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Effects of acute sleep deprivation on motor and reversal learning in mice

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ABSTRACT

Sleep supports the formation of a variety of declarative and non-declarative memories, and sleep deprivation often impairs these types of memories. In human subjects, natural sleep either during a nap or overnight leads to long-lasting improvements in visuomotor and fine motor tasks, but rodent models recapitulating these findings have been scarce. Here we present evidence that 5 h of acute sleep deprivation impairs mouse skilled reach learning compared to a matched period of ad libitum sleep. In sleeping mice, the duration of total sleep time during the 5 h of sleep opportunity or during the first bout of sleep did not correlate with ultimate gain in motor performance. In addition, we observed that reversal learning during the skilled reaching task was also affected by sleep deprivation. Consistent with this observation, 5 h of sleep deprivation also impaired reversal learning in the water-based Y-maze. In conclusion, acute sleep deprivation negatively impacts subsequent motor and reversal learning and memory.

1. Introduction

Mounting evidence supports a role for sleep in both declarative and non-declarative forms of learning and memory (Diekelmann & Born, 2010; Havekes, Vecsey, & Abel, 2012). In human subjects, one of the most robust and reproducible benefits of sleep has been observed with improved motor performance as assessed through a finger tap motor sequence test (MST) (Fischer, Hallschmid, Elsner, & Born, 2002; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). In addition, a greater benefit of sleep was appreciated with increasing complexity of the MST (Kuriyama, Stickgold, & Walker, 2004). Disruption of sleep as a consequence of obstructive sleep apnea is associated with deficits in MST performance (Djonlagic, Saboisky, Carusona, Stickgold, & Malhotra, 2012) and in motor cortex plasticity induced by theta burst stimulation (Opie, Catcheside, Usmani, Ridding, & Semmler, 2013). Anatomically, performance of a MST after sleep preferentially activated the contralateral primary motor cortex, medial prefrontal lobe, hippocampus, and ipsilateral cerebellum (Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005).

A motor learning paradigm in rodents that engages similar circuits to the MST in humans is skilled reach learning, in which an animal learns to reach through a narrow window for a sugar reward pellet (Whishaw, O'Connor, & Dunnett, 1986) with increases in accuracy over time. A previous study investigating how sleep architecture changes as a function of intensive skilled reach learning in rats showed an increase in slow wave activity in the cortex contralateral to the trained paw (Hanlon, Faraguna, Vyazovskiy, Tononi, & Cirelli, 2009); however, change in performance as a function of subsequent sleep or sleep loss was not tested. In this study, we determined the effects acute sleep deprivation mice on subsequent skilled reaching performance.

Cortical circuits mediating reversal learning may also be affected by sleep deprivation. There is evidence both supporting and refuting a role for sleep deprivation on reversal learning, depending on the exact nature of the reversal task. Because the skilled reaching task we utilized herein incorporates a form of reversal learning, we determined the effects of acute sleep deprivation on reversal learning in this task. Choice reversal in a water-based Y-maze is a behavioral task that also allows for assessment of reversal learning by training animals to locate a rescue platform in one arm of the Y-maze and subsequently testing the frequency of reversing this behavior when the rescue platform is moved to the untrained arm. The results of our studies indicate that 5 h of sleep deprivation after task acquisition impaired motor accuracy and reversal learning during skilled reaching as well as reversal learning in a water-based Y-maze.

2. Methods

2.1. Subjects

Adult C57BL/6 male mice (3–6 months of age) were kept on a 12 h/12 h light/dark schedule with lights on at 7:00 AM (zeitgeber

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time (ZT) 0) (8:00 AM during daylight savings). Mice were generally group housed (3–4 mice per cage) but were singly housed during skilled reach experiments. Food and water were generally available ad libitum, but food was limited during skilled reach experiments (see Section 2.3.3 below for details). All experiments were approved by the Institution of Animal Care and Use Committee of the New York University and were carried out in accordance with all National Institutes of Health guidelines.

2.2. Sleep deprivation and sleep quantification

To achieve sleep deprivation (SD) in mice, we used the gentle handling technique involving graded interventions of manual cage tapping, bedding disturbance, and gentle animal stroking (Havekes et al., 2012). Electroencephalographic recordings have shown that these interventions effectively retain animals in a state of wakefulness for several hours (Meerlo, de Bruin, Strijkstra, & Daan, 2001) without substantial changes in serum cortisol (Hagewoud et al., 2010; Vecsey et al., 2009). Acute SD always lasted 5 h in duration. During skilled reach experiments, SD occurred between ZT 5 and ZT 10. SD during this circadian time was selected based on prior work showing changes in memory behavior, electrophysiology, and cellular signaling as a consequence of SD (Vecsey et al., 2009). Because of the extended duration of the Y-maze experiments, SD occurred between ZT 1 and ZT 6 during those experiments.

Quantification of sleep time in control mice was estimated in real time by a direct observer. Sleep was characterized by behavioral arrest, eye closure, and huddled body posture, or behavioral arrest for >40 s if accompanied by huddled body posture without eye closure. Prior work assessing the inactivity of C57BL/6 mice for >40 s showed 92% agreement with sleep/wake states evaluated by polysomnography (Pack et al., 2007).

2.3. Skilled reaching task

2.3.1. Skilled reaching chamber

We designed a skilled reaching chamber for mice as previously described (Diep et al., 2012; Farr & Whishaw, 2002). The chamber is a rectangular box constructed of clear acrylic measuring 23 cm long × 6.25 cm wide × 25 cm tall. A 1 cm wide window that runs up the front of the box was centered on the front (narrowest) wall. A shelf (6.25 cm long × 4 cm wide) was mounted at the base of this window outside of the box and was 1.2 cm above the floor. Two indentations spaced 1 cm away from the window and centered on its edges were placed in the shelf to hold sucrose pellets (this placement was intended to urge the mice to use their forepaw to obtain pellets and prevent reaching pellets simply with their tongue).

2.3.2. Habituation and motivation

A 13-day protocol was used. Single-housed mice were placed on a diet on day 1 in order to achieve 85–90% of their baseline body weight (typically, grams of chow equal to 10% of their baseline weight). Water was available ad libitum throughout. Weights were monitored 6 times across the 13 days. During days 1 and 2, mice were habituated to the skilled reaching chamber for 10-min periods twice per day. On days 1 and 2, mice were separately habituated to 20 mg sucrose pellets by placing 10 pellets/mouse in the home cages. On days 3 and 4, mice were maintained on the diet but did not undergo further habituation.

2.3.3. Initial training

Beginning on day 5, mice spent two 15-min sessions per day in the skilled reaching chamber, once between ZT 3 and ZT 5 and once between ZT 10 and ZT 12. During the initial sessions in the skilled reach chamber, sucrose pellets were available on the floor, on the shelf within tongue-distance, and on the shelf within reaching distance. As the mice learned that pellets existed within reaching distance across trials, the pellets on the floor and on the shelf within tongue distance were removed, thus making pellets only accessible through reaching. In addition, as mice displayed paw-preference, pellets within reaching distance were placed in only one of the two indentations to reinforce use of the preferred paw. In some instances, mice would experience one rather than two sessions in a day, but all mice completed 11–14 total training sessions across days 5–11.

2.3.4. Skilled reach training and testing with the non-preferred paw

In order to better isolate the effect of sleep deprivation on the motor component of the task (independent of the novel taste and contextual learning), on days 12 and 13 mice were given 10 min to reach for sucrose pellets with the *non-preferred* paw by placing the pellet in the indentation opposite to the one the mouse had been trained on. On day 12, a training session with the non-preferred paw occurred between ZT 4 and ZT 5. Immediately after this, mice experienced conditions of either sleep deprivation via gentle handling or ad libitum sleep for 5 h. For those mice that were allowed to sleep ad libitum, estimations of total sleep were made by direct observation. An initial immediate 10-min testing session occurred between ZT 9 and ZT 10 (T5). On day 13, a delayed 10-min testing session occurred between ZT 4 and ZT 5 (T24). Each 10-min testing session was recorded with a digital video camcorder (Sony). Primary performance metrics recorded were gain in total success rate (i.e. number successfully consumed pellets per total number of reaches) and fraction of non-preferred paw reaches (i.e. number of reaches with the non-preferred paw per total number of reaches).

2.4. Water Y-maze reversal task

A slightly modified version of the water Y-maze reversal task previously described was utilized (Hoeffer et al., 2008). Mice were habituated to the maze for 15 min on day 1 and then returned to their home cage. On day 2 the mice were trained to locate a submerged escape platform (in a pool of obscured water) in either arm of a Y-shaped maze (simple always right or always left arm pattern) for 20 trials. The mice were returned to their home cages after day two of training. On day 3, the mice were tested to determine whether they achieved an escape success criterion of 4/5 correct. For mice that achieved this criterion, the escape arm was reversed on day 4. Mice had two initial opportunities to find the new escape location before undergoing a period of 5 h of either ad libitum sleep or sleep deprivation via gentle handling. After this 5-h period, mice underwent another 30 trials to find the new escape location. Mice were allowed a maximum of 60 s to make an arm choice. Mice were not directed to the correct arm if they made an error. If mice made an error in arm choice, they were trapped in the incorrect arm for 20 s before being rescued. The inter-trial interval during Days 2 through 4 was 10 min. Mice were assigned randomly to either left or right arms at the beginning of training and the researcher was blind to sleep condition during testing.

2.5. Data analysis

Data were analyzed using SigmaPlot version 11.0. For normally distributed data (gain in fraction of non-preferred paw reaches), analysis consisted of using a two-way repeated measures ANOVA with sleep group (SD vs. ad libitum sleep) as the between-subjects independent variable and time (T5 vs. T24) as the within-subjects independent variable. Post-hoc analyses were completed with Bonferonni correction. Because gain in total success rate was continuous but not normally distributed, Wilcoxon signed rank tests