Objective Measures are Useful in Subtyping Chronic Insomnia

Commentary on Edinger et al. Does physiological hyperarousal enhance error rates among insomnia sufferers? *SLEEP* 2013;36:1179-1186.

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The diagnosis of chronic insomnia, the most prevalent sleep disorder, is based solely on subjective complaints, whereas objective measures are currently considered of little use in the diagnosis, differential diagnosis, severity assessment, or therapeutic response of insomnia.¹

The article by Edinger et al.² in this issue of *SLEEP* adds to the accumulated recent evidence that objective measures can be useful in predicting the impact of chronic insomnia on health, and in particular, on neurocognitive performance. The authors examined the association between physiological hyperarousal and response accuracy in reaction-time tasks measuring switching attention in a large sample of insomniacs and normal sleepers. The multiple sleep latency test (MSLT) was used as a measure of physiological hyperarousal (i.e., values > 8 minutes were associated with “alertness,” whereas values < 8 minutes were associated with “sleepiness”).

Edinger et al. found that “alert” participants showed lower objective sleep efficiency, suggesting 24-h hyperarousal in this chronic insomnia group. The authors found that the group with the highest number of errors were the alert insomniacs. The authors concluded that physiological hyperarousal, although associated with higher alertness, adversely affects neuropsychological performance requiring attention. The authors also interpreted their results as consistent with recent findings of Fernandez-Mendoza et al.³ that chronic insomnia with physiological hyperarousal is associated with neurocognitive deficits in switching attention. Fernandez-Mendoza et al. conducted a population-based study in which physiologically hyperaroused insomniacs were ascertained by objective short sleep duration.³

For more than 40 years, both cognitive-emotional and physiological hyperarousal have been suggested as characteristics of chronic insomnia. From the pioneering studies of Peter Hauri, Lawrence Monroe, and Anthony Kales, until today, insomnia has been associated with emotional arousal as well as increases in physiological measures including core body temperature, skin resistance, power in electroencephalographic fast frequencies, 24-h whole body and brain metabolic rate and heart rate, as well as impaired heart rate variability and increased secretion of stress hormones (i.e., catecholamines and cortisol).⁴⁻⁹ This has led to the concept that insomnia is a disorder of cog-

nitive-emotional and physiological hyperarousal and not a result of sleep loss. However, these physiological findings were confirmed in several but not all studies, which raised doubts about the universality of the physiological hyperarousal model. Furthermore, proposed sleep lab measures did not appear to be clinically useful, and there has been throughout the years an emphasis on a thorough clinical evaluation and assessment of patients with chronic insomnia.¹ Inadvertently, this may have resulted in a relative neglect of the neurobiology of the disorder.

In 1998 and 2001, Vgontzas et al. reported that catecholamine excretion and cortisol plasma levels were directly related to the degree of objective sleep disturbance in individuals with insomnia.^{10,11} Specifically, increased levels of cortisol and catecholamines were observed in those insomniacs with objective short sleep duration but not in those with “normal” sleep duration. These findings led to the hypothesis that there are two types of insomnia—the first associated with physiological hyperarousal (i.e., short sleep duration and activation of the stress system), and the second not associated with physiological hyperarousal or activation of the stress system. If this hypothesis was true, these two subtypes would be associated with distinct effects on the cardiometabolic and neurocognitive systems, given the adverse impact of chronic activation of both limbs of the stress system (e.g., hypercortisolemia) on physical and mental health. This hypothesis was tested in several recent studies that showed that insomnia with objective short sleep duration, but not insomnia with normal sleep duration, is associated with a higher risk for hypertension,¹²⁻¹⁴ impaired heart rate variability and pre-ejection period,¹⁵⁻¹⁷ type 2 diabetes,¹⁸ glucose or insulin sensitivity alterations,^{19,20} neurocognitive impairment,³ poorer depression outcome,²¹ increased mortality in men,²² and a higher risk for chronicity and unremitting course.^{23,24}

The results of the study by Edinger et al.² represent a significant step forward, since the authors used another measure of physiological hyperarousal (i.e., MSLT) and reached very similar findings. Several studies have shown that patients with insomnia—despite their complaints of lack of adequate sleep and daytime fatigue—have increased sleep latencies during daytime MSLT sleep, which contrasts with the significantly shortened sleep latencies of sleep-deprived normal sleepers.²⁵⁻²⁸ The findings of Edinger et al.² confirm that at least one form of chronic insomnia involves a disorder of physiological hyperarousal, and that measures of physiological hyperarousal can be useful in subtyping this disorder by detecting its more severe form.

We believe that among all the proposed measures of physiological hyperarousal, sleep duration from nighttime PSG, sleep latency from daytime MSLT, and peripheral cortisol levels, are available and useful in routine clinical practice. However, nighttime PSG and daytime MSLT are expensive and incon-

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venient and also limited by phenomena such as night-to-night variability and first-night effect. Also, usefulness of cortisol in predicting the severity of insomnia (e.g., its association with cardiovascular and psychiatric morbidity) has not been tested in large studies. Obviously there is a need for development and validation of more practical and cost-effective tests as measures of physiological hyperarousal, including such candidate measures as 1-2 weeks of nightly actigraphy, peripheral measures of sympathetic activity, peripheral saliva cortisol levels, or others. Despite these current limitations and challenges, the accumulating scientific literature illustrated in the study by Edinger et al.² suggest that objective measures are useful in subtyping chronic insomnia, and whenever available they can guide our diagnostic and treatment recommendations. For example, in a patient with insomnia and short sleep duration, the goal would be to decrease physiological hyperarousal and lengthen sleep time, most likely with biological methods, whereas in a patient with insomnia and normal sleep duration, the goal would be to address the cognitive-emotional and behavioral underpinnings of insomnia.²⁹ We believe that the time is ripe for our field to pursue and test these hypotheses and questions on the psychological pathophysiology of insomnia.

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