Published in final edited form as:

Mov Disord. 2015 March ; 30(3): 293–295. doi:10.1002/mds.26095.

The cortico-pallidal projection: An additional route for cortical regulation of the basal ganglia circuitry

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Keywords

globus pallidus; glutamate; hyperdirect; subthalamic nucleus; diffusion tensor imaging

Our current view of the functional circuitry of the basal ganglia is largely based on data from rodents and non-human primates using various tract-tracing methods combined with immunohistochemistry and *in situ* hybridization¹⁻³. These approaches demonstrated that cortical information flows through the basal ganglia via two major projection systems; the so-called “direct” and “indirect” striatofugal pathways that originate from segregated populations of striatal projection neurons and elicit opposite effects upon basal ganglia outflow. Although this dual network model has been greatly refined since its introduction in the late 1980s, it remains a highly useful organizational framework for clinical and basic basal ganglia research. In addition to the striatum, the subthalamic nucleus is also considered as a major entry for cortical information to the basal ganglia network. Because information may be more rapidly conducted to the basal ganglia output nuclei via the cortico-subthalamic projection than via the direct and indirect pathways, the trans-subthalamic route is commonly referred to as the “hyperdirect” pathway⁴⁻⁶.

In a recent study published in *Movement Disorders*, Milardi et al. suggest the existence of a cortico-pallidal projection in humans⁷. Their evidence for this projection is based on imaging data obtained from brain images from normal human volunteers, using a High Angular Resolution Diffusion Imaging-Constrained Spherical Deconvolution (CSD)-based technique. Although diffusion tensor imaging (DTI) is the most commonly used approach to trace white matter tracts in the human CNS⁸⁻¹⁰, this technique suffers from a number of limitations including relatively poor spatial resolution, and a limited capacity to characterize neural projection systems consisting of fibers with distinct orientation¹¹. The CSD method allows for a better discrimination of fiber orientation in neural networks with intravoxel orientation heterogeneity¹²⁻¹⁴. Using this approach, Milardi et al. provide imaging data suggesting the existence of a direct connection between Brodmann's areas 4, 5, 6, 11, 12, 11, 46, and 48 and both segments of the globus pallidus in humans. Although the imaging

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Financial disclosure/conflicts of interest: The authors have no conflict of interest and financial issues to disclose related to the content of this manuscript.

data shown in this study do not provide information about the pattern of innervation and synaptic connections of cortical projections with specific neuronal populations in the external (GPe) and the internal (GPi) segments of the human pallidum, they suggest that GPe receives a more massive cortical innervation than GPi⁷. They also demonstrate that this cortico-pallidal system is separate from the descending cortico-spinal and cortico-pontine axons that travel through the internal capsule. As discussed by the authors, the existence of a direct glutamatergic “*cortico-pallidal*” system that bypasses the traditional direct, indirect and hyperdirect pathways could have a significant impact on our understanding of transmission and processing of information through the basal ganglia circuits in normal and diseased states.

Although this study is the first to highlight the possible existence of a cortico-pallidal projection in humans, such a connection has previously been suggested from different tracing studies in rodents and lampreys. In rats, Naito and Kita reported the existence of a cortico-pallidal (and cortico-nigral) projection(s) based on data obtained after injections of the anterograde tracer biotinylated dextran amine (BDA) in various cortical regions^{15,16}. 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 anterogradely labeled varicosities in the ipsilateral GP. At the electron microscopic level, BDA-labeled boutons formed asymmetric (likely excitatory) synapses with small dendrites and spines of GP neurons¹⁶. They also showed that the cortico-pallidal projection is topographically organized and that its density is about 10% of that of the corticostriatal projection¹⁶. In the lamprey, Stephenson-Jones et al. demonstrated that pallido-habenular neurons receive direct excitatory projections from the pallium (i.e., the homologue of the cerebral cortex in mammals), and suggested that this connection may be part of a distinct reward-evaluation circuit used to select actions across vertebrates¹⁷.

Using vesicular glutamate transporter 1 (vGluT1), as a preferential marker of cortical terminals in the telencephalon¹⁸⁻²⁰, preliminary data from our laboratory strongly support the existence of a direct glutamatergic cortico-pallidal projection in rodents, monkeys and humans²¹⁻²². In line with the aforementioned rodent data¹⁶, we found that the vGluT1 terminals target almost exclusively dendritic spines and small dendrites in the monkey pallidum, a pattern of synaptic connectivity strikingly different from that of vesicular glutamate transporter 2 (vGluT2) terminals that originate predominantly from the STN²². Another interesting feature of this cortico-pallidal system is the differential pattern of localization of cortical terminals between the two pallidal segments in monkeys and humans²¹⁻²². As suggested by the imaging data of Milardi et al., the cortico-pallidal projection to the GPe is more extensive than to GPi⁷. In the GPe, vGluT1 terminals are distributed along the full extent of the nucleus, while they are exclusively found in the peripallidal region of GPi in monkeys and humans²². Taking into consideration that peripallidal cells in GPi are the main sources of the pallido-habenular projection²³⁻²⁵, these results suggest that the cortical inputs to GPi may preferentially target pallido-habenular neurons, a pattern reminiscent of that recently described in the lamprey¹⁷ (Fig. 1).

Altogether these observations strongly suggest the existence of a glutamatergic cortico-pallidal projection in mammals, including humans (Fig. 1). Future studies are needed to characterize more precisely the exact source(s) of this input to GPe or GPi. According to the imaging data of Milardi et al., this projection originates from prefrontal associative regions and sensorimotor cortices⁷. However, care must be taken in interpreting these findings, because of the massive input prefrontal associative cortices provide to basal forebrain cholinergic neurons^{26,27}. Because some of these cholinergic cells reside along the internal and external medullary lamina, between the two pallidal segments and the putamen, it cannot be ruled out that some of the cortical areas suggested as sources of the cortico-pallidal projection by Milardi et al. are, in fact, targeting cholinergic basal forebrain neurons. Tract-tracing studies in primates are needed to address this issue.

Thus, although preliminary, the findings of Milardi et al. are a timely and important demonstration of the existence of the cortico-pallidal projection in humans, which may provide cortical access to the basal ganglia output nuclei, bypassing the striatum. Obviously, the functional relevance of this projection strongly depends on the source(s) and target(s) of the information that reaches the basal ganglia via this pathway. It will be important to evaluate whether the cortico-pallidal projection supports some of the currently favored roles of the basal ganglia in the control of motor and non-motor behaviors. Finally, it will be important to assess potential changes of this system in disease conditions such Parkinson's disease or Huntington's chorea, using animal models of these disease and advanced tract tracing imaging studies, such as CSD.

Acknowledgments

Funding sources: This work was supported by the following grants by the National Institutes of Health: P50 NS071669 (Udall Center grant, TW, YS), R01 NS037948 (YS), and P51 OD011132 (infrastructure grant to the Yerkes National Primate Research Center).

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Figure 1.

Proposed organization of the cortico-pallidal glutamatergic projection in primates based on findings presented in references 7,16,17,21,22. Glutamatergic cortical afferents innervate the whole extent of the GPe, while they preferentially target peripallidal neurons in the GPi. Sensory-motor cortices are suggested as the main sources of the cortico-pallidal projection, although additional sources cannot be ruled out. Abbreviations: CM: Centromedian nucleus; GPe: Globus pallidus, external segment; GPi: Globus pallidus, internal segment; LHb: Lateral habenular nucleus; PPN: Pedunculo pontine nucleus; SNr: Substantia nigra pars reticulata; STN: Subthalamic nucleus; STR: Striatum; VA/VL: Ventral anterior/ventral lateral nucleus.