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# Methodology in clinical sleep research

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**Abstract.** This review presents traditional and cutting-edge interventions in sleep research, including descriptions of the relationship of rapid eye movement-non-rapid eye movement sleep with the autonomous nervous system, and dream research methodology. Although sleep and dreaming are overlapping and non- separable phenomena, they are not typically addressed simultaneously in the scientific sleep research literature. Therefore, a more extensive overview of dream research has been included with a focus on objective dream content analysis and the theory of neurocognitive analysis. A bridge is made between dream content analysis and current sleep research methodologies.

**Keywords.** Sleep, REM-NREM, ANS, dreams, sleep and dreaming.

## REM and non-REM sleep as targets for interventions

Different approaches to manipulate rapid eye movement (REM) and non-REM (NREM) sleep have been used to pursue physical and psychological effects. Experimental and clinical interventions are of three kinds: behavioral, pharmacological, and physical.

### Behavioral interventions

Multiple behavioural interventions have been used to manage sleep disturbances [1, 2]. These approaches are particularly explored for insomnia, a very prevalent condition in adult population [1]. Stimulus control is aimed at training the insomniac to reassociate the sleeping environment with a rapid sleep onset by creating a relaxing bedroom environment [2]. Sleep restriction therapy consists of curtailing the amount of time spent in bed to more nearly match the subjective amount of sleep [2]. Sleep restriction creates a mild state of sleep deprivation and thereby promotes rapid sleep onset. Generally, time in bed is not less than 5 h to prevent daytime sleepiness [1]. Relaxation interventions are designed to reduce the levels of arousal in insomniac patients. Progressive muscle relaxation, biofeedback, abdominal breathing and cognitive techniques are used for this purpose [1]. Cognitive therapy seeks to transform detrimental beliefs and attitudes about sleep. It consists of identifying dysfunctional sleep cognitions and replacing them with more adaptive substitutes. Paradoxical intention is a technique that engages the patient in staying awake, thus reducing anxiety and improving sleep onset [2]. Sleep hygiene education targets improving health practices and environmental factors. Multiple studies have shown that behavioural techniques produce reliable and sustained improvement in about 70 % – 80 % of patients with chronic insomnia. There may be additional improvement when a behavioral strategy is combined with pharmacological treatment [2].

Sleep deprivation has historically been used as a major tool in manipulating sleep and circadian rhythms affecting different physiological variables. [3 – 6] Sleep loss can affect various circadian rhythms [5, 6]. It can be altered by multiple factors like physical activity, exposure to bright light, noise and temperature, body position, interest, motivation and drugs

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[3, 4]. Repeated periods of sleep loss have multiple psychological effects [3,4]. The most common psychopathological changes associated with sleep deprivation are sleepiness, fatigue, irritability, difficulty concentrating and disorientation. Perceptual distortions and hallucinations may also occur. Some individuals show psychotic symptoms [3,4]. Sleep deprivation has been shown to lead to a REM sleep and slow-wave sleep (SWS) rebound during recovery [3]. When there is a large REM-sleep rebound, increase in slow-wave activity may be reduced, delayed, or absent, especially in the later stages of sleep recovery, suggesting that a longer recovery period is needed in some cases [4].

According to most authors, memory consolidation is dependent on sleep [7]. In humans, there is evidence of sleep-dependent consolidation in both declarative and procedural non-declarative consolidation domains [7]. There is strong evidence for consolidation of both perceptual and motor skill memory [7]. Correlation and sleep-deprivation studies have implicated all stages of sleep except stage 1 in maintaining cognitive and motor skill function [7]. The role of sleep in these domains appears to be more to enhance performance than to stabilize it [7, 8]. Neuroimaging studies have demonstrated that sleep-dependent learning is associated with plastic reorganization of memory within the human brain [9]. Learning of complex logical games and development of mathematical insight have also demonstrated sleep-dependent overnight improvements. Evidence for human declarative memory is not so clear, but recent findings suggest a strong role for SWS, when the concurrent reductions in glucocorticoid and acetylcholine release may contribute to the consolidation process [9]. Declarative memory has also been associated with sleep spindles [10]. In fact, all stages of sleep except stage 1 are associated with declarative memory [11]. Firing patterns of cells in neuronal ensembles seen during learning are replayed during subsequent sleep in both rats and songbirds [7]. Manipulations including sleep deprivation may affect both declarative and procedural memory in humans [7]. The role of slow wave sleep is probably related to reactivation of the hippocampal-neocortical circuits activated during a waking learning period, while REM sleep is responsible for consolidation of this new learning into long-term memory [17]. Contrary to these negative effects of sleep deprivation, it is the only known intervention that has proven antidepressant benefits within 24 h, albeit transitory [12]. The antidepressant effects of sleep deprivation have been demonstrated in patients who range in age from adolescence to late life. Total sleep deprivation significantly improves mood in about 60 % of all depressed patients. The 'depressiogenic' effect of short sleep periods depends on time of day: morning naps have a stronger tendency to provoke relapses of depressive symptoms than naps in the afternoon [2]. In this context, it is of interest that studies involving a total of 20 patients demonstrated that merely advancing the phase of the sleep period to 5:00 p.m. to 12:00 midnight for 2–3 weeks led to an improvement of depression in 75 % of the patients [3, 4]. Some studies show that the antidepressant effect is related to a reduction in cingulate cortex metabolism [13]. Sleep deprivation can also improve the effect of pharmacological treatment in geriatric patients. Mood amelioration is associated with reduced glucose metabolism in anterior cingulate cortex and medial prefrontal cortex [14]. There is some evidence that sleep deprivation might exert its antidepressant properties by involving serotonergic mechanisms. Tryptophan depletion did not reverse the antidepressant effects of sleep deprivation but prevented relapse beyond a night of recovery sleep. These findings suggest that sleep deprivation does not act via a single monoamine-related mechanism but probably by wider neurochemical alterations [15]. According to some authors sleep deprivation during the second half of the night improves mood more effectively [16]. Probably differences between the first and second halves of the night are related to the relative amount of REM sleep in these periods. Selective REM sleep deprivation by selective awakenings and REM sleep augmentation by rebound-based methods can also influence mood disturbances [17].

**Pharmacological interventions**

Multiple pharmacological interventions that affect sleep have been developed. Basically, they can be divided into the following categories: hypnotics and sedatives, stimulants and memory-enhancing drugs. Ideal hypnotics must have the following characteristics: absence of cognitive and attentional effects, rapid absorption, specific receptor binding, good-quality physiologic sleep, absence of residual effects, absence of active metabolites, absence of respiratory depression, absence of interaction with central nervous system depressant drugs, absence of tolerance, absence of dependance, absence of abuse potential and optimum half-life [18, 19]. Benzodiazepines have sedative, hypnotic, amnesic, anticonvulsant and myorelaxing effects [19]. Because they are more sedative than anxiolytic, benzodiazepines are not primarily classified as hypnotics. The first benzodiazepine synthesized was chlordiazepoxide, followed by diazepam, oxazolam and nitrazepam [19]. In the 1970s flurazepam and flunitrazepam appeared. Benzodiazepines are known to alter sleep structure [18, 20, 21] in multiple ways, sleep including latency reduction,

increased stage 2, slow wave sleep reduction, REM sleep latency augmentation and REM density reduction. Benzodiazepines also affect sleep electroencephalogram (EEG), reducing delta activity and enhancing rapid frequencies. Benzodiazepine dependency and tolerance after prolonged usage have been described [22], but generally, its dosage tends to increase in order to obtain similar effects. Tolerance potential is dissimilar among different benzodiazepine molecules. Benzodiazepine dependency may be due to two main mechanisms: altered metabolism of the endogenous ligand of the benzodiazepine receptor and downregulation of benzodiazepine receptors. In some cases the hypnotic effect disappears while the anxiolytic effect remains. Abrupt benzodiazepine withdrawal can cause specific symptoms defined as abstinence syndrome, especially concerning short half-life and intermediate compounds such as lorazepam and alprazolam. In some cases rebound anxiety may occur, which tends to increase sleep difficulties. Benzodiazepines have specific binding sites that interact with GABA (X-aminobutyric acid) receptor sites, causing chloride ion influx and hyperpolarization. There is evidence to suggest that hypnotic effect depends both on postsynaptic chloride influx and on presynaptic voltage-gated calcium channels [23, 24]. Benzodiazepine binding is stereospecific, so enantiomeric forms can have opposite blocking effects. Among different types of GABA receptors, BZD1 or ω1 seems to be the most related to hypnotic effect. Triazolam microinjection into dorsal raphe nucleus produces paradoxical effects in different structures: it promotes arousal and induces sleep in the media preoptic area. This area receives afferents from prosencephalus and brainstem, coordinating multiple systems involved in homeostatic and reproductive functions. During the 1990s new hypnotics were synthesized, such as ciclopirolones (zopiclone and eszopiclone), imidazopiridines (zolpidem and alpidem), zaleplon and imidazobenzodiazepines. These compounds are more selective at the sleep-promoting GABA-BDZ receptor, thus having fewer of the generalized central nervous system (CNS) depressant effects of the less-selective benzodiazepines. More recently, the first melatonin-receptor agonist, ramelteon, has come to market in some countries. This compound promotes sleep onset and is also chronobiologically active. Sedative hypnotic drug development is currently in a very active phase.

While hypnotics promote faster sleep onset, stimulants promote arousal generally [25–27]. Xantines, including caffeine and teophilinem antagonize adenosine receptors. Adenosine is an important sleep promoter. Many other stimulants enhance monoaminergic activity, promoting arousal. Amphetamines increase central dopaminergic activity [28]. Stimulants are used in the treatment of sleep because they reduce REM sleep and total sleep time. Abrupt interruption may cause REM-sleep rebound. Modafinil has been introduced as stimulant for the treatment of excessive somnolence in narcolepsy. Although not completely understood, some mechanisms proposed to explain its effect include increased dopamine liberation through the inhibition of GABAergic neurons, altered GABA-glutamate balance in brain areas involved in sleep-wake cycle, and possibly inhibition of histaminergic neurons in the posterior hypothalamus and activation of adrenergic α1 receptors [29, 30]. Antidepressant drugs generally reduce REM sleep [31]. This action depends on the noradrenergic stimulation [31, 32]. The antidepressant effect, parallel to behavioural techniques of REM sleep deprivation are probably due to some common mechanism [31]. Some antidepressants, like trazodone, mirtazapine doxepine and amitryptiline, have sedative action [31, 32]. Proposed mechanisms for the sedative effect are histaminergic H1 antagonism, and anticholinergic and α-adrenoceptor action [33]. Cholinergically active drugs affect REM sleep [34–36]. The effects of many cholinergic agents on sleep in normal and pathological situations has been widely studied [37–46]. Studies with galantamine and rivastigmine have reported increased REM sleep in normal, alcohol-dependent and depressed patients [37, 39, 43, 44]. Polysomnography studies in which donepezil was given to normal elderly and young healthy subjects consistently reported increases in REM sleep percentage and REM density, with reduced REM latency after a single 5-mg dose [40, 41]. These findings correlated with findings on memory performance, although the studies were not double-blind or placebo controlled. REM sleep increment has also been observed in depressed patients treated with donepezil [41]. Studies of the effects of tacrine on REM sleep were not conclusive probably because doses higher than 100 mg/day could not be used due to liver toxicity [42]. A recent placebo-controlled study of the effect of donepezil on sleep in Alzheimer's patients showed that donepezil treatment increases REM sleep percentage, whereas it decreases EEG slowing ratio and REM-sleep slow-band power in specific brain areas in Alzheimer's disease patients [47]. Potentiation of cholinergic transmission induced a change in REM-sleep EEG frequency bands. There was a more pronounced reduction of theta band absolute power in the frontal area, which is similar to what has been reported for long-term donepezil treatment in mild to moderate Alzheimer's patients during wakefulness [47]. Decreased cholinergic input is believed to be a require-

ment for the generation of EEG slow-wave activity; thus, by increasing cholinergic transmission we would expect a decrease in EEG slow-wave activity and what is expected in terms of sleep or sleep disturbances. Improvement of the ratio between slow and fast REM-sleep EEG frequencies after donepezil treatment in occipital leads resulted mainly from a decrease in slow frequencies [34, 47]. According to this study, donepezil-related cognitive improvement in Alzheimer's disease may be predicted by REM-sleep EEG alpha-band power in spectral analysis before treatment [47]. REM-sleep rapid frequencies may reflect a less-deteriorated cholinergic system [47]. Anatomical structures affected by Alzheimer's disease overlap with those related to the genesis and control of REM sleep to some degree [47]. This has prompted some authors to speculate that there might be a functional relationship between REM sleep and Alzheimer's disease pathogenesis [48]. There is an extensive but controversial literature relating REM sleep to cognitive function, which is impaired in Alzheimer's disease [35, 45]. It is still unclear whether cholinergic drugs are valuable interventions in sleep disturbances of non-demented patients. [34].

**Physical interventions**

Continuous positive airway pressure (CPAP) is the most important therapeutic physical intervention that can affect sleep. There is strong evidence that patients with sleep apnea hypopnea syndrome treated with CPAP improve daytime function and quality of life, as well both subjective and objective measures of sleep [49]. Patients treated with CPAP present increased SWS percentage and decreased stage 1. Sleep efficiency is also improved by treatment. A placebo-controlled study found no significant increase in REM sleep during prolonged treatment. REM sleep rebound generally occurs immediately after instauration of CPAP treatment [49, 50]. It is possible that REM-sleep rebound correlates with improved oxygen saturation after CPAP treatment [49]. Possibly physiologic functions of REM may fail if oxygen saturation falls below a critical level [49]. If CPAP can affect sleep stage distribution, sleep stages can affect CPAP treatment; positional apnea patients cease to benefit from lateral decubitus during REM sleep due to chest wall muscle atonia, thus altering CPAP titration [51]. Higher CPAP pressure is required to abolish upper-airway obstruction generally during REM sleep, which is clearly observed in an auto-CPAP device. Uninterrupted SWS is usually associated with the lowest CPAP level. This finding is in agreement with the notion that airway collapsibility is least in this sleep state [52].

**REM and non-REM sleep with ANS interactions**

Sleep stages and sleep/wake transition affect cardiovascular function [53]. There is a close relationship between sleep, sleep stages and autonomic regulation. It is known that there is a tonic increase in parasympathetic activity during NREM and REM sleep. However, there have also been findings of bursts of high-amplitude sympathetic activity during REM sleep compared to wakefulness in normal subjects [54, 55], characterizing a special state in which autonomic nervous system (ANS) component interaction is peculiar. The balance between both arms of the ANS low frequency/high frequency (LF/HF) ratio is increased in the 5 min of state 2, NREM sleep, preceding REM sleep, compared with the 5 min of state 2 preceding slow-wave sleep [56]. Arousal from sleep is associated with a sudden increase in sympathetic tone [57, 58]. All these data together suggest that there is a relationship between sleep EEG and ANS regulation during sleep [59]. In fact, an increase in delta activity, reaching maximal values during SWS, correlates with increase in parasympathetic tonus, but inversely with a sympathetic component [60]. The sympathetic/parasympathetic balance during desynchronized EEG, seen during REM sleep, is sometimes similar to wakefulness [61].

ANS activity, which can be monitored with beat-by-beat heart-rate variability (HRV) in baseline condition or in response to a given stimuli, is an objective measure and quantification of the autonomic state during physiological or pathological conditions [62] and has been used for many years as a research tool. By applying time domain analysis to the electrocardiogram signal it is possible to obtain measures of RR variability to evaluate autonomic physiology and pharmacology and to predict cardiovascular outcome in cardiac patients. The frequency domain technique is also routinely applied to the RR interval, in three main frequency bands, 1 – the HF component – ranging from 0.15–0.40 Hz; 2 – the LF – 0.04–0.15 Hz; and 3 – very low frequency (VLF) – 0.0033–0.4 Hz [63]. The period of time of ECG signal analyzed in the literature ranges from 5 minutes to 24 h [64] Five minutes is a commonly used interval in sleep studies in different sleep stages [36]. The interpretation of HRV results is not always simple. The LF range of HRV may difficult to interpret, since both sympathetic and parasympathetic components might be involved. However, it has been accepted that an increase in its power provides insight into the activity of the sympathetic tone, and administration of beta blockers could reduce it [65]. Respiratory patterns may influence the sympathovagal balance and sometimes the LF component to the HF band; therefore the phys-

iological interpretation of LF component should be done in association with the HF component [66]. In the case of periodic breathing patterns seen in some elderly, one may find large oscillations in the VLF frequency band during REM sleep [66]. In these elderly subjects during periodic breathing, the standard deviations of NN intervals (normal to normal RR intervals) and of the LF component are increased; however, during normal breathing most parameters of HRV are decreased in the elderly compared with young adults [67], implying that in some cases it is critical to have simultaneous respiratory monitoring for optimal sleep analysis. Recent studies have proposed simultaneous analysis of respiration (flow or thoracic impedance plethysmography) and HRV, suggesting that this will improve recognition of the respiratory component of HRV [68]. The former applied Wavelet transform (time and frequency domain technique) to both, respiratory signal and RR intervals, thus improving time resolution [69]. The later study evaluated HRV and thoracic impedance signal compared with pneumotachography and concluded that this analysis improves recognition of central and obstructive apneas. Thus, the integrity of all mechanisms involved in ANS activation is then necessary, making sleep and arousal testing situations for the ANS critical for normal sleep homeostasis and sleep function [70]. Since we acknowledge that REM sleep is generally subject to distinct ANS control, and sleep is a state of low susceptibility to external stimuli, some authors have recently explored the sleep states particularly as targets of interventions and outcomes using HRV. For example, Yamizaki et al. [71] studied HRV during REM, NREM sleep, and during arousal in cardiac transplant patients. They characterized the reactive group, as those patients in whom HRV changed with sleep-stages alternation, even when their absolute HRV indices were greatly decreased in wakefulness compared with controls. On the other hand, when the central sympathetic activity was pharmacologically inhibited, heart failure patients were able to increase their parasympathetic tone related to NREM and REM sleep, improving ANS balance and sleep quality [72]. HRV during sleep in recent myocardial infarction compared with controls shows a significant increase in LF/HF ratio, a sympathetic component, only during sleep, associated with a loss in the capability of the vagus to physiologically activate during sleep. The authors suggest that this important ANS alteration during sleep may provide insights into the causes of nocturnal occurrence of sudden death in these patients [73]. Henessy et al. [74] studied a series of 12 epileptic patients with medically intractable seizures that underwent abrupt carbamazepine withdrawal in order to facilitate seizure recording. The authors found that this intervention led to enhanced sympathetic activity during sleep that was associated with seizure-induced hypoxia; they concluded that this relationship may predispose epilepsy patients to sudden unexpected death. Additionally, HRV analysis has helped finding ANS abnormalities during sleep in patients with other medical disorders. A study of vasovagal syncope patients in whom 24-h HRV and other diagnostic approaches performed after the episode of syncope were negative or showed conflicting results found that the LF component is decreased during REM sleep, suggesting alteration of sympathetic activation. The authors hypothesize that if patients are unable to physiologically increase their sympathetic tone, this may partially explain the autonomic reflex during syncope episodes. In this study, an index of LF component variation across SWS and REM sleep was utilized as possible marker of abnormal ANS activity during sleep. Parameters of HRV, LF and LF component variation across SWS and REM all exhibited good sensitivity and specificity compared with the clinical judgment diagnostic of vasovagal syncope as the gold standard in this same study [36]. If this finding is confirmed, future ANS interventions targeting REM sleep may restore the physiological sympathetic tonus in these patients. Likewise, Viola et al. [75] studied a patient with second-degree atrioventricular blocks during REM sleep and stage 2 preceding REM sleep, and compared him with normal controls. They found a similar lack of increase in sympathetic tonus during REM sleep. The authors suggested that sleep processes, particularly during REM sleep, create a specific neurological background that prevents surges in sympathetic activity and triggers cardiac pauses. Finally, it has been extensively shown in the literature that obstructive sleep apnea syndrome (OSAS) is associated with increased sympathetic activity during sleep, and increased cardiovascular mortality risk [76, 77]. Moreover, it has been argued that routine Holter-monitor evaluation of ECG together with HRV analysis is able to identify obstructive sleep apnea syndrome (OSAS) patients [78], since they present a high LF and LF/HF ratio during sleep hours and a pattern of brady-tachycardia [79]. Effective treatment with continuous positive airway pressure (CPAP) may restore more normal physiological ANS regulation during sleep. CPAP has been reported to alter both parasympathetic and sympathetic activity during sleep in patients with OSAS of differing severity [80–82]; however, controlled studies with large numbers of individuals are still needed.

### Objective versus subjective assessment

Objective assessment of sleep studies has been standardized by the sleep stages scoring manual [83], and more recently characterization of sleep stability was systematized by the Cyclic Alternating Pattern Atlas [84]. The most widely used subjective sleepiness scores are the Epworth Sleepiness Scale (ESS) [85] and the Stanford Sleep Scale (SSS) [86]. Sleep quality has been assessed by the Global Sleep Assessment Questionnaire [87]. Objective characterization of dreaming is mostly done using the Hall/Van de Castle classification system [88–90]. Subjective or interpretative assessment has been described by many different systems, but most of them lack a sound scientific methodology [91–93]. Objective dream content analysis can be associated with changes in the sleep EEG, namely alpha rhythm [94].

### Studies of dreams, content and objective outcomes

The central point of dream study is based on or tests a dream theory or paradigm. Here we present a brief description of the main theories of dreams. Content analysis has been improved by the Hall/van de Castle analysis paradigm [89–91] with consistent and reproducible results in many studies, but it is considered a simple and limited tool [92, 93]. Cognitive function during sleep has been neglected in past sleep studies, but it is now an important component of sleep homeostasis, namely in REM sleep.

### Introduction to dream theories

Ancient Egypt and China [94] addressed the meaning of dreams from a religious or mythical perspective. The modern scientific approach was promulgated by Freud [95], whose self-analysis led to investigation of his own dreams and childhood memories. Adler argued that dreams were designed to reveal the content of social and compensatory strivings of the individual [96]. Jung forwarded the idea that dreams are manifestations of the collective unconscious and archaic images [97, 98]. With few exceptions, more than a hundred years of case studies have done little to support the specific hypotheses put forward by Freud, Jung or any other psychoanalytic theorist. A more recent physiological theory known as the activation-synthesis paradigm describes dreams as simply cortical response triggered by the temporal-limbic region and regularly stimulated by periodic bombardments of random stimuli from the pontine region of the brainstem during REM sleep [99–102].

New neurocognitive theory suggests that dreams are essentially a continuation of waking mental activities that depends upon the maturation and maintenance of a specific network of forebrain structures. This theory integrates physiological and content-based approaches to understand the meaning of functions of dreams.

A recent dream study demonstrated that dreaming cannot be triggered by external stimuli [92], and that dream content is by and large impervious to the wide range of pre-sleep and concurrent stimuli that have been used in an attempt to influence it. The brain's higher centers are inactive during sleep, and no correlation between specific REM sleep events and dream content variables have been reported [103]. Ontological studies of dreaming have reported low levels of dreaming in the REM sleep of children [104–109], similarities of waking and dreaming cognition [110–114], realistic dream content, consistency of dream content over years and decades in adults [115–117], and the manipulation of dream content by drugs. Recent work in neuropsychology and neuro-imaging [118–121] suggests there may be a fairly specific neural network for dreaming that can be studied in a variety of ways, namely the presence of 'canonical' maps of cerebral activities for typical dream features during REM sleep. Relevant findings come from assessments of patients with brain injuries which show that lesions in different areas have differential effects on dreaming and thereby imply the contours of the neural network necessary for dreaming [121]. The interactions and neurochemistry of dream formation implicate acetylcholine, serotonin, norepinephrine, histamine, dopamine and others, and are still controversial and confusing [122]. It is known that alkaloids and dopamine intensify the dream experience. Patients suffering from epilepsy or Parkinson's disease might be potential candidates for such content studies. It is known that medications that eliminate epileptic seizures also reduce or eliminate the patients' nightmares and that L-dopa potentiates the dream experience [123]. Different studies have described opposing results [124]; however, the fact that dreams can be made more vivid and frightening by drugs affecting the dopaminergic system suggests that the relationship between neural networks for dreaming and dream content can be studied through determining the influence of various drugs on specific aspects of dream content [125, 126].

Dreaming appears to be the result of the normal functioning of a relatively specific neural network located primarily in the limbic, paralimbic, and associational areas of the forebrain, although the brainstem or the midbrain, namely the ventral tegmental area, may be responsible for dream generation [127]. If there are defects in these areas, dreaming can

be lost temporarily or permanently, or be impaired in some way, such as loss of visual dream imagery [128]. There is a large clinical literature on the repetitive nightmares of people suffering from post-traumatic stress disorder that fits well with the idea of a repetition principle [129]. This supports a potential linkage between dream content and the neural network for dreaming, particularly in terms of its possible relationship with the vigilance/fear system, nightmares in post-traumatic stress disorder sometimes happen in stage 2 of NREM and seem to parallel the nightmares suffered by epileptics due to seizures in NREM [130, 131]. Both dreams and the vigilance/fear system seem to provide a neurocognitive record of traumas, upsets, and tensions over a lifetime [132, 133]. And both may be impaired even when the person seems emotionally recovered and unhampered by the past during waking life.

## Summary

Many interventions may affect sleep, causing or improving sleep disturbances and sleep physiology. The literature is more extensive where pharmacological approaches are concerned. We have attempted to summarize how the main classes of drugs and CPAP (the main physical intervention aimed at treating sleep respiratory disorders) affect sleep and cognition. We have also provided a brief review of how technical approaches during sleep, assessing autonomic tonus and dreaming function, may have potential application in recognizing, monitoring, and treating medical disorders.

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