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The implications of sleep disruption for cognitive and affective processing in methamphetamine abuse

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ABSTRACT

Sleep is disrupted during active use of methamphetamine (MA), during withdrawal from the drug, and during abstinence from its use. However, relatively little is known about possible mediatory functions of disrupted sleep in the emergence, manifestation, and maintenance of cognitive and affective symptoms of MA abuse. We hypothesise that sleep functions as a mediator for stimulant drug effects. Specifically, we propose that objectively-measured sleep parameters can be used to explain some of the variability in the experience and presentation of memory deficits and emotion dysregulation in MA abusers. After describing how important healthy sleep is to unimpaired cognitive and affective functioning, we review literature describing how sleep is disrupted in MA abuse. Then, we provide a conceptual framework for our hypothesis by explaining the relationship between MA abuse, sleep disruption, memory deficits, emotion dysregulation, and changes in reward-related brain networks. We conclude by discussing implications of the hypothesis for research and treatment.

Introduction

Abuse of the synthetic psychostimulant methamphetamine (MA) is of particular concern to medical and mental health professionals. Globally, MA abuse has been widespread for several decades [1], and it trails only cannabis as the most widely abused illicit drug [2,3]. In the United States, estimates from a 2012 survey indicate that more than 12 million people aged 12 years and older (almost 5% of that population) have used MA, in some form, at some point in their lives. The same survey noted that 1.2 million people in the US reported using methamphetamine in the past year [4]. The drug is most popular in East and Southeast Asia, however: almost two-thirds of the world's users live there, with the Mekong region being particularly heavily affected (e.g., in Laos, there is a lifetime use prevalence of approximately 5%, and in Thailand three-fourths of substance-related clinic admissions are due to MA) [5]. In South Africa, estimates from surveys conducted between 2005 and 2011 report that MA is responsible for more than 5% of all substance abuse-related admissions to government-funded treatment (the third most frequent reason for admission, following only alcohol and cannabis), and that up to 12% of adolescents in the Western Cape province report having used the drug [6,7].

Prolonged MA abuse is associated with a host of long-term physical, behavioural, cognitive, and mental health problems [8–13]. These profound changes in the individual have a deep societal impact: MA abuse is associated with marked disruptions in family, school, and work environments, and with drug-related crime and violence, particularly in low socioeconomic status communities [14–18].

The acute effects of MA use are marked by a state of general hyperarousal; enhancement of various affective, physiological, and cognitive functions results in, for instance, positive mood, cardiac stimulation, and acute improvement in attention and psychomotor coordination [8,19]. Long-term, chronic MA abuse is, however, marked by a state of general dysregulation of arousal; affect, physiology, and cognition are dampened, and individuals present with symptoms such as severe weight loss, increased risk of seizures, episodes of uncontrollable rage, hallucinations, paranoia, depression, panic attacks, and impaired concentration and memory, poor decision making, and disinhibition [20,21].

Although the symptoms listed above are commonly reported in MA abuse, there are frequently large individual differences in symptom presentation [22,23]. Such individual differences are not unique to MA abuse; they are present in the symptom presentation associated with many other addictive substances. Consistent with a neurobiological model of addiction, a substantial literature has explored biological predictors of these individual differences. Human and animal studies have described relationships between symptom presentation in MA abuse and (a) genetic factors

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[24,25], (b) structural changes to specific brain regions [26,27], (c) changes in functional brain activation in response to particular stimuli [28,29], (d) changes in neurotransmitter systems [30,31], and (e) electrophysiological changes, including during sleep [32,33]. In other substances of abuse (e.g., alcohol, opiates), sleep disruption is often considered a predictor of outcome: for instance, the more sleep is disrupted, the greater the risk of relapse [34,35].

With specific regard to MA, numerous studies have shown that sleep is disrupted during active use, during withdrawal, and during abstinence. Generally speaking, the patterns of sleep disruption that accompany MA abuse follow, at least initially, the same trajectory as described above for cognitive, affective, and other physiological functions. That is to say, at the higher doses (>50 mg) typically ingested during illicit use, MA produces insomnia as part of the general hyperarousal that marks acute effects. Numerous clinical reports and empirical studies chart the changes in sleep patterns that accompany withdrawal and subsequent abstinence [36–38]. During acute withdrawal stages, which typically last 7–10 days but can persist for up to 2 weeks, hypersomnia is common (reflecting rebound sleep compensating for previous hyperactivity during the intoxication period). If patients continue to abstain from MA abuse, hyposomnia/insomnia is a common residual symptom associated with neurotoxicity, consistent with general dampening of affect, cognition, and physiology. Specifically, sleep during this period is characterised by (a) frequent awakenings and arousals, (b) longer latency to onset, and (c) frequent nightmares. Subjective reports suggest that compromised sleep quality may persist for weeks to years after the onset of abstinence [9,39,40].

For medical and mental health professionals treating patients who are active MA abusers, or who are in withdrawal or abstinent, the importance of these drug-associated sleep disturbances is that they are treatable by a variety of pharmacological and psychological interventions [41,42]. Furthermore, numerous substance abuse treatment studies suggest that decreased sleep disturbance is related to (a) decreased risk of relapse, and (b) improvement in other symptoms [35,43–45]. Hence, there might be great value in investigating relationships between MA-related sleep disruptions and impaired affect and cognition: Such investigations might enable interventions to focus on specific targets, and they might allow insight into why particular clusters of symptoms arise together (e.g., why sleep disruption, memory impairment, and impulsivity-aggression co-occur in many individuals who abuse MA).

Hypothesis

Emerging evidence suggests that sleep disturbances are more than a secondary consequence of psychopathology: quality of sleep is an important diagnostic marker and of prognostic value in evaluating psychiatric illness, including substance abuse [46–49]. Relatively little is known about possible mediatory functions of sleep in the emergence, manifestation, and maintenance of psychiatric illness, however [50,51]. Furthermore, because most psychiatric research into disordered sleep focuses on affective disorders [46,52–54], relatively little is known about ways in which sleep is disrupted in substance abuse, and about mechanisms driving associations between disrupted sleep, substance abuse, and cognitive-affective impairment.

We hypothesise that sleep functions as a mediator for stimulant drug effects. Specifically, we propose that objectively-measured sleep parameters (e.g., those generated by polysomnographic studies) can be used to explain some of the variability in the experience and presentation of memory deficits and emotion dysregulation in MA abusers. We investigate the grounds for this hypothesis by describing how central healthy sleep is to unimpaired cognitive and affective functioning. We then review literature detailing how sleep is disrupted in MA abusers. Next, we provide a conceptual framework explaining the relationship between MA abuse, sleep disruption, memory deficits, emotion dysregulation, and changes in reward-related brain networks. Finally, we discuss implications of the hypothesis for research and treatment.

The importance of healthy sleep for memory functioning and emotion regulation

Healthy sleep consists of four stages of Non-Rapid Eye Movement (NREM) sleep and a physiologically distinct Rapid Eye Movement (REM) stage of sleep. Within NREM sleep, stages 3–4 are considered Slow Wave Sleep (SWS). The complete cycle of four stages of NREM sleep followed by REM sleep repeats 4–5 times through the night. However, the first half of the night is dominated by SWS (i.e., healthy individuals typically spend most of their early-night sleep in SWS), while the second half of the night is dominated by REM sleep (i.e., healthy individuals typically spend most of their later-night sleep in REM sleep).

Sleep and memory

An established body of knowledge shows that previously encoded neutral declarative memories are strengthened during sleep in three important ways [55,56]. First, during SWS, slow-wave oscillations driven by the prefrontal cortex (PFC) synchronise with sharp-wave ripples in the hippocampus. The result of this synchronisation is that memories encoded during waking are redistributed from hippocampal areas to the neocortex [57–60]. Second, also during SWS, those connections that are weakly potentiated at synapses are eliminated, leaving intact only those connections that are strongly potentiated. The result of this synaptic downscaling is that relatively more important and salient memory traces are spared at the expense of those that are relatively insignificant [61]. Third, during REM sleep, a process of gene expression results in further strengthening of synaptic connections so that they form long-lasting representations in the brain [62]. The result of this process is, again, that relatively more important and salient memory traces are strengthened.

Sleep and emotion

In contrast to the literature on sleep and memory, that regarding sleep's role in emotion regulation is not as well developed; certainly, there are few overarching theoretical frameworks guiding its discussion. A number of independent empirical studies show, however, that healthy sleep is important for emotion regulation [63,64]. Specifically, healthy sleep serves to attenuate emotional reactivity to valenced stimuli, so that people who sleep normally do not show exaggerated reactions to emotion-laden events in their everyday waking lives. REM sleep might be particularly important in facilitating this emotion regulation [65,66]. To illustrate these points, Gujar and colleagues [67] showed that participants' reactivity to fear- and anger-laden stimuli increased over the course of a day. However, a nap blocked and reversed this response: participants did not show increased reactivity to fear- and anger-laden stimuli, and concurrently showed increased responsiveness to happy stimuli. Importantly, however, this reversal in response to emotional stimuli was only true for participants who had experienced REM sleep during the nap.

Neuroimaging investigations have allowed further insight into the mechanisms driving the association between sleep and emotion regulation. For instance, Yoo and colleagues [68] demonstrated that sleep-deprived participants, in contrast to those who