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# It's a Storm, It's a Gale: Epilepsy Initiation From the Corticostriatal Circuit

**Impaired Cortico-Striatal Excitatory Transmission Triggers Epilepsy**

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*STXBP1* and *SCN2A* gene mutations are observed in patients with epilepsies, although the circuit basis remains elusive. Here, we show that mice with haplodeficiency for these genes exhibit absence seizures with spike-and-wave discharges (SWDs) initiated by reduced cortical excitatory transmission into the striatum. Mice deficient for *Stxbp1* or *Scn2a* in corticostriatal but not corticothalamic neurons reproduce SWDs. In *Stxbp1* haplodeficient mice, there is a reduction in excitatory transmission from the neocortex to striatal fast-spiking interneurons (FSIs). Fast-spiking interneurons activity transiently decreases at SWD onset, and pharmacological potentiation of AMPA receptors in the striatum but not in the thalamus suppresses SWDs. Furthermore, in wild-type mice, pharmacological inhibition of corticostriatal FSI excitatory transmission triggers absence and convulsive seizures in a dose-dependent manner. These findings suggest that impaired corticostriatal excitatory transmission is a plausible mechanism that triggers epilepsy in *Stxbp1* and *Scn2a* haplodeficient mice.

**Keywords**
striatum, stxbp1, scn2a, spike-and-wave discharge, fast-spiking neurons

## Commentary

Nothing is as simple or—as complicated—as it seems. The role of basal ganglia in seizure control has been appreciated for many years and significantly since the pioneering paper of Iadarola and Gale in rats pointed to the controlling role of the substantia nigra pars reticulata in provoked seizures.[1] The topic of basal ganglia circuitry (as well as its outputs[2]) and its role in seizures have been further approached from many different points of view with inclusion of other components of basal ganglia pathways,[3-5] surveying developmental aspects as well as sex and regional specificity.[6,7] Striatum, especially its dorsal (dorsolateral) part, has been identified as one of the structures participating in the spread of provoked (pentylenetetrazole) seizures, especially those of clonic character.[8] In all these studies, striatum was considered as a part of complex basal ganglia circuitry containing several loops and several disinhibitory synaptic links that after inhibition (or excitation) may lead to surprising outcomes.[9-11] Thus, effects on seizures afforded by any activation or inhibition within the basal ganglia pathways and their outputs should be considered with utmost attention because of intricate pathways, as several inhibitory projections including interpolation of additional local inhibition (and locally projecting excitation!) are involved. Indeed, the thalamus is also included in this circuitry and adding to the complexity of the system.[12]

It is thus not surprising that there is a variety of seizures evolving from this complicated system. In experimental rodents (for simplicity), there are at least 3 major seizure patterns that arise from forebrain structures and are more or less affected by activity in the basal ganglia circuits. If one follows these epileptic phenomena in a provoked seizure model such as systemic pentylenetetrazole,[13] the first pattern consists of a few seconds long spindle-shaped (or crescendo–decrescendo) spike-and-wave episodes in the electroencephalography (EEG) with frequency in the narrower θ range (4-6 Hz; here referred to as spike-and-wave discharges [SWD]). The EEG activity is accompanied by a motionless stare (freezing episodes). Later on, a second pattern is observed, which encompasses isolated whole-body myoclonic twitches frequently (but not always) associated with large amplitude spikes in the EEG. Finally, pure clonic motor seizures develop involving in their classical appearance forelimbs and head muscles while the animal keeps (or preserves) upright position. There may be loss of posture due to the clonic seizure severity, but no loss of righting ability.

Parallel EEG usually consists of decrescendo spike-and-wave pattern which slows over time. Ultimately, these seizures propagate out of the forebrain and basal ganglia-thalamic circuitry, and when reaching the brain stem, the righting ability is lost and frequently a prominent tonic component precedes long-lasting all limb clonus.[14]

Now inserting genetics into this complex picture, the authors investigated the mechanisms of epilepsy source in *Stxbp1*$^{+/-}$ *and Scn2a*$^{+/-}$ mutations in mice. For that they used a combination of pharmacologic, genetic, and electrophysiological tools. Initially, they identified that *Stxbp1*$^{+/-}$ mice display SWD on the EEG associated with freezing (behavioral quiescence) and sometimes also myoclonic or clonic seizures. Ethosuximide abolished the SWDs. Local field potential recordings also indicated significant in-phase involvement of the dorsal striatum (CPu) together with somatosensory cortex and ventroposterior thalamus. If the GABAA receptor agonist muscimol was microinfused individually into these 3 brain structures, it suppressed occurrence of SWDs in the somatosensory cortex. Muscimol microinfusions in the CPu even suppressed SWDs in the medial prefrontal cortex, somatosensory cortex, and striatum itself showing a powerful inhibitory force stemming from the dorsal striatum. In contrast, CPu microinjections of GABAA receptor antagonist bicuculline was able to trigger myoclonic twitches and clonic seizures, and similarly, a single pulse electrical stimulation of one side of the CPu elicited SWDs in all the above-mentioned brain areas and CPu contralaterally. Interestingly, this effect is in contrast with published reports on striatal microinfusion as Cavalheiro showed that microinfusion of excitatory NMDA as well as bicuculline into the striatum suppresses seizures induced by amygdala kindling or systemic pilocarpine[9,10,15] and does not correspond to the effects of focal excitation and inhibition in individual basal ganglia nuclei as reviewed in the study by Velíšková and Moshé.[16] Thus, this effect requires further investigation and explanation.

Introduction of global deletion of *Stxbp1* in inhibitory neurons (driven by *Vgat*-Cre) reproduced the occurrence of myoclonic twitches and jumps while specific deletion of *Stxbp1* (driven by *Emx1*-Cre) in dorsal telencephalic (minus striatum, globus pallidus, and thalamus) excitatory neurons reproduced SWD with behavioral freezes. Similarly the other mutants, *Scn2a*$^{+/-}$ (and *Scn2a*$^{+/-}$*/Emx* but not *Scn2a*$^{+/-}$*/Vgat*) had SWDs with behavioral arrests. Accordingly, striatal glutamate release was decreased in *Stxbp1*$^{+/-}$ compared to wild-type mice. These findings strongly suggest that impairment of the corticostriatal glutamatergic pathway significantly contributed to the induction of specific SWDs with behavioral arrest. When the impairment was counteracted by ampakine (CX516), which is a positive allosteric modulator inhibiting deactivation of glutamate AMPA receptors, there was a reduction in SWDs. The notable finding here is that even focal intra-CPu injection of ampakine provided this effect. The authors then used specific genetic deletion (driven by *Trpc4*-Cre) of *Stxbp1* or *Scn2a* in either cortical layer V pyramidal neurons (excitatory projection to the striatum) or cortical layer VI (driven by *Ntsr1*-Cre; excitatory projection to the thalamus). From these 2 layer-specific deletions, only that involving the striatal projection was associated with SWS occurrence. The opposite approach used retrograde lentivirus injected to CPu, which in association with adenovirus injected into the cortex induced Cre expression in cortical neurons projecting to the CPu. When applied to *Stxbp1* floxed (*Stxb1*$^{fl/fl}$) mice, the mice developed SWS in contrast to wild-type or *Stxbp1*$^{fl/+}$ heterozygous mice.

Then the authors electrophysiologically (patch clamp) identified striatal fast-spiking and medium spiny neurons and measured cortical excitatory drive onto these neurons. In the fast-spiking neurons in the *Stxbp1*$^{+/-}$ mice (but not in the *Scn2a*$^{+/-}$ mice), there was faster rundown in the excitatory postsynaptic currents (EPSCs) after repetitive 10 Hz somatosensory cortex stimulation (without effects on miniature potentials and absolute amplitude of EPSCs). This result again indicates impairment of the presynaptic component of neurotransmission, hence the weakening of the cortical glutamatergic input into the fast-spiking neurons of the CPu. When wild-type mice were injected in the CPu with 1-napthyl acetyl spermine, which selectively blocks calcium-permeable AMPA receptors and is expressed in the fast-spiking neurons, SWDs appeared in the CPu. Finally, the authors expressed designer receptors specifically in these CPu fast-spiking (parvalbumin positive) neurons in the *Stxbp1*$^{+/-}$ mice. Then administration of the designer receptor agonist was able to suppress SWDs in these mice. Finally, to expand their hypothesis of CPu driving the SWDs, the authors used another rodent model of SWDs, the genetic absence epilepsy rats from Strasbourg, and showed that ampakine indeed reduced the number of SWDs while 1-napthyl acetyl spermine increased the occurrence of SWDs.

Thus, the authors propose a new view on the neural circuitry responsible for generation of SWDs, with heavy and likely decisive involvement of corticostriatal excitatory projections ending at fast-spiking striatal interneurons, which express parvalbumin. There are several issues to be reconciled: The SWD genesis associated with behavioral arrest is a classic feature of absence seizures. Human *STXBP1* and *SCN2A* mutations appear in patients with epileptic encephalopathies expressing atonic and myoclonic seizures with the closest phenotype of atypical absences. An explanation here may be an additional effect of the mutation. Second, clinical studies find involvement of striatum in juvenile myoclonic epilepsy,[17] and according to our genetic model, parvalbumin-expressing striatal neurons play a significant role in juvenile myoclonic epilepsy as well.[18] Since this type of epilepsy in humans is characterized by myoclonic twitches, it appears that the striatal inhibitory systems rather than corticostriatal excitatory connections may be involved. Finally, the authors build their proposal of basal ganglia circuitry on structures observed in cats, monkeys, and humans (containing globus pallidus internus and externus) rather than in rodents, which is a weakness of the manuscript. Yet the authors established a solid link between the impairment of corticostriatal excitation and the phenotypic expression of SWS associated with behavioral arrest.

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