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Determinants of Cortical Synchrony

Commentary on Bachmann et al. The BDNF Val66Met polymorphism modulates sleep intensity: EEG frequency- and state-specificity. SLEEP 2012;35:335-344.

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It has been recognized for almost a century that sleep plays a critical role in learning because it allows the brain to optimize memory formation and consolidation.[1] It is only more recently, however, that the molecular mechanisms of brain plasticity involved in learning are being directly linked to the regulation of sleep intensity.[2] The most reliable index of sleep intensity is measured in the electroencephalogram (EEG) as the activity in delta frequencies (1-4 Hz) during NREM sleep. Sleep deprivation, which results in increased homeostatic pressure for sleep, results in a proportional increase in delta activity (or slow wave activity [SWA]) in the next sleep opportunity. Indeed, factors known to change the properties of neuronal communication at the synaptic level, like BDNF (brain-derived neurotrophic factor), have been implicated in regulating SWA in animals.[3] This is an intriguing connection, because an important function of BDNF is that it facilitates long term potentiation (LTP), which represents a synaptic correlate of learning and memory.[4]

In the current issue of *SLEEP*, Bachmann and colleagues[5] examine the role of BDNF on sleep regulation by comparing humans that differ in a functional *BDNF* polymorphism. This polymorphism results in an amino acid change (Val66 to Met66) that impairs the activity-dependent secretion of BDNF and has been associated with reduced performance on memory tasks.[6] Importantly, Bachmann et al.[5] find that individuals carrying a copy of the allele producing the impaired Met66 variant have decreased sleep intensity compared to non-Met66 carriers. Indeed, the Met66 carriers spent less time in slow wave sleep, had lower delta activity during NREM sleep, a blunted build-up of SWA at the beginning of the first sleep cycle, and a slower dissipation of SWA in the course of a baseline sleep episode.

Interestingly, however, the Met66 and non-Met66 carriers were similar in their relative EEG response to sleep deprivation (i.e., equivalent increases in SWA after prolonged wakefulness). The authors confirmed that the Met66 variant impaired working memory in their subjects, but also found that this effect did not depend on the duration of previous wakefulness. Memory performance was decreased by ~10% following sleep deprivation, regardless of BDNF genotype. Thus, the Met66 BDNF variant altered both the absolute level of sleep intensity and memory performance, but had little influence on the build-up of homeostatic sleep pressure or magnitude of impairment due to sleep loss. As a result, the Bachmann et al. data point towards a general role for BDNF in regulating NREM sleep neuronal synchrony rather than regulating the homeostatic response to sleep deprivation.

Genetic studies in animals have already made great progress in identifying genes that influence measures of sleep intensity. It is evident from work in rodents that genes influencing the absolute level of delta power can be different from those influencing the dynamic response of delta to sleep deprivation.[7] In addition, human genetic approaches, enabled by the Human Genome Project, the HAPMAP consortium, and other genomic initiatives also provide insight into the basic mechanisms of sleep regulation by exploiting variations in the human genome. Notably, recent work from this same research group also point to a role of adenosine in regulating absolute delta power by comparing individuals with specific polymorphisms in the adenosine deaminase gene.[8] Clock genes, such as *PER3*, have also been shown to modulate the absolute level of cortical synchrony during sleep.[9] On the other hand, *DEC2* is another clock-related gene linked to sleep regulation in humans, which has also been implicated in the EEG response to sleep deprivation in a mouse model.[10] The combined effects of such genetic variants, in addition to those in proteins involved in core synaptic processes of learning, such as BDNF, are largely unknown and likely to be the basis of inter-individual differences in sleep intensity.

As further studies examine how specific genetic variants influence EEG activity during sleep and in response to sleep deprivation, additional analyses are needed to assess the effect on individual NREM sleep slow wave properties. Indeed, slow wave occurrence and precise slow wave characteristics, for instance the slope between the negative and positive peaks, were shown to also track sleep pressure level in both rodents and humans.[11-13] Furthermore, their measurement greatly refines our knowledge of network wiring by informing about which parameters of cortical synchrony are affected by the given genotype (e.g., duration of the hyperpolarization phase [i.e., down state] of neuronal firing, synchrony of neurons in entering the depolarizing phase [i.e., up state]). In parallel, such refinements might also help understanding why the observed changes in neuronal synchrony are in some circumstances independent (like those reported by Bachmann and colleagues), or rather dependent upon the duration of prior wakefulness.

In sum, it is once more reassuring for researchers to note that an impactful study still leads to numerous novel questions. Bachmann et al.[5] undoubtedly revealed that a precise genetic

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variant in the *BDNF* gene represents a determinant of brain cortical synchrony as measured with EEG. However, it is still not clear whether the reduced SWA in Met66 carriers is entirely due to the acutely reduced activity-dependent secretion of BDNF, or whether there are developmental/anatomical changes to the brain as a result of the polymorphism. Several studies have found anatomical differences in the brain associated with this BDNF polymorphism, particularly in the hippocampus.[14] Future studies should also expect a stronger effect in the rare individuals who are homozygous for the Val66Met substitution. Yet the current findings of Bachmann et al.[5] reveal that a functional change in BDNF, a crucial mediator of neuronal plasticity, can alter both baseline sleep intensity and memory performance in humans, which supports the hypothesis that sleep both serves and depends on plasticity-related functions of the central nervous system.

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DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.

REFERENCES

1. Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci 2010;11:114-26.
2. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. Sleep Med Rev 2006;10:49-62.
3. Faraguna U, Vyazovskiy VV, Nelson AB, Tononi G, Cirelli C. A causal role for brain-derived neurotrophic factor in the homeostatic regulation of sleep. J Neurosci 2008;28:4088-95.
4. Cowansage KK, LeDoux JE, Monfils M-H. Brain-derived neurotrophic factor: a dynamic gatekeeper of neural plasticity. Curr Mol Pharmacol 2010;3:12-29.
5. Bachmann V, Klein C, Bodenmann S, Schäfer N, Berger W, Brugger P, Landolt HP. The *BDNF* Val66Met polymorphism modulates sleep intensity: EEG frequency- and state-specificity. Sleep 2012;35:335-44.
6. Egan MF, Kojima M, Callicott JH, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 2003;112:257-69.
7. Andretic R, Franken P, Tafti M. Genetics of sleep. Annu Rev Genet 2008;42:361-88.
8. Bachmann V, Klaus F, Bodenmann S, et al. Functional ADA polymorphism increases sleep depth and reduces vigilant attention in humans. Cereb Cortex 2011; in press.
9. Viola AU, Archer SN, James LM, et al. PER3 polymorphism predicts sleep structure and waking performance. Curr Biol 2007;17:613-8.
10. He Y, Jones CR, Fujiki N, et al. The transcriptional repressor DEC2 regulates sleep length in mammals. Science 2009;325:866-70.
11. Vyazovskiy VV, Olcese U, Lazimy YM, et al. Cortical firing and sleep homeostasis. Neuron 2009;63:865-78.
12. Carrier J, Viens I, Poirier G, et al. Sleep slow wave changes during the middle years of life. Eur J Neurosci 2011;33:758-66.
13. Mongrain V, Carrier J, Paquet J, Bélanger-Nelson E, Dumont M. Morning and evening-type differences in slow waves during NREM sleep reveal both trait and state-dependent phenotypes. PLoS ONE 2011;6:e22679.
14. Bueller JA, Aftab M, Sen S, Gomez-Hassan D, Burmeister M, Zubieta J-K. BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. Biol Psychiatry 2006;59:812-5.