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Commentary: Gilles de la Tourette's and the disruption of interneuron-mediated synchrony

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Abstract

The article by Hashemiyoony et al is a masterful synthesis of the clinical, genetic, and neurobiological aspects of Gilles de la Tourette's syndrome that provides unique insights into the neural state dysfunctions that underlie this enigmatic disorder. In particular, the authors make a powerful argument for the disorder arising from hyposynchronization within cortico-basal ganglia-thalamocortical systems which may result from a genetically-driven developmental insult to interneuron regulation, and suggest deep brain stimulation as a valuable tool to assess how balance may be restored to the system and reverse the pathological state.

Gilles de la Tourette's syndrome (GTS) is an enigmatic disorder of childhood onset, in which interest has waxed and waned over the years due to its heterogeneous nature and comparatively low incidence (McNaught & Mink [2011] *Nature Rev Neurology* 7: 667–676); however, the impact on those children afflicted with the disorder can be devastating. Nonetheless, even basic aspects of whether it is a voluntary or involuntary movement disorder and the neurobiological underpinnings have not generated substantial agreement among those that study the disorder or are involved in diagnosis and treatment. While the hallmark of GTS is the tics, these are presented as a complex constellation of symptoms that are often preceded by a premonitory sensation (Leckman et al [1993] *Amer. J. Psych.* 150:98–102). The article “Putting the pieces together in Gilles de la Tourette syndrome: Exploring the link between clinical observations and the biological basis of dysfunction” by Rowshanak Hashemiyoony and colleagues, shines an important light on GTS, providing both a novel yet comprehensive review and leading to an innovative synthesis of a broad literature relating clinical, scientific, and therapeutic aspects of GTS. Importantly, it provides the first truly comprehensive synthesis of factors underlying tic expression, an in-depth analysis of the nature of the link between premonitory urges and tics, and a circuit-level explanation to account for the physiological bases of GTS and its treatment.

GTS itself is often characterized by an onset of an impelling urge that is relieved by expressing the tic; in this way it shares many characteristics seen with obsessive-compulsive disorder (OCD), in which compelling and insistent obsessional urges engender anxiety states which drive the compulsive behavior (Leckman et al [1993] *Amer. J. Psych.* 150:98–102). Although GTS and OCD are often comorbid and run in families, the timing of the onset, the nature of the illness, and the pharmacotherapy are distinct (Albin & Mink [2006] *Trends Neurosci* 29: 175–182). GTS has been proposed to involve dysfunction across multiple systems, which are pointed out in this article as involving the neocortex, the thalamus, and

the basal ganglia. Treatments are chosen to impact these circuits, primary among them being dopamine antagonist drugs; however, these are fraught with severe side effects that occur with drug doses much lower than elicit these symptoms in schizophrenia patients (McNaught & Mink [2011] *Neurology* 7: 667–676), suggesting an increased responsivity of the dopamine regulatory systems in this disorder. However, drug treatments are often ineffective, in which case surgical intervention can be employed. In the Hashemiyoon et al article, a case is made for the use of deep brain stimulation (DBS) for treating severe GTS. While highly invasive, DBS has the advantage over other surgical approaches because it is adjustable and reversible. Unlike drugs that block receptors throughout the brain, DBS can be applied to targeted pathways in order to treat the disorder. More importantly, DBS impacts the brain in a specific manner i.e., by delivering high-frequency stimulation, it can modulate activity and synchrony in the network. Oscillatory activity is appreciated as a measure of more informative metric of systems interaction, in that oscillations control information flow within local circuits as well as provide a functional link between distal brain regions (Buzsaki & Draguhn [2004] *Science* 304: 1926–1929). In this way, oscillatory activity can provide a macroscopic organizational influence that can coordinate activity among functionally linked circuits. In animal models, DBS has been found to produce changes both in oscillatory power and in oscillation coherence between brain regions that requires stimulation over extended periods of time (Ewing & Grace [2013] *Brain Stimulation* 6:274–285), thereby altering how activity patterns can be synchronized between brain regions. We have found that this occurs via changing the activity state of interneurons (McCracken & Grace [2007] *J. Neurosci* 27: 121601–12610), since interneurons have been shown to underlie the control of oscillatory patterns within brain regions (Buzsaki [2001] *Neurochem Res* 26: 899–905). Indeed, given that excitatory circuits in the brain are the first to be laid down in ontogeny, with interneurons coming in later to stabilize the system (Sultan et al. [2013] *Front. Cell Neurosci* 7: 221), the interneuron population will likely be highly vulnerable to late developmental insults leading to disease states (Grace [2016] *Nature Neurosci Rev* 17: 524–532). Therefore, by altering interneuron dynamics, one can change the brain state in a manner that could reverse pathological conditions at the core of the illness.

A powerful assertion of the Haseimiyooun et al manuscript is the synthesis provided linking interneurons, oscillatory activity, GTS and DBS. Specifically, the authors show that in chronic recordings of the thalamus, there is a significant correlation that is present between gamma band power/theta-gamma coherence and alleviation of symptoms. They further posit that this hyposynchronization among brain regions drives the underlying pathophysiology observed in the disease, consisting of an abnormal informational link between premonitory urges and tics. Such dysfunction can be derived from genetic disruptions related to interneuron development, which would affect the balance of excitation and inhibition necessary for information processing and coordinated oscillatory activity among these brain regions. DBS can thereby act to break the hyposynchronized oscillatory state that is proposed to drive tic expression (Maling, Hashemiyoon et al [2012] *PLoS One* 7: e44215). As a result, this manuscript provides a unique functional basis for systemwide dysfunction in interneuron control of network activity leading to abnormal associations between premonitory urges and tic expression that lie outside of the voluntary control of the

individual. This provides a testable model for future studies on the predictive power of DBS-induced alterations on circuit function.