (Beswick et al., 2003). In alcohol and cocaine-abusing populations, disturbed sleep is an important predictor of relapse (Brower et al., 1998; Conroy et al., 2006), and

there are many indications that this is true in opiate-dependent populations as well (Gossop and Bradley, 1984; Staedt et al., 1996; Oyefeso et al., 1997).

To test whether deficits in cognitive functioning may be exacerbated by acute sleep disturbance, the present study examined impulse inhibition, psychomotor speed, subjective mood, sleep quality and sleep quantity before and after one baseline night of sleep, one night of total sleep deprivation (SD), and two recovery sleep nights (RE). To assess differences based on the duration of MM, secondary analyses divided participants into short- and long-term MM treatment duration groups. Finally, to assess differences based on methadone dose, secondary analyses divided participants were divided into low- and high-dose groups. A priori hypotheses were that all MM participants would perform more poorly on cognitive tasks than HCs at baseline, and that baseline differences would be exacerbated by SD. Short-term MM participants would perform most poorly, however after SD both long- and short-term groups would perform at a similar level. Finally, participants on a high dose of methadone would perform the most poorly, however after SD both high- and low-dose groups would perform at a similar level. These data were collected as part of a larger study to assess the effects of SD on sleep architecture and brain bioenergetics in MM participants (Trksak et al., 2010).

2. METHODS

2.1 Participants

HCs and opiate-dependent participants actively enrolled in a MM program were recruited via newspaper, radio, online advertisements, or from the North Charles Mental Health and Addiction Services (Cambridge, MA). After initial phone screens, they visited the Sleep Research Laboratory at McLean Hospital where IRB approved informed consent was obtained. They underwent a physical examination (EKG, complete blood panel and test of liver function), drug urine screen (QuickTox Drug Screen Dipcard, Branan Medical Corporation, Irvine, CA), and pregnancy testing for females (Stanbio QuPID, Studio Laboratory, Boerne, Texas). Pregnant participants were excluded. Participants were free of any current Axis I disorders (Structured Clinical Interview for DSM-IV Disorders; First et al., 1997), except opiate dependence for MM participants. Participants were free of primary sleep disorders, including sleep apnea and periodic limb movement disorder assessed with polysomnography. On study nights participants were again tested for drugs and pregnancy. Positive drug test results: Baseline- 3 cocaine, 3 benzodiazepines, 1 morphine, 1 THC; SD- 2 cocaine, 4 benzodiazepines, 1 morphine, 1 THC, 2 PCP; RE 1- 1 cocaine, 3 benzodiazepines, 1 THC; RE 2- 4 cocaine, 5 benzodiazepines, 2 morphine, 1 PCP. The percentage of drug positive urines were not different between groups (short-term MM: 38%; long-term MM: 29%; low-dose methadone: 33%; high-dose methadone: 33%).

Participant completers were 14 HC adults (34 ± 3.1 years; $n=7$ females), and 22 MM adults (39.5 ± 2.1 years; $n=10$ females). There were no significant age or sex differences between HC and MM groups. Average treatment duration for the MM group was 16.1 ± 2.4 months. Within the MM group, 8 participants were categorized as short-term (MM ≤ 12 months; age= 38 ± 3.6 years; 4 female), and 14 as long-term (MM > 12 months; age= 40.3 ± 2.8 years; 6 female). This differentiation is based on previous findings and clinical relevance (Oviedo-Joekes et al., 2009; Peles et al., 2011a). There were no significant age or sex differences between short-and long-term treatment groups. Within the MM group, 9 participants were categorized as low-dose (dose <80 mg; age= 45.6 ± 6.0 years; 6 female), and 13 as high-dose (dose ≥ 80 mg; age= 35.2 ± 10.2 years; 4 female). This differentiation is based on previous findings and clinical practices (Mohamad et al., 2010; Peles et al., 2011b). Low-dose participants were older than high-dose participants ($p=0.014$), but there was no sex difference between MM groups. Participants in the short-term group were not more likely to

be receiving a higher dose of methadone. The short-term MM group contained 6 participants on a high dose and 2 participants on a low dose of methadone. The long-term MM group contained 7 participants on a high dose and 7 participants on a low dose.

2.2 Experimental Procedures

The Continuous Performance Task (CPT) is designed to assess selective attention and impulsivity (Conners, 1994). 360 stimuli are presented in random order (10% targets). One key indicates the stimulus is a target; a different key indicates it is not a target. The Digit Symbol Substitution Task (DSST) is designed to assess psychomotor performance (Lezak et al., 2004). The participant completes a worksheet with a key containing symbols paired with numbers. Participants fill in as many symbols next to corresponding numbers as possible in 120 seconds.

On SD nights, participants remained awake for 36 hours, supervised by a technician. On all other non-deprivation nights, total time in bed was 8 hours. To assess cognitive function, participants were administered the CPT in the morning after a baseline night of sleep, a night of total SD, and two RE nights. The DSST was administered at bedtime and in the morning each day. To assess mood, participants were administered the Profile of Mood States (POMS; McNair et al., 1971) at bedtime and in the morning each day. To assess subjective sleep, participants were administered the Stanford Sleepiness Scale (SSS; Hoddes et al., 1972) and a visual analog scale (VAS) on which participants rated their current level of sleepiness (anchors: sleepy, alert). All tests were assessed in the morning before participants' daily dose of methadone or in the evening immediately before bed. All participants were stably medicated, and attended regular methadone clinic visits at the usual dosing time. Therefore, side effects and withdrawal symptoms were not measured.

2.3 Analysis

Differences in demographic characteristics were analyzed by t-tests. Cognitive task performance, subjective sleep, and mood data were analyzed with linear mixed model ANOVAs with sleep night and treatment group as fixed factors. Alpha was $p < 0.05$ with Bonferroni corrections. All data are expressed as mean $\pm$ SEM.

3. RESULTS

3.1 All Methadone Maintained Participants and Cognitive Performance

At baseline, MM participants had slower reaction times (RTs) on correct responses (hits) on the CPT (Figure 1D; $F_{[1,33]}=7.68$; $p=0.009$), more variable hit RTs (Figure 1D inset; $F_{[1,33]}=9.25$; $p=0.005$), and completed fewer accurate substitutions on morning DSST (Figure 1E; $F_{[1,33]}=6.07$; $p=0.019$), than HCs. There were no baseline differences on errors of omission (Figure 1A), errors of commission (Figure 1B), or hits (Figure 1C) on the CPT or the number of accurate substitutions on the evening DSST (Figure 1E). There was no effect of sleep night, and no sleep night by group interaction, but when all four days of assessment were included in the analysis, MM participants made more errors of omission (Figure 1A; $F_{[1,130]}=8.43$; $p=0.004$), had fewer hits (Figure 1C; $F_{[1,130]}=4.90$; $p=0.029$), had slower hit RTs on the CPT (Figure 1D; $F_{[1,130]}=32.19$; $p<0.0001$), had more variable hit RTs (Figure 1D inset; $F_{[1,130]}=17.64$; $p<0.001$), and completed fewer accurate substitutions on the evening (Figure 1E; $F_{[1,136]}=15.49$; $p<0.0001$) and morning DSST (Figure 1F; $F_{[1,132]}=27.87$; $p<0.0001$). However, MM participants made fewer errors of commission on the CPT (Figure 1B; $F_{[1,129]}=10.10$; $p=0.002$). Visual inspection of errors of omission suggest that a group difference exists between baseline and study nights, however this is likely due to the increased variability in MM participant data (Figure 1D inset).

3.2 Length of Methadone Maintenance and Cognitive Performance

At baseline, analysis of duration of MM revealed that short-term MM participants responded more slowly than HCs (Figure 2D; $F_{[2,32]}=4.85$; mean difference=102.69; 95% CI=17.19–188.19; $p=0.014$), long-term MM participants had more variable hit RTs than HCs (Figure 2D inset; $F_{[1,32]}=4.498$; mean difference=2.46; 95% CI=0.19–6.72; $p=0.035$), and short-term MM subjects correctly completing fewer substitutions (Figure 2F; $F_{[2,32]}=3.68$; mean difference=16.25; 95% CI=0.62–32.07; $p=0.039$) on the morning DSST than HCs. There were no group differences on errors of omission (Figure 2A), errors of commission (Figure 2B), or hits (Figure 2C) on the CPT, or on the evening DSST (Figure 2E).

There was no effect of sleep night, and no sleep night by group interaction, but when all four days of assessment were included in the analysis, long-term MM participants made more errors of omission than HCs (Figure 2A; $F_{[2,126]}=5.32$; mean difference=20.26; 95% CI=5.18–35.34; $p=0.004$). Surprisingly, HCs made more errors of commission (Figure 2B; $F_{[2,125]}=6.44$; mean difference=5.03; 95% CI=1.57–8.50; $p=0.002$) than short-term MM participants, however examination of the data reveals that when both types of errors are summed, HCs still made fewer errors across all sleep nights than short-term MM participants (55.9 and 74.3 errors, respectively). Long-term MM participants had fewer hits (Figure 2C; $F_{[2,126]}=3.94$; mean difference=17.77; 95% CI=2.0–33.54; $p=0.021$), exhibited slower hit RTs (Figure 2D; $F_{[2,126]}=20.36$; mean difference=67.10; 95% CI=27.27–106.92; $p<0.0001$), and had more variable hit RTs (Figure 2D inset; $F_{[2,126]}=8.68$; mean difference=5.75; 95% CI=2.17–9.36; $p<0.0001$) than HCs; however short-term MM participants had slower hit RTs than both HCs (mean difference=119.38; 95% CI=72.66–166.11; $p<0.0001$) and long-term MM participants (mean difference=52.29; 95% CI=6.11–98.46; $p=0.021$), and had more variable hit RTs than HCs (Figure 2D inset; mean difference=5.32; 95% CI=1.10–9.54; $p=0.008$). Similarly, long-term MM participants correctly completed fewer substitutions than HCs on the evening DSST (Figure 2E; $F_{[2,132]}=10.86$; mean difference=7.71; 95% CI=0.37–15.06; $p=0.036$), however short-term MM participants correctly completed fewer substitutions than both HCs (mean difference=15.40; 95% CI=7.79–25.00; $p<0.0001$) and long-term MM participants (mean difference=8.68; 95% CI=0.07–17.88; $p=0.047$) on the evening DSST. Finally, both long-term MM (Figure 2F; $F_{[2,128]}=15.18$; mean difference=12.83; 95% CI=5.21–21.45; $p<0.0001$) and short-term MM participants (mean difference=18.80; 95% CI=9.91–27.70; $p<0.0001$) correctly completed fewer substitutions on the morning DSST than HCs.

3.3 Dose of Methadone and Cognitive Performance

At baseline, analysis of dose of methadone revealed that participants on a low dose of methadone had significantly longer reaction times than HCs on the CPT (Figure 3D; $F_{[2,32]}=4.94$; mean difference=103.74; 95% CI=18.42–189.056; $p=0.013$), and low-dose MM participants had more variable hit RTs than HCs (Figure 3D inset; $F_{[1,32]}=5.68$; mean difference=4.77; 95% CI=1.07–8.48; $p=0.008$). There was no effect of sleep night or sleep night by group interaction, but when all four days of assessment were included in the analysis, participants on a high dose of methadone made more errors of omission on the CPT than HCs (Figure 3A; $F_{[2,126]}=4.17$; mean difference=15.88; 95% CI=0.30–31.46; $p=0.044$). HCs made more errors of commission than low-dose MM participants (Figure 3B; $F_{[2,125]}=8.00$; mean difference=5.59; 95% CI=2.20–8.98; $p<0.0001$), however examination of the data reveals that when both types of errors are summed, HCs still made fewer errors across all sleep nights than low-dose MM participants (55.9 and 71.1 errors respectively). Both low-dose (Figure 3D; $F_{[2,126]}=20.43$; mean difference=117.68; 95% CI=71.65–163.70; $p<0.0001$) and high-dose (mean difference=67.79; 95% CI=27.95–107.63; $p<0.0001$) MM participants had slower RTs than HCs, but low-dose MM participants also had slower RTs than high-dose MM participants (mean difference=49.89; 95% CI=4.26–95.52; $p=0.027$).

Both low-dose (Figure 3D inset; $F_{[2,126]}=9.25$; mean difference=5.57; 95% CI=1.49–9.65; $p=0.004$) and high-dose (mean difference=5.72; 95% CI=2.19–9.25; $p<0.001$) MM participants had more variable hit RTs than HC. Finally, both low-dose and high-dose MM participants correctly completed fewer substitutions on the evening DSST (Figure 3E; $F_{[2,132]}=7.66$; low-dose mean difference=9.96; 95% CI=1.18–18.73; $p=0.020$; high-dose mean difference=11.39; 95% CI=3.91–18.88; $p=0.001$) and on the morning DSST (Figure 3F; $F_{[2,128]}=13.63$; low-dose mean difference=15.92; 95% CI=6.95–24.91; $p<0.0001$; high-dose mean difference=15.93; 95% CI=6.78–22.17; $p<0.0001$) than HCs.

3.4 Subjective Sleep and Mood

When MM participants were analyzed as a group, there were no baseline differences in subjective sleep or mood. SD did increase evening ratings of sleepiness on the SSS (Fig 4A; $F_{[3,130]}=18.18$; $p<0.0001$), however there was no difference between groups. SD did not affect ratings of depression or tension on the POMS in either group (Fig 4D, 4G). When MM participants were separated into short- and long-term MM periods, there were no baseline differences in subjective sleep or mood. SD increased evening ratings on the SSS (Fig 4B; $F_{[3,126]}=20.04$ $p<0.0001$), however there was no difference between groups. SD did not affect ratings of depression or tension in any of the groups (Fig 4E, 4H). Finally, when MM participants were separated by dose of methadone, there were no baseline differences in subjective sleep or mood. SD increased evening ratings on the SSS (Fig 4G; $F_{[3,126]}=19.71$; $p<0.0001$), but there were no differences between groups. SD did not affect ratings of depression or tension in any of the groups (Fig 4F, 4I).

4. DISCUSSION

Overall, MM participants performed more poorly on the DSST assessment of psychomotor performance and the CPT assessment of selective attention and/or impulsivity. MM participants responded less quickly (slower hit RT on the CPT and fewer correct substitutions on the DSST), were not as alert (fewer hits on the CPT), and did not attend to the tasks as well as HCs (more errors of omission on the CPT), and were more variable in the time it took to make correct responses (higher standard errors on hit RTs on the CPT). On the CPT at baseline, rates of errors of omission and commission for MM participants were in the 50th and 22nd percentile respectively, and hit RTs were in the 63rd percentile. For HC participants, rates of omission and commission were in the 20th percentile and 16th percentile respectively, and hit RTs were in the 29th percentile. The convention for reporting CPT data is that lower percentile values indicate better performance (Connors, 1994). This indicates that, other than errors of commission, task performance of these MM individuals was reduced when compared to both standard normative data and to the enrolled HCs in this study. Both the DSST and the CPT assess skills that are likely to be clinically and functionally relevant as they are often used in a variety of daily tasks such as driving a motor vehicle, riding a bicycle, or crossing the street-- all skills that are likely to be involved with everyday functioning such as arriving at a clinic for a daily dose of methadone. These findings are consistent with the majority of previous research that demonstrates poorer performance by MM participants when compared with HCs (Darke et al., 2000; Ornstein et al., 2000; Mintzer et al., 2005; Pirastu et al., 2006; Prosser et al., 2006).

Analysis of the impact of treatment duration revealed that the long-term, (i.e., more stably medicated) MM participants' performance approached and sometimes became statistically indistinguishable from HCs. This too, fits with previous research findings of improved cognitive performance with long-term methadone stabilization (Gruber et al., 2006; Soyka et al., 2008; 2010). The focus of these previous studies was largely on differences between the beginning weeks of methadone initiation and the first few weeks of methadone maintenance (~6 months). In the present study, short-term MM participants were on a stable dose for up

to 12 months (average length of MM=6 months). Participants in the long-term group were medicated for 12–24 months (average length of MM=22 months). Because short-term MM was defined as less than 12 month, the results in the present study indicate that the poorer performance associated with shorter-term MM is not simply due to initial adjustment to methadone, but that deficits continue to be apparent after what many deem as initial stabilization. One alternative interpretation of these is that participants who remained in treatment long enough to be considered long-term were better off cognitively than participants in the short-term group. However, because we do not have data from these participants during early treatment we cannot address this possibility.

Finally, when participants were divided into low- and high-dose methadone groups, a lower dose of methadone was associated with worse performance on the CPT, and there was no difference between low- and high-dose methadone groups on DSST performance. This is in direct contrast to previous research that found that lower doses of methadone were associated with better performance (Curran et al., 2001; Rapeli et al., 2007; Loeber et al., 2008). One possible explanation for this is that in other studies, a higher dose of methadone was associated with participants who were just recently introduced to a MM program, and that once participants were stabilized on methadone, the dose was tapered. In the present study, the dose was not correlated with length on MM (See Methods section 2.1; $R^2=0.04$), and it is not possible to determine if this is the case in these previous studies as a dose by length of MM correlation was either not addressed (Rapeli et al., 2007; Loeber et al., 2008), or a crossover design was used in which participants received 50% versus 100% of their daily methadone dose (Curran et al., 2001).

Surprisingly, performance on the CPT and DSST was not affected SD for either MM or HC participants. SD produced highly significant changes in measures of subjective sleep in all participant groups, so it is unlikely that our lack of a significant effect of SD on cognitive measures is due to participants not experiencing the typical effects of SD. However, we had originally hypothesized that poorer cognitive performance in MM groups would be exacerbated by SD. It is possible that the relatively short period of deprivation used in this study was not long enough to exacerbate performance decrements. Studies using longer periods of deprivation will be necessary to assess this. Additionally, previous studies found that tasks that require more attention are less affected by SD (Pilcher et al., 2007). Both the CPT and the DSST are complex cognitive tasks that require the participant to pay close attention. Finally, although previous studies have found that poor mood in MM participants may contribute to poorer performance (Darke et al., 2000), in this study mood did not differ in MM participants, so the observed performances were not secondary to an effect on mood.

Aside from the relatively short period of SD, there are several other limitations to the current study. First, several participants did use other drugs (See Methods section 2.1), which may affect cognitive performance. While this indicates that the cognitive impairment in these participants may not have been completely due to methadone, many individuals on MM continue to use other drugs, so the findings in the current study are likely generalizable to the larger MM population. A more serious limitation is the low number of participants in the secondary analyses. Because cognitive effects are often subtle, results from analysis of length of MM and dose of methadone should be treated with caution. However, although higher dose participants performed more similarly to HCs than low-dose participants, contrary to the original hypotheses, longer-term MM participants performed more similarly to HCs than short-term MM participants, which is consistent with results from several previous studies (Gruber et al., 2006; Soyka et al., 2008; Soyka et al., 2010).

These data were collected as part of a larger study assessing effects of SD on sleep architecture (polysomnography) and brain bioenergetics (magnetic resonance spectroscopy)

(Trksak et al., 2010). These previous analyses found no effect of methadone dose, but an effect of MM duration with long-term MM participants recovering from SD more similarly to HCs. In contrast, short-term MM participants did not experience an increase in total sleep time and sleep efficiency that is commonly associated with recovery night sleep, and that was seen in the other two groups (Trksak et al., 2010). Our original hypothesis was, similar to the PSG results, that MM participants would be more affected by SD with higher ratings of sleepiness and fatigue than HCs, and that long-term MM participants would be more similar to HCs than short-term MM participants. However, we found MM and HC ratings to be indistinguishable regardless of how MM groups were stratified. Previous results assessing agreement between subjective and objective measures of sleep are mixed, with some studies finding a mismatch (Silva et al., 2007), and others finding significant correlations even among opiate dependent participants (Sharkey et al., 2011). So, even though the performance of our MM participants on the CPT and the DSST fit with our prior PSG data (Trksak et al., 2010), it is not unusual that subjective ratings of sleep do not match objectively obtained sleep measures.

In addition, Trksak et al. (2010) found that after SD nucleotide triphosphate levels (a direct measurement of adenosine triphosphate, ATP) were increased more in MM participants than HCs, but there was no difference when participants were separated by length of MM or dose of methadone. It is possible that a reason there was not a corresponding worsening of cognitive performance is that the brain was successfully able to adapt and compensate for SD by increasing energy production.

Collectively, the findings indicate that MM subjects exhibit a disruption in cognitive performance. Long-term MM subjects were more similar to HCs, which may indicate that with longer MM deficits in cognitive task performance may begin to normalize. These changes may have direct implications for daily functioning and furthermore may influence decision-making. Although immediate changes following SD were not identified in the performance data, comparisons with previous studies indicate that the brains of these individuals may have been able to compensate for SD with increased energy production. One day of SD was enough to alter sleep, but cognitive function may be more resilient and so longer episodes of SD may be too much for the brain to compensate. Future studies will need to find the threshold of the number of hours of SD needed to see comparative changes in sleep architecture, brain bioenergetics, subjective sleep and mood, and cognitive performance.

Acknowledgments

We thank Ronna Shostak, Carol Buchanan, and Barbara Beake for administrative support in conducting these studies.

ROLE OF FUNDING SOURCE Funding for this study was provided by NIDA grants DA016542, T32DA15036, 5K01DA025125, and K05DA00343. The NIDA had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

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Figure 1.

Differences between healthy control and all methadone maintained (MM) participants in the number of errors of omission (A), errors of commission (B), the number of correct responses (hits; C), the hit reaction time (RT; D), the standard error of hit RTs (D inset) on the Continuous Performance Task, and the number of correct substitutions on the evening (E) and morning (F) Digit Symbol Substitution Task (DSST).

Figure 2.

Differences between healthy control and MM participants maintained < 12 months and MM participants maintained ≥ 12 months in the number of errors of omission (A), errors of commission (B), the number of correct responses (hits; C), the hit reaction time (RT; D), the standard error of hit RTs (D inset) on the Continuous Performance Task, and the number of correct substitutions on the evening (E) and morning (F) Digit Symbol Substitution Task (DSST).

Figure 3.

Differences between HC, low-dose (> 80mg methadone), and high-dose (< 80mg methadone) participants in the number of errors of omission (A), errors of commission (B), the number of correct responses (hits; C), the hit reaction time (RT; D), the standard error of hit RTs (D inset) on the Continuous Performance Task, and the number of correct substitutions on the evening (E) and morning (F) Digit Symbol Substitution Task (DSST).

Figure 4.

Effects of sleep deprivation on ratings of subjective sleep (Stanford Sleepiness Scale) by HC and all MM participants (A), HC, long-term and short-term MM participants (B), and HC, low-dose, and high-dose MM participants (C). Effects of sleep deprivation on evening ratings of "depression" by HC and all MM participants (D), HC, long-term and short-term MM participants (E), and HC, low-dose, and high-dose MM participants (F). Effects of sleep deprivation on evening ratings of "tension" by HC and all MM participants (G), HC, long-term and short-term MM participants (H), and HC, low-dose, and high-dose MM participants (I).