Commentary - The Future of Deep Brain Stimulation

Many people comment on the remarkable success of DBS (*see Commentary - The Case for DBS*). However, the real question is, why are they so surprised at this success? The brain is basically an electrical device. Information is processed by integrating excitatory and inhibitory post-synaptic *electrical* potentials and information is encoded in the subsequent train of *electrical* action potentials. Neurotransmitters, released at the synaptic junctions, are just the messengers; they are not the message. One merely has to consider the time scale of operations to understand the difference between electrical and pharmacological effects. DBS operates on the order of milliseconds. For example, the time difference between effective DBS at 130 pps and ineffective DBS at 100 pps is 2.3 ms, which is the difference in the inter-stimulus pulse intervals. Yet this small difference of 2.3 ms is sufficient to cause a difference in efficacy, with 130 pps DBS being effective and 100 pps not. Pharmaceutical agents operate over minutes to hours and cannot replicate the precise timing of information in the brain.

It is the message in the brain that is abnormal, save for the most peripheral motor and sensory functions of the brain, and it is the misinformation that causes the symptoms and signs of disease (*see Chapter 20 - The Basic Unit of Information in the Brain, Montgomery Jr. EB, Deep Brain Stimulation Programming: Mechanisms, Principles, and Practice, Oxford University Press 2016*). Because the message is fundamentally electric, the message should be manageable electrically (*see Chapter 4 - The Principles of Electrophysiology, Montgomery Jr. EB, Deep Brain Stimulation Programming: Mechanisms, Principles, and Practice, Oxford University Press 2016*).

Theoretically, several electrophysiological approaches could be applied to treat misinformation, depending on the nature of the misinformation. One type of misinformation may be a low signal-to-noise ratio. In this case, the actual information is present but buried in noise. The signal-to-noise ratio can be improved, along with symptoms and signs, by resonance amplification using DBS. There may also be two types of resonance amplification. The first depends on a specific frequency and on a regular or constant inter-stimulus DBS interval. Resonance then depends on the frequency of DBS relative to the fundamental carrier frequency of the neural oscillators involved (*see Chapters 17 - Oscillator Basics and Chapter 18 - Discrete Neural Oscillators, Montgomery Jr. EB, Deep Brain Stimulation Programming: Mechanisms, Principles, and Practice, Oxford University Press 2016*).

A second type of resonance amplification is stochastic resonance, which is the counterintuitive notion of adding noise to a signal to improve the signal-to-noise ratio (Hanggi 2002). Although the noise added to the signal has to be a certain bandwidth (the range of frequencies contained in the noise), the advantage of stochastic resonance is that the precise fundamental frequencies of the underlying neural oscillators do not have to be known precisely. Stochastic resonance has been implicated in improved speech perception in patients undergoing cochlear implants (Chatterjee and Robert 2001; Zeng, Fu et al. 2000) and in balance control (Priplata, Niemi et al. 2002).

Another approach to correcting misinformation is to overwrite the misinformation with no information. Overwriting can be accomplished by stimulating and driving the neurons to fire in a highly regular manner so as to strip the neuronal spike trains of any information (Montgomery and Baker 2000; Grill, Snyder et al. 2004).

Other novel approaches to correcting misinformation include attempts to replicate the normal patterns of neuronal spike trains, although this replication is a great challenge. Another approach consists of closed-loop DBS, in which sensors in the brain detect specific brain states and then trigger a brief train of DBS.

Another major challenge for DBS is to identify new targets for an expanding number of neurological and psychiatric disorders. In the past, DBS targets were identified but targeting those structures previously surgically ablated; an approach called "chasing lesions." If this approach were to remain the only means of identifying DBS targets, the future would be very limited indeed. Fortunately, other methods for defining DBS targets have been tried. For example, Positron Emission Tomographic (PET) scans of patients with medically refractory depression reveal areas of increased and decreased metabolism. Although the target, the hyper-metabolic area, was chosen on the basis of what is now an outdated notion of how DBS works (that inhibiting the stimulated target is the goal of therapy), the subgenu cingulum with increased metabolic activity was selected for DBS (Mayberg, Lozano et al. 2005).

Perhaps the most common conception of how functions are represented in the brain is modular in nature. Specific areas in the brain perform specific functions and while these functions are integrated to cause the final behaviors, the integration is piecemeal and often sequential. An alternative conception, the *Systems Oscillators theory* (Montgomery 2004, Montgomery 2007, Montgomery 2008, Montgomery and, Gale 2008), is that the brain is sets of loosely coupled interconnected networks (*see Chapter 8 - Pathophysiological Mechanisms, Montgomery Jr. EB, Deep Brain Stimulation Programming: Mechanisms, Principles, and Practice, Oxford University*

Press 2016). While specific networks or aspects of networks vary in their anatomical location, they act more as a whole and virtually simultaneously or in parallel. In the case of physiological functions being distributed throughout the network rather than restricted to a specific structure implies that a physiological function to be targeted by DBS anywhere within that network. The advantage of targeting a system rather than a specific structure is that other targets may be identified in the system and that some of these targets might be better surgical candidates, given ease of approach and risks. It would be interesting to extend the *Systems Oscillators theory,* in which DBS affects systems, not just structures, to determine whether DBS to areas of decreased metabolism would improve depression.

Another approach to developing DBS targets is to thoroughly explore the neurophysiology. Schiff and colleagues developed such an approach in minimally conscious patients on the basis of preliminary imaging and electrophysiological studies in non-human primates (Schiff, Giacino et al. 2007).

The potential for electrophysiological treatments of neurological and psychiatric disorders is just beginning to be appreciated. DBS and related technologies have tremendous potential, given both the spatial and temporal specificity of the therapies. In contrast to bathing the entire brain in pharmacological therapies for extended periods, DBS has a spatial resolution measured in millimeters and a temporal resolution measured in milliseconds. DBS differs markedly from pharmacological therapies, and in those differences lie its unique advantages in the treating neurological and psychiatric disorders.

References:

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