The relation between sleep and violent aggression

Kamphuis, Jeanine

Publication date:
2017

Chapter 5

Chronic sleep restriction has little effect on the expression of violent behavior in aggressive rats

Authors:
Jeanine Kamphuis
Jaap M. Koolhaas
Marike Lancel
Peter Meerlo

ABSTRACT

Human studies imply a strong association between sleep problems and impaired control of aggression, especially in populations at risk, such as forensic psychiatric patients. Experimental studies in animals investigating the effect of sleep deprivation on aggressive behavior so far provided inconsistent results, which may be related to the methods of sleep deprivation and variation in the aggression measurements. We aimed to examine the effect of sleep restriction on the development of abnormal, violent aggressive behavior in Wild-type Groningen (WTG) rats. Eight male rats, selected for comparable high aggression levels, were subjected to a sleep restriction protocol of 9 days by placing them in rotating drums for 20h per day. Compared to home cage and forced activity controls, sleep restricted rats did not show more aggression, did not attack faster, did not significantly reduce their introductory threatening behavior before the attack, did not attack more vulnerable body parts, and did not attack unfamiliar females and anesthetized intruders more frequently. The results of this study indicate that sleep restriction does neither alter general aggression nor induce pathological forms of aggression in WTG rats. Possibly, like in humans, only few animals are vulnerable to developing this type of abnormal behavior after sleep loss.

INTRODUCTION

Poor sleep can negatively affect emotional function (Banks and Dinges, 2007), potentially resulting in greater irritability and diminished anger control (Kamphuis et al., 2012). Anecdotal information and correlational evidence from studies in both humans and animals suggest that disrupted sleep may contribute to the development of aggressive behavior. For example, short sleep and a higher number of nighttime awakenings have been correlated to conduct disorders and aggressive behavior in children (Gregory et al., 2004; Reid et al., 2009). In adults, poor subjective sleep quality has been associated with increased hostility and anger (e.g. Pilcher et al., 1997; Shin et al., 2005; Granö et al., 2008).

Despite a fair number of studies that have been devoted to this topic, available data from controlled studies remain inconsistent. Sleep deprivation studies in humans investigating the effect of sleep loss on escalation of aggression have been inconclusive. Sleep deprived healthy individuals respond with increased verbal aggression to frustrating situations (Kahn-Greene et al., 2006) and are less able to inhibit a response to negative emotional stimuli (Anderson and Platten, 2011). However, studies using behavior in a computer game to assess aggression, defined by the amount of noise blasted at the opponent in the game (Vohs et al., 2011) or the amount of money taken from an opponent without monetary gain for the experimental subject itself (Cote et al., 2013), did not find increased aggression levels after sleep deprivation. These inconsistent findings in humans may in part be due to the varying and often indirect measures of aggression.

There are several animal studies that have assessed effects of sleep deprivation on aggressive behavior more directly. Yet, even in these cases the results are sometimes still difficult to interpret because of the different methods of sleep deprivation employed, some of which may be confounded by factors unrelated to sleep loss. For example, a number of studies report increased aggression following selective deprivation of rapid-eye-movement (REM) sleep using the flower pot method in rats (Sloan, 1972; Hicks et al., 1979; Peder et al., 1986; de Paula and Hoshino., 2002; Marks and Wayner, 2005) and mice (Benedetti et al., 2008). Yet, since in this method animals are placed on small platforms surrounded by water, it has often been criticized for inducing high levels of stress, which must be taken into consideration when interpreting the findings. Webb (1962) found more aggressive behavior when rats were confronted with a conspecific after treadmill-induced sleep deprivation. In another study, rats displayed increased irritability after treadmill-induced sleep deprivation, an effect due to sleep loss as the authors controlled for the physical exercise by adding a forced activity control group (Tartar et al., 2009). Rather unexpectedly, in an experiment executed in our own laboratory we found no effects on resident intruder offensive aggressive behavior after repeated sleep restriction for 8 days by forced locomotion in rats (unpublished).

When investigating the effect of sleep loss on aggression in animal research and producing clinically relevant data it is vital to investigate forms of animal aggression that can be considered as escalated and perhaps pathological aggression. Thus, aggression that is no longer subject to inhibitory control and has lost its adaptive function in social communication. Although reports on violent outbursts in animals under controlled laboratory conditions are rare (Miczek et al., 2013), some violent behavioral characteristics have been postulated: a disappearance of normal investigatory and threatening behavior, orienting bite attacks on more vulnerable parts of the opponent's body such as the head or abdomen, and losing the ability to discriminate context and/or type of opponent, leading to the attack of dominant males, females or even anesthetized/dead conspecifics (de Boer et al., 2003; de Boer et al., 2009; Miczek et al., 2013). Approximately 8-12% of Wilde-type Groningen (WTG) rats displays such pathological aggressive behavior after repeatedly allowing them dominate a conspecific (de Boer et al., 2009).

The aim of this study was to investigate the effect of sleep loss on the expression of such pathological forms of aggression in WTG rats. To be able to detect acute and chronic effects we used a repeated sleep restriction schedule. We hypothesized that sleep restricted animals will display escalated and out-of-context aggression, reflected in faster attacks, bite wounds on more vulnerable body parts of the opponent and attacking anesthetized and female intruders. We expected stronger effects after exposure to chronic sleep restriction than after acute sleep deprivation.

METHODS

Animals and Housing

The study was performed with 24 medium to high aggressive male adult WTG rats. Animals were housed under a 12h light/ 12h dark cycle with lights on from 9.00 to 21.00 h. Housing rooms had stable temperature (21 ± 1 °C) and humidity (60 ± 2 %). Water and food were provided ad libitum throughout the experiment. Experiments were approved by the animal ethics committee of the University of Groningen.

Selection and grouping of animals

To obtain 24 medium to high aggressive rats, we exposed four batches of 24 three-month old WTG rats to four resident intruder (RI) tests. Wistar rats were used as intruder. Attack latencies were scored in each test. During the fourth test, the amount and type of aggressive behavior was evaluated for ten minutes after the first attack. Aggressive behaviors that were scored were: 1) lateral threat, 2) keep down, 3) clinch, 4) chase, and 5) upright posture. All RI tests were executed during the first hour of the dark phase. See for RI test procedure video publication by Koolhaas et al., 2013.

Animals that showed aggressive behavior for more than 45% of the time during the fourth RI test were selected and randomly distributed over three groups: sleep restriction, forced activity control or home cage control (n=8 in each group). The procedures for sleep restriction and the control procedures were applied as described previously (e.g., Roman et al. 2005, Novati et al. 2008). The rats in the sleep restriction group were subjected to repeated partial sleep deprivation for 9 days by placing them in motorized drums slowly rotating at a speed of 0.4 m/min, for 20h per day. Drums were not rotating during the first 4 hours of the light phase. The rats in the forced activity control group were placed in rotating drums similar to the sleep restriction group but only for 10h per day, divided in 5x2h blocks, during the experimental period. Drums were rotating at double speed (0.8/min) and therefore these animals walked the same distance as animals in the sleep restriction condition. This condition was added to control for the mild physical activity sleep restricted animals performed. Finally, the animals of the home cage control condition were placed in regular cages, and underwent the same tests for violent behavior as animals in the sleep restriction and forced activity condition. The sleep restriction protocol as applied above has been shown to significantly reduce non-rapid-eye-movement (NREM) and REM sleep: Barf et al. (2012) measured EEG while rats were in the rotating drums and found that rats showed occasional micro sleeps (< 20 seconds), adding up to one hour of sleep during a 20h sleep deprivation period.

Experimental procedure

Prior to the start of the experiment, aggression levels of the selected 24 animals were measured again by exposing them to the same procedure used in the selection phase, namely four RI tests on consecutive days, using Wistar intruders, with video scoring the fourth test for ten minutes after the first attack. This was done because up to three months passed between selecting animals from the first and fourth batch. During this waiting period animals were housed with their paired female. After the re-characterization, animals were habituated to the drums (for sleep restriction and forced activity condition) or to new regular cages (for the control condition). The habituation took place on three days for 2-3h during the second half of the light phase. The next day (day 0 of the experiment) drums started rotating. At the start of the light phase, all animals were taken out of their drums/regular control cages and placed in their own RI test cage to allow them to rest and to spend time with their paired female, which was housed in this RI test cage during the entire experiment. On day 1, 7, 8, and 9 tests for violent behavior were executed, in the first hour of the light phase.

Tests for violent behavior

To investigate whether sleep restriction lead to forms of aggressive behavior no longer subject to inhibitory control and with no adaptive function in social communication, all animals were subjected to the following series of tests:

Regular RI tests on day 1 and day 7 with a male Wistar intruder:

All animals were confronted with a male Wistar intruder on day 1 and day 7 of the sleep restriction protocol, shortly after they were removed from their drums/regular cages at the start of the light phase and placed in their own RI test cage. Their paired female was already removed. About 5-10 minutes later, a Wistar rat was introduced. Video recordings were made for ten minutes after the first attack. Within the first half hour of the light phase all tests were finished and females were returned and placed with the experimental rats. The video recordings were analyzed and the following behaviors and outcome measures were assessed:

- Attack latencies: the development of abnormal aggressive behavior may be associated with a gradual disappearance of normal investigatory and threatening behavior and may result in immediate attacks reflected in shorter attack latencies.
- Lateral threat/clinch ratios: normally a bite attack is preceded by introductory threatening behavior during which the resident animal moves toward the intruder while performing lateral threatening postures. The actual bite attack or clinch, only follows after a period of lateral threat. This usually leads to the intruder taking a submissive posture (signaling defeat) when approached and/or kept down by the resident. The resident will no longer bite the intruder as long as it remains passive. Persistence of bite attacks or clinching and diminished lateral threatening result in lower lateral threat/clinch ratios. A ratio below 1 shows that animals attack without any introductory behavior and forewarning which is a reliable indicator of violence (out of control) (Koolhaas et al., 2013).
- Bite wound locations: normally, bite attacks are directed toward the back and neck regions of the intruder. Orienting the attack bites towards more vulnerable body parts, such as the head or ventral surface, is considered a sign of out of context, escalated

aggression (Haller et al., 2001, de Boer et al., 2009). After each test, Wistar intruders were anaesthetized by Isoflurane (Pharmachemie BV, Harlem, The Netherlands) and checked for bite wound locations. A distinction was made between four target areas: head (the area anterior to the ears), dorsal areas (the dorsal part of the neck, back and flanks), ventral areas (throat and belly) and extremities (legs, paws and tail) (Haller et al., 2001).

RI test on day 8 with un unconscious male Wistar intruder:
Territorial aggression in male rats is normally directed towards unfamiliar conspecific intruder males (Miczek et al., 2013). An opponent that is completely immobile and non-responsive displays no threat and will usually not be a strong trigger for aggression and presumably will not evoke bite attacks. We therefore performed an RI test on day 8 with a Wistar intruder that was anesthetized with an intraperitoneal injection of pentobarbital. The anesthetized animal was removed immediately after an attack of the resident or after 10 minutes when no attack occurred.

RI test on day 9 with an unfamiliar female:
Territorial aggression in male rats is normally only directed towards male conspecifics and not to females. Attacking a female is considered to be a form of deviant aggression, as it has no evolutionary advantages. To test for abnormal aggression, the experimental animals were subjected to a RI test with an unfamiliar wild type female as an intruder. Females were removed after the first attack, or after 10 minutes when no attack occurred.

Statistical analysis
One-way ANOVA was performed to assess the effects of sleep restriction on the various outcome measures of the aggression tests (attack latencies, total amount of aggressive behavior, time spent with lateral threat, time spent with clinch/attack, time spent with inactivity, the lateral threat/clinch ratio, the time spent with no activity, bite wounds number and location). Effects found on day 1 of the experiment were considered acute and on day 7 chronic effects. Fisher's exact tests were used to analyze the effect of condition (sleep restriction, forced activity, control) on whether or not an anesthetized and/or female intruder was attacked (yes/no). To get a better understanding of the behavioral profile of animals that attacked a female or anesthetized intruder, differences in total aggression scores and specific aggressive behaviors, lateral threat/clinch ratios, number of bite wounds and locations between attackers and non-attackers were analyzed with an independent Student *t* test. All analyses were performed with the software PASW Statistics 18. Statistical significance was set to $p<0.05$.

Table 1. Scores on outcome measures for the control group (n=8), sleep restriction group (n=8) and the forced activity group (n=8). Scores for total time spent with aggressive behavior, attack latency, time spent with lateral threat and clinch, the lateral threat/ clinch ratio and time spent being inactive are shown for the characterization phase prior to the start of the experiment, day 1 and day 7. Bite wounds, shown separately for day 1 and day 7, are separated for the different bite wound locations, anterior (head), dorsal (back), ventral (neck and abdomen) and extremities (paws and tail). *Abbreviations*: an = number of animals, wo = number of wounds.

		Control	Sleep restriction	Forced Activity
% total aggression	Characterization	38,05 ± 22,82	36,85 ± 20,34	37,91 ± 12,98
	Day 1	27,14 ± 11,36	20,81 ± 13,47	28,69 ± 19,98
	Day 7	35,90 ± 15,55	24,13 ± 24,12	25,00 ± 16,10
Attack latency	Characterization	96,38 ± 82,64	71,03 ± 67,12	67,69 ± 33,09
	Day 1	118,14 ± 63,67	114,00 ± 47,13	90,86 ± 37,19
	Day 7	89,00 ± 94,71	97,38 ± 89,96	119,00 ± 56,15
% lateral threat	Characterization	25,55 ± 15,89	22,64 ± 13,36	27,23 ± 12,85
	Day 1	20,04 ± 7,12	11,50 ± 8,40	19,41 ± 15,74
	Day 7	26,73 ± 14,76	18,69 ± 21,06	17,19 ± 13,53
% clinch	Characterization	3,96 ± 2,61	4,84 ± 4,17	4,08 ± 2,72
	Day 1	3,00 ± 2,32	4,11 ± 4,59	4,84 ± 5,39
	Day 7	3,50 ± 2,18	2,36 ± 1,40	4,56 ± 2,01
% lateral threat/ % clinch	Characterization	7.61 ± 7.35	15.19 ± 28.75	12.95 ± 15.67
	Day 1	8.91 ± 6.47	4.71 ± 3.76	6.79 ± 6.06
	Day 7	9.23 ± 6.60	8.00 ± 6.44	5.55 ± 7.24
% inactivity	Characterization	8,26 ± 12,54	4,73 ± 5,19	4,81 ± 3,58
	Day 1	5,41 ± 4,24	4,83 ± 4,27	9,28 ± 15,11
	Day 7	7,36 ± 7,76	7,74 ± 8,76	6,91 ± 7,54
Bite wounds day 1	Anterior	3 an / 8 wo	4 an / 5 wo	1 an / 1 wo
	Dorsal	5 an / 35 wo	7 an / 42 wo	7 an / 20 wo
	Ventral	4 an / 6 wo	2 an / 3 wo	1 an / 1 wo
	Extremities	4 an / 9 wo	0 an / 0 wo	1 an / 1 wo
Bite wounds day 7	Anterior	2 an / 2 wo	1 an / 1 wo	2 an / 2 wo
	Dorsal	8 an / 65 wo	7 an / 27 wo	7 an / 53 wo
	Ventral	2 an / 5 wo	3 an / 3 wo	3 an / 4 wo
	Extremities	1 an / 8 wo	2 an / 6 wo	3 an / 7 wo

Abbreviations: an, number of animals; wo, number of wounds

RESULTS

Most animals showed lower levels of aggression immediately prior to the experiment than they had done during the initial selection phase (total aggression time during the RI test 37.6 ± 18.3% and 55.6 ± 11.4%, respectively; $t(38.4)=4.1$, $p=0.000$). This was the case for all groups. Thus, at the start of the experiment average aggression score fell in the medium category (between 15% and 45%).

Aggression scores on day 1 and 7

The results of the standard RI tests on day 1 and 7 of the sleep restriction protocol are shown in Table 1.

Although sleep restricted animals on average displayed less aggressive behavior, a lower percentage of lateral threat, and lower lateral threat/clinch ratios than animals in the forced activity control and home cage control conditions on day 1 of the experiment, these differences did not reach statistical significance (ANOVA $p>0.05$ in all cases). On day 7, sleep restricted animals and animals from the forced activity group had lower total aggression scores and lower lateral threat/clinch ratios, than the control group, but this was also not statistically significantly different.

With regard to the lateral threat/clinch ratios, none of the control animals reached a ratio <1. In the sleep restriction group one animal had a ratio <1 on day 1 of the experiment, another animal on day 7, indicating these animals attacked without proper introductory behavior. For the forced activity group, there was one animal on day 1 and two other animals on day 7. There were no statistically significant differences between groups.

Bite wounds

Animals in all groups attacked their opponent mostly on the dorsal part of the body. The total number of bite wounds was highest in the opponents of the control group (Mean ± SD: 7.3 ± 7.1 on day 1, and 10.0 ± 7.9 on day 7; sleep restriction: 6.5 ± 5.9 on day 1, and 5.3 ± 4.3 on day 7: forced activity: 2.9 ± 3.1 on day 1, and 8.3 ± 7.3 on day 7). The differences between the groups were not statistically significant (ANOVA: $F_{2,23}=1.33$, $p=0.287$ on day 1, and $F_{2,22}=0.91$, $p=0.420$ on day 7). Sleep restriction did not affect bite wound locations. With regard to the severity of the wounds, more Wistar opponents needed surgical suturing after the test in the control group than in the sleep restriction group (control: four on day 1 and three on day 7; sleep restriction: two on day 1 and one on day 7; forced activity: two on day 1 and two on day 7).

Attack of the anesthetized intruder

During the test with an anesthetized intruder on day 8, a majority of animals from all 3 groups attacked the immobile opponent (control: n=7; sleep restriction: n=6, forced activity: n=6). Fisher's exact test yielded p=0.999, indicating no group differences. Irrespective of treatment group, animals attacking an anesthetized intruder made significantly more bite wounds on day 7 (t(19.6)=-4.4, p=0.000), especially dorsally located wounds (t(21)=-2.6, p = 0.017). They did not differ in other outcome measures from non-attackers.

Attack of the unfamiliar female intruder

Only a few animals in each group attacked the unfamiliar female on day 9 (control: n=2; sleep restriction: n=3, forced activity: n=1) and the number of animals did not significantly differ between the groups (p=0.837). Animals that did attack a female showed a trend towards more inactivity during the test on day 1 and 7 (t(22=-2.1, p = 0.051; t(6.3)=-2.3, p = 0.056, respectively). They did not differ from non-attackers in total aggression scores, attack latencies, bite wound locations, lateral threat or clinching behavior.

DISCUSSION

In the present study, we examined the influence of acute and chronic sleep restriction on the expression of pathological forms of aggression in WTG rats. Contrary to our expectation, sleep restriction neither increased the amount of aggression in our rats nor did it significantly affect the nature of the aggression. Sleep restricted rats did not show more signs of aberrant, pathological aggression than control animals. These data do therefore not support the hypothesis that sleep loss promotes violent behavior in rats.

The lack of the effect of sleep restriction may be due to the highly important survival function of territorial aggression. Having a territory leads to access to resources and mating partners, thus contributes to fitness and survival of the species. Perhaps the drive and motivation for territorial aggression is so strong that it is one of the last things that will fail under conditions of sleep loss. One may wonder whether the present negative results can be considered as scientifically conclusive. Our results contradict findings in experimental studies where aggressive behavior changed after sleep restriction. In fact sleep deprivation in fruit flies has been found to decrease fighting behavior, in both offensive and defensive aggression (Kayser et al., 2015). The authors actually claim that sleep deprivation places the fruit flies at a competitive disadvantage towards finding a partner, thus negatively affecting their reproductive fitness.

Another explanation for the lack of effects of sleep restriction on aggression in our study as opposed to some other studies may be the method of sleep deprivation employed. Most studies finding aggression-promoting effects of sleep loss, used selective REM sleep deprivation (Sloan, 1972; Hicks et al., 1979; Peder et al., 1986; de Paula and Hoshino., 2002; Marks and Wayner, 2005; Benedetti et al., 2008). It might be that there is a specific effect for REM sleep on aggression control, since this sleep stage is involved in emotional regulation (Goldstein and Walker, 2014). However one has to take into account that the flower pot method used for REM sleep deprivation leads not only to the loss of REM sleep, but also largely to loss of slow wave sleep (Machado et al., 2004). A study in mice using a 3 cm platform for 24h resulted in a 78% reduction of slow wave sleep and a 96% decrease of REM sleep (Silva et al., 2004). It is possible that especially the sleep fragmentation caused by this method affected aggression, whereas our sleep restricted animals were confronted with a continuous, perhaps more predictable sleep restricting situation, allowing better adaptation. Finally, the sleep restriction protocol employed in this study has been shown to produce an altered stress response (Meerlo et al., 2002). Whether or not this response is different from the effects seen in selective REM sleep deprivation is not known.

Perhaps in animals, like in humans, only a small proportion reacts with more abnormal and escalated aggression to sleep loss. Although in healthy human populations significant correlations have been found between poor sleep, hostility and anger (see for review Kamphuis et al., 2012), it is likely that the relation with violent acts and crimes is only relevant for certain individuals, such as forensic psychiatric patients (Kamphuis et al., 2014). When examining combinations of abnormal aggressive behavior, we detected one animal in the sleep restriction group that showed the combination of increased total aggression scores on day 1 and 7, attacking more vulnerable body parts leading to suturing of the opponent, an increase of clinching and lateral threat/clinch ratio <1. No animal in the home cage control and forced activity groups had this behavioral combination. Whether or not this behavior was due to restricted sleep, perhaps in combination with un underlying vulnerability, or if this animal would have displayed this behavior regardless of the group he was in, is not clear. Only bigger studies using more animals per group might shed some light on this question.

Animals that attacked unfamiliar females were few, but did not seem to be the most aggressive animals. In fact, two days prior to the test, they spent significantly more time than the other animals being inactive. Four out of the six animals attacking a female had a total aggression score < 10% in the test on day 7. Thus, attacking a female is not necessarily combined with faster attacks, higher levels of aggression and decreased introductory and forewarning behavior. This is not in line with literature on pathological aggression in these rats (Miczek et al., 2013). Why these females are attacked remains a question. Most of our animals in all groups attacked the anesthetized intruder. Although one can presume all of them are thus violent animals, no clear effect on other aggression parameters was found in the attackers, except for making more bite wounds than the five non-attacking animals. Therefore, we considered attacking an anesthetized intruder in this experiment not as a good marker for pathological, abnormal aggression.

Another puzzling finding was the reduction in aggression levels from the initial selection phase to the characterization immediately prior to the experiment. On a group level the high aggressive group we started with, were then medium aggressive. Some individual rats were even low aggressive (<15%) prior to the start of the experiment. This may be caused by older age, since there was up to three months between the selection phase and start of the experiment for animals of the first batch. But earlier studies did not show an effect of age on displayed aggression (Blanchard et al., 1984). Whatever the explanation, it is possible that the diminished aggression affected our results, since we know from other studies that only a proportion of the high aggressive rats start displaying violent behavior after repeated winner experiences (de Boer et al., 2009). Nonetheless, we were not able to show increased violent aggression after sleep restriction in the group of rats used in this study.

In conclusion, we did not find an effect of sleep restriction on the expression of violent behavior in WTG rats. It may be that a higher number of animals per group and the use of rats with stable high aggressive traits give an indication whether there are individual rats sensitive to developing abnormal aggression after sleep loss. Speculatively, in humans the potential causal relation between poor sleep and violent behavior is just true for a group of vulnerable people.

REFERENCES

Anderson C, Platten CR. Sleep deprivation lowers inhibition and enhances impulsivity to negative stimuli. Behavioral Brain Research 2011;217:463-66.

Banks S, Dinges DG. Behavioral and physiological consequences of sleep restriction. J Clin Sleep Med 2007;3:519-528.

Barf RP, Van Dijk G, Scheurink AJ, Hoffmann K, Novati A, Hulshof HJ, Fuchs E, Meerlo P. Metabolic consequences of chronic sleep restriction in rats: changes in body weight regulation and energy expenditure. Physiol Behav 2012;107(3):322-8.

Benedetti F, Fresi F, Maccioni P, Smeraldi E. Behavioral sensitization to repeated sleep deprivation in a mice model of mania. Behav Brain Res 2008;187(2): 221-27.

Blanchard RJ, Flannelly KJ, Layng M, Blanchard DC. The effect of age and strain on aggression in male rats. Physiol Behav 1984;33:857-861.

Cote KA, McCormick CM, Sleep deprivation lowers reactive aggression and testosterone in men. Biological Psychology 2013; 92: 249-256.

De Boer SF, van der Vegt BJ, Koolhaas JM. Individual variation in aggression of feral rodent strains: a standard for the genetics of aggression and violence? Behav Genet 2003;33:485-501.

De Boer SF, Caramaschi D, Natarajan D, Koolhaas JM. The vicious cycle towards violence, focus on the negative feedback mechanisms of brain serotonin neurotransmission. Frontiers in Behavioral Neuroscience, 2009; 52: 1-6.

Granö N, Vahtera J, Virtanen M, Keltikangas-Jarvinen L, Kivimaki M. Association of hostility with sleep duration and sleep disturbances in an employee population. Int J Behav Med 2008;15(2): 73-80.

Goldstein AN, Walker MP. The role of sleep in emotional brain function. Annu Rev Clin Psychol 2014;10:679-708.

Gregory AM, Eley TC, O'Connor T, Plomin R. Etiologies of Associations between childhood sleep and behavioral problems in a large twin sample. J Am Acad Child Adolesc Psychiatry 2004;43(6):744-51.

Gujar N, Yoo SS, Hu P, Walker MP. Sleep deprivation amplifies reactivity of brain reward networks, biasing the appraisal of positive emotional experiences. J Neurosci 2011;31:4466-4474.

Haller J, van de Schraaf J, Kruk M. Deviant forms of aggression in glucocorticoid hyporeactive rats: a model for 'pathological' aggression? J Neuroendocrinol 2001;13:102-107.

Hicks RA. Moore JD, Hayes C, Phillips N, Hawkins J. REM sleep deprivation increases aggressiveness in male rats. Physiol Behav 1979;22(6):1097-1100.

Ireland JL, Culpin V. The relationship between sleeping problems and aggression, anger,

5

and impulsivity in a population of juvenile and young offenders. J Adolesc Health 2006;38(6):649-55.

Kahn-Greene ET, Lipizzi EL, Conrad AK, Kamimori GH, Killgore WDS. Sleep deprivation adversely affects interpersonal responses to frustration. Personality and Individual Differences 2006;41:1433-1443.

Kamphuis J, Meerlo P, Koolhaas JM, Lancel M. Poor sleep as a potential causal factor in aggression and violence. Sleep Med 2012;13:327-334.

Kamphuis J, Dijk DJ, Spreen M, Lancel M. The relation between poor sleep, impulsivity and aggression in forensic psychiatric patients. Physiol Behav 2014;123:168-173.

Kayser MS, Mainwaring B, Yue Z, Sehgal A. Sleep deprivation suppresses aggression in Drosophilia. Elife 2015;4:e07643.

Killgore WD. Self-reported sleep correlates with prefrontal-amygdala functional connectivity and emotional functioning. Sleep 2013;36:1597-1608.

Koolhaas JM, Coppens CM, de Boer SF, Buwalda B, Meerlo P, Timmermans PJA. The Resident-intruder Paradigm: A Standardized Test for Aggression, Violence and Social Stress. J Vis Exp 2013;77:4367.

Machado RB, Hipolide DC, Benedito-Silva AA, Tufik S. Sleep deprivation induced by the modified multiple platform technique: quantification of sleep loss and recovery. Brain Res 2004;1004:45-51.

Marks CA. Wayner MJ. Effects of sleep disruption on rat dentate granule cell LTP in vivo. Brain Res Bull 2005;66(2):114-9.

Meerlo P, Koehl M, Van der Borght K, Turek FW. Sleep restriction alters the hypothalamic-pituitary-adrenal response to stress. J Neuroendocrinol 2002;14:1-11.

Miczek KA, de Boer SF, Haller J. Excessive aggression as model of violence: a critical evaluation of current preclinical methods. Psychopharmacology (Berl) 2013;226:445-458.

Novati, A., Roman, V., Cetin, T., et al. Chronically restricted sleep leads to depression-like changes in neurotransmitter receptor sensitivity and neuroendocrine stress reactivity in rats. Sleep, 2008, 31: 1579–85.

Paula de HM, Hoshino K. Correlation between the fighting rates of REM sleep deprived rats and susceptibility to the 'wild running' of audiogenic seizures. Brain Res 2002;926(1-2):80-85.

Peder M, Elomaa E, Johansson G. Increased aggression after rapid eye movement sleep deprivation in Wistar rats is not influenced by reduction of dimensions of enclosure. Behav Neural Biol 1986;45(3):287-91.

Pilcher JJ, Ginter DR, Sadowsky B. Sleep quality versus sleep quantity: relationships between sleep and measures of health, well-being and sleepiness in college students.

J Psychosom Res 1997;42(6):583-96.
Raine A, Yang Y. Neural foundations to moral reasoning and antisocial behavior. Soc Cogn Affect Neurosci 2006;1(3):203-13.
Reid GJ, Hong RY, Wade TJ. The relation between common sleep problems and emotional and behavioral problems among 2- and 3-year-olds in the context of known risk factors for psychopathology. J Sleep Res 2009;18(1):49-59.
Roman, V., Van der Borght, K., Leemburg, S. A., Van der Zee, E. A. and Meerlo, P. Sleep restriction by forced activity reduces hippocampal cell proliferation. Brain Res., 2005b, 1065: 53–59.
Semiz UB, Algul A, Basoglu C, Ates MA, Ebrinc S, Cetin M, et al. The relationship between subjective sleep quality and aggression in male subjects with antisocial personality disorder. Turk Psikiyatri Derg 2008;19(4):373-81.
Silva RH, Abilio VC, Takatsu AL, kameda SR, Grassl C, Chehin AB, et al. Role of hippocampal oxidative stress in memory deficits induced by sleep deprivation in mice. Neuropharmacology 2004;46(6):895-903.
Shin C, Kim J, Yi H, Lee H, Lee J, Shin K. Relationship between trait-anger and sleep disturbances in middle-aged men and women. J Psychosom Res 2005;58(2):183-89.
Sloan MA. The effects of deprivation of rapid eye movement (REM) sleep on maze learning and aggression in the albino rat. J Psychiatr Res 1972;9(2):101-11.
Tartar JL, Ward CP, Cordeira JW, Legare SL, Blanchette AJ, McCarley RW, et al. Experimental sleep fragmentation and sleep deprivation in rats increases exploration in an open field test of anxiety while increasing plasma corticosterone levels. Behav Brain Res 2009;197(2):450-53.
van der Helm E, Gujar N, Walker MP. Sleep deprivation impairs the accurate recognition of human emotions. Sleep 2010;33(3):335-42.
Vohs KD, Glass BD, Todd Maddox WT, Markman AB. Ego depletion is not just fatigue: evidence from a total sleep deprivation experiment. Social Psychological and Personality Science 2011;2(2):166-173.
Webb WB. Some effects of prolonged sleep deprivation on the hooded rat. J Comp Physiol Psychol 1962;55:791-93.
Yoo SS, Gujar N, Hu P, Jolesz FA, Walker MP. The human emotional brain without sleep--a prefrontal amygdala disconnect. Curr Biol 2007;17(20):877-78.