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CLINICAL REVIEW

The hyperarousal model of insomnia: A review of the concept and its evidence

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SUMMARY

Primary insomnia is defined as difficulties in falling asleep, maintaining sleep or non-restorative sleep accompanied by significantly impaired daytime functioning in the absence of a specific physical, mental or substance-related cause. The current review provides substantial support for the concept that hyperarousal processes from the molecular to the higher system level play a key role in the pathophysiology of primary insomnia. Autonomous, neuroendocrine, neuroimmunological, electrophysiological and neuroimaging studies demonstrate increased levels of arousal in primary insomnia during both night and daytime. In the light of neurobiological theories of sleep–wake regulation, primary insomnia may be conceptualized as a final common pathway resulting from the interplay between a genetic vulnerability for an imbalance between arousing and sleep-inducing brain activity, psychosocial/medical stressors and perpetuating mechanisms including dysfunctional sleep-related behavior, learned sleep preventing associations and other cognitive factors like tendency to worry/ruminate.

Introduction

Insomnia as a diagnostic entity is defined as a complaint of prolonged sleep latency, difficulties in maintaining sleep, the experience of non-refreshing or poor sleep coupled with impairments of daytime functioning, including reduced alertness, fatigue, exhaustion, dysphoria and other symptoms. The complaints have to endure for at least 4 weeks to be diagnosed as insomnia. The Diagnostic and Statistical Manual of the American Psychiatric Association (DSM)[1] classifies insomnias into primary insomnia (PI), insomnia related to a medical or mental disease and insomnia related to the intake or abuse/dependency from substances. The International Classification of Sleep Disorders (ICSD)[2] goes beyond that approach and specifies 11 insomnia subtypes encompassing among others acute, psychophysiological, paradoxical, idiopathic and substance-induced insomnia.

Insomnia as a symptom is a highly prevalent health complaint afflicting up to 50% of the general population depending on criteria applied. Estimates for the prevalence of PI as a diagnostic entity in the general population range from 3 to 5%.[3] Research diagnostic criteria for insomnia[4] now provide operationalized and standardized criteria for the diagnosis of insomnia and its subtypes.

Polysomnographic research on insomnia revealed a remarkable discrepancy between the subjective experience of insomnia and polysomnographically rather undisrupted sleep in many patients with primary insomnia.[5,6] Thus, polysomnography (PSG), in contrast to other fields of clinical sleep medicine, has not become the via regia to the diagnosis of insomnia.[7] Insomnia diagnosis and assessment is based on subjective reports (sleep questionnaires) of sleep behavior and relies on sleep diaries filled out every evening and morning (for an overview of relevant instruments see[8,9]).

The effectiveness of cognitive-behavioral treatment for insomnia (CBT-I)[10–12] compared to the risks inherent with pharmacological insomnia treatment (e.g., benzodiazepines[13]) may have added to the conceptualization of PI as primarily a psychological disorder and negligence to study its biological aspects (compared to other sleep disorders or other disorders in the field of mental health).

The "hyperarousal" perspective of insomnia[14–16] has gained widespread attention as an integrative approach to the pathophysiology of insomnia (especially primary insomnia (PI) or psychophysiological

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Nomenclature

AASM	American Academy of Sleep Medicine
AIE	Attention–intention–effort model
APA	American Psychiatric association
BZ	Benzodiazepine
CAP	Cyclic alternating pattern
CNS	Central nervous system
CBT-I	Cognitive-behavioral therapy for insomnia
CREB	Cyclic AMP-response element binding protein
CRH	Corticotropin releasing hormone
DEX	Dexamethasone
DSM	Diagnostic and Statistical Manual of the American Psychiatric Association
ECG	Electrocardiogram
EEG	Electroencephalogram
ERP	Event-related potential
FFT	Fast Fourier Transformation
fMRI	functional Magnetic Resonance Imaging
GABA	Gamma-amino-butyric acid
GSC	Good sleeper control
GSR	Galvanic skin response
HPA	Hypothalamic–pituitary–adrenal axis
ICSD	International Classification of Sleep Disorders
Il	Interleukin
MRI	Magnetic Resonance Imaging
MSLT	Multiple sleep latency test
NREM	Non-REM sleep
PET	Positron emission tomography
PGO	Ponto-geniculo-occipital waves
PI	Primary insomnia
PSG	Polysomnography
REM	Rapid eye movement sleep
R&K	Rechtschaffen and Kales
SPECT	Single photon emission computed tomography
SWS	Slow wave sleep
TNF	Tumor necrosis factor
VLPO	Ventrolateral Preoptic Nucleus

insomnia), assuming an interplay between psychological and physiological factors in the etiology and perpetuation of chronic insomnia. Accordingly, acute episodes of insomnia are triggered by acute stressors ("threat", i.e., psychosocial, medical, drug factor). In many cases, with the cessation of the influence of the stressor, the sleep complaint resolves. Only a subpopulation of afflicted patients develops persistent, chronic insomnia which becomes independent of the initial stressors.[17]

The hyperarousal concept postulates that subjects who tend to focus cognitively on the insomnia and start to ruminate about their sleep complaint are prone to develop "learned sleep preventing associations" which explain the chronicity of the disorder. Maladaptive behaviors (i.e., prolongation of bedtime, daytime napping, increased alcohol consumption, etc.) are postulated to contribute additionally to the perpetuation of insomnia. The hyperarousal concept from early on encompassed physiological phenomena as it was demonstrated that chronic insomnia is accompanied by indices of increased autonomic activity.[14,18] The term "psychophysiological" insomnia as it was coined by Hauri[19] indicated that "psychophysiological insomnia… develops secondary to chronic, somatized tension and negative conditioning". Yet, 20 years later, when considering the description of psychophysiological insomnia in the ICSD-2,[2] not much knowledge seems to have been accumulated concerning the "physiological" (=somatized tension) aspect.

It is the aim of the present article to review the hyperarousal concept of primary insomnia and to discuss the underlying evidence with an emphasis on neurobiological studies. Furthermore we aim to integrate these findings with neuroscientific knowledge on sleep–wake regulation.

The hyperarousal concept of insomnia

Perlis and colleagues[16,20] provided a comprehensive review of the hyperarousal perspective including neurobiological variables which they termed "neurocognitive" theory of insomnia (modified version see Fig. 1).

The model is based on the behavioral perspective that insomnia occurs acutely in association with predisposing and precipitating factors (for example psychosocial stressors), and chronically in association with perpetuating factors[17] (for example extension of time in bed). The behavioral perspective is extended by explicitly allowing the possibility that conditioned arousal may act as a perpetuating factor. Arousal is expressed in terms of somatic, cognitive and cortical activation. Hence, the bed and the sleep environment and its circumstances become stimuli for arousal instead of "de-arousal". It is hypothesized that the cortical arousal (experienced subjectively as increased cognitive activity and measurable on an electroencephalographic level by increased fast frequencies of the sleep Electroencephalogram (EEG), (see section Electro- and neurophysiology of insomnia)) occurs as a result of classical conditioning and promotes abnormal levels of sensory and information processing, and of long-term memory formation. These phenomena are directly linked to sleep continuity disturbances and/or sleep state misperception (i.e., paradoxical insomnia). Specifically, enhanced sensory processing around sleep onset and during sleep is thought to render the insomniac individual especially vulnerable to perturbation by environmental (or other) stimuli, and these events may directly interfere with sleep initiation and/or maintenance. Enhanced information processing during sleep may distort the distinction between sleep and wakefulness and might thus account for the tendency of many insomniac patients to judge PSG measured sleep as wakefulness. Enhanced memory formation for the events around sleep onset and arousals during sleep may interfere with the subjective experience of sound and uninterrupted sleep. An increased ability to encode and retrieve information in insomnia would be expected to correlate with altered assessments about sleep latency, wakefulness after sleep onset and sleep duration.

The model assumes that the experience of chronic insomnia may have a decisive impact on the development of relevant psychopathology, i.e., depression, addiction and anxiety disorders. From a psychological point of view depressed mood as a consequence of chronic insomnia might be explained with the model of "learned helplessness". Not unsurprising, dependence on alcohol, hypnotic and sedating drugs is more common in patients with insomnia compared to subjects not afflicted with chronic sleep complaints. The relationship to anxiety disorders on a psychological level is less clear: yet, there is considerable anxiety about sleep, insomnia and its consequences in many afflicted patients which might lead to a generalization of increased levels of anxiety.

Espie and colleagues[21] provided a cognitive model for the development and maintenance of chronic insomnia which they called the AIE (attention–intention-effort) pathway. The focus of this model lies on cognitive mechanisms that accompany or underly the assumed hyperarousal in insomnia patients. By taking a perspective of sleep normalcy as its starting point the model

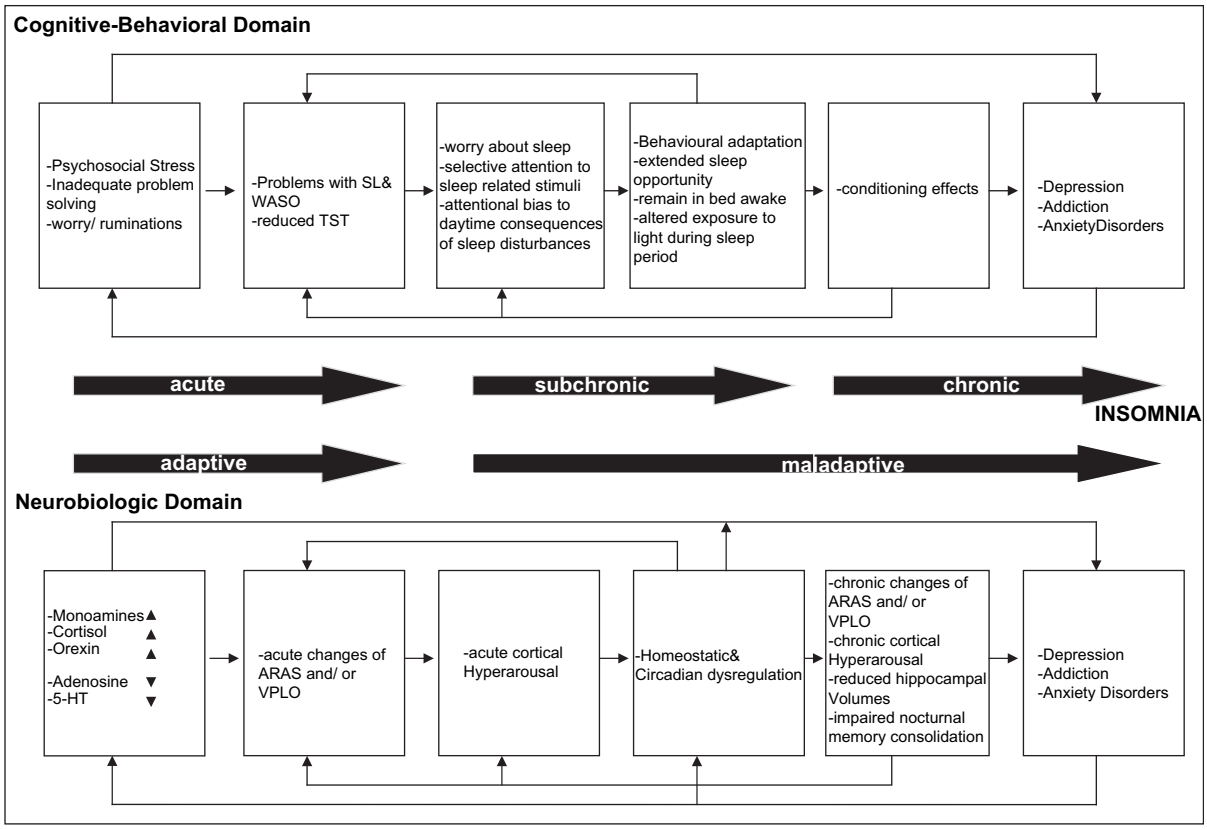

Fig. 1. Neurocognitive model of insomnia (modified according to Perlis et al., 16, 20; Pigeon and Perlis, 141). 5-HT: Serotonin; ARAS: ascending reticular activating system; SL: sleep latency; TST: total sleep time; VLPO: ventrolateral preoptic area of the hypothalamus; WASO: wake after sleep onset. Acute insomnia: 1–90 days; subchronic: 3–6 months; chronic >6 months. Note: the cognitive-behavioral and the neurobiologic domain are depicted in a parallel way – it is assumed (see text) that both domains are strongly interconnected and not independent of each other.

suggests attention on sleep as well as explicit intention and effort to fall asleep as crucial factors for the development and maintenance of insomnia.[22] The basic idea is that normal sleep is a largely automatic and involuntary process that first can be inhibited by selectively directing attention to it. Secondly, the automaticity is further compromised by an explicit intention to sleep and finally by an increased effort to fall asleep resulting in the development of maladaptive sleep-preventing behaviors.

The "neurobiologic domain" as depicted in Fig. 1 is the main focus of this review and will be outlined in detail in the sections devoted to the different areas of biological hyperarousal.

In order to critically review and update this model of chronic insomnia we will review empirical evidence from human studies (mostly comparing good sleepers to chronic insomniacs) including genetic, neurophysiological, neuroendocrine, neuroimmunological and neuroimaging variables. As all of these studies are cross-sectional in design, no conclusions about cause–effect relationships between psychological and physiological events can be drawn. Conceptually, insomnia may result from top-down processes, as proposed by Perlis and Espie and colleagues, emphasizing the etiological importance of dysfunctional cognitive processes resulting in physiological hyperarousal. Yet in extension, not necessarily in contradiction to this perspective, insomnia might – in a bottom-up approach – result (at least in part) from a genetically determined dysfunction in sleep–wake regulating neural circuitries originating from the brainstem leading to sleep disruptions and cognitive and emotional disturbances. It will also be discussed whether the described alterations can be seen as a direct expression of hyperarousal or should be viewed as a consequence of (albeit minor) chronic sleep loss. Insofar the important question arises whether hyperarousal leads to insomnia or vice versa insomnia provokes arousal or whether there is a bi-directional relationship. Data from studies on neuropsychological and psychopathological consequences of insomnia will complement the review as they bear relevance for the hyperarousal concept.

Empirical evidence related to insomnia and the hyperarousal perspective

(Molecular-)genetic studies

As in other areas of medicine the ultimate goal of this line of research is to delineate one or several genes whose presence/absence is highly predictive that a given subject will develop a certain disorder/disease. As sleep and sleep disorders are complex phenotypes, regulated by many genes, gene interactions, environment and gene–environment interactions, it is extremely unlikely that there is a clear-cut single gene relationship for insomnia.[23] It seems more likely that several genes and their polymorphism serve as vulnerability factors determining that predisposed individuals with a given physiological "make-up" will develop chronic insomnia under adverse circumstances, such as stressful live events. This putative interplay may be further elucidated by different approaches of genetic studies, i.e., family and twin studies, population- and family-based association studies of candidate genes or genome-wide scan studies in representative populations.

Bastien and Morin[24] investigated a group of 285 patients evaluated for insomnia at a sleep disorders clinic and found that 35%

had a positive family history for a sleep disturbance (which in 76% of cases was insomnia). Dauvilliers and colleagues[25] described that of 77 patients with primary insomnia, 72.7% reported familial insomnia compared to 24.1% in a non-insomnia control group in a French population. Similar results were obtained from a larger dataset in a Canadian population.[26] A study in mono- and dizygotic twins indicated significantly higher concordance rates for insomnia in the monozygotic twin pairs.[27] Drake and colleagues[28] showed that 37% of the variance in vulnerability to stress-related insomnia in siblings was accounted for by familial aggregation.

These few investigations support the idea of a genetically transmitted vulnerability for insomnia, though further replications in larger samples are needed to underpin this concept. At this point it needs to be stressed that none of the above cited studies demonstrated a 100% genetic dominance – beyond that family studies do not exclude that especially environmental factors play an important role. The genetic approach per se seems very promising, because a high heritability of EEG sleep patterns was reported recently.[29]

No studies have been conducted yet to identify genes of specific relevance for insomnia. First-line candidate genes may include adenosine and Gamma-amino-butyric acid (GABA) receptor polymorphisms. Retey et al.[30] reported that a genetic variant of adenosine deaminase in humans is specifically coupled with enhanced slow wave activity during sleep. In contrast, a distinct polymorphism of the adenosine A_2 receptor gene, which is associated with interindividual differences in anxiety reactions to caffeine, was found to be associated with an increased frequency of subjectively experienced sleep problems and less slow wave sleep as measured by polysomnography. Similar interesting results have been reported for a subunit gene of the $GABA_A$ receptor.[31]

As there is some evidence for altered sleep homeostasis (as manifested by decreased slow wave sleep either during baseline or after sleep deprivation/restriction) at least in a subgroup of patients with chronic insomnia,[32] exact phenotyping of insomniac patients according to ICSD-2 criteria[2] and by EEG sleep analyses including polysomnography and spectral analysis might prove a valuable strategy to discover relationships between insomnia subtypes and genes/polymorphisms involved in the regulation of sleep homeostasis.

So-called clock genes, named clock, Bmal, Per1, Per2 and Cry1 and Cry2 and their mutations have been shown to be involved in the regulation of circadian rhythms in animals, humans and in patients with circadian rhythm disorders.[33] As there is evidence for a contribution of circadian factors at least in a subgroup of insomniac patients,[34] it seems worthwhile to include these genes in genetic studies on insomnia.

Another interesting candidate for studying molecular mechanisms of insomnia might be CREB (cyclic AMP-response element binding protein) as it has been shown that by manipulating CREB through molecular genetic techniques in mice massive differences in wakefulness and Non-REM Sleep (NREM) time could be elicited,[35] suggesting that CREB is involved in sustained arousal.

Genetic research on insomnia may benefit largely from systematically orienting itself towards the current neurobiological knowledge about sleep–wake regulation (see section The neurobiology of sleep–wake regulation) and investigating genes that are implicated in the process of arousal/de-arousal. The strategy of genome-wide scans of well-defined samples of insomnia patients and good sleeper controls will require intensive phenotyping of insomniac samples on a clinical and PSG level. The high potential of this research strategy has already been demonstrated for the restless legs syndrome.[36] Furthermore, the development of valid animal models of insomniac behavior will be of invaluable help to determine the genetic basis and molecular mechanisms of the disorder. Based on the observation that transient insomnia is a ubiquitous human experience whereas chronic insomnia afflicts only a small subgroup of the total population, the assumption of genetic factors being involved to set "the wheel in motion" besides psychological and behavioral factors seems to be reasonable and worth looking into it.

Electro- and neurophysiology of insomnia

PSG research in insomniac patients was of limited value insofar as many studies revealed that PSG derived sleep variables indicated far less pronounced differences to good sleepers than expected from subjective reports of patients. Studies using the Multiple Sleep Latency Test (MSLT) in insomniac samples surprisingly showed that these subjects did not show signs of previous sleep loss (as should have been evidenced by reduced sleep latencies during daytime naps) but normal or increased sleep latencies during daytime, thus stimulating the hypothesis of 24-h hyperarousal in PI (see below). In consequence of the insufficient explanation of subjective complaints in primary insomnia by conventional PSG data, spectral analysis of EEG sleep and the registration of event-related potentials prior to and during sleep and the application of the CAP (cyclic alternating pattern) method became of high interest for the hyperarousal concept. These techniques allow more fine-grained and sophisticated analyses of EEG sleep than traditional epoch by epoch visual scoring according to Rechtschaffen and Kales (R & K) criteria.[37]

Classical sleep EEG (R&K) and MSLT

As of now there is a plethora of studies including polysomnographic data on patients with insomnia (registered and scored according to Rechtschaffen and Kales criteria[37]) especially PI, it would be beyond the scope of this report to review all of these investigations and discuss them. Instead, we will rely on several overviews on the topic.[38–40] According to these reviews, PSG derived sleep continuity in PI is compromised by prolonged sleep latency (SOL), increased wake time after sleep onset (WASO) and reduced sleep efficiency. Absolute differences are not large (ca. 30–60 min. with respect to total sleep time) but of statistical significance. One of the most consistent findings is that the PSG differences are of much lesser magnitude than subjectively estimated differences in sleep continuity between PI and good sleepers. There is also evidence that subtypes of primary insomnia (for example psychophysiological vs. paradoxical insomnia) are not homogeneous with respect to their PSG findings, with patients with paradoxical insomnia not differing at all from good sleeper controls in some studies. Further complicating the picture is the finding of marked night-to-night variability in some insomniacs.

With respect to sleep architecture, only a minority of investigations describe either SWS (slow wave sleep) or REM (rapid eye movement) sleep reductions in insomniac samples. REM latency, the classical variable from sleep research in depression,[41] was never found to be reduced in insomnia patients compared to good sleepers.

The Multiple Sleep Latency Test (MSLT) consists of 5 brief 20 min nap opportunities with EEG sleep monitoring. The latencies to stages 1, 2 and REM are determined and are thought to reflect daytime sleepiness or alertness. Earlier work[42–45] indicated that contrary to expectations derived from studies on the impact of sleep loss on MSLT sleep latencies, patients with insomnia did not show reduced but prolonged sleep latencies. Bonnet and Arand have thoroughly investigated this phenomenon[46–48] confirming increased sleep latencies during the day in spite of disturbed nocturnal sleep. The authors conclude that the results of the MSLT in insomniac patients reflect a combination of sleep tendency and a high level of arousal during daytime, thus arguing strongly for

a 24-h hyperarousal. It has also been speculated that the demand characteristics of the MSLT ("try to sleep") contribute to these surprising results in insomniacs for whom the conscious effort to attain sleep might constitute a provocation method for arousal.

Spectral analysis

This method is based on the insight that any actual signal can be decomposed into a series of harmonic waves.[49] It quantifies EEG signal amplitude (or its square: power) and separates slower and faster rhythms. Spectral analysis precisely assesses the amount of delta waves, which are "censored" by R&K criteria[37] through a threshold criterion. Beyond, spectral analysis encompasses other frequencies that are not exactly quantified by R&K criteria,[37] such as alpha activity or fast (beta/gamma) EEG components in both REM and NREM sleep. The observation of large slow wave amplitudes during deep NREM sleep was one of the basic findings for the development of R&K[37] sleep staging. Consequently, the relative amount of higher frequency (beta and gamma) EEG power was found to be increased in waking, stage 1 and REM sleep relative to stages 2–4 in early studies,[50] establishing a phenomenological link to the degree of cortical arousal. The use of relative spectral power in this way, however, is controversial: since EEG power is dominated by slow frequencies, separating actual high-frequency effects in one direction from actual slow-wave effects in the other direction can be problematic with relative power values. On the other hand, dividing by total power reduces intersubject variance caused by global variations in EEG amplitude.

In 12 patients with sleep onset insomnia compared to 12 good sleeper controls (GSC), Freedman[51] found absolute EEG beta power increased during wake, stage 1 and REM sleep but not during NREM stages 2–4. Merica et al.[52] investigated 20 chronic sleep maintenance insomnia patients and 19 GSC and described increased beta power throughout the night (maximally in REM sleep), in addition to reductions in slower EEG frequencies in both REM and NREM sleep. Perlis et al.[53] contrasted relative spectral power in three groups (sample size each: $n = 9$): Primary insomnia (PI), insomnia secondary to major depressive disorder (MDD) and GSC and found beta and gamma power specifically increased in PI in both REM and NREM sleep. Relative slow-wave power did not show significant differences in this study. Krystal et al.[54] examined both absolute and relative spectral power in 12 "subjective" and 18 "objective" patients with insomnia as well as 20 GSC subjects and found decreased relative delta and increased relative alpha, sigma and beta power during NREM sleep in the "subjective" insomniacs but not in the "objective" insomnia group. No differences were found in REM sleep. Buysse et al.,[55] examining absolute and relative NREM sleep EEG power in 48 PI patients and 25 GSC subjects, found no general difference between the groups but increased absolute delta and beta power specifically in the female PI patients.

Since cortical electrophysiological signals in the beta and especially gamma band have been hypothesized to be a main feature of coherent cortical processing of sensory information ("feature binding"[56,57] and possibly of all cognitive activity[58,59]), an EEG power increase in this frequency range can be interpreted as a sign of cortical hyperactivity or hyperarousal. As the cortical state is part of a complex feedback system, a classical "chicken and egg" dilemma arises: is it the ongoing attentive cortical activity leading to aroused and permeable subcortical systems or vice versa?

Benzodiazepine hypnotics cause changes of the NREM sleep EEG spectrum known as the "GABA-Benzodiazepine signature" (reduction of frequencies below 10 Hz and a clear increase of sigma band power[60,61]; frequencies below 1 Hz are rather increased by acute intake[62]). After a 4-week intake of different BZ (Benzodiazepine)-hypnotics, average NREM beta power tends to be increased, while a low-frequency reduction remains.[63] Therefore, both acute and continued use of benzodiazepine hypnotics result in increased relative amount of beta power within the whole spectrum, while continued use may even result in increased absolute beta power. Bastien et al.[64] examined absolute NREM spectral EEG power in 46 older adults ($\geq$55 yrs) in three groups: insomnia with and without chronic use of benzodiazepines as well as self-defined good sleepers. No spectral power differences were found between insomnia patients without benzodiazepine use and the GSC group but only between chronic benzodiazepine users and non-users. Spectral analysis studies in insomnia therefore require very strict criteria regarding previous and current use of BZ-hypnotics in order to exclude previous BZ use as a confounding factor.

Given the strong, partially hereditary variability in spectral sleep EEG composition,[29,65] large and well-controlled studies are needed to resolve the partially contradictory findings. In particular, it is currently unclear whether EEG spectral power differences in insomnia are more pronounced within NREM or REM sleep, since several studies were restricted to NREM sleep and the remaining studies reported contradictory results for REM sleep.

Event-related potentials (ERPs) in sleep

This technique involves the frequent presentation of stimuli and the computation of the average EEG around the stimulus times, thereby statistically eliminating ongoing EEG activity unrelated to the stimulation. During wakefulness, different ERP components (peaks) from about 70 ms to several 100 ms index different stages of cortical processing of the stimulus. The amplitude of early components increases with increasing stimulus intensity, while the amplitude of later components is linked to stimulus salience (see for example Picton et al.[66]).

In contrast, the exact functional meaning of sleep-ERP components is unclear, since most of the methods for corresponding studies during wakefulness are unavailable in sleep (i.e., tasks and response instructions). Components are sometimes assessed by analogy to the well-examined wake state counterparts. In comparison to sleep, stimulus processing in the wake state is very homogeneous, driven by the necessity to respond to stimuli quickly and reliably. The amplitude of ERPs during sleep onset or in a given R&K sleep stage can be used to assess the state of the subject's input channels or the arousal threshold.

For auditory stimuli, the waking EEG shows components labeled N100, P200, N200 and possibly P300, named after their polarity (negative or positive going, usually measured on Cz relative to linked ears) and their approximate latency (100, 200 or 300 ms). The P300 topography usually shows a medial and centroparietal maximum. Although responses often occur before the P300 reaches its peak, the link to conscious decisions has made the P300 a major research tool for cognitive neurophysiology. During NREM sleep, the P300 component largely disappears. Following a reduced N1 component, components called P220, N350, P440, N550 and P900 can be discerned, the positivities having a more anterior distribution and a different target/nontarget variation than the P300.[67] There is a substantial overlap between these components and the peaks of the K complex, a typical graphoelement of NREM sleep (evoked K complex[68]). It can be noted from the latencies that the effect of a stimulation takes longer to subside in sleep than in wakefulness, possibly because the components reflect the perturbation in the arousal system more than the actual cortical processing.[69]

In patients with insomnia, Devoto et al.[70] related the waking P300 amplitude in 11 PI patients and 11 GSC subjects to the PSG sleep quality of the previous night (contrasting a good and a bad night) and found that nights with impaired sleep led to higher P300 amplitudes. Devoto et al.[71] were able to replicate these results in another dataset of 7 PI patients and 7 GSC subjects: PI patients but

not GSC subjects showed increased P300 amplitudes after "bad" nights relative to good nights. The increase is difficult to interpret because, as noted above, the maximum P300 amplitude is usually obtained on centroparietal sites. If subjects are required to inhibit a prepotent motor response, a more frontal contribution can be observed (No-Go anteriorization[72]) which may be due either to frontal inhibitory process or a contribution of the motor execution in the "Go" trials.[73] Devoto et al.[70,71] interpreted the increased P300 amplitudes as a sign of hyperarousal following "bad" nights in the PI group, being a state marker of hyperarousal rather than a trait-marker.

Sforza and Haba-Rubio[74] examined the waking ERP amplitudes (evening and morning) of 15 PI patients, 45 patients with sleep-related breathing disorder and 13 healthy controls. No significant differences between the PI and GSC groups were found for the analyzed components (N100, P200 and P300). Furthermore, evening to morning differences in ERP components were not related to indices of sleep loss/sleep fragmentation in any of the studied groups.

In another interesting approach Wang et al.[75] related waking ERP baseline to peak measurements to performance in a distracter task and found that in poor sleepers larger amplitudes at frontal sites were correlated with depression and impulsivity scores.

Bastien et al.[76] studied waking ERP amplitudes (evening and morning) as well as ERP during sleep onset in 15 PI patients and 16 GSC subjects. During wakefulness, PI patients showed increased N100 amplitudes; during sleep onset, P220 was increased and N350 was reduced. The authors interpreted their data more in favor of "inhibition deficits" (to disengage from waking processes) of the insomniac sample than as direct evidence for hyperarousal.

During sleep, Yang and Lo[77] examined auditory ERPs of 15 PI patients and 15 GSC controls and found a larger N100 as well as a smaller P220 amplitude to rare tones and a smaller N350 to standard tones during the first 5 min of continuous stage 2. No differences across the whole night were found. The results were interpreted as an enhancement of attention and a reduction in the inhibitory process at sleep onset in insomnia.

To summarize, ERP studies in insomnia are scarce and most available studies focused on the wake state or sleep onset. ERPs during the whole night were assessed in a single study, with negative results. The existing studies, however, appear to show an increased sensitivity to auditory stimuli in PI patients during both wake and sleep onset. An increased N100 amplitude is also observed intraindividually when slow negative potentials such as the contingent negative variation (CNV) are modulated, reflecting increased expectation and lowered response threshold (i.e., increased cortical excitability[78–80]). Alternatively, the described results may also be viewed as a consequence of a compromised ability of insomniacs to inhibit wakefulness when trying to fall asleep.

CAP (cycling alternating pattern)

The cyclic alternating pattern (CAP[81]) is a phenomenon of the NREM sleep EEG and has some overlaps with R&K events (mostly arousals). CAP is based on the observation that certain EEG elements, distinct from background EEG, recur with a periodicity of 20–40 s.[82] CAP marks an arousal fluctuation, containing unstable or aroused parts of sleep and consolidated, well-maintained sleep. Correspondingly, a large CAP rate marks disturbed sleep with poor sleep quality.[83]

Terzano et al.[84] compared 47 PI patients and 25 GSC subjects and showed an increased number of arousals and an increased CAP rate, as well as increased nocturnal wake time, in the PI group. Despite the comparatively large number of patients examined in this study, the interpretation of the results is limited by the inclusion of various patient subgroups on active hypnotic medication. The same group of authors concluded[85] that CAP rate reflects a measure of the stability of sleep with increased CAP frequencies indicating a "destabilization" of sleep in insomnia.

Summarizing, the different quantitative electrophysiological methods can potentially highlight deviations in the states of different subsystems of the brain, while normal sleep staging considers the whole subject to be in one of few well-defined states in every single moment. In this way, these studies hold promise of explaining why the macro-analysis of EEG sleep according to Rechtschaffen and Kales criteria[37] often fail to fully reflect the subjective complaints of disrupted sleep in insomniac patients.

Most of the electrophysiological studies noted above are generally limited by small sample sizes as well as inhomogenity in selected patient subgroups and concomitant intake of medication. There is, however, a common trend towards signs of increased arousal or cortical excitability. As mentioned earlier, there is a "chicken and egg" dilemma in that it is unclear whether the cortical state determines subcortical activity or vice versa. This could turn out to be an academic question since daytime worrying adjusts subcortical gating, as for example occurring in subjects trying to sleep while expecting danger, increasing the alertness of the whole system. In contrast to external threat, patients with insomnia are under "internal" threat, i.e., they fear being unable to sleep and the associated consequences.

Autonomous, neuroendocrine and neuroimmunological measures of insomnia

Autonomous variables

Since the classical study of Monroe,[14] the validity of the hyperarousal concept in patients with insomnia has been tested by measuring autonomous variables, including electrocardiogram (ECG)-derived heart rate and heart rate variability, body temperature, whole-body metabolism and galvanic skin response (GSR).

There is some evidence that heart rate is elevated in patients with primary insomnia both in the presleep period and during nighttime sleep.[86–88] However, these results have been challenged by other studies that failed to find significant between-group differences.[14,15,18,89] Using indices of heart rate variability, nocturnal sympathetic activity was found to be enhanced in insomnia patients, while parasympathetic activity was reduced.[87] However, altered indices of heart rate variability have not been found during wakefulness in patients suffering from insomnia.[89,90]

Recently, Lack et al.[91] provided a review of the literature concerning insomnia and elevated body temperature as a marker of physiological hyperarousal. Considering the few studies that have been conducted under constant routine conditions.[89,92] the authors came to the conclusion that core body temperature seems to be elevated in elderly insomnia patients during the night but not during daytime.

Investigating whole-body metabolism by measuring body oxygen use, Bonnet and Arand[46] found an increased basal metabolic rate in patients with insomnia providing a possible measure for physiological hyperarousal.

Concerning galvanic skin response, results are inconsistent. Broman and Hetta[93] found higher electrodermal activity in a daytime study implying a higher arousal level in insomnia patients. However, during the night Monroe[14] found an increase in basal skin resistance in insomnia patients while Freedman and Sattler[15] found no significant between-group differences.

In summary, the majority of studies measuring autonomous variables in insomnia documented an increased arousal tone in this patient group. Unfortunately, most findings were not replicated

unequivocally. A major caveat for clear-cut conclusions are small sample sizes and the use of a wide variety of insomnia definitions. It is also unclear whether increased autonomic activity is causing insomnia or whether vice versa, insomnia and its sleep loss triggers increased autonomic activity.

Neuroendocrine variables

This line of research focuses on the hormone cortisol as an indicator of the activity of the HPA (hypothalamic–pituitary–adrenal) axis. Cortisol has been a target hormone in research on stress and on the biology of depression for more than 30 years.[94] It is widely acknowledged that in major depression, cortisol excretion is enhanced in about 60% of the population. Increased cortisol secretion can be determined by urinary measures, cortisol plasma or saliva assessments or with challenge tests (e.g., dexamethasone test, DEX-CRH test). There is also substantial literature on the relationships between cortisol and sleep–wake regulation in normal and depressed sleepers.[95,96] Experimental sleep loss stimulates the HPA-axis as evidenced by enhanced evening cortisol secretion after short-term total sleep deprivation or subchronic restriction of sleep time in healthy young volunteers.[97–99]

Compared to these areas of investigation, neuroendocrine research in insomnia is still in its infancy. Vgontzas et al.[100] found a positive correlation between the amount of nocturnal wake times and urinary cortisol excretion in a sample of young patients with insomnia. The same group[101] confirmed increased evening and early night cortisol secretion in another sample of insomniacs compared to healthy sleepers. Rodenbeck et al.[102] were able to replicate this finding in a sample of 7 middle-aged insomniacs. Unfortunately, there is also conflicting evidence: Riemann et al.[103] were unable to detect any difference in evening and nocturnal cortisol secretion between 10 patients with PI and good sleepers. In the same vein, Varkevisser et al.[89] using a 24 h constant routine protocol were unable to find significant elevations of cortisol in 13 insomniacs compared to good sleepers. By using salivary cortisol measurements at home, Backhaus et al.[104] came to somewhat mixed results: in their sample of 14 patients with PI morning cortisol upon awakening was significantly decreased and correlated negatively with prior waking times during the night. The authors speculatively interpreted their results of decreased morning cortisol in insomnia as evidence for increased nocturnal cortisol secretion.

Given the database above, it seems premature to conclude that cortisol excretion in PI is generally enhanced either during day- or nighttime. Pursuing this line of research seems of specific interest since it provides a link to the frequent observation that patients with insomnia are more prone to an elevated risk of lifetime depression (see section Psychopathology and insomnia), Future work on the stress/HPA-axis will have to encompass larger sample sizes, and include "real life" measurements at home by using salivary measures of the hormone (which are easier to perform than blood sampling throughout 24 h in the sleep laboratory). Additionally, inclusion of challenge tests (like the dexamethasone test or the dexamethasone-CRH test) is strongly suggested as these tests are easier to conduct than longitudinal serial cortisol sampling and because it was the introduction of these tests into clinical research that became the fundament for the cortisol-depression link. As there is already such a strong database on cortisol, sleep–wake regulation and a psychopathological condition which is linked tightly with insomnia, a thorough evaluation of cortisol excretion in PI is needed. Sophisticated designs will be necessary to disentangle whether it is the chronic (mostly minor) sleep loss of many insomniacs driving the cortisol abnormalities or whether a primarily hyperactive cortisol axis contributes to the development of insomnia.

Neuroimmunology

As with research on cortisol, parameters of the immune system have been a major target of sleep research for more than two decades.[105,106] In brief, changes in sleep are hallmarks of the acute phase response to infectious challenge, and on the other hand it is assumed that parameters of the immune system such as interleukins (IL) or tumor necrosis factor (TNF) are involved in the regulation of spontaneous sleep. Furthermore, fatigue and sleep disturbances are very common in cancer patients receiving therapy with cytokines.[107] Additionally, neuroendocrine and neuroimmunological systems are interrelated and both are influenced by sleep loss.[108] Experimental sleep loss seems to compromise innate immunity.[106]

Irwin et al.[109] demonstrated an association between insomnia and nocturnal sympathetic arousal and declines of nocturnal immunity (reduction of natural killer cell responses). Vgontzas et al.[110] found that the daytime secretion of Interleukin-6 (IL-6) is reduced by the duration and quality of previous nighttime sleep. The same group[111] demonstrated increased Il-6 levels in insomnia, though mainly during daytime, hypothesizing that this might explain the experience of increased daytime fatigue in insomniac patients. In a study by our group[112] we were able to show increased levels of Il-6 during nighttime sleep in primary insomniacs. In a community study it was found[113] that morning measured Il-6 levels correlated positively with the previous night's amount of wake time and negatively with sleep efficiency (both measured with PSG) in a sample of 70 healthy subjects.

Due to the small number of studies performed and due to methodological differences between studies, clear-cut conclusions on the interplay between chronic insomnia and the function of the immune system cannot be drawn. It is also unclear if the findings mentioned above relate directly to hyperarousal (increased sympathetic activity leads to increased IL-6 production from adipocytes) or represent epiphenomena of chronic sleep loss experienced by insomniacs. It is most likely that the interaction between immunological parameters and sleep is bi-directional. This avenue merits further pursuit as it has been shown that increased levels of Il-6 signals are associated with an increased risk for inflammatory and cardiovascular disease.[114]

Summarizing, data from this research avenue covering autonomous, neuroendocrine and neuroimunological variables in primary insomnia are compatible (though not unequivocal) with the hyperarousal concept. Again, as with the electro- and neurophysiological findings described above, the direction of cause–effect relationships between these alterations, the insomnia disorder and hyperarousal, have yet to be determined. It has also been speculated that the sleep loss due to insomnia may "drive" the neuroendocrine and neuroimmunological alterations, as it has been shown that short-term experimental sleep loss/sleep restriction may have sequelae similar to those described in chronic insomnia.[99]

In order to clarify this important question, longitudinal studies in insomniac patients seem necessary to determine the extent of autonomous, neuroendocrine and -immunological abnormalities during early stages, chronic course and successful treatment of insomnia.

Neuroimaging studies in insomnia

In contrast to neuroendocrine or neurophysiological studies allowing only indirect conclusions about the function of the human brain, neuroimaging methods such as single photon emission computed tomography (SPECT), positron emission tomography (PET) and magnetic resonance imaging (MRI) allow a more direct approach to brain structure and function. Neuroimaging methods

are now widely used in human basic sleep research and have been utilized with varying degrees of success in studying different types of disorders in the field of sleep medicine.[115]

In a SPECT study[116] imaging was conducted around the sleep onset interval in patients with primary insomnia and good sleeper subjects ($n = 5$). Contrary to expectation, patients with insomnia exhibited a consistent pattern of hypoperfusion across 8 preselected regions of interest, with the most marked effect being observed in the basal ganglia. The frontal, medial, occipital and parietal cortices also showed significant decreases in blood flow compared to good sleepers. After successful behavioral therapy abnormal values in insomniacs returned to baseline.[117]

A PET study[118] acquired data from 7 patients with chronic insomnia and 20 good sleeper controls from an interval during wakefulness and during consolidated NREM sleep. PI patients exhibited increased global glucose metabolism during wakefulness and Non-REM sleep. Patients with insomnia exhibited smaller declines in relative glucose metabolism from wakefulness to NREM sleep in wake promoting regions including the ascending reticular activating system, the hypothalamus and thalamus. Similar effects were observed in areas associated with cognition and emotion including the amygdala, hippocampus, insular cortex, and the anterior cingulate and prefrontal cortices. Reduced relative metabolism in the prefrontal cortex was found in insomniacs while awake. Thus, this study gave, for the first time, direct evidence for the hypothesis of central nervous hyperarousal in insomnia. In an extension of this work, Nofzinger and colleagues[119] by using PET again, described a correlation between increased brain metabolism in the pontine tegmentum, thalamocortical networks in a frontal, anterior temporal and anterior cingulate distribution and waking time after sleep onset (WASO) in a sample of 15 patients with primary insomnia.

The apparent contradictions between the SPECT and PET studies as cited above may be related to a variety of reasons. First of all, the PET studies allowed a 20 min "window" of measured brain activity versus 2 min in the SPECT studies. It is hitherto unknown whether the assumed hyperarousal is a dynamic process with periods of instability, switching from normal or reduced to increased brain metabolism or whether we have to deal with a stable process throughout the entire night. Given the cyclic nature of the sleep process itself with well-known oscillations between slow wave and REM sleep and other dynamic changes with even shorter period lengths during sleep, it seems reasonable to assume that the hypothetical hyperarousal also fluctuates, which might explain that neuroimaging methods with different sampling times may produce divergent results.

Our own work,[120] using manual morphometry of structural magnetic resonance images (performed during daytime wakefulness), showed that out of several regions of interest only one significant difference between 8 chronic insomniacs and 8 healthy control sleepers was found, i.e., a bilateral reduction of hippocampal volumes. This finding is in line with animal studies on the effects of sleep loss and sleep deprivation on functional and structural plasticity in the hippocampus[121] and corresponds well to empirical data on cognitive deficits and impaired nocturnal memory consolidation in insomnia (see below). It remains to be determined whether these alterations of hippocampal structures are directly related to the insomnia (i.e., a consequence of chronic sleep loss), the associated increased cortisol excretion, or predate the development of insomnia. Interestingly, a combined neuroimmunological/neuroimaging study in a large community sample of healthy subjects described an inverse relationship between interleukin-6 levels and hippocampal grey matter volume,[122] thus also linking the aforementioned finding of increased nocturnal Il-6 in primary insomnia[112] with structural brain alterations.

The first fMRI (functional magnetic resonance imaging) study in 21 patients with primary insomnia used a category and a letter fluency task as stimulation paradigms during the wake state in the MRI scanner.[123] This study revealed a hypoactivation of the medial and inferior prefrontal cortical areas in primary insomnia (in the absence of behavioral differences) compared to good sleepers. Rescanning after successful cognitive-behavioral therapy revealed a normalization of these patterns of activation in the patients with insomnia. The authors interpreted their data as evidence for a differential recruitment of brain regions for successful task completion in those insomniac patients considered as "high achievers" on a behavioral level (as evidenced by improved performance on rather simple tasks but decreased performance on more complex tasks relative to controls).

Using Proton Magnetic Resonance Spectroscopy to determine brain GABA (gamma-amino-butyric-acid) levels in vivo in a sample of 16 patients with Primary Insomnia, Winkelman and colleagues[124] demonstrated a global reduction of GABA in the brains of insomniac patients compared to good sleepers. Given the fact that GABA is the most prevalent inhibitory neurotransmitter in the Central Nervous System (CNS),[125] these data further support the assumption that in primary insomnia the central nervous balance between inhibition and excitation might be compromised.

Given the heterogeneity of neuroimaging methods applied and the small sample sizes in the cited studies, it is not surprising that up to now no clear-cut picture arises. Nevertheless, the few studies referred to above have taught us that chronic insomnia is associated with directly measurable alterations of brain function pointing to CNS hyperarousal and potentially even altered brain structure. The findings by Winkelmann et al.[124] of reduced GABA levels in the brains of untreated insomniacs for the first time give direct evidence for the widespread clinical practice to treat insomnia with benzodiazepines. Future fRMI studies will allow to combining studies on memory function, neuropsychology and emotions in insomnia with a brain research approach, thus opening the perspective not only to describe the phenotype of this disorder but also to relate the phenotype to brain (dys-)function. Furthermore, studies with SPECT or PET using specific ligands should be able to test whether neurotransmitters/neuropeptides related to sleep homeostasis, such as adenosine or orexin, are altered in insomniacs during baseline conditions or experimentally modulated sleep–wake manipulations including sleep deprivation/restriction paradigms. Another important avenue will be the longitudinal study of brain anatomy and function with these methods before, during and after successful and unsuccessful therapies of the insomnia.

Daytime performance and nocturnal memory consolidation in insomnia

The study of daytime performance in patients with insomnia has been driven by the assumption that short-term or chronic sleep loss has a negative impact on daytime functioning. This assumption is supported by the observation that many patients suffering from chronic insomnia subjectively report deficits in various neuropsychological domains, including alertness and memory functioning. However, neuropsychological studies investigating daytime performances often failed to detect robust impairments. This has generally been explained by the opposing effects of sleep deficits and hyperarousal that both might influence daytime performance in insomnia patients. Additionally, compensatory effort might play a crucial role in the experimental situation. An alternative explanation might be that the neuropsychological tests mainly used were just not sensitive enough to detect differences between patients with insomnia and good sleeper controls.

Some studies described no impairments at all in objective measures of cognitive performance in insomnia patients with a discrepancy between subjective reports of deficits and objective neuropsychological tests.[126] Accordingly, two review articles on this topic[127,128] concluded that there are only minor deficits in this population with significant group differences to controls in only 20–25% of all comparisons in the literature. However, investigating neuropsychological performance with challenging and naturalistic tests in large sample sizes might reveal stable deficits in the insomnia patients population.[129]

Given the ambiguous results, it needs to be emphasized that further research on this issue is needed to determine whether cognitive and memory function during daytime is impaired in primary insomnia. The incorporation of everyday and longer lasting challenges (as for example in the study of Altena et al.,[123] see section Neuroimaging studies in insomnia) into the experimental paradigms seems necessary to draw a realistic picture of insomniacs' cognitive status. It also needs to be determined to what extent differences between insomniacs and good sleepers are due to previous sleep loss or if and what other mechanisms are involved.

A novel line of research, based on the well-founded concept of sleep's function for brain plasticity and memory consolidation,[130] investigated overnight, sleep-related memory consolidation (both declarative and procedural) in patients with primary insomnia and good sleeper controls. Two studies have been performed to date in primary insomnia and demonstrated impairments in procedural[131] and declarative[132] memory consolidation in this patient group compared to good sleepers.

Conceptually, sleep-related deficits in memory consolidation as a consequence of hyperarousal might result from different, not necessarily exclusive pathophysiological processes. First, ongoing hyperarousal during sleep might interfere with uniquely sleep-dependent brain activity implicated in the strengthening of labile memory traces acquired during preceding daytime wakefulness. Thus, animal[133] and human studies[134] indicate that newly acquired memories are replayed and further processed during sleep, presumably contributing to brain plasticity underlying long-term memory formation.[135] Other studies demonstrate that sleep-specific brain activity patterns, such as sleep spindles[136] or ponto-geniculo-occipital (PGO) waves related to rapid eye movements,[137] foster the transition from unstable into sustainable memories. The extent of sleep disruptions and hyperarousal present in at least subtypes of insomnia (i.e., psychophysiological insomnia) should predict some deficiencies in overnight memory consolidation. Second, given the link between chronic alterations of functional neural plasticity and structural alterations, chronic sleep disruptions due to hyperarousal might lead to persistent alterations in brain circuits critical for memory functioning. In line with this concept bilaterally reduced volumes in the hippocampus, a highly plastic brain structure, were described in primary insomna.[120] Third, ongoing hyperarousal during sleep might disrupt basic mechanisms of brain plasticity and synaptic homeostasis. The synaptic homeostasis hypothesis of sleep[138,139] proposes that synapses strengthened during daytime wakefulness undergo a process of generalized downscaling during sleep, specifically during EEG slow wave activity (SWA), refining the information/noise ratio in neural networks and restoring the brain's ability to acquire new information under conditions of limited energy and space. The synaptic homeostasis hypothesis includes that functional alterations might lead to learning deficits during wakefulness and possibly also during sleep under conditions of hyperarousal during sleep, such as in primary insomnia. Combined behavioral, electrophysiological and functional and structural brain imaging studies are needed to further elucidate the interplay between sleep and memory formation in insomnia, two integral parts of health and functioning.

Consequences of primary insomnia for psychopathology

The most consistent interrelationship between insomnia and psychopathology has been demonstrated for depressive disorders.[140] It is well-known that almost all patients with depression display disturbances of sleep continuity including an increased latency to fall asleep, increased frequency of nocturnal awakenings or early morning awakening. Beyond this, depressed patients show more specific alterations of sleep like a decrease of slow wave sleep, a shortening of REM latency (interval between sleep onset and the occurrence of the first REM period) and an increase of REM density.[41] Whereas traditional psychiatric thinking assumed that insomnia almost exclusively reflects an underlying depressive disorder, in the meantime a change of concept has occurred postulating that insomnia in its own right might represent an independent risk factor for the development of depression.[141] This perspective is reflected by the proceedings of the NIH State of the Science Conference on insomnia[142] that strongly argues for giving up the concept of secondary insomnia in favor of "comorbid" insomnia, thus giving more weight to insomnia as an independent disorder. Two recent studies targeted insomniac symptoms in primarily depressed patients (who received standard antidepressant treatment with medication) with either additional hypnotic pharmacotherapy or specific cognitive-behavioral treatment for insomnia.[143,144] Both studies found that additional treatment of insomnia accelerated the improvement of the depressive disorder. These preliminary findings underline the importance of specifically treating insomniac symptoms in the context of psychiatric disorders. On the other hand, treatment of primary insomnia with sedating antidepressants[145] with good success has become a widespread practice.

Given the high public health relevance, more dedicated efforts seem adequate to disentangle the role of insomnia for psychopathology. Primary Insomnia, as a "pure" form of insomnia without medical or mental comorbidity seems to constitute the ideal model to clarify this role. It needs to be noted that Primary Insomniacs are at an increased statistical risk to develop relevant lifetime psychopathology (compared to good sleepers), however, probably the majority of these subjects will not develop signs of clinically relevant psychophathology. The question is why there is an increased risk and who out of the population of subjects with Primary Insomnia will develop signs of psychopathology. As already mentioned in the introduction the concept of "learned helplessness" as a psychological model can offer some explanation for those suffering chronically and experiencing no relief from standard therapies. Hypercortisolism, present in both depressive disorder (see section Neuroendocrine variables) and at least in some Primary Insomniacs, could provide a biological link between both conditions.

The neurobiology of sleep–wake regulation: consequences for the understanding of insomnia

Based on the early work of von Economou[146] and Moruzzi and colleagues[147] it is widely acknowledged that the ascending reticular activating systems (ARAS), originating in the brainstem, plays a major role in the regulation of sleep–wake states and is the major source of cortical arousal. Saper and colleagues[148,149] have elegantly summarized up to date knowledge about the neurobiology and neurochemistry of sleep–wake regulation. In short, according to their model (see Fig. 2), wakefulness depends on a network of cell groups in the hypothalamus (encompassing orexinergic neurons) activating the thalamus and the cerebral cortex. The major input to the hypothalamic neurons stems from cholinergic cells in the upper pons and other areas of the brainstem. Another activating input to

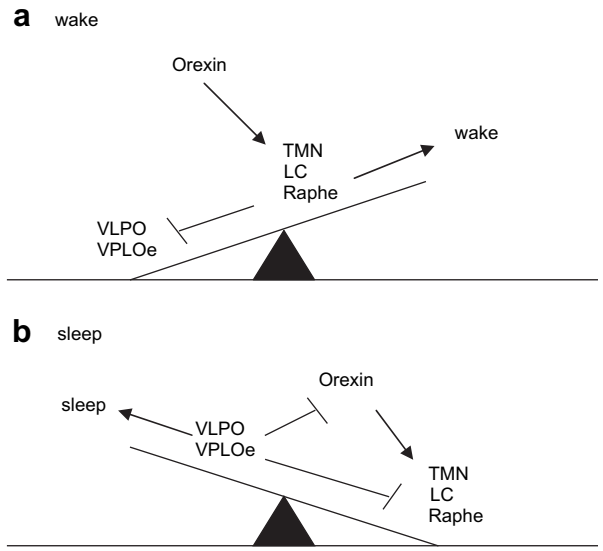

Fig. 2. Flip-flop switch model of sleep–wake regulation (modified from Saper et al., 2005). Neurons of the ventrolateral preoptic nucleus (VLPO) are active in sleep, and loss of VLPO neurons produces sleep fragmentation and insomnia. The VLPO contains 2 different types of neurons, VLPO that projects most heavily to the tuberomammillary nucleus (TMN), whereas VLPOe projects more heavily to the locus coeruleus (LC) and the dorsal and median raphe nuclei. The interaction between the VLPOe and components of the arousal systems is mutually inhibitory, and for instance these pathways function analogously to a flip-flop switch. The lateral hypothalamic (LH) orexin neurons likely play a stabilizing role of the switch.

the cortex, facilitating the processing of inputs from the thalamus, arises from neurons in monoaminergic cell groups, among others in the dorsal and median raphe nuclei and the locus coeruleus, containing histamine, dopamine and noradrenaline.

A "key switch" in the hypothalamus has the capacity to shut off this arousal system during sleep. Other hypothalamic neurons serve to stabilize the switch and their absence (loss of orexin neurons) results in an inappropriate switching of behavioral states, as it happens in narcolepsy with sudden sleep attacks, cataplexy and increased daytime sleepiness. It may be speculated that a dysfunctional "key switch" is involved in the pathogenesis of primary insomnia. This might be evidenced by an imbalance between sleep-promoting areas in the brain (i.e., the VLPO: ventrolateral preoptic nucleus; neurotransmitter: GABA) and arousal-promoting neurons (among others orexin neurons in the lateral hypothalamus) with a relative overactivity of the orexin system or a hypofunction of the VLPO.

Cano et al.[150] introduced a stress-induced insomnia model in rats. With a sophisticated design and experimental procedures they were able to show that rats which were subjected to the insomnia model (cage exchange) revealed a pattern of Fos expression (the expression of Fos is an indirect marker of neuronal activity because Fos is often expressed when neurons fire action potentials) demonstrating simultaneous activation of sleep-promoting and arousal-related brain regions. The authors hypothesize that during insomnia the VLPO is fully activated as a result of homeostatic and circadian pressure but cannot turn off the arousal system which at the same time is intensely excited by the limbic system. This leads to the unique situation where sleep circuitry shows Fos activation like in the sleeping rat but the activation of Fos in the cortex and arousal system resembles the fully awake state. These data in rats bear similarities to the phenomenology of human insomnia with the simultaneous subjective experience of daytime fatigue/exhaustion (probably due to insufficient sleep) and the inability to "de-arouse" when intending to sleep and the phenomenon of sleep state misperception.

Present neurobiological knowledge about sleep–wake regulation derived from animals studies in vivo and in vitro offers explanations for the hitherto mainly descriptive hyperarousal concept of insomnia. It needs to be conceded that animal studies cannot simulate the subjective experience of insomnia as it is accessible through the introspective self-reports of insomniac patients, but this should not avert the synthesis of insomnia concepts with basic neuroscience. This may foster the development of new pharmacological strategies to combat insomnia as has already been demonstrated by the development of orexin-antagonists.[151] Beyond, animal models of insomnia are also well suited to test the impact of behavioral manipulations.

Synthesis

Till recently, insomnia, especially primary insomnia, was mainly conceptualized as a psychological disorder caused by psychosocial stress and maintained by maladaptive behaviors and conditioned arousal leading to the subjective experience of disturbed sleep which could, however, not be corroborated by objective measures of sleep like polysomnography. It was the aim of this review to demonstrate that by basing our theoretical reasoning on the concept of hyperarousal and linking it with the accumulated empirical evidence on several levels of neurobiological research, insomnia can be conceptualized as a **psychobiological disorder** which is linked not only with alterations on a psychological level, but which is associated with measurable deviations of neuroendocrine and neuroimmunological variables, as well as electro- and neurophysiological, structural and functional alterations of the brain. A psychobiological perspective seems more adequate than a pure psychological concept alone. This conceptualization does not devalue the psychological models of insomnia which have proven extremely fruitful, especially with respect to developing cognitive-behavioral treatment concepts. We also do not argue for a dominance of biology over psychological processes. Both levels are highly interdependent and interrelated.

Given the ubiquitous nature of transient insomnia, it seems reasonable to assume that only those individuals with a certain genetic vulnerability for sustained hyperarousal are prone to develop chronic insomnia. It is yet unknown which genes are involved in this susceptibility, but research approaches like for example genome-wide scans might help to solve this riddle. We are still very far from understanding how this putative genetic vulnerability triggers and maintains the measurable hyperarousal on biological and psychological levels. Animal models of insomnia seem the decisive tool to shed light on these interrelationships. Stressors like critical life events, i.e., medical or psychosocial burden, may "set the wheel in motion", causing hyperarousal with sleep disruption and ensuing daytime impairments and sleep-related anxieties. Chronic sleep loss which occurs at least on a minor level in most insomniacs may in turn counteract the hyperarousal and lead to the experience of daytime tiredness/sleepiness coupled with interspersed good nights due to increased sleep drive as expression of the sleep homeostat. The "paradox" of chronic insomnia, i.e., the pronounced subjective experience of nocturnal sleep loss and daytime fatigue and impairments in performance in contrast to the only minor documented PSG sleep abnormalities and mild neuropsychological deficits, may be thus explained by the simultaneous activation of the sleep homeostat and arousal systems reflecting a dissociation between these two processes.

It is widely accepted that maladaptive behaviors like extension of time in bed, increased alcohol consumption etc. contribute to perpetuate the insomnia. However, it is also known that chronic insomnia may occur without these behaviors, and vice versa,

execution of these maladaptive behaviors per se does not necessarily lead to insomnia. This also applies to cognitive hyperactivity: many chronic insomniacs indeed display cognitive hyperactivity or anxiety about sleep, but not all.

Large-scale longitudinal studies are needed encompassing behavioral, psychological and neurobiological variables during the natural course of the disorder and during different types of treatment. This type of study might also help to understand the intimate connection of insomnia to depression: why is it that patients with insomnia do have a 2–4-fold incresed risk to develop depression? Is it the experience of learned helplessness with respect to the chronic nature of insomnia? Or is insomnia-related increased cortisol excretion involved as an important pathway? With this approach it can also be clarified whether biological abnormalities and the assumed underlying hyperarousal have state- or trait- or even vulnerability-marker characteristics.

With the availability of modern state of the art combined psycho-neurobiological research methods such an approach is timely and needed in order to improve our armamentarium of insomnia treatments.

Practice points

- Chronic primary insomnia is a disorder of 24-h hyperarousal as evidenced by data from several types of research
- Chronic sleep loss due to the insomnia may mask the hyperarousal and explain daytime fatigue and occasionally good nights
- Insomnia diagnosis should be based on a longitudinal approach
- The experience of chronic insomnia is not a misperception on the patients' side but may be the result of a dissociation between arousal and sleep-inducing brain systems

Research agenda

- A genetic approach using different types of investigation should be applied to PI
- Animal models for insomnia need to be pursued
- Chronic insomnia needs to be studied multi-dimensionally with different types of methods (autonomous, neuroendocrine and -immunological, electrophysiological, neuropsychological and neuroimaging)
- Longitudinal therapy studies with long-term follow-ups should incorporate different types of neurobiological measures

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COMMENTARY

Hyperarousal and insomnia

The reader of this issue is presented with a conundrum in understanding the role of hyperarousal in insomnia. Riemann et al.[1] discuss the development of hyperarousal in insomnia from a psychological and behavioral view while Bonnet and Arand[2] present a more physiologic basis for hyperarousal and insomnia. Readers may 'agree' more or less with either view, but, in the final analysis, many will find that similarities in the two approaches outweigh differences.

Riemann et al. correctly emphasize that behavior such as irregular sleep patterns and response to stress do play a role in the production of insomnia in individual cases. Certainly there are personality types that lend themselves to stress and arousal just as there are personality types that recognize the disruptive role of stress and schedule irregularity and live more carefully controlled lives that may also help to avoid insomnia despite underlying predisposition. However, as seen in the evolution of treatments for depression, behavioral approaches such as psychotherapy often give way to pharmaceutical approaches as understanding of the brain advances.

Of course, we are a combination of our behavioral milieu and our genetic predispositions. The high heritability of insomnia suggests a significant neural substrate for the development of insomnia that has already moved to an examination of brain sites and receptor systems. Both of the reviews end with exciting findings that presage the development of an animal model complete with neurophysiology and lesion studies that show how the animal situational insomnia can be blocked.[3] Such findings almost certainly set the stage for the development of a true neurobiology of insomnia that should provide a wealth of treatment suggestions and targets.

However, even if we had a complete knowledge of the neurobiology of insomnia, that does not mean that behavioral therapies will have no use. Just as behavioral control of diet and weight remain significant therapies for diabetes, behavioral treatment will certainly continue to play a prominent role in the prevention and treatment of insomnia. Of more importance, a complete knowledge of the interaction of sleep and arousal systems in the brain in itself will not demonstrate the risks of chronic insomnia and the risk/benefit ratio of chronic treatment with current or future medications.

Both reviews have carefully stressed the importance of many-year placebo-controlled insomnia treatment studies and research to determine whether the findings of insomnia as a risk factor in the development of depression[4] and hypertension[5] can be replicated in developmental studies and controlled by treatment without equally significant side effects. Many other important studies, like the relationship of chronic insomnia to the development of abnormal glucose control, remain to be done. Regardless, the development of new means of measuring brain function will actually improve our ability to differentiate behavioral versus neural components of insomnia and result in more targeted treatment strategies.

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