Toward a Deeper Understanding of Blepharospasm:

It's About Time

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For most blepharospasm patients, the symptoms are not present all of the time. They may be alleviated when speaking, singing, or touching the face and they are generally absent during sleep. Although the brain is clearly in a very different mode while sleeping, the subtle dependency on certain actions while awake is puzzling. In this case, certain tasks can temporarily alleviate the symptoms. In other forms of focal dystonia, such as focal hand dystonia, an opposite effect can be seen. Those patients may show symptoms only during certain tasks, in some cases of musician's dystonia only while performing certain passages of specific pieces. This feature of focal hand dystonia is commonly referred to as "task specificity". At a gross level, blepharospasm patients exhibit the same phenomenon but with the opposite effect, in which the symptoms are alleviated by certain tasks. Thus, both forms of focal dystonia exhibit features of task specificity. What clues can this provide about the brain circuits involved in the disease? While this remains one of the greatest mysteries in dystonia research, neuroscience is beginning to assemble the pieces of the puzzle.

One of the most important neural pathways for controlling voluntary behavior is the circuit from the cortex through the basal ganglia and thalamus back to the cortex. Although the details are complex, there are a few simple features that should be recognized. First, the basal ganglia receive input from virtually all of the cortex. Thus, it receives information not only from areas of the cortex involved in planning and preparing movement, but also from areas representing sensory input. This combination of sensory information and "motor plan" can be collectively thought of as "state". Second, the basal ganglia send outputs to two major destinations: the brain stem and, by way of the thalamus, the frontal cortex. Both of these, in turn, exert control over a wide variety of motor systems, including the brain stem nuclei controlling the muscles involved in blepharospasm. What exactly is the basal ganglia doing in this circuit? While this remains an intense area of research, the contemporary view in neuroscience is that the basal ganglia are doing "action selection". In other words, given the "state" input, what should be chosen as the next "action?" The third feature is critically important but also more complex. The basal ganglia role in action selection plays out over multiple time scales. This can be most easily understood from the anatomy. The pathways from frontal cortical areas through basal ganglia and thalamus go back to the same frontal cortical areas. Those frontal cortical areas are involved in motor planning over longer

time scales as you go anteriorly (toward the front of the head) from the primary motor cortex. Although historically viewed as separate, parallel loops, contemporary refinements of our understanding of this circuit indicate that there are several forms of complex connections between them. In principle, then, the basal ganglia could play a key role in how a given time scale's motor plan influences a shorter time scale's motor plan, eventually cascading down to the level of the timing of specific muscle activation patterns. Similarly, the basal ganglia projections to brain stem nuclei are combined with projections from cortex, with different timing. Collectively these pathways determine, for a given context or "state", which specific actions are chosen in which sequence and with what timing. As with other forms of dystonia, the specific muscle activations that give rise to the symptoms are not abnormal per se. Rather, it is their timing, relative to each other and the patient's current "state", that is abnormal.

To develop a deeper understanding of blepharospasm, we will need to understand the relative timing of influences through these various pathways, and how that goes awry in the disease. My overarching strategy is to try to link evidence for abnormalities in the neurobiology with detailed clinical information. For example, thanks to support from the BEBRF, we are using evidence for dopamine abnormalities in the basal ganglia to construct computer simulations of how those abnormalities modify the response of neurons in the basal ganglia to cortical inputs. The most striking effect is in the relative timing of spiking patterns in those neurons. We are in the process of embedding these effects into large scale simulations of the basal ganglia network, incorporating basic research on the connections between those loops. Through support from the Dystonia Coalition, of which the BEBRF is a key contributor, we are also using computer-based video processing software, known as the Computer Expression Recognition Toolbox (CERT), to assess symptoms in patient videos. The first stage of this research is to determine whether CERT gives ratings of symptom severity that are similar to clinician evaluations. In the long term, we envision using the frame-by-frame information from CERT to measure the time course of activation of periocular muscles with unprecedented temporal resolution. Ultimately, this information can be linked with the computer simulations of the neural circuitry to provide a complete, coherent picture of the exquisite timing with which symptoms are evoked. This will also give us a principled basis for designing new treatments aimed at the pathophysiology of the disease rather than just the symptoms.

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