April 17, 2019

Neurobiology

"Peeling back the onion": a multi-layered approach to understand the dynamics of sleep

by **Maxime Jan**[1] | Postdoctoral Research Fellow; **Paul Franken**[2] | Professor

[1]: Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland

This Break was edited by Reinier Prosee, *Scientific Editor* - TheScienceBreaker

ABSTRACT

We have taken a systems genetics look at sleep to peel back the many layers regulating sleep. Using this approach, we could connect specific DNA variations to sleep traits and track the layer-to-layer information flow. Peeling back the –omics onion of sleep is thus revealing a number of new insights that can now be followed up on.

Sleep phenome, metabolome, proteome, transcriptome, genome: sleep as a multi layered-omics onion
Image credits: Pixabay – CC0

We now know that a good night's sleep is essential for maintaining optimal brain functioning and health. Many will have experienced the acute detrimental effects of 'pulling an all-nighter' on attention and performance, which are usually quickly remedied by sleep. Chronically curtailed or disrupted sleep can, however, have severe long-lasting negative health consequences as both epidemiological and experimental studies have found it to predispose for e.g. metabolic disorders such as type-2 diabetes and obesity. The biological substrates through which sleep protects us from the harmful effects of excess wakefulness remain largely unknown.

To gain insight into the problem of sleep, researchers have taken advantage of the genetic variability in how individuals cope with sleep loss. Although identifying DNA-variants that are associated with sleep traits can lead to important discoveries, this approach does not directly inform on how the information encoded in the DNA affects a trait of interest. Therefore, researchers are now complementing these genetic data with more information on the organism, to study sleep using a "systems approach". This approach uses data from many different aspects of an organism's biology in order to determine how each aspect affects the others. A lot like peeling back the layers of an onion.

In our study, we took this approach to peel back the many layers regulating sleep [***PMID: 30091978***].

We based our research on a widely used and well-characterized genetically diverse collection of mouse lines. Using these mice, we established a map of 11'000 DNA variants that affected sleep. These served as the '*genome'* data, and the core of our systems analyses. The outermost layer of our "onion" was the '*sleep phenome*': data on the many aspects of sleep and related phenotypes such as brain activity and locomotion.

Classical genetic studies are usually based solely on these two layers. For our systems approach, we added several intermediate layers. Connected to the genome, we added the *'transcriptome'* layer, which contains information on how genes were expressed in two tissues, the brain and liver. These data connected the gene sequence data of the *'genome layer'* to the way these genes are expressed. Finally, 124 metabolites (substances produced for and by metabolic reactions) were measured in the blood, forming the '*metabolome*' layer of our –omics onion. This additional layer allowed us to relate gene expression (the '*transcriptome'* layer) to its effects on the organism's metabolism.

All data were collected either under undisturbed conditions - during which mice could sleep as they pleased - or after a 6-hour period during which we kept the mice awake. In this multi-layered system we then determined *i*) the wiring of the many connections within and between layers, and *ii*) the influence of both DNA variants and sleep loss on this complex, multi-layered wiring.

With this resource in hand we could ask which genetic aspects are required to have an adequate response to sleep loss. We were first surprised by the sheer magnitude of the effect of eliminating sleep during the first half of the normal sleeping period: the levels of 78% of all genes expressed in the brain, 60% of liver genes, and 60% of blood metabolites significantly changed. Even more surprising was that for a number of sleep phenotypes and molecules, levels increased with sleep deprivation in one mouse line but decreased in another, attesting to the pervasive effects of genetic factors shaping how we cope with sleep loss.

For several of these remarkable changes we could connect the *'genome'* layer all the way to the *'sleep phenome'* level, through all intermediate levels. For example, a DNA variant (*'genome'*) affecting the expression of a gene called *Acot11* (*'transcriptome'*), which encodes an enzyme that helps regulate free fatty acids and other blood metabolites (*'metabolome'*), also determined how much of the lost sleep mice were able to recover during the next day (*'sleep phenome'*). Interestingly, *Acot11* is known to have a role in obesity and type-2 diabetes, conditions that in humans are known to be associated with insufficient sleep, likely through a dysregulation of free fatty acids.

Peeling back the –omics onion of sleep already revealed a number of new insights that we are now following up on, such as the role of *Acot11* in sleep homeostasis. Thus far, we only managed to uncover a fraction of the novel information still hidden in the resource. Because we made our data publically accessible (https://bxd.vital-it.ch/), we invite all to further mine this resource. In the meantime, we continue to add extra layers to the onion.