Current Trends in Neurology
Vol. 5, 2011

Review

Nightmares as predictors of psychiatric disorders in adolescence

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ABSTRACT

Adolescence is a critical period for neural and psychological development, during which sleep plays an important functional role. Nightmares are a prominent feature of sleep in adolescence, and are proposed to reflect social, emotional and affective problems specific for this developmental period. Nightmares occur typically during rapid eye movement (REM) sleep. Furthermore, the mechanisms of REM sleep and its dreaming state are associated with the consolidation of emotional memories with negative valence as well as with many affective disorders. Thus, adolescents with high prevalence of nightmares may be at risk for psychiatric disorders such as anxiety, posttraumatic stress disorder, obsessive compulsive disorder, and depression, all of which often cross into more heavy forms in adulthood leading to serious cognitive, mood-related and psycho-social problems, poor academic achievement and invalidation. In this review, we first summarise data about the neurobiology and role of REM sleep for cognition, psychology and emotional processing in normal and psychopathological conditions. Second, we focus on the maturation of REM sleep and its regulatory mechanisms in adolescence. Third, we provide evidence for existing close relationships between nightmares and a number of psychiatric disorders that commonly occur during adolescence. Since adolescence is critical for neurodevelopment, these relationships between nightmares and increased risk for psychiatric illnesses will be discussed in the context of understanding and prevention of psychiatric disorders in adolescence.

KEYWORDS: nightmares, REM sleep, psychiatric disorders, development, adolescence

INTRODUCTION

Sleep is a common biological feature in all mammal species including man, and represents a state of immobility with greatly reduced responsiveness to environmental stimuli, which can be distinguished from coma or anaesthesia by its rapid reversibility. Sleep is by no means a dormant state. When it is prevented, the body tries to recover the lost amount. Thus, the existence of sleep 'rebound' after deprivation reveals that sleep is not simply a period of reduced activity or alertness regulated by circadian or ultradian rhythms [1]. Furthermore, the magnitude of the changes in brain metabolism and neuronal activity during sleep exceeds those which occur during most waking periods [2]. Also, many data show that dramatic changes in brain electrophysiology, neurochemistry and functional anatomy biologically distinguish the different sleep stages from one another [3]. This is evident from the electrophysiological characteristics of human polysomnography (PSG). Overnight sleep

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is characterized by the cyclic occurrence of rapid eye movement (REM) sleep and Non-REM sleep, which includes lighter sleep stages 1 and 2 and stages 3 and 4 of deeper, slow wave sleep (SWS) [4]. Whereas SWS dominates the first half of the night, REM sleep and stage 2 dominate the second half. This dynamics reflects the so called circadian regulation of sleep that is distinguishable from its homeostatic regulation seen after sleep deprivation [5]. A hypnogram of normal adolescent overnight sleep is presented in Figure 1.

Although the role of sleep is still beyond a comprehensive understanding [6], data clearly show its beneficial effect on many physiological, cognitive and psychological functions. Sleep serves metabolic, immune, respiratory, and cardio-vascular functions responsible for the normal body homeostasis [7-11]. Further, sleep is shown to be important for many cognitive processes such as learning and off-line consolidation of memory [12-14], cognitive abilities [15, 16], emotional processing [17, 18], and human insight [19]. Last, but not least, sleep is shown to sustain the so called default mode network of the brain during quiet wake, which is important for adequate cognitive processes [20]. Importantly, a close relationship exists between metabolic and cognitive functions of sleep [21-25]. It is therefore the mind-body interaction rather than separate functions that sleep regulates. The vital importance of sleep is well documented by the fact that its deprivation in rodents and flies can cause death faster than food deprivation [26].

One of the most attractive mental features of sleep is its dreaming state [27, 28]. Since the discovery of a relationship between REM sleep and dreaming [29], many researchers have investigated dream production and its intensity and quality in distinct sleep stages. Now it is well documented that REM sleep is the brain state characterizing with the most intense and delusive dream content including the occurrence of bad dreams or nightmares [30-33]. These mental signatures of REM sleep are proposed to serve resolution of emotional and social conflicts, and also to be involved in affective psychiatric disorders such as posttraumatic stress disorder (PTSD) and anxiety depression [17, 34].

However, the possible role of nightmares, as a sleep disturbance in these and other psychiatric conditions has so far received little attention. Since nightmares are a prominent feature in childhood and adolescence [35], and because adolescence is characterized by dramatic changes in psychological functioning including emotionality [36-38], it might be suggested that frequency of nightmare occurrence may be one important factor for many psychiatric disorders that occur during these developmental periods. Further support for this suggestion is the existence of a bi-directional

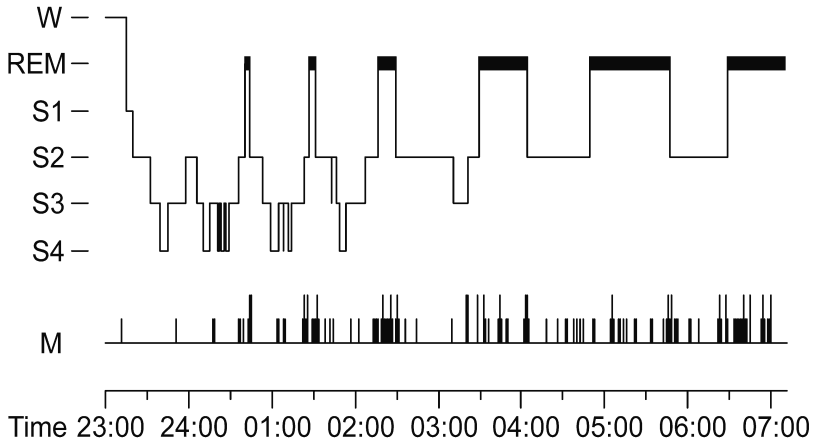

Figure 1. Hypnogram of a healthy adolescent overnight sleep. W, wake; REM, rapid eye movement sleep; S1, stage 1 of Non-REM sleep; S2, stage 2 of Non-REM sleep; S3, stage 3 of Non-REM Sleep; S4, stage 4 of Non-REM Sleep; M, movement time.

relationship between waking and dreaming mental activity proposed by the so called continuity hypothesis. This hypothesis posits that cognitive and emotional processes generated, developed and used during wakefulness do continue and evolve during sleep and dreaming [39, 40]. For example, it has been reported that the dream content of 1348 Canadian students was focused on five prevalent themes: (1) being chased, (2) sexual experiences, (3) falling, (4) school, teachers, and studying, and (5) arriving late [41, 42]. There is also evidence that dream content and dream recall may affect waking life [43, 44]. Thus, though speculative, nightmares may reflect amplification of current concerns and worries during dreaming, and may be a key for a better understanding of the daily mental activity in normal and psycho-pathological conditions.

In this review, we first summarise data about the neurobiology and role of REM sleep for cognition, psychology and emotional processing in normal and psychopathological conditions. Second, we focus on the maturation of REM sleep and its regulatory mechanisms in adolescence. Third, we provide evidence for existing close relationships between nightmares and a number of psychiatric disorders that commonly occur during adolescence. These relationships further suggest that high prevalence of nightmares may be a predictor for the occurrence of psychiatric illnesses in adolescence.

1. REM-sleep and its role for cognition, psychology and emotional processing

The discovery of REM sleep [45] has initiated extensive sleep research in all domains of neurosciences. Unlike the electrophysiology of lighter sleep stages and SWS, those of REM sleep are characterized by swift occurrence of low-amplitude and desynchronized electroencephalogram (EEG) activity comprising both theta (~ 5 Hz) and much higher beta and gamma (~ 15-70 Hz) EEG oscillations [46, 47]. This is accompanied by large magnitude saccadic or rapid eye movements, increase in heart and breathing rate and complete loss of muscle tone [4, 45]. The electrophysiological signatures of REM sleep are shown and compared to those of stage 2 of Non-REM sleep and SWS in Figure 2.

1.1. The neurobiology of REM-sleep

The neurobiology of REM sleep should be reviewed together with the processes governing the other sleep-wake stages [3, 48]. During wake, acetylcholine (Ach), noradrenaline (NA), serotonin (5-hydroxytryptamine, 5-HT), and histamine (H) projecting to the cortex are all active, thus sustaining a balance between cortical excitation and inhibition [3, 48]. As sleep deepens, all these neurotransmitters progressively decrease their activities with their lowest levels occurring during SWS, which results in cortical inhibition [48, 49]. In REM sleep, all NA, 5-HT and H neurons stop working. Instead, an Ach excessive over-activity emerges projecting to the cortex and almost all sub-cortical structures, which creates a hyper-excitability of the brain [3, 48, 50-52]. Concomitantly, hypothalamo-pituitary-adrenal (HPA) activity as indicated by cortisol release is suppressed to a minimum during early, rich in SWS sleep portion of night, while it is drastically increasing during late, rich in REM sleep night [53]. Importantly, REM sleep provides the most sound basis for neurotransmitters and modulators that are diversely involved in numerous synaptic plastic changes [54, 55]. Moreover, REM sleep is characterized by higher levels of the cerebral blood metabolism than the other sleep stages [56]. Thus, it is not surprising that REM sleep can serve more cognitive and psychological functions than non-REM sleep stages.

1.2. Cognitive and psychological functions of REM-sleep

It is generally recognized that REM sleep consolidates mostly procedural (motor skills, habits, implicit learning, etc.) memory [57-61]. Even the portion of REM sleep in a daily nap may be sufficient for gain in the off-line consolidation of procedural memory [62]. Further, REM sleep selectively facilitates access to weak associations [63, 64], promotes creativity [65], and late-night REM sleep preserves previously acquired implicit knowledge [66]. Also, the role of REM sleep is proposed to be related to integration of recently acquired memory in a more general and individually specific context [14], and a recent study shows that REM sleep promotes the transfer of implicit knowledge into explicit solving of a task following meta-cognitive learning [67].

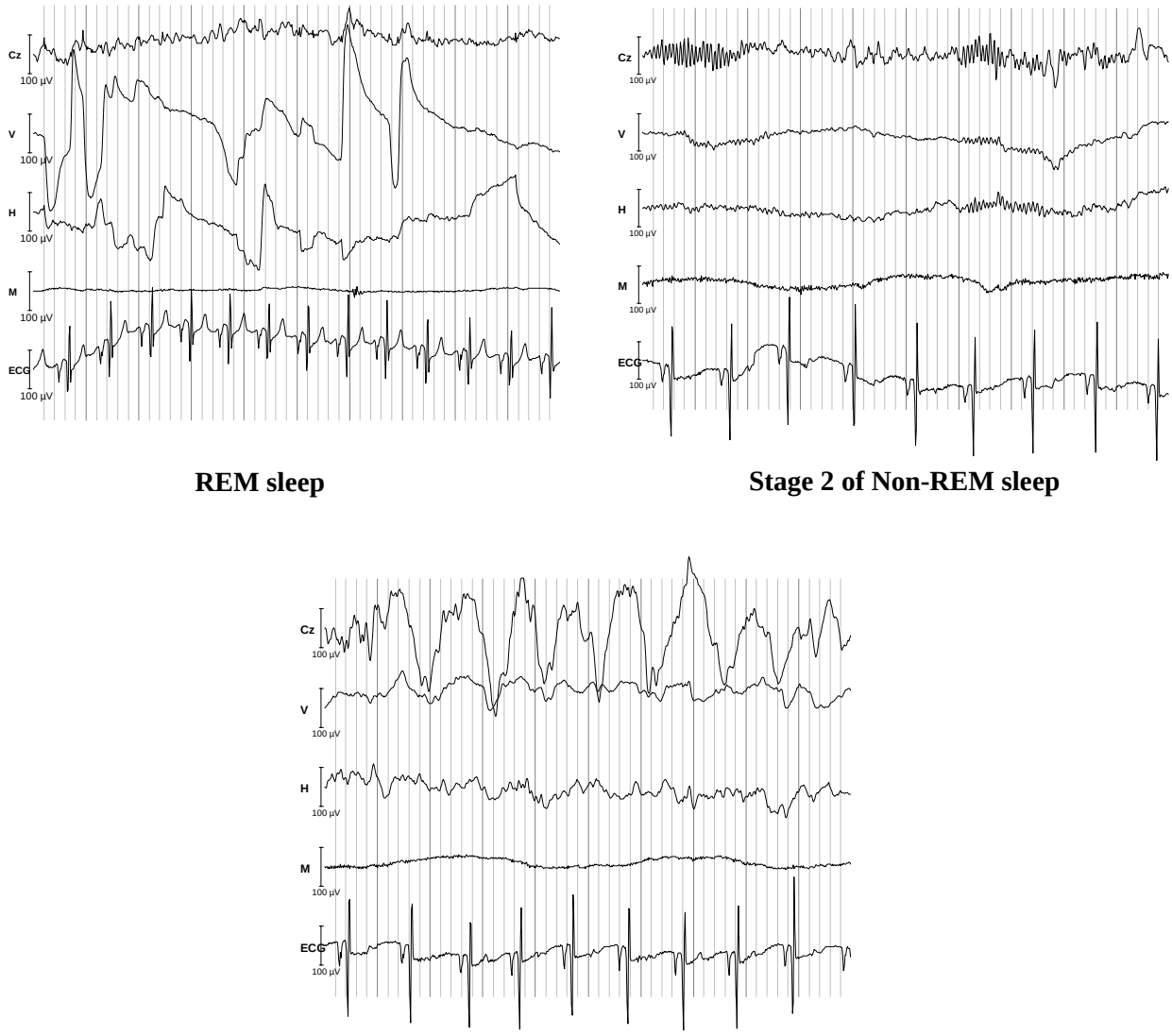

Figure 2. The electrophysiological characteristics of rapid eye movement (REM) sleep, stage 2 of Non-REM sleep and slow wave sleep (SWS). For a better visualization, epoch of 10-sec are presented. Five signals are shown as follows: Cz, elecroencephalogram; V, vertical eye movements; H, horizontal eye movements; M, electromyogram; ECG, elecrocadrigram.

1.3. REM-sleep and emotional processing

REM sleep may have an important role in selective facilitation of affective memory. Some studies have revealed the social aggression interaction signature of dreams during REM sleep compared to those during non-REM sleep [33, 68-69]. This also suggests that the process of REM sleep mental activity aids in the resolution of previous emotional conflict [33, 70]. Indeed, REM sleep and its EEG signature (theta EEG activity) were shown to benefit consolidation of fact-based information with negative emotional valence, thus suggesting that REM sleep has an important role for emotional processing [71-74]. On the other hand, these features of REM sleep and their respective neural grounds, if improperly set, may lead to the development of a variety of psychiatric disorders with affective component [17, 18, 34].

Given the latter, psychological functions of REM sleep, it is notable that REM sleep pressure or overdrive (increased REM sleep amount and shortened latency to REM sleep) is recognized to hallmark a spectrum of child, adolescent and adult psychiatric disorders. For example, REM sleep overdrive is a major, incapacitating symptom commonly observed in schizophrenia, depression, anxiety, PTSD, obsessive compulsive disorder (OCD) as well as in many affective disorders [75-83]. To conclude, REM sleep and its regulatory mechanisms are very important for many cognitive and psychological functions, and their alterations can induce a number of psychiatric diseases.

2. REM-sleep and the importance of its maturation in adolescence

Sleep and its regulatory mechanisms maturate from infancy to late adolescence [84]. The human newborn exhibits an even distribution of waking, REM sleep, and SWS, spending about 8 hours in each state. After birth, there is a gradual decrease in REM sleep from about 8 hours at birth to about 1 hour by 15 years of age, beyond which there is a small decrease until senescence. SWS may increase transiently after birth, and then gradually decrease from 8 hours per day to 6 to 7 hours per day by 15 years of age. The gain observed in total waking time, from about 8 hours at birth to about 16 hours at maturity, is mostly at the expense of REM sleep duration [84]. The neural substrates responsible for these developmental decrease in REM sleep are located in brain-stem nuclei and the neurotransmitters involved include Ach, excitatory amino acids such as n-methyl-d-aspartic acid, the inhibitory gamma amino-butyric acid, NA, and serotonin, all comprising the so called developmental REM sleep suppressing mechanisms [78, 79, 85]. These REM sleep suppressing mechanisms may be altered and/or not adequately matured in a spectrum of psychiatric disorders during development including pubertal schizophrenia, panic attacks, PTSD, OCD, and anxiety depression, all exhibiting REM sleep overdrive [79, 85]. Moreover, if not properly treated, these disorders can cross into adulthood. Also, the impaired REM sleep regulation during development may lead to occurrence of major depression, insomnia, schizophrenia, and Alzheimer's, and Parkinson's diseases later in life [79, 85]. For example, one of the most common child psychiatric disorders, attention-deficit/ hyper-activity disorder (ADHD) frequently crosses into adolescence depression [86-88], and among the many sleep alterations reported in ADHD, an increased REM sleep amount is found [89-91].

Notably, it has been suggested that REM sleep serves to direct the course of brain maturation [92]. Since that activity-dependent development may direct neural connectivity throughout the brain, REM sleep could provide endogenous activation at a time when the brain has little or no exogenous input [93].

Further, it is to be emphasized that adolescence is characterized by drastic hormonal changes [38, 94], which are associated with substantial alterations of the sleep-wake cycle [84, 85, 95, 96] and sleep habits [97, 98]. Also, during this period of development many psychological functions such as social brain [37, 99], emotional processing [36, 38] and executive control [100] undergo dramatic changes. Whereas data about plausible association between REM sleep and executive control are only inferred [20], such between REM sleep and social brain and emotionality are discussed above [17, 34]. Importantly, the changes in these functions during adolescence are related to onset of a spectrum of psychiatric disorders. This includes psychiatric diseases including high neuroticism and emotional liability such as anxiety and PTSD, bipolar disorder (BPD), depression, schizophrenia, borderline disorders, OCD, and anorexia nervosa [101-112], each one accompanied by serious sleep disturbances and cognitive deficits [95, 113] and most of them characterized by REM sleep overdrive [79, 85].

Given the above arguments, adolescence is a very critical period for neurodevelopment, during which sleep, and REM sleep in particular, plays an important role. Therefore, some common child and adolescent sleep disorders including parasomnias such as nightmares during this period may be significant factors for decrement of cognitive and psychological development and occurrence of psychiatric illnesses [79, 85, 97, 98, 114].

3. Definition, prevalence and reasoning of nightmares in adolescence

Nightmares have fascinated mankind for centuries and have often appeared in literature. A failure to understand that they are not real may result in significant behavioral problems. For example, it has been described that a 13-year-old girl who dreamed she had intercourse with her father. Months afterward, this girl was so horrified that she could not communicate with her father [115]. Nightmares are traditionally defined as extremely frightening dreams leading to awakening that may cause a sleeping subject to cry or experience distress during sleep, and commonly induce negative emotional tone, accompanied by sleepiness and worsened cognitive abilities during the succeeding day [35, 116-119]. However, definitions of nightmares vary. For instance, the definition in the International Classification of Sleep Disorder, 2nd edition [116] does not limit negative emotions in nightmares to fear alone, as anger or sadness are also prevalent in nightmares. There is considerable discussion and debate over the definition of disturbed dreaming among children and adolescents. Different operational terms are employed across studies: bad dreams, anxiety dreams, scary dreams, dysphoric dreams, and nightmares. Also, definitional criteria, such as whether or not disturbing dreams cause awakenings, are frequently cited as a means of distinguishing nightmares, which produce awakenings and distress from bad dreams or not [120]. Nightmares typically occur during REM sleep, mostly in the second half of the overnight human sleep [35, 116].

Most studies concern mainly adolescents and children aged 5 years or older as having the highest prevalence of nightmares. In fact, disturbed dreams are reported to be common in childhood and adolescence [35, 116]. There is no sex difference in nightmare prevalence among children under 12 years of age, but nightmares are more prevalent in girls than in boys at 13 years. This gap becomes more pronounced at 16 years, and probably, reflects hormonal and associated developmental gender differences [121]. No other socio-demographic correlates of bad dreams during these developmental periods have been well documented [120].

Diagnostically, nightmares are distinguished from night terrors or pavor nocturnus, a parasomnia occurring prevalently in children and young adolescents. Unlike nightmares, which occur during REM-sleep in the second half of the night, night terrors occur during the first non-REM-sleep cycle approximately 15 to 60 minutes after sleep onset. The sleeper sits up in bed, screams out in fear, and wakes up with eyes wide open and breathing fast. In this state, children do not respond to comfort or consolation, and typically, they do not recognize their parents. After the attack, children fall asleep again, and on the next day normally they do not remember what has happened [35].

Although nightmares are a prominent sleep feature in children in adolescence, they have so far received very little attention in the literature. The precise psychological meaning of nightmares is still poorly understood. Yet, they are shown to be a usual sleep disturbance resulting from previously experienced social and emotional problems as well as traumatic and stressful events [122-125]. Adolescence is characterized by hyper-emotionality and high neuroticism [36, 38]. Furthermore, nightmares are traditionally associated with the most intense, delusive and affective/aggressive signatures of dream content characterizing REM sleep [32, 33], and it has been shown that the neurobiological regulatory mechanisms of REM sleep and intense dream production have much in common [30, 31, 48]. Also, adolescence is characterized by dramatic changes in hormonal status and accompanying alterations of many psychological processes [36-38, 94, 99, 100] and sleep-wake cycle, particularly affecting REM sleep [84, 95]. Thus, the high prevalence of nightmares during this developmental period can have neurobiological and psychological grounds. Yet, it is difficult to distinguish the dream content incorporated in nightmares and the neurobiology of REM sleep from each other. Studies in this direction deserve attention, because the frequent nightmare occurrence in adolescence may have an important role for both normal psychological development and psychiatric conditions.

4. Nightmares and common adolescent psychiatric disorders: Close relationships

As mentioned above, nightmares are a prominent feature of sleep in children and adolescents.

Several considerations should be taken into account concerning this issue. First, given that in these periods of development, REM sleep maturates [84], the related dream production may undergo dramatic changes. Second, since a REM sleep overdrive hallmarks a number of childhood and adolescent psychiatric disorders [78, 79, 85], excessive prevalence of nightmares during these stages of development may be associated with psychiatric conditions emerging in adolescence. Furthermore, if REM sleep regulatory mechanisms during development were insufficient, REM sleep-related mentality, as reflected by dream content might be impaired. Third, as mentioned above, adolescence is characterized by dramatic and rapid changes in hormonal status paralleled by alterations in many psychological functions [36-38, 94, 99, 100], which can substantially alter the sleep-wake cycle [95, 97, 98]. Therefore, close relationships between nightmares and common adolescent psychiatric disorders can be suspected. Indeed, existing data concerning such relationships are reported. However, they are still overlooked.

We will first present existing data about nightmare occurrence in children and adolescents with ADHD. Sleep complaints in children and adolescents with ADHD frequently engage nightmares [126-129]. Importantly, childhood ADHD frequently crosses into adolescent depression [86-88], and sleep complaints in depressive adolescents typically include nightmares [107, 112, 130-134]. Given the high prevalence of nightmares in both childhood ADHD and adolescent depression and the link between the two psychiatric conditions, it might be tentatively proposed that the frequent nightmares in ADHD children may be one of the risk factors for the occurrence of depression in adolescence.

Further, nightmares are usually reported to be very frequent and stressful in vulnerable adolescents and in adolescents suffering from many psychiatric disorders. For example, nightmares are a common sleep feature in adolescents suffering from anxiety disorders including high neuroticism and emotional liability, separate anxiety, parental abuse, episodes with panic attacks, and PTSD [120-125, 135-137]. Further, nightmares are typically reported in depression and manic symptoms [107, 112, 130-134, 138]. High prevalence of nightmares is also found in anorexia nervosa, BPD and OCD in adolescence [139-141]. Importantly, increased frequency of nightmares is reported in adolescents with schizophrenia, personal borderline disorders and schizoid phenotype, and suicidal behavior [133, 142-151]. All these data point to a close relationship between nightmares and psychiatric disorders commonly observed in adolescence. Thus, a predictive value of nightmares for later occurrence of psychopathology could be proposed. Indeed there are reports citing both REM sleep dreams and nightmare content indicators as significant predictors of suicidal ideation in depressed individuals [121, 130, 136, 151].

Most of the listed above psychiatric illnesses with high nightmare incidence in adolescence are hallmarked by REM sleep overdrive [79, 85]. Therefore, one major question is whether the frequent nightmare occurrence in these psychiatric disorders is simply an epiphenomenon resulting from the REM sleep overdrive, or alternatively, nightmares may predict occurrence of psychiatric conditions in adolescence. In order to answer this question, some empirical results should be reviewed. There is a wealth of data linking dream content variables to specific clinical outcomes, such as depression, nightmares, recurrent dreams, and unpleasant everyday dreams [118, 152-155]. It is also fairly well established that specific content indicators, that is, fearful or unpleasant emotional imagery in REM sleep-related mentation of persons with PTSD predicts the severity of the disorder [156]. Consistently, incorporation of trauma-related memories into dreams is one of the criteria for the PTSD [35]. REM dream content variables are also strongly correlated with selected personality dispositions, such as attachment status [68], extraversion [157, 158], neuroticism [137], and psychological boundaries [159, 160]. Furthermore, REM sleep and its mental experiences are shown to consolidate memories with negative valence, thus being involved not only in successful emotional processing, but also in a spectrum of psychiatric disorders with affective component [17, 18, 34, 71-74]. Therefore, although REM sleep overdrive hallmarks a number of developmental psychiatric disorders [79, 85], the personal characteristics of the mental experience in REM sleep, as incorporated in nightmares, may be transformed into one or another psychiatric

condition. Given these arguments, we hypothesize that nightmares are not simply an epiphenomenon of the REM sleep overdrive characterizing these psychiatric disorders. Rather, they may appear as an early predictor of psychopathological conditions in adolescence, whereas the corresponding symptoms and related sleep alterations may occur later. Yet, the precise role of nightmares for psychiatric disorders in adolescence needs further clarification.

In conclusion, adolescence is a very critical period for the normal cognitive and psychological development, in which REM sleep and the related dream mentality may have an important role. Nightmares are a prominent sleep feature during this period and may be predictors of many psychiatric conditions in adolescence. Therefore, their frequent occurrence in adolescents should be treated with increased attention by the parents, pediatricians, mental health professionals, and sleep researches.

ABBREVIATIONS

PSG, polysomnography; REM, rapid eye movement; SWS, slow wave sleep; PTSD, posttraumatic stress disorder; EEG, electro-encephalogram; Ach, acetylcholine; NA, nor-adrenaline; 5-HT, serotonin; H, histamine; OCD, obsessive compulsive disorder; ADHD, attention-deficit/hyperactivity disorder; BPD, bipolar disorder.

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