The neurobiology, investigation, and treatment of chronic insomnia

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Chronic insomnia is defined by difficulties in falling asleep, maintaining sleep, and early morning awakening, and is coupled with daytime consequences such as fatigue, attention deficits, and mood instability. These symptoms persist over a period of at least 3 months (Diagnostic and Statistical Manual 5 criteria). Chronic insomnia can be a symptom of many medical, neurological, and mental disorders. As a disorder, it incurs substantial health-care and occupational costs, and poses substantial risks for the development of cardiovascular and mental disorders, including cognitive deficits. Family and twin studies confirm that chronic insomnia can have a genetic component (heritability coefficients between 42% and 57%), whereas the investigation of autonomous and central nervous system parameters has identified hyperarousal as a final common pathway of the pathophysiology, implicating an imbalance of sleep–wake regulation consisting of either overactivity of the arousal systems, hypoactivity of the sleep-inducing systems, or both. Insomnia treatments include benzodiazepines, benzodiazepine-receptor agonists, and cognitive behavioural therapy. Treatments currently under investigation include transcranial magnetic or electrical brain stimulation, and novel methods to deliver psychological interventions.

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For the **British sleep survey** see http://www.sleepio.com/-2012report/

Introduction

In 2002, about 6% of the adult population in high-income countries had chronic insomnia.[1] If acute insomnia is considered, the diagnostic prevalence rises to almost 50% of the population. Thus, as a transient phenomenon, insomnia is commonplace and frequently remits spontaneously. In its chronic form, insomnia is associated with several negative health outcomes and a severely reduced quality of life.[2] In a 2009 longitudinal study,[3] 181 out of 244 individuals who fulfilled the DSM-IV diagnostic criteria for at least 4 weeks, still had insomnia 1 year later. Gender has a strong effect on the prevalence of insomnia, with women having insomnia more frequently than men at a ratio of 1·4:1.[1] This difference becomes even more pronounced after the age of 45 years, reaching a ratio of 1·7:1. Epidemiological data from a British sleep survey indicate that the inability to relax or unwind (a racing mind) is reported as the main reason for inability to sleep.

Prospective longitudinal studies have shown that individuals with insomnia show a heightened risk for developing acute myocardial infarction (relative risk 1·5; 95% CI 1·2–1·8).[4] An important mediator for this association might be the short sleep duration, which has been linked to cardiovascular disease both when assessed subjectively[5] or polysomnographically.[6] Insomnia also arises frequently in the context of neurological disorders. Mayer and colleagues report that insomnia as a symptom ranges in prevalence from 25% to 60% in patients with multiple sclerosis, Parkinson's disease, Alzheimer's disease, stroke, traumatic brain injury, or epilepsy.[7] Moreover, insomnia is involved in the development of cognitive impairment,[8] and a cross-sectional correlation between poor sleep quality and cortical atrophy has been shown in community dwelling elderly adults.[9]

The epidemiological literature describing the association between insomnia and mental disorders, especially depression, shows a particularly strong correlation. One meta-analysis[10] showed that insomnia independently confers a two times increased risk of development of depression in subsequent years. In other meta-analyses, insomnia also specifically conferred a two times increased risk for suicidal ideation and behaviour, although this risk was not moderated by depression.[11,12] Insomnia is increasingly regarded as an independent risk factor for work disability, sick leave, and reduced work performance.[13] These data are complemented by economically driven analyses concluding that insomnia is associated with high direct and indirect costs for the health-care system and society.[14]

In this Review, we aim to summarise the basic research on sleep–wake regulatory mechanisms that are of relevance for the understanding of chronic insomnia. These findings will be contextualised within evidence from clinical studies. This approach is expected to help provide a conceptualisation of insomnia as a disorder of the brain with long-lasting negative consequences for somatic and mental health. Our introductory overview regarding the epidemiology, diagnosis, and public health effects underscores the necessity to develop a comprehensive psycho-neurobiological understanding of insomnia. This Review will focus only on chronic insomnia with duration of at least 3 months, and not on acute or transient insomnia.[15]

Diagnostic classification of insomnia

With respect to diagnostic classifications, an important change in the way insomnia is diagnosed was recently defined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders[16] and the third edition of the International Classification of Sleep Disorders.[17] Instead of classification of insomnia into primary or secondary forms, this distinction was removed in favour of an umbrella category for insomnia disorder which could be used in cases when insomnia is comorbid with medical or psychiatric conditions. This

change reflects understanding that although insomnia frequently accompanies other disorders, it can also precede the comorbid condition, persist despite effective treatment of the comorbid condition, or aggravate the symptoms of the comorbid condition. For a diagnosis of chronic insomnia, the DSM-5 and ICSD-3 criteria require a subjective report of a sleep complaint (difficulty initiating or maintaining sleep, or early morning awakening) occurring at least three times per week over a period of 3 months, as well as at least one related daytime impairment (fatigue, attention impairment, mood disturbance, or impaired performance). With the introduction of this umbrella category, the disorder is expected to receive increased clinical and scientific attention. Both clinically and in many research studies, insomnia is primarily diagnosed by the measurement of subjective symptoms and not by the determination of sleep parameters through polysomnography. This strategy might partly be attributable to economic reasons, but is also a consequence of the widely replicated finding that many patients with insomnia display a mismatch between subjective estimates of their sleep parameters in comparison to those parameters derived from polysomnography. This phenomenon has been termed sleep state misperception or paradoxical insomnia.[18] Therefore, a large subjective overestimation of the sleep difficulty might exist, perhaps relating to the effect of the associated patient-reported daytime complaints. Patients diagnosed with insomnia showing polysomnographically determined short sleep duration might constitute the most biologically severe phenotype of the disorder.[19]

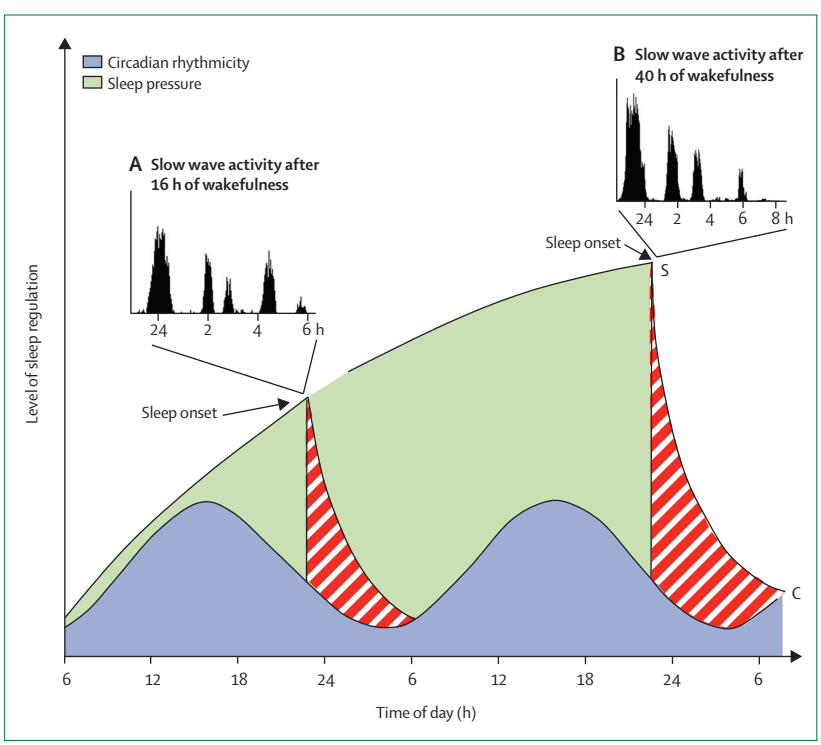

Figure 1: **Two-process model of sleep regulation[20]**
Two central processes are relevant for sleep–wake regulation: process C, a circadian process and process S, reflecting sleep pressure. Process C reflects the circadian rhythmicity of physiological functions (eg, core body temperature). Process S can be measured retrospectively by analysis of the slow wave activity in the sleep electroencephalogram. The interaction between processes C and S determines the sleep–wake cycle, its timing, and the sleep depth. The difference between S and C reflects the likelihood for falling asleep, whereas the moment that S reaches C signals a high propensity for termination of sleep (ie, awakening). If no sleep occurs, the S process does not get reduced. The red-white pattern shows the decline of sleep pressure when people sleep. The inserts show slow wave activity over the course of the night after 16 h of wakefulness (A) and after 40 h of wakefulness (B). After longer periods of wakefulness, slow wave activity is increased over the course of the night. Modified with permission from Borbély.[20]

Sleep–wake regulation

The basic tenets of sleep–wake regulation have been formulated in the two-process model.[20] According to this model, two major processes govern sleep–wake rhythms: a circadian (chronobiological) process and a homoeostatic process. The circadian process reflects the fact that, from the cellular to the system level, the variation in intrinsic activity over 24 h follows a sinusoidal curve. This activity is controlled by an internal clock located in the suprachiasmatic nuclei and synchronised to the time of day by external cues, predominantly the light–dark cycle. The homoeostatic process, which is the need for sleep (sleep pressure) as a function of the time since the last adequate sleep, is an indicator of homoeostatic sleep drive. This process can be measured retrospectively by the amount of slow wave activity during sleep; the longer someone has been awake, the more slow wave activity will be recorded in his or her electroencephalogram (EEG) when they do sleep (figure 1). A recent longitudinal study suggested that some of the general principles of the two-process model also hold true for individuals with insomnia: several nights of poor sleep were regularly followed by single nights of good sleep.[21] Two other studies reported that high night-to-night variability in sleep quality might be a typical sleep pattern in insomnia, and that there may be different subtypes of insomnia based on specific night-to-night sleep patterns.[22,23]

Consistent with the two-process model, levels of melatonin[24] and adenosine[25] have been reported as relevant for sleep–wake regulation. Melatonin, a hormone produced by the pineal gland, is suppressed by light. Its secretion starts at twilight and peaks during the middle of the night. This hormone has been associated with the circadian process. The neuropeptide adenosine has been identified as a sleep promoter and can inhibit arousal by blocking the activity of the orexin system, known to induce arousal and wakefulness. It has been hypothesised that adenosine is associated with the homoeostatic process, as its production is closely linked to the amount of time awake.[26]

Important insights on the neuroanatomy of sleep–wake regulation have been identified from the study of agrypnia, which is a syndrome of organic insomnia resulting from neuronal lesions or dysfunction of neuronal circuits involved in sleep regulation and motor and sympathetic overactivation.[27] Fatal familial insomnia, Morvan's syndrome, and delirium tremens are examples of diseases

that induce severe agrypnia and are frequently fatal.[27] In fatal familial insomnia, for example, autonomic and hormonal (eg, cortisol) output increases, circadian rhythmicity disappears together with a parallel reduction in melatonin secretion, and hypometabolism in the thalamic structures spreading to the cerebral cortex and basal ganglia is seen on ^{18}F-fluorodeoxyglucose PET. Traumatic brain injury is also accompanied by insomnia in 30–70% of patients.[28] In patients with focal brain lesions resulting from traumatic brain injuries, the strongest associations exist between insomnia and left dorsomedial prefrontal damage.[29] Advances at the level of brain structures and molecules governing the regulation of sleep and wakefulness were reviewed in 2010 (figure 2).[30]

The sleep–wake cycle is mostly controlled by the ascending reticular activating system, the ventrolateral preoptic nucleus, the median preoptic nuclei, and a group of orexinergic neurons in the lateral hypothalamus. The ascending reticular activating system comprises cholinergic, monoaminergic, histaminergic, and glutamatergic neurons in the brainstem, especially in the laterodorsal pontine tegmentum and pedunculopontine tegmentum, locus coeruleus, tuberomammilary nucleus, and dorsal raphe. These structures project to the thalamus, basal forebrain, and cerebral cortex, and are crucially involved in the generation of wakefulness. The ventrolateral median preoptic nuclei (which both contain GABAergic neurons) inhibit the ascending reticular system and, thus, constitute the main sleep-promoting system. Orexinergic neurons in the lateral hypothalamus modulate sleep–wake regulation by reinforcement of arousal pathways in the brainstem, and have a direct excitatory input to the cerebral cortex and basal forebrain. The reciprocally inhibitory systems of sleep-inducing and wake-inducing brain pathways constitute a flip-flop switch that is responsible for creation of fast and complete transitions between sleep and wakefulness. The cycling between non-rapid eye movement (NREM) and rapid eye movement (REM) sleep has been assumed to be caused by a different neuronal switch (figure 2).[30]

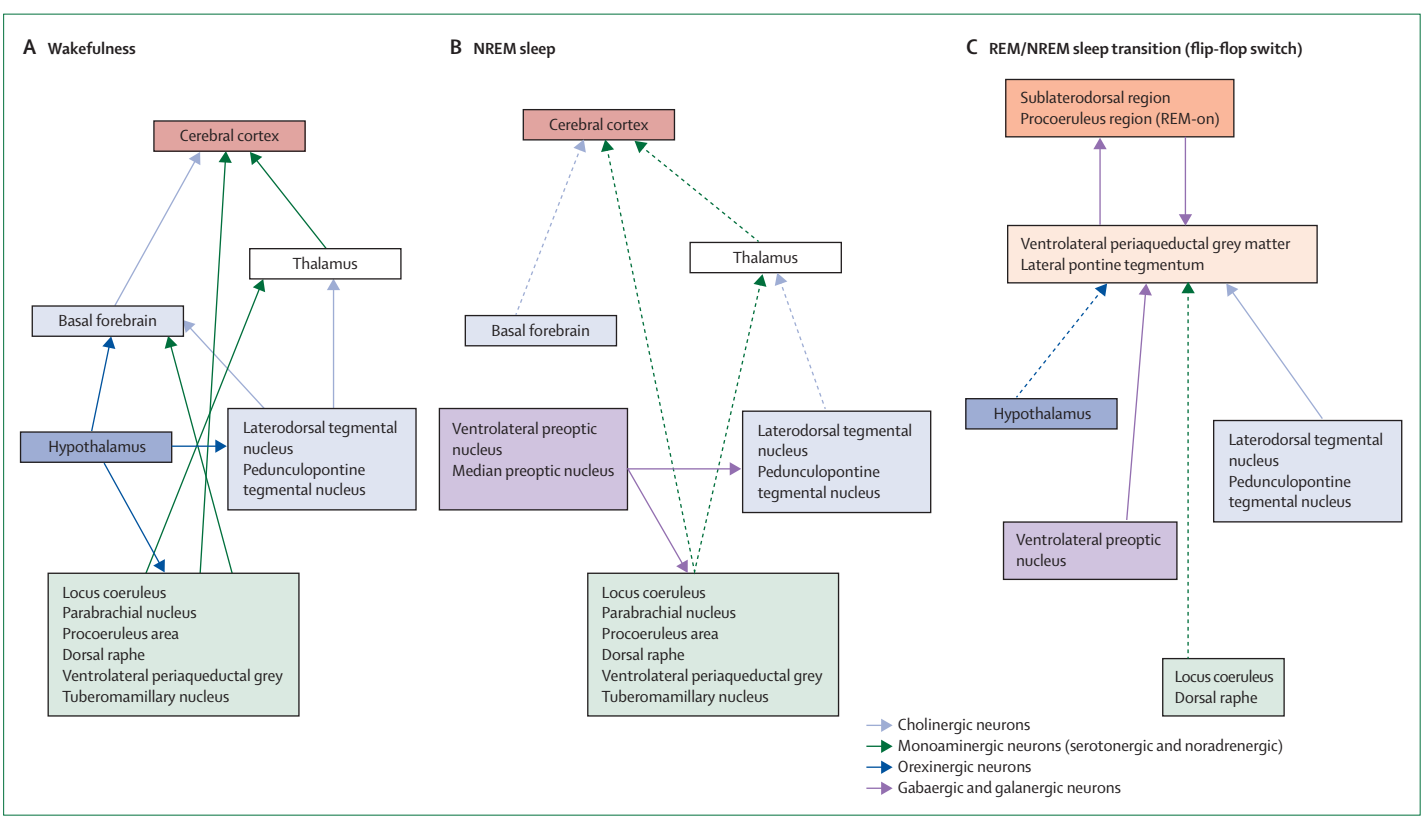

Figure 2: **Sleep–wake regulation according to the flip-flop switch model[30]**
Wakefulness (A) is governed by neurons in the upper brainstem projecting to higher brain areas. Cholinergic neurons provide input to the thalamus and basal forebrain whereas monoaminergic neurons directly innervate the thalamus, basal forebrain, and cerebral cortex. Orexinergic neurons in the lateral hypothalamus (dark blue) reinforce the activity of these brainstem arousal pathways and also directly excite the basal forebrain. Non-rapid eye movement (NREM) sleep (B) is promoted by the ventrolateral and median preoptic nuclei (magenta) which inhibit the ascending arousal pathways at the level of hypothalamus and brainstem (green and light blue broken lines). Rapid eye movement (REM)-on (sublaterodorsal region and precoeruleus area) and REM-off (ventrolateral periaqueductal grey matter and the adjacent lateral pontine tegmentum) neuronal populations are mutually inhibitory and form a flip-flop switch for control of the transitions between REM and NREM sleep (C). During REM sleep, noradrenergic neurons in the locus coeruleus and serotonergic neurons in the dorsal raphe are inhibited; cholinergic neurons from the laterodorsal and pedunculopontine tegmental nuclei promote REM sleep by having opposite actions on the REM-on and REM-off populations. Orexinergic neurons (dark blue) inhibit entry into REM sleep by exciting neurons in the REM-off population, whereas the ventrolateral preoptic nucleus neurons promote entry into REM sleep by inhibition of this same target. Pathways that are inhibited or inactive are presented as broken lines. Modified with permission from Saper and colleagues[30] with kind permission from the author and Elsevier.

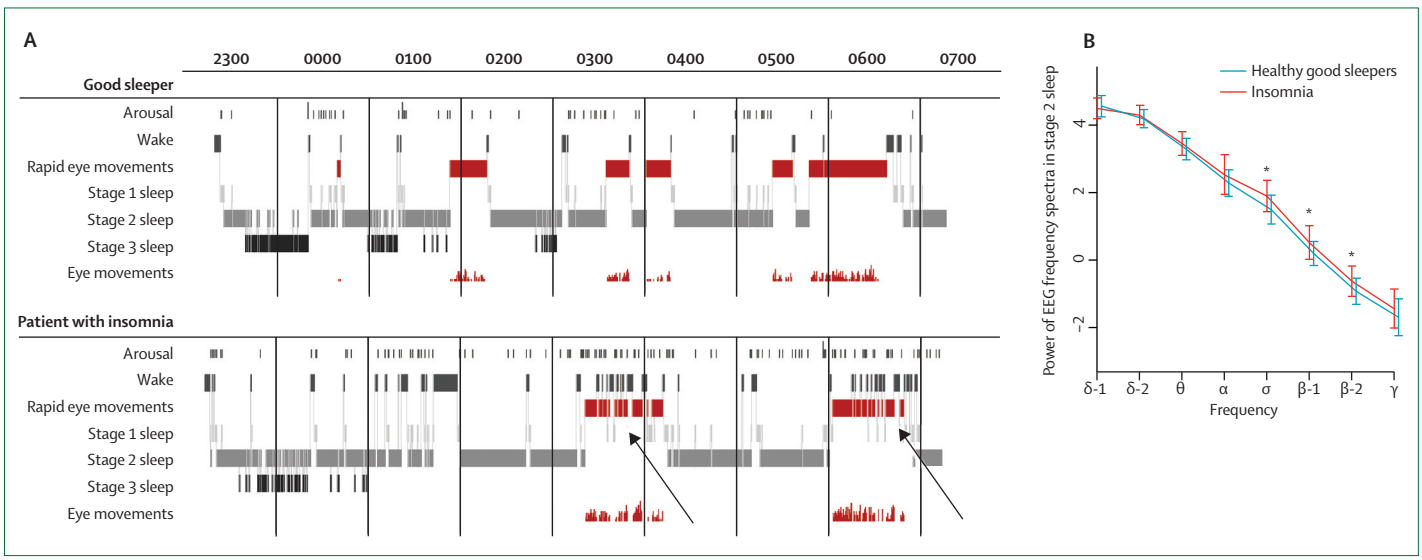

Figure 3: **Polysomnographic and power density differences between good and poor sleepers**
(A) Comparison of the polysomnogram of a good sleeper and a patient with insomnia. With respect to the macrostructure of sleep, the sleep pattern of this patient with insomnia is mostly intact—the disturbance is mainly expressed through an increased frequency of stage shifts and increased brief waking periods and microarousals (arrows) as previously reported in our studies.[31] Data are taken from the database of the University of Freiburg Sleep Laboratory (Freiburg, Germany). (B) Asterisks show significant (p<0·05) alterations in the sleep electroencephalogram of patients with insomnia as compared with healthy good sleepers, as shown by enhanced power in fast frequencies (derived from spectral analysis). Redrawn from Spiegelhalder and colleagues.[33]

Figure 3 displays the polysomnographically determined sleep pattern of a healthy sleeper. NREM (stages 1–3) and REM periods alternate in 90–120 minute cycles. Approximately 5% of the night is spent in stage 1 sleep, 50% in stage 2 sleep, 20% each in stage 3 and REM sleep, whereas 5% of the night is spent awake.

A number of functional changes to the known sleep–wake regulatory mechanisms (figure 2) could have a role in insomnia. On a chronobiological level, a misalignment of the circadian process leading to phase delays or advances might lead to either prolonged sleep onset latency (the length of time that it takes to go from full wakefulness to sleep) or early morning awakening. These changes might also be shown by delayed or advanced melatonin secretion. Dysfunction of the homoeostatic process could explain both sleep onset and sleep maintenance difficulties. The homoeostatic process has been specifically linked to extracellular adenosine concentration in the basal forebrain, which rises as sleep pressure increases. Maladaptive behaviours (eg, prolonged time in bed to counteract insomnia) might reduce the homoeostatic process. Conversely, behavioural changes such as bedtime restriction could enhance the homoeostatic process and improve sleep. Any brain lesion in areas relevant for sleep regulation, caused by either neurotrauma or neurological disease, might also be capable of inducing insomnia.

At the neurochemical level, several mechanisms of sleep–wake regulation have been identified. For example, reduced GABAergic activity or orexinergic overactivity might be associated with a weakening of the sleep-promotion system or a strengthening of the arousal system, respectively. The polysomnographic sleep of many patients with insomnia is characterised by an increased frequency of brief events such as shifts in sleep stages between NREM and REM sleep and among NREM stages, brief periods of awakening and microarousals (brief and transient changes in EEG frequency suggestive of an awake state), and not by extremely long periods of wakefulness.[31] Thus, although the macrostructure of sleep (cycling between NREM and REM periods) is only mildly affected,[32] the microstructure within both NREM and REM periods strongly shows a disturbance of the switch between sleep and wakefulness. This disturbance is also exemplified by power spectral analysis of the sleep EEG, a method that can be used to quantify the amount of frequency power in any prespecified frequency band. As compared with healthy sleepers, people with insomnia, have the most pronounced differences in the EEG fast frequency range (β power).[33] This type of instability has also been suggested to be relevant for the disruption of REM sleep, which is known to be especially fragmented in insomnia patients, with microarousals.[31,34,35] It should be noted, however, that some patients with insomnia do show strong disturbances in sleep continuity, including long sleep latencies or protracted periods of wakefulness occurring during the night. A 2014 meta-analysis of polysomnographic data[32] showed that, on average, the sleep of patients with insomnia is shortened by about 25 min when compared with good sleepers.

The study of animal models of insomnia, such as those using immobilisation, the grid-over-water method,

or sensory stimulation, are promising approaches to enhance understanding of the neurobiology of the disorder.[36] In these models, animals are exposed to psychosocial stressors that result in pronounced sleep disturbances with mild effects on sleep macrostructure and strong effects on sleep microstructure. Cano and colleagues[37] used a cage exchange paradigm, in which adult wild-type male Sprague-Dawley rats were placed into a dirty cage that was previously occupied by another male rat. At the neurobiological level, this resulted in the simultaneous activation of sleep-inducing and arousal-promoting brain areas during the sleep period. Thus, although basic sleep regulatory mechanisms seemed to remain intact (as might be the case in human insomnia), overactivity of the arousal system caused by stress resulted in a hybrid sleep–wake sleep state. This hybrid sleep–wake state can be viewed in terms of localised central regulation suggesting that circumscribed regions of the brain can independently be in different states of sleep and wakefulness. Huber and colleagues[38] have shown that sleep homoeostasis has a local component; specific learning tasks administered to animals or humans have been shown to induce changes in the slow wave activity of specific brain regions and not simultaneously in the whole brain. Moreover, the role of small specific neuronal networks and the importance of prior activation within each network have been emphasised as playing a substantial role in sleep regulation.[39] Synchronisation of local networks implicated in sleep occurs through both humoral and neuronal connections and thereby results in whole-organism sleep. In this context, several characteristics in the sleep of patients with insomnia, such as increased frequency of brief awakenings, microarousals, and fast EEG frequencies, might be interpreted as reflecting a mixed or hybrid sleep–wake state.

Genetics and epigenetics of insomnia

Family studies undertaken in infants, adolescents, and adults have provided solid evidence for a familial aggregation of insomnia.[40,41] In afflicted individuals, between 35% and 55% of first-degree relatives also have insomnia, which is a substantially higher rate of insomnia than that seen in first-degree relatives of good sleepers. To separate genetic and environmental factors, several twin studies have been done yielding heritability coefficients between 42% and 57%.[42–44] Moreover, a twin study[45] suggests that the vulnerability for the development of stress-induced sleep disturbances, as measured by the Ford Insomnia Response to Stress Test (FIRST), is genetically influenced, with heritability estimates of about 29% for women and 43% for men.

The search for specific genotypes of insomnia has identified various candidate genes (table 1). Mutations have been identified in *CLOCK* genes,[47] genes coding for the β3 subunit of the $GABA_A$ receptor,[46] and serotonin transporter genes.[48] However, none of these results have been replicated in independent samples. Two published genome-wide association studies failed to validate these results.[49,50]

Various investigators, including ourselves, have recently suggested that epigenetic mechanisms might be involved in the development and maintenance of insomnia.[51,52] In brief, we hypothesise that stressful life events could have the capability to change the activity of stress-regulatory systems (ie, the hypothalamic-pituitary-adrenal axis). This change, in turn, might induce long-term changes in brain structures such as the hippocampus. The hippocampus is an especially plastic brain region vulnerable to stress and a target of stress hormones; furthermore, it has been shown that hippocampal neurogenesis, and in consequence memory performance, is impaired by acute and chronic stress.[51,52] Re-exposure to some stressors

	Type of study	Gene identified	Gene function	Results
Buhr et al (2002)[46]	Case study	*GABRB3*	Regulation of GABAergic inhibition	Missense mutation Arg192His of the gene detected in the insomnia case but not in 115 healthy controls
Serretti et al (2003)[47]	Candidate gene study of 620 patients with major depressive disorder or bipolar disorder	*3111T/C CLOCK*	Timing of the circadian rhythm	p<0·001 for association between the C allele and insomnia
Deuschle et al (2010)[48]	Candidate gene study of 157 patients with primary insomnia and 827 healthy controls	*5-HTTLPR*	Regulation of serotonin in the synapse	p<0·05 for association of short allele (44 base-pair deletion polymorphism in the 5′ regulatory region) with insomnia
Ban et al (2011)[49]	Genome-wide association study of 8719 participants, including 1439 patients with insomnia	*ROR1, PLCB1*	Modulation of neurite growth and synapse formation (*ROR1*), regulation of calcium signalling (*PLCB1*)	p<0·001 for rs1120830 (*ROR1*), p<0·001 for rs718712 (*PLCB1*)
Byrne et al (2013)[50]	Genome-wide association study of 2323 people from the general population	*CACNA1C*	Regulation of calcium signalling	p<0·001 for association between rs7304986 and subjective sleep onset latency; results not replicated in an independent sample (2034 patients) within the same study

Table 1: **Genes implicated in the neurobiology of insomnia**

could therefore constitute a vulnerability factor for the development of chronic insomnia.

Pathophysiological markers of insomnia

The pathophysiology of insomnia has been mainly investigated from the perspective of the hyperarousal model.[53] This approach is based on a long-standing history of clinical observation and empirical findings that patients with insomnia display signs of increased arousal either on a cognitive-emotional`, behavioural, autonomous, or central nervous system level. A substantial number of cross-sectional case-control studies have been undertaken to investigate the hypothalamic-pituitary-adrenal axis (with cortisol as the major stress response hormone) and the activity of the autonomic nervous system (heart rate, heart rate variability) as indicators for increased arousal levels. Most of the evidence suggests an overactivity of these systems in insomnia, supporting the assumption that hyperarousal contributes to insomnia in these patients (table 2).

EEG and neuroimaging

Many studies have been done in which EEG-derived sleep parameters were used to compare the sleep of patients with insomnia with that of healthy good sleepers. A meta-analysis of this literature showed that, on average, patients with insomnia sleep 25 min less than do healthy good sleepers and show reduced amounts of both slow wave and REM sleep.[32] Polysomnographically documented disturbances of sleep continuity have long been known to be far less pronounced than those expected from subjective reports of patients with insomnia.[18] Thus, increasingly sensitive methods are needed to uncover the neurobiological factors underlying the subjective experience of insomnia,

	Study participants	Output parameters
Cortisol		
Zhang et al (2014)[54]	69 patients with insomnia; 175 controls without insomnia from a community-based sample (~10% with medication)	Cortisol awakening response increased in patients with insomnia
Xia et al (2014)[55]	30 patients with primary insomnia; 30 healthy controls	Morning (0730–0800 h) cortisol increased by about 82% in patients with primary insomnia
Seelig et al (2013)[56]	13 female patients with primary insomnia; 12 female healthy controls	Midnight cortisol increased by about 100%; 0600 h cortisol not different between groups
Heart rate variability		
Farina et al (2014)[57]	85 patients with primary insomnia; 55 healthy controls	Sympathetic and parasympathetic activity during N2 increased in patients with primary insomnia; slow wave sleep and REM not different between groups
Maes et al (2012)[58]	17 female patients with primary insomnia; 11 female healthy controls	Heart rate variability parameters during the sleep-onset period not different between groups
Israel et al (2011)[59]	54 patients with primary insomnia; 22 healthy controls	Heart rate variability parameters during sleep not different between groups
Spiegelhalder et al (2011)[60]	58 patients with primary insomnia; 46 healthy controls	Bedtime parasympathetic activity decreased in patients with primary insomnia; bedtime sympathetic activity not different between groups
De Zambotti et al (2011)[61]	Eight patients with primary insomnia; eight healthy controls	Parasympathetic activity during the sleep-onset period not different between groups
Yang et al (2011)[62]	47 patients with primary insomnia; 88 healthy controls	Daytime and bedtime parasympathetic activity decreased in patients with primary insomnia
EEG β power		
Maes et al (2014)[58]	17 patients with primary insomnia; 11 healthy controls	Sleep-onset period β EEG decreased in patients with primary insomnia; slow wave sleep β EEG increased in patients with primary insomnia
Wu et al (2013)[63]	50 patients with primary insomnia; 32 healthy controls	NREM β EEG not different between groups
St-Jean et al (2013)[64]	26 patients with primary insomnia; 20 patients with paradoxical insomnia; 21 healthy controls	β EEG during sleep not different between groups
Spiegelhalder et al (2012)[33]	25 patients with primary insomnia; 29 healthy controls	NREM β EEG increased in patients with primary insomnia; REM β EEG not different between groups
Israel et al (2012)[59]	54 patients with primary insomnia; 22 healthy controls	NREM β EEG increased in patients with primary insomnia
Corsi-Cabrera et al (2012)[65]	Ten patients with primary insomnia; ten healthy controls	Pre-sleep wakefulness β EEG increased in patients with primary insomnia; β EEG during sleep not different between groups

Changes indicated in output parameters were statistically significant. EEG=electroencephalogram. N2=stage 2 sleep. REM=rapid eye movement sleep. NREM=non-rapid eye movement sleep.

Table 2: **Studies investigating cortisol, heart rate variability parameters, and EEG β power (power spectral analysis) in adult patients with insomnia and healthy controls**

such as power spectral analysis of the sleep EEG, which shows an increase of EEG β power during NREM sleep in insomnia patients (table 2, figure 3).[33,58,59,63,64,65] This finding is thought to reflect increases in arousal levels beyond the macroclassification of polysomnographically determined sleep stages.[53] Nevertheless, EEG studies in insomnia are insufficient to determine the spatial localisation of the increased sleep EEG β power noted, its associated mechanism, or the manner by which arousal-promoting or sleep-promoting brain circuits are involved in the subjective experience of chronic insomnia.

Neuroimaging methods provide better spatial resolution than does EEG and allow the investigation of the morphometry (MRI), neurochemical (magnetic resonance spectroscopy), and functional aspects (functional MRI, PET, and SPECT) of the human brain during wakefulness and sleep.[66] A major methodological constraint during such types of imaging is that sleep in a scanner is difficult to achieve. Further, more concomitant monitoring of EEG or deployment of tasks within MRI scanners requires specialised equipment. Thus, only a few studies have directly studied patients with insomnia during sleep with brain imaging. SPECT and PET, albeit within specific limits, have the advantage over MRI that the patients can be injected with the contrast agent during sleep (eg, in the sleep laboratory), while the scan can be performed at a later time when patients are awake.

Daytime investigations

Morphometric studies with conventional T2-weighted MRI images have shown inconsistent results and have methodological limitations. Several cross-sectional studies have suggested a grey matter reduction in the frontal lobe of patients with insomnia.[67–70] However, the results of one study[70] were not corrected for multiple testing and other studies have not noted any brain morphometric abnormalities in the frontal cortex of patients with insomnia.[71] Some studies further suggest that hippocampal volumes are reduced in insomnia,[72–74] although other research could not replicate such an effect.[67,69–71,75] The anterior cingulate gyrus volume of insomnia patients was reportedly increased in two independent samples,[69] and the volume of the pineal gland was reduced in one investigation.[76] However, both of these findings have not been replicated in a separate study.[71] Altogether, the data from these cross-sectional morphological studies fail to produce consistent findings. Because all these studies were undertaken in rather small samples (≤40 patients per group), future research using larger sample sizes, data pooling, and longitudinal designs is deemed necessary.

Three studies using ^{1}H-MRS have suggested an association between insomnia and decreased daytime cortical GABA levels,[77–79] although conflicting findings have been reported.[80] Another study reported lower grey matter phosphocreatine concentrations to be associated with insomnia.[81] GABA, the most important inhibitory neurotransmitter in the CNS, is crucially involved in the regulation of sleep and wakefulness, whereas low levels of phosphocreatine suggest an increased demand for cellular energy. These studies therefore suggest that a decreased sleep drive in patients with insomnia leads to disinhibition of the arousal-promoting brain centres. Future longitudinal studies that assess patients before and after treatment on the basis of the aforementioned mechanisms might help to advance our knowledge on the use of evidence-based pharmacological and non-pharmacological treatments.

fMRI has been used in several studies to study daytime performance deficits in patients with insomnia.[82–84] Performance in neuropsychological tasks has been consistently associated with a hypoactivation of task-related areas, especially in frontosubcortical networks. A diffusion tensor imaging study also revealed reduced integrity of white matter tracts in the anterior internal capsule of patients with insomnia, thereby further showing that disturbed frontosubcortical connectivity might be a cause or consequence of the disorder.[85] Stoffers and colleagues[84] suggested that insomnia pathophysiology involves reduced recruitment of the caudate nucleus—a key structure for the regulation of arousal levels—in combination with an attenuated input from the orbitofrontal cortex to the caudate nucleus. In another fMRI study, patients with insomnia, as compared to healthy good sleepers, showed increased cue-induced amygdala reactivity to sleep-related pictures of individuals lying awake in bed at night.[86] This finding is in line with previous literature on high levels of negative emotions associated with insomnia and the phenomenon known as sleep-related attentional bias.[87,88] Finally, in a study[83] on daytime performance, reduced deactivation of the default mode network was noted in patients with insomnia during a working memory task. This finding may hence be a neurobiological correlate of the increased self-referential processing, introspection, worry, and rumination all usually found in patients with insomnia.[89]

Investigations during sleep

Most investigations of brain function in patients with insomnia during sleep states have used PET neuroimaging, despite SPECT scanners having substantially improved spatial and temporal resolution, as well as detection efficiency. The most frequently cited PET study during sleep states used ^{18}F-fluorodeoxyglucose as a radiotracer and reported increased brain metabolism during stage 2 sleep in relation to the waking state in insomnia patients, as compared with good sleepers.[90] Specifically, an inhibition of the usual activity decline occurring in the waking to sleep switch in patients with insomnia was noted in the following brain regions: ascending reticular activating system, hypothalamus,

thalamus, amygdala, hippocampus, insula, and anterior cingulate and prefrontal cortices. These findings suggest that a general overactivity of the arousal, emotion-regulating, and cognitive systems are all involved in the pathophysiology of insomnia. Insomnia has therefore been conceptualised as a disorder of corticolimbic overactivity that interferes with sleep-promoting brain structures. A promising approach to increase the temporal resolution in future investigations of sleep-related brain activity might be the combined use of fMRI together with EEG measurements. This method will probably provide important insights into undisturbed human sleep.[91] Figure 4 shows an overview of the key results of all brain imaging studies (summarising daytime and sleep investigations) in insomnia highlighting those brain areas that are likely implicated in the pathophysiology of the disorder.

Insomnia treatment

Despite striking progress in the understanding of the neurobiology of sleep–wake regulation, primary treatments for insomnia such as cognitive behavioural therapy for insomnia (CBT-I), benzodiazepines, and benzodiazepine-receptor agonists were all introduced into clinical practice at least three decades ago. About 40% of patients with chronic insomnia do not reach sustained remission with these treatments.[92]

At present, CBT-I is the first-line treatment for chronic insomnia.[93] This treatment comprises advice on sleep–wake behaviour (sleep hygiene), stimulus control and sleep restriction, and relaxation and cognitive techniques. The efficacy of CBT-I has been shown in meta-analyses[94] of randomised controlled trials. It has been shown to be equal to pharmacotherapy during acute treatment and more effective for long-term treatment.[94] One strength of these approaches, particularly sleep restriction therapy, is that the mechanism of action is consistent with models of sleep–wake regulation such as the two-process model. For example, increased time out of bed and wakefulness, enhanced sleep drive (homoeostatic process), and less curtailed, more intense subsequent sleep are all related to increased slow wave activity.[95] Recent developments in CBT-I include abbreviated behavioural treatments,[96] internet-based versions,[97] and stepped-care models ranging from self-help to individualised psychotherapy.[98] These variants aim to improve the dissemination of standard face-to-face CBT-I. However, the core components have remained largely unchanged in the past two decades.

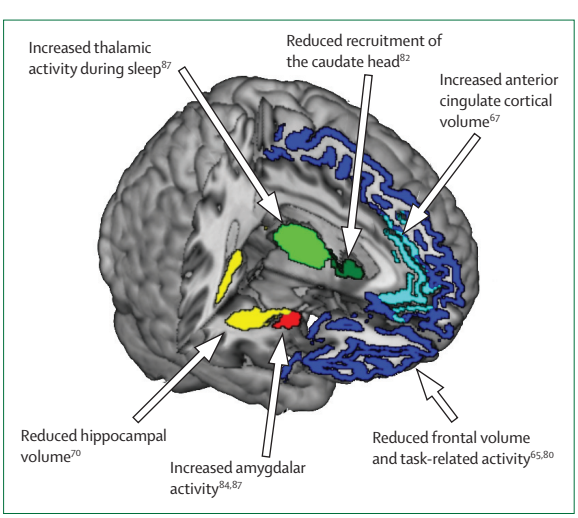

Figure 4: **Key neuroimaging findings in insomnia research**
The location of important brain areas that may be involved in insomnia pathophysiology as identified by neuroimaging studies are shown: hippocampus (yellow),[71] amygdala (red),[85,88] thalamus (light green),[88] caudate head (dark green),[83] anterior cingulate cortex (light blue),[68] and frontal cortex (dark blue).[66,81]

The most widely prescribed classes of medication for insomnia, benzodiazepines and benzodiazepine receptor agonists, act by strengthening the flip-flop sleep switch. More specifically, these drugs bind to the benzodiazepine-receptor binding site of the $GABA_A$ receptor, increase intrinsic activity of the inhibitory neurotransmitter GABA, and enhance inhibitory outputs to all of the major cell groups in the brainstem and hypothalamus that promote arousal.[36] According to meta-analyses of randomised controlled trials, benzodiazepines and benzodiazepine receptor agonists are safe and effective short-term treatments for acute insomnia.[94,99] However, their safety and efficacy are substantially restricted by the development of tolerance and an elevated risk of dependency with long-term use. Several million people worldwide are dependent on these drugs,[100] with many of them having long-term side-effects and increased morbidity and mortality.[101] Whether increased morbidity and mortality is a direct effect of benzodiazepines or benzodiazepine receptor agonists intake or whether these findings are confounded by other comorbid conditions such as insomnia or depression is a controversial topic.[101] The long-term use of benzodiazepines or benzodiazepine receptor agonists is not approved or recommended for chronic insomnia in Europe.

An alternative pharmacological approach is to directly block wake-promoting aminergic and cholinergic neurotransmission. Antihistamines and tricyclic antidepressants (with anticholinergic and anti-histaminergic properties) have been increasingly used over the past decades, although few data support this treatment option.[102] A major advantage is that these drugs do not cause addiction. However, these compounds are associated with substantial side-effects, such as rebound insomnia after withdrawal, liver dysfunction, and heart rhythm disturbances. They may further require medical monitoring and are not approved for long-term use.[102]

Novel treatments

The most exciting novel pharmacological treatment is the orexin receptor antagonist suvorexant, for which there are encouraging first safety and efficacy data in insomnia.[103,104] Suvorexant is the first available drug

which acts on the orexin system by suppressing the wake-stimulatory network of sleep–wake regulation. This is in contrast to the traditional pharmacological approach, which is to strengthen the sleep drive by the augmentation of gabaergic activity (eg, with benzodiazepines). Highly relevant clinical phenomena such as risk of dependency might thus be avoided. Another promising therapeutic target is the adrenergic neurotransmitter system, an important arousal pathway with an underexplored drug development potential for insomnia. Some clinical evidence suggests that antihypertensive drugs with alpha-adrenergic antagonistic properties can induce sleep.[105] As of date of writing, no adrenergic antagonist has been tested specifically for hypnotic properties.

Complementary to psychotherapy and pharmacotherapy, non-invasive brain stimulation approaches including thermostimulation and transcranial direct current stimulation, might also have the potential to improve sleep. These techniques can induce local activity changes in selected areas of the human cortex which could modulate arousal and sleep via cortico-thalamo-cortical feedback loops. First proof-of-concept studies have reported the short-term induction of EEG slow waves by transcranial direct current stimulation in healthy subjects,[106] and a dose-dependent improvement of sleep latency and efficiency by frontal cerebral thermostimulation in patients with insomnia.[107] Besides their therapeutic potential, non-invasive brain stimulation techniques can be used as probes of brain function to provide novel information about the mechanisms of healthy and disrupted sleep.

Another emerging treatment approach is the transformation of descriptive recordings of brain activity patterns, such as EEG or real-time fMRI signals, via biofeedback. Insomnia-related brain activity can be characterised and patients can be trained to directly control their brain activity in a training session with biofeedback.[108,109] Further trials are warranted to determine if neurofeedback can be considered to be an effective treatment for insomnia. Biofeedback could thus be used to downregulate hyperarousal, either in its traditional approach which measures parameters of the autonomic nervous system, or by targeting CNS parameters.

Conclusions and future directions

This Review aimed to delineate neurobiological aspects of chronic insomnia, thus adding to and complementing the existing literature on psychological aspects of the disorder. Whereas the psychological aspects can be considered as a top-down perspective in the understanding of chronic insomnia, the search for neurobiological origins is a bottom-up approach. The reviewed evidence suggests a genetic component for the development of insomnia, probably in the form of an inherited vulnerability developing after stressful life events. Investigations examining both peripheral and central nervous variables implicated in the pathophysiology of chronic insomnia continue to suggest that hyperarousal is a fundamental mechanism. Whereas basic sleep–wake regulation, as reflected by classical polysomnography, is rather unperturbed in patients with chronic insomnia, more fine-grained analysis of the sleep EEG in these patients suggests a hybrid or mixed-state sleep with ongoing signs of increased arousal. Neuroimaging studies, although often showing mixed evidence, do generally support this notion. Hence, in the context of basic sleep–wake neurobiology, chronic insomnia is an imbalance in the sleep–wake switch (figure 2), with frequent switching to the waking state during sleep. This type of disturbance might also have a negative effect on healthy brain plasticity, a possible function of sleep that has received much attention in recent years.[110] The development of novel therapeutics (ie, orexin antagonists) has been driven by recent neurobiological discoveries. Further options for drug development in the treatment of insomnia are likely to follow. These neurobiological aspects of chronic insomnia require integration with current psychological knowledge. Thus, a psychoneurobiological approach towards the understanding and treatment of chronic insomnia is necessary for effective improvement of our treatment modalities.

Increased awareness for effective insomnia treatment is fundamentally important. The ultimate goal is to successfully select and implement personalised treatment pathways on the basis of individual neurobiological and clinical characteristics. These treatments are expected to comprise a broad combination of psychotherapy techniques, pharmacological interventions, non-invasive brain stimulation techniques, and psychobiological interventions such as neurofeedback, which can be delivered in a stepped-care setting ranging from internet-based self-help to intensive personal care. Another important issue will be the ability to use treatment outcomes in clinical studies beyond classical sleep-related

Search strategy and selection criteria

We identified studies on the neurobiology of chronic insomnia through a search of PubMed with the term "insomnia" linked to any of the following terms: "neurobiology", "brain", "central nervous system", "genetics", "cortisol", "heart rate variability", "power spectral analysis", "polysomnography", "MRI", "fMRI", "PET", "SPECT", "spectroscopy", "treatment", or "therapy". We searched Pubmed from Jan 1, 1980 to Jan 31, 2015. Further relevant studies were found by examination of reference lists of identified papers. Criteria used to include or exclude information were based on the relevance and significance of studies to the aim of this Review. We had no language restrictions. Due to space limitations, we have included only the most recent evidence and preferentially selected published overviews, review articles, or meta-analyses that were deemed adequate.

parameters. These outcomes might include, for example, daytime functioning, measures of arousal (heart rate or heart rate variability), cortisol excretion, and neurobiological parameters derived from neuroimaging.

Contributors

All authors contributed to the writing of the manuscript and to the design of the figures. DR and KS conceived the structure of the Review and handled communications between all the authors.

Declaration of interests

DR received an honorarium from Abbvie in 2013 for consultation on the development of new drugs for neurodegenerative disorders. CN has received speaker honoraria from Servier. MLP, LP, AO, and KS declare no competing interests.

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