Translational neurophysiology of Parkinson’s disease: can’t blink on an eye blink

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TO THE EDITOR: Complex motor abnormalities in disorders of basal ganglia, such as parkinsonism, often coexist with deficits of eyelid movements. Modest physiology and accessibility have enticed several investigations of eyelid movements in Parkinson’s disease. These endeavors are not only useful to characterize phenomenology of degenerative disorders of basal ganglia, but they also have paramount importance in objectively characterizing the course of the disease and understanding the physiological basis of its treatment. Three types of eyelid movement abnormalities are notable in the experimental models of Parkinson’s disease: blink hyperreflexia, impaired blink reflex plasticity, and reduced rate and impaired rhythm of the spontaneous blinks (Basso et al. 1993; Kaminer et al. 2011, 2014, 2015).

In a recent elegant study of the rodent model with Parkinson’s disease, Kaminer et al. (2015) stimulated the subthalamus with beta-band (15-20 Hz) and high-frequency (130 Hz) electrical pulses. The idea was that if the hypersynchrony in beta band is the cause for eyelid abnormality in Parkinson’s disease, then the low-frequency stimulation in the beta band might cause or worsen the eyelid abnormalities. The suppression of beta-band oscillations with high-frequency stimulation might treat the blink abnormalities. Indeed, high-frequency stimulation of the subthalamus resolved blink hyperreflexia and restored blink reflex plasticity, but it did not affect the abnormal rate and rhythm of the spontaneous blinks (Kaminer et al. 2015).

There are various ways to interpret these results. One possibility is the complex interplay between two models of altered basal ganglia physiology in Parkinson’s disease. The rate model depicts an increase in the firing rate of subthalamic and pallidal neurons. This phenomenon could increase the neural response gain and cause cardinal parkinsonian symptoms such as elevated muscle tone, increased eyelid reactivity leading to blepharospasm, and impaired suppression of undesired movements causing dystonia. Alteration in the pallidal output gain might disrupt motor adaptation by affecting cerebellothalamic connections. Such maladaptation can also lead to dystonia, blepharospasm, and impaired eye-blink plasticity in subjects with Parkinson’s disease. Subthalamic or pallidal deep brain stimulation might improve the blink reflex hyperactivity and plasticity by instantaneously suppressing the gain of the pallidal output. However, the change in the steady-state neural response gain might not affect dynamic motor function such as rate or rhythmicity of the spontaneous blinks. This concept is compatible with the recent report by Kaminer et al. (2015).

The pattern model, in contrast, departs a change in firing patterns, particularly increasing the bursting behavior of subthalamic, pallidal, and substantia nigra pars reticulata neurons in the Parkinson’s disease. High-frequency stimulation of either subthalamic or pallidum restores their abnormal bursting behavior but does not affect the discharge patterns of substantia nigra pars reticulata neurons. It is therefore possible that firing patterns of substantia nigra pars reticulata determine the spontaneous blink rate and rhythmicity, just like eye movements. This prediction is also supported by the recent findings that subthalamic deep brain stimulation did not restore abnormal spontaneous blink rate and rhythm (Kaminer et al. 2015).

Finally, the clever analytical approach for the blink analysis presented by Kaminer and colleagues (2011, 2015) has substantial clinical implications. Strategies of such kind have a potential to allow early differentiation of Parkinson’s disease from its atypical forms such as progressive supranuclear palsy. For example, the ratio of frequency of square-wave jerk (denominator) to spontaneous eye blink robustly increases in patients with progressive supranuclear palsy compared with Parkinson’s disease. Objective assessment of the pattern and frequency of spontaneous blinks can also sharpen our ability to precisely differentiate Parkinson’s disease from progressive supranuclear palsy early in their courses. Such distinction is one of the most outstanding challenges in the contemporary practice of neurology. Early differentiation of Parkinson’s disease from progressive supranuclear palsy have critical importance in preventing devastating comorbidities of parkinsonism, such as falls leading to intracranial hemorrhage. The objective measures will also strengthen our ability to noninvasively, yet precisely and objectively, follow the course of parkinsonism and the outcome of neuromodulation therapy for degenerative neurological disorders. These experimental strategies will also foster development of satellite programs to objectively assess parkinsonism, a concept analogous to that of telediagnosis. In such a scheme, only a simple recording device will be needed at the peripheral clinical location to capture eyelid movements. The recordings can be transferred electronically to the centralized analysis site for the quantitative expert assessment in an effort to yield accurate diagnosis.

DISCLOSURES
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