

ASK NOT WHAT THE BRAIN CAN DO FOR SLEEP – ASK WHAT SLEEP CAN DO FOR THE BRAIN

By Philip Low

Advanced Sleep Analysis for the sole purpose of identifying sleep disorders, such as apnea, or merely counting sleep stages would be akin to doing a blood test for nothing more than diagnosing sepsis or tabulating red and white blood cells: sleep is an untapped opportunity to study the brain, an opportunity which neuroscientists, the medical community, the pharmaceutical industry and most of you - and us - have yet to wake up to.

Several neuropathologies are already known to have an effect on certain sleep metrics: schizophrenic patients have fewer sleep spindles, clinical depression is positively correlated with increases in REM sleep, and Alzheimer patients can suffer from a fragmentation of REM sleep; to name just a few. Interestingly, while REM sleep appears important to form new memories, REM deprivation has been shown to abate symptoms of depression. It has even been proposed that more sleep is positively correlated with shorter lifespan. None of these observations (Ferrarelli et al., 2007; Feinberg et al., 1982; Kripke et al., 2002) make much sense if one is led to arbitrarily believe that particular sleep stages are always good for you, that we all need the same eight hours of sleep and that “light sleep” (where spindles take place) is insignificant.

While sleep may provide a mirror of a vast array of conditions, conversely, treating sleep with the assumption that side effects may be self-contained within the realm of sleep is again akin to suggesting that injecting a compound into the bloodstream may only affect the blood. Several drug companies have realized the cost of such dangerous assumptions when some sleep inducing drugs were found to generate profound mood disorders and even amnesia. More recently, the FDA asked a dozen drug manufacturers of sleep inducing drugs to write on their drug bottles that the compounds may cause “sleep driving”, i.e., that the drug may still have an effect in the form of impairment on waking behavior.

This raises the following questions:

- 1) Can we leverage the dynamic oscillations produced during sleep in order to systematically detect severe neuropathologies?
- 2) Can we use sleep to make safer drugs?

Yes, we can.

Currently, the sleep diagnostics market is driven by the sleep disorders market. While there are over 70 million individuals in the United States estimated to suffer from sleep disorders, of those, only 4 million are followed clinically, leading to 7 million tests per year, mostly for apnea. These tests require protracted hospital stays wherein a patient has to sleep tethered to a wall with electrodes glued on the scalp, chin, abdomen and around the eyes. The data are then analyzed by hand by human scorers who agree with one another 75% of the time. The discomfort, inaccuracy, time and cost requirements of this setup have been a major bottleneck in the clinical evaluation and treatment of the vast majority of sleep patients.

This entire clinical setup can be reduced to a single channel of EEG (Low, 2007). This channel can be used to create a frequency coded map of brain activity and has revealed the presence of a new sleep state, which offers far more information than the hypnogram, a stair step plot of sleep stages and its associated statistics. In this map, the hippocampus, thalamus, basal ganglia, septum, cortex, cerebellum, etc., produce different signatures throughout the sleep/wake cycle depending on whether they are diseased or not, or whether they are being adversely affected by medication. Contributions of these structures can be teased out by contrasting these results with analysis from animals with a differing genetic make-up or neuroarchitecture, as well as human stroke patients. Many of the animal recordings can now be performed using a single channel as in the human recordings, and some even non-invasively. Work with zebra finches has shown that certain brain patterns, which are associated with the neocortex in mammals, do not, in fact, necessarily require a neocortex (Low et al., 2008).

Toy, gadget, sensor, lifestyle, consumer, FDA and non-FDA regulated companies and others appear to have done a responsible and promising effort in order to develop dry non-contact sensors which do not require electrogel, collodion glue, etc.

The combination of algorithms, wireless sensors, databases and regulatory approval will prove necessary to create a simple portable wireless neurodiagnostics system for neuropathologies of interest. We have embarked upon this path, with the development of an iPod for the brain - the iBrain - as well as with the construction of a database of sleep derived biomarkers, in partnership with leading research institutions and pharmaceutical companies who test their drugs for efficacy and side effects on the brain, which at low doses may not produce noticeable symptoms over the course of a short clinical trial.

Brain activity during sleep is a mosaic of highly variable patterns, which will serve as a magnifying glass for the non-invasive detection of neuropathologies and drug side effects, well before the onset of symptoms, while providing important boundary

conditions for comparative, clinical, cognitive neuroscience and pharmaceutical research.

Ferrarelli, F., Huber, R., Peterson, M. J., Massimini, M., Murphy, M., Riedner, B. A., Watson, A., Bria, P., and Tononi G. (2007). Reduced sleep spindle activity in schizophrenia patients. *Am. J. Psychiat.* 164, 483-492.

Feinberg, M., Gillin, J. C., Carroll, B. J., Greden, J. F., and Zis, A. P. (1982). EEG studies of sleep in the diagnosis of depression. *Biol. Psychiat.* 17, 305-316.

Kripke, D. F., Garfinkel, L., Wingard, D. L., Klauber, M. R., and Marler, M. R. (2002). Mortality associated with sleep duration and insomnia. *Arch. Gen. Psychiat.* 59, 131-136.

Low, P. S. (2007). A New Way to Look at Sleep. *Ph.D. thesis, UC San Diego*, 1.

Low, P. S., Shank, S. S., Sejnowski, T. J., and Margoliash, D. (2008). Mammalian-like features of sleep structure in zebra finches. *Proc. Natl. Acad. Sci. USA* 105, 9081-9086.

Philip Low is Chairman, Chief Scientific and Chief Executive Officer of NeuroVigil, Inc., Adjunct Professor at Stanford School of Medicine, Research Affiliate at the M.I.T. Media Lab and the Salk Institute and the President of the 1st International Conference on Alzheimer's Disease and Advanced Neurotechnologies, to be held in Monaco in February 2010. Dr. Low is well-known for his many groundbreaking contributions to the neuroscience of sleep, which include a new sleep state and a 1 page Ph.D. dissertation. To bring his innovations to the market, Dr. Low founded NeuroVigil, an award-winning Computational Neurodiagnostics company headquartered in La Jolla, California.

philip@neurovigil.com