Physiological Correlates of Insomnia

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Abstract Insomnia is a prevalent sleep disorder that is typically comorbid with medical, psychiatric, and other sleep disorders. Yet, it is a disorder with its own course and morbidity that can persist if untreated. This chapter describes the physiological correlates of insomnia expressed during sleep and during the daytime. Together, the data from nighttime and daytime electrophysiology, event-related brain potential recording, neuroimaging studies, sympathetic nervous system, and HPA axis monitoring all suggest that insomnia is a 24 h disorder of hyperarousal.

Keywords Polysomnography · Event related potentials · Multiple Sleep Latency Test · Sympathetic nervous system · HPA

Contents

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1 Introduction

Insomnia is the most prevalent sleep disorder in the population with approximately 30 % of respondents reporting insomnia symptoms and 20 % meeting diagnostic criteria (Roth et al. 2007). Over the past decade there has been a major paradigm shift in understanding the pathophysiology, diagnosis, and treatment of insomnia. It is now recognized that insomnia is a disorder with significant morbidity and its own course that can persist for years if untreated (NIH 2005). It typically coexists with any number of medical and psychiatric disorders and other primary sleep disorders. Of particular relevance to the focus of this book is the fact that persistent insomnia is a risk factor for the development of major depressive disorder (MDD), is an important symptom predictive of MDD relapse, and can remain after successful treatment of the MDD (Krystal 2006). Unlike MDD, insomnia coexisting with anxiety disorders typically follows the onset of the specific anxiety disorder and follows relapse of the anxiety disorder (Johnson et al. 2006). This chapter will describe the physiological correlates of *insomnia,* expressed both during sleep and during the daytime. As this chapter will indicate, insomnia can be considered a 24 h disorder of arousal.

2 Insomnia Diagnosis

The *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition (DSM-V) defines *insomnia* (see Table 1) as difficulty initiating sleep, maintaining sleep, and/or early awakening with inability to return to sleep. These complaints are present despite there being an adequate opportunity and circumstances to sleep (American Psychiatric Association 2013). The sleep disturbance must have a frequency of at least three nights per week, a duration of at least 3 months, and cause clinically significant impairment in daytime functioning. The sleep disturbance cannot occur *exclusively* during the course of another sleep disorder and is not attributable to drugs of abuse or medications. When coexisting with a psychiatric or medical disorder the insomnia symptom is prominent and can persist after resolution of the psychiatric or medical disorder.

The DSM-V reflects a number of significant changes from the DSM-IV-R. First, *insomnia* is no longer dichotomized into *primary insomnia* and *comorbid insomnia* (i.e., insomnia related to another disorder). This change in nomenclature moves from the causal attribution that is inherent in a primary versus secondary distinction. DSM-V then directs that any comorbid psychiatric or medical disorder

Table 1 DSM-V diagnostic criteria for insomnia 780.52

(A) A predominant complaint of dissatisfaction with sleep quantity or quality associated with one (or more) of the following symptoms
1. Difficulty initiating sleep
2 Difficulty maintaining sleep
3. Early-morning awakening awakening with inability to return to sleep
(B) The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning
(C) The sleep difficulty occurs at least 3 nights per week
(D) The sleep difficulty is present at least 3 months
(E) The sleep difficulty occurs despite adequate opportunity for sleep
(F) The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia)
(G) The insomnia is not attributable to the direct physiological effects of a substance (e.g., a drug of abuse, a medication)
(H) Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia

be listed. A minimal frequency criteria of insomnia symptoms, three times per week, has been added and the necessary duration of symptoms has been increased from 1 to 3 months. Both of these changes better establish the severity and clinical significance of an insomnia complaint. The DSM-IV-R symptom of "non-restorative" sleep has been removed as it is poorly defined and nonspecific.

A critical feature of *insomnia* carried over from the DSM-IV-R is the inclusion of daytime symptoms in addition to any nighttime sleep symptoms. These daytime symptoms may vary from patient to patient and the diagnostic criteria lists impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning as examples. Importantly, these daytime symptoms cause the patient significant distress and impairment and often are the motivation for a patient to seek treatment. Recognition of the clinical importance of daytime consequences associated with sleep disturbance and the emerging understanding of the pathophysiology of insomnia, which is expressed during the daytime as well as at night (see discussion) has lead to the view that insomnia is a 24 h disorder of arousal (NIH 2005).

3 Electrophysiological Assessment of Insomnia

3.1 Polysomnography

Polysomnography (PSG) is the term used to refer to the continuous recording of multiple physiological parameters during sleep including orbital electrooculograms, at least a centrally derived electroencephalogram, and submental electromyogram, which are the basic parameters used to differentiate sleep and wake and

to score the standard NREM and REM sleep stages (Carskadon and Dement 2011). Clinically, to identify other sleep disorders additional physiologic measures are recorded, such as tibialis electromyograms to assess restless legs and periodic leg movements during sleep and respiratory airflow, effort, and oximetry for sleep-related breathing disorder.

Numerous PSG studies of people with insomnia, defined using various diagnostic criteria and recruited from clinics or the general population, have compared them to volunteers without sleep complaints variously described as "good sleepers" or "normal sleepers". The results have been inconsistent, but some studies have shown increased wake after sleep onset and reduced overall sleep efficiency (e.g., min of wake /min of recording time) in people with insomnia (Bonnet and Arand 2006). One reason for the inconsistency of results is revealed in a frequently referenced early study. Carskadon et al. showed considerable overlap in the sleep efficiency distribution of 122 drug-free people with insomnia to the sleep efficiency distribution of those without insomnia (Carskadon et al. 1976). Insomnia is a symptom-based diagnosis and as currently done PSG is not needed for a diagnosis of insomnia. Consequently, by expert consensus PSG is not performed in the routine evaluation of insomnia unless there is suspicion of sleep-related breathing disorder or restless legs/periodic leg movement disorder (Schutte-Rodin et al. 2008).

The PSG also yields information regarding what is termed "sleep architecture," which refers to the amount of the various sleep stages and the progression through NREM to REM sleep cycles across the night. Some studies have reported reduced amounts of REM and NREM stage 3–4 sleep in insomniacs compared to age-matched controls (Mendelson et al. 1986; Gillin et al. 1979; Roth et al. 2014; Baglioni et al. 2014). Parenthetically, age-matching in such studies is critically important as the amount of stage 3–4 sleep normally declines as a function of age (Carskadon and Dement 2011). Some studies have also found elevated amounts of stage 1 NREM sleep, particularly when multiple nights of sleep are sampled (Salin-Pascual et al. 1992).

Several other analytic approaches to the PSG have assessed what is referred to as the "microstructure" of sleep or "sleep continuity". Identification of primary sleep disorders such as sleep apnea and periodic leg movements raised attention to the clinical significance of the brief (3–15 s) EEG arousal during sleep that follows a breathing disturbance or leg movement event. Brief EEG arousal scoring rules have been developed, which have produced reliable and valid results (Bonnet et al. 2007). Some studies of people with insomnia have found elevated arousal frequencies compared to people without insomnia (Terzano et al. 2003), while other studies have not (Stepanski et al. 1984). Brief arousal frequency relates well to the level of excessive daytime sleepiness (Bonnet et al. 2007), and as will be seen in the next section, excessive daytime sleepiness is not the problem of a majority of people with insomnia.

The issue in insomnia may not be the frequency of arousal, but rather the inability to return to sleep after the arousal. A recently developed analytic approach assesses sleep and wake bout frequency and duration using the standard 30 s PSG epoch-by-epoch sleep versus wake scoring. The number and duration of

each bout of consecutive epochs scored during sleep or wake is tabulated. A recent paper compared fibromyalgia and rheumatoid arthritis patients with comorbid insomnia to age-matched controls and found comparable sleep efficiency among the patients, which was lower than that of the controls (Roehrs et al. 2013). The wake bout duration of both patient groups was twice as long as that of controls. A much larger study (n = 293) comparing people with primary insomnia and people with fibromyalgia to healthy controls showed those with primary insomnia compared to the controls had more frequent and longer wake bouts, as in the previous study of comorbid insomnia (Roth et al. 2014). The larger study also showed those with insomnia had more frequent and shorter sleep bouts than controls. Compared to those with insomnia, the people with fibromyalgia had more sleep bouts and more and longer wake bouts. As in the smaller study, the sleep efficiency of both patient groups was comparable and lower than that of the controls.

3.2 EEG Spectral Analyses

The EEG signal during sleep has been submitted to EEG spectral frequency analyses. Spectral frequency analysis separates the EEG signal into frequency bands and then quantifies signal amplitude over a given frequency band, which is defined as signal power. Some studies have failed to find differences in EEG power in the delta (0.5–3.5 Hz) and theta (3–7 Hz) bands (Buysse et al. 2008), whereas others have reported declines among people with insomnia (Mercia et al. 1998). One of the more consistent EEG spectral findings is an increase in beta (14–35 Hz) and gamma (>35 Hz) EEG activity in people with insomnia compared to age-matched controls (Mercia et al. 1998; Perlis et al. 2001). The International Classification of Sleep Disorders, 2nd edition (ICSD-II) includes the diagnostic entity "paradoxical insomnia" to account for people who report disturbed sleep, but show normal PSGs. Spectral analyses of the sleep EEG of patients with "paradoxical" insomnia have found lower delta and greater alpha (8–12 Hz), sigma (12–14 Hz), and beta activity than controls (Krystal et al. 2002). In such studies the sleep efficiency and sleep architecture of the patients with "paradoxical" insomnia appears normal, despite a patient complaint of disturbed sleep. Since beta and gamma frequencies are a waking EEG component associated with the processing of sensory information or with attentional focus, observing such frequencies during sleep suggests people with insomnia continue to process information while asleep, suggesting an elevated state of arousal (i.e., are "hyperaroused").

3.3 Multiple Sleep Latency Test

As noted earlier, a critical feature of insomnia is the inclusion of daytime symptoms in addition to any nighttime sleep symptoms. The Multiple Sleep Latency

Test (MSLT) uses standard PSG technology and scoring to assess level of sleepiness/alertness, calculated as the average time to fall asleep on 4–5 tests conducted at 2 h intervals across the day. Data are now emerging to indicate that people with insomnia have unusually high MSLT latencies relative to control subjects (Bonnet and Arand 1995; Stepanski et al. 1988; Roehrs et al. 2011). Difficulty falling asleep during the daytime after a night of disturbed sleep, despite feeling fatigued, is a frequent daytime symptom reported by people with insomnia. A large study (n = 95) of people with insomnia, diagnosed by DSM-IV-R criteria, and the additional criterion of a sleep efficiency $\leq$85 %, found that elevated MSLT scores were stable for over 8 months (Roehrs et al. 2011). Importantly, those with the highest MSLTs had the shortest total sleep times, which is opposite to what is seen in control subjects (e.g., short sleep times produce short MSLTs). Parenthetically, the study also showed that there is a wide distribution of MSLT latencies among people with insomnia and that there is a small subset of people with insomnia who are "sleepy" by MSLT (e.g., average latency <8 min) criteria.

Given that among healthy controls, reduced nocturnal sleep duration is associated with greater sleepiness (e.g., shorter sleep latencies) on the MSLT (Drake et al. 2001), it was hypothesized that homeostatic sleep mechanisms are weakened in people with insomnia (Stepanski et al. 2000). To test the homeostatic mechanisms in insomnia, the effects of total sleep deprivation on the MSLT and on recovery nocturnal sleep were compared to age-matched healthy controls (Stepanski et al. 2000). Although elevated at baseline relative to controls, the average daily sleep latency on the MSLT after total deprivation was reduced in those with insomnia to similar levels as controls. The total sleep time of people with insomnia was less than that of controls at baseline (6.1 versus 7.6 h), and it increased to that of the controls (7.5 versus 7.8 h) on the recovery night, suggesting normally responsive homeostatic sleep mechanisms. These data then support the hypothesis that most people with insomnia show a reliable disorder of "hyperarousal" (see discussion) with increased wake drive both at night and during the day.

3.4 Auditory Evoked Potentials

Another method to assess hypothesized "hyperarousal" in insomnia is analysis of event-related brain potentials (ERPs), which is a classic electrophysiological method employed in a variety of psychiatric disorders. The electrophysiological response to any stimuli presented repeatedly and then averaged, yields a wave form with consistent negative and positive polarity components at different temporal points (ms) after stimulus onset. ERPs to auditory tasks have been measured in people with insomnia during the daytime, at sleep onset, and during sleep. Using an oddball paradigm (i.e., stimuli presented during a reading task) in people with insomnia, a self-rated bad night of sleep was followed during the day by an enlarged amplitude P300 (e.g., a positive wave at 300 ms) and a lower P300 after a good night (Devoto et al. 2003, 2005). In comparing people with insomnia to self-described

"good sleepers" heightened N1 (most negative peak between 60 and 110 ms) amplitudes were seen in those with insomnia on both morning and evening testing (Bastien et al. 2008). Recently, the ERPs of night workers with insomnia were compared to night workers with sleepiness and asymptomatic night workers (Guymenyuk et al. 2014). Tested during their night shift, the night workers with only insomnia showed an enhanced N100 amplitude and a decreased P200 amplitude relative to asymptomatic night workers and to those with sleepiness in addition to insomnia (see Fig. 1). During sleep onset people with insomnia only showed increased P2 (most positive peak between 120 and 200 ms) amplitudes and decreased N350 (most negative peak between 250 and 350 ms) amplitudes, interpreted by the investigators as an inability to "disengage from waking sensory processing" during the sleep onset process (Bastien et al. 2008). In another study the oddball paradigm was applied during sleep and the study found increased N1 (most negative peak between 76 and 150 ms) and decreased P2 (most positive peak between 150 and 260 ms) amplitudes during the first 5 min of stage 2 NREM sleep, but thereafter during the remainder of the night *no* ERP differences from the control subjects were seen (Yang and Lo 2007). These studies of ERPs in people with insomnia, while differing in methodology and specific ERP findings, do suggest increased sensitivity to auditory stimulation during waking and reduced sensory inhibition during the sleep onset process. These ERP data are consistent with the MSLT data of people with insomnia, both assessments suggesting hyperarousal.

4 Sympathetic Nervous System (SNS) and Hypothalamic-Pituitary-Adrenal (HPA) Correlates

Insomnia is hypothesized to reflect a 24 h state of hyperarousal. As discussed earlier, this hyperarousal is evident in the prolonged sleep latencies (i.e., about one standard deviation above the mean of a representative population sample) on the MSLT during the day, despite disrupted and shortened nocturnal sleep the previous night seen in people with insomnia (Bonnet and Arand 1995; Stepanski et al. 1988; Roehrs et al. 2011). Evidence also suggests that this physiologic hyperarousal is associated with activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis. Insomniacs show elevated levels of circulating daytime and nighttime catecholamines (Vgontzas et al. 1998), increased metabolic rates (Bonnet and Arand 1995), increased body temperature (Lushington et al. 2000), decreased high frequency heart rate variability (Lichstein et al. 1994), and altered pupillometry patterns (Lichstein and Johnson 1994). HPA augmentation in insomnia is indicated by elevated levels of nighttime urinary free cortisol proportional to the amount of wakefulness during the night (Vgontzas et al. 1998). An activated SNS and HPA axis suggests there may be an underlying central mechanism for the hyperarousal of insomnia, possibly involving corticotropin releasing factor (CRF) neurons.

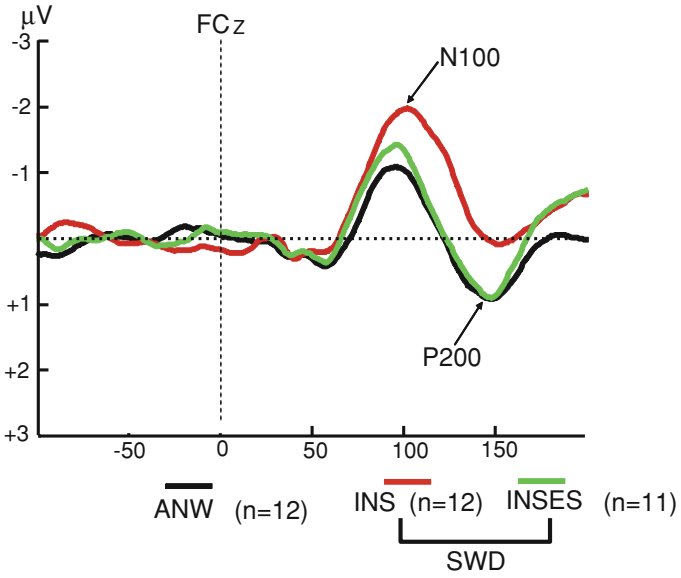

Fig. 1 ERPs at FCz electrode, elicited by tones (1200 Hz, 100 ms duration) in three groups of participants: asymptomatic night workers (ANW) and shift work disorder (SWD) patients with insomnia only (INS) and with insomnia/excessive sleepiness (INSES). Enlarged N100 and decreased P200 are indicators of cortical hyperarousal in insomnia without excessive sleepiness

All these studies have compared people with insomnia to people without insomnia, rather than assessing individual differences among those with insomnia as a function of level of hyperarousal. As noted earlier, the presence of hyperarousal is seen in some people with insomnia, about two-thirds, as defined by the MSLT (Roehrs et al. 2011). In a large sample of people with insomnia it was found that MSLT elevation in insomnia is a stable "trait-like" finding (Roehrs et al. 2011). Recently, it was reported that elevated MSLTs were associated with elevated levels of daytime urinary norepinephrine (see Fig. 2) (Roehrs et al. 2012). This is a first validation of the construct of hyperarousal in insomnia using two concurrent "independent" physiological measures.

5 Neuroimaging

Neuroimaging findings in people with insomnia also support a hyperarousal hypothesis. In PET studies primary insomniacs, relative to healthy controls, showed greater cerebral glucose metabolism during sleep, while awake, and at the transition from wake to sleep and particularly in the ascending reticular activation system (ARAS) (Nofzinger et al. 2004). The hypothalamus, thalamus, amygdala, hippocampus, and prefrontal cortices were also activated during sleep. In a follow-up study also using PET, it was shown that there was a positive correlation between the amount of wake time after sleep onset and the level of cerebral glucose metabolism in the pontine tegmentum and thalamocortical networks in a frontal, anterior temporal, and anterior cingulate distribution (Nofzinger et al. 2006).

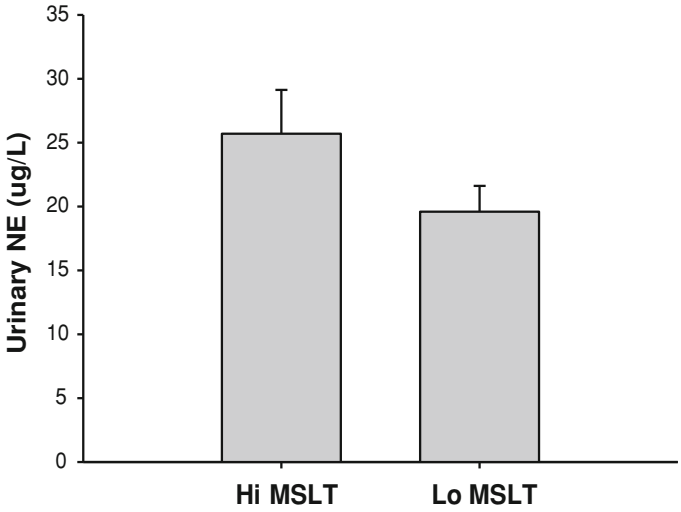

Fig. 2 Daytime (0700–1500 h) urinary NE (ug/L) level in people with insomnia and high MSLT latencies versus those with low MSLT latencies ($p < 0.01$)

6 Pathophysiology of Insomnia

It is hypothesized that the pathophysiology underlying the hyperarousal and sleep disturbance of insomnia is at least in part a HPA axis dysfunction, specifically increased corticotrophin releasing factor (CRF) activity (Richardson and Roth 2001; Drak et al. 2003). First, studies in normal volunteers without insomnia have shown IV administration of cortisol or adrenocorticotropic hormone (ACTH) reduces rapid eye movement sleep (Born et al. 1989) and IV administration of CRF reduces slow wave sleep (Holsboer et al. 1988), both of which are consistent with PSG findings in insomnia (Baglioni et al. 2014). In other words, HPA axis activation including CRF elevation is disruptive of sleep in healthy volunteers. In addition, a study comparing people with chronic primary insomnia to control subjects showed that those with insomnia had increased evening and nocturnal plasma ACTH and cortisol concentrations (Vgontzas et al. 2001; Vgontzas et al. 2013). Moreover, among those with insomnia the level of cortisol was proportional to the level of the degree of objective PSG-defined sleep disturbance (Vgontzas et al. 2013). In a study of severe chronic insomnia, the area under the curve of cortisol levels was strongly correlated ($r = -0.91$) with the level of sleep efficiency (Rodenbeck et al. 2002). Some of the studies that have failed to find cortisol elevations in people with insomnia relative to controls, also do not show PSG-defined sleep disturbances. For example, in one negative study the sleep efficiency of subjects with insomnia was 88.2 % and that of the controls was 88.6 % (Riemann et al. 2002). This suggests that cortisol elevation may be a marker of severe insomnia.

Data from animal studies suggest that CRF functions centrally as a neurotransmitter in the locus coeruleus. Microinjection of CRF into the locus coeruleus of the rat elicits fear-specific behaviors and a general behavioral activation (Butler et al. 1990) and local CRF infusion increases locus coeruleus cell firing and the release of norepinephrine (Page and Abercombie 1999). In addition, CRF positive cells and fibers have been localized to the locus coeruleus through immunohistochemical

labeling (Swanson et al. 1983). That brain CRF has a sleep-disruptive effect has been shown in several animal models. Stress normally reduces sleep time and an antagonist of CRF blocks the stress-induced reduction of sleep time; that is, sleep time normalizes (Matsumoto et al. 1997). Importantly, the antagonist itself has no effect on baseline sleep.

7 Insomnia, Hyperarousal, and Mood and Anxiety Disorders

As noted in the introduction, insomnia is a risk factor for the development of major depressive disorder (MDD), is an important symptom predictive of MDD relapse, and can remain after successful treatment of the MDD (Krystal 2006). This raises questions as to how insomnia and MDD are related (e.g., whether insomnia causes MDD, MDD causes insomnia, or either condition can cause the other) or rather than a cause-effect relation, whether insomnia and MDD share components of a common pathophysiology. It should be noted that not all insomnia leads to MDD and that MDD is not highly predictive of the development of new insomnia. An epidemiological study in adolescents explored the strength of the directionality of the insomnia and MDD association (Johnson et al. 2006). Prior insomnia carried a 3.8 times greater risk of MDD, adjusting for gender, race/ethnicity, and anxiety, while prior depression was not associated with onset of insomnia.

In attempting to understand the relation of hyperarousal, CRF/HPA axis dysregulation and insomnia comorbid with MDD, it also must be noted that MDD is not a homogeneous entity. MDD has been clinically characterized as two distinct subtypes of contrasting psychological and neurovegetative symptoms (Gold and Chrousos 2002). Melancholic patients are anxious, anorectic, unresponsive to psychosocial stimuli, more depressed in the morning and exhibit insomnia. Patients with atypical depression are lethargic, fatigued, hyperphagic, reactive to the environment, more depressed in the evening and exhibit hypersomnia. These two subtypes exhibit two distinct CRF/NE states (Gold and Chrousos 2002). Melancholic patients show an overactive CRF/HPA axis, while atypical patients show a down-regulated CRF/HPA axis.

It was also noted in the introduction that insomnia coexisting with anxiety disorders (AD) follows, rather than precedes, the onset of the specific AD. The epidemiological study cited earlier also assessed the directionality of the insomnia AD association (Johnson et al. 2006). Prior AD carried a 3.5 risk for subsequent insomnia adjusting for gender, race/ethnicity, and depression, while prior insomnia was not associated with the development of AD. As to hypothesized pathophysiology, regardless of the specific AD, it is critical to note that this literature has not distinguished AD with and without insomnia. The focus of the hypothesized pathophysiology of the various ADs has been on central NE dysfunction (Gold and Chrousos 2002). In addition to neglecting the possible role of comorbid insomnia,

peripheral measures of resting NE (i.e., plasma, urine) are assessed to reflect central NE. But, such measures predominantly reflect peripheral, not, central NE. The literature has not consistently shown that resting NE measures in the various ADs are different from those of controls (Gold and Chrousos 2002). NE challenge studies, in which drugs (e.g., yohimbine) are administered producing NE dysfunction, have been more successful. Relative to controls, patients with panic disorder have shown increased panic attacks, increased ratings of anxiety or nervousness, and increases in various physiological measures reflecting arousal (i.e., blood pressure, pulse, and cortisol) (Kalk et al. 2011). The extent to which the daytime NE challenge that also disrupts nocturnal sleep has not been documented. As noted, we also are unaware of studies that have assessed patients with ADs and comorbid insomnia versus those without comorbid insomnia.

8 Summary

There has been a major paradigm shift over the last decade in understanding the pathophysiology, diagnosis, and treatment of insomnia. That shift is reflected in the way insomnia is defined and diagnosed according to DSM-V. Insomnia is viewed as a disorder with its own course and morbidity that is typically coexistent with other medical, psychiatric, and sleep disorders. Electrophysiological study of the sleep of people with insomnia using standard methods termed polysomnography (PSG) in which sleep/wake and sleep stages are scored in 30 s epochs have not consistently found elevated wake time or disrupted sleep stage progression relative to age-matched controls. Studies using analyses of the microstructure of the PSG have found increased fragmentation of sleep with brief arousals (<15 s) and spectral analyses of the sleep EEG has shown increased fast frequency [e.g., beta (15–35 Hz) and gamma (>35 Hz)] EEG activity. Testing speed of sleep onset during the daytime using PSG methods [Multiple Sleep Latency Test (MSLT)] have shown usual daytime alertness, not sleepiness, particularly given short nocturnal sleep times and daytime sleepiness/fatigue symptoms. Auditory evoked potential (ERP) assessment during sleep and during the day have suggested increased sensitivity to auditory stimulation during waking and reduced sensory inhibition during sleep. This increased CNS activation is also reflected in neuroimaging studies. Sympathetic nervous system and hypothalamic-pituitary-adrenal assessments also support the hypothesis that insomnia reflects a 24 h state of hyperarousal. Given that insomnia is a common symptom in both mood and anxiety disorders, a future focus on understanding the relation of insomnia and its hyperarousal and CRF/HPA axis dysregulation in mood and anxiety disorders will be important. It may be that insomnia shares components of a common pathophysiology with depression or anxiety?

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