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### The relation between sleep and violent aggression

Kamphuis, Jeanine

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## Chapter 9

# General discussion

The general hypothesis underlying this thesis was that sleep problems are a potential risk factor for aggressive, violent behavior. The aim of this thesis was twofold: 1) to investigate the clinical relevance of sleep problems in an aggressive population, namely forensic psychiatric patients and 2) explore the causal direction of the relation between sleep and violent aggression in several animal studies. The findings in this thesis will be discussed with these aims in mind.

## RELEVANCE OF SLEEP PROBLEMS IN FORENSIC PSYCHIATRY

In chapter 3 we concluded that poor sleep is highly prevalent among forensic psychiatric inpatients. For 30% of our participants the scores on the Sleep Diagnosis List indicated the presence of one or more sleep disorders, most often chronic insomnia. An even larger proportion (almost 50%) was dissatisfied with their sleep quality. Causes for these problems varied, especially suboptimal sleep hygiene, stress or ruminating, negative sleep conditioning and side effects of psychotropic medications appeared to play a role. Almost half of the poor sleepers habitually napped during the day. Over 40% of the poor sleepers received a hypnotic drug, but were still not satisfied with their sleep quality. In chapter 4 a significant association was shown between sleep problems, impulsivity and aggression. Forensic psychiatric inpatients with a poor sleep quality and higher scores on an insomnia scale, rated themselves as being more impulsive and aggressive, had a higher chance of being involved in aggressive incidents within the clinic, and were more likely to be evaluated as hostile by their treating clinicians. Since most cross-sectional studies looking at the relationship between sleep and aggression in populations with a history of violence only investigated self-rated aggression (Ireland and Culpin, 2006; Semiz et al., 2008), this was one of the first studies to show a significant relation between sleep problems and actual overt aggressive behavior in a group of forensic patients.

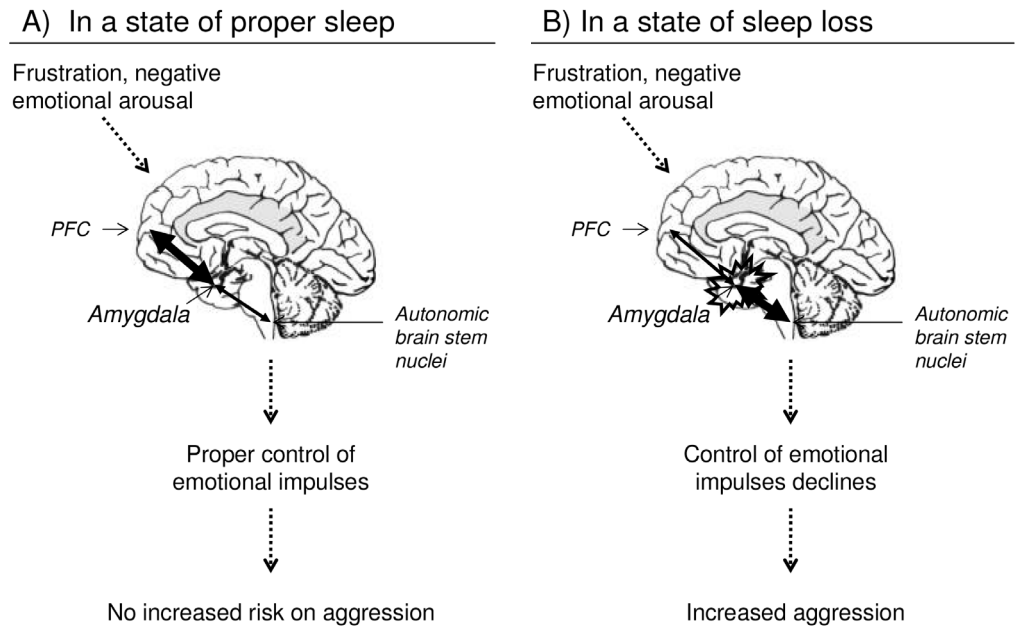
Even though this correlation does not give any direction to causality, some case reports and small clinical studies suggest that treatment of sleep problems and disorders improves not only quality of sleep but also diminishes daytime aggressive behavior (Mitchell and Kelly, 2005; Mitchell and Kelly, 2006; Mulvaney et al., 2006; Pakyurek et al., 2002; Booth et al., 2006; Haynes et al., 2006). That treatment of sleep problems has a positive effect on daytime symptoms is increasingly being recognized in general psychiatric practice. It receives more and more attention that is important to target treatment on co-morbid sleep problems, in parallel to treatment of the psychiatric disorder. Combining treatment for sleep disorders with psychiatric treatment often has a larger effect on psychiatric

recovery than psychiatric treatment alone. This has been shown in many patient groups in well-controlled studies, such as major depressive disorder (Fava et al., 2006; Manber et al., 2008; Manber et al., 2016), post-traumatic stress disorder (Krakow et al., 2001; Bishop et al., 2016) and anxiety disorders (Londborg et al., 2000; Ye et al., 2015). Especially cognitive behavioral therapy for insomnia is highly efficacious and has long term positive effects, also for psychiatric patients suffering from insomnia (Riemann and Perlis, 2009; Smith et al., 2005; Wu et al., 2015). Importantly, cognitive behavioral therapy for insomnia is devoid of the many disadvantages of pharmacological treatment, such as the development of tolerance and dependence (Riemann and Perlis, 2009). Whether treatment of sleep disorders in forensic psychiatric patients may positively affect their psychiatric outcome, especially the problematic impulsive and aggressive behavior, has not been studied yet. The strong association between poor sleep and aggression in this group, combined with the few case reports suggesting that adequate treatment of sleep disorders decreases problematic aggressive behavior, and the well-controlled studies in other fields of psychiatry showing additional reduction of the severity of psychiatric symptoms when sleep treatment is included, are promising. Paying attention to sleep complaints, treatment of sleep disturbances, and promoting a proper sleep quality may have aggression-reducing effects in forensic psychiatric populations. This is an important direction for future research.

## REMARKS ON CAUSALITY

With the forensic psychiatric patients in mind and the hypothesis that sleep loss negatively affects prefrontal cortex (PFC) functioning, further impeding their often already poor impulse control, one can assume causality in the direction of sleep problems causing violence (see Figure 1 for a schematic overview of the hypothesis).

On the other hand, aggressive behavior or even the stress of angry feelings may affect nocturnal sleep quality and quantity, thus assuming the causal direction the other way around. There is scientific support for both directions, indicating the complexity of the inter-relations between sleep and aggression. How the findings of this thesis adds to this field of research is discussed below.



**Figure 1.** Hypothesized causal mechanism between sleep loss and increased aggressiveness: loss of prefrontal cortical inhibition of emotional responses.

A In a state of proper sleep the prefrontal cortex has a strong connectivity to the amygdala, thereby inhibiting its activity, resulting in context-appropriate, socially acceptable behavior.

B In a state of sleep loss, the connectivity between the prefrontal cortex and amygdala weakens, resulting in disinhibition and therefore greater activity of the amygdala in response to frustrating or emotional arousing situations. This may contribute to a stronger response of the autonomic brain stimuli and thereby increase the risk of impulsive, emotional and aggressive responses.

### **Is sleep loss a potential risk factor for aggressive and violent behavior?**

If this is the case one would expect to find increased aggression after sleep deprivation. However, sleep deprivation studies assessing aggression in humans (Kahn-Greene et al., 2006; Vohs et al., 2011; Cote et al., 2013) and animals (Webb, 1962; Sloan, 1972; Hicks et al., 1979; Peder et al., 1986; de Paula and Hoshino, 2002; Marks and Wayner, 2005; Benedetti et al., 2008; Tartar et al., 2009; Kayser et al., 2015) are inconclusive. The results on the study presented in chapter 5 add a new negative finding to this discussion. We were not able to show the development of abnormal and escalated aggression after acute and chronic sleep restriction in male Wild-type Groningen rats. This may indicate that there is no causal relationship at all, but this contradicts the sleep deprivation studies that did find an effect.

In humans, the sleep deprivation study which did reveal an effect, examined the written responses to cartoons displaying frustrating situations (Kahn-Green et al., 2006; see Figure 2 for examples). Authors found that 55h sleep deprived subjects were more aggressive in their responses, less willing to take the blame and had a higher tendency to assign blame to others. Although this indicates a lower frustration tolerance, it does not necessarily mean that an actual aggressive physical outburst will occur. It may increase the risk for violent behavior, but probably other factors mediate this as well, such as prior experiences of the individual. Examples from forensic psychiatric practice of such experiences are frequently witnessing violence between the primary caretakers or repeatedly being molested as a child and discovering that physical aggression is an effective defence strategy. The results of studies on the influence of sleep deprivation on aggressive behavior seem to depend highly on the operationalization of aggression. Cote et al. (2013) used the well-validated Point Subtraction Aggression Paradigm (PSAP), in which aggression is defined as stealing points from a fictitious opponent. PSAP aggression in violent parolees exceeds that of non-violent parolees (e.g., Cherek et al., 1996), and it is also higher in clinical groups, who are known to exhibit more aggressive behavior than non-clinical populations (e.g., Zhou et al., 2006, Kivisto et al., 2009; New et al., 2009), and is thus considered a well-validated test. Sleep deprivation in healthy males appeared to decrease aggression in this paradigm. Thus, sleep deprivation lowers frustration tolerance in healthy adults, but did not produce an increase of aggressive behavior in the respective computer game. It may be interesting to repeat these experiments in forensic psychiatric patients or other antisocial populations, considering the option that they represent a subgroup highly vulnerable to these consequences. However, it is unlikely that an ethical commission would approve such a study.

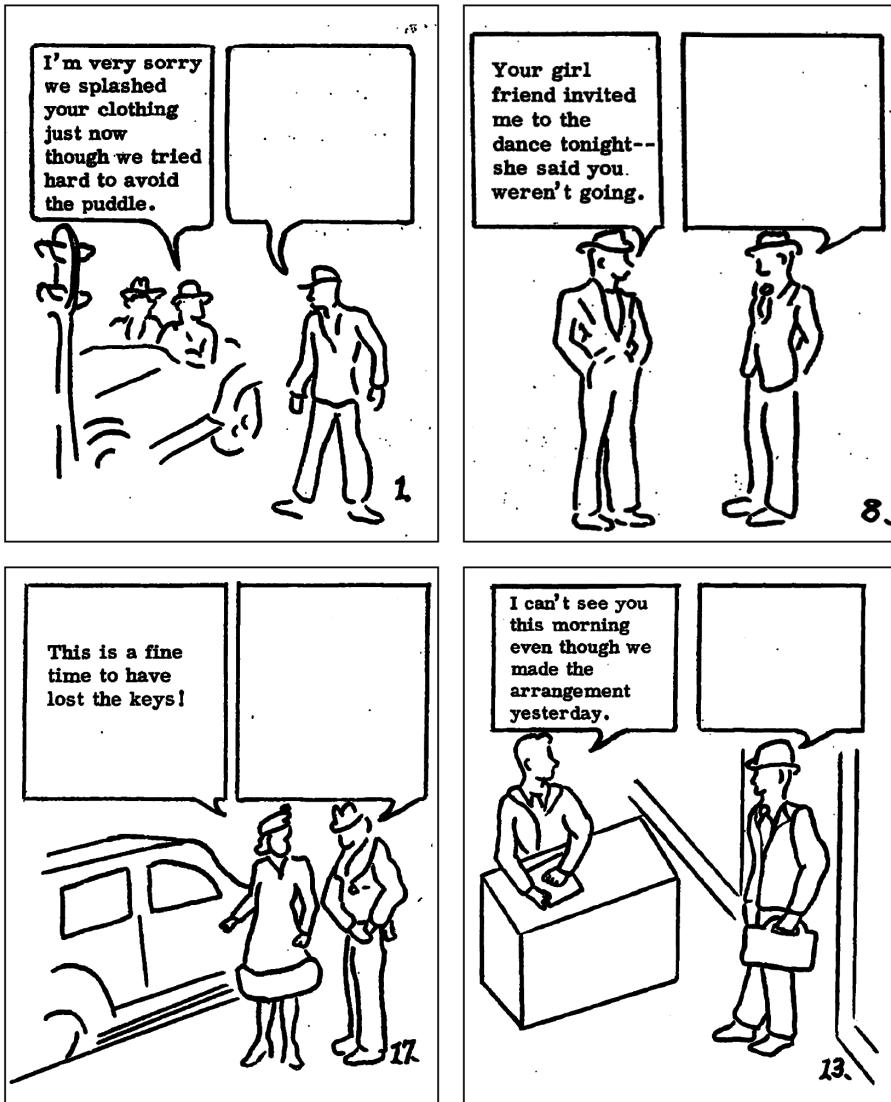


Figure 2. Examples from cartoons used in the Rosenzweig Picture Frustration Study (Rosenzweig, 1945; Rosenzweig, 1946).

Most animal studies that found aggression-promoting effects of sleep deprivation used selective rapid-eye-movement (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). Although the platform method, usually applied for selective REM sleep deprivation, not only reduces REM sleep, but also non-rapid-eye-movement (NREM) sleep (Machado et al., 2004; Silva et al., 2004), it is likely that some other, perhaps not sleep-related factors contributed to the development of increased aggression. This may be the stress this method is known to induce, when animals continuously fall in the water, or the high frequency of sleep disruptions. It may also be that the observed aggression does not display increased aggression per se, but hyperactivity in general, comparable to the euphoric, irritable state some people experience after one night without sleep. The selective REM sleep deprivation studies did not focus specifically on pathological forms of aggression, as we have done in the study presented in chapter 5. In fact, some animal studies using the platform technique for sleep deprivation suggest hypersexuality, hyperactivity and stereotypy after sleep deprivation (Fratta et al., 1987; Gessa et al., 1995). It may thus be interesting to investigate the effect of selective REM sleep deprivation on pathological forms of aggression such as studied in chapter 5.

In chapter 6 we did show a negative effect of acute and chronic sleep restriction on PFC-functioning, reflected in diminished timing ability, attention control and decreased behavioral inhibition. The latter may reflect impulsivity. Although this adds to the large amount of human data demonstrating decreased activity of the PFC after sleep loss, leading to elevated amygdala activity, it does not directly answer our question whether sleep loss contributes to actual overt violent behavior.

There is probably no simple answer to this question. Data presented in this thesis do not support a one-on-one relationship between sleep and violent behavior. The relation showed in forensic psychiatric inpatients, presented in chapter 4, suggests that in certain vulnerable individuals sleep difficulties may contribute to aggressive acts, but causality was not investigated. Although we tried to select high-aggressive rats in our study presented in chapter 5, expecting them to be potentially vulnerable subjects for developing abnormal aggression after sleep deprivation, we did not succeed in this. Perhaps, similar to humans, only a very small proportion of animals is susceptible for developing violent behavior as a consequence of too short sleep. For the general public it seems that sleep loss may contribute to increased emotional reactivity, decreased frustration tolerance, but not to out-of-context, rule breaking behavior.



### **Does aggressive behavior cause poor sleep?**

The idea that aggression may cause sleep difficulties is not so hard to comprehend. An intense argument with your partner right before going to bed may make it harder to fall asleep. A fight induces a stress response in most people. Stress in the pre-sleep period is thought to act on sleep quality through increased cognitive and somatic arousal (Krystal and Edinger, 2008). Whether angry feelings and aggressive acts can directly disrupt sleep quality via this mechanism, has scarcely been examined. In this thesis we showed in chapter 7 that a social conflict has a large impact on the post-conflict sleep period in rats. It causes a significant increase in NREM sleep slow wave activity (SWA), much more than keeping them awake for an hour during the same period of the light/dark phase. Importantly, we found that not only losers of the social conflict exhibited elevated NREM sleep SWA, winners displayed a comparable elevation. This finding suggests that regardless of the outcome of a conflict, participating in a conflict influences the following sleep period. The increase in NREM sleep SWA after the conflict may reflect recovery processes in the brain. Approximately 6 hours after the conflict NREM sleep SWA returned to baseline levels. Thus, we found that a conflict clearly influences sleep-EEG, but the question is whether this represents poor sleep or, more likely, a well-functioning recovery processes.

The few human studies suggesting that aggressive daytime interactions may negatively influence sleep were based on questionnaires and interviews. Brissette and Cohen (2002) asked 47 healthy adults in the US to report the level of disagreement or conflict during their daily social interactions and positive as well as negative affect for a period of 7 days. During this time the subjects also reported on their sleep quality. Higher levels of conflict significantly correlated with reporting more problems with sleep continuity, such as lying awake after waking up in the night, on the following night. However, on the days participants reported more conflicts, they also experienced more sleep problems on the previous night. This effect was partially mediated by negative affect during the day. A conflict may be considered as an (often verbal) aggressive interaction. These findings may support a bidirectional relationship between sleep and aggression.

As aggressive interactions may influence sleep quality, it is interesting to investigate the sleep of violent subjects. In chapter 8 data on the sleep-wake pattern and NREM sleep SWA, measured by EEG, in violent and non-violent rats were presented. There were no differences in baseline measurements. Violent animals seemed to slightly differ in how exposure to challenging situations, like sleep deprivation and restraint stress, were

processed during the following sleep period compared to the non-violent group. Violent rats tended to show a delay in the NREM sleep increase after restraint and in the REM sleep increase after sleep deprivation. Human studies in violent offenders also found differences in sleep quality and sleep EEG. Lindberg et al. (2003) investigated the night time sleep of 19 male violent offenders with an antisocial personality disorder. They found more night time awakenings and lower sleep efficiency compared to healthy controls. These offenders also had a lower self-reported sleep quality. Results were not explained by alcoholism, sleep deprivation, or head injuries. With regard to sleep stages, they had more slow wave sleep (SWS) compared to controls. No differences in REM sleep were found. Together with our finding that especially patients with an antisocial personality disorder or antisocial traits are dissatisfied with their sleep quality compared to non-antisocial forensic psychiatric patients presented in chapter 3 and to some extent the results presented in chapter 8, these observations may suggest that antisocial patients differ in their vulnerability to developing sleep problems and disorders.

Taken together, involvement in conflicts affects the subsequent sleep period. In both animals and humans there are probably inter-individual differences in the conflict-evoked sleep changes. Hostile and antisocial individuals may represent a subgroup in which daytime social interactions are differently processed during the night than in healthy subjects.

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## COMPARING HUMAN AND ANIMAL DATA

This thesis combines data from human studies with findings from animal studies. The experiences in clinical practice and findings in the human studies presented in chapter 3 and 4 have contributed to or were even leading in the planning of the animal experiments. Working with a feral rat strain, with a large heterogeneity in levels of aggression and where some animals even develop abnormal and escalated aggressive behavior, strengthened the validity and therefore the selection of this animal model.

Although findings on EEG differences between violent and non-violent rats, were not statistically significantly relevant, - perhaps due to a too low number of animals per group -, it is interesting that grouping animals of the same strain merely based on behavioral differences revealed small differences in REM and NREM sleep patterns. This corresponds somewhat to psychiatric practice, where disorders are classified based on a set of behavioral and psychological criteria. That in a feral animal strain the approach of

including animals based on behavioral criteria leads to potentially interesting findings is exciting, and contributes to the possibility to extrapolate animal results to humans.

In chapter 6 we demonstrated a negative effect of chronic sleep restriction on the function of the PFC, in line with fMRI findings in humans (e.g. Yoo et al., 2007).

The findings of the study presented in chapter 5 indicate that the relation between sleep and violent behavior is more complex than simply a one-on-one causal sequence. Although it is possible that our selected animals were basically not aggressive enough (not the extreme end of the spectrum we studied in humans) to find a clear relation, an alternative explanation is that some factors are a prerequisite, that must be present for poor sleep to contribute to violent outbursts. Our main underlying hypothesis, was based on increased impulsivity due to impaired PFC function as a consequence of sleep loss. But, although we found increased behavioral disinhibition on an operant conditioning task in sleep restricted rats, indicative of increased impulsivity (chapter 6), we were still not able to demonstrate in an experimental design more violent behavior after chronic sleep restriction (chapter 5). Thus, maybe only increased impulsivity is not enough to evoke violent outbursts. It is interesting to consider the consequences of poor sleep on the level of 'emotional perception of the world', and that this may be a critical step towards the relationship with violent aggression, rather than behavioral disinhibition per se.

Several studies suggest that the effect of disturbed sleep on the PFC-amygdala network contributes to increased reactivity towards emotional stimuli (Yoo et al., 2007; Gujar et al., 2011), and blunted recognition of subtle facial emotional expressions (van der Helm et al., 2010). Baseline emotional functioning seems to influence the way people are affected by sleep loss: individual differences in emotional intelligence predicted the influence of sleep deprivation on written responses to cartoons displaying frustrating situations (Kahn-Greene et al., 2006). When people, due to their life time experiences, already view the world as hostile and unsafe, this may worsen when poor sleep is present. In some people sleep problems may lead to feelings of being unwanted and unloved, without any value, feelings of guilt, contributing to depressive symptomatology; many studies show a causal link between insomnia and major depressive disorder (e.g. Baglioni and Riemann, 2012). In people with already a low impulse control and hostile view of the world, this increased negative emotional state and less adequate processing of surrounding stimuli as a consequence of poor sleep, may further increase violent tendencies and the risk of uncontrolled aggression. With regard to aggression control, childhood experiences, specifically childhood maltreatment (Chen et al., 2012a) and a hostile attributional bias (Chen et al., 2012b) are significantly linked to adult aggression, and it may be necessary to take such factors into account when examining the relation

between sleep and violent behavior. The impact of chronic sleep problems not only on impulse control but also on a hostile perception of the surrounding (for example caused by early life maltreatment), may be essential for the assumed relation between sleep and violence. Perhaps, only individuals with an unfortunate combination of this may be at risk of developing escalated aggression in a state of sleep loss. Forensic psychiatric patients, but also prisoners, are potential groups at-risk.

Designing animal studies investigating this individual vulnerability hypothesis is challenging and may ask for a fundamentally different approach, but is highly relevant. Individual variation has been shown to be stable over time and across situations and has been investigated in a wide variety of animals, such as primates, rodents, insects, fish and birds (Koolhaas, 2008). Humans and rodents may differ in the complexity of experienced emotions, but as they have comparable emotional brain circuitry (Koolhaas et al., 2016), experiments in animals offer great possibilities of more directly investigating these systems on molecular levels. The effect of early-life stress is currently being explored in animal models for depression (Schmidt, 2011). These models may also be employed in fundamental research exploring the effects of early-life experience on the susceptibility for sleep deprivation and behavioral output this will gain. Another factor to consider in designing future animal studies may be to take into account or even select for certain coping styles. We have selected animals based on their aggression levels in a standard resident intruder paradigm. Recently Koolhaas et al. (2016) proposed that this trait-aggressiveness is merely a part of the qualitative coping style of the animal. This coping style can be disentangled in multiple quantitative behavioral domains, like flexibility/impulse control, emotional reactivity and harm avoidance/reward processing, each encoded into selective neural circuitries. With this model in mind, it becomes possible to determine the position of each individual on these domains. How this may interact with early-life experience is highly interesting. In humans, we have the impression that such factors are essential for a causal link between sleep and violence. For example, forensic psychiatric patients may represent individuals on the extreme ends of the proposed behavioral domains, with low impulse control, high emotional reactivity and high reward seeking. In future animal studies, it may be relevant to detect and select animals with such a profile when investigating violence and factors causing this.

## LIMITATIONS

Some limitations of the studies presented in this thesis have already been mentioned. In short, we only collected cross-sectional data in our forensic psychiatric participants,

which does not allow us to draw any conclusions on causality between sleep and aggression. Data on objective sleep quality is still lacking. In chapter 5 and 6 a repeated sleep restriction protocol was used. Although this sleep restriction protocol has been shown to lead to a significant loss of NREM and REM sleep (Barf et al., 2012) and is designed to model the chronic sleep loss often seen in human society, one may question how well it corresponds to sleep disorders, such as chronic insomnia. In chronic insomnia not just extrinsic factors (such as noise or an uncomfortable bed) are present, but especially intrinsic psychological factors, such as ruminating, determine this syndrome. Such psychological factors are hard to investigate in an animal model. Finally, a higher number of animals per group in the experiment presented in chapter 8 may produce more clear and statistically significant results.

## CONCLUSIONS

In conclusion, the inter-relations between sleep and violence are complex. Only in certain vulnerable individuals sleep loss may contribute to an increased risk of violent outbursts. Forensic psychiatric patients likely represent such a group. Many forensic psychiatric patients suffer from sleep problems and chronic sleep disorders. Poor sleep quality and higher insomnia rates are significantly linked to higher self-rated aggression and impulsivity, increased involvement in aggressive incidents within the clinic and a higher chance of being evaluated as hostile by the treating clinicians. It is of great importance to investigate the effect of treatment of sleep problems in these patients on their impulse control, hostility and aggression. Experimental studies investigating the effect of sleep deprivation on aggression in humans and animals remain inconclusive. We found no direct effect of sleep restriction on expression of violent aggression in rats. We did confirm in an animal model that sleep loss negatively impacts PFC function, diminishing behavioral inhibitory capacities in addition to negative effects on attentional control and timing ability. Aggressive interactions affect the following sleep period. Whether a fight is lost or won is not that relevant for the effect on subsequent sleep. How this finding may relate to the development of poor sleep quality, that is suggested by observations and some studies in humans, is not clear. Finally, individuals with violent traits seem to slightly differ in sleep regulation and sensitivity towards stressful events compared to non-violent subjects. The clinical relevance of this is not yet clear, but since antisocial individuals are particularly dissatisfied with their sleep it is an interesting direction to pursue.

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