Sleep Medicine Reviews 18 (2014) 237–247

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Who is predisposed to insomnia: A review of familial aggregation, stress-reactivity, personality and coping style

Christopher-James Harvey [a,*], Phil Gehrman [b], Colin A. Espie [a]

[a] Nuffield Department of Clinical Neurosciences, Sleep & Circadian Neuroscience Institute, University of Oxford, Level 6 West Wing, John Radcliffe Hospital, Oxford OX3 9DU, UK
[b] Department of Psychiatry, 3535 Market Street, Suite 670, Philadelphia, PA 19104, USA

ARTICLE INFO

Article history:
Received 12 April 2013
Received in revised form
5 November 2013
Accepted 20 November 2013
Available online 28 November 2013

Keywords:
Insomnia
Stress-reactivity
Personality
Neuroticism
5HTTLPR
Vulnerability

SUMMARY

Insomnia is a common health complaint world-wide. Insomnia is a risk factor in the development of other psychological and physiological disorders. Therefore understanding the mechanisms which predispose an individual to developing insomnia has great transdiagnostic value. However, whilst it is largely accepted that a vulnerable phenotype exists there is a lack of research which aims to systematically assess the make-up of this phenotype. This review outlines the research to-date, considering familial aggregation and the genetics and psychology of stress-reactivity. A model will be presented in which negative affect (neuroticism) and genetics (*5HTTLPR*) are argued to lead to disrupted sleep via an increase in stress-reactivity, and further that the interaction of these variables leads to an increase in learned negative associations, which further increase the likelihood of poor sleep and the development of insomnia.

Introduction

Spielman in 1987 [1] states in his behavioural model, that the development of insomnia is dependent on three factors: predisposing factors; precipitating factors (life stressors [2]) and perpetuating factors (attention biases [3,4] and hyperarousal [5] for example). In 1988 Coren devised the arousal predisposition scale (APS), in an attempt to illustrate that 'arousability' predicted sleep disruption [6]. In 1998 Perlstrom and Wickramasekera [7] further hypothesised that night time arousal is associated with four predisposing factors: high neuroticism, susceptibility to hypnosis, repression and a tendency to catastrophise. The notion of phenotypes of predisposition to develop insomnia is also alluded to in more contemporary models, such as Harvey's cognitive model [8] in 2002 and Espie's attention–intention–effort pathway in 2006 [4].

At a theoretical level it is well established that a vulnerable phenotype exists. Experimentally, it is only in the last 10 years that the existence of a trait-like vulnerability to sleep disruption has been investigated [9,10]. Bonnet and Arand [11] have shown sleep disruption to be consistent across different stressors:

1) 'first night effect': spending the night in a new environment is considered a mild stressor, and leads to sleep disruption in good sleepers.
2) caffeine prior to sleep onset: caffeine represents a mild physiological stressor. Being a stimulant, it is known to disrupt sleep. Participants were given 400 mg half an hour prior to sleep onset.
3) 3 hour phase advance: participants' lights out (bedtime) is 3 hour earlier. This means that they are trying to sleep at a time when their circadian rhythm would not normally allow.
4) 6 hour phase advance: participants' lights out is 6 hours earlier.

It was found that those who demonstrated sleep disruption on the first night in the sleep laboratory also demonstrated greater sleep disruption across the other three conditions, despite being good sleepers at screening and on baseline night (second night in the lab). The 'situational insomniacs' (i.e., those who demonstrated sleep disruption in response to the three stressor conditions, relative to baseline) compared to the 'super sleepers' (those whose sleep maintained across all conditions relative to baseline) also demonstrated increased heart-rate and increased low-frequency (indicative of sympathetic nervous system activity) and decreased

* Corresponding author. Tel.: +44 1865 234 957.
E-mail addresses: Christopher-james.harvey@ndcn.ox.ac.uk, cjay.harvey@gmail.com (C.-J. Harvey).

1087-0792/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.smrv.2013.11.004

high-frequency (a decrease in parasympathetic nervous system activity) electrocardiogram (ECG) spectral power. They also showed a pattern on the multiple sleep latency tests (MSLT) similar to what has been found in primary insomnia (PI): greater MSLT scores suggesting a difficulty with de-arousal. This suggests that the situational insomnia group was more sensitive to stressors, both physiological (caffeine) and psychological (first night effect), and hence more vulnerable to insomnia. Further, the observed sleep disruption seen may have been secondary to increased sympathetic nervous system activity, which may serve as a marker for vulnerability to sleep disruption. It is worth bearing in mind that sensitivity of the sleep system to caffeine may be driven by certain polymorphisms which drive adenosine production, which has implications when using caffeine to measure sleep sensitivity [12].

Drake et al. [13] devised the Ford insomnia responsivity to stress test (FIRST), which has been shown to differentiate those likely to show objective sleep disruption in response to stress, vs. 'stable' sleepers. The same group [10] found that those scoring high on the FIRST demonstrated greater MSLT scores, in accordance with the previously mentioned study. Polysomnography (PSG) scores during the first night in a sleep laboratory were also worse in those scoring higher on the FIRST. The PSG results remained significant even after exclusion of those with a past complaint of insomnia. Groups showed no differences on sleep diary measures obtained for two weeks prior to coming to the lab, indicating that the sleep disruption is likely due to 'the first night effect', rather than a faulty basal sleep system. Differences in MSLT scores became non-significant when those with a past complaint of insomnia were excluded. This is not surprising given the evidence suggesting that a past episode of insomnia is the greatest predictor of a new episode [2,14]. Taken as a whole, the work suggests that individuals who are good sleepers at any given time possess a range of vulnerability to sleep disruption in the absence of current insomnia that is quantifiable.

Evidence to date is supportive of the existence of a trait-like vulnerability to insomnia and suggests that this is driven by an augmented response to stress. Despite these findings there is still very little work assessing the make-up of the vulnerable phenotype. Therefore, the aetiology of insomnia from symptom through to the development of an insomnia syndrome is poorly understood.

Epidemiological studies suggest that life stress [2,15], and a predisposition to arousability [16] are amongst the strongest predictors of insomnia. This suggests that an individual's reaction to stress predicts the likelihood that they will develop insomnia. The hyperarousal theory of insomnia [17] purports that the insomnia population shows increased activation of the central nervous system throughout the 24 h cycle. Such hyperarousal has been indexed via cortisol output [18,19], increased brain activation [20] and increased heart-rate [21,22]. This further implicates the role of the stress-system in the development of insomnia syndrome.

Stress-reactivity is not solely a physiological construct, but rather a psychobiological one. So far, there has been no attempt to understand how biology and psychology interact to create an individual who is more prone to developing insomnia symptoms, and therefore insomnia syndrome. This review aims to evaluate the evidence supporting the existence of a vulnerable phenotype, referencing studies on familial aggregation of sleep and insomnia, and a discussion of which genes may be involved. There will be a particular focus on genetics which may control response to stress, specifically the *5HTTLPR* serotonin transporter polymorphism.

Lastly, psychological factors will be considered, concluding that a vulnerable phenotype does exist and that it is likely characterised by faulty stress-management, at both the physiological and psychological levels. The merit of a more profound understanding of predisposing factors is in the ability to help prevent insomnia in those who are vulnerable, the development of education programmes, and in the provision of further insights into developing more robust, individually tailored, treatment programmes.

Familial aggregation: at risk from birth

A moderate genetic component has been demonstrated in healthy sleep, both in humans and in animals, leading to the mapping of several loci which may be involved in sleep regulation. Studies on normal sleep in twins have demonstrated strong concordance in slow wave sleep, suggesting about 50% heritability, as well as similarities in sleep onset latency and in sleep disruption that are not solely accounted for by environmental factors [23–26]. There seems to be a strong familial component in other sleep disorders such as narcolepsy, parasomnias, sleep apnoea, idiopathic insomnia, hypersomnia and delayed sleep phase syndrome. It is therefore likely that other sleep disorders i.e., primary insomnia, also have genetic/familial components: this has an obvious bearing when considering predisposing factors and in understanding the psychobiology of insomnia syndrome.

Work on familial aggregation of sleep is somewhat sparse (Table 1 provides a summary of published studies which have a particular focus on familial aggregation of primary insomnia (PI)); however, work to date suggests PI is heritable and related to anxiety, depression and stress-reactivity. LeBlanc et al. [2] point out that family history was the second strongest predictive factor in new cases of insomnia syndrome. The implication here is that there may be a familial predisposition in some: a vulnerable phenotype.

Bastien and Morin [27] found in a well-defined sample of patients reporting to a sleep clinic that 35% have a first or second degree relative with a current or past sleep problem. The mother was the most commonly affected member, with 45% of mothers having a past problem and 39% a current problem with insomnia. Further, there was a trend towards a higher familial incidence in those reporting earlier onset vs. those reporting a later onset. Speculatively, this suggests that certain subtypes of insomnia may have different aetiologies i.e., idiopathic insomnia which is defined in the international classification of sleep disorders (ICSD-2) as a sleep complaint with an insidious onset during infancy may develop differentially from psychophysiological insomnia which typically starts in young adulthood [28]. Neither of these subtypes is differentiated in the diagnostic and statistical manual of mental disorders (DSM-IV). There was no attempt in this study to follow-up family members, or to verify the existence or severity of insomnia.

Dauvilliers et al. [29] investigated individuals with either primary insomnia ($n = 77$) or insomnia due to a psychiatric disorder ($n = 104$), in order to differentiate aetiologies (methods of assessment are outlined in Table 1). This is the only study to exclude other sleep disorder on the basis of PSG and a physical examination was also carried out by sleep-specialist physicians, thus allowing for assessment of the relative contribution of psychological, behavioural and medical factors to insomnia. This cohort represents the most thoroughly defined group within the published work in this field.

Results from the primary insomnia group suggest that the risk of developing insomnia is 6.65 times greater in those who have a first-degree relative with PI compared to those who do not. Consistent with Bastien and Morin the mother was found to be the most commonly affected relative (42%). Interestingly, the risk value decreased to 1.63 for insomnia related to psychiatric disorder, suggesting differing degrees of genetic contribution.

This work is the first work to verify the existence of insomnia in a family member by asking the indicated family members to complete the insomnia severity index (ISI), and also to employ a control group of proband spouses ($n = 90$) who were also assessed with the ISI, and via clinical interview. This goes someway to controlling for environmental factors i.e., if the current sleeping