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The Cerebellum and Basal Ganglia are Interconnected

Andreea C. Bostan and
Center for the Neural Basis of Cognition, Systems Neuroscience Institute, and Department of Neurobiology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261, USA

Peter L. Strick
Pittsburgh Veterans Affairs Medical Center, Pittsburgh, PA 15240, USA, Center for the Neural Basis of Cognition, Systems Neuroscience Institute, and Department of Neurobiology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261, USA

Andreea C. Bostan: acb42@pitt.edu

Abstract

The cerebellum and the basal ganglia are major subcortical nuclei that control multiple aspects of behavior largely through their interactions with the cerebral cortex. Discrete multisynaptic loops connect both the cerebellum and the basal ganglia with multiple areas of the cerebral cortex. Interactions between these loops have traditionally been thought to occur mainly at the level of the cerebral cortex. Here, we review a series of recent anatomical studies in nonhuman primates that challenge this perspective. We show that the anatomical substrate exists for substantial interactions between the cerebellum and the basal ganglia. Furthermore, we discuss how these pathways may provide a useful framework for understanding cerebellar contributions to the manifestation of two prototypical basal ganglia disorders, Parkinson's disease and dystonia.

Keywords

Cerebellum; Basal ganglia; Virus tracing; Parkinson's disease; Dystonia

Introduction

The cerebellum and the basal ganglia are groups of subcortical nuclei with long-established roles in motor control. The traditional view has been that both of these structures integrate inputs from widespread cortical areas in the prefrontal, parietal, and temporal lobes and provide output exclusively to the primary motor cortex via the thalamus (Kemp and Powell 1971; Allen and Tsukahara 1974; Brooks and Thach 1981). Over the past three decades, many investigators have challenged this view. Leiner et al. (1986, 1989, 1991, 1993) were among the first to postulate that cerebellar output targets not only the primary motor cortex, but also areas in the prefrontal cortex that are involved in language and other cognitive functions. Similarly, Alexander et al. (1986) hypothesized that basal ganglia output targets not only the primary motor cortex, but also several areas in the prefrontal cortex that are involved in cognitive and limbic functions. Recent advances in anatomical circuit tracing using neurotropic viruses (Strick and Card 1992; Kelly and Strick 2000) have provided strong support for this new perspective on the roles of the cerebellum and the basal ganglia (Lynch et al. 1994; Middleton and Strick 1994, 1996, 2001, 2002; Hoover and Strick 1999;

Correspondence to: Andreea C. Bostan, acb42@pitt.edu.

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Clower et al. 2001, 2005; Kelly and Strick 2003, 2004; Akkal et al. 2007; Prevosto et al. 2010).

Viral tracers are ideally suited for unraveling multi-synaptic circuits like those that link the cerebellum and basal ganglia with the cerebral cortex. This approach has been used to demonstrate that the cerebellum and the basal ganglia do not simply funnel information from a variety of cortical areas to the primary motor cortex. Rather, the output of the basal ganglia and cerebellum reaches not only the primary motor cortex, but also areas of premotor, oculomotor, prefrontal, posterior parietal, and temporal cortex (Lynch et al. 1994; Middleton and Strick 1994, 1996, 2001, 2002; Hoover and Strick 1999; Clower et al. 2001, 2005; Kelly and Strick 2003, 2004; Akkal et al. 2007; Prevosto et al. 2010). Furthermore, different cortical areas project to specific cerebellar and basal ganglia territories. These territories have been shown to project back to many of the same cortical areas that are the origin of their input. This pattern of connections creates multiple closed-loop circuits (Middleton and Strick 2000; Dum and Strick 2003; Kelly and Strick 2003; Strick et al. 2009). These loops provide the anatomical substrate for the output from the cerebellum and basal ganglia to affect a much more widespread array of cortical regions than previously recognized and to have an impact on motor as well as nonmotor functions.

The loops that link the cerebellum with the cerebral cortex have traditionally been considered to be anatomically and functionally distinct from those that link the basal ganglia with the cerebral cortex (Doya 2000; Graybiel 2005). As the projections from the cerebellum and basal ganglia to the cerebral cortex are relayed through distinct thalamic nuclei (Percheron et al. 1996; Sakai et al. 1996), any interactions between cortico-cerebellar and cortico-basal ganglia loops were thought to occur primarily at the cortical level. In this review, we describe results from a series of recent studies that challenge this perspective.

First, we describe a disynaptic projection that links an output stage of cerebellar processing, the dentate nucleus, to the striatum, an input stage of basal ganglia processing (Hoshi et al. 2005; Fig. 1). Second, we describe a comparable pathway that links the subthalamic nucleus of the basal ganglia to the cerebellar cortex (Bostan et al. 2010; Fig. 1). Our results indicate that the pathways linking the cerebellum with the basal ganglia are topographically organized and that they may be involved in integrating cerebellar and basal ganglia functions in both the motor and nonmotor domains. These pathways provide evidence for substantial communication between the cerebellum and the basal ganglia that is independent of the cerebral cortex. Communication between these major subcortical nuclei is likely to have important clinical implications. As examples, we discuss how the pathways linking the cerebellum with the basal ganglia may provide a useful framework for understanding cerebellar contributions to the manifestation of two prototypical basal ganglia disorders, Parkinson’s disease and dystonia.

Virus Tracing

Earlier attempts to unravel the complex connections that link the basal ganglia and cerebellum to the cerebral cortex relied on the use of conventional tracers. While these methods have provided remarkable insights into the organization of these circuits, they are capable of displaying only the direct inputs and outputs from a site. Basal ganglia and cerebellar circuits with the cerebral cortex are multi-synaptic. As a consequence, our ability to examine these circuits has been greatly enhanced with the development of tracing techniques that use neurotropic viruses as transneuronal tracers. Specific strains of viruses are transported transneuronally in the anterograde or retrograde direction. The viruses that are useful for tracing experiments move from neuron to neuron exclusively at synapses, in a time-dependent fashion. By adjusting the survival time after virus injections, it is possible to

study neural circuits composed of two or more synaptically connected neurons (Strick and Card 1992; Ugolini 1995; Kelly and Strick 2000, 2003, 2004).

For the results described below, we used transneuronal transport of the N2c strain of rabies virus in nonhuman primates to examine the connections between the cerebellum and the basal ganglia. Prior studies have demonstrated that rabies virus is transported exclusively in the retrograde direction in a time-dependent fashion (Ugolini 1995; Kelly and Strick 2000; Hoshi et al. 2005; Bostan et al. 2010). Virus is transported between neurons exclusively at synapses and virus is not transported by fibers of passage or grow in glia (Ugolini 1995; Kelly and Strick 2000). A 40-hour survival time is sufficient for uptake and retrograde transport of the N2c strain of rabies virus by the synapses of first-order neurons that project to the injection site and then, retrograde transneuronal transport from these first-order neurons to the second-order neurons that innervate them (Hoshi et al. 2005; Bostan et al. 2010). A 50-hour survival time is sufficient for another stage of retrograde transneuronal transport from second-order neurons to the third-order neurons that project to them (Hoshi et al. 2005).

All of the procedures used during these experiments were approved by the appropriate Institutional Animal Care and Use and Biosafety committees. Biosafety practices conformed to the biosafety level 2+ regulations outlined in the “Biosafety in Microbiological and Biomedical Laboratories” (Department of Health and Human Services publication 93-8395). For technical details of the experimental methods and the procedures for handling virus and virus-infected animals see Kelly and Strick (2000), Hoshi et al. (2005) and Bostan et al. (2010).

The Disynaptic Projection from the Cerebellum to the Basal Ganglia

To explore whether the cerebellum projects to the basal ganglia, in two monkeys we injected the N2c strain of rabies virus into a localized region of the putamen. The injection sites in both animals were localized largely to the “sensorimotor territory” of the striatum (Parent and Hazrati 1995a). We set the survival time to allow for two stages of virus transport. We observed retrograde transport of the virus from the injection site to first-order neurons in the thalamus, and then, retrograde transneuronal transport from these first-order neurons to second-order neurons in the deep cerebellar nuclei (Fig. 1). The neurons in the cerebellar nuclei that were labeled by virus transport were located largely in the dentate nucleus. Thus, an output stage of cerebellar processing, the dentate, projects via the thalamus to an input stage of basal ganglia processing, the putamen.

In another two monkeys, we injected rabies virus into the external segment of the globus pallidus (GPe). In these animals, we set the survival time to allow for three stages of rabies virus transport. We observed retrograde transport of the virus from the injection site to first-order neurons in the striatum, retrograde transneuronal transport from these first-order neurons to second-order neurons in the thalamus, and retrograde transneuronal transport from the second-order neurons in the thalamus to third-order neurons in the deep cerebellar nuclei. We again found that most of the labeled neurons in the cerebellar nuclei were confined to the dentate (Figs. 1 and 2). Thus, not only does the output from the cerebellum influence the striatum, but the target of this influence includes striatal neurons in the so-called “indirect” pathway which projects to GPe (Alexander and Crutcher 1990).

The injections of rabies virus into GPe involved two different regions of the nucleus. The injection in one animal labeled neurons primarily in ventral and caudal regions of dentate. The injection site in the other animal was placed approximately 1 mm caudally in GPe and labeled neurons in more dorsal regions of dentate. These observations suggest that the projection from the dentate to the basal ganglia is topographically organized.

The dentate is a major source of projections to motor, premotor, prefrontal and parietal areas of cortex. Based on the topography of these projections, the dentate has been divided into distinct motor and nonmotor domains (Fig. 2; Dum and Strick 2003; Strick et al. 2009). These domains are also recognized by immunohistochemical staining with a monoclonal antibody, “8B3” (Pimenta et al. 2001; Dum and Strick 2003; Akkal et al. 2007). Projections from the dentate nucleus to the primary motor and premotor areas originate from the motor domain. In contrast, projections from the dentate nucleus to prefrontal and parietal areas originate from its nonmotor domain (Fig. 2). In the current experiments, virus transport from the basal ganglia labeled neurons in both the motor and nonmotor domains of the dentate (Fig. 2). These observations suggest that the cerebellar projection to the input stage of basal ganglia processing influences motor and nonmotor aspects of basal ganglia function.

The Disynaptic Projection from the Basal Ganglia to the Cerebellum

To explore whether the basal ganglia project to the cerebellum, in three monkeys we injected the N2c strain of rabies virus into selected sites within the cerebellar cortex. We set the survival time to allow for two stages of virus transport. We observed retrograde transport of the virus from the injection site to first-order neurons in the pontine nuclei, and then, retrograde transneuronal transport from these first-order neurons to second-order neurons in the subthalamic nucleus (STN) of the basal ganglia (Figs. 1 and 3).

Our rabies virus injections were placed in two areas within the hemispheric expansion of cerebellar lobule VII: the posterior aspects of Crus II (Crus IIp) (n=2) and the hemispheric lobule VIIB (HVIIB) (n=1). In all of these animals, virus transport labeled substantial numbers second-order neurons in the STN (Fig. 3a, b). The second-order neurons labeled from virus injections into Crus IIp and HVIIB differed in their rostro-caudal and dorso-ventral distributions within the STN. The Crus IIp injections labeled larger numbers of neurons in ventromedial portions of rostral STN, whereas the HVIIB injections labeled larger numbers of neurons in the dorsal aspects of caudal STN (Fig. 3a). Thus, a disynaptic connection links the STN with cerebellar cortex and this connection is topographically organized.

The STN can be subdivided into sensorimotor, associative, and limbic territories based on its interconnections with regions of the globus pallidus and the ventral pallidum (Fig 3c; Parent and Hazrati 1995b; Joel and Weiner 1997; Hamani et al. 2004). Our results provide evidence that the projections from the STN to the cerebellar cortex originate from all three of its functional subdivisions. Specifically, most of the STN neurons that project to Crus IIp were found in the associative territory, in regions that receive substantial inputs from the frontal eye fields and regions of the prefrontal cortex (Fig. 3d; Monakow et al. 1978; Stanton et al. 1988; Inase et al. 1999; Kelly and Strick 2004). In contrast, most of the STN neurons that project to HVIIB were found in the sensorimotor territory, in regions that receive substantial inputs from the primary motor cortex and premotor areas of the frontal lobe (Fig. 3d; Monakow et al. 1978; Nambu et al. 1996, 1997; Inase et al. 1999; Kelly and Strick 2004). Therefore, the anatomical substrate exists for both motor and nonmotor aspects basal ganglia processing to influence cerebellar function.

Implications for Disorders of Motor Control

Our results provide the anatomical substrate for two-way communication between the cerebellum and the basal ganglia (Fig. 1). One prediction from these findings is that activity in one of these major subcortical systems may directly affect the function of the other. Such interactions between the cerebellum and the basal ganglia are likely to have important implications for motor and cognitive functions. Similarly, the interconnections between the

two structures may enable abnormal activity at one site to propagate to the other and have negative consequences. As examples, we will discuss how the pathways linking the cerebellum with the basal ganglia may contribute to our understanding of cerebellar involvement in two prototypical basal ganglia disorders: Parkinson's disease and dystonia.

Parkinson's Disease

In Parkinson's disease the loss of dopaminergic neurons of the substantia nigra pars compacta of the basal ganglia results in the manifestation of its characteristic motor signs: resting tremor, rigidity and akinesia/bradykinesia (Wichmann and DeLong 2003). Resting tremor is the most common initial sign of Parkinson's disease, present in approximately half of the patients at the time of diagnosis (Fishman 2008). The loss of dopaminergic neurons results in abnormal oscillatory activity in the basal ganglia. Tremor-related activity has been recorded in the STN and the internal segment of the globus pallidus (GPi) of Parkinson's disease patients (Hurtado et al. 1999; Amtage et al. 2008). It has also been observed in monkey models of Parkinson's disease that exhibit tremor (Bergman et al. 1994; Wichmann et al. 1994). However, the source of the tremor remains unclear.

We would like to present the evidence that one potential source of the tremor-related oscillations seen in Parkinson's disease is the cerebellum. As mentioned previously, the cerebellum and the basal ganglia project to different thalamic nuclei (Percheron et al. 1996; Sakai et al. 1996). In Parkinson's disease patients (Ohye et al. 1974; Lenz et al. 1994) and in monkey models of Parkinson's disease (Guehl et al. 2003) oscillatory activity at tremor frequencies has been recorded in the region of the motor thalamus that receives cerebellar efferents, the ventralis intermedius nucleus (VIM). Such activity is not observed in thalamic nuclei that are the target of basal ganglia efferents. Furthermore, VIM has been established as one of the most effective surgical sites for treating parkinsonian tremor (Narabayashi et al. 1987; Lenz et al. 1988). In contrast, thalamic regions that are the target of basal ganglia efferents are not especially effective in treating tremor. These findings provide strong evidence that abnormal activity in cerebellar circuits may account for the tremor in Parkinson's disease.

In Parkinson's disease, the STN exhibits significant increases in firing rates, oscillatory and bursting activity (Bergman et al. 1994; Wichmann et al. 1994; Hutchison et al. 1998; Magarinos-Ascone et al. 2000; Magnin et al. 2000; Rodriguez-Oroz et al. 2001; Steigerwald et al. 2008; Theodosopoulos et al. 2003; Schrock et al. 2009). Based on our findings, the disynaptic connections may transmit abnormal STN activity to cerebellar cortex. In support of this proposal, several neuroimaging studies have reported abnormal cerebellar activity in Parkinson's disease (Rascol et al. 1997; Catalan et al. 1999; Ghaemi et al. 2002; Turner et al. 2003; Wu and Hallett 2005; Yu et al. 2007). Deep brain stimulation of the STN is recognized as a very effective treatment for the motor symptoms of Parkinson's disease (Limousin-Dowsey et al. 1999; Krack et al. 2002). In addition, deep brain stimulation has been shown to normalize cerebellar activity (Hilker et al. 2004; Payoux et al. 2004; Grafton et al. 2006; Trost et al. 2006; Geday et al. 2009). Thus, the effectiveness of deep brain stimulation as a treatment may be due, in part, to altering STN activity and reducing STN abnormal output to the cerebellum.

Dystonia

Dystonia is a movement disorder characterized by involuntary muscle contractions, twisting movements and abnormal postures (Fahn et al. 1998). Several lines of evidence indicate that the basal ganglia represent a key structure in the pathophysiology of both primary and secondary dystonias. Primary dystonias develop spontaneously, without an apparent cause and have a hereditary component. Although no overt degeneration has been identified in

primary dystonias, abnormalities in basal ganglia activity have frequently been reported (Brakefield et al. 2008).

Secondary dystonias result from diseases or brain injury and are most often associated with lesions of the basal ganglia (Bhatia and Marsden 1994; Geyer and Bressman 2006; Brakefield et al. 2008). Lesions and pharmacological manipulations of the basal ganglia in animal models have produced various forms of dystonia (Guehl et al. 2009). Furthermore, injections of GABA-A anatagonist bicuculline into the rostral motor thalamus, which relays basal ganglia projections to the cerebral cortex, can induce dystonic postures (Guehl et al. 2000; Macia et al. 2002).

On the other hand, cerebellar abnormalities have also been implicated in both primary and secondary dystonias. Carriers of genetic mutations that are associated with primary dystonia exhibit abnormalities in metabolic brain activity not only in the basal ganglia, but also in the cerebellum (Eidelberg 1998; Trost et al. 2002; Ghilardi et al. 2003; Carbon et al. 2008, 2010; Carbon and Eidelberg, 2009). Diffusion tensor imaging data suggests that in these individuals, the integrity of the cerebello-thalamo-cortical tract is reduced and this reduction is correlated with the clinical penetrance of their genetic mutations (Argyelan et al. 2009).

Damage to the cerebellum can result in some forms of secondary dystonia (Bhatia and Marsden 1994; LeDoux and Brady 2003; Geyer and Bressman 2006; Brakefield et al. 2008). Animal models provide further support for cerebellar contributions to secondary dystonia. In mice, pharmacological stimulation of the cerebellar vermis has been shown to elicit dystonic postures of the trunk and limbs (Pizoli et al. 2002). Furthermore, abnormal oscillations have been reported in the cerebellar cortex of tottering mice, a genetic mouse model of dystonia (Chen et al. 2009). In these mice, abnormal cerebellar output appears to be essential for the generation of dystonic movements (Campbell and Hess 1998; Campbell et al. 1999; Neychev et al. 2008). These findings indicate that dystonia is associated with abnormalities in both the basal ganglia and cerebellum and these two structures may interact in the expression of this disorder.

Our results showing interconnections between the cerebellum and the basal ganglia may help explain how these structures interact in the expression of dystonia. The disynaptic link from the dentate nucleus to the striatum may allow abnormalities in cerebellar activity to affect he basal ganglia. Similarly, abnormal activity in the basal ganglia, particularly in the STN, may impact cerebellar function. The STN of patients with primary dystonia exhibits significant increases in firing rates, oscillatory and bursting activity (Schrock et al. 2009). These abnormal signals could be transmitted from STN to the cerebellar cortex and contribute to the manifestation of dystonia.

Summary and Conclusions

We have described a disynaptic projection from the cerebellum to the basal ganglia and a reciprocal projection from the basal ganglia to the cerebellum (Fig. 1). These newly identified pathways provide a direct route for cerebellar activity to influence and be influenced by basal ganglia activity. We have provided a couple of relevant examples of how the pathways linking the cerebellum and basal ganglia may contribute to our understanding of two major motor disorders, Parkinson’s disease and dystonia.

Evidence has been accumulating for important roles of the cerebellum and the basal ganglia not only in motor control, but also in nonmotor functions (e.g., Middleton and Strick 2000; Strick et al. 2009). Our results indicate that both the motor and nonmotor domains of the dentate nucleus provide disynaptic inputs to the basal ganglia. Similarly, the motor and nonmotor territories of the STN provide disynaptic inputs to the cerebellar cortex. These

findings indicate that cerebellar and basal ganglia functions may be integrated across motor and nonmotor domains.

Clinically, interactions between the cerebellum and the basal ganglia in the nonmotor domain are likely to have important implications for a wide variety of disorders. Alterations in cerebellar and basal ganglia loops with nonmotor cortical areas have been identified in numerous neuropsychiatric disorders including schizophrenia, Tourette's syndrome, autism, attention deficit disorder, and addiction (e.g., Andreasen et al. 1998; Middleton and Strick 2000; Grabli et al. 2004; François et al. 2004; Temel and Visser-Vandewalle 2004; Krain and Castellanos 2006; Amaral et al. 2008; Andreasen and Pierson 2008; Strick et al. 2009; Rouaud et al. 2010; Simpson et al. 2010; Tobe et al. 2010). It may be important for future studies to consider the potential contributions of both the basal ganglia and cerebellum in the manifestation of these disorders. The interconnections between the basal ganglia and cerebellum mean that the substrate exists for dysfunction in one structure to be propagated to the other.

Of course our results raise another important question: What are the implications of the interconnections between the cerebellum and basal ganglia for normal function? So far, research has focused primarily on differentiating between cerebellar and basal ganglia contributions to behavior (e.g., Doya 2000). We believe our findings suggest that new insights will come from considering how these two nuclei cooperate to influence movement, cognition and affect.

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Acronym Key

Cerebellar areas

Crus IIp	posterior Crus II (a component of hemispheric lobule VII)
HVIIB	hemispheric lobule VIIB

Basal ganglia areas

GPe	external segment of the globus pallidus
GPi	internal segment of the globus pallidus
STN	subthalamic nucleus

Thalamic areas

VIM	ventralis intermedius nucleus

References

Akkal D, Dum RP, Strick PL. Supplementary motor area and presupplementary motor area: targets of basal ganglia and cerebellar output. Journal of Neuroscience. 2007; 27(40):10659–10673. [PubMed: 17913900]

Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends in Neurosciences. 1990; 13(7):266–271. [PubMed: 1695401]

Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking the basal ganglia and cortex. Annual Review of Neuroscience. 1986; 9:357–381.

Allen GI, Tsukahara N. Cerebrocerebellar communication systems. Physiological Review. 1974; 54(4):957–1006.

Amaral DG, Schumann CM, Nordahl CW. Neuroanatomy of autism. Trends in Neurosciences. 2008; 31(3):137–145. [PubMed: 18258309]

Amtage F, Henschel K, Schelter B, Vesper J, Timmer J, Lücking CH, et al. Tremor-correlated neuronal activity in the subthalamic nucleus of Parkinsonian patients. Neuroscience Letters. 2008; 442(3):195–199. [PubMed: 18634849]

Andreasen NC, Pierson R. The role of the cerebellum in schizophrenia. Biological Psychiatry. 2008; 64(2):81–88. [PubMed: 18395701]

Andreasen NC, Paradiso S, O'Leary DS. "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? Schizophrenia Bulletin. 1998; 24(2):203–218. [PubMed: 9613621]

Argyelan M, Carbon M, Niethammer M, Ulug AM, Voss HU, Bressman SB, et al. Cerebellothalamocortical connectivity regulates penetrance in dystonia. Journal of Neuroscience. 2009; 29(31):9740–9747. [PubMed: 19657027]

Bergman H, Wichmann T, Karmon B, DeLong MR. The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. Journal of Neurophysiology. 1994; 72(2):507–520. [PubMed: 7983515]

Bhatia KP, Marsden CD. The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain. 1994; 117(4):859–876. [PubMed: 7922471]

Bostan AC, Dum RP, Strick PL. The basal ganglia communicate with the cerebellum. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107(18):8452–8456. [PubMed: 20404184]

Brakefield XO, Blood AJ, Li Y, Hallett M, Hanson PI, Standaert DG. The pathophysiological basis of dystonias. Nature Reviews Neuroscience. 2008; 9(3):222–234.

Brooks, VB.; Thach, WT. Cerebellar control of posture and movement. In: Brooks, VB., editor. Handbook of physiology, Section I. The nervous system. Vol. 2. Bethesda: Am. Physiol. Soc; 1981. p. 877-946.Motor Control, Part II

Campbell DB, Hess EJ. Cerebellar circuitry is activated during convulsive episodes in the tottering (tg/tg) mutant mouse. Neuroscience. 1998; 85(3):773–783. [PubMed: 9639271]

Campbell DB, North JB, Hess EJ. Tottering mouse motor dysfunction is abolished on the Purkinje cell degeneration (pcd) mutant background. Experimental Neurology. 1999; 160(1):268–278. [PubMed: 10630211]

Carbon M, Eidelberg D. Abnormal structure-function relationships in hereditary dystonia. Neuroscience. 2009; 164(1):220–229. [PubMed: 19162138]

Carbon M, Ghilardi MF, Argyelan M, Dhawan V, Bressmann SB, Eidelberg D. Increased cerebellar activation during sequence learning in DYT1 carriers: an equiperformance study. Brain. 2008; 131(1):146–154. [PubMed: 17947338]

Carbon M, Argyelan M, Eidelberg D. Functional imaging in hereditary dystonia. European Journal of Neuroscience. 2010; 17(Suppl 1):58–64.

Catalan M, Ishii K, Honda M, Samii A, Hallett M. A PET study of sequential finger movements of varying length in patients with Parkinson's disease. Brain. 1999; 122(3):483–495. [PubMed: 10094257]

Chen G, Popa LS, Wang X, Gao W, Barnes J, Hendrix CM, et al. Low-frequency oscillations in the cerebellar cortex of the tottering mouse. Journal of Neurophysiology. 2009; 101(1):234–245. [PubMed: 18987121]

Clower DM, West RA, Lynch JC, Strick PL. The inferior parietal lobule is the target of output from the superior colliculus, hippocampus, and cerebellum. Journal of Neuroscience. 2001; 21(16):6283–6291. [PubMed: 11487651]

Clower DM, Dum RP, Strick PL. Basal ganglia and cerebellar inputs to "AIP". Cerebral Cortex. 2005; 15(7):913–920. [PubMed: 15459083]

Doya K. Complementary roles of basal ganglia and cerebellum in learning and motor control. Current Opinion in Neurobiology. 2000; 10(6):732–739. [PubMed: 11240282]

Dum RP, Strick PL. An unfolded map of the cerebellar dentate nucleus and its projections to the cerebral cortex. Journal of Neurophysiology. 2003; 89(1):634–639. [PubMed: 12522208]

Eidelberg D. Functional brain networks in movement disorders. Current Opinion in Neurology. 1998; 11(4):319–326. [PubMed: 9725077]

Fahn S, Bressman SB, Marsden CD. Classification of dystonia. Advances in Neurology. 1998; 78:1–10. [PubMed: 9750897]

Fishman PS. Paradoxical aspects of parkinsonian tremor. Movement Disorders. 2008; 23(2):168–173. [PubMed: 17973325]

François C, Grabli D, McCairn K, Jan C, Karachi C, Hirsch EC, et al. Behavioural disorders induced by external globus pallidus dysfunction in primates II. Anatomical study. Brain. 2004; 127:2055–2070. [PubMed: 15292054]

Geday J, Østergaard K, Johnsen E, Gjedde A. STN-stimulation in Parkinson's disease restores striatal inhibition of thalamocortical projection. Human Brain Mapping. 2009; 30(1):112–121. [PubMed: 18041743]

Geyer HL, Bressman SB. The diagnosis of dystonia. Lancet. 2006; 5(9):780–790.

Ghaemi M, Raethjen J, Hilker R, Rudolf J, Sobesky J, Deuschl G, et al. Monosymptomatic resting tremor and Parkinson's disease: a multitracer positron emission tomographic study. Movement Disorders. 2002; 17(4):782–788. [PubMed: 12210876]

Ghilardi MF, Carbon M, Silverstri G, Dhawan V, Tagliati M, Bressman S, et al. Impaired sequence learning in carriers of the DYT1 dystonia mutation. Annals of Neurology. 2003; 54(1):102–109. [PubMed: 12838525]

Grabli D, McCairn K, Hirsch EC, Agid Y, Féger J, François C, et al. Behavioural disorders induced by external globus pallidus dysfunction in primates: I. Behavioural Study. Brain. 2004; 127:2039–2054. [PubMed: 15292053]

Grafton ST, Turner RS, Desmurget M, Bakay R, Delong M, Vitek J, et al. Normalizing motor-related brain activity: subthalamic nucleus stimulation in Parkinson disease. Neurology. 2006; 66(8):1192–1199. [PubMed: 16636237]

Graybiel AM. The basal ganglia: learning new tricks and loving it. Current Opinion in Neurobiology. 2005; 15(6):638–644. [PubMed: 16271465]

Guehl D, Burbaud P, Boraud T, Bioulac B. Bicuculline injections into the rostral and caudal motor thalamus of the monkey induce different types of dystonia. European Journal of Neuroscience. 2000; 12(3):1033–1037. [PubMed: 10762334]

Guehl D, Pessiglione M, François C, Yelnik J, Hirsch E, Féger J, et al. Tremor-related activity of neurons in the "motor" thalamus: changes in firing rate and pattern in the MPTP vervet model of parkinsonism. The European Journal of Neuroscience. 2003; 17(11):2388–2400. [PubMed: 12814370]

Guehl D, Cuny E, Ghorayeb I, Michelet T, Bioulac B, Burbaud P. Primate models of dystonia. Progress in Neurobiology. 2009; 87(2):118–131. [PubMed: 19022333]

Hamani C, Saint-Cyr JA, Fraser J, Kaplitt M, Lozano AM. The subthalamic nucleus in the context of movement disorders. Brain. 2004; 127(1):4–20. [PubMed: 14607789]

Hilker R, Voges J, Weisenbach S, Kalbe E, Burghaus L, Ghaemi M, et al. Subthalamic nucleus stimulation restores glucose metabolism in associative and limbic cortices and in cerebellum: evidence from a FDG-PET study in advanced Parkinson's disease. Journal of Cerebral Blood Flow & Metabolism. 2004; 24(1):7–16. [PubMed: 14688612]

Hoover JE, Strick PL. The organization of cerebellar and basal ganglia outputs to primary motor cortex as revealed by retrograde transneuronal transport of herpes simplex virus type 1. Journal of Neuroscience. 1999; 19(4):1446–1463. [PubMed: 9952421]

Hoshi E, Tremblay L, Féger J, Carras PL, Strick PL. The cerebellum communicates with the basal ganglia. Nature Neuroscience. 2005; 8(11):1491–1493.

Hurtado JM, Gray CM, Tamas LB, Sigvardt KA. Dynamics of tremor-related oscillations in the human globus pallidus: a single case study. Proceedings of the National Academy of Sciences of the United States of America. 1999; 96(4):1674–1679. [PubMed: 9990083]

Hutchison WD, Allan RJ, Opitz H, Levy R, Dostrovsky JO, Lang AE, et al. Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. Annals of Neurology. 1998; 44(4):622–628. [PubMed: 9778260]

Inase M, Tokuno H, Nambu A, Akazawa T, Takada M. Corticostriatal and corticosubthalamic input zones from the presupplementary motor area in the macaque monkey: comparison with the input zones from the supplementary motor area. Brain Research. 1999; 833(2):191–201. [PubMed: 10375694]

Joel D, Weiner I. The connections of the primate subthalamic nucleus: indirect pathways and the open-interconnected scheme of basal ganglia-thalamocortical circuitry. Brain Research Brain Research Reviews. 1997; 23(1–2):62–78. [PubMed: 9063587]

Kelly RM, Strick PL. Rabies as a transneuronal tracer of circuits in the central nervous system. Journal of Neuroscience Methods. 2000; 103(1):63–71. [PubMed: 11074096]

Kelly RM, Strick PL. Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. Journal of Neuroscience. 2003; 23(23):8432–8444. [PubMed: 12968006]

Kelly RM, Strick PL. Macro-architecture of basal ganglia loops with the cerebral cortex: use of rabies virus to reveal multisynaptic circuits. Progress in Brain Research. 2004; 143:449–459. [PubMed: 14653187]

Kemp JM, Powell TPS. The connexions of the striatum and globus pallidus: synthesis and speculation. Philosophical Transactions of the Royal Society of London. 1971; 262(845):441–457. [PubMed: 4399123]

Krack P, Fraix V, Mendes A, Benabid AL, Pollak P. Postoperative management of subthalamic nucleus stimulation for Parkinson's disease. Movement Disorders. 2002; 17(Suppl 3):S188–S197. [PubMed: 11948776]

Krain AL, Castellanos FX. Brain development and ADHD. Clinical Psychology Review. 2006; 26(4): 433–444. [PubMed: 16480802]

LeDoux MS, Brady KA. Secondary cervical dystonia associated with structural lesions of the central nervous system. Movement Disorders. 2003; 18(1):60–69. [PubMed: 12518301]

Leiner HC, Leiner AL, Dow RS. Does the cerebellum contribute to mental skills? Behavioral Neuroscience. 1986; 100(4):443–454. [PubMed: 3741598]

Leiner HC, Leiner AL, Dow RS. Reappraising the cerebellum: what does the hindbrain contribute to the forebrain? Behavioral Neuroscience. 1989; 103(5):998–1008. [PubMed: 2679667]

Leiner HC, Leiner AL, Dow RS. The human cerebro-cerebellar system: its computing, cognitive, and language skills. Behavioural Brain Research. 1991; 44(2):113–128. [PubMed: 1751002]

Leiner HC, Leiner AL, Dow RS. Cognitive and language functions of the human cerebellum. Trends in Neurosciences. 1993; 16(11):444–447. [PubMed: 7507614]

Lenz FA, Tasker RR, Kwan HC, Schnider S, Kwong R, Murayama Y, et al. Single unit analysis of the human ventral thalamic nuclear group: correlation of thalamic "tremor cells" with the 3–6 Hz component of parkinsonian tremor. The Journal of Neuroscience. 1988; 8(3):754–764. [PubMed: 3346719]

Lenz FA, Kwan HC, Martin RR, Tasker RR, Dostrovsky JO, Lenz YE. Single unit analysis of the human ventral thalamic nuclear group. Tremor-related activity in functionally identified cells. Brain. 1994; 117(3):531–543. [PubMed: 8032863]

Limousin-Dowsey P, Pollak P, Van Blercom N, Krack P, Benazzouz A, Benabid A. Thalamic, subthalamic nucleus and internal pallidum stimulation in Parkinson's disease. Journal of Neurology. 1999; 246(Suppl 2):II42–II45. [PubMed: 10526001]

Lynch JC, Hoover JE, Strick PL. Input to the primate frontal eye field from the substantia nigra, superior colliculus, and dentate nucleus demonstrated by transneuronal transport. Experimental Brain Research. 1994; 100(1):181–186.

Macia F, Escola L, Guehl D, Michelet T, Bioulac B, Burbaud P. Neuronal activity in the monkey motor thalamus during bicuculline-induced dystonia. European Journal of Neuroscience. 2002; 15(8):1353–1362. [PubMed: 11994129]

Magarinos-Ascone CM, Figueiras-Mendez R, Riva-Meana C, Córdoba-Fernández A. Subthalamic neuron activity related to tremor and movement in Parkinson's disease. European Journal of Neuroscience. 2000; 12(7):2597–2607. [PubMed: 10947834]

Magnin M, Morel A, Jeanmonod D. Single-unit analysis of the pallidum, thalamus and subthalamic nucleus in parkinsonian patients. Neuroscience. 2000; 96(3):549–564. [PubMed: 10717435]

Middleton FA, Strick PL. Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. Science. 1994; 266(5184):458–461. [PubMed: 7939688]

Middleton FA, Strick PL. The temporal lobe is a target of output from the basal ganglia. Proceedings of the National Academy of Sciences of the United States of America. 1996; 93(16):8683–8687. [PubMed: 8710931]

Middleton FA, Strick PL. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Research Brain Research Reviews. 2000; 31(2–3):236–250. [PubMed: 10719151]

Middleton FA, Strick PL. Cerebellar projections to the prefrontal cortex of the primate. Journal of Neuroscience. 2001; 21(2):700–712. [PubMed: 11160449]

Middleton FA, Strick PL. Basal-ganglia "projections" to the prefrontal cortex of the primate. Cerebral Cortex. 2002; 12(9):926–935. [PubMed: 12183392]

Monakow KH, Akert K, Künzle H. Projections of the precentral motor cortex and other cortical areas of the frontal lobe to the subthalamic nucleus in the monkey. Experimental Brain Research. 1978; 33(3–4):395–403.

Nambu A, Takada M, Inase M, Tokuno H. Dual somatotopical representations in the primate subthalamic nucleus: evidence for ordered but reversed body-map transformations from the primary motor cortex and the supplementary motor area. Journal of Neuroscience. 1996; 16(8): 2671–2683. [PubMed: 8786443]

Nambu A, Tokuno H, Inase M, Takada M. Cortico-subthalamic input zones from forelimb representations of the dorsal and ventral divisions of the premotor cortex in the macaque monkey: comparison with the input zones from the primary motor cortex and supplementary motor area. Neuroscience Letters. 1997; 239(1):13–16. [PubMed: 9547160]

Narabayashi H, Maeda T, Yokochi F. Long-term follow-up study of nucleus ventralis intermedius and ventrolateralis thalamotomy using a microelectrode technique in parkinsonism. Applied Neurophysiology. 1987; 50(1–6):330–337. [PubMed: 3329871]

Neychev VK, Fan X, Mitev VI, Hess EJ, Jinnah HA. The basal ganglia and cerebellum interact in the expression of dystonic movement. Brain. 2008; 131(9):2499–2509. [PubMed: 18669484]

Ohye C, Saito U, Fukamachi A, Narabayashi H. An analysis of the spontaneous rhythmic and non-rhythmic burst discharges in the human thalamus. Journal of the Neurological Sciences. 1974; 22(2):245–259. [PubMed: 4829196]

Parent A, Hazrati LN. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. Brain Research Brain Research Reviews. 1995a; 20(1):91–127. [PubMed: 7711769]

Parent A, Hazrati LN. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Research Brain Research Reviews. 1995b; 20(1):128–154. [PubMed: 7711765]

Payoux P, Remy P, Damier P, Miloudi M, Loubinoux I, Pidoux B, et al. Subthalamic nucleus stimulation reduces abnormal motor cortical overactivity in Parkinson disease. Archives of Neurology. 2004; 61(8):1307–1313. [PubMed: 15313852]

Percheron G, François C, Talbi B, Yelnik J, Fénelon G. The primate motor thalamus. Brain Research Brain Research Reviews. 1996; 22(2):93–181. [PubMed: 8883918]

Pimenta AF, Strick PL, Levitt P. Novel proteoglycan epitope expressed in functionally discrete patterns in primate cortical and subcortical regions. Journal of Comparative Neurology. 2001; 430(3):369–388. [PubMed: 11169474]

Pizoli CE, Jinnah HA, Billingsley ML, Hess JE. Abnormal cerebellar signaling induces dystonia in mice. Journal of Neuroscience. 2002; 22(17):7825–7833. [PubMed: 12196606]

Prevosto V, Graf W, Ugolini G. Cerebellar inputs to intraparietal cortex areas LIP and MIP: functional frameworks for adaptive control of eye movements, reaching, and arm/eye/head movement coordination. Cerebral Cortex. 2010; 20(1):214–228. [PubMed: 19465740]

Rascol O, Sabatini U, Fabre N, Brefel C, Loubinoux I, Celsis P, et al. The ipsilateral cerebellar hemisphere is overactive during hand movements in akinetic parkinsonian patients. Brain. 1997; 120(1):103–110. [PubMed: 9055801]

Rodriguez-Oroz MC, Rodriguez M, Guridi J, Mewes K, Chockkman V, Vitek J, et al. The subthalamic nucleus in Parkinson's disease: somatotopic organization and physiological characteristics. Brain. 2001; 124(9):1777–1790. [PubMed: 11522580]

Rouaud T, Lardeux S, Panayotis N, Paleressompoulle D, Cador M, Baunez C. Reducing the desire for cocaine with subthalamic nucleus deep brain stimulation. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107(3):1196–1200. [PubMed: 20080543]

Sakai ST, Inase M, Tanji J. Comparison of cerebellothalamic and pallidothalamic projections in the monkey (Macaca fuscata): a double anterograde labeling study. Journal of Comparative Neurology. 1996; 368(2):215–228. [PubMed: 8725303]

Schrock LE, Ostrem JL, Turner RS, Shimamoto SA, Starr PA. The subthalamic nucleus in primary dystonia: single-unit discharge characteristics. Journal of Neurophysiology. 2009; 102(6):3740–3752. [PubMed: 19846625]

Simpson EH, Kellendonk C, Kandel E. A possible role for the striatum in the pathogenesis of the cognitive symptons of schizophrenia. Neuron. 2010; 65(5):585–596. [PubMed: 20223196]

Stanton GB, Goldberg ME, Bruce CJ. Frontal eye field efferents in the macaque monkey: I. Subcortical pathways and topography of striatal and thalamic fields. Journal of Comparative Neurology. 1988; 271(4):473–492. [PubMed: 2454970]

Steigerwald F, Pötter M, Herzog J, Pinsker M, Kopper F, Mehdorn H, et al. Neuronal activity of the human subthalamic nucleus in the parkinsonian and nonparkinsonian state. Journal of Neurophysiology. 2008; 100(5):2515–2524. [PubMed: 18701754]

Strick, PL.; Card, JP. Transneuronal mapping of neural circuits with alpha herpesviruses. In: Bolam, JP., editor. Experimental neuroanatomy: a practical approach. Oxford: Oxford University Press; 1992. p. 81-101.

Strick PL, Dum RP, Fiez JA. Cerebellum and nonmotor function. The Annual Review of Neuroscience. 2009; 32:413–434.

Temel Y, Visser-Vandewalle V. Surgery in Tourette syndrome. Movement Disorders. 2004; 19(1):3–14. [PubMed: 14743354]

Theodosopoulos PV, Marks WJ, Christine C, Starr PA. Locations of movement-related cells in the human subthalamic nucleus in Parkinson's disease. Movement Disorders. 2003; 18(7):791–798. [PubMed: 12815658]

Tobe RH, Bansal R, Xu D, Hao X, Liu J, Sanchez J, et al. Cerebellar morphology in Tourette syndrome and obsessive-compulsive disorder. Annals of Neurology. 2010; 67(4):479–487. [PubMed: 20437583]

Trost M, Carbon M, Edwards C, Ma Y, Raymond D, Mentis MJ, et al. Primary dystonia: is abnormal functional brain architecture linked to genotype? Annals of Neurology. 2002; 52(6):853–856. [PubMed: 12447944]

Trost M, Su S, Su P, Yen RF, Tseng HM, Barnes A, et al. Network modulation by the subthalamic nucleus in the treatment of Parkinson's disease. NeuroImage. 2006; 31(1):301–307. [PubMed: 16466936]

Turner RS, Grafton ST, McIntosh AR, DeLong MR, Hoffman JM. The functional anatomy of parkinsonian bradykinesia. NeuroImage. 2003; 19(1):163–179. [PubMed: 12781736]

Ugolini G. Specificity of rabies virus as a transneuronal tracer of motor networks: transfer from hypoglossal motoneurons to connected second-order and higher order central nervous system cell groups. Journal of Comparative Neurology. 1995; 356(3):457–480. [PubMed: 7642806]

Wichmann T, DeLong MR. Pathophysiology of Parkinson's disease: the MPTP primate model of the human disorder. Annals of the New York Academy of Sciences. 2003; 991:199–213. [PubMed: 12846988]

Wichmann T, Bergman H, DeLong MR. The primate subthalamic nucleus. I. Functional properties in intact animals. Journal of Neurophysiology. 1994; 72(2):494–506. [PubMed: 7983514]

Wu T, Hallett M. A functional MRI study of automatic movements in patients with Parkinson's disease. Brain. 2005; 128(10):2250–2259. [PubMed: 15958505]

Yu H, Sternad D, Corcos DM, Vaillancourt DE. Role of hyperactive cerebellum and motor cortex in Parkinson's disease. NeuroImage. 2007; 35(1):222–233. [PubMed: 17223579]

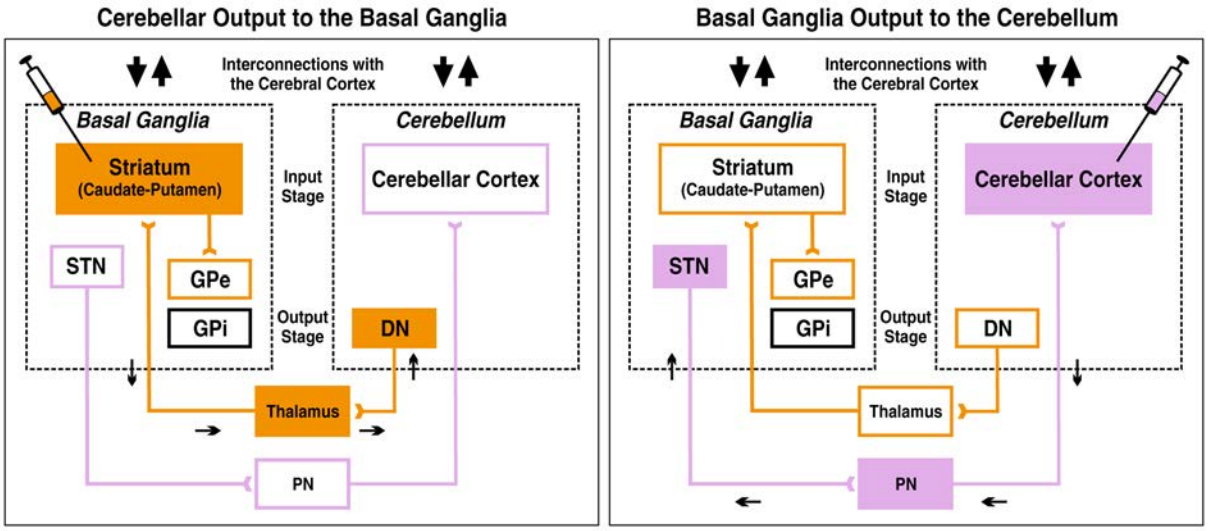

Fig. 1.

Experimental paradigms and circuits interconnecting the cerebellum and basal ganglia: The left panel depicts the experimental paradigm and results from Hoshi et al. 2005, describing cerebellar output to the basal ganglia (orange circuit). We injected rabies virus into the striatum. The virus went through two stages of transport: retrograde transport to first-order neurons in the thalamus that innervate the injection site and then, retrograde transneuronal transport to second order neurons in the dentate nucleus (DN) that innervate the first-order neurons. Striatal neurons that receive cerebellar inputs include neurons in the "indirect" pathway that send projections to the external globus pallidus (GPe). The right panel of the figure depicts the experimental paradigm and results from Bostan et al. 2010, describing basal ganglia output to the cerebellum (purple circuit). We injected rabies virus into the cerebellar cortex. The virus went through two stages of transport: retrograde transport to first-order neurons in the pontine nuclei (PN) that innervate the injection site and then, retrograde transneuronal transport to second-order neurons in the subthalamic nucleus (STN) that innervate the first-order neurons. These interconnections enable two-way communication between the basal ganglia and the cerebellum. Each of these subcortical structures has separate parallel interconnections with the cerebral cortex (up and down large black arrows). The small black arrows in both panels indicate the direction of virus transport. DN: dentate nucleus; GPe: external segment of the globus pallidus; GPi: internal segment of the globus pallidus; PN: pontine nuclei; STN: subthalamic nucleus

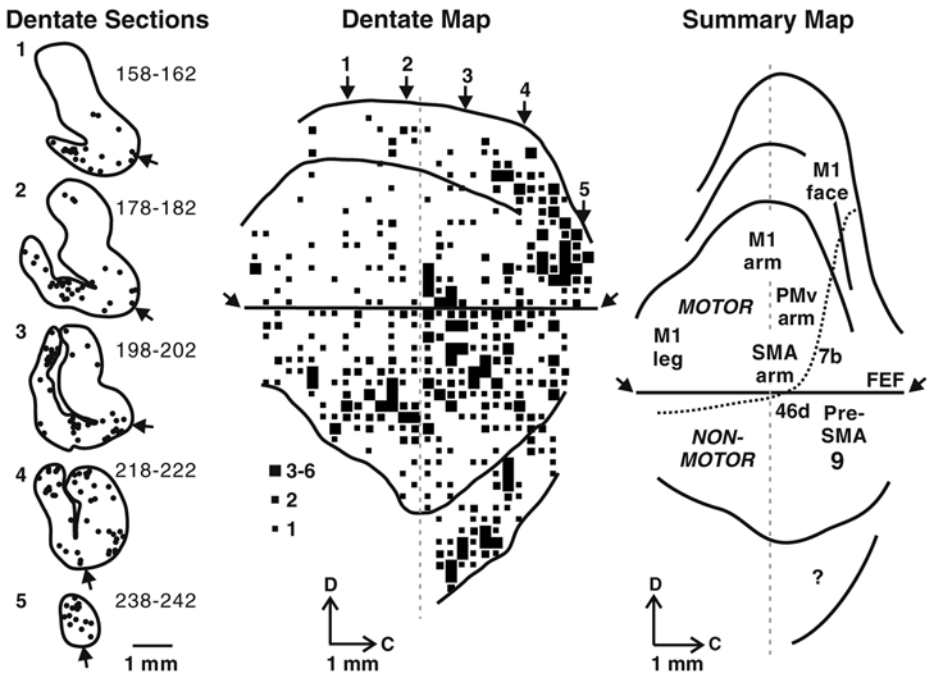

Fig. 2.

Dentate nucleus projection to the external segment of the globus pallidus: The left panel shows selected cross-sections of the dentate nucleus. Dots represent the location of third-order neurons labeled by retrograde transneuronal transport of rabies virus from the external segment of the globus pallidus. Black arrows indicate the level of the horizontal line through the middle of the dentate in the middle and right panels. The middle panel shows the distribution of labeled neurons on an unfolded map of the dentate. The arrows at the top of the map indicate the locations of slices in the left panel. The vertical dashed line marks the rostro-caudal center of the nucleus. Filled squares indicate the density of labeled neurons found in 200 μm×200 μm bins through the nucleus. The right panel shows the motor and nonmotor domains of the dentate. This map shows the origin of dentate projections to different cortical areas (M1 face, M1 arm, M1 leg: face, arm and leg representations in primary motor cortex; PMv arm: arm representation in the ventral premotor area; SMA arm: arm representation in the supplementary motor area; 7b: area 7b in the posterior parietal cortex; FEF: frontal eye fields; pre-SMA: pre-supplementary motor area; 9, 46d: areas 9 and dorsal area 46 in the prefrontal cortex). The curved dotted line indicates the border between motor and nonmotor domains of the dentate. The vertical dashed line marks the rostro-caudal center of the nucleus. C: caudal; D: dorsal. (The left and middle panels of this figure are from Hoshi et al. 2005; the right panel is modified from Hoshi et al. 2005 to include additional data, see Strick et al. 2009)

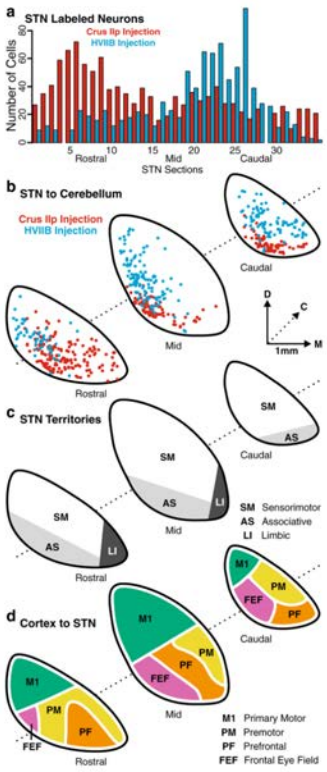

Fig. 3.

STN projection to the cerebellar hemisphere: **a** Histogram of the rostro-caudal distribution of second-order neurons labeled in the STN by retrograde transport of virus from Crus IIp (red bars) and HVIIB (blue bars). Missing bars correspond to missing sections. **b** Charts of labeled neurons in STN after rabies virus injections into Crus IIp (red dots) and HVIIB (blue dots) are overlapped to illustrate the topographic differences in distribution of STN second-order neurons in the two cases. **c** Schematic representation of STN organization, according to the tripartite functional subdivisions of the basal ganglia (Parent and Hazrati 1995b; Joel and Weiner 1997; Hamani et al. 2004). **d** Schematic summary of the known connections between STN and areas of the cerebral cortex. C: caudal; D: dorsal; M: medial; STN: subthalamic nucleus. (Figure from Bostan et al. 2010)