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The relation between sleep and violent aggression

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Chapter 6

Sleep restriction in rats leads to changes in operant behavior indicative of reduced prefrontal cortex function

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ABSTRACT

Sleep deprivation has profound effects on cognitive performance and some of these effects may be mediated by impaired prefrontal cortex function. In search of an animal model to investigate this relationship we studied the influence of restricted sleep on operant conditioning in rats, particularly the performance in a differential reinforcement of low rate responding (DRL) task, which is highly dependent on an intact prefrontal cortex. Animals were trained to withhold a lever press until an imposed delay of 30 seconds after the last press had passed in order to achieve a food reward. Once the animals had mastered the task, they were sleep restricted for seven days with 20h of sleep deprivation per day. At the end of each daily sleep deprivation session, performance on the DRL task was assessed. The results show that sleep restricted animals were less able to correctly time their responses, started pressing the lever more randomly and showed signs of behavioral disinhibition, the latter possibly reflecting enhanced impulsivity. Our data support the hypothesis that a sleep debt has disruptive consequences for the functioning of the prefrontal cortex. This model offers possibilities for future studies investigating the underlying biochemical and molecular mechanisms of this relationship.

INTRODUCTION

Sleep loss has profound disruptive effects on cognitive performance (Abel et al., 2013; Diekelmann and Born, 2010; Killgore, 2010). Many cognitive capacities, such as planning, decision-making, behavioral inhibition and working memory, depend highly on adequate functioning of the prefrontal lobe. Therefore, the prefrontal cortex (PFC) may be one of the brain structures that play a key role in the negative influence of sleep loss on cognitive functions. Indeed, there are data suggesting that the PFC is sensitive to a lack of sleep (Muzur et al., 2002). Imaging studies show a reduced blood flow and cerebral metabolism in the prefrontal area after sleep deprivation (Thomas et al., 2000; Drummond and Brown, 2001; Yoo et al., 2007). Also, neuropsychological sleep deprivation studies reveal impairments on tasks that are considered to be mediated by the PFC (e.g. Harrison and Horne, 1999; Wimmer, 1992).

While much of this work has been done in humans, it remains difficult to develop well-controlled, reproducible prefrontal tasks for human subjects. Some tasks are too simple, leading to low motivation of the participants, whereas more complicated and highly motivating tasks with financial or other gains may dampen the effect of sleep deprivation (Muzur et al., 2002). Animal models provide several potential advantages to investigate the relationship between sleep loss and prefrontal cortical functioning because it allows for experimental manipulation under controlled conditions as well as detailed studies of underlying molecular mechanisms. One commonly used behavioral task to test several executive functions in animal research is the 'differential reinforcement of low rate responding' (DRL) task. In this task an animal is required to withhold a response, like lever pressing or nose poking, until an imposed delay after the last response has passed in order to achieve a food reward. A premature response resets the timing clock and therefore delays the availability of the next reward (i.e., penalizing premature lever presses). This DRL task requires an intact PFC as evidenced by lesion studies. For example, rats on a DRL-10 schedule (required delay between presses is 10 seconds) with 50% reinforcement rate showed significantly increased premature lever presses (<2 seconds) after surgical removal of their medial PFC (Nalwa and Rao, 1985). This suggests a diminished capacity of behavioral inhibition in the lesioned animals. Also, in mice on a DRL-10 schedule, a neurotoxic lesion of the PFC leads to a diminished ability to properly time the responses, more random pressing and consequently a lower number of food rewards (Cho and Jeantet, 2010). Moreover, another study in mice by Rossi et al. (2012) showed that lesions of the medial PFC, but not of the nucleus accumbens and rostral dorsal hippocampus, disrupted the performance in a modified DRL task. These

findings clearly indicate that optimal performance on a DRL task is dependent on an intact functioning PFC. Therefore, we selected the DRL task in rodents to study the consequences of insufficient sleep on prefrontal function.

The aim of this study was to investigate the effect of acute and chronic sleep restriction on DRL schedule performance in rats. We were particularly interested in the consequences of chronically restricted sleep because this is a common problem in human society and also because this may have cumulative effects that are not seen after acute sleep deprivation (Roman et al., 2005a, Novati et al. 2008). Based on the earlier findings that sleep loss reduces prefrontal metabolic activity, we expected to find behavioral impairments in the same directions as those previously observed in PFC lesion studies.

METHODS

Animals

The study was performed with 24 adult male wild-type Groningen (WTG) rats (Rattus Norvegicus), originally wild-trapped animals and bred under laboratory conditions for over 50 generations in the animal facility of the University of Groningen. Body weight of the animals at the start of the experiment was on average 408±5.4 gr. They were individually housed under stable humidity (60±2%) and temperature (21±2 °C) conditions in a 12h light/12h dark cycle with lights on from 12.00 to 24.00 h. Animals were food deprived to 90% of their free-feeding body weight during the operant conditioning training and experiment in order to motivate them for lever pressing: animals were weighed every day and the amount of chow food (Arie block Diervoeding B.V.,Woerden, NL) was adjusted daily to ensure they remained on the required body weight. Water was available ad libitum. Experiments were approved by the Groningen University Committee of Animal Experiments.

Operant conditioning: the DRL-30 task

In order to ensure that the DRL task would be a sufficient challenge for PFC functions, such as working memory and behavioral inhibition, we used a required delay between responses of 30 seconds. The DRL-30 task was conducted in twelve identical operant conditioning chambers (45x30x50 cm, lengthxweightxheight; Med Associates Inc., St. Albans, VT, USA) controlled by a computer located outside the experimental room (MEDPC IV acquisition software, Med Associates Inc). These chambers were the home cages for the animals during the training. Animals were first trained to press the lever of a food dispenser for a 45 mg pellet of food (Dustless Precision Pellets, Product F0165;

Bioserv, Frenchtown, USA) in a daily 60-min session (during the last hour of the dark cycle; from 11.00-12.00 h) for 5 consecutive days. Each lever press resulted in the delivery of one food pellet in the food tray receptacle located next to the lever. After this initial training phase, the rats were subjected to a DRL-30 schedule, that is, the animals had to learn that lever presses needed to be separated by at least 30 seconds to result in the delivery of a food pellet. Animals were trained until performance on the DRL-30 schedule had stabilized at an average efficiency of around 40% (after 12 weeks of daily training), which is in accordance with efficiency levels reached in other rodent studies (Cho and Jeantet, 2010; Rossi et al., 2012). Subsequently, we tested how this performance level was affected by sleep deprivation.

The DRL task generates several outcome measures. We obtained the number of lever presses and number of food rewards from each session. Efficiency was calculated as the number of obtained rewards divided by the number of presses. The range of interresponse times during the 1h sessions can be visualized in an interresponse-time (IRT) distribution, showing ascending IRT time bins on the x-axis and the frequency of occurrence of these IRT durations on the y-axis. The highest frequency is expected around the IRT bin corresponding to the imposed delay. A quantitative method for describing important characteristics of this IRT distribution is the peak deviation analysis, as described by Richards et al. (1993). Peak deviation analysis compares the IRT distribution of each rat with a theoretical distribution, which would have occurred if the rat had emitted the same number of presses randomly in time. This expected distribution curve is called the corresponding negative exponential (CNE). By comparing this corresponding negative exponential to the obtained IRT distribution we calculated the values for the following parameters: peak area and burst ratio. The peak area is the area of the obtained IRT distribution above the CNE, hence the area that cannot be explained by random lever pressing. Therefore, decreases in the peak area indicate loss of schedule control since the IRT distribution then becomes more similar to random performance. The burst ratio was used to investigate the tendency of the rats to respond in bursts, or in other words, press the lever with very short time intervals in between. It is calculated as the number of obtained IRT durations in the burst category (IRT<3 seconds) divided by the number of IRT durations predicted to occur in the burst category by the CNE. More bursting behavior is considered to reflect diminished behavioral inhibition.

Sleep restriction

To assess the effects of acute and chronic sleep restriction on DRL performance, rats were subjected to a schedule of repeated partial sleep deprivation for 7 days, allowing them

to sleep 4h every day at the beginning of the light phase (Novati et al., 2008; Roman et al., 2005). Animals were subjected to daily sleep deprivation by placing them in slowly rotating drums (40 cm diameter) driven by an engine at constant speed (0.4 m/min). During the DRL-30 training phase animals were habituated to the drums as their home cage. Throughout the experimental phase, rats were taken from the drums at 11:00 and placed in their own operant conditioning chamber in order to perform the DRL-30 task for 60 min during the last hour of the dark phase. The daily 20h sleep deprivation thus consisted of 19h in the rotating drums and 1h in the DRL task. Immediately after finishing this task at the beginning of the light phase, rats were weighed and placed back in their drum for their daily 4h rest (the drum was not rotating during this time). The 7d sleep restriction period was followed by a recovery week, where the same procedure of testing DRL performance was followed but the drums were not moving.

The experiment was conducted using a cross-over design, performed twice with two batches of 12 rats. For each batch, 6 animals were first subjected to sleep restriction while the remaining 6 animals served as a control group (non-rotating drums during the complete experiment). Between the end of the recovery phase and the start of the next sleep restriction phase two weeks were scheduled in order to allow the animals to reach stable weight and performance again. See Figure 1 for experimental protocol.

Sleep restriction and control animals were paired based on their weight and food intake prior to the start of sleep restriction. In each pair, the daily amount of chow the sleep restricted animal received was similar to the amount the control animal received, which maintained 90% of the pre-experimental body weight. This was done because sleep restriction itself may cause a mild drop in body weight (e.g. Barf et al., 2012). Trying to compensate for this by providing more food might reduce motivation for lever pressing and performance in the DRL task, independent of an effect of sleep loss on the PFC. Thus, when a sleep restricted animal dropped in body weight below 90% of its pre-experimental weight, it did not receive more food but, instead, it always received the same amount of food as its paired control. The daily food was provided at random times but at least 3 hours after finishing the DRL-30 session.

Forced activity control

Since the sleep deprivation procedure included mild forced locomotion, we used a forced activity control procedure to test whether changes in DRL performance following sleep deprivation might be caused by forced activity rather than by sleep loss per se. The cross-over experiment was repeated with the same animals but now with the drums rotating

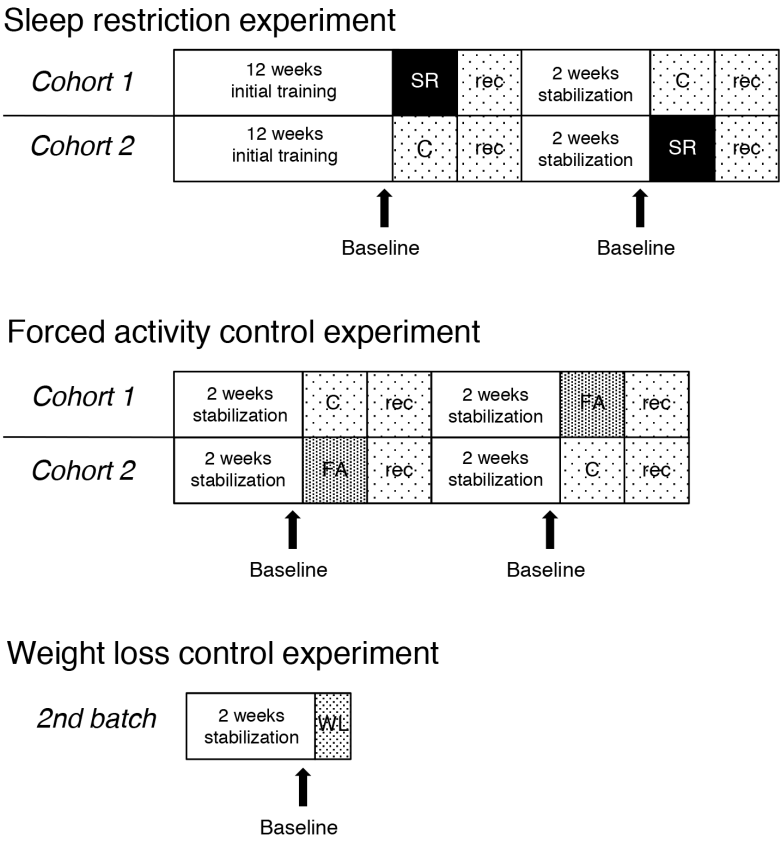

Figure 1. Experimental protocol.
The sleep restriction experiment and forced activity control experiment were performed twice with two batches of 12 animals. Based on weight and DRL-performance animals were paired and grouped to cohort 1 and cohort 2 (each N=6). DRL-performance on the three days preceding each experimental phase was used as baseline measurement (baseline). Each batch was trained for 12 weeks after which the sleep restriction experiment was conducted in a cross-over design. Animals were exposed to one week of sleep restriction by forced locomotion in a slow rotating drum (SR) or one week of control condition in a non-rotating drum (C). The SR and C condition were followed by one week of recovery (rec). The recovery week was followed by two weeks in which weight and DRL-performance stabilized (2 weeks stabilization). After this, the groups were again subjected to either the SR or the C condition and a week of recovery. Two weeks after completing the sleep restriction experiment exactly the same protocol was used for the forced activity control experiment, in which animals were exposed to the forced activity condition (FA). Only the second batch was subjected to the weight loss control experiment, after the completion of the forced activity control experiment. All 12 animals of this batch were exposed to weight loss (WL) for three days and subjected to DRL-testing on these days.

at double speed (0.8 m/min) for half the duration (see Figure 1). Instead of 19h, the drums were rotating for only 9.5h, divided in 5 blocks (1x1.5h block at the end of the light phase and 4x2h blocks in the dark phase, with 1h resting in between). Thus, in the forced activity control experiment, the animals walked the same distance as in the sleep restriction experiment but had sufficient time to sleep.

Weight loss control

While we aimed to maintain body weight at 90% of the pre-experimental body weight by restricting food availability, in many animals the sleep restriction procedure resulted in a small additional loss of weight. To assess whether this additional loss of weight might partly explain the deficits in DRL performance, we performed an additional control experiment with the animals of the second batch. The rats were subjected to body weight loss up to 85% of pre-experimental body weight by additional food restriction, after which their performance on the DRL-30 task was investigated for 3 consecutive days (see Figure 1).

Statistical analysis

All data for the different DRL outcome measures are expressed as a percentage of baseline (the average of the last 3 days of training before the start of the experiment). The number of lever presses, the amount of rewards and efficiency were analyzed for the 7d experimental period and the subsequent 7d recovery period using repeated measures ANOVA with a between-subjects factor condition (sleep restriction or forced activity versus control) and a within-subjects factor time (7 successive days). When the overall repeated measures ANOVA revealed a significant effect of treatment or a significant treatment x time interaction, post hoc *t*-tests were applied to determine at which days the differences occurred. The percentages of the peak area and burst ratio compared to baseline were analyzed using a repeated measures ANOVA, separately for the experimental and recovery period, in the same manner as described above. For the weight loss control the average for all outcome measures of the 3 days before the decrease in body weight and the average of the 3 days after that, were compared using Student *t*-tests. All analyses were performed with the software PASW Statistics 18. Statistical significance was set to $p<0.05$.

RESULTS

Sleep restriction

There were no baseline differences in number of presses, rewards, efficiency, peak area, burst ratio and body weight between control and experimental groups.

Results for the number of presses, the number of rewards, and the efficiency are depicted in Figure 2A-C. For the amount of lever presses during the 7d treatment period, repeated measures ANOVA revealed a strong trend towards an overall effect of treatment ($F_{1,46}$=3.79, p=0.058) and a significant treatment x time interaction ($F_{6,276}$=5.56, p<0.001), suggesting that there was a gradual increase in lever pressing during the week of sleep restriction (Figure 2A). Also, during the 7d recovery period, a significant treatment effect was found ($F_{1,44}$=6.76, p<0.05). The increase in lever presses that occurred during the sleep restriction phase persisted throughout the entire recovery period (Figure 2A).

During the experimental week animals received significantly less rewards in the sleep restriction condition than in the control condition ($F_{1,45}$=6.97, p<0.05). This effect rapidly disappeared and ANOVA did no longer indicate an effect of treatment for the 7d recovery period (Figure 2B).

Concerning efficiency during the 7d treatment period, repeated measures ANOVA revealed a significant effect of sleep restriction ($F_{1,46}$=4.88, p<0.05), indicating that animals who were sleep restricted had a lower efficiency than animals who were allowed to sleep when they pleased (Figure 2C). No significant treatment effect was found for the recovery period.

Peak deviation analyses were performed for the three days prior to the start of the experiment and for all the days of the experimental and recovery period. Results are shown in Figure 3A-C. The IRT distribution averaged for the 7 days of the experiment shows that under the influence of sleep restriction the peak shifted to the left and became wider and more flat (Figure 3A). Indeed, repeated measures ANOVA revealed a significant overall effect of treatment on the peak area during the 7d sleep restriction period ($F_{1,46}$=30.13, p<0.001). The sleep restricted animals displayed an immediate decrease in peak area after the first day of sleep restriction, which persisted throughout the 7d experimental period (Figure 3B). During the recovery period the peak area quickly normalized and remained stable thereafter.

The burst ratio was significantly increased in animals subjected to sleep restriction ($F_{1,43}$=5.94, p<0.05), indicating that these animals were bursting more than their controls (Figure 3C). This effect lasted throughout the entire recovery period ($F_{1,40}$=6.09, p<0.05).

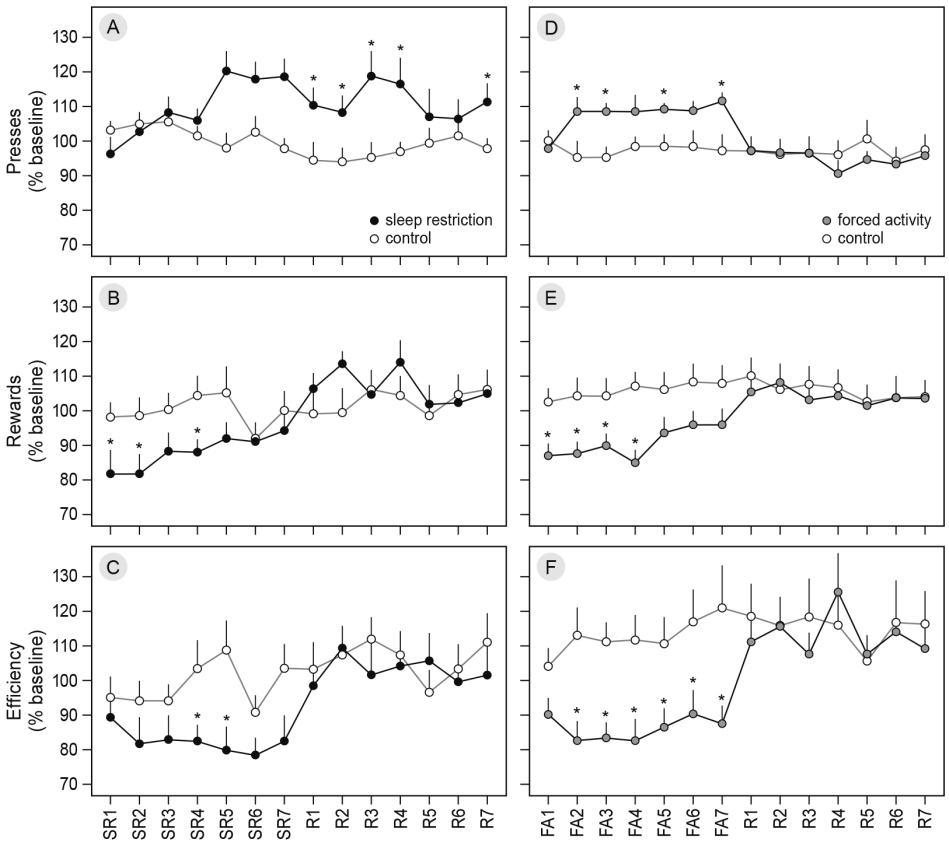

Figure 2. DRL-30 performance of rats exposed to 7 days of sleep restriction (left panels, A-C) or forced activity (right panels, D-F) followed by a 7-day recovery period (N=24 for each condition). All data are expressed as a percentage of baseline performance (the average of the last 3 days of training before the start of the experiment). Days of the experiment: SR = sleep restriction, FA = forced activity, R = recovery. Only when repeated measures ANOVA revealed a significant effect of condition or a condition x time interaction effect, were the successive days compared using Student *t*-tests. Significant differences are indicated by an asterisk * ($p < .05$).

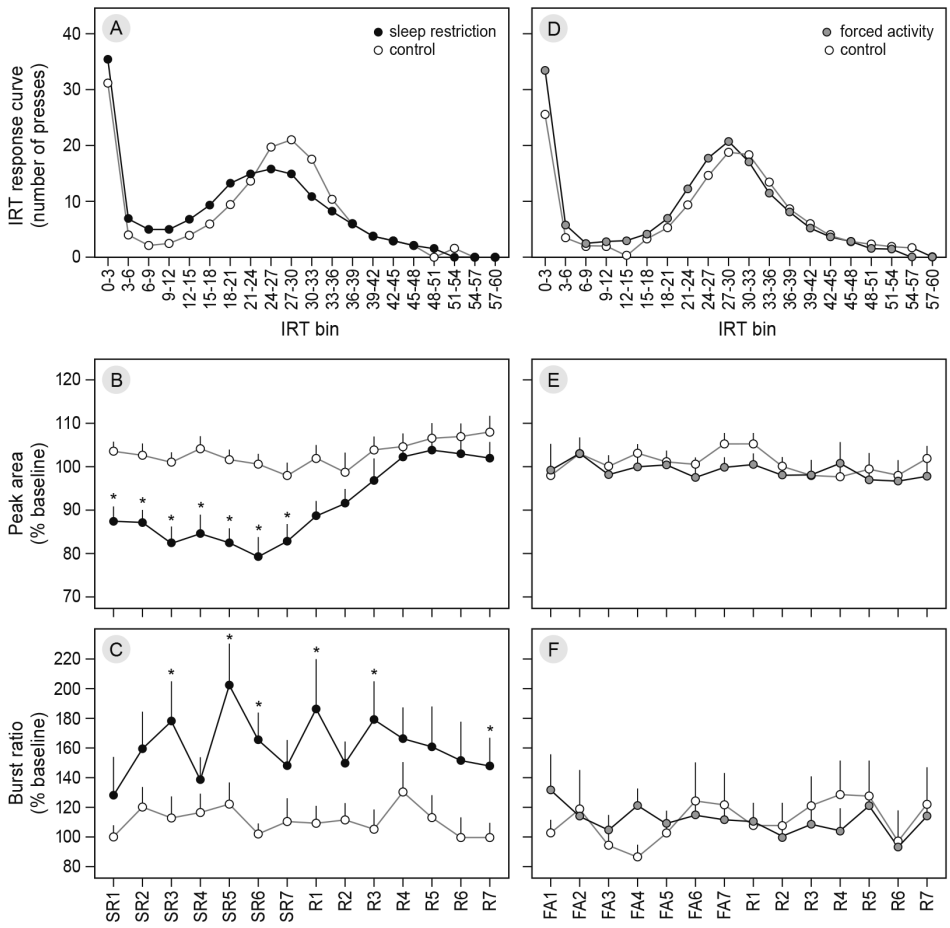

Figure 3. Results of the peak deviation analyses, showing the inter-response time (IRT) distribution, changes in peak area and in burst ratio for the sleep restriction experiment (left panels, A-C) and forced activity control (right panels, D-F) (N=24 for each condition). Data for the peak area and burst ratio are expressed as a percentage of baseline performance (the average of the last 3 days of training before the start of the experiment). Days of the experiment: SR = sleep restriction, FA = forced activity, R = recovery. Only when repeated measures ANOVA revealed a significant effect of condition or a condition x time interaction effect, were the successive days compared using Student *t*-tests. Significant differences are indicated by an asterisk * ($p<0.05$).

Forced activity control

Results for presses, rewards and efficiency under conditions of forced activity are shown in Figure 2D-F. Compared to baseline, the number of presses increased with approximately 10% during forced activity and remained at this level for the complete forced activity period. This was a significant difference compared with the control group ($F_{1,46}$=6.90, p<0.05). No condition effect for number of presses was found for the recovery period.

Comparable findings were found for number of rewards, which decreased significantly during the forced activity period ($F_{1,46}$=8.80, p<0.01), and were restored to baseline levels at the start of the recovery period.

Forced activity significantly lowered efficiency as indicated by a significant treatment effect during the forced activity period ($F_{1,46}$=10.55, p<0.01). During the recovery period efficiency of the animals subjected to forced activity immediately came back to levels comparable to the controls: no significant differences were found. There were no significant treatment x time effects for number of presses, rewards and efficiency.

The IRT response curve for the forced activity experiment shows that there were no striking changes in the shape of the forced activity curve compared to the control curve (Figure 3D). Hence, there were also no significant effects on the peak area (Figure 3E). Also the burst ratio was not significantly affected by forced activity (Figure 3F).

Weight loss control

Sleep restricted animals displayed a small additional drop in body weight to 88.3±0.2% of the pre-experimental body weight after the first experimental day up to 83.4±0.4% on the seventh experimental day. For the weight loss control experiment, animals of the second batch were food deprived and gradually reached a body weight of 84.7±0.4% pre-experimental weight on the 3rd day. Table 1 shows the performance of the animals during this 3-day period of extra body weight loss compared to their performance in the 3 days prior to the start of the additional food deprivation. Student t-tests showed no significant differences between the baseline performance and the additional weight loss performance.

Table 1. Results of the weight loss control experiment. Body weight of the animals was lowered from 90% free-feeding body weight to approximately 85% free-feeding body weight, by means of extra food restriction. Baseline scores (the average of the scores of the 3 days prior to the start of the additional food restriction) on the different outcome measures and the average score of the 3 days after were compared using Student *t*-tests. Values are expressed as mean ± standard error of the mean.

	Baseline	Body weight control	*p*
% of free-feeding body weight	90.5 ± 0.7	86.4 ± 0.9	0.000*
Efficiency	40.2 ± 24.7	37.7 ± 22.6	0.801
Number of presses	167.1 ± 82.2	163.7 ± 87.6	0.925
Number of rewards	52.8 ± 19.2	48.2 ± 18.5	0.578
Peak area	0.52 ± 0.12	0.50 ± 0.11	0.713
Burst ratio	3.00 ± 3.72	3.02 ± 3.66	0.991

* $p < .001$

DISCUSSION

This study investigated the influence of sleep restriction on operant conditioning behavior in rats, using a DRL-30 task. Several DRL outcome measures were affected by sleep loss. Although some measures were also affected by forced locomotion, the effects on the peak area and burst ratio seem to be a direct effect of sleep restriction itself. The decreased peak area in sleep restricted animals indicate that they were less able to correctly time their lever presses as required by the DRL-30 schedule and pressed more randomly. This was an acute effect, directly visible after the first sleep restriction session. Sleep restriction also caused a significant increase in burst ratio, thus animals were responding more often with very short time intervals (<3 seconds). While the peak area and burst ratio did not change significantly in the forced activity control experiment, the number of lever presses, the amount of rewards and efficiency did. In fact, the changes in these outcome measures were comparable for the sleep restriction and forced activity condition. Thus, for these specific measures we cannot distinguish between effects of sleep disruption and forced activity. Although the forced activity control procedure allowed sufficient time for sleep it still constituted a disruption of the normal sleep-wake rhythm. The changes in DRL performance that were similar for the sleep restriction group and forced activity control condition might therefore be due to sleep disturbance, forced activity or both.

Interestingly, the sleep restriction-specific changes in peak area and bursting behavior are very similar to what has been reported in PFC-lesion studies using a DRL paradigm (Cho and Jeantet, 2010; Nalwa and Rao, 1985). Therefore, our results support the hypothesis that sleep loss affects prefrontal cortical functioning. In the study of Cho and Jeantet (2010) it was especially the peak area that was affected by a lesion in the prefrontal area and not so much the number of responses, rewards and efficiency. It may be that the peak area is a more specific marker for prefrontal cortical functioning than the number of presses, rewards, and efficiency, which are possibly sensitive to a broader range of factors. In fact, mice with a lesion in their hippocampus made more responses, acquired fewer reinforcements and were less efficient than mice with a lesion in their prefrontal cortex (Cho and Jeantet, 2010). Since hippocampal functioning is highly sensitive to both sleep loss and stress (Kim and Diamond, 2002; Kreutzmann et al., 2015) this may offer an explanation why sleep restriction as well as forced activity affected these outcome measures.

Why animals show bursting behavior in a DRL task is still a subject of discussion. One could think of autoshaped responses (Monterosso and Ainslie, 1999), meaning behavior that animals spontaneously engage in without obvious reinforcement, or perseverative behavior (Sokolowski and Salamone, 1994), thus being part of a response pattern where the animal is unable to break out of. However, it is tempting to consider the increased bursting behavior in our sleep restricted animals as a form of enhanced impulsivity. Due to the broad and often poorly defined construct of impulsivity (Monterosso and Ainslie, 1999), the relation between sleep and impulsivity is still under debate. Lack of sleep seems to negatively affect especially emotional impulse control. For example, Anderson and Platten (2011) showed that one night of sleep deprivation in healthy volunteers led to enhanced impulsive responses towards negative emotional stimuli. Furthermore, impaired control of emotional responses after sleep deprivation has been linked in an imaging study to reduced top-down control of the PFC over the amygdala (Yoo et al., 2007). The impulsivity-PFC paradigm as an explanation for the increased burst ratio in our experiment seems to fit well with our hypothesis. Follow up studies may particularly focus on unravelling the nature of increased bursting behavior as a consequence of sleep loss.

Our findings of changes in operant conditioning and the presumed underlying prefrontal impairment in rats are in agreement with studies showing reduced blood flow and cerebral metabolism in the prefrontal area after sleep deprivation in humans (Thomas et al., 2000; Drummond and Brown, 2001; Yoo et al., 2007). Sleep deprivation

may directly affect neuronal function in the prefrontal cortex function, e.g., by impairing cAMP signaling (Vecsey et al. 2009). In addition, sleep restriction could perhaps affect prefrontal cortex function through indirect pathways and changes elsewhere in the brain and body, e.g. effects on other brain areas functionally connected to the PFC or changes in neuroendocrine factors that reach the PFC through the blood. One potential indirect mechanism that requires further study is a disruption of circadian rhythmicity. Although in an earlier study sleep deprivation by forced locomotion did not alter the phase or period of the free-running rest-activity rhythm in rats (Strijkstra et al. 1999), other studies in rats showed that sleep deprivation can have pronounced effects on neuronal firing of the suprachiasmatic nucleus or biological clock in the hypothalamus (Deboer et al. 2003). It is not excluded that such altered neuronal activity of the biological clock might ultimately affect activity and function of the PFC (Sylvester et al. 2002). Also stress hormones might in theory mediate some effects of sleep restriction on operant conditioning (Olausson et al., 2013), although in previous studies we have shown that levels of the stress hormone corticosterone in our sleep restricted rats are not or only mildly elevated (e.g. Roman et al., 2005a; Novati et al., 2008). Stress does not seem to be the common denominator since some effects were specific for sleep restriction and were not seen in forced activity controls, which have equally high or even higher levels of stress hormones (Novati et al., 2008).

Interestingly, there were individual differences in the extent to which rats were affected by sleep restriction. Some rats showed just a minor change in peak area, while others were only able to reach around 60% of their baseline peak area. Inter-individual differences in vulnerability to the effects of sleep loss have been described before in humans (e.g. Van Dongen et al., 2004) and animals (Córdova et al., 2006). One hypothesis is that the level of prefrontal cortical functioning determines how susceptible an individual is to the effects of sleep deprivation (Kamphuis et al., 2012), meaning that lower PFC function under baseline conditions may result in a higher vulnerability to disruptive effects of sleep loss. Given the involvement of PFC functional impairments in several behavioral and psychiatric disorders (Lewis and Lieberman, 2000; Drevets, 2001; Raine et al., 2000) and the high prevalence of sleep problems among such individuals (Tsuno et al., 2005; Cohrs et al., 2008; Kamphuis et al., 2013) it may be worthwhile to further explore this vulnerability hypothesis.

Sleep restriction affected DRL-30 schedule performance in rats, reflected in a diminished timing ability and attention control, working memory problems and reduced behavioral inhibition. Since behavioral efficiency in the DRL paradigm is highly dependent

on proper functioning of the PFC, our data support the hypothesis that sleep loss has a negative impact on prefrontal cortical functioning. This model may be employed in future studies investigating this relation on a biochemical and molecular level using advanced neurobiological techniques.

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