specific RNA-binding protein to prevent deleterious phase separation. For example, bait RNAs can effectively solubilize TDP-43 and counter neurodegeneration driven by cytoplasmic TDP-43 aggregation (Mann et al., 2019). Since bait RNAs are similar in size and character to ASOs, they could be readily delivered to degenerating neurons in patients. Clearly, further studies are urgently needed to understand how the exciting findings of Lester et al. might empower therapeutic strategies to mitigate neurodegeneration in tauopathies.

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Basal ganglia reign through downstream control of motor centers in midbrain and brain stem while updating cortex with efference copy information

Sten Grillner[1,*] and William Scott Thompson[1]
[1]Department of Neuroscience, Karolinska Institutet, 17177 Stockholm, Sweden
*Correspondence: sten.grillner@ki.se
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In this issue of *Neuron*, McElvain et al. (2021) show that the major output of the basal ganglia, the substantia nigra pars reticulata, targets no fewer than 42 midbrain and brainstem structures and conveys an efference copy of the downstream commands back via thalamus to the cortex and striatum.

Much of the interest in the basal ganglia has been focused on the information fed back via thalamus to cortex, although it has long been known that there are important downstream connections to motor-related targets. The results that McElvain et al. (2021) report in this issue change, in a radical way, our understanding of the downstream control of movements and the type of information that is channeled back to cortex. The major output nucleus of the basal ganglia in rodents is the GABAergic substantia nigra pars reticulata (SNr). The authors show that neurons in the SNr target no fewer than 42 distinct regions, mostly in the midbrain and at the pontine and medullary brainstem level, consisting of, e.g., centers for the control of eye and orienting movements (Hikosaka and Wurtz 1983), posture, and locomotion, as well as orofacial structures. These projections are found to be highly segregated and support the notion of parallel channels of information processing through the basal ganglia.

The different SNr subpopulations are arranged in an orderly fashion from lateral to medial in the SNr (Figure 1). While all SNr neurons are spontaneously active, they exhibit heterogeneous physiological properties. McElvain et al. show that the lateral ones directed to the superior colliculus and the pontine and medullary reticular formation have a higher level of activity and briefer action potentials, whereas the medial ones projecting to, e.g., the raphe nuclei have longer-lasting action potentials and a lower rest rate. This topographic segregation within the SNr supports a model in which parallel modules exist throughout the basal ganglia (Figure 1; Grillner and Robertson 2016). Under resting conditions, SNr neurons continuously inhibit all their targets. An increased

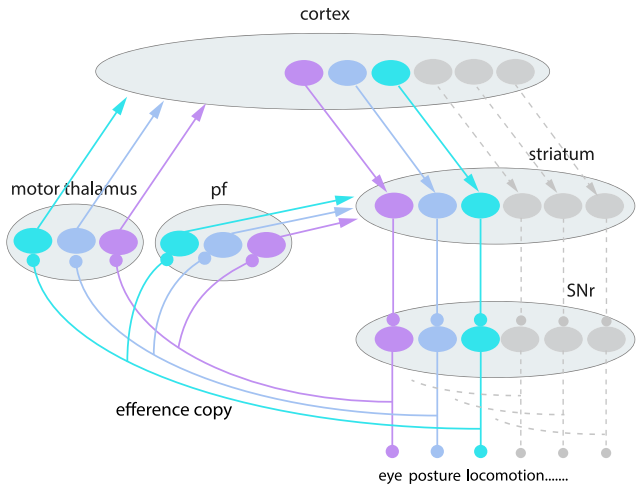

Figure 1. Schematic representation of the basal ganglia downstream control of motor structures in the midbrain-brainstem with specific efference copy information transmitted back via thalamus to cortex and striatum

Subpopulations of neurons in the cortex project to subpopulations in the striatum that in turn inhibit discrete groups of neurons in the substantia nigra pars reticulata (SNr; Foster et al., 2020). Each circle indicates groups of neurons. Note that the upstream axonal branches to the motor thalamus and the parafascicular nucleus (pf) forward efference copies about the specific activity in the output channels. Only the "direct pathway" connectivity between the striatum and SNr is included in this scheme. McElvain et al.'s contribution is that SNr is subdivided into subpopulations with specific motor targets and that each conveys an efference copy to different parts of the motor thalamus or pf and further to cortex and striatum.

SNr activity leads to deepened inhibition. Conversely, cessation of activity in any of the SNr subpopulations leads to disinhibition of its particular target structure and promotion of the specific action generated by this structure, whether eye movements or postural adjustments.

SNr neurons are also known to project heavily to the motor thalamus, which projects to the cortex, and to the parafascicular nucleus (pf) in thalamus, which projects back to the striatum. Some SNr neurons have been known to have two axonal branches: one downstream to motor centers and another to the thalamus. McElvain et al. now show that all the downstream-projecting SNr neurons also have a thalamic axonal branch. This means that the upstream thalamic branches carry information about the commands issued to the different motor centers in the midbrain and brainstem. As important, the different SNr subpopulations each project to discrete sections of the thalamic nuclei, such that the information projected back to the cortex and striatum is forwarded in a subpopulation-specific manner (see Figure 1). Hence, the cortex and striatum are continuously receiving updated information regarding the downstream commands issued from different parts of SNr to the motor centers. This type of information can be described as an efference copy.

The efference copy information forwarded to the cortex and striatum will be important for the planning of upcoming movements or the next phase of a movement sequence, rather than the actual movement being executed at that particular moment. With regard to the information fed back to the cortex, it is noteworthy that lesions of the motor thalamus performed clinically for reducing Parkinsonian symptoms, particularly in the pre-DOPA era (e.g., Duval et al., 2006), had no effects on deficits of gait and posture, but only on hand tremor. No cognitive or emotional symptoms were reported, despite the extensive projections back from the parts of the striatum concerned with emotional and cognitive processing located in the dorsomedial and ventral striatum (Alexander et al., 1986). These findings suggest that the information carried back via the thalamus is of the efference copy character, whereas motor symptoms of Parkinson's disease with regard to gait and posture are due primarily to the immediate downstream effects exerted from the basal ganglia.

The dorsomedial striatum is influenced by limbic areas and talks to the medial part of SNr, which, as McElvain et al. show here, projects preferentially to targets such as the dorsal raphe. The somato-motor part of striatum, the dorsolateral part, projects mainly to the lateral part of SNr, which affects different motor structures. A very precise projection pattern between the cortex, striatum, and SNr has recently been established (Foster et al., 2020). Thus, discrete parts of cortex project to distinct striatal subpopulations that in turn project to specific SNr subpopulations (see Figure 1; Grillner et al., 2020). The striatal projection neurons (with D1 dopamine receptors) of the "direct pathway" will, when activated, inhibit the target SNr neurons, which in turn will act to elicit a specific motor pattern through disinhibition. The current study builds upon this framework by showing that these specific SNr subpopulations are also specific in a precise targeting pattern. In addition to the disinhibition produced by a cessation of SNr activity directed to a specific brainstem-midbrain motor center, additional excitatory input might also be received from other structures like projections from cortex. Most likely, a movement is as a rule initiated through a combination of SNr-induced disinhibition and excitation from, for example, cortex.

In addition to the specific upstream projection from the SNr via thalamus or downstream to the many different targets, the authors identify a third category of SNr projections, comprising the pedunculopontine nucleus (PPN) and the midbrain reticular formation. In contrast to the orderly arranged input to the thalamic nuclei from SNr, the axonal branches to PPN appear to converge from across the different SNr subpopulations. If activity is reduced in any of the SNr subpopulations, PPN will receive less inhibition, and its activity will thus be enhanced. Therefore, increases in PPN activity will reflect the activation of any of the motor centers that are activated from the SNr. The PPN is subdivided into two parts, one mainly ascending and another descending. Each part consists of a glutamatergic and a cholinergic portion, and both have been implied in the control of locomotion (see Grillner et al., 2020).

McElvain et al.'s results were obtained in the mouse. In rodents, the SNr is responsible for around 89% of the output of the basal ganglia, while the smaller globus pallidus interna (GPi; in rodents often called the entopeduncular nucleus) is responsible for the remainder. The latter has not been studied in detail, but some of these neurons are known to have both an ascending and a descending branch, as in SNr. Whether most have multiple axonal branches is not known. In cats, a parcellation of the SNr into separate parts controlling eye, postural, and locomotor movements have been documented (Takakusaki et al., 2004). In primates, the SNr has a similar downstream projection pattern. Kim and Hikosaka (2013) have, for instance, shown that different types of eye movements are handled by different parts of the primate SNr. In the macaque, SNr represents but 45% of the output of the basal ganglia and GPi the remainder (Hardman et al., 2002). The latter has thus increased in relative size. The GPi and SNr are present in all vertebrates (Grillner and Robertson 2016). The SNr is clearly concerned with the control of different midbrain and brainstem motor structures, but the role of GPi is less clear, and it has been suggested that it may be concerned also with the strength or intensity of the movement.

In conclusion, the view that some major motor centers like the superior colliculus are under tonic inhibition from the SNr and that the basal ganglia contributes to action selection through disinhibition of downstream motor targets has been established for many years (Hikosaka and Wurtz 1983; Grillner et al., 2020; Takakusaki et al., 2004). These data have nevertheless often been overlooked in many parts of current and previous basal ganglia literature that, to a large degree, have been focused on effects transmitted back to the cortex via thalamus. What McElvain et al. have importantly contributed to is (1) an understanding of the detailed and precise projection pattern to many different parts of the midbrain and brainstem—more than could have been imagined—and (2) that the information fed back to the cortex from SNr is of efference copy character and carries information regarding the activity in each of the different downstream channels. This study should have a significant impact on the thinking of the function of the basal ganglia.

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