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It's not just the basal ganglia: cerebellum as a target for dystonia therapeutics

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Abstract

Dystonia is a common movement disorder that devastates the lives of many patients but the etiology of this disorder remains poorly understood. Dystonia has traditionally been considered a disorder of the basal ganglia. However, growing evidence suggests that the cerebellum may be involved in certain types of dystonia raising several questions. Can different types of dystonia be classified as either a basal ganglia disorder or a cerebellar disorder? Is dystonia a network disorder that involves the cerebellum and basal ganglia? If dystonia is a network disorder, how can we target treatments to alleviate symptoms in patients? A recent study by Chen *et al.*, using the pharmacological mouse model of Rapid-onset dystonia Parkinsonism (RDP), has provided some insight into these important questions. They showed that the cerebellum can directly modulate basal ganglia activity through a short latency cerebello-thalamo-basal ganglia pathway. Further, this paper and others have provided evidence that in some cases, aberrant cerebello-basal ganglia communication can be involved in dystonia. In this review we examine the evidence for the involvement of the cerebellum and cerebello-basal ganglia interactions in dystonia. We conclude that there is ample evidence to suggest that the cerebellum plays a role in some dystonias, including the early-onset primary torsion dystonia DYT1 and that further studies examining the role of this brain region and its interaction with the basal ganglia in dystonia are warranted.

Introduction

Dystonia is the third most common movement disorder behind only Parkinson's disease and essential tremor¹. In dystonia abnormal muscle contractions result in unwanted movements or postures². The movements are often patterned and twisting but may be tremulous as well. Further, they are usually exaggerated by voluntary movement and are associated with muscle activation overflow, resulting in the characteristic co-contraction of agonist-antagonist muscle pairs³. Unfortunately, the neural substrates of dystonia are not completely understood and therefore therapeutic options available to patients remain limited⁴. While dystonia has been considered a disorder of the basal ganglia, there is evidence to suggest that

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other brain areas may also play a role⁵⁻⁷. Importantly, two recent studies have provided compelling evidence for a cerebello-thalamo basal ganglia pathway.

A 2011 study by Calderon *et al.*, demonstrated that the rare genetic dystonia Rapid-onset dystonia Parkinsonism (RDP) can be pharmacologically modeled in the rodent by targeting both the cerebellum and basal ganglia⁸. It was also shown that the most common inherited dystonia, DYT1, can be modeled in the mouse by targeting only the cerebellum⁹. Further, it was suggested that abnormal cerebellar output may cause dystonia by altering basal ganglia activity through a di-synaptic pathway connecting these two brain areas (Figure 1). In 2014, Chen *et al.*, showed that basal ganglia activity can be modulated by input from the cerebellum via this direct cerebello-thalamo-basal ganglia pathway¹⁰. In this perspective, we will address the evidence for a role of the cerebellum and cerebello-basal ganglia communication in dystonia. We will also discuss the implications of the paper by Chen *et al.* and how they add to our understanding of the pathophysiology underlying dystonia. Finally, we will address how these results can improve our therapeutic approach to dystonia.

The Basal Ganglia in movement and movement disorders

Clinically, it has been known for a number of years that dysfunction in the basal ganglia can cause movement disorders¹¹. Multiple lines of reasoning suggest that the basal ganglia are involved in dystonia. Because damage to the basal ganglia can lead to secondary dystonia in human patients, this area is traditionally considered to underlie this disorder. Dystonia can be associated with abnormalities in dopamine as seen in patients with DYT5 who are highly responsive to treatment with levodopa¹². In addition, some patients with Parkinson's disease present initially with dystonia^{13,14}. Since normal dopamine signaling is vital to basal ganglia function, dopamine involvement suggests an important link between the basal ganglia and dystonia^{15,16}. Finally, many dystonic patients experience an alleviation of symptoms after lesions or deep brain stimulation (DBS) of nuclei in the basal ganglia¹⁷⁻²¹.

Animal models have demonstrated that a number of manipulations to the basal ganglia can result in dystonia. Early studies showed that applying a GABA_A antagonist to the striatum induced dystonia in cats or rats, indicating that impaired inhibition of the striatum is important in this disorder²²⁻²⁴. Recently, specific pharmacologic block of striatal fast spiking interneurons (FSIs) was performed in rodents and resulted in dyskinesia²⁵. Although the activity of FSIs was uniformly decreased in mice with dyskinesia, the activity change in MSNs was more variable, suggesting that dystonia may not be caused simply by changes in firing rate of MSNs but rather by more complicated changes in firing^{25,26}. Another study showed that abnormal bursting evident in striatal field potentials and the subsequent inhibition of activity in substantia nigra pars reticulata (SNr) were associated with dystonic movements²⁷. In a rat model of kernicterus-induced striatal dystonia, neurons in the globus pallidus (GP), subthalamic nucleus (STN), and entopeduncular nucleus fired in a more irregular manner with many exhibiting bursts of activity uncommon under normal conditions²⁸. Dystonic muscle contractions in this model were shown to correlate with periods of bursting of specific neurons, suggesting that burst firing in the basal ganglia may be an electrophysiological signature of dystonia²⁸.

Studies in humans have corroborated this notion of abnormal firing in the basal ganglia. In a seminal 1999 study, Vitek *et al.*, demonstrated that GPi neurons in patients with dystonia predominantly fire bursts of action potentials with intermittent pauses²⁹. Since then, this finding has been replicated a number of times and burst firing has also been identified in the STN of patients with dystonia^{30–33}. There is also evidence from humans that changes in the rate of firing of the different nuclei of the basal ganglia may contribute to dystonia. Specifically, neurons in the output nuclei of the basal ganglia exhibit a decreased firing rate in dystonic patients^{29,31,33–35}. Still, the effectiveness of pallidotomy in alleviating dystonia rather than worsening it, suggests that a decrease in the rate of basal ganglia output neurons alone does not cause dystonia. Further, whether rate is decreased in the GP at all in dystonia is disputed by some groups³⁶.

The Cerebellum and its role in movement and movement disorders

Cerebellar abnormalities are associated with ataxia in which patients exhibit gross incoordination of muscles³⁷. However, there has been evidence for some time that cerebellar dysfunction and tumors of the cerebellum can result in hyperkinetic disorders as well. Wurffbain probably provided the first description of this phenomenon in 1691 when he identified a child with a cerebellar tumor who exhibited fits of opisthotonus and head retraction. In fact, head retractions and abnormal head postures have been seen numerous times in patients with cerebellar tumors³⁸. There is evidence that cases of secondary focal neck dystonia are most often associated with lesions of the cerebellum and brainstem rather than of the basal ganglia³⁹.

However, the involvement of the cerebellum is not limited to focal neck dystonia. In 1988, a series of patients was presented with degenerative cerebellar ataxias who also displayed prominent dystonia⁴⁰. It is now clear that in some inherited ataxias, dystonia is a prominent feature^{37,41,42}. In fact, some patients with these disorders present initially with dystonia^{43–45}. Because these disorders are primarily associated with pathology of the cerebellum, the identification of dystonia in these patients is consistent with the hypothesis that dystonia can originate in the cerebellum. Further support came from other patients with familial dystonia associated with cerebellar atrophy⁴⁶. Based on these findings, it was suggested that at least in some cases abnormalities in the cerebellum might result in dystonia.

There is also evidence that the cerebellum is abnormal in patients with hereditary dystonias. Changes in cerebellar metabolism in patients with inherited dystonia have been reported⁴⁷. Studies in patients with DYT1, the most common hereditary dystonia, demonstrate that patients exhibit specific changes in cerebellar connectivity compared to controls and non-affected mutation carriers⁷. A recent study in patients with DYT11 highlighted that there are changes in the metabolism of the cerebellum of patients compared to non-symptomatic carriers⁶. In fact, there is evidence that transcranial magnetic stimulation of the cerebellum may alleviate symptoms in some dystonic patients⁴⁸.

Pioneering work in the 1960s and 1970s demonstrated that in some cases interventions involving the cerebellum could alleviate dystonia and other hyperkinetic disorders^{49,50}. In

one case, cerebellar lesion surgery was performed on a patient exhibiting an athetoid movement disorder. During surgery, Purkinje cells exhibited abnormal burst firing with the caveat that the patient was under anesthesia at the time of the recording⁵¹.

Further evidence for the role of the cerebellum in hyperkinetic disorders, specifically dystonia, has come from animal models. Both the tottering mouse and the *dt* rat exhibit dystonia that has been shown to originate in the cerebellum^{52–54}. Also, recent optogenetic studies have shown that stimulation of the cerebellum can elicit involuntary movements⁵⁵. In the *dt* rat and tottering mouse, abnormal bursting of cerebellar Purkinje cells and neurons of the CN underlies dystonia, a firing pattern similar to that identified in the athetoid patient of Slaughter, Nashold, and Somjen^{51,56}. In addition, neurons of the deep cerebellar nuclei in cerebellar-induced mouse models of RDP and DYT1 also display abnormal high frequency bursts during dystonic postures^{9,57,58}. Therefore, it is possible that abnormal burst firing may be a common mechanism by which the cerebellum contributes to dystonia.

Evidence for the cerebello-basal ganglia connection

Thus far, compelling evidence has been provided for involvement of the basal ganglia and the cerebellum in dystonia. However, the question still remains whether both areas can be simultaneously involved in dystonia since some inherited dystonias demonstrate abnormal function of both the cerebellum and basal ganglia⁵⁹. There is also evidence that the cerebellum can affect activity in the basal ganglia. In 1969, Ratcheson and Li demonstrated that electrical stimulation of the CN evoked either excitation or inhibition of activity in neurons of the striatum of the basal ganglia⁶⁰. This response was dependent on the intralaminar nuclei of the thalamus, areas deep in the thalamus now known to connect a number of regions throughout the brain and thought to be involved in attentional awareness^{61,62}. Nearly 30 years later, this idea was resurrected when a direct di-synaptic connection between the cerebellum and basal ganglia was identified in rodents which could underlie these responses⁶³. The pathway was found to connect the lateral cerebellar nucleus to the striatum of the basal ganglia via the intralaminar nuclei of the thalamus. In rodents, the pathway primarily traversed the centrolateral nucleus of the thalamus (CL), a small area that has been implicated in normal motor coordination^{62,64}. Subsequently, it was shown that this pathway is conserved in primates and recent evidence suggests it is also present in humans^{65,66}. Therefore this pathway could provide a substrate through which abnormal cerebellar output may affect the basal ganglia.

Could abnormal cerebellar output alter activity in the basal ganglia through the cerebello-basal ganglia connection?

There has been a growing interest in understanding whether a cerebello-basal ganglia circuit could play a role in dystonia^{54,67–70}. Using a pharmacologic rodent model of RDP, Calderon *et al.* addressed this question and systematically demonstrated that the dystonic features in these mice were due to changes in cerebellar output^{67,71}. Further, abnormal bursts of cerebellar EEG activity correlated with dystonic postures. The Parkinsonism-like features of RDP was recapitulated in the rodent model by infusing ouabain to the basal ganglia whereas dystonia was elicited by infusing ouabain to the cerebellum alone. Likewise, the use of

shRNAs specifically targeting the $\alpha 3$ isoform of the sodium pump either in the substantia nigra or in the cerebellum produced the same phenotype described above⁵⁷. Interestingly, dystonia could be alleviated in the pharmacologic rodent model of RDP by preventing cerebellar output, either by electric lesions of the CN, silencing the cerebellum with infusions of tetrodotoxin, or even increasing inhibitory tone by infusing GABA into the cerebellum (Figure 2). Since infusion of ouabain to both the cerebellum and basal ganglia was necessary to recapitulate all the features of RDP, one hypothesis is that abnormal cerebellar output in this pharmacologic model alters activity in the basal ganglia, resulting in dystonia. Additionally, in some cases where dystonia is thought to be secondary to cerebellar dysfunction, DBS of the basal ganglia can alleviate dystonic postures^{72,73}. Although there are multiple interpretations of this phenomenon, it is consistent with the hypothesis that in some cases the cerebellum can drive aberrant activity in the basal ganglia to induce dystonia. Since several lines of evidence already discussed indicate that burst firing of basal ganglia neurons occurs in dystonia, an obvious question is whether or not such firing is present in cerebellum-induced dystonia.

Short latency cerebellar modulation of the basal ganglia and its implications in dystonia

Using the established pharmacological model of RDP, Chen *et al.* recorded neurons in the dorsolateral striatum (DLS) of awake, freely moving animals with cerebellar-induced dystonia¹⁰. The DLS receives the majority of input from the di-synaptic pathway connecting the cerebellum to the basal ganglia⁶²⁻⁶⁴. They showed that in cerebellar-induced dystonia neurons of the DLS exhibited abnormal high-frequency burst firing (Figure 3). This abnormal firing was exaggerated during periods of severe dystonia. Notably, the abnormal firing pattern observed in the DLS was also recorded in cells of the CN in the RDP mouse model⁵⁸. Additionally, because the recordings in the DLS were performed using microarrays, there was the added advantage of simultaneously recording cells in close proximity to each other. They found that the activity of nearby neurons in the DLS was highly correlated during cerebellar-induced dystonia, in agreement with the hypothesis that the cells in the DLS receive a strong common drive (Figure 4). To determine whether the cerebellum is the instigator of the aberrant firing in the DLS, the centrolateral nucleus of the thalamus was electrically lesioned or silenced optogenetically, thereby disrupting communication between the cerebellum and basal ganglia. Remarkably, by severing the disynaptic pathway in dystonic mice, Chen *et al.*, found that the dystonic postures were alleviated, suggesting that the cerebellum could be the source of aberrant drive that modifies activity in the striatum thereby resulting in dystonia. Together, these findings support the hypothesis that abnormal cerebellar output drives high-frequency bursting activity in the DLS to cause dystonia. This is the first study showing that abnormal cerebellar output can result in burst firing within the basal ganglia, which has been shown to be a prominent feature of human dystonia^{29,31}.

Could interventions targeting a direct cerebello-basal ganglia connection have any therapeutic relevance in dystonia?

In recent years, DBS of the basal ganglia and especially the globus pallidus has become a mainstay of dystonia treatment because of its proven efficacy^{4,74–77}. Although this treatment has been shown to be effective in a variety of different dystonia patients, a common feature of basal ganglia DBS is that it often takes weeks to months for the alleviation of symptoms to occur^{75,77,78}. It is unknown why there is such a marked delay between implantation of DBS stimulating electrodes and the alleviation of symptoms. One hypothesis to explain this phenomena is that dystonia is a disorder of plasticity and the delay in symptom alleviation represents the time it takes for plastic changes in the motor circuitry to occur⁷⁹. However, it is clear that the delay in alleviation of symptoms is not present for all movement disorders. For example, DBS of GP in Parkinsonian patients has an immediate effect on symptoms⁸⁰. In patients with tremor, DBS of the ventralis intermedius thalamus can immediately alleviate symptoms⁸¹. In fact, early evidence suggested that interventions involving the thalamus could acutely alleviate dystonia as well⁸². This finding has been recently corroborated for some focal dystonias where lesioning the ventro-oral region of the thalamus results in immediate improvement of symptoms⁸³. Together, these studies suggest that acute alleviation of dystonia can be attained if the right area is targeted.

The findings presented in the ouabain mouse model by Calderon *et al*, 2011 and Chen *et al*, 2014 show that acutely silencing or lesioning the centrolateral nucleus of the thalamus (CL) in rodents with cerebellar-induced dystonia alleviates abnormal postures. This suggests that interventions involving the human equivalent of CL may also be effective in immediately alleviating dystonia in some patients. Based on our findings, if the thalamic area analogous to CL in rodents can be identified in humans, then alleviation of dystonia on a fast time scale should be attainable in patients with cerebellar-induced dystonia. Therefore, it would be especially important to examine whether some of the thalamic sites previously used to acutely alleviate dystonia in patients are intermediates in the cerebello-thalamo-basal ganglia pathway in humans. Further investigation into the role of the thalamus as an intermediary in the cerebello-thalamo-basal ganglia pathway and what form this pathway takes in humans is warranted. Therapeutic approaches targeting the cerebellum are also plausible. Calderon *et al*. 2011 additionally showed that dystonia in their rodent model of RDP could be improved by silencing the cerebellar output either by electrolytic lesions of the CN or by infusions of TTX. Furthermore, GABA infusions into the cerebellum were also sufficient to alleviate the dystonic postures.

In the pharmacologic model of RDP, Chen *et al*, found that burst firing within the DLS is associated with dystonia. Studies in other rodent models where dystonia is thought to originate from the basal ganglia itself show that burst firing occurs throughout this area and is associated specifically with abnormal muscle contractions^{28,84–87}. Although abnormal bursting activity in DLS is correlated with dystonia, it is unclear whether bursting of the basal ganglia alone is sufficient to cause dystonic postures. However, one study demonstrated that pharmacologically inhibiting FSIs of the striatum results in dystonic-like postures in the rodent²⁵. Recordings from this area showed that while all FSIs demonstrated

a decrease in firing rate after infusion of the drug, the response of MSNs was more variable with some cells increasing and others decreasing their firing rate. Although the authors did not specifically test for abnormal burst firing, they suggest in a later publication that abnormal patterns of activity may underlie the dyskinesia generated in this model²⁶. It is clear that we are just beginning to understand the relationship between the cerebellum and the basal ganglia and its role in movement disorders. The fact that aberrant neuronal activity is seen in the cerebellum of two different mouse models of RDP^{57,58} and in a mouse model of DYT1⁹ and given that there is a disynaptic connection from the cerebellum to the basal ganglia¹⁰, it is likely that this irregular activity is also present in the basal ganglia. While the current study addresses some questions, a more thorough understanding of how these areas communicate under physiological and pathological conditions in various mouse models of dystonia is vital.

Concluding Remarks

Recent evidence suggests that the cerebellum and cerebello-basal ganglia interactions have a role in dystonia that may be crucial in understanding this movement disorder. Chen *et al.*, 2014 has shown that the cerebellum can directly modulate the basal ganglia over a short time scale and has provided a mechanism by which abnormal cerebellar output may cause dystonia. Based on the resurgence of interest in the involvement of the cerebellum in dystonia, groups have started reconsidering cerebellar interventions for this disorder. The study by Koch *et al.*, 2014 demonstrated that cerebellar stimulation could alleviate some symptoms in patients with cervical dystonia⁸⁸. Another study last year by Sokal *et al.* demonstrated that bilateral deep anterior cerebellar stimulation in patients with secondary dystonia reduces both dystonic symptoms and spasticity⁸⁹. Future studies should examine whether DBS of the cerebellum may alleviate other types of dystonia as suggested by the results of Calderon *et al.* in the rodent model of RDP. Further, post mortem studies have suggested that patients with this disorder have marked changes in the cerebellum⁹⁰. Therefore, it will be important to determine whether patients with RDP and potentially patients with other genetic dystonias could benefit from interventions involving the cerebellum.

There is also a growing body of evidence that interactions between the cerebellum and basal ganglia are important in some dystonias. One case study of a patient with myoclonus dystonia showed that during dystonic episodes there was marked changes in the activity of the cerebellum and thalamus⁵⁹, suggesting that these areas are involved in this disorder. However, a number of studies have shown that this same syndrome can be alleviated by DBS of the basal ganglia^{91,92}. The recent work by Chen *et al.*, provides one explanation of how dystonic syndromes may be caused by changes in cerebellar output and alleviated by interventions involving the basal ganglia. Whether these same changes are present in other forms of dystonia is at present unknown, and needs to be studied experimentally. Additionally, this study suggests that interventions involving the cerebellum itself or the thalamic intermediate in the di-synaptic cerebello-basal ganglia connection may provide better and faster relief for some dystonic patients. Hopefully, as we discover more about the etiology of dystonia, better interventions can be developed to treat this disorder.

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A Pathway for short latency communication between the cerebellum and basal ganglia

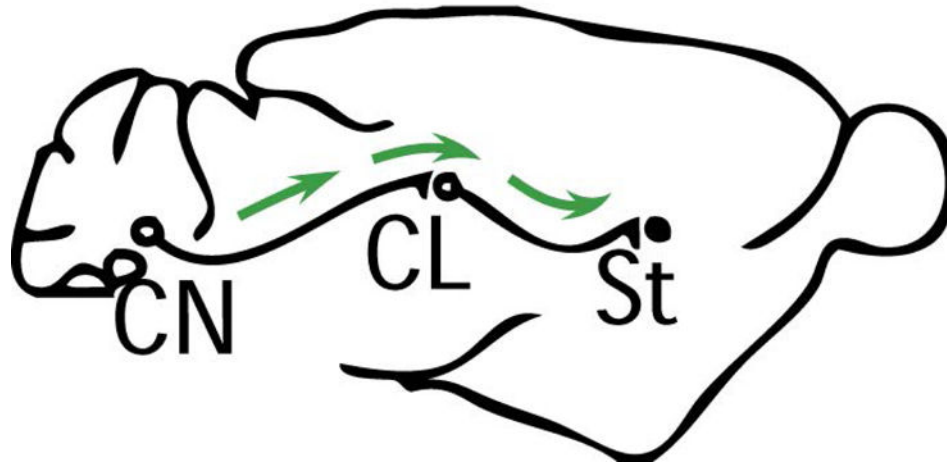


Figure 1. A disynaptic pathway connects the cerebellum to the basal ganglia

There is a disynaptic cerebello-basal ganglia connection that is conserved between rodents and humans. Fibers from the deep cerebellar nuclei (CN) pass through the intralaminar nuclei of the thalamus (in rodents primarily the centrolateral nucleus, CL) to the dorsolateral striatum (St, top image).

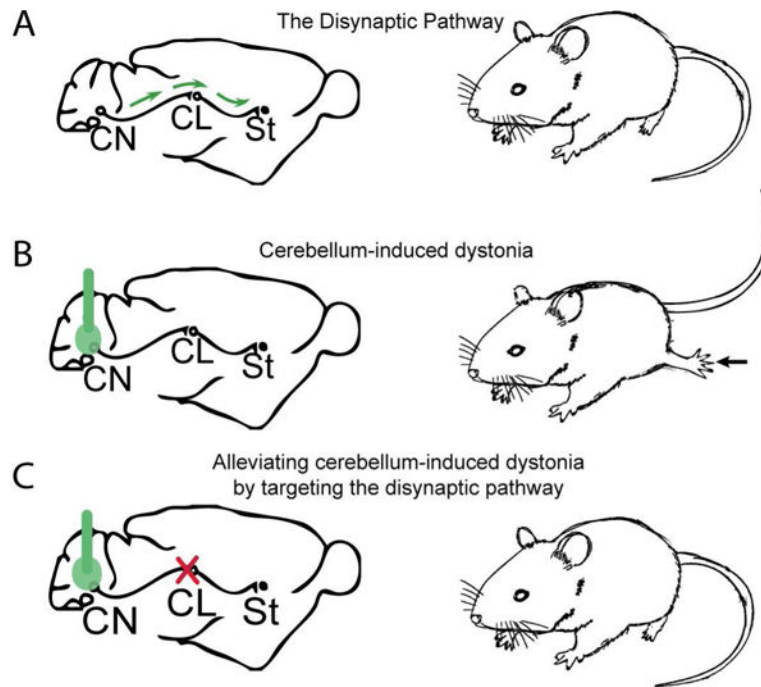
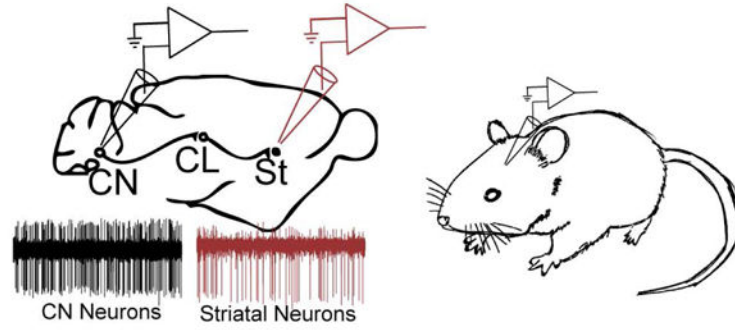


Figure 2. The disynaptic pathway connecting the cerebellum to the basal ganglia is implicated in dystonia

(A) A disynaptic pathway connects the cerebellum to the basal ganglia (B) When the $\alpha 3$ isoform of the sodium potassium ATPase is disrupted pharmacologically (left) with ouabain delivered by an osmotic pump or by shRNA injected stereotaxically in the cerebellum (green), there is a change in cerebellar output and the animal exhibits dystonia. (C) Remarkably, when the disynaptic pathway is disrupted either with (1) electrolytic lesions or (2) optogenetically, dystonic postures in the animal is relieved (right).

A Single unit extracellular recordings of neurons in an awake wild-type mouse



B Single unit extracellular recordings of neurons in an awake dystonic mouse

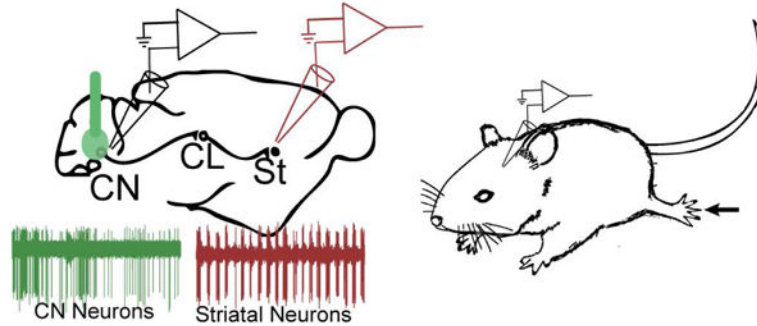


Figure 3. Electrophysiological signature in the cerebello-basal ganglia connection under physiological and pathological conditions

(A) Under physiological conditions cells in the deep cerebellar nuclei (CN) of awake mice fire regularly with a rate of around 40-50 Hz as seen by the raw trace (black), whereas cells in the striatum (St) fire with more variability and at a slower rate (red) compared to cells in the CN. (B) Fremont *et al.* 2014 showed that when ouabain is infused into the cerebellum, neurons in the CN fire in erratic bursts in the dystonic mouse (green trace). Similarly, Chen *et al.* 2014 also showed that neurons in the striatum fire in high frequency bursts (red trace) during dystonic postures.

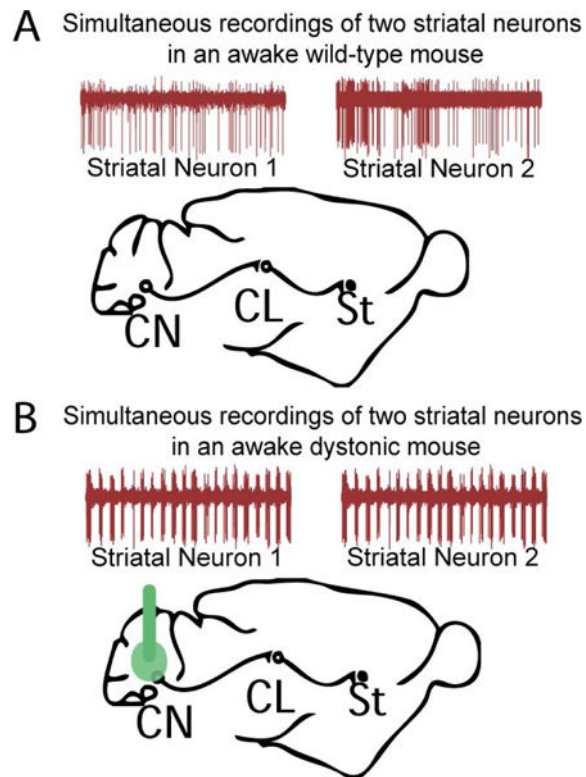


Figure 4. Under pathological conditions simultaneously recorded neighboring neurons in the striatum fire in bursts

Using a microarray to record single unit activity of neurons in the striatum Chen *et al.*,2014 found that striatal neurons recorded simultaneously during dystonic postures in the pharmacological model of RDP showed high frequency burst firing, which suggests that these neurons receive a common aberrant input from the cerebellum that could be driving this abnormal activity.