Chapter 2

Poor sleep as a potential causal factor in aggression and violence

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ABSTRACT

Clinical observations suggest that sleep problems may be a causal factor in the development of reactive aggression and violence. In this review we give an overview of existing literature on the relation between poor sleep and aggression, irritability and hostility. Correlational studies are supporting such a relationship. Although limited in number, some studies suggest that treatment of sleep disturbances reduces aggressiveness and problematic behavior. In line with this, is the finding that sleep deprivation actually increases aggressive behavior in animals, and angriness, short-temperedness and the outward expression of aggressive impulses in humans. In most people poor sleep will not evoke actual physical aggression, but certain individuals, such as forensic psychiatric patients, may be particularly vulnerable to the emotional dysregulating effects of sleep disturbances. The relation between sleep problems and aggression may be mediated by the negative effect of sleep loss on prefrontal cortical functioning. This most likely contributes to loss of control over emotions, including loss of the regulation of aggressive impulses to context-appropriate behavior. Other potential contributing mechanisms connecting sleep problems to aggression and violence are most likely found within the central serotonergic - and the hypothalamic-pituitary-adrenal-axis. Individual variation within these neurobiological systems may be responsible for amplified aggressive responses induced by sleep loss in certain individuals. It is of great importance to identify the individuals at risk, since recognition and adequate treatment of their sleep problems may reduce aggressive and violent incidents.

INTRODUCTION

It is well known that sleep loss can have serious detrimental effects on cognitive performance. For example, sleep deprivation reduces sustained attention, executive functioning and memory (Maquet, 2001; Walker, 2008). Moreover, sleep loss may also affect emotional function (Walker and van der Helm, 2009) and chronically disrupted sleep may even sensitize individuals to mood disorders (Baglioni et al., 2011; Meerlo et al., 2008). However, relatively little attention has been paid to the effects of sleep loss on other areas of affective functioning. Yet, many people have the experience that disturbed sleep is accompanied by emotional instability, expressed for instance by a greater irritability and short-temperedness. In most people this will not result in physical outbursts of aggression. However, this may be different in vulnerable individuals, such as psychiatric patients, who often experience serious sleep problems. For example, about 80% of patients suffering from a depressive disorder experience sleep problems (Abad and Guilleminault, 2005) and sleep disturbances are found in 30-80% of schizophrenic patients (Corhs, 2008). Similar numbers may apply to forensic psychiatric patients, but published data are lacking. Forensic psychiatric hospitals treat patients who committed (violent) offences, but have diminished responsibility due to a mental disorder. The most important treatment goal for this specific group of patients is to reduce the risk of (violent) recidivism. Based on clinical observations in forensic psychiatry, we have the impression that poor sleep may contribute to the loss of emotional control, including the regulation of aggression. If sleep problems are a potential risk factor for hostile and (reactive) aggressive behavior, treating sleep disturbances and promoting good sleep in mentally disordered offenders may be beneficial in crime-preventing treatment programs. Therefore, in this paper we present an overview of existing literature concerning the relationship between sleep and aggression / hostility.

METHODS

A literature search was performed in PubMed and Ovid with the following search terms: sleep, sleep disturbances, sleep problems, sleep deprivation, sleep architecture, aggression and aggressive behavior. The search terms were used in different combinations. Cross-references were checked for relevant papers. We included studies that covered sleep and its effects on aggression, anger and irritability.

With regards to the interpretation of relevant studies, it is important to bear in mind

that aggression is often defined and measured in different ways, including self-report questionnaires, observed behavior by family or experimenters, or endpoints measured in an experimental task. These measures are not necessarily analogous. In addition, in several studies it is not aggression that is measured, but anger, hostility or irritability by means of mood questionnaires. However, hostility, irritability, anger and rage appear to play an important role in violent behavior and individuals with a poor regulation of these emotions are at greater risk for actual aggression. Furthermore, aggressive acts do not occur as frequently as aggressive feelings. Therefore, only studying aggressive behavioral actions reduces the ability to detect relationships.

We will first discuss studies investigating correlations between sleep quality and aggression and/or angriness, separately for children/adolescents and adults. Secondly, we will discuss studies performed in aggressive individuals, including studies employing polysomnography. We will then review studies examining the effects of treatment of sleep disorders on daytime vulnerability to the emotional effects of poor sleep.

RESULTS

Correlations between sleep and aggression

Childhood populations

In addition to the more obvious consequences - such as sleepiness, inattention, and poor cognitive performance and anxiety - poor sleep in children and adolescents appears to be associated with aggression and conduct problems (O'Brien, 2009; Dahl, 2006). In a large group of 2- to 3-year-old children the number of night time awakenings was positively correlated with parent-rated aggressive behavior (Reid et al., 2009). Parent-reported sleep problems in 3-4 year-old twins correlated positively with conduct problems, anxiety and hyperactivity (Gregory et al., 2004). In a sample of older children (mean age 7) suffering from insomnia, parents were asked to rate daytime problematic behavior with the Childhood Behavior Checklist (CBCL). Shorter total sleep-time was associated with higher scores on delinquent behavior (Velten-Schurian et al., 2010). A similar observation was made in a large group of 2- to 5-year-old children in the US (Lavigne et al., 1999). In contrast, in a large Canadian population those children who slept more than other children were rated as more aggressive on a parent-rated scale (Coulombe et al., 2009). However, the item used to assess sleep time, asked the parents to include both night sleep and day sleep. More sleep during the day could of course be a sign of inadequate night sleep quality, independent of sleep duration. In fact, children who were assessed as being overtired also had higher scores on aggressive behavior. Comparable

observations were made in adolescents: both total sleep time and self-rated tiredness correlated positively with self-rated aggression, also after accounting for other risk factors (Coulombe et al., 2011). In a large 2- to 14-year-old population, those children at high risk for sleep-disordered breathing-problems or periodic leg movements during sleep (as measured by the Pediatric Sleep Questionnaire) had significantly more parent-reported aggression and conduct problems (Chervin et al., 2003). In a large group of US schoolchildren symptoms of sleep-disordered breathing were significantly correlated with parent- and/or teacher-rated conduct problems, bullying behavior and discipline referrals (O'Brien et al., 2011).

Interestingly, sleep problems at young age predicted, though modestly, conduct behavior, anxiety and hyperactivity several years later (Gregory et al., 2004). In addition, parent-rated sleep problems in childhood are correlated with higher scores on an aggression behavior scale later in life (Gregory et al., 2008). The authors state that sleep problems during childhood may constitute risk indicators of behavioral difficulties later in life.

Taken together, multiple studies in healthy and insomniac children show correlations between inadequate sleep (in sleep duration as well as in sleep quality) and daytime problematic behavior, such as aggression and conduct problems.

Adult populations

In two groups of healthy young men, with one group habitually sleeping 7-8 hours per night and the other 9.5-10.5 hours per night, the group with the shorter sleep duration scored significantly higher on anger and hostility on a mood scale (Taub, 1977). Other studies failed to show a significant positive correlation between sleep duration and self-rated aggression, hostility or angriness (Schubert, 1977; Pilcher et al., 1997; Shin et al., 2005). Yet, Granö et al. (2008) found an association between shorter sleep duration and higher hostility, which was partially related to psychiatric problems. In Israeli medical residents, work-induced sleep deprivation and fragmentation, measured with actigraphy, amplified the negative emotional consequences of disruptive daytime events, while reducing the positive effect of goal-enhancing events (Zohar et al., 2005). In a Polish study, the difference between desired sleep duration and actual self-reported sleep time correlated positively with mood complaints (including irritability) in adolescents and students, but not in young working adults (Oginska et al., 2006). To summarize, the studies in adults correlating short sleep duration to daytime aggression are not conclusive.

One complication in many of the studies that rely on indices of sleep duration is that sleep quality is not taken into account. In fact, sleep quality may be even more important

than actual sleep time with regard to the relationship between sleep problems and negative emotions, such as angriness and hostility. In a large group of Finnish hospital employees a hostility scale was used to assess proneness for angriness, irritability, and argumentativeness (Granö et al., 2008). Sleep problems during the past four weeks were assessed with a four-item scale. The authors found that sleep disturbances, sleep-onset and sleep-maintenance insomnia, and unrefreshing sleep correlated independently with self-reported hostility. This relationship remained after adjusting for several potential confounders, including psychiatric disorders. A large adult Korean population was asked whether they were suffering from sleep problems. In addition, trait-anger was measured with the Spielberger Trait Anger Scale, which measures the general disposition toward angry feelings (referred to by the authors as temperament) and the tendency to express anger (referred to as reaction). Difficulties maintaining sleep, excessive daytime sleepiness, a bad condition in the morning after awakening and awakening late in the morning were all significantly associated with trait-anger (Shin et al., 2005). Unfortunately, the authors did not differentiate between the angry temperament and angry reaction.

A small group of US students with insomnia complaints were asked how angry they would react to a number of potential provocative situations, using the Novaco Provocative Inventory (Waters et al., 1993). As the authors expected, the insomniacs scored higher than controls. The subjects also underwent a stress elicitation test with the simultaneous recording of electrophysiological measures: sleep problems, such as difficulty falling asleep and overall diminished sleep quality, were correlated with higher skin conductance and heart rate, both signs indicative of higher arousal. In two studies US college students were asked how often they experienced mood changes, during the last weeks, using the Profile of Mood States (POMS) (Pilcher et al., 1997; Lund et al., 2010). The POMS is a questionnaire which assesses the severity of active fluctuating mood states as depression, tension, fatigue, confusion, vigor and anger. Those students with poor subjective sleep quality, as measured by the Pittsburgh Sleep Quality Index (PSQI; used cut of > 8), experienced significantly more anger during the last weeks.

All together, poor sleep quality in both healthy and insomniac adults indeed correlates with increased frequency and intensity of self-reported anger, hostility and aggression.

Aggressive individuals

Correlations

The correlation between disturbed or short sleep and disturbed control of aggression could even be stronger in subjects with a high anger-trait being a part of their character.

A condition in which aggression and angriness are core symptoms and can be considered part of the character is the antisocial personality disorder (ASPD). Individuals with ASPD probably suffer from sleep problems comparable to other psychiatric patients. In fact, in a group of Turkish male military subjects diagnosed with ASPD approximately 80% scored > 5 on the PSQI, indicating poor sleep quality (Semiz et al., 2008). As expected these subjects had significantly higher levels of aggression compared to the control group, but also more subjective sleep complaints. Aggression was assessed with the Aggression Questionnaire, in which subjects have to judge how applicable statements on aggression and angriness are to themselves, measuring trait aggression. Ireland and Culpin (2006) studied an adolescent prison population. Since 50-80% of incarcerated offenders have diagnosable ASPD (Hare, 1983), it is reasonable to assume that a majority of these prisoners met the criteria for ASPD. In the adolescent offenders sleep disturbances and short sleep duration were associated with increased hostility. Female victims of domestic violence reported significantly more sleep problems in their abusive partners as compared to controls (Hoshino et al., 2009). Intriguingly, significantly more of the abused women reported increased aggression from their partners after a poor night's sleep (58% vs 7% in controls) and half of them remembered being battered on those days. The authors suggest that sleep deprivation could be an important causal factor for aggression in domestic violence. To our knowledge, there are no studies on aggressive populations, such as ASPD patients or a prison population, using objective measures of aggression or employing more provocative inventories to measure reactive aggression. Also no correlational studies were found in which objective measures of aggression were employed.

Taken together, aggressive populations seem to have serious sleep problems which correlate positively with increased self-reported aggression/hostility and partner-reported aggressive outbursts.

Measuring sleep in aggressive individuals

Though limited in number, there are some studies suggesting that polysomnographically recorded night sleep is different in aggressive individuals. In healthy adults certain sleep variables appeared to correlate with specific personality factors: aggressive tension and impulsiveness, including a lack of affect control and frustration tolerance and a need to dominate and criticise others, correlate positively with the amount of superficial sleep during the night (Schubert, 1977). No correlation was found with deep, slow wave sleep (SWS). In another study, 19 male psychiatric patients with ASPD, who committed violent crimes, exhibited significantly more night time awakenings and consequently lower

sleep efficiency than control subjects (Lindberg et al., 2003). These results remained after correction for alcoholism, sleep deprivation and head injuries. On the other hand, the ASPD patients also had more SWS, which is supposed to be the most refreshing part of sleep; yet they had a lower self-reported sleep quality. No differences in rapid eye movement (REM) sleep parameters were found. A higher amount of SWS was also observed in 3 female psychiatric patients with ASPD charged for violent crimes (Lindberg et al., 2006) and in preadolescent boys with conduct disorder (Coble et al., 1984), a childhood psychiatric disorder which may develop into ASPD after the age of 18 years.

Measurements of autonomic physiological functions suggest that hyperarousal might mediate the relationship between sleep problems and aggression. In a small study, male subjects with so-called type A behavior - characterized by impatience, hostility, aggression and ambition - and high scores on a trait-anger-scale were compared with males with the exact opposite, type B behavior and low scores on a trait-anger-scale (Madigan et al., 1997). Compared to the latter group, the angry type A scorers showed cardiovascular hyper-reactivity even when asleep.

All together, sleep and physiological recordings suggest that sleep patterns are different in aggressive individuals compared to controls. The causes and implications of these observations remain to be elucidated.

Effects of treatment of sleep problems

An interesting case report describes two boys (6 and 8 year old), both admitted to a psychiatric unit for increasingly aggressive and violent behavior towards peers and family members (Pakyurek et al., 2002). During admission, they were diagnosed with obstructive sleep apnea syndrome (OSAS), which in children is most often due to enlarged tonsils. After adenotonsillectomy, both children had, as expected, a significant reduction in their apneic episodes. But more importantly, prominent reductions both in the number and severity of violent outbursts were observed. After several months this effect was still present and improvements had taken place in other areas as well, including school performance and social interactions. In unreferred schoolchildren nighttime breathing problems correlated positively with aggression and oppositional behavior (Mulvaney et al., 2007). In addition, children with OSAS receiving adenotonsillectomy showed long-term improvement in parent-reported aggression (Mitchell and Kelly, 2005; Mitchell and Kelly, 2006). Furthermore, a small sample of sex offenders suffering from OSAS showed significantly lower scores on an aggression questionnaire after OSAS treatment with continuous positive airway pressure (CPAP) (Booth et al., 2006).

Treatment of sleep disturbances other than OSAS may also lead to a reduction of aggression. This is suggested by a study in adolescents recently treated for substance abuse, who also experienced sleep problems (Haynes et al., 2006). These adolescents received weekly sessions of behavioral sleep therapy during 6 weeks. Adolescents with greater improvements in total sleep time reported significantly less aggressive ideations and fewer aggressive actions, as compared to those with less change in total sleep time. A case report on an aggressive and severely mentally retarded adult male describes that he showed increased aggression during demand conditions, especially after having slept for less than 5 hours (O'Reilly, 1995). After implementation of a support plan, explicitly including rest periods, his aggressive behavior diminished.

Taken together, although limited in number and not always properly controlled, these studies suggest that treatment of sleep problems can reduce daytime aggression and problematic behavior.

Laboratory findings

Animal studies

Various experimental studies in rats suggest that sleep deprivation may increase aggression: rats subjected to enforced wakefulness by placing them together on top of a rotating drum surrounded by water, died after 3-14 days, not directly from sleep loss per se, but from fighting (Licklider and Bunch, 1946). These rats became so hyper-reactive that even slight physical contacts precipitated vicious, aggressive behavior. This behavior was not always directed against the actual offender, and occasionally several innocent rats would become involved in a fight, while the original aggressor stood by and watched. Webb (1962) kept 6 rats continuously awake by individually forced locomotion for 27 days. After 16 days the animals began to exhibit aggressive behavior, when they were paired in an observation cage during 5 minutes. Treadmill-induced total and partial sleep deprivation in rats increases exploratory behavior in an open field test of anxiety (Tartar et al., 2009). According to the authors this can be interpreted as a reduction in anxiety, loss of fear, and increase in locomotor activity, but possibly also as irritability. Whether changes in aggression in these studies were a direct result of sleep loss or, instead, physical activity or other confounding factors involved in the procedures remains a question.

Several studies report increased aggressive behavior following selective REM-sleep deprivation 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). Although these findings suggest that manipulative changes in sleep patterns can produce aggression, the results

are hard to interpret, since only REM-sleep is deprived. In addition to this, the flower pot method, by which REM-sleep is selectively deprived, is often criticized because it induces high levels of stress.

The animal studies discussed so far differ in the type of aggressive outcome measured (proactive versus reactive, fighting with conspecifics versus rats that display mouse killing, pain-induced aggression, irritability towards experimenters, etc.). It is important to realise that this in itself is another source of variability, thereby further complicating comparability and extrapolation to human aggressiveness.

Another view on the direction of the relation between sleep and aggression is offered by studies using a model of social stress in which animals are placed in the territory of an older, bigger and more aggressive male animal and are attacked and defeated. Immediately following defeat, rats (Meerlo et al., 1997; Meerlo et al., 2001) and mice (Lancel et al., 2003; Meerlo and Turek, 2001) show increased amounts of NREM sleep or increased NREM sleep intensity as reflected in elevated slow wave activity in the electroencephalography. This was not seen after a sexual interaction, a non-aversive social interaction (Meerlo and Turek, 2001).

So, results of animal studies support a potential causal relationship between sleep disturbances and aggressive discharges, but future studies are needed to elucidate the exact effect and type of behavior observed after total sleep deprivation.

Human studies

In 1964 a 17-year old male in the US stayed awake for 264 hours, thereby setting the record for prolonged wakefulness. Psychiatric and neurological consequences were investigated during the entire sleep deprivation period. In addition to becoming intermittently delusional and paranoid after several days, he became irritable and uncooperative (Ross, 1965). This course of symptom development has been observed in more cases of long-lasting total sleep deprivation in humans (Orzel-Gryglewska, 2010). Understandably, most of these experiments used shorter sleep deprivations. In fact, already after one night of sleep deprivation healthy young men scored higher on the aggression scale of a mood check list (Roth et al., 1976). But, the subjects also showed higher scores on the friendly subscale, which makes the results difficult to interpret.

In a small British sample subjects who were sleep deprived for 30 hours scored higher on the Profile of Mood subscales of depression and fatigue, but not on the subscales

anger and tension (Scott et al., 2006). Another study investigated the effect of chronic insufficient sleep on mood (Haack and Mullington, 2005). Both the experimental and control group slept for 16 days in the laboratory. The experimental group was allowed 4 hours of sleep per night, the control group 8 hours. Four factors of mood and physical symptoms, namely optimism-sociability, tiredness-fatigue, anger-aggression and bodily discomfort, showed significant effects. Anger-aggression was moderately, but significantly elevated in the 4-hour sleep group compared to the 8-hour sleep group. Unfortunately, the authors do not discuss this finding.

In a US healthy adult sample, 56 hours of total sleep deprivation induced significant changes in psychopathological symptoms, measured with the Personality Assessment Inventory (Kahn-Greene et al., 2007). Scores on the antisocial subscale changed significantly in 8.3 % of the sample. Changes on other subscales were seen in more subjects, especially paranoia, which represented a subtle elevation of interpersonal mistrust and hostility toward others.

The studies discussed so far use self-report questionnaires to assess the mood state of aggression and anger. To our knowledge only two studies tried to measure aggression objectively. Kahn-Greene et al. asked their 55 hour sleep deprived subjects to write a response for a cartoon character that is confronted with a frustrating situation (Kahn-Greene et al., 2006), e.g. he gets splashed from a water puddle by a passing car. The responses after sleep deprivation showed a significantly greater tendency to assign blame to others. Sleep deprivation was also associated with increased outward expression of aggressive responses and a reduced willingness to take the blame or offer amends to the other party. The authors suggest that sleep deprivation weakens the inhibition of aggression. Contrary, Vohs et al. (2011) did not measure higher aggression after sleep deprivation. Participants played an aggression-game where level of noise blasted at the opponent (the computer) was the measure of aggression. A part of the study group was also deprived of emotional regulation abilities, the so-called ego depletion, by watching a disgusting video while they were not allowed to show any emotion on their face. Ego-depleted subjects behaved more aggressively in the game, but there was no additional effect of sleep deprivation. Unfortunately, the authors only deprived sleep for 24 hours. Possibly, longer total sleep deprivation or a longer period of partial sleep deprivation is needed in humans to elicit the effect of a failing inhibition of aggressive urges.

Failing behavioral inhibition: sleep deprivation and impulsivity

The failing inhibition of aggressive urges possibly reflects enhanced impulsivity. There

are different forms of impulsive behavior, such as delay discounting, risk taking and sensation seeking, but also lack of behavioral response inhibition. The latter is in our view most important in discussing the relationship between sleep problems and aggressive behavior. Although the detrimental effects of sleep deprivation on decision-making (Harrison and Horne, 2003) and risk-taking (McKenna et al., 2007; Venkatraman et al., 2007) are quite clear, the effect of sleep deprivation on behavioral response inhibition, has not been studied extensively. In healthy 24 hour sleep deprived subjects no effect was found on a behavioral response inhibition task, namely the Stop Task (Acheson et al., 2007). This task uses neutral signals, such as a tone or a letter on a computer screen, to measure a response. Anderson and Platten (2011) sleep deprived healthy subjects for 36 hours and had them perform a behavioral inhibition task using positive and negative emotional stimuli, in addition to neutral stimuli. They also did not find a significant difference in ability to suppress the response to neutral stimuli after sleep deprivation. But, interestingly and more importantly, sleep deprived subjects were less able to inhibit the response to negative emotional stimuli.

Speculatively, loss of behavioral inhibition to negative emotional circumstances mediates the relationship between sleep deprivation and unwanted or context-inappropriate aggressive responses.

Potential mechanisms

Prefrontal cortical functioning

One hypothesis on the relationship between poor sleep and aggression is that sleep deprivation results in poor prefrontal cortical (PFC) functioning. When PFC functioning is reduced, the ability to anticipate, delay and initiate behavioral responses based on cognitive and social context declines (Dahl, 1996). That sleep deprivation affects the PFC is supported by the finding that sleep deprivation as short as 24 hours leads to significant declines in PFC metabolic activity (Thomas et al., 2000). In addition, after sleep deprivation, behavior comparable to PFC neuropsychological anomalies is observed, which is reversed after recovery sleep (Dahl, 1996). Among these anomalies are the weakening or diminution of goal directed behaviors and instability in emotional responses (Horne, 1993). The instability in emotional responses is reflected by a study showing that healthy volunteers had decreased emotional intelligence after 50 hours of sleep deprivation (Killgore et al., 2008). Emotional intelligence includes the ability to understand one's own and others emotions, effectiveness in dealing with interpersonal relationships and capacity to cope with environmental needs (Kahn-Greene et al., 2006) and can be considered a reflection of the level of PFC functioning. In a group of US

healthy subjects, 30 hours of sleep deprivation impaired accurate recognition of human facial emotions (van der Helm et al., 2010). Extreme emotional faces were still correctly recognized, but the ability to recognize moderately angry and happy faces was reduced after sleep deprivation. The blunted recognition could reflect the susceptibility of the prefrontal lobe to sleep deprivation. A specific region of the prefrontal lobe, the anterior cingulate cortex, is implicated in the emotions anger and happiness (van der Helm et al., 2010; Blair, 2009).

PFC dysfunctioning is also associated with the loss of inhibition of context-inappropriate responses, which is also seen after sleep deprivation (Horne, 1993). A potential mechanism for this loss of inhibition and changed emotional reactions after sleep deprivation is provided by an fMRI study of Yoo et al. (2007). During scanning, subjects performed an emotional viewing task: 35 hour of sleep deprivation significantly weakened the connectivity between the amygdala and the medial PFC and elevated amygdala activation in response to negative pictures. The authors suggest that as the medial PFC is proposed to exert top-down control of amygdala activity, resulting in context-appropriate emotional responses, sleep deprivation leads to a failure of top-down, prefrontal control (Yoo et al., 2007).

Although aggression may in some situations be considered appropriate and meaningful behavior, most often it is not compatible with the rules in modern society. Raine and Yang (2006) hypothesize that rule-breaking behavior is in part due to impairments in brain structures belonging to the PFC. In this regard the PFC can be considered as the cortical region where context-inappropriate aggression is kept under control. Speculating further, when PFC control is lost or diminished as a consequence of sleep deprivation, this could potentially lead to uncontrolled, impulsive aggressive responses (primitive reactions).

Serotonin

Evidence from both animal (de Boer et al., 2009) and human (Dolan et al., 2001; Stolpmann et al., 2010) studies strongly support an important role for serotonin in aggressive behavior. Emphasizing the importance of serotonin is the finding that selective serotonin reuptake inhibitors decrease irritability, angriness, impulsivity and assault in violent offenders (Butler et al., 2010). An etiological hypothesis states that lower brain serotonin (5-HT) neurotransmission in the orbitofrontal cortex contributes to reduced cortical top-down control, which is implicated in the development of aggression and violence (Siever, 2008). The serotonin deficiency hypothesis of aggression

is currently debated (de Boer et al., 2009). Booij et al. (2010) showed that male adult individuals with a history of childhood physical aggression had currently low 5-HT brain synthesis, measured with positron emission tomography, but despite this, no differences in measures of aggression, emotional intelligence and impulsivity compared to control subjects. The authors suggest that low 5-HT does not mediate current behavior, but should be considered a vulnerability factor for impulsive-aggressive behavior that may or may not be expressed depending on other variables. For example, trait aggression has been shown to be significantly higher in men with decreased 5-HT availability in combination with high testosterone levels, but also in men with increased 5-HT availability and low testosterone, reflecting the interaction of 5-HT functioning with other variables, in this case testosterone (Kuepper et al., 2010). Thus, although serotonin seems to have an important role in aggression, it is almost certainly not the only causal factor for the development of aggression.

Sleep and wakefulness are associated with clear changes in serotonergic activity (Monti, 2011). Particularly, wakefulness and sleep deprivation are associated with higher serotonergic activity than during sleep, as established by numerous microdialysis studies (Portas et al., 2000). Total sleep deprivation in rats seems to increase 5-HT turnover in the frontal cortex, hippocampus, hypothalamus and brain stem (Asikainen et al., 1997). Whether this is also true in humans remains to be elucidated. Moreover, experimental studies in rats have shown that chronically restricted and disrupted sleep leads to gradual changes in serotonin-receptor sensitivity (Roman et al., 2005; Novati et al., 2008). To our knowledge, there are no studies investigating the relation between sleep problems, serotonergic dysfunctioning and aggression directly. However, indirect evidence supporting such a relationship comes from studies on suicidal behavior. Both sleep loss and decreased serotonergic activity are associated with suicide and suicidal behavior (Singareddy and Balon, 2001; Kohyama, 2001; Goodwin and Marusic, 2008). The association between low cerebrospinal fluid 5-HIAA (the principal metabolite of 5-HT) and suicide is most prominent in or may even be confined to patients who use particularly violent methods in their suicide attempts (Singareddy and Balon, 2001). In addition, lifetime externally directed aggression is more frequent in suicide attempters and criminal offenders also have increased suicidal behavior. Singareddy and Balon (2001) suggest that decreased serotonergic function in suicidal patients and criminal offenders may predispose to reduced inhibitive capabilities or to increased impulsive behavior. This can be self-directed (suicidal behavior) or externally directed (impulsive and aggressive behavior toward property or other persons).

In conclusion, both preclinical and clinical evidence supports the view that serotonin may be an important causal or modulatory link between sleep problems and aggression.

The Hypothalamic-Pituitary-Adrenal (HPA) axis system

HPA axis dysfunctioning contributes to aggressive behavior in antisocial and conduct-disordered individuals (van Goozen and Fairchild, 2009). However, the generally accepted hypothesis is that this is explained by the hypo-arousal driven aggression model. This is not compatible with the hyperarousal seen in insomniacs: Waters et al. (1993) observed that insomniac subjects exhibited signs indicative of hyperarousal, namely higher skin conductance and heart rate, and also scored higher on an anger scale compared to non-insomniac controls. Animal studies focusing on the involvement of the HPA system in aggressive behavior produce contradicting results (Koolhaas et al., 2010).

Sleep, particularly deep sleep, has an inhibitory influence on the HPA axis, whereas HPA axis activation produces arousal and sleeplessness (Meerlo et al., 2008; Steiger, 2002, Vgontzas and Chrousos, 2002). Insomnia is associated with higher levels of ACTH and cortisol, especially during the evening and first part of the night, suggesting central nervous system hyperarousal (Vgontzas and Chrousos, 2002). A rat study which showed increased exploration in an open field test of anxiety after sleep deprivation - possibly reflecting irritability - did not reveal differences in plasma corticosterone levels (Tartar et al., 2009). This suggests that sleep deprivation-induced explorative behavior is not mediated by HPA activation.

In conclusion, sleep disturbance may affect the HPA axis but whether this contributes to the relation between sleep problems and aggression remains to be elucidated. To our knowledge no study exists specifically addressing the role of the HPA-system in this relation.

Individual vulnerability

It is possible that certain individuals are more susceptible to the emotional consequences of poor sleep. For example, individual differences in emotional intelligence predict the influence of sleep deprivation on written responses to cartoons displaying frustrating situations (Kahn-Greene et al., 2006). This could indicate that individuals with low emotional intelligence are more vulnerable for the negative effects of sleep deprivation on mental functioning. Speculatively, individuals with poor prefrontal functioning, such as certain psychiatric patients, are potentially more vulnerable to the effects of sleep deprivation. This may imply that individuals with an aggressive trait, such as many

forensic psychiatric patients, may represent a group with poor prefrontal inhibition of aggressive impulses. In fact, researchers have found lower volumes of blood flow in the frontal lobes of people with various kinds of impulse-control disorders (Hollander and Cohen, 1996). A meta-analysis of brain-imaging studies confirmed prefrontal structural and functional impairments in antisocial populations (Yang and Raine, 2009). Possibly, poor sleep exacerbates the loss of their already low impulse control leading to verbal or even physical acting out of aggressive impulses. This makes the relationship between sleep and aggression of special importance in these subgroups.

In addition to individual differences in prefrontal cortical functioning, interindividual differences in serotonergic function may also contribute to the variability in effects of sleep loss on aggression. Variability in central serotonin function is associated with individual differences in affect, temperament and personality: for example, high-aggressive male rats respond in a more sensitive way to a 5-HT_{1A}–receptor agonist compared to low-aggressive animals (Koolhaas et al., 2010). As discussed earlier, low central 5-HT may be a vulnerability factor for impulsive-aggressive behavior (Booij et al., 2010). Sleep deprivation most certainly has an effect on serotonergic activity in the brain, but to what degree this effect differs between individuals is not clear. Thus, although we know that individual variation in the serotonergic system is associated with differences in aggressiveness, the potential role for sleep in this relation remains to be elucidated.

Similar speculations can be made for individual variation in the HPA axis. Differences in behavioral coping style between high and low aggressive mice have been associated to differences in the HPA stress system (Veenema et al., 2004). Overall, the general picture of the relationship between aspects of variation in coping style and HPA-axis activity is rather complicated and results are not conclusive (Koolhaas et al., 2010); yet, the possibility that certain variations in the HPA-axis make individuals vulnerable to the effect of sleep problems on behavioral problems can not be excluded.

CONCLUSIONS

Clinical and anecdotal observations in forensic psychiatric patients suggest that sleep loss is a potential risk factor for impulsive, reactive aggression. The larger part of the reviewed literature concerning the relationship between poor sleep and emotional regulation supports this hypothesis. Yet, most studies measured correlations and thus, do not provide information on causality: poor sleep may affect aggressiveness and/or

aggressiveness may produce sleep problems. Another option is that both sleep problems and aggressive tensions/behavior are due to a shared risk factor, such as a psychiatric disorder. However, the limited number of studies showing that adequate treatment of sleep problems reduces daytime aggression support the hypothesis that sleep problems are in fact a risk factor for aggression. Unfortunately, relevant animal research on sleep deprivation and aggression is largely confined to the influence of REM-sleep deprivation. Moreover, many of these studies have not taken into account various confounding factors associated with the sleep deprivation procedures. Sleep deprivation in humans appears to exert profound effects on mood, including increased irritability and altered reactions to frustrations. Whether or not these effects actually result in physically acting out aggressive urges is still obscure.

Sleep problems may impair prefrontal cortical functioning and thereby weakening the top-down inhibition of aggressive impulses. This offers a neurobiological mechanism explaining how sleep problems may be a risk factor for aggression and violent behavior. Possibly, some individuals may be more vulnerable to the emotional consequences of poor sleep. If so, it is highly important to identify these individuals, because promoting good sleep in these people may reduce the frequency and/or severity of aggressive outbursts. People known to be aggressive such as violent delinquents and some ASPD patients, are most likely to belong to this risk group.

In view of the fact that most existing literature supports an association between sleep loss and aggression, it seems worthwhile to investigate in more detail the impact of sleep problems and experimental sleep deprivation on aggression and hostility. Studies exploring individual vulnerability for the negative consequences of poor sleep on the regulation of emotions are also of particular interest. Moreover, there is a need for studies elucidating the neurobiological mechanisms that may mediate the influence of poor sleep on aggressive feelings and behavior. Speculatively, when evidence in support of the relationship between sleep and aggression is substantiated, it is of utmost importance to pay attention to sleep complaints, correctly diagnose and adequately treat sleep disturbances in individuals at risk. The treatment of sleep problems may be a valuable, innovative element in aggression-reducing and crime-preventing treatment programmes.

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