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Translational Neuroscience

From the bench to the bedside: Sleeping when you're awake, lasers and the blood-brain barrier, neurons with a taste for lactate, and more…

Jason S. Hauptman

Department of Neurosurgery, Geffen School of Medicine at UCLA, Los Angeles, CA

E-mail: *Jason S. Hauptman - jhauptman@mednet.ucla.edu
*Corresponding author

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COULD SOME OF YOUR NEURONS BE ASLEEP EVEN WHEN YOU'RE AWAKE?[5]

Neurosurgeons, perhaps above all others, are familiar with prolonged periods of wakefulness, routinely sacrificing sleep for the practice of their art. Sleep deprivation is known to have detrimental cognitive effects, and neuroimaging experiments have shown dramatic changes in activation of brain areas. Despite these observations, it is not known how these changes correlate to alterations in neuronal activity. In this study, Vyazovskiy *et al*., recorded from ensembles of neurons in the deep layers of the frontal motor cortex of awake, behaving rats. After characterizing neuronal activity during spontaneous awake and sleep states, rats were kept awake for prolonged periods of time. They found that the longer the rats were kept awake, the more frequently neuronal activity resembled periods seen during non-rapid-eye-movement (NREM) sleep. These periods, termed "off states," were characterized by groups of neurons showing brief periods of silence and overall slow activity. Interestingly, when rats were then allowed to sleep, those that were kept awake the longest also had the longest "off states" during sleep as well. When the recording electrodes were moved to other brain areas, similar effects were observed. In animals kept awake the longest, there were periods when all recorded areas went offline, though most of the time the "off states" were local. Within a local cortical region, they found that groups of neurons could go completely silent while others fired normally, suggesting that during sleep deprivation certain neurons "go to sleep" while others remain awake. All of this occurred while the animal was awake! The take-home message: ultimately, regardless of how long you want to stay awake, neuron eventually give up and go offline. The next question: can a cup of coffee wake them back up again?

ADULT HIPPOCAMPAL NEUROGENESIS: A CURE FOR AGE-RELATED COGNITIVE IMPAIRMENT?[3]

The dentate gyrus, the "inner sanctum" of the hippocampus, is important for the formation of new episodic memories, pattern separation (the process by which similar events are encoded as separate, non-overlapping memories), and modulation of some antidepressant effects. Another characteristic about the dentate gyrus that is unique is that it has been a proposed site of adult neurogenesis. It is known that ablation of neurogenesis in the dentate gyrus results in alterations in responses to antidepressant medications and impairments in pattern separation. In this study by Sahay *et al*., the effects of augmentation of dentate gyrus

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neurogenesis are assessed. They accomplished this by designing a way to "turn off" the genes responsible for programmed cell death in neural stem cells within the adult dentate gyrus, thus ensuring greater neurogenesis. They found that this strategy not only resulted in greater number of adult-born neurons, but these neurons were appropriately integrated into the hippocampal circuit. They found that animals with increased dentate gyrus neurogenesis had no changes in object recognition or spatial learning or memory. These animals did, however, show enhanced pattern separation (meaning they were better able to distinguish between similar contexts, which in this case was a subtle change in odor). Interestingly, voluntary exercise has also been shown to increase adult hippocampal neurogenesis. When this intervention was applied to the mice with increased adult hippocampal neurogenesis, even greater cognitive improvements were noted (an increase in exploratory behavior and a decrease in anxiety-related behavior). Because normal aging has been shown to be related to impairments in dentate gyrus function and pattern separation, it is possible that increasing adult hippocampal neurogenesis may have a role in improving memory. I do not know about you, but I am heading back to the gym!

BREAKING THROUGH THE BLOOD-BRAIN BARRIER USING OPTICS[2]

The blood-brain barrier, a veritable fortress that keeps the brain and spinal cord in an immunological sanctuary, has been a challenge for those looking to peripherally deliver drugs and other active biomolecules to the central nervous system. In this PNAS study by Choi *et al*., a novel method is described to non-invasively deliver large molecules in a spatially-specific manner that utilized a near-infrared ultrashort pulsed laser. First, the authors showed that using extremely short (femtosecond) laser pulses, specific blood vessels could be targeted, with resultant transient increases in vascular permeability to macromolecules (but not red blood cells). They also showed that a variety of peripherally administered molecules could be induced to penetrate outside the vessel lumen, including nanoparticles and dyes. Even more interesting, the authors showed that genetically engineered viruses could also be induced to cross the blood-brain barrier. This method has the potential of revolutionizing a number of *in vivo* procedures, particularly given that it is noninvasive and has subcellular resolution. Despite its technical drawbacks (which may be addressed in future work), this has tremendous potential in the treatment of brain tumors or in the study of brain function.

NEURONS PREFER LACTATE TO GLUCOSE AS AN ENERGY SOURCE *IN VIVO*[7]

Many may recall being taught that glucose was the most important [even only] metabolic substrate in healthy brains. Recently, evidence has come to light that challenges this concept, particularly in regards to the use of lactate in both healthy and diseased neurons. In this study, Wyss *et al*., used a combination of voltage-sensitive dyes and radiolabeling to investigate the role of lactate in sustaining neural activity *in vivo*. The authors found that after inducing severe glucose deprivation, animals receiving lactate infusions maintained neuronal activity equivalent to those receiving glucose and greater than those receiving a saline control. To examine how lactate was being utilized, authors use a radiolabeled form of lactate and found that lactate metabolism increased in parallel with increases in neuronal activity. Interestingly, when animals were given intravenous lactate without glucose deprivation, there was a dose-dependent reduction in glucose metabolism, suggesting the neurons preferred lactate over glucose according to its availability. They also showed that the reduction in glucose utilization occurred as neuronal activity increased, suggesting that during high period of activation neurons preferred lactate to glucose as well. This study puts a fascinating spin on what has been traditionally considered with regards to neuronal metabolism (though a role in the metabolism of astrocytes cannot be excluded).

TREATING CHRONIC LOW BACK: MORE EFFECTS THAN MEET THE EYE[4]

All neurosurgeons are likely familiar with the diagnosis and treatment of chronic low back pain (CLBP). It has been known that chronic pain syndromes result in alterations in brain structure and function, including reductions in cortical gray matter, abnormal cortical function, and cognitive impairments. In this study, Seminowicz *et al*., followed CLBP patients longitudinally to examine these changes before and after treatment. Their primary methodology was Magnetic Resonance Imaging (MRI) (both structural and functional). The authors found that prior to treatment, CLBP patients experienced reductions in cortical thickness in the left dorsolateral prefrontal cortex (DLPFC), an area known to be involved in pain modulation. These patients also had thinning of the insula, temporal cortex, and cingulate cortex. Interestingly, following treatment (either spine surgery or facet block), patient who experienced reductions in pain or pain-related disability exhibited recovery of DLPFC thickness. Importantly, this change in DLPFC was found to be independent of depression, a common comorbidity in these patients. Perhaps even more interesting is that the degree of thickness increase in the DLPFC correlated to the extent of pain reduction, suggesting that the better the treatment the more the DLPFC recovers. Along with these structural changes in the DLPFC, the researchers showed that DLPFC function changes as well. Prior to treatment,

CLBP patients had abnormal DLPFC function that reversed following successful treatment. Their preliminary data suggested the functional changes preceded the anatomical changes. Something to think about next time you are treating a CLBP patient: treatment choices not only will affect their back, but their brain too!

NEW WAYS OF ASSESSING CONSCIOUSNESS IN VEGETATIVE PATIENTS[1]

When considering patients in coma, two different diagnoses are possible, albeit difficult to distinguish clinically: vegetative state (VS), defined by arousal without any evidence of awareness, and minimally sconscious state (MCS), defined as purposeful behavior without the ability to communicate. Differentiating between these two states, which is essentially pinpointing a marker of consciousness, has been difficult. Some have used event-related potentials, particularly those with long latencies, as an indicator of conscious perception (thought to reflect processing of information in the frontal and parietal cortices). In this study by Boly *et al*., investigators tried to correlate level of consciousness with the function of "top-down", or backward connectivity. This connectivity describes the way target areas, such as somatosensory cortex, modulate information flowing through the pathways leading up to it (such as thalamic and brainstem relays). This connectivity is reflected in changes in long-latency responses of event-related potentials. Using a test that elicits pre-attentive responses and some elaborate mathematical modeling (termed dynamic causal modeling), authors examine responses in healthy, MCS, and VS subjects. They found a statistically significant interaction between level of consciousness and the characteristics of event-related potentials. In particular, they found that MCS and VS can be differentiated by event-related potentials. Patients with MCS exhibit near-normal connectivity with higher-order cortex, whereas VS patients do not. This approach could have significant clinical implications (with regards to prognosis). Furthermore, these findings demonstrate selective loss of top-down connectivity in VS patients, suggesting this loss may account for alterations of consciousness.

GADOLINIUM GETS AN UPGRADE: NOVEL METHODS FOR TRACING BRAIN CONNECTIONS *IN VIVO*[6]

There is no doubt that true understanding of neuroanatomy has less to do with the study of individual regions but instead with connections between regions. Traditional approaches require the injection of special tracers in living animals followed by sacrifice, tissue processing, and examination under the microscope. One new strategy in the study of *in vivo* connections is diffusion tensor imaging (DTI), an MRI protocol used to estimate the location of large white matter tracts. There are several limitations to DTI, including lack of information about the direction of connection, poor resolution where several tracts converge, and problems with tract estimation in abnormal brains. In this study, Wu *et al*., document the development of a unique tracer that labels monosynaptic connections between brain regions. This tracer, cholera-toxin subunit B (CTB), was conjugated to gadolinium and injected into living animals. Through an elegant array of experiments, the authors demonstrated that after local injection of this compound into the rat somatosensory cortex, connected thalamic nuclei showed gadolinium enhancement. Enhancement occurred by 5 days after injection, peaked at 7 days, remained stable for 4 weeks, and returned to baseline by 8 weeks. Histological studies verified these findings and also demonstrated that the tracer did not significantly harm surrounding tissue. In addition to enhancement of thalamic nuclei, authors also showed that connecting white matter tracts enhanced as well. In a final experiment, the authors showed this tracer could be used in other brain regions, such as the olfactory system. This paper shows an exciting and ingenious new method that could be used to trace anatomical connections *in vivo*. Despite the need for more technical improvement, this strategy could have interesting applications in studies of neuromodulation and functional brain disorders.

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