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THEORETICAL REVIEW

Neurophysiological aspects of primary insomnia: Implications for its treatment

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Summary Insomnia has usually been studied from a behavioral perspective. Somatic and/or cognitive conditioned arousal was shown to play a central role in sleep complaints becoming chronic, and was used as a starting point for the development of treatment modalities. The introduction of the neurocognitive perspective, with its focus on cortical or CNS arousal, has given rise to a renewed interest in the neurophysiological characteristics of insomnia. Recent research, using quantitative EEG, neuroimaging techniques and the study of the microstructure of sleep, suggests a state of hyperarousal with a biological basis. Furthermore, insomnia might not be restricted to sleep complaints alone because it appears to be a 24-h disorder, affecting several aspects of daytime functioning as well. These new findings have implications for the treatments used and indicate that a focus on cortical or CNS arousal should be pursued. As such, the use of EEG neurofeedback, a self-regulation method based on the paradigm of operant conditioning, might be a promising treatment modality. Preliminary results for insomnia and successful applications for other disorders suggest that this treatment can have the necessary stabilizing effects on the EEG activity, possibly resulting in a normalizing effect on daytime as well as nighttime functioning.

Introduction

Insomnia has received much attention the last few decades, since it has become a growing and complex problem in our society. It has long been, and still is, an under-recognized and under-treated problem. Unfortunately, approximately 60% of the people suffering from insomnia do not talk about their sleeping disturbances with their physician, which only contributes to the fact of being an under-treated disorder.[1] Insomnia is defined as the complaint of difficulty initiating or maintaining sleep, early awakening, and interrupted or non-restorative sleep. Furthermore, it must be accompanied by clinically significant impairment in daytime function, for which there is no identifiable cause such as another sleep, psychiatric or medical disorder.[2] However, insomnia is not always

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the primary disorder, but can present itself in a context of other underlying maladies. As such, comorbid insomnia can be accompanied by a diversity of medical and psychiatric conditions, such as chronic painful physical conditions (CPPC's),[3] affective disorders, [1,4,5] like depression and anxiety, and other psychiatric pathologies,[6] including substance abuse disorder.[3,7-9]

There have been many studies concerning the prevalence and epidemiology of insomnia, but the lack of systematic assessment makes it difficult to compare and review these studies in a meaningful way.[9,10] Overall, it is suggested that about 10–20% of the general population reports insomnia complaints and consequently impairment of daytime functioning. Furthermore, the prevalence seems to be higher in woman and increases with age.[1,7,9,11]

One of the characteristics of insomnia is the discrepancy between the objective polysomnographic (PSG) sleep measures and the subjective report of sleep complaints. Insomniacs tend to overestimate these objective sleeping problems in their subjective report on their sleeping pattern. Sometimes however, there seems to be a total lack of evidence of sleep disturbances in contrast to the subjective report of the patient, in which case it is diagnosed as Paradoxical insomnia (formerly known as sleep state misperception).[12] The most important characteristics that determine the clinical significance of primary insomnia are its severity, frequency, duration and daytime consequences.[13,14] The frequency and duration of the complaints are two very important factors to evaluate the severity of this sleep disorder. A frequency of at least three times a week is regarded as clinically significant, especially for research inclusion criteria.[15,16] When the sleep disturbances are present for less than 1 month, it is referred to as transient insomnia. Generally, it is triggered by situational stressors and will resolve itself after the individual has adjusted to the stressful event. Insomnia lasting between 1 and 6 months is referred to as subacute or short-term insomnia. Finally, when the sleep complaints persist for more than 6 months, it is classified as chronic insomnia.[12] In addition, there should be an impairment of daytime functioning. Unfortunately, there seems to be a lack of objective evidence, and only subjective reports show a possible impairment of various aspects of daytime functioning. Generally, studies suggest that insomnia patients experience an increase in fatigue, but not in sleepiness.[17-21] Although insomniacs complain of concentration and/or attention deficits, there seems to be no consensus on the objective existence of these cognitive impairments.[18,21-23] One hypothesis introduced by Edinger et al.[24] concerns possible interference of the sleep setting itself the night before daytime testing. The results surprisingly showed that insomnia patients who slept at home prior to daytime testing generally appeared the most alert on the multiple sleep latency test (MSLT) and differed significantly from normal sleepers. Although alternative explanations are possible, these findings could suggest that the insomnia patients were too aroused to fall asleep. Furthermore, post-hoc analysis in this latter study revealed that the participants' relative ease or difficulty with nocturnal sleep onset persisted into the daytime and explained their MSLT differences. This suggests that the arousal is a 24-h phenomenon, which raises the question whether insomnia is in fact only a disorder of nighttime sleep, since there seem to be substantial daytime as well as nighttime symptoms.[25]

Clearly, insomnia can be understood as a disorder or a comorbidity with a high prevalence in our society. Therefore it is necessary that the understanding of developing and maintenance (predisposing, precipitating and perpetuating factors), as well as its pathophysiology are better understood.

Neurophysiological characteristics

Insomnia and arousal

The behavioral model of insomnia posits that trait and precipitating factors result in acute insomnia, which in turn becomes sub-acute because of the reinforcement of maladaptive coping strategies. Finally, these strategies result in conditioned arousal and chronic insomnia.[26] Since, this theoretical framework has been dominantly used since the 1980s, the somatic and cognitive components of the conditioned arousal have received much attention. The somatic hyperarousal has been evidenced by elevated heart rate, body temperature, cortisol levels and whole body metabolic rate, which in turn is associated with chronic sympathetic hyperactivity.[18,27,28] Furthermore, Bonnet and Arand [18] have shown that insomnia patients are not only aroused during the sleep onset period and PSG sleep, but also during the day. Additionally, it appears that verbal and physical activities consistently produce a characteristic EEG arousal response and a return to wakefulness for a period of time, which is related to the magnitude of physiological arousal.[29]

Cognitive hyperarousal is reflected by intrusive and negative cognitions and their association with sleep complaints.[30-32] In a study with normal sleepers, De Valck et al.[33] also showed that experimentally induced cognitive arousal resulted in significant increases in sleep latency as measured by the MSLT, thus having a substantial effect on the ability to fall asleep.

Recently, Perlis et al.[26] introduced a neurocognitive perspective that focuses on cortical arousal, which is measured by EEG activity. It has been suggested that the presence of high frequency EEG activity, namely beta and gamma power, is correlated with cognitive processes.[34-36] This perspective offers a possible explanation for a number of paradoxes, which characterize insomnia patients. First of all, there is a discrepancy between the objective measure and the subjective report of sleep. Insomnia patients tend to overestimate their sleep latency and underestimate their total sleep duration. Secondly, when awakened shortly after sleep onset from polysomnographically-verified sleep, they often report having been awake. Thirdly, they tend to report greater benefits from treatment with hypnotic medication than can be explained by objective measures of sleep improvement, because benzodiazepine hypnotics do not normalize sleep.[26,37] According to Perlis and his colleagues [26] the high frequency EEG activity during the sleep onset period affects the mesograde amnesia related to the sleep onset. Consequently, sleep and wakefulness are more difficult to distinguish because of the high level of information and/or memory processing. The preliminary results of a recent study indeed suggest an enhanced recognition memory for information presented at the initial sleep onset period with insomnia patients.[38]

These findings imply that hyperarousal in insomnia is a multidimensional construct consisting of three relatively independent components, interfering with the normal process of sleep and consequently leading to sleep complaints and impairment of daytime functioning.[26,39] As research already showed a 24-h impact of the somatic component, an evaluation of cognitive and cortical arousal during the day might give more clarity about the relationship between the different arousal components.

Quantitative EEG (qEEG) characteristics in insomnia

The transition from wakefulness to sleep is normally characterized by a decrease of high frequency and an increase of slow frequency EEG activity.[40] However, insomnia patients appear to display other EEG changes during the sleep onset period (SOP) and PSG sleep, which makes differentiation from comorbid insomnia and normal sleepers possible.[41]

First of all, insomniacs show heightened levels of relative beta power during wakefulness at the SOP.[42] They furthermore appear to exhibit higher beta and gamma power during NREM sleep in comparison with comorbid insomnia and good sleeper controls,[43] especially during the latter portion of the night.[44] Merica et al.[45] also found increased levels of beta power during the REM periods of sleep. Secondly, insomnia patients exhibit reduced levels of alpha power during wakefulness and these levels remain rather constant during the SOP. They do not show the sharp decrease in alpha power in comparison to comorbid insomnia and normal sleepers.[41,42] Merica et al.[45] observed significantly decreased levels of alpha power during NREM sleep and increased levels of alpha power during REM sleep. Thirdly, one study also reported a deficit in the theta power during NREM and REM sleep.[45] Finally, during the SOP the delta power appears to be lower in insomniacs and does not show a dramatic increase at the sleep onset.[41,42] This delta deficit also appears to persist into the NREM and REM periods.[45] Taken together, these findings suggest an EEG profile opposite to that of normal sleepers, namely elevated levels of high frequency and a reduction of slow frequency EEG activity, which suggest a state of CNS hyperarousal. Furthermore, the results also showed an inverse relationship between the beta and delta activity,[46] which good sleepers appear to maintain for the entire night, while insomnia patients apparently lose this characteristic pattern between 3 and 4 h after sleep onset. It is suggested that this may correspond to their increased number and/or duration of awakenings after sleep onset.[44] Moreover, Perlis et al.[43] also observed a positive correlation between the presence of beta activity during unambiguous sleep and the tendency to underestimate total sleep time.

Although these results suggest the presence of an EEG profile associated with CNS hyperarousal during the SOP and PSG sleep in insomnia patients, it still remains a topic of discussion. First of all, most studies only used the first few minutes of the sleep onset period [42] or the first three NREM cycles.[43] Secondly, not all studies addressed the possible influences of arousal after sleep onset and EMG artifacts.[42,45] Therefore, future research should focus on a standard assessment method, carefully remove all artifacts and use whole-night EEG data.

Clearly, replications of these studies are necessary to come to a consensus about the EEG profile of insomniacs. Furthermore, other methods, such as neuroimaging techniques, that can enlighten the neurophysiological and pathophysiological characteristics of insomnia should be encouraged and further explored.

Neuroimaging data

Insomnia certainly can be understood within a behavioral framework, assessed by subjective sleep reports and polysomnographic measures, but research into the underlying neurobiological mechanisms is also evolving. The recent introduction of cortical arousal, as well as the use of neuroimaging techniques, gave rise to a growing interest in these latter aspects.

The advantage of qEEG techniques lies in the excellent temporal resolution when mapping dynamic changes in cortical activity over time. The lower spatial resolution, however, makes it difficult to measure subcortical activity. This shortcoming might be compensated by using neuroimaging techniques because they can provide a better spatial resolution to identify CNS abnormalities during sleep. Smith et al.[47] performed a preliminary Tc-99-HMPAO SPECT study in insomnia patients and found a decreased cerebral blood flow during NREM sleep in comparison to healthy controls. This hypoperfusion was observed in the basal ganglia, the frontal medial, occipital and parietal cortices. These results appear to contradict the proposed hyperarousal theory of insomnia. However, it must be pointed out that there were some limitations that could interfere with the results, such as the fact that the insomnia patients received the blood flow assessments after a longer duration of NREM sleep than the healthy subjects. This may be crucial because it is known that blood flow tends to decline with increasing duration of NREM sleep. Furthermore, only a 2-min window of perfusion during the first NREM cycle was sampled. Therefore it remains possible that the insomnia patients, while hypoaroused during the initial phases of NREM sleep, are more aroused over the entirety of NREM sleep cycles. This could be supported by the research of Perlis et al.[44] since they found an increase of beta EEG activity more pronounced in the latter portion of the night. A second study by Nofzinger et al.[48] investigated the neurobiological basis of poor sleep and daytime fatigue in seven insomnia patients and 20 healthy controls using a fluorodeoxyglucose positron emission tomography (PET) during waking and NREM-sleep. Results indicated a significantly increased whole-brain metabolism in insomnia patients during the transition from waking to sleep onset, which suggests a state of hyperarousal during the SOP. They also showed a smaller decrease than did healthy subjects in relative metabolism from waking to NREM sleep states in the ascending reticular activating system (ARAS), the hypothalamus, the amygdale, the hippocampus, the anterior cingulate and in the prefrontal cortex. A higher metabolism was also seen in the thalamus, which could be related to sensory processing and information processing, as well as faster frequencies in the cortical EEG and subsequent shallower sleep.[49] A reduced relative waking metabolism was also observed in the prefrontal cortex in insomnia patients, which has also been observed in healthy subjects after sleep deprivation.[50] In summary, these studies reveal a hypermetabolism in certain brain regions related to the arousal system, as well as a hypometabolism in specific areas suggesting a chronic sleep deprivation. Nofzinger et al.[48] proposed that interacting neural networks play an important role in the neurobiology of insomnia, including a general arousal system (ascending reticular formation and hypothalamus), an emotion-regulation system (hippocampus, amygdala, and anterior cingulate cortex), and a cognitive system (prefrontal cortex).

Microstructure of sleep: the cyclic alternating pattern

Conventional assessment of sleep occurs through the variables that form the macrostructure of sleep, namely duration, number and extension of nocturnal awakenings and stage representation.[51] For insomnia research, the presence of arousals has always been of interest due to its association with sleep disruption, complaints of non-restorative sleep, increased wake time after sleep onset and impairment of daytime functioning. An EEG arousal is characterized by a sudden frequency shift toward faster rhythms (can be theta, alpha, beta, but not spindles) that shortly interrupts sleep continuity for at least 3 s.[52] However, since arousals are also spontaneous manifestations of sleep and not necessarily increased in insomnia,[53,54] another variable is thought to play an important role in the complaint of poor sleep.

A relatively new approach in sleep assessment is the examination of the microstructure of sleep.[55] At this level of analysis the cyclic alternating pattern (CAP), a marker of arousal instability, appears very interesting for insomnia research. This phenomenon is defined as a periodic EEG

activity in NREM sleep, distinguished from background EEG activity by changes in amplitude and frequency. In order to identify CAP, two phases need to occur within 1 min intervals: [52] (1) the repetitive element that is represented by the recurring EEG feature (phase A), and (2) the intervening background identified as the interval that separates the repetitive elements (phase B). A CAP cycle is defined as the sum of phase A and phase B duration given that each phase is 2–60 s in length. A succession of two or more CAP cycles is then defined as a CAP sequence. Concerning phase A, there are three different subtypes, which are differentiated on the basis of the presence of synchronized or desynchronized EEG patterns. Subtype A1 consists of dominantly synchronized EEG patterns, subtype A2 is composed of a mixture of synchronized and desynchronized EEG patterns, and subtype A3 is characterized by the dominant presence of desynchronized EEG patterns.[55] Regarding their functional significance, subtype A1 accompanies the transition from superficial sleep to deep sleep and seems to be responsible for the process of building up and maintaining EEG synchronization. Subtypes A2 and A3, on the other hand, are more dominantly present in the latter part of the sleep cycle and prepare the desynchronized background necessary for the onset of REM sleep.[56,57] This suggests that subtypes A2 and A3 represent central nervous system (CNS) arousal.[52] The periodic arousal fluctuation reflected by CAP is of course a natural phenomenon of NREM sleep which varies across the lifespan, but it has been shown that CAP parameters provide more detailed information than conventional objective measures.[58] CAP variables appear to be very sensitive in differentiating insomniacs from normal controls, as well as in differentiating between placebo and active medication groups in insomnia patients.[59] The mean duration of CAP sequences and the increased amount of CAP cycles observed in insomnia patients indicate a difficulty to maintain consolidated sleep. Furthermore, the alterations of CAP variables in untreated insomniacs were consistent with the subjective report of poor sleep. Research has also examined the efficacy of hypnotic medication and found a significant effect on sleep quality and CAP subtypes A1 and A2. Subtype A3 and EEG arousals, however, were weakly affected by the medication, which might suggest that sleep medication has only a limited effect on the variables reflecting CNS arousal. Finally, the highest significance for the correlation between sleep quality and PSG variables was found for CAP rate.[59] These results suggest that the analysis of CAP seems more sensitive in detecting sleep quality problems, which might be of great importance in research concerning the discrepancy between subjective reports and objective PSG data on sleeping complaints. Further research is necessary since the extension of conventional sleep measures to CAP variables may improve our knowledge on the diagnosis and management of insomnia.

Treatment implications

Regarding the pharmacological treatment, it is recommended to limit its usage for short-term or transient insomnia, since there are some concerns about potential side-effects in the long-term. It is advised not to exceed the standard limit of 4 weeks to avoid tolerance and dependence.[60,61] Consequently, pharmacotherapy is contraindicated for the treatment of chronic insomnia. Cognitive-behavioral therapies (CBT), however, seem to be quite efficient for treatment of this latter type of insomnia. They focus primarily on maladaptive sleeping habits, conditioned arousals, and dysfunctional beliefs.[62] Only 8 weeks of treatment resulted in an improvement of the subjective as well as the objectified sleep complaints.[63] However, CBT has limitations. First of all, the majority of insomnia patients following CBT show an average improvement that does not bring them into the good sleeper range, which means that they still show some impairment after treatment.[64–66] Secondly, the CBT-effect sizes obtained for insomnia are markedly lower in comparison to the CBT-effect sizes obtained for other psychological disorders.[65] Thirdly, the combined use of CBT and active medication may result in better progress ,[67] but, on the other hand, Hauri [68] showed that the improvements obtained during a combined therapy are not maintained over a follow-up period of 10 months in comparison with those patients who followed CBT without the use of medication. Fourthly, it requires much effort and dedication by the patients to produce the desired effects.[64] Finally, a significant group of patients (19–26%) does not respond at all to CBT.[64,65]

These findings suggest that there exists a group of insomnia patients who do not benefit from the focus on cognitive or somatic characteristics. It is also assumed that the three components of the arousal system are quite independent of each other. In this regard, De Valck et al.[33] showed that an experimentally induced cognitive arousal only resulted in somatic arousal, but not in cortical arousal. In light of this finding one could speculate that this component must be managed separately

and it may therefore be of interest to find a treatment modality, which focuses on the CNS arousal (high frequency EEG activity) and sleep EEG instability (CAP parameters).

EEG neurofeedback training

EEG neurofeedback training is a self-regulation method that makes use of learning theory, more specifically, the paradigm of operant conditioning.[69] While the EEG is measured, the patient receives instant feedback (visual and/or auditory) on the cortical activity of the brain. The goal of this treatment modality is to normalize the functioning of the brain by inhibiting and/or reinforcing specific frequency bands.

In a pioneering study Sterman et al.[70] showed that cats learned to voluntarily enhance 12–14 Hz activity in their wake EEG through operant conditioning, which resulted in changes in the sleep EEG. More specifically, a facilitation of sleep spindle bursts, as well as an increase of quiet sleep was observed. Furthermore, motor activity, which is suppressed by the presence of 12–15 Hz in the waking state, was also reduced during sleep. Since, an intervention in the wake EEG resulted in alterations of the sleep EEG, it was suggested that certain aspects of sleep physiology could be associated with the nature of the waking experience. Sustained behavioral immobility appears to be a shared factor in the presence of both rhythms, and suggests the existence of a common mechanism that might be involved in the suppression of movement.[70,71] This 12–14 Hz rhythm found in the waking EEG during sustained behavioral immobility and localized in the sensorimotor cortex, was named after its location, namely the sensorimotor rhythm (SMR).[70,71]

It is thought that the thalamus plays an important role in the production of several frequency bands. The EEG rhythmic patterns are thought to reflect the properties of the thalamocortical networks, which include brainstem and cortical processes. They are topographically localized in relation to nervous system organisation, and their frequency and spatio-temporal expression is determined by the interaction between sensory, neuro-modulatory, and corticothalamic influences.[72–75]

The thalamus is divided into different nuclei, which in turn receive information that is projected to specific areas of the cortex. Most neural input to the cerebral cortex travels this way, which means that the thalamus has an important gating function and consequently can block information from going to the target area in the cortex.[72] The thalamus contains three types of neurons which can display oscillatory behavior, reflecting the EEG frequencies measured at the scalp: (1) the thalamocortical neurons (TCR) which function in two different modes, namely as depolarizing relay cells which transmit ascending sensory input, or as oscillatory cells which fire in a phasic bursting mode, consequently blocking the input to the cortex; (2) the reticular nucleus neurons (RE) which provide the TCR neurons with inhibitory feedback control; and (3) local interneurons which play an important role in the coordination of the interactions between the first two types of neurons.[76]

Early studies suggest that the rhythmic activity associated with immobilization, namely EEG SMR activity and possibly sleep spindles, are mediated by a series of distinct thalamic generators.[71] SMR was observed in the EEG of the somatosensory nuclei of the thalamus, namely the ventrobasal (VB) nuclei. Consequently, the connections between these thalamic nuclei and the somatosensory cortex are necessary for the existence of this rhythmic EEG activity in the cortex. Furthermore, it appears that the presence of SMR activity results in a suppression of the conduction of somatosensory information through the ventrobasal thalamus. Ventrobasal thalamocortical elements appear to display an intrinsic, rhythmic discharge that is mediated by a recurrent feedback mechanism. Consequently, an attenuation of somatosensory afferent activity and a reduction in motor excitability takes place.[75]

Concerning sleep spindles, recent research has indicated two types of spindles, differentiated on the basis of their frequency and topographical location. First, there are the low frequency spindles (LFS) around 12 Hz dominantly present in frontal areas. Secondly, the high frequency spindles (HFS) around 14 Hz are more pronounced in the parietal regions.[77,78] Considering the cortical connections to the thalamus, it has been suggested that the LFS are probably generated in the mediodorsal nucleus of the thalamus, while the HFS are generated at the ventral nuclei related to sensory inputs.[78] Additionally, a temporal difference in their appearance was observed, namely the later emergence of 12 Hz sleep spindles in comparison to the 14 Hz sleep spindles. It is assumed that this is associated with the amount of cortical de-arousal, more specifically heightened levels of delta activity, which is necessary for the appearance of the 12 Hz sleep spindles.[79] Anderer et al.[77] used low-resolution brain electromagnetic tomography (LORETA) to localize the source of cortical electrical spindle activity more precisely. They identified two main brain areas, namely the precuneus (Brodmann's

area 7) and the medial prefrontal gyrus (Brodmann's areas 9 and 10), which are directly connected to the dorsal part of the thalamus, and are known to produce spindle activity.

It has also been suggested that the thalamus is responsible for the generation of slow oscillations, in particular delta waves (1–4 Hz) and low frequency oscillations (<1 Hz).[80–82] Throughout SWS a significant decrease in regional cerebral blood flow (rCBF) was observed in certain central core structures, such as the thalamus.[82] An interesting perspective in light of these findings has been offered by Merica and Fortune.[83] These authors have proposed a so-called neuronal transition probability model explaining the evolution of power in the sigma (12–15 Hz = SMR/sleep spindle frequency) and delta frequency bands of the sleep EEG. They have suggested three modes of neuron oscillation, namely beta frequency, sigma frequency and delta frequency, reflecting wake/REM sleep, sleep spindles and slow-wave sleep, respectively. During deepening of sleep, a systematic shift in the oscillatory mode occurs going from beta to sigma to delta, and this process reverses when sleep becomes lighter during the second half of the night. Other findings support this perspective such as the inverse relationship between beta and delta power [46,44] and the presence of sleep spindles preceding an increase in delta waves during NREM sleep.[76,81,84]

Insomnia and EEG neurofeedback

In light of the proposed hyperarousal theory, a direct intervention on the CNS arousal may have beneficial effects on the sleep complaints as well as the subjective impairments of daytime functioning. Recent research suggests that insomnia is not limited to sleep complaints, but should be considered as a 24-h disorder.[29] The heightened level of arousal appears to result in impairments of daytime functioning such as the subjective report of increased fatigue and reduced quality of life. Moreover, a resolution of the sleeping problem after treatment does not always result in an improvement of daytime functioning.[20] Hence, it seems important to look for a treatment modality with a 24-h effect and a focus on the suppression of arousal day and night. As mentioned before, an alteration in the wake EEG using EEG neurofeedback training resulted in changes of the sleep EEG.[70] When we reconsider some of the neurological underpinnings of neurofeedback, one might suggest that an intervention was made on the thalamocortical mechanisms and networks, which play an important role in sleep and arousal. They are responsible for the production of sleep rhythms (sleep spindles and delta waves), as well as information processing during the awake and attentive state.[72,74]

Concerning the possibility of treating insomnia with EEG neurofeedback, only two studies have investigated this possibility. In 1981 Hauri [85] compared three biofeedback modalities and one control group. Forty-eight psychophysiologic insomnia patients were assigned at random to one of the following groups: (1) frontalis EMG feedback, (2) feedback of frontalis EMG followed by theta feedback, (3) SMR feedback, or (4) control. Their main interest was focused on possible interaction effects and comparison of the different feedback groups. Results showed no significant difference in sleep improvements between the neurofeedback groups, but only the SMR group showed a positive correlation between the amount of SMR learning and improvements in laboratory measured sleep. Post-hoc analyses revealed a correlation between the amount of tension during baseline and the effects of a specific neurofeedback protocol. Namely, relaxation training by means of frontalis EMG and theta feedback was considered appropriate only for those who had initial tension problems, while the SMR training resulted in improvements with insomniacs who were not initially tense. In a replication study [86] 16 psychophysiologic insomnia patients were randomly assigned to either theta feedback or SMR feedback. However, because of methodological issues, they performed both trainings with eyes open, while in the first study the theta was trained in an eyes closed condition receiving only auditory feedback. The results of the home sleep logs showed an equal improvement in sleep of both feedback training modalities. The sleep laboratory findings indicated that participants with tension problems were most helped with the theta training, while the participants without tension problems reacted best on SMR feedback. In summary, EEG neurofeedback seems to have significant effects on sleep complaints. However, there are some limitations in these two studies that need to be considered. The first study only examined the difference between the neurofeedback groups and paid less attention to the clinical significance of certain sleep improvements. For example, only the SMR training resulted in a normal sleep latency, both subjective as well as objective (<30 min). Furthermore, no post-measurements were performed for the control group, only a follow-up after 9 months was done. In the replication study the sleep latency at baseline was <30 min in both groups, and even

<20 min in the theta group. Consequently, it was difficult to find significant changes since they already were in the good sleeper range. Future research should focus on strict inclusion criteria to ensure the presence of a disrupted sleeping pattern. Finally, a recent pilot study about sleep continuity in 15 primary insomnia patients has demonstrated that after 4 weeks sleep latency, wake after sleep onset, and total sleep time were significantly improved.[87]

In view of the cortical arousal theory, it may be of interest to examine the existence of cortical arousal, and its evolution after neurofeedback, both on daytime and nighttime functioning.

The development and widespread application of quantitative EEG (qEEG) techniques has led to the discovery of specific EEG profiles accompanying certain disorders. This, in turn, has resulted in the exploration of new applications of EEG neurofeedback training. Attention deficit hyperactivity disorder (ADHD), for example, appears to be characterized by a cortical slowing reflected in the higher ratio of slow-wave activity relative to fast EEG activity dominantly present in frontal and central regions, especially when cognitive processing is demanded. The consistent observation of heightened levels of theta power and the lack of beta EEG activity, suggest a central nervous system dysfunction probably reflected by a cortical hypoarousal.[88-91] Recent research has indicated that EEG neurofeedback resulted in significant improvements in attention, impulse control, speed of information processing and consistency of attention, as well as a decline in internalizing and externalizing psychopathology. These findings reflect significant reductions on both cognitive and behavioral symptoms in ADD/ADHD.[92,93] Another possible interesting application of neurofeedback training examined by Saxby and Peniston[94] is the treatment of alcoholics with depressive symptoms. They combined the alpha–theta EEG training with relaxation and biofeedback training, which resulted in significant reductions in self-assessed depression, as well as corresponding changes in Millon Clinical Multiaxial Inventory (MCMI) and Minnesota Multiphasic Personality Inventory (MMPI) scales. Only one of the 14 subjects reported a relapse after a 21-month follow-up period, which indicates an efficiency rate of 92%. Egner and Gruzelier [95] even demonstrated the effect of neurofeedback training on the musical performance of students from the Royal College of Music in London. They compared several neurofeedback protocols, as well as other techniques assumed to improve artistic performance. The findings showed that only the alpha–theta protocol resulted in a significant musical improvement. Finally, there has also been some interesting work done with brain computer interface (BCI), an EEG feedback method that allows 'locked-in' patients to communicate again with their environment. People who are completely paralyzed learn to regulate their EEG slow cortical potentials (SCP's) to drive an electronic spelling device, and thus formulate written messages.[96,97]

Possible limitations of neurofeedback therapy

A final important remark concerns the possibility of generalizing the effects as well as the time and cost investments. First of all, specific equipment is used during these sessions, which might interfere with generalization of the desired effects. However, neurofeedback can be considered as a form of cognitive behavior modification. Throughout the training, patients gradually will become more aware of the shifts in state during the sessions and during the day, as such resulting in the recognition of the desired mental state which accompanies a certain EEG pattern.[98] But more importantly, the fact that neurofeedback improves attention, impulse control, information processing and reduces internalizing and externalizing psychopathology in ADHD, suggests that the effects of this treatment modality does generalise to other aspects of behavior and cognition. Monastra et al.[99] showed that, in comparison to methylphenidate, the positive effects of neurofeedback remain present even when the therapy has ended.[99] Notwithstanding, more research on its long-term effects seems necessary to evaluate the generalisation of the outcome after treatment. Since neurofeedback is a learning procedure, it is obvious that many sessions are required to consolidate the desired effects. In general, 20–40 sessions are necessary for an optimum training outcome. This means of course an investment of time and money, which can be hindered by a lack of motivation and engagement. For this reason, the use of secondary reinforcement, especially with children, might be helpful in maintaining motivation.

Summary of neurofeedback and insomnia

In summary, studies of neurofeedback therapy in other patient populations show a possible new tool for treatment of disorders with a neurophysiological or—biological basis. Considering qEEG research and the few studies, although not recent, examining the impact of neurofeedback on insomnia, we

believe that this treatment modality might have great potential in the management of CNS arousal. The beneficial effects of both SMR and theta training illustrate that hyperarousal might be a future focus of treatment, since both rhythms play an important role in sleep and consequently cortical de-arousal. Sterman et al.[70] showed that the enhancement of SMR has an influence on the sleep-EEG and more specifically the appearance of sleep spindles. Furthermore, looking back at the neurological underpinnings of neurofeedback, the appearance of sleep spindles is related to the function of the thalamus, which in turn plays an important role in information processing. Theta power, on the other hand, is associated with drowsiness and relaxation, which in turn might have a positive effect on the cortical as well as the somatic arousal, the latter component reflected by high tension levels. These research findings support the hypothesis that neurofeedback might be a potential tool in the treatment of insomnia.

Conclusions

Insomnia is a common disorder in our society and seems to have a significant impact on both nighttime and daytime functioning. A disruption of the sleeping pattern, as well as the subjective report of fatigue, impairment of daytime functioning and a low quality of life is often reported. Several attempts have been made to create a model that would explain this disorder and could be used as a foundation for treatment. However, it appeared that no model can fully comprehend and clarify all aspects of insomnia. The introduction of cortical arousal or CNS arousal by Perlis et al.[26] has given rise to increasing research in the field of neurophysiology in order to identify possible neurobiological characteristics of insomnia. Growing evidence supports the assumption that insomnia is not limited to a sleeping complaint, but should be considered as a 24-h disorder. QEEG studies of the SOP have revealed an EEG profile opposite to that of normal sleepers associated with CNS hyperarousal.[39] An attempt was made to clarify and support these findings by means of neuroimaging techniques. Preliminary findings indeed suggest a neurobiological basis for hyperarousal, but should be interpreted with caution, since only two studies were performed using different techniques. Furthermore, the analysis of sleep microstructure, and more specifically the CAP parameters, has revealed a new variable to measure the stability and/or disruption of sleep. It appears to provide more detailed information and is more sensitive than conventional objective measures. Research showed that the best differential diagnosis of insomnia was made with the use of CAP variables.[59] These neurophysiological findings led to the search for other treatment modalities that might address the CNS/cortical arousal and sleep EEG instability. Neurofeedback, a self-regulation method based on learning theories, appears to be a promising application. By means of enhancement and/or suppression of brain waves of certain frequencies, a normalization of brain functioning is pursued. Literature shows that neurofeedback might have a 24-h influence, as well as altering arousal impairments of the CNS. Since recent research has suggested that a treatment modality with these characteristics might be of interest,[18,100] and preliminary studies with insomnia patients have revealed a possibly significant effect, future research in this area should be encouraged.

Practice points

1. Clinicians should keep in mind that insomnia might be a 24-h disorder, and should also pay sufficient attention to daytime functioning.[21,100]
2. Standard assessment and research methods should be developed to ensure adequate comparison of different insomnia studies.
3. Treatments for insomnia focussing on a reduction of arousal day and night should be considered.[100]

Research agenda

1. It could be of interest to examine the possible relation between somatic, cognitive and cortical arousal in insomnia.[39]
2. The hypothesis of cortical hyperarousal in insomnia should be further examined by means of qEEG and neuroimaging techniques.[49]
3. The cyclic alternating pattern appears to be a sensitive measure for insomnia. Further research to support this suggestion should be encouraged. Since CBT seems to have beneficial effects on insomnia, it might be of interest to examine its potential influence on CAP.

4. Some insomnia patients do not benefit from CBT that focuses on cognitive arousal. Research examining the possible relation between cortical arousal and therapeutic outcome after CBT might enlighten the relationship between cognitive and cortical arousal.
5. Since, neurofeedback may have an influence on both the wake and sleep EEG, it seems a good intervention for insomnia. Therefore, further research on its therapeutic effect in this medical condition is warranted.

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