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Genetic Influences Contribute To Neurobehavioral Response To Acute Sleep Deprivation

Commentary on Kuna et al. Heritability of performance deficit accumulation during acute sleep deprivation in twins. SLEEP 2012;35:1223-1233.

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Sleep deprivation as an experimental protocol allows for the investigation of the underlying processes of sleep as well as characterising potential functional impairments during and following prolonged wakefulness. Numerous studies have investigated the consequent neurobehavioral impairments in performance on tasks of sustained attention, typically using the psychomotor vigilance task (PVT). Performance deterioration on the PVT is considered to represent impaired behavioral alertness and sleep tendency,[1] and hence can be considered an indicator of sleep-homeostatic drive. The impact of sleep deprivation is considered to be in part dependent on sleep/circadian influences, arousal system influences, and individual characteristics,[2] suggesting that resulting neurobehavioral impairments are likely to show vast interindividual differences. One factor considered to influence interindividual response to sleep deprivation is genetics.

In this issue of *SLEEP,* Kuna and colleagues[3] present the first twin study to assess the heritability of response to experimentally induced total sleep deprivation. The authors assessed the accumulation of performance deficits on the PVT (defined as lapses > 500 msec per trial, at regular 2-hour intervals) following 38 hours of total sleep deprivation. The accumulation of "sleep drive" demonstrated substantial genetic influence, with broad-sense heritability estimated at 83%.

One of the main strengths of the paper by Kuna et al.[3] is the use of three complimentary methods of analysis to assess heritability. First, heritability was assessed using classical methods comparing intra-class correlation coefficients between monozygotic (MZ) and dizygotic (DZ) twin pairs. Second, ANOVA based methods were used to test the validity of the twin model (testing the assumption that the phenotype of interest does not differ as a function of zygosity). Finally, standard biometrical model-fitting approaches of maximum likelihood estimation were used to allow for the examination of possible modes of genetic transmission (i.e., allowing variance to be parsed into additive and non-additive [dominance] genetic influences). Additionally, the stability of the trait in question was assessed by comparison of the grand mean of performance lapses in the final 24 hours of the deprivation protocol within MZ twin pairs. This method of analysis allows for the direct comparison of earlier work by Van Dongen and colleagues,[4] who used within-individual test-retest reliability methods to assess trait stability. The resulting estimates from these different methods of analysis led to the same conclusion: that response to sleep deprivation is a highly stable, genetically determined trait.

As well as observing a robust behavioral indicator of the sleep homeostatic drive, the report by Kuna and colleagues also reveals a circadian mechanism, as indicated by a plateau in performance deficits after 24 hours.[3] This plateau reflects the input of the circadian alerting signal on performance ability. Accordingly, this demonstrates that behavioral response to sleep deprivation is partly influenced by the interaction between sleep-homeostatic and circadian processes. Further research using multivariate model-fitting approaches within the twin design will be important to determine whether the genes influencing the sleep homeostatic process are shared with those influencing the circadian process. One such study using subjective measures of sleep and circadian rhythmicity suggests substantial genetic overlap between phenotypes.[5] This research points to the possibility that these two interacting processes may be orchestrated by common genes. Indeed, Kuna and colleagues attempted to identify molecular genetic polymorphisms predicting individual differences in neurobehavioral response to sleep deprivation. The candidate gene association approach was used to assess associations with a variable number tandem repeat (VNTR) in PERIOD3 (PER3), and a single nucleotide polymorphism (SNP) in adenosine deaminase (ADA). While these genes were selected because of their proposed role in measures of sleep homeostasis and circadian rhythmicity,[6-9] the authors found no associations with measures of vigilance performance over the sleep deprivation protocol. However, given the inconsistencies within the field regarding the genes that control sleep and components of the molecular clock (in particular PER3), further research should consider the possibility that interactions between genes, and indeed environmental influences, may account for these inconsistencies.

A subsidiary aim of Kuna et al.[3] was to assess heritability of properties of the sleep polysomnogram (PSG) at baseline. Their study represents one of the largest investigations of PSG in twins. In accordance with previous studies, there was evidence of substantial genetic influences on: (i) the proportion of sleep stages across the night; (ii) sleep efficiency; and (iii) wake after sleep onset. While there is accumulating evidence from twin studies of the heritability of EEG parameters during wakefulness and sleep,[10,11] the authors note that no previous studies have attempted to assess heritability of the sleep

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homeostatic drive in humans (as indicated by changes in EEG NREM delta power). Future twin studies using power spectral analysis to assess changes in frequency and amplitude characteristics will enable us to determine whether, like characteristics of the waking EEG, SWA, and delta power during sleep are under genetic control. In addition, multivariate genetic model fitting analyses will enable researchers to determine the extent to which individual components of the sleep EEG share underlying genetic factors.

In addition to assessing EEG activity *prior* to sleep deprivation, further research assessing EEG characteristics *during* sleep deprivation will allow us to identify correlates of the decrements in neurobehavioral performance. Earlier studies noted reduced alpha activity and increased delta and theta activity in the waking EEG during sleep loss.[12] It is also well documented that recovery sleep *following* sleep deprivation is characterised by significant changes in EEG activity compared to baseline sleep, in particular an increase in SWA, and power density in the delta band.[13,14] De Gennaro et al. observed high intraindividual stability and heritability of NREM sleep EEG in the 8-16 Hz range in a small sample of twins.[15] Further studies assessing the heritability and stability of EEG *changes* during and following sleep deprivation, as well as examining its synchronicity with performance deficits, will be an important adjunct to the current results of Kuna et al., potentially enabling us to identify specific characteristics of brain activity responsible for the objective changes in neurobehavioral performance. This may provide further steps towards identifying biological markers of sleepiness.

CITATION

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DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.

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