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Behavioral and Genetic Markers of Sleepiness

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Neurobehavioral responses to acute total and chronic partial sleep deprivation occur in healthy adults and are particularly evident in vigilant attention performance. There are large inter-individual differences in the degree of cognitive deficits—such differences are manifested in proportionality between the mean and variance as sleep loss progresses. It has recently been demonstrated via laboratory experiments that differential neurobehavioral vulnerability to sleep deprivation is not random—but rather is stable and trait-like—strongly suggesting a phenotypic response with possible genotypic involvement. These experiments also showed that vulnerability was not explained by subjects' baseline functioning or a number of other potential predictors. Differential vulnerability has been shown to extend to chronic partial sleep deprivation. One potential genetic biomarker for such differential vulnerability is the human leukocyte antigen (HLA) *DQB1*0602*, an allele which we recently demonstrated predicts interindividual differences in sleepiness, physiological sleep, and fatigue to chronic partial sleep deprivation in healthy adults. Determination of biomarkers of individual differences to sleep loss will help identify those individuals in the general population who are most in need of prevention of sleep debt and in need of effective countermeasures for sleep loss; will further understanding and management of vulnerability to excessive sleepiness due to common sleep and medical disorders; and will inform public policies pertaining to the need for adequate sleep.

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SUPPLEMENT

Prevalence and Consequences of Sleep Loss

Studies estimate that 20% to 40% of the adult US population sleep less than 7 hours per night[1]—the minimum sleep duration necessary to prevent cumulative deterioration in performance on a range of cognitive tasks.[2,3] The proportion of people curtailing their sleep due to lifestyle is increasing,[1] and is likely higher than surveys indicate, since physiological sleep duration is typically at least one hour less than self-reported sleep duration.[4,5] Moreover, sleep loss has become a significant public health concern as population studies have found reduced sleep duration (less than 7 hours) associated with increased risks of obesity, morbidity, and mortality.[6-8]

Sleep loss, including chronic partial sleep deprivation (PSD)—a condition experienced by millions of people on a consecutive and daily basis—can result from medical conditions, sleep disorders, work demands, stress/emotional distress, and social/domestic responsibilities.[1] In addition, for the majority of people, sleep loss directly causes significant risks via increased fatigue and sleep propensity, and via deficits in mood and neurocognitive functions including vigilant and executive attention, cognitive speed and working memory, and executive functions.[1,9,10]

Stable Trait-like Individual Differences in Response to Sleep Loss

Our laboratory was the first to experimentally demonstrate that subjects undergoing acute total sleep deprivation (TSD)—in which no sleep is obtained—show differential vulnerability to sleep loss, demonstrating robust inter-individual (trait-like, phenotypic) differences in response to the same laboratory conditions, as measured by various physiological and subjective sleep measures and neurobehavioral tasks sensitive to sleep loss.[11,12] The intraclass correlation coefficients (ICCs)—which express the proportion of variance in the data explained by systematic interindividual variability—revealed that stable responses accounted for 58% and 68% of the overall variance in Psychomotor Vigilance Test (PVT) lapses (greater than 500 ms reaction times) between multiple sleep-deprivation exposures in the same subjects.[2,12-14] Thus, individuals who showed high PVT lapse rates during TSD after one exposure also showed high PVT lapse rates during a second exposure; similarly, those with low PVT lapse rates during one exposure showed low PVT lapse rates during a second exposure. Most importantly, because these high ICCs were found when the subjects were exposed to TSD 2-3 times under markedly different conditions (e.g., high versus low stimulation[13]; 6 h versus 12 h sleep time per night[11]), the vast differences in cognitive vulnerability to sleep deprivation are considered trait-like. While some individuals are highly vulnerable to cognitive performance deficits when sleep deprived (Type 3 responses), others show remarkable levels of cognitive resistance to sleep loss (Type 1 responses), and others show intermediate (Type 2) responses.[12]

Other researchers have confirmed our findings of large, stable differences in cognitive responses to acute TSD.[15,16] Notably, such differences have not been accounted for by baseline functioning, by circadian morningness-eveningness, by demographic factors (e.g., age, sex, IQ), or by habitual sleep timing; psychometric scales also have not reliably identified cognitively vulnerable individuals.[2,11,14] Our group[2,17] and others[18] have found similar differential vulnerability to chronic PSD, in which sleep is restricted to 3-7 hours time in bed per night.

Genetic Biomarkers of Individual Differences in Response to Sleep Loss

The stable, trait-like inter-individual differences observed in response to acute TSD, with intraclass correlation coefficients accounting for 58%-92% of the variance in neurobehavioral measures,[11,12] point to an underlying genetic component. Despite this link, however, relatively little is known about the genetic basis of differential vulnerability in healthy subjects undergoing deprivation.[9,19]

Available data suggest that common genetic polymorphisms (variations) involved in sleep-wake, circadian, and cognitive regulation may underlie these large phenotypic differences in neurobehavioral vulnerability to sleep deprivation and may thus represent biomarkers in healthy adults.[9,19,20]

To this end, we investigated the role of the human leukocyte antigen (HLA) *DQB1*0602* allele in response to chronic PSD. The *DQB1*0602* allele is closely associated with narcolepsy, a neurological sleep disorder characterized by excessive daytime sleepiness, fragmented sleep, and shortened REM latency,[21] and is also found in 12-38% of healthy adult sleepers in the general population.[21,22] During baseline, although *DQB1*0602* positive subjects were significantly sleepier and more fatigued by self report, they showed greater sleep fragmentation, and decreased sleep homeostatic pressure (measured by slow-wave energy; SWE) and differentially sharper declines during the night.[23] During chronic PSD, despite SWE elevation comparable to *DQB1*0602* negative subjects, *DQB1*0602* positive subjects were sleepier and showed more fragmented sleep. Moreover, they showed differentially greater reductions in REM latency and smaller reductions in stage 2 sleep, along with differentially greater increases in fatigue. Both groups demonstrated comparable cumulative decreases in cognitive performance and increases in physiological sleepiness to chronic PSD.[23]

*DQB1*0602* positivity in a healthy population may represent a continuum of some sleep-wake features of narcolepsy. *DQB1*0602* was associated with inter-individual differences in sleep homeostasis, physiological sleep, sleepiness and fatigue, but not in cognitive measures, during baseline and chronic PSD.[23] Therefore, *DQB1*0602* may represent a genetic biomarker for predicting individual differences in both basal and sleep loss conditions. The influence of the *DQB1*0602* allele on sleep homeostatic and neurobehavioral responses has not been examined in healthy subjects undergoing acute TSD nor have our findings been replicated in an independent sample of individuals undergoing chronic PSD.

Future Directions in the Search for Biomarkers to Sleep Loss

Currently, it remains unknown whether the same individuals vulnerable to the adverse effects of acute TSD are also vulnerable to chronic PSD. The handful of published reports comparing responses to both acute TSD and chronic PSD have used small sample sizes and limited assessments,[2,24,25] and only one published study[24] has systematically studied the same subjects in both types of sleep loss. Considering this, specific candidate genes may play different roles in the degree of vulnerability and/or resilience to the neurobehavioral and homeostatic effects of acute TSD and chronic PSD. Future studies are needed to explore this avenue of research and to determine predictors of those individuals most vulnerable to the neurobehavioral effects of both types of sleep loss.

With the exception of two recent studies,[17,23] all candidate gene studies involving sleep physiological and neurobehavioral variables have employed small sample sizes and have only examined homozygotic individuals.[26-31] Larger sample sizes and assessment of phenotype-genotype relationships in both homozygous and heterozygous individuals are needed to definitively determine whether such candidate genes involved in regulation of sleep-wake, circadian, and cognitive functions are associated with inter-individual neurobehavioral responses to sleep loss across an entire population. This is particularly critical given that individuals are necessarily categorized into different genotypes, reducing sample sizes in each subgroup. Thus, future candidate gene studies must employ sample sizes in the hundreds to detect statistically reliable differences across genotypes. In addition, replication of findings in independent samples is needed to determine whether findings are genuine and are not due to chance. Ideally, studies should also be replicated in different ethnic groups to increase generalizability of the findings. Finally, other genetic approaches, including GWAS and linkage studies, are needed to complement candidate gene methods, for assessing individual differences at baseline as well as in response to sleep deprivation.

Conclusions

The impairing effects of sleep loss on a variety of neurobehavioral functions are well-established consequences of sleep deprivation. However, there are substantial differences in the extent to which individuals experience such deficits when sleep deprived. In recent years—since our group originally identified such stable, phenotypic neurobehavioral vulnerability to sleep loss in healthy adults—a rapidly growing search for biomarkers of this neurobehavioral vulnerability has emerged in an effort to identify this large and critical source of variance in human neurobehavioral responses to sleep deprivation. Indeed, recent seminal findings employing candidate gene techniques highlight the feasibility of such efforts, but future research in this area must employ both initial and replicate sample sizes large enough to ensure that findings are reliable.

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DISCLOSURE STATEMENT

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