RESEARCH ARTICLE

# Basal Ganglia Network by Constrained Spherical Deconvolution: A Possible Cortico-Pallidal Pathway?

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**ABSTRACT:** In the recent past, basal ganglia circuitry was simplified as represented by the direct and indirect pathways and by hyperdirect pathways. Based on data from animal studies, we hypothesized a fourth pathway, the cortico-pallidal, pathway, that complements the hyperdirect pathway to the subthalamus. Ten normal brains were analyzed by using the high angular resolution diffusion imaging—constrained spherical deconvolution (CSD)-based technique. The study was performed with a 3T magnetic resonance imaging (MRI) scanner (Achieva, Philips Healthcare, Best, Netherlands); by using a 32-channel SENSE head coil. We showed that CSD is a powerful technique that allows a fine evaluation of both the long and small tracts between cortex and basal ganglia, including direct, indirect, and hyperdirect pathways. In addition, a pathway directly connecting the cortex to the globus pallidus was seen. Our results confirm that the CSD tractography is a valuable technique allowing a reliable reconstruction of small- and long-fiber pathways in brain regions with multiple fiber orientations, such as basal ganglia. This could open a future scenario in which CSD could be used to focally target with deep brain stimulation (DBS) the small bundles within the basal ganglia loops. © 2014 International Parkinson and Movement Disorder Society

**Key Words:** basal ganglia; subthalamic nucleus; brain; tractography; CSD

Our knowledge of basal ganglia–related disorders has increased enormously during the last two decades. Despite the large amount of published data in the neurological literature, the primary function of basal ganglia remains highly speculative.[1,2]

The basal ganglia circuitry was commonly simplified as represented by direct, indirect, and hyperdirect pathways. The pathophysiology of movement disorders was explained by firing rate changes through those pathways.[3] However, full understanding of this scenario is actually under debate and far from being fully identified.

Basal ganglia anatomo-physiology has been obtained in animal studies by using neuroanatomical tract-tracing methods,[4-7] whereas most human data are derived mainly from clinical and neuroradiological observations in patients with small lesions within basal ganglia circuits, and only recently from functional neuroimaging studies.

By using diffusion tensor imaging (DTI) as computed from magnetic resonance imaging (MRI), basal ganglia circuits can now be visualized in vivo in humans.[8] However, DTI is unable to adequately characterize a system consisting of several distinct fiber orientations. Consequently, a number of more complex diffusion reconstruction schemes have been proposed to overcome the limitations associated with the DTI model.[9]

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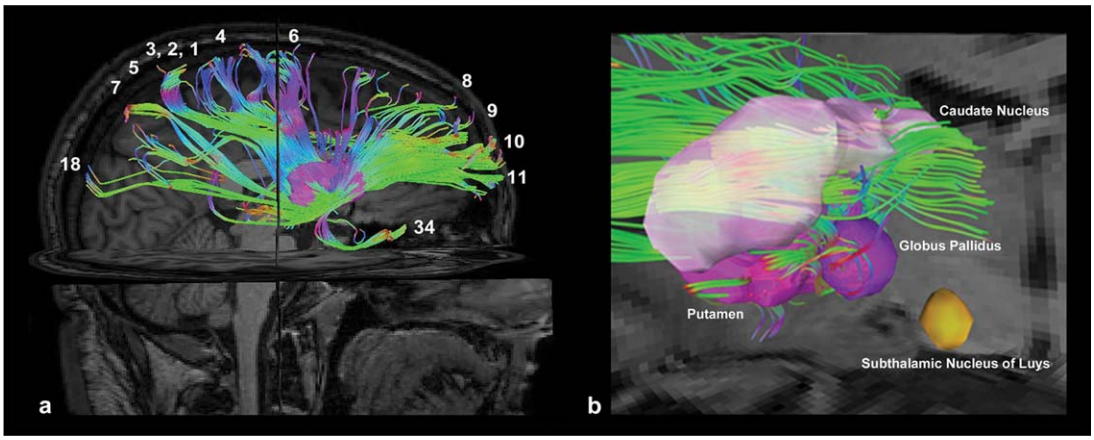


**FIG. 1.** Cortico-neostriatal pathway. Sagittal view of the cortico-striatal projections and connected Brodmann areas (**A**). GP, PU, and CN are represented with red, purple, and pink VOIs, respectively. Focused view (**B**) of the short tracts' connections between neostriatum and GPi (arrowheads).

One promising approach is constrained spherical deconvolution (CSD), a fast computation method that allows reliable estimation of one or more fiber orientations in the presence of intravoxel orientational heterogeneity.[10-12]

Despite the fact that CSD has substantially improved standard tractography, it suffers from major drawbacks intrinsically related to the technique, such as the inability to demonstrate synaptic or gap junction connections. Nevertheless, in this study we suggest that the globus pallidus (GP) not only is a part of the basal ganglia network, but it could be also connected with cortex. The aim of this paper is to present preliminary data on the possible existence of direct cortico-pallidal fibers in humans by using CSD.

## Material and Methods

### Participants

A local ethical committee approved the study, and written informed consent was obtained from all subjects before MRI examination. A total of 10 human subjects (6 males, 4 females; mean age, 29; age range, 25-32 years) were recruited; thus, 20 brain hemispheres were studied. No participants had a history of any overt neurological or psychiatric disease.

### Data Acquisition and Preprocessing of Diffusion Weighted Data

The study was performed with a 3T MRI scanner (Achieva, Philips Healthcare, Best, Netherlands), using a 32-channel SENSE head coil. We performed MRI sequences whose parameters are detailed in the Supplemental Data section.[13-24]

### Tractography

All data for each subject were spatially normalized to Montreal Neurological Institute stereotactic space using the SPM8 segmentation toolbox (www.fil.ion.ucl.ac.uk/spm). We used a modified high angular resolution diffusion imaging technique, called non-negativity CSD. This technique estimates the fiber orientation distribution function (fODF) directly from the diffusion weight (DW) signal by means of positive (avoiding the unreal negative regions) spherical deconvolution.[10] We reconstructed a color-coded map in which red, blue, and green indicated the principal eigenvector's directions.[25] Specifically, red indicates a left–right pattern; green, an anterior–posterior pattern; and blue, a caudal–cranial pattern. Intensity and pureness of these colors vary according to the behavior of fibers in all intermediate positions, indicating voxel-by-voxel each tract's direction. More details on this topic are provided in the Supplemental Data.

### Basal Ganglia Segmentation

Segmentation was carried out manually by a trained researcher using Analyze 11.0 (AnalyzeDirect, Inc.; Kansas City, KS, USA). We registered all subjects' brains on the Montreal Neurological Institute atlas, using a 12 degrees of freedom registration algorithm to obtain specific coordinates of each nucleus for appropriate region of interests (ROIs) positioning. Details about this procedure are described in the Supplemental Data section (See Fig. 2, Supplemental Data).

### Intra- and Inter-subjects Variability

Tract-specific measurements were extracted (number of streamlines = N.) and a lateralization index calculated[26,27] according to the following formula:

$$(\text{N. Right}-\text{N. Left})/(\text{N. Right}+\text{N. Left})$$

Statistical significance was determined using a two-tailed $t$ test; $P$ values less than 0.05 were considered to indicate statistically significant differences.

## Results

We reconstructed the following components of the basal ganglia network:

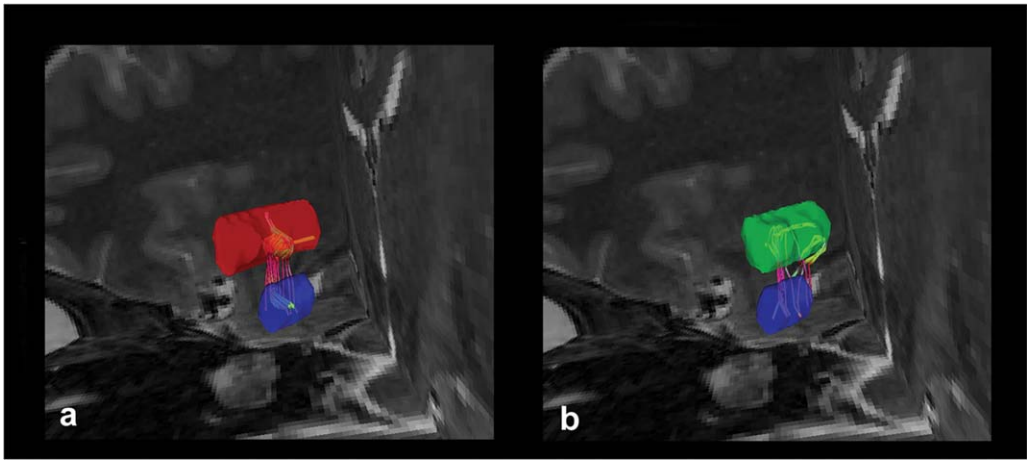


**FIG. 2.** Subthalamo-pallidal pathway. The subthalamo-pallidal pathway can be seen as a short white matter bundle connecting STN (blue VOI) both with GPi (**A**) and GPe (**B**) (green and red VOIs, respectively).

1. Long tracts white matter bundles between cortex and striatum (cortical-neostriatal pathway) and short white matter bundles between GP and striatum (direct pathway) (Fig. 1)
2. White matter bundles between sub thalamic nucleus (STN) and GP (subthalamo-pallidal pathway) (indirect pathway) (Fig. 2)
3. White matter bundles between STN and cortex (hyperdirect pathway) (Fig. 3)
4. White matter bundles between cortex and GP (Fig. 4)

## Cortico-neostriatal Pathway

We were able to reconstruct white bundles running between caudate nucleus (CN) and cortical areas: 11, 10, 9, 5, 7 and between putamen (Pu) and several cortical areas, namely 11, 10, 9, 8, 6, 4, 3, 2, 1, 5, 7, 19, 18, 17, and 34. These areas include orbitofrontal, premotor and supplementary motor, primary motor, primary somatosensory, secondary somatosensory, visual, and limbic areas (Fig. 1A). No significant lateralization of these tracts was found.

## Neostriatum-Pallidal Pathway

Figure 1B plots the reconstruction of the fibers running between CN and Pu (neostriatum) GP, which are implicated in a direct pathway.

## Subthalamo-Pallidal Pathway

The subthalamo-pallidal tract is part of the indirect pathway. The white matter tract running between STN and GP is shown in Figure 2. It crosses the internal capsule at a right angle, as previously reported.[28] The largest part of this pathway is interposed between STN and Globus Pallidus external (GPe) (Fig. 2A). However, by using separate segmentation of internal and external globus pallidus (Globus Pallidus internal (GPi) and GPe), a small bundle of fibers tracing up to the GPi was also detected (Fig. 2B). The difference between the STN-GPe and STN-GPi white matter tracts was statistically significant ($P > 0.05$).

## Hyperdirect Pathway

The hyperdirect pathway passes through the internal capsule. This is shown in sagittal rotated view (Fig. 3A)

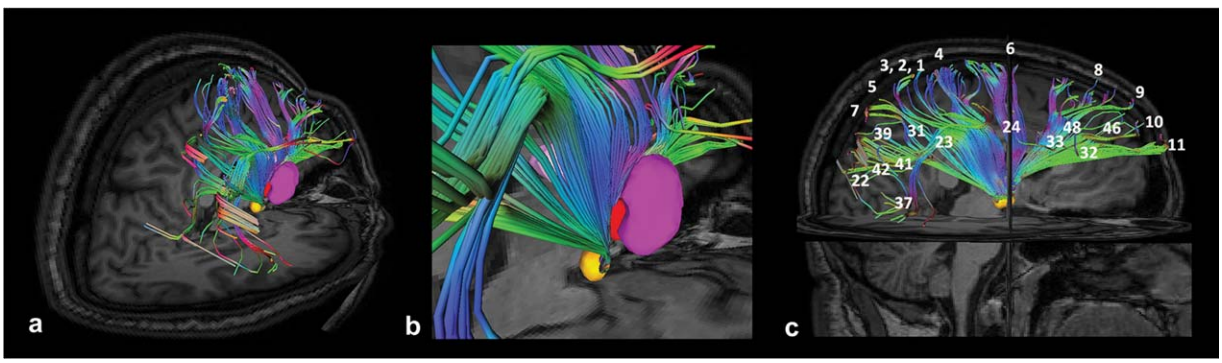


**FIG. 3.** Hyperdirect pathway. (**A**) Oblique sagittal view of hyperdirect pathway appears as a large bundle that from the cortex reach STN (yellow VOI). (**B**) Enlarged view shows its passage through the internal capsule. GP, PU, and CN are represented with red, purple, and pink VOIs, respectively. (**C**) Sagittal view of Brodmann's areas involved.

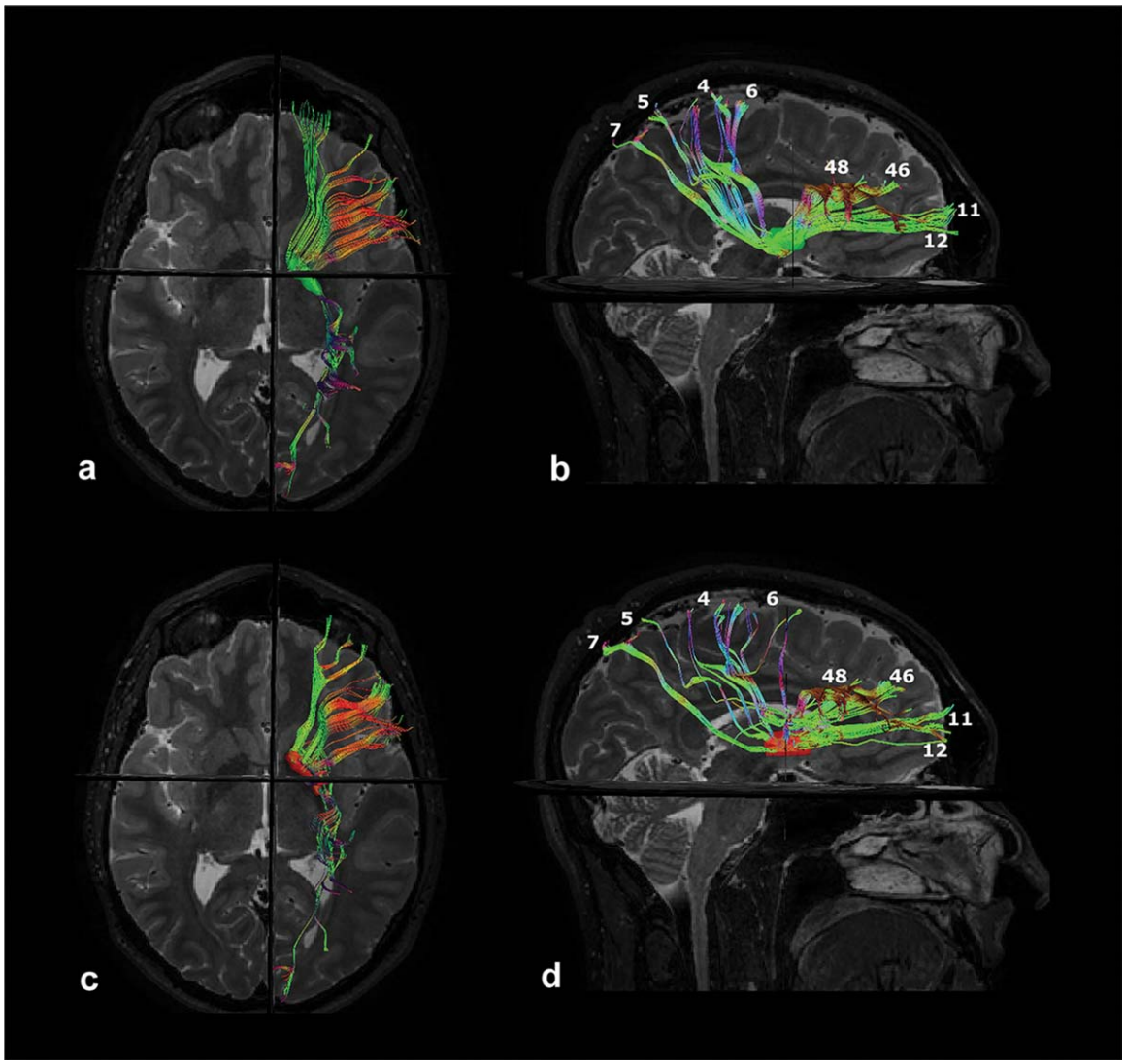


**FIG. 4.** Cortex-GP connections. (**A**) Axial view of fibers bundles connecting GPi (green VOI) and cortex. The connected Brodmann's areas are indicated on the sagittal view (**B**). Axial (**C**) view of fiber bundles connecting GPe (red VOI) and cortex. The connected Brodmann's areas are indicated on the sagittal view (**D**).

and in detail (Fig. 3B). We were able to reconstruct white matter fibers running between STN and the following Brodmann's areas: 3-1-2 (primary somatosensory cortex), 4 (motor cortex), 5, 6 (premotor cortex, supplementary motor cortex and pre-supplementary motor cortex), 7, 8 (frontal eyes fields), 9, 10, 11, 22, 23, 31, 32-33-24 (anterior cingulate cortex), 39, 41-42 (auditory cortex), 46, and 48 (Fig. 3C).

We observed intrasubject and intersubject variability, because the percentage of reconstructed white bundles in the examined 20 brain hemispheres was 100% for areas 4, 6, 7, 8, 32, and 33; 90% for areas 24 and 46; 85% for areas 3, 1, 2; 80% for areas 9, 10, and 11; 70% for areas 5 and 23; 65% for areas 41 and 42; and 50% for areas 22, 39, and 48.

## Possible Direct Cortico-pallidal Connection

We found white matter fibers running through the corona radiate between both the GPe and GPi and the following cortical Brodmann's areas: 12, 11, 46, 48, 6, 4, 5 (Fig. 4A, B, C, and D). These fibers are well separated from the cortico-pontine fibers running through the internal capsule (see Supplemental Data Fig. 1).

The computed mean number of streamlines of these fibers was 355.5, with a standard deviation of $\pm 18.65$, with a maximum and a minimum number of streamlines of 381 and 327, respectively, and a mean length of 9.65 cm with a standard deviation of $\pm 0.60$ (Table 1).

In all subjects the density of the streamlines between cortex and GPe was higher than that to GPi ($P < 0.05$).

**TABLE 1.** Streamlines analysis of the cortico-pallidal pathway

| Healthy Subject Number (n = 10) | Mean Number of Streamlines (mean of all = 355.5 ± 18.65) | Mean Streamlines Length (mean of all = 9.65 cm ± 0.60) |
|---|---|---|
| 1 | 327 | 8.94 |
| 2 | 371 | 9.32 |
| 3 | 335 | 10.44 |
| 4 | 368 | 9.19 |
| 5 | 375 | 9.87 |
| 6 | 354 | 9.75 |
| 7 | 381 | 10.34 |
| 8 | 362 | 9.81 |
| 9 | 343 | 8.66 |
| 10 | 339 | 10.18 |

The mean number of streamlines and the mean streamlines length of the cortico-pallidal pathway has been shown for each healthy subject (10 healthy subjects). Mean and standard deviation of all subjects' streamlines number and length are 355.5 ± 18.65 and 9.65 ± 0.60 cm, respectively.

In each of 10 examined brains, these bundles were reconstructed in both sides without statistically significant lateralization. However, in one subject, we were not able to trace, on both sides, the connection with area 48. These differences may have been attributable to the well-known intersubject variability of white matter tracts. Indeed, a variability of cortico-spinal tracts, optic radiations, uncinate fasciculus, and inferior fronto-occipital fasciculus has been reported in both postmortem anatomical studies and in vivo tractography.[29,30]

## Discussion

A fundamental premise to our discussion is that tractography represents a method based on the preferential anisotropic diffusion along the myelinated white matter; therefore, the reconstructed fibers can be considered a reasonable approximation of the highest mathematical probability of the existence of the anatomical pathway. In addition, the existence of synapsis and gap junctions as well as the directionality of the signal transmission cannot be established by tractography.

By using in vivo CSD tractography, we demonstrated that the basal ganglia network is far more complicated than expected, by showing the existence of fibers running from the vicinity of the cerebral cortex to the vicinity of the globus pallidus.

In addition, the CSD approach provided a detailed mapping of the whole basal ganglia network, including the small tracts of the direct and indirect pathways.

The presence of a direct cortico-pallidal connectivity has never been demonstrated in humans with tractography. Although our results do not represent the proof of evidence of cortico-pallidal connectivity, they do indicate the probability of the existence of this pathway (Fig. 4).

The idea of the existence of a direct cortico-pallidal pathway is not entirely new, considering that it has been already observed in lamprey,[31] rat,[32] and monkey.[33]

In lamprey, habenula-projecting globus pallidus neurons receive direct excitatory projections from the pallium (corresponding to the cortex in mammals). The habenula-projecting globus pallidus neurons are glutamatergic and provide an indirect inhibitory influence on midbrain dopamine neurons. In rat, the cortical projections to the GP originate in the primary motor cortex, the supplementary motor area, and a part of the somatosensory cortex. In rhesus and squirrel monkeys, fibers were traced caudally in a path, which descended through the internal capsule and entered the dorsal region of both lateral and medial pallidal segments. Using adenosine 3′:5′-monophosphate–regulated phosphoprotein of M(r) 32 kDa in rhesus monkeys, Ghashghaei and Barbas[34] found that the neural tracer retrogradely labeled from orbitofrontal and prefrontal cortices into the ventral.[34]

Additional clues on the existence of a direct cortico-pallidal connection in monkeys and humans is provided by the comparison of the results of two further papers.

In 2007, Akkal et al.[35] studied connections between supplementary and presupplementary motor area with globus pallidus in cebus apella monkeys using retrograde transneuronal transport of neurotropic viruses and found connections between cortical areas and GPi. The authors stated the connections were disynaptic via the thalamus. However, in 2012, Zhang et al.[36] studied in humans the functional connectivity of supplementary motor area (SMA) and pre-SMA areas and found that pre-SMA areas had no functional connection with thalamus; conversely, they found that posterior pre-SMA area was strongly functionally connected to pallidum. Consequently, the connections between pre-SMA and globus pallidus demonstrated by Akkal et al.[35] could be partially attributable to a direct anatomical pathway between pre-SMA and globus pallidus.[35,36]

Direct cortico-pallidal fibers has been also postulated and demonstrated 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."[37]

An alternative explanation is that these fibers actually represent bundles from the ventrolateral thalamus passing through the GP and in route back to the

cortex, because the use of volume of interest (VOI) in the tractography technique can potentially flaw the reconstruction of the "passing through fibers." This has been demonstrated by the antidromic activation of ventro-thalamic neurons with deep brain stimulation (DBS) of the GPi.[38-40] Conversely, we cannot exclude that at least part of these fibers may really reach the GP.

In keeping with previous DTI studies, we showed that the hyperdirect pathway is connected to STN with many cortical areas, including primary motor cortex, premotor cortex, supplementary motor cortex, presupplementary motor cortex, frontal eyes fields, anterior cingulate cortex, primary somatosensory cortex, and dorsolateral prefrontal cortex. The existence of such a hyperdirect pathway in humans using DTI has been reported in the literature. In 2007, Aron et al.,[41] using probabilistic tractography, performed with a 1.5 T scanner, showed that right STN was connected with inferior frontal cortex and presupplementary motor area.[41] In 7 of 10 healthy adult subjects, Brunenberg et al., using a 3 T scanner and high angular resolution diffusion imaging tractography, showed hyperdirect pathways connecting STN with cortical motor areas.[42] Direct connections between the ventro medial prefrontal cortex, anterior cingulate cortex, presupplementary motor cortex, and inferior frontal cortex with STN also have been reported.[43,44] Finally, in a recent work, Lambert et al.[45] obtained, using a 7 T scanner and tractography, a very accurate reconstruction of the STN connections, including the hyperdirect pathway.[45]

## Neurophysiological Considerations

Before inferring any physiological consideration, two issues need to be considered: first, physiology cannot be derived only from anatomical connectivity, and second, our speculations could be valuable if, from the number of possible alternative explanations, we assume direct connections between the cortex and GP.

In the classical view, the basal ganglia circuitry was simplified to be composed of two major projection systems: the "direct" and "indirect" pathways.[46]

The direct and indirect pathways originate from separate populations of striatal medium spiny neurons (MSNs), the activity of which is differentially modulated by dopamine. Indeed, the two-striatal output pathways are affected differently by the dopaminergic projection from the substantia nigra pars compacta to the striatum. Striatal neurons that project directly to the two output nuclei have D1 dopamine receptors that facilitate transmission, whereas those that project in the indirect pathway have D2 receptors that reduce transmission.[47]

The core of the model resides in the concept that "direct" and "indirect" striatal projections modulate the main output structures (GPi and substantia nigra (SNr)) exerting opposite functional effects on the movement. These output structures have in turn GABAergic neurons firing almost in a tonic manner, keeping targeted structures in the thalamus and brain stem under tonic inhibitory control.

Indeed, the recent introduction of transgenic animal models, in which the direct and indirect pathways can be selectively targeted and visualized, have allowed direct testing of the validity of this model. Selective stimulation of MSNs expressing D2 receptors ("indirect circuit") induced movement arrest, whereas activation of MSNs expressing D1 receptors ("direct circuits") led to movement activation.[48,49] As a result, activation of the direct pathway facilitates movement, whereas activation of the indirect pathway inhibits movement.

According to this model, in Parkinson's disease, the more GPi activity is decreased, the more thalamic activity is enhanced and the more severe and generalized dyskinesias should be. Therefore, blockade of GPi activity, for example, by pallidotomy, would be expected to bring down GPi efferent activity and worsen dyskinesias. However, in apparent contradiction to this prediction, dyskinesias disappear after pallidotomy, as shown in the monkey and also as typically observed in Parkinson's disease patients with severe levodopa-induced dyskinesias.[50]

A partial solution to this paradox has been recently provided by Dybdal and co-workers,[51] who showed that chemical blockade of the SNr in monkeys does in fact induce choreiform dyskinesias, which is exactly the expected consequence of reducing basal ganglia output.[51]

In addition, likely the pallidotomy paradox is also related to a substantial rearrangement of the basal ganglia circuits after several years of disease and replacement therapy.[52] An alternative explanation could be related to the removal of the oscillatory activity of the basal ganglia in this condition.[53] The presence of direct cortico-subthalamic projections constituting a third pathway was demonstrated first in primates by tracer studies. Later, an electrophysiological study by Nambu et al.[54] confirmed the existence of this ''hyperdirect'' pathway.[1,54] The cortico–STN–GPi "hyperdirect" pathway conveys strong excitatory signals from the cortex to the GPi with faster conduction velocity than the direct and indirect pathways; in this way the excited STN generates an excitatory signal directed to the GPi and a fast stop signal of the motor gesture inhibiting irrelevant motor programs or changing motor plans.[1,43,46]

In line with these findings, Forstmann and co-workers[55] demonstrated that increased white matter strength between the anterior cingulate cortex and the STN resulted in better stopping behavior in a go/no-go task.[55]

We speculate that, because the hyperdirect pathway allows a faster connection of cortex with STN with respect to the direct and indirect pathways, so the cortico-pallidal fibers could represent a fast connection between cortex and GP. This hypothesis would meet the vision that the cortico-basal ganglia circuit is composed of several, parallel, segregated, and functionally distinct, but homologous loops.[56]

Future studies, using postmortem microsurgery dissection or tracer injection or in vivo functional MRI, are necessary to confirm the existence of this postulated pathway and to clarify its function.

## Limitations of the Study and Future Perspectives

Several limitations of this study are related to the intrinsic weakness of the tractography technique and in particular the inability to demonstrate the existence of synapsis and gap junctions as well as the directionality of the signal transmission.[57]

Nevertheless, tractography should be considered only as the highest mathematical probability of the existence of a given anatomical pathway.

In keeping with previous findings of our group, we confirmed that CSD tractography is a valuable technique allowing a reliable reconstruction of long fiber pathways in brain regions with multiple fiber orientations[12,58] using 3T MRI scanners, which are more available than 7T scanners. In addition, we demonstrated that the CSD technique is able to identify even the short tracts within the basal ganglia network. Data on animal Parkinson's disease models suggest that DBS may act either on local STN neurons and more likely via an antidromic activation of the "hyperdirect" pathway from motor areas to the STN.[59] Given the growing body of evidence implicating white matter as the main target for DBS, the identification of small bundles with CSD could be used in the near future to focally target short tracts within the basal ganglia loops. ■

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## Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's website.