New insights into cortico-basal-cerebellar connectome: clinical and physiological considerations

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Running head: The novel cortico-basal-cerebellar connectome model

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Abstract

The current model of the basal ganglia system based on the “direct”, “indirect” and “hyperdirect” pathways provides striking predictions about basal ganglia function that have been used to de**velop** deep brain stimulation approaches for Parkinson’s disease and dystonia.

The aim of this short article is to challenge this scheme in light of new tract tracing information that has recently come available from the human brain using MRI-based tractography, thus providing a novel perspective on the basal ganglia system. We will also explore the implications of additional direct pathways running from cortex to basal ganglia and between basal ganglia and cerebellum in the pathophysiology of movement disorders.

Keywords: basal ganglia; connectivity; deep brain stimulation; movement disorders;

Introduction

Current knowledge of the functional circuitry of basal ganglia (BG) and cerebellum is mostly derived from data collected in rodents and primates with tract-tracing invasive approaches, immunochemistry and in situ hybridization techniques (DeLong, 1990) . Although they still represent the gold standard for anatomical brain connectivity studies, these techniques are restricted to animals (Nambu *et al.*, 2000; Lu, 2011) and have limitations (Ugolini, 2011). The development of diffusional resonance imaging (dMRI) and tractography has provided a new, powerful tool to explore, noninvasively, anatomical brain connectivity in humans (Henderson, 2012) allowing us to reconstruct major white matter (WM) fiber pathways with directional information provided by diffusion weighted images (DWI) (Basser *et al.*, 2000). While accuracy and reliability of streamline tractography are currently a matter of debate, efforts have been made to understand its limits (Nucifora *et al.*, 2007; Ciccarelli *et al.*, 2008) and have prompted research groups to **develop** and improve tractographic outcomes (Côté *et al.*, 2013).

One of the most promising **approaches** is Constrained Spherical Deconvolution (CSD), a modeling technique that overcomes the well-known limitations of classic Diffusion Tensor Imaging (DTI) by solving partial volume effects and allowing a faithful reconstruction of complex fibers configurations within a single voxel (Tournier *et al.*, 2007, 2008). In the present review, we will summarize the results of recent work in humans on the cortico-basal-cerebellar connectome using the non-invasive DWI-based approach with subsequent CSD-based tractography. The physiological and clinical relevance is also discussed.

The "classical" cortico-basal ganglia-cerebellar connectome

According to the classical view, cortical outflow reaches basal ganglia via two major projection systems: the direct and the indirect pathways that originate from segregated populations of striatal neurons and have opposite **effects** upon the basal ganglia output (Alexander *et al.*, 1986).

Superimposed on this system, is the "hyperdirect pathway" that conveys input from the cortex to the pallidal outflow neurons via the subthalamic nucleus (STN) (Nambu *et al.*, 2002; Sano *et al.*, 2013). In this scheme, the basal ganglia lie in an information loop whose major function is to take input from the cortex and return it, once processed, via the thalamus back to both the cortex and directly back to the striatum via a direct thalamo-striatal connection. Despite its apparent simplicity, this model provides striking accurate predictions about basal ganglia function that have been used to devise deep brain stimulation (DBS) approaches to the basal ganglia diseases such as Parkinson's disease (PD) and dystonia.

In the past ten years it has become possible using DWI and tractography to visualize this connectivity within the human brain, and even to distinguish variation in connectivity between individual brains. Thus, all the main pathways, including direct, indirect and hyperdirect pathways, plus the pallidothalamic, nigropallidal and thalamo-striatal projections, have all been successfully characterized to allow an in vivo, comprehensive reconstruction of the basal ganglia connectome (Lehéricy *et al.*, 2004; Draganski *et al.*, 2008; Verstynen *et al.*, 2011; Forstmann *et al.*, 2012; Lenglet *et al.*, 2012).

Additional connections identified with CSD-tractography in human brain

The overall pattern of basal ganglia connectivity has been strikingly preserved over evolution and can be demonstrated even in the primitive brain of the lamprey. In the present note we wish to draw attention to additional pathways identified in the human that superimpose a more direct cortical control on basal ganglia output that bypasses the major relay in the striatum.

Our recent work using High Angular Resolution Diffusion Imaging CSD-based tractography has allowed us to identify a direct connection between cortex and the external and internal segment of globus pallidus (GP). (see Figures 1-2). In particular there are extensive inputs from frontal (paracentral, precentral, middle –MFG-, superior -SFG- and inferior frontal gyri) and parietal (inferior, medial, supramarginal and precentral gyri) lobes to the external segment of the globus pallidus (GPe) and a smaller range of connections from SFG and pre/postcentral cortex to internal segment of the globus pallidus (GPi) (Milardi *et al.*, 2015, Cacciola *et al.*, 2017*a*)**.**

However, some caution is needed in interpreting these findings, as cholinergic cells reside along the internal and external medullary lamina between the two pallidal segments. Therefore, it cannot be ruled out that some of the presumed cortico-pallidal projections are, instead, fibers targeting these cholinergic neurons (Milardi *et al.*, 2015; Smith and Wichmann, 2015). Nevertheless, the presence of a direct cortico-pallidal pathway has been confirmed by a recent study using probabilistic tractography (Middlebrooks *et al.*, 2018) and also by recent DBS data from GPi-implanted dystonic patients showing a robust band of coherence in the beta band linking the motor cortex with GPi that could be mediated by a direct cortico-pallidal connection (Neumann *et al.*, 2015, Cacciola *et al.*, 2016*b*).

Although our data were the first to highlight the possible existence in vivo of a cortico-pallidal projection in humans, such a connection has previously been suggested from different tracing studies in a variety of animal species (Kornhuber *et al.*, 1984; Naito and Kita, 1994; Milardi *et al.*, 2015; Cacciola *et al.*, 2016*a*, 2017*b*)**. In rats, Naito and Kita reported the existence of a cortico-**

pallidal projection(s) after injecting the anterograde tracer biotinylated dextran amine (BDA) in various cortical region (Naito and Kita, 1994)**. They found that BDA injections into the precentral medial and lateral cortices (homologues of the supplementary motor area, and primary motor/portions of the somatosensory cortices in primates, respectively) resulted in anterograde labeling of the ipsilateral GP** (Naito and Kita, 1994)**. In the lamprey, Stephenson-Jones and co-workers showed that pallido-habenular neurons receive direct excitatory projections from the pallium (i.e., the homologue of the cerebral cortex in mammals), and proposed that this pathway is implicated in a reward-evaluation circuit used to select actions across vertebrates** (Stephenson-Jones *et al.*, 2013)**. The presence of direct glutamatergic cortico-pallidal projections has been demonstrated in monkeys and in humans using vesicular glutamate transporter 1 (vGluT1), as a preferential marker of cortical terminals in the telencephalon** (Smith and Wichmann, 2015)**.**

Direct cortico-pallidal fibers have also been noted by the French anatomist Testut who, in a classical textbook of anatomy, comments: "Ascending and descending cortico-caudal, cortico-putaminal, and cortico-pallidal connections do exist. Cortico-caudal and cortico-putaminal fibers are indicated together as cortico-striatal pathway: they are less than cortico-pallidal fibers. The cortico-pallidal fibers are prevalently but not exclusively cortico-fugal (efferent). These fibers (demonstrated both by anatomic dissection and by neuronography), originate from area 6 (Testut and Latarjet, 1971)**. Finally**, in DBS-implanted dystonic patients, GPi stimulation may increase corticospinal excitability tested 6ms later with transcranial magnetic stimulation (TMS) (Ni *et al.*, 2018). Since GPi-DBS does not activate corticospinal fibers directly, these results also would be compatible with the presence of a fast, direct connection between GPi and primary motor cortex (Milardi *et al.*, 2015; Cacciola *et al.*, 2018; Ni *et al.*, 2018).

In addition to cortico-pallidal connections**, we also described, using tractography, the existence of a cortico-nigral connection (Figure 3)** (Cacciola *et al.*, 2016*a*)**. The highest connectivity profile was between SN and the SFG, which is known to be an important prefrontal area; in addition, lower values of connectivity were found between SN and other prefrontal areas such as pars opercularis, pars orbitalis, pars triangularis, and rostral MFG.**

Our findings are in line with data regarding prefrontal cortex (PFC)-SN connectivity described in rodents (Bunney and Aghajanian, 1976; Kornhuber *et al.*, 1984; Sesack *et al.*, 1989) **and primates** (Leichnetz and Astruc, 1977; Frankle *et al.*, 2006)**, and with the few existing results obtained in humans by means of DTI-based techniques** (Menke *et al.*, 2010; Kwon and Jang, 2014)**. Interestingly, connections between PFC and SN in humans appear to be more prominent than the sparse dorso-lateral PFC/SN projections described by Frankle and colleagues in macque**

monkeys. On the other hand, compared to primates we unable to find any connectivity between the orbitofrontal cortex and SN (Frankle et al., 2006). We also found a well-represented structural link between SN and cortical areas related with motor functions, such as paracentral lobule and precentral gyrus: this finding is in line with the existing literature showing sparse connections between motor cortex, premotor cortex and SN in primates (Künzle, 1978; Monakow *et al.*, 1979)**.**

The cerebellum is another important subcortical structure controlling multiple aspects of motor and cognitive behavior. For many years, it was thought that circuits linking cerebellum to the cortex were anatomically and functionally segregated from those connecting basal ganglia to cortex (Sakai *et al.*, 1996). Therefore, all interactions between cerebellum and basal ganglia were thought to occur primarily at the cortical level. Studies in primates and, more recently, in humans by our group have challenged this model by showing the anatomical existence of an extensive subcortical network connecting basal ganglia and cerebellum. In primates, Hoshi and co-workers demonstrated the existence of a topographically organized di- and trisynaptic system originating from dentate nucleus, passing via the thalamus, ending in the putamen and the external segment of GP (Hoshi *et al.*, 2005). In addition, the same authors reported the presence of a disynaptic afferent pathway running from the STN to the cerebellar cortex with a relay in the pontine nuclei (Bostan *et al.*, 2010). In this regard, we have recently confirmed, for the first time in vivo in humans, the existence of connections running from the STN to the cerebellar cortex with a relay in the pons (Milardi *et al.*, 2016).

As an extension of the results of the studies in primates, our data also appear to demonstrate the presence of a direct route linking the dentate nucleus to the GPi and the SN (Figures1-3). **Although dentato-pallidal pathways have not been directly documented in animal studies, there is some evidence in rats suggesting the presence of a direct route linking the dentate with substantia nigra** (Snider *et al.*, 1976; Nieoullon *et al.*, 1978)**. In addition, a** recent study using a combination of magnetoencephalography and direct recordings of the GPi local field potential from DBS electrodes implanted in dystonic patients (Neumann *et al.*, 2015) **showed robust alpha band a coherence between GPi and cerebellum, although it was impossible to exactly localize the source of electrical activity over the cerebellum**.

The presence of direct connections between the dentate nucleus and GPi and SN, bypassing the thalamus, is very provocative considering the existence of direct cortico-pallidal and cortico-nigral connections bypassing the striatum both in human and monkeys (Cacciola *et al.*, 2017*b*). It is tempting to hypothesize that the two systems may interact in the GPi and GPe, bypassing the striatum and the thalamus, respectively. **In keeping with this hypothesis, we have recently demonstrated that the area of the GPi receiving from the cortex significantly overlaps with that receiving**

input from the dentate nucleus (Cacciola *et al.*, In Press, Mov Disord) **(Cacciola et al 2019 in press Mov. Dis.).** A similar overlap may apply to the cortico-nigral and dentato-nigral systems **although this remains to be demonstrated. However, due to the intrinsic limitation of tractography (see below), the existence of such direct connections between cerebellum and basal ganglia, by-passing the thalamus, should to be viewed with some caution.**

Physiological relevance of these new connections

A good deal more work needs to be done to define the functional role of these connections. Our working hypothesis is that they may be a phylogenetically new projection superimposed onto the older conserved cortico-basal ganglia anatomy. A parallel would be the development in primates of the monosynaptic component of the corticospinal tract. In rodents and cats, the motor cortex projects only to interneurons of the spinal grey matter, which then contact the spinal motoneurons to drive muscle contraction. In primates this is supplemented by an additional direct connection to spinal motoneurons, particularly those controlling the arm and hand. This direct connectivity is thought to allow the flexibility and fractionation of movement that is typical of hand control in higher primates. It could be that the direct cortical input to pallidum similarly allows a more direct influence on pallidal output.

Indeed, it is suggestive that the most direct projections to GPi come from sensorimotor areas of cortex and cerebellum, indicating a prominent role of the "new" connectivity in motor control. The frontal areas projecting to the dorsal aspect of GPe are also highly involved in goal-directed behavior (Middleton and Strick, 1994; Parent and Hazrati, 1995; Akkal *et al.*, 2007; Saga *et al.*, 2011, 2013), again consistent with the notion that these connections may have a particular relevance to flexible motor behavior.

A similar consideration can be applied to cortico-nigral connections exerting a supervision on direct and indirect pathways. This system could provide in humans a short-latency route, superimposed on old pathways, for fast interaction between the cerebellum, basal ganglia and the motor cortex, thus allowing them to quickly harmonize their outputs in real-time. This interpretation does not conflict with the findings in primates described above, if we assume that the appearance of this fast conducting system occurred phylogenetically later, in humans, triggered by the emergent importance of manual dexterity (Cacciola *et al.*, 2017*b*) (Figure 3).

The basal ganglia can be viewed as circuits organized to select desired actions and to inhibit potentially competing unwanted actions. The majority of outputs from basal ganglia arise from GPi and SNpr and are inhibitory to thalamic nuclei, superior colliculus, and the pedunculopontine area of the brainstem. Thus, the output of the basal ganglia resembles to a

braking system (Mink, 1996)**.When a desired action is initiated by a particular motor pattern generator in the cerebral cortex or brainstem, basal ganglia output neurons projecting back to that generator decrease their discharge, thereby removing tonic inhibition "releasing the brake" on that generator. Simultaneously basal ganglia output neurons projecting to other motor pattern generators, involved in competing actions, increase their firing rate and thereby apply the "brake" to those generators. In this way competing motor tasks are inhibited and the net result is the focused selection of desired actions and surround inhibition of competing actions. Disruption of the ability to facilitate desired movements and inhibit unwanted movements results in slow voluntary movements (parkinsonism), abnormal involuntary movement (chorea, dystonia, tics), or both** (Mink, 2003)**.**

The model we propose here would reinforce the old vision where basal ganglia are characterized by the presence of discrete, parallel, segregated and functionally distinct but homologous circuits (Alexander *et al.,* 1986) (Figure 4). **Within this new framework the possibility of direct control of basal ganglia output neurons through a direct cortico-pallidal pathway to GPe and GPi would allow more flexible control of direct and indirect pathways modulating surround inhibition of competing actions. Cortico-nigral pathways would provide an additional direct system modulating action selection according to the model proposed by Mink** (Mink, 1996, 2003)**.** Our hypothesis is that direct cortico-GP and SN pathways, in cooperation with those from the dentate nucleus, give the cortex an ability to fine-tune decision making and motor action selection. In addition, they could give more rapid flexibility to any unexpected changes in the environment, which is prerogative of human species. Future studies are needed to disentangle the exact physiological role of these new circuits and how they might influence the firing patterns of neurons in the motor network.

Clinical relevance of these new connections: adaptive and maladaptive plasticity within the cortico-BG-cerebellar connectome on basal ganglia disorders.

The proposed model, with the presence of parallel direct and indirect projections running between the cortex, basal ganglia and cerebellum, complements new ideas that view movement disorders as disorders of a complex motor network rather than a limited disruption of individual nuclei in the basal ganglia. In this scenario it becomes easier to understand why stereotactic lesions of the globus pallidus and thalamus are not accompanied by severe motor dysfunction. A lesion within the BG will trigger reorganization within the cortico-basal-cerebellar connectome recruiting alternative pathways (such as cortico-nigral pathway for instance) which may compensate (or worsen) the primary deficit. In

this respect DTI tractography is a promising tool to study anatomical connectivity of basal ganglia disorders and shed new light on the pathophysiology of movement disorders.

Although most investigations on movement disorders have focused on the BG, increasing anatomical and pathophysiological evidence suggests that the cerebellum plays a substantial role of in the genesis of the clinical symptoms of both Parkinson's disease and dystonia (Caligiore *et al.*, 2017). Indeed, there is a significant rearrangement within the cortico-BG-cerebellar connectome in patients with Parkinson's disease. For instance, it has been reported that during timed motor exercises, compared to normal controls, patients with Parkinson's disease have significantly greater activation bilaterally in the cerebellum, in the right thalamus and in the left midbrain/SN (Jahanshahi *et al.*, 2010). Moreover, in Parkinson's disease during self-initiated movement, the measures of striatum–cortical and striatum–cerebellar effective **connectivity are** weakened, whereas the motor cortico-cerebellar connectivity is strengthened (Wu *et al.*, 2011).

The nature of such hyperactivation or strengthened connectivity of the cerebellum in Parkinson's disease is still a matter of debate. Several lines of evidence indicate that it may have a compensatory role: cerebellar hyperactivity may counterbalance hypoactivity in some other regions, such as the supplementary motor cortex (SMA) and the striatum (Sabatini *et al.*, 2000; Haslinger *et al.*, 2001; Buhmann *et al.*, 2003; Wu and Hallett, 2005). In fact it is possible that cerebellum may compensate for GPi hypoactivity in PD via our recently described dento-pallidal and dento-nigral pathways or through the traditional cerebello-thalamo-cortical circuit (Sen *et al.*, 2010). As Parkinson's disease is preceded by a long prodromal phase without overt clinical symptoms, it is likely that compensatory effects of cerebellum and other brain regions within the cortico-basal-cerebellar connectome may delay the onset of motor symptoms, keeping performance within normal range.

Although compensation may occur early in the disease, it could be that changes in the cerebellum later in disease progression become maladaptive. One example could be the occurrence dyskinesia. The pathophysiology of levodopa-induced dyskinesia (LID) is not completely understood; however, the cerebello-thalamo-cortical circuit seems to contribute to the appearance of LID in the later stages of the diseases (Wu and Hallett, 2013) (Wu et al). Aberrant neuronal synchrony in Parkinson's disease with LID may propagate from the STN to the cerebellum and "lock" the cerebellar cortex in a hyperactive state (Kishore and Popa, 2014; Rajan *et al.*, 2017). In keeping with this hypothesis, DBS of the STN and GPi, the surgical procedures that alleviate levodopa-induced dyskinesia (Krack *et al.*, 2003; Anderson *et al.*, 2005), modulate neural activity or metabolism in the cerebellum and reduce this hyperactivity (Hilker *et al.*, 2004; Payoux *et al.*, 2004, 2009; Asanuma *et al.*, 2006; Grafton *et al.*, 2006; Geday *et al.*, 2009). The effects are likely mediated by the subthalamic-pontine-cerebellar pathways described in monkeys and by our group in vivo humans using DTI (Bostan *et al.*,

2010; Milardi *et al.*, 2016). The contribution of the cerebellum to LID is also consistent with the therapeutic effect of repetitive transcranial magnetic stimulation (rTMS) over the cerebellum in LID. These clinical improvements were paralleled by a reduction of 18F-fluorodeoxyglucose metabolism in the cerebellum (Brusa *et al.*, 2012).

Although the involvement of BG in the pathophysiology dystonia is indisputable, the mechanisms producing dystonia are incompletely understood, with recent evidence pointing to the involvement of a variety of brain areas including the cerebellum (Quartarone and Hallett, 2013; Jinnah *et al.*, 2017). As it is possible that the etiological heterogeneity of dystonias reflects the relative importance of different nodes in this extended motor network, one major challenge is determining first, the role and contribution of the different brain regions in the various forms of dystonia with a comprehensive model; second, if there is a final common pathway for all dystonias (Quartarone and Ruge, 2018). One important area again appears to be the cerebellum (Neychev *et al.*, 2011; Caligiore *et al.*, 2017; Quartarone and Ruge, 2018) particularly in contribution to sensorimotor integration. This is not surprising considering that cerebellum relays sensory afferent inputs to the motor cortex (M1) (Butler *et al.*, 1992) and processes proprioceptive information for both temporal and spatial discrimination of sensory signals, mechanisms that are altered in primary dystonia (Restuccia *et al.*, 2001; Pastor *et al.*, 2004).

In a recent MEG study Neumann and associates recorded direct local field potentials, from the human pallidum, simultaneously with whole head magnetoencephalography to characterize functional connectivity in the cortico-BG-cerebellar network in nine patients with idiopathic dystonia (Neumann *et al.*, 2015) (Neumann et al 2016). The authors found that the cerebellum is interconnected with the internal pallidum through 7– 13 Hz alpha band oscillations. Interestingly, the degree of pallido-cerebellar coupling was inversely correlated with the severity of dystonic symptoms, as indexed by the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), suggesting a compensatory role for the cerebellum in dystonia (Neumann *et al.*, 2015). The pathways involved may include the dentato-thalamic connection or the dentato-pallidal connections described in human DTI studies (Cacciola *et al.*, 2016*b*, 2017*b*; Milardi *et al.*, 2016).

The same authors found a negative correlation between cerebellar alpha band power (7–13 Hz) (see above) and motor cortical beta band power (Neumann and Kühn, 2016). It is possible that reduced cerebellar alpha band activity, which may be caused by a loss of structural fibre integrity (dento-pallidal or dentato-thalamic), could lead to increased motor cortical beta oscillatory activity in patients with dystonia. In this framework the cortico-pallidal system may act as an important node involved in the functional interactions of beta signalling in the cortex-basal ganglia-cortex feedback loops for motor control (Cacciola *et al.*, 2016*b*).

The data published in the last 10 years suggests the basal ganglia are part of a motor network involved in movement disorders. In this network it becomes difficult to localize the primary dysfunction since, as the pathological process starts, reorganization occurs within the whole circuit so that no part necessarily behaves as in the healthy brain. The picture is made more complicated by the existence of an extensive direct and indirect sub-cortical cross-talk between the cerebellum and basal ganglia. Thus localizing dysfunction to one part of the network becomes impossible.

In such a scheme, tractography becomes important for defining subject-specific connectivity targets for the GPi or other sub-cortical structures, as suggested by a pilot study, where segmentation of GPi, based on probabilistic tractography, was used in the setting of DBS in PD patients (Middlebrooks *et al.*, 2018). In keeping with anatomical and physiological studies in primates and in humans (Parent and Hazrati, 1995; Tisch *et al.*, 2007), the best clinical results were achieved when electrodes were implanted in the voxels connected with M1 which corresponded to ventral-posterior sensorimotor territory (Middlebrooks *et al.*, 2018).

This is in line with our recent findings in which we segregated the GPe into a ventral associative cluster, a dorsal sensorimotor cluster and a caudal "other" cluster on the base of its cortical connectivity. Dentato-pallidal connections clustered only in the GPi, together with associative and sensorimotor clusters. Thus, we represented, for the first time, the topographical organization of both GPi and GPe according to cortical and cerebellar connections. Such descriptions could be useful in DBS and FUS targeting for treating motor and non-motor symptoms in movement disorders (Cacciola *et al.*, In Press, Mov Disord)**.**

Intrinsic limitations of tractography

Although several algorithms for tractography have been developed and applied to the study of the human connectome, such computational reconstruction suffers from some intrinsic methodological limitations.

First, the spatial resolution of DWI is inherently lower than the one achieved with conventional tract-tracing techniques that can establish synaptic connectivity. Indeed, classical diffusion weighted images used for tractographic reconstruction usually have a voxel resolution of 2x2x2 mm^3 which is notably higher than the axonal diameter (Jbabdi and Johansen-Berg, 2011), whilst traditional anatomical tracers can track the projections of single axons. Another major drawback of tractography is the inability to determine the polarity of a given connection and thus to establish whether a given fiber pathway is afferent or efferent (Parker *et al.*, 2013)**.**

In addition, simple diffusion signal modelling approaches cannot reliably disentangle the complex white matter architecture consisting of twisting, bending, crossing and kissing fibers thus failing in representing any of their orientations. To overcome this issue, "model-free" approaches have been developed in the last decade, such as Diffusion Spectrum Imaging (DSI) (Wedeen *et al.*, 2005)**, Q-ball Imaging** (Tuch *et al.*, 2003) **and CSD** (Tournier *et al.*, 2007)**.**
More recently, it has been argued that most tractographic algorithms are able to produce tractograms containing 90% of the ground truth bundles, recovering about one-third of their volumetric extent, while producing, at the same time, large amounts of false-positive bundles, even though they are not part of the ground truth (Maier-Hein *et al.*, 2017)**.**
Despite the abovementioned limitations, DWI and tractography are the only existing techniques able to investigate anatomical connectivity in the human brain in vivo and non-invasively. Indeed diffusion tractography has been extensively recognized as the first "in vivo dissection" approach to map the major fiber bundles in the human brain with extreme precision as well as to show the existence of new associative pathways that have been subsequently replicated using the traditional post-mortem Kingler dissection (Klingler, 1935; Klingler and Gloor, 1960).
As final remark, the anatomical validity and reproducibility of DWI tractography have been assessed in vitro in a highly gyrated model of the porcin brain, demonstrating that tractography is able to reliably detected specific white matter pathways and therefore to be a precise and powerful tool in investigating anatomical brain connectivity (Dyrby *et al.*, 2007)**. With these concepts in mind, tractographic results should always be interpreted with caution and we believe that there is an urgent need for methodological advances in diffusion tractography in order to ameliorate our knowledge of human brain structural connectivity.**

Authors' Contribution

AQ: Study concepts/study design, guarantor of integrity of entire study, draft the initial version of the manuscript, manuscript revision for important intellectual content. AlbC: Study concepts/study design, literature research, draft the manuscript, manuscript and figures preparation. DM: Literature research and interpretation. MFG: Literature research and interpretation, figures preparation. AleC: Literature research and interpretation. GC: Literature research and interpretation. GA: Guarantor of integrity of entire study, data interpretation, and manuscript revision for important intellectual content. JR: Study concepts/study design, guarantor of integrity of entire study, data interpretation, and manuscript revision for important intellectual content. All the authors approved the final version of the manuscript.

Competing Interest

The Authors declare no conflicts of interest.

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Figure Legends

Figure 1. Cortico- and dento-GPe connections. A) 3D axial view of the GPe (green VOI) and GPi (red VOI); B) Parasagittal view of the streamlines connecting different areas of the cerebral cortex with the GPe (green VOI in transparency); the same view allows to visualize the streamlines that link the dentate nucleus (light brown VOI) with the caudal-posterior area of the GPe running via the superior cerebellar peduncle; C) zoomed inset showing the streamlines at the level of the GPe. The streamlines are depicted according to a color-coded map in which red, blue and green colors indicate the principal streamline directions, according to the traditional nomenclature.

Figure 2. Cortico- and dento-GPi connections. A) 3D axial view of the GPe (green VOI) and GPi (red VOI); B) Parasagittal view of the streamlines connecting the motor-related cortex with the GPi (red VOI); the same view allows to visualize the streamlines that link the dentate nucleus (light brown VOI) with the most posterior area of the GPi running via the superior cerebellar peduncle; C) zoomed inset showing the streamlines at the level of the GPi. The streamlines are depicted according to a color-coded map in which red, blue and green colors indicate the principal streamline directions, according to the traditional nomenclature.

Figure 3. Cortico- and dento-SN connections. A) 3D axial view of the SN (purple VOI) at the level of the midbrain; B) Parasagittal view of the streamlines connecting mostly frontal and parietal areas with the SN (purple VOI); the same view allows to visualize the streamlines that link the dentate nucleus (light brown VOI) with the most posterior area of the GPi running via the superior cerebellar peduncle; C) zoomed inset showing the streamlines at the level of the GPi. The streamlines are depicted according to a color-coded map in which red, blue and green colors indicate the principal streamline directions, according to the traditional nomenclature.

Figure 4. Proposed model integrating "classical" and "novel" cortico-basal ganglia-cerebellar pathways. This figure shows both the "classical" and "novel" cortico-basal ganglia-cerebellar pathways, thus pointing out the presence of discrete, parallel, segregated and functionally distinct but homologous circuits involved in the complex organization of the basal ganglia network.

The most basic circuit model of basal ganglia function involving the "direct" and "indirect" pathways originally proposed by Albin and co-workers in 1989. Solid black lines highlight the "direct" pathway funnelling information from the cerebral cortex to the striatum and then to GPi/SNr via GABAergic inhibitory projections thus selectively reducing GPi/SNr activity and releasing the thalamocortical

circuits involved in motor pattern generators. The dashed black lines depict the “indirect” pathway: when excited by the glutamatergic inputs of the cerebral cortex, striatal D2 receptors allow the cells of the striatal matrix to send inhibitory signals to the GPe, thus exerting its tonic GABAergic inhibition on the STN. Therefore, the glutamatergic neurons of the STN can then excite the GPi/SNr thus suppressing thalamic activity on the cerebral cortex and increasing inhibitory influences on the upper motor neurons. More recently, a “hyperdirect” pathway has been described (blue lines between the cerebral cortex and STN), conveying excitatory stimuli from motor, associative and limbic brain areas on the STN, bypassing the “indirect” inhibitor circuit and leading to excited GPi/SNr activity. The same figure shows the connections between the cerebellum and basal ganglia as revealed by retrograde tracing studies in monkeys. Red lines indicate the output of the cerebellum on the basal ganglia via the dentate-thalamo-striatal pathway as well as the control of basal ganglia on the cerebellum via the STN-ponto-cerebellar cortex pathway. Green lines highlight the newly identified connections between the cerebral cortex, GPi, GPe and SN as well as the complementary circuits between the dentate nucleus and such nuclei as described in recent tractographic studies in humans.