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Imbalance of the direct and indirect pathways in focal dystonia: a balanced view

This scientific commentary refers to 'The direct basal ganglia pathway is hyperfunctional in focal dystonia' by Simonyan *et al.* (doi:10.1093/brain/awx263).

Imagine that you sign a cheque or order a glass of wine at a restaurant. How does the brain control these actions? According to the traditional model, motor control is regulated by the so-called direct and indirect basal ganglia-thalamocortical pathways (Alexander and Crutcher, 1990). From a functional standpoint, these pathways are well balanced in health, but are thought to exhibit specific forms of imbalance in hypokinetic movement disorders such as Parkinson's disease and in hyperkinetic ones such as dystonia. Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal movements or postures. The term focal dystonia is used when the abnormal movements are localized to a single site. Focal dystonia is exemplified by writer's cramp and laryngeal dystonia, in which either the hand or the larynx are exclusively involved. These types of focal dystonia are also task-specific in that abnormal movements are triggered stereotypically by a specific action. In this issue of *Brain*, Simonyan and colleagues elegantly demonstrate the imbalances of the direct and indirect pathways in these focal, task-specific forms of dystonia (Simonyan *et al.*, 2017).

Let us take a brief look at a simple (but useful) early model of the motor circuit (Alexander and Crutcher, 1990). The major input area of the basal ganglia is the corpus striatum, which for the motor circuit principally involves the putamen. The striatum receives excitatory input from widespread cortical regions, including the supplementary motor area, premotor cortex, and primary motor cortex. The direct and indirect pathways are two major pathways connecting the striatum to the major output area of the basal ganglia, i.e. the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr). Striatal medium spiny neurons of the direct pathway express dopamine D_1 family receptors and are inhibitory to GPi/SNr output structures. The medium spiny neurons of the indirect pathway express D_2 family receptors and, via the globus pallidus external segment (GPe) and subthalamic nucleus, excite the GPi/SNr. Basal ganglia output is inhibitory to the pallidoreceptive thalamic nuclei, which in turn convey excitatory output to the relevant cortical regions. Thus, the direct pathway is net excitatory and the indirect pathway is net inhibitory to the cortical regions (Fig. 1A).

Although the precise pathophysiology of focal dystonia remains unclear, an imbalance of the direct and indirect pathways has been suggested, which results in net increased excitation and reduced inhibition in motor cortical regions. On the one hand, reduced indirect pathway activity resulting in loss of inhibition is expected based upon the diminution in striatal D_2 receptor binding seen with ^{11}C-raclopride PET (Berman *et al.*, 2013; Simonyan *et al.*, 2013). On the other hand, direct pathway overactivity, resulting in increased cortical excitation, has been proposed as the underlying mechanism in dystonia based upon the abnormal metabolic network seen in patients with the disorder (Eidelberg *et al.*, 1995; Trost *et al.*, 2002; Carbon and Eidelberg, 2009; Fujita *et al.*, 2016). Indeed, the dystonia-related metabolic network was characterized by metabolic increases in the lentiform nucleus (the putamen and globus pallidus), and in the lateral premotor, supplementary motor regions (with abnormal dissociation of activity in the lentiform and thalamic regions). While this distinctive metabolic topography is compatible with overactivity of the direct pathway, the demonstration of increases in striatal D_1 binding affinity remained elusive.

In the current study, Simonyan *et al.* used ^{11}C-NNC-112 [(+)-8-chloro-5-(7-benzofuranyl)-7-hydroxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine] in conjunction with high resolution PET to measure striatal D_1 receptor binding in focal dystonia patients with writer's cramp and laryngeal dystonia and compared the results to analogous measurements in healthy subjects. They observed that subjects in both dystonia groups exhibited abnormal increases in striatal D_1 receptor binding involving the putamen bilaterally in writer's cramp and the right caudate and putamen in laryngeal dystonia.

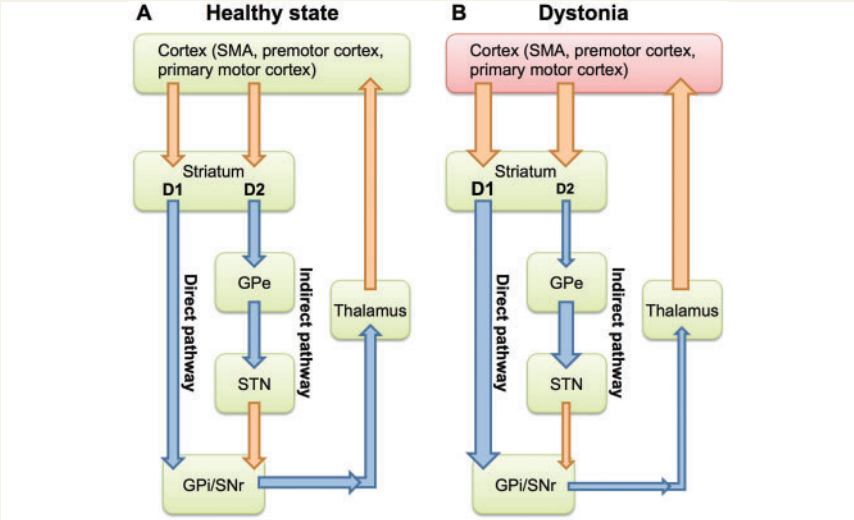

Figure 1 A simplified model of the motor circuit. (**A**) Healthy state. The striatum receives excitatory (orange) input from widespread cortical regions, including the supplementary motor area (SMA), premotor cortex, and primary motor cortex. The direct pathway is D_1 receptor-enriched and inhibitory (blue) to the globus pallidus internal segment and substantia nigra pars reticulata (GPi/SNr). The indirect pathway is D_2 receptor-enriched and via the globus pallidus external segment (GPe) and subthalamic nucleus (STN), excitatory to the GPi/SNr. The GPi/SNr is inhibitory to the thalamus, which sends excitatory output to the cortical regions. In aggregate, the direct pathway is net excitatory and the indirect pathway is net inhibitory to the cortical regions. Other relevant structures such as the substantia nigra pars compacta (SNc) are omitted for simplification. (**B**) In dystonia, upregulation of D_1 receptors (hyperactivity of the direct pathway) and downregulation of D_2 receptors (hypoactivity of the indirect pathway) can together add to the hyperexcitability of the cortical regions. The wide and thin arrows indicate increased and decreased output, respectively.

The changes seen in both groups were distributed along the anterior-posterior axis of the striatum, involving associative as well as sensorimotor subdivisions. Thus, in aggregate, the findings point to hyperactivity of the direct pathway in both types of focal dystonia (Fig. 1B).

The authors then determined how the striatal D_1 abnormalities related to the changes in D_2 receptor binding that were observed previously in focal dystonia. To this end, they combined the current findings with those from their previous reports in which decreased striatal D_2 receptor binding at rest and reduced dopamine release during task performance were seen in subjects with writer's cramp or laryngeal dystonia (Berman *et al.*, 2013; Simonyan *et al.*, 2013). Using combined D_1 and D_2 receptor binding data, Simonyan and colleagues now compared the spatial distribution of both radiotracers in the two focal dystonia groups with respect to the corresponding distribution in healthy subjects. The authors found substantial overlap between areas of D_1 and D_2 receptor binding and zones of task-induced dopamine release in healthy subjects, as well as smaller non-overlapping areas with D_1 or D_2 receptor binding. This contrasted with the findings in focal dystonia in which a remarkable spatial separation was present for the two radiotracers, with discrete zones of increased striatal D_1 binding, reduced D_2 binding, and attenuated dopamine release. These findings suggest that the normal interface between the direct and indirect pathways visualized as areas of receptor overlap is disrupted in focal dystonia.

Simonyan *et al.* asked another important question: are these abnormalities associated with somatotopic distribution of body representation within the striatum? As in the sensorimotor cortex, each body part, including hand and larynx, is represented by a discrete subregion of the striatum. In fact, the observed disorganization of dopaminergic function largely followed a known somatotopic distribution of body representation within the striatum. In writer's cramp, dopaminergic function with both direct and indirect pathways was mainly altered within the hand representation, which is localized to the mid-portion of the putamen. In laryngeal dystonia, by contrast, the abnormalities corresponded to the striatal representation of the larynx, which is localized to the ventral portion of the putamen. These findings nicely correspond to the distribution of clinical manifestations observed in the subjects with focal dystonia. The results may also be relevant to treatment assuming that a similar spatial distribution is evident in the GPi, which is the main target of deep brain stimulation in dystonia.

The contribution of Simonyan and colleagues provides evidence for an imbalance in neurotransmission along the direct and indirect pathways in focal dystonia. The current work should also stimulate research into other mechanisms mediating this condition and related neurodevelopmental disorders. Indeed, other organizational dualities exist within the striatum. The division of this structure into striosomal (patch) and matrix compartments has attracted great attention in recent years (Crittenden and Graybiel, 2011), and imbalance of striosomal and matrix compartments has also been proposed as an important pathobiological feature of dystonia (Goto *et al.*, 2005; *cf.* Holton *et al.*, 2008). Both compartments contain medium spiny neurons that project to the target nuclei of the direct and indirect pathways. That said, the target structures receive more inputs from matrix than striosomal medium spiny neurons, because the matrix compartment is much larger than the striosomal compartment.

Glossary

Laryngeal dystonia (spasmodic dysphonia): A task-specific focal dystonia that is characterized by involuntary spasms in the laryngeal muscles. It leads to uncontrolled voice breaks predominantly during speaking (Simonyan *et al.*, 2013).

Writer's cramp: A task-specific dystonia of writing, characterized initially by an abnormally tight grip while writing with progressive difficulty in performing the task as writing continues (Torres-Russotto and Perlmutter, 2008).

On the other hand, it is likely that only striosomal medium spiny neurons have direct projections to the substantia nigra pars compacta, which supplies dopamine to the entire dorsal striatum. As the balance between the direct and indirect pathways is largely governed by dopamine, it may be regulated by striosomal medium spiny neurons and their critical projection to the substantia nigra pars compacta. In this regard, it would then be interesting to learn how D_1 and D_2 receptor-expressing medium spiny neurons in the striatum are integrated within the striosomal and matrix compartments under normal conditions and in various forms of dystonia.

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Functional brain network architecture may route progression of Alzheimer's disease pathology

This scientific commentary refers to 'Distinct influence of specific versus global connectivity on the different Alzheimer's disease biomarkers', by Mutlu *et al.* (doi:10.1093/brain/awx279).

The last decades of neuroimaging research have shed major light on the temporal and spatial evolution of Alzheimer's disease pathology in the human brain. It is now well established that amyloid-β accumulates preferentially across heteromodal association cortices that show constitutively high metabolic activity across the lifespan. Of these regions, the posterior parietal association cortex in particular is vulnerable to synaptic dysfunction as indexed by glucose hypometabolism. Brain atrophy, on the other hand—which is thought to be mostly driven by tau pathology—shows a different spatial evolution as it initiates predominantly in medial and inferior temporal brain regions, after which it spreads systematically throughout the cortex (Sepulcre *et al.*, 2017). Strikingly, the spatial evolution of Alzheimer's disease-related brain abnormalities partly resembles the topology of functional networks that have been characterized by the use of functional MRI (Buckner *et al.*, 2005). This spatial overlap between Alzheimer's