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Research Report

Differential effects of duration of sleep fragmentation on spatial learning and synaptic plasticity in pubertal mice

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ABSTRACT

Study objective: To examine the differential effects of acute and chronic sleep fragmentation (SF) on spatial learning and memory, and hippocampal long-term potentiation (LTP) in pubertal mice.

Methods: Two studies were performed during which adolescent C57/Bl6 mice were subjected to acute-SF 24 h a day × 3 days or chronic-SF for 12 h a day × 2 weeks using a programmable rotating lever that provides tactile stimulus with controls housed in similar cages. Spatial learning and memory was examined using the Morris water maze, and long-term potentiation (LTP) was evaluated after stimulation of Schaffer collaterals in CA1 hippocampus post SF. Actigraphy was used during the period of SF to monitor rest-activity patterns. Electroencephalographic (EEG) recordings were acquired for analysis of vigilance state patterns and delta-power. Serum corticosterone was measured to assess stress levels.

Results: Acute-SF via tactile stimulation negatively impacted spatial learning, as well as LTP maintenance, compared to controls with no tactile stimulation. While actigraphy showed significantly increased motor activity during SF in both groups, EEG data indicated that overall sleep efficiency did not differ between baseline and SF days, but significant increases in number of wakeful bouts and decreases in average NREM and REM bout lengths were seen during lights-on. Acute sleep fragmentation did not impact corticosterone levels.

Conclusions: The current results indicate that, during development in pubertal mice, acute-SF for 24 h a day × 3 days negatively impacted spatial learning and synaptic plasticity. Further studies are needed to determine if any inherent long-term homeostatic

Abbreviations: SF, sleep fragmentation; NREM, non rapid eye movement; REM, rapid eye movement

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mechanisms in the adolescent brain afford greater resistance to the deleterious effects of chronic-SF.

1. Introduction

Sleep is a complex, yet fundamental, physiological state necessary for neuronal maturation (Meerlo et al., 2009), plasticity (Peirano and Algarín, 2007) and survival (Dinges and Chugh, 1997) in all animal species. Sleep disruption in childhood and adolescence results in a significant spectrum of adverse neurobehavioral consequences, including reduced learning (Carskadon et al., 1998; Randazzo et al., 1998), abnormal behavior (Paavonen et al., 2009), and mood disturbances (Aronen et al., 2000). Unlike total sleep deprivation or restriction, SF is a problem in many sleep disorders such as obstructive sleep apnea (Carreras et al., 2014), and restless leg syndrome (Trenkwalder and Paulus 2010). In animal models, sleep loss impairs spatial learning and memory in the Morris water maze and radial arm water maze (Smith and Rose, 1996; Youngblood et al., 1999a, 1999b: Kopp et al., 2006; Tartar et al., 2006). Initial studies have focused on either acute sleep deprivation, lasting hours or days, or chronic sleep disruption, the later studies focusing on SF and its effects on learning and memory. No studies have methodically tested the consequences of SF duration within the same model, especially in a maturing brain. Furthermore, there is limited work evaluating the neurobiological effects of sleep alterations in the developing brain. Directly assessing the cognitive effects of multiple forms of sleep disruption via behavioral and electrophysiological assay within a common model is important to better understand the neurobiological relation between sleep loss and cognition. LTP is a form of neural plasticity that has been implicated as a cellular mechanism of memory formation (Malenka and Nicoll, 1997). In vitro studies show that LTP is impaired in various models of sleep deprivation and sleep fragmentation. For example, impaired LTP has been observed with both acute (Patti et al., 2010; Fernandes-Santos et al., 2012; Romcy-Pereira and Pavlides, 2004; Alhaider et al., 2010; Vecsey et al., 2009) and chronic sleep loss (Kim et al., 2005) in adult animals. However, differential effects of sleep fragmentation duration on LTP in the developing brain have not been well investigated.

The goal of this study was to assess the effects of acute- and chronic-SF on spatial learning and memory and LTP in pubertal mice. Actigraphy was used to monitor rest-activity patterns and electroencephalograms (EEGs) were obtained for sleep/wake analysis and to validate the actigraphy findings and effect of our SF protocols. We also examined whether stress was a factor in the SF methodology used by measuring serum corticosterone levels.

2. Results

2.1. Actigraphy

Actigraphy was utilized to examine rest-activity patterns. Control animals had low activity levels during lights-on whereas they had high activity levels during lights-off (Fig. 1A, top).

2.1.1. Acute-SF

In contrast to controls, acute-SF animals did not show a significant difference between lights-on and -off [control: $F(1,12)=9.55$, $p<0.01$]; acute-SF: $F(1,12)=2.4$, $p>0.14$] and there was no statistically significant decline in locomotor activity across the 3 days of SF [$F(2,15)=0.52$; $p>0.6$]. Moreover, the lack of a significant difference in the locomotor activity counts in the experimental group between lights- on and -off suggests that the acute-SF protocol achieved perturbation of expected rest-activity cycles. While we cannot exclude the possibility that the acute-SF group may have been getting some recovery sleep during the dark phase, the fact that activity counts in the dark-phase did not differ significantly from controls ($F(1,12)=3.94$, $p>0.07$), suggest that they did not (Fig. 1B, top).

2.1.2. Chronic-SF

In the chronic-SF group, locomotor activity was significantly increased in the lights-on period compared to controls [$F(1,18)=4.47$, $p<0.05$] (Fig. 1A bottom and 1B bottom), but not different in dark period compared to controls [$F(1,19)=1.23$, $p>0.28$], suggesting that no recovery sleep was experienced when the lever was not rotating.

2.2. Morris water maze studies

2.2.1. Acute-SF

There was a day main effect for distance [$F(4,56)=12.30$; $p<0.0001$], with scores decreasing across days, demonstrating learning of the task. Mice given acute-SF exhibited poorer overall performance, showing higher distance scores, collapsed across all 5 testing days, as compared to controls [$F(1,14)=5.02$; $p<0.05$] (Fig. 2A). For overnight amnesia, neither acute-SF nor control animals increased their swim distance during the overnight interval (data not shown).

For the probe trial, assessing memory of the platform location (northeast (NE) quadrant), there was a main effect of Quadrant [$F(1,14)=88.142$; $p<0.0001$]. We confirmed that each group spent more percent of total swum distance in the target NE quadrant as compared to the opposite southwest (SW) quadrant, showing localization of the platform location [Control: $F(1,7)=36.949$; $p<0.001$; acute-SF: $F(1,7)=59.894$; $p<0.0001$]. Control and acute-SF animals did not differ in the percent of total swum distance in either the NE or SW quadrant (Fig. 2C).

2.2.2. Chronic-SF

There was a day main effect for distance [$F(4,68)=23.51$; $p<0.0001$], with scores decreasing across days, demonstrating learning of the