Neuron
Previews

Looking at the Trees in the Central Forest: A New Pallidal-Striatal Cell Type

Ana M. Vicente[1] and Rui M. Costa[1,*]
[1]Champalimaud Neuroscience Programme, Champalimaud Center for the Unknown, Av. De Brasília, 1400-038 Lisbon, Lisbon, Portugal
*Correspondence: ruicosta@fchampalimaud.org
DOI 10.1016/j.neuron.2012.06.003

The glopus pallidus is a central nucleus of the basal ganglia, pivotal to their function in health and disease. In this issue of *Neuron*, Mallet et al. (2012) reveal that this structure is more diverse than previously thought, and identify a novel cell type that projects from pallidum to striatum providing massive GABAergic innervation. These findings invite new views on basal ganglia processing.

Corticobasal ganglia loops, and the basal ganglia in particular, have long been associated with action control, action selection and reinforcement learning (Graybiel, 2005; Balleine et al., 2007). Basal ganglia circuits have also been implicated in learning new skills, as well as in both goal-directed and habitual actions (Balleine et al., 2007; Yin and Knowlton, 2006). The basal ganglia encompass several nuclei that contribute to a large interconnected network. The regions that form the basal ganglia are the striatum, the globus pallidum, the subthalamic nucleus (STN), and the substantia nigra. The major input into the basal ganglia is through the striatum, its largest region. It receives input from cortical, thalamic and limbic structures (such as amygdala), and it is composed of projection GABAergic medium spiny neurons (95%) and several populations of interneurons. Some striatal medium spiny neurons project directly to basal ganglia output nuclei, like the substantia nigra pars reticulata (SNr) or the internal globus pallidum (GPi; entopeduncular nucleus in rodents) giving rise to the so-called direct pathway. Other medium spiny neurons project to the external globus pallidum (GPe), which is a central basal ganglia nucleus that projects to other basal ganglia nuclei, like the STN, giving rise to the indirect pathway (Gerfen et al., 1990).

These corticobasal ganglia loops appear to have a parallel organization that connects specific topographic regions of cortex, striatum, and thalamus (Groenewegen et al., 1990). There are different models of how circuit organization in basal ganglia relates to information processing in these loops. The most influential model poses that the direct and the indirect pathways have orthogonal effects on basal ganglia output (Albin et al., 1989): activity in direct pathway striatal neurons would directly inhibit basal ganglia output and hence disinhibit the thalamus, while activity of the indirect pathway would disinhibit basal ganglia output, and therefore inhibit thalamus. According to this view, the output of basal ganglia would be a balance of the activity in these two pathways. This model has been used to provide a mechanistic explanation of the symptoms associated with several basal ganglia disorders, most notably Parkinson disease (PD), (Albin et al., 1989). In PD, loss of dopamine input mainly from substantia nigra pars compacta, would have opposing effects on direct and indirect pathway neurons, which express mostly D1 versus D2-type dopamine receptors, respectively (Gerfen et al., 1990). This would result in overactivation of the indirect pathway (and the consequent inhibition of GPe) and less activation of the direct pathway and to lack of movement (Kravitz et al., 2010). Other studies show that PD is accompanied by the emergence of abnormal oscillations in basal ganglia, most notably prominent beta oscillations in STN and GPe (Mallet et al., 2008; Nini et al., 1995), which are thought to constitute a pacemaker circuit (Plenz and Kital, 1999).

The GPe, central to basal ganglia function, has been traditionally portrayed as a structure organized in different domains of homogeneous cell populations of projection neurons, all projecting to the STN with some collaterals reaching other structures. In this issue of *Neuron*, Mallet and colleagues (Mallet et al., 2012) demonstrate that the organization of the GPe is more complex than previously thought, and that it is composed of at least two populations of GABAergic projection neurons. The authors had previously shown that in a PD rat model, two different types of GPe neurons could be identified based on their entrainment to different phases of cortical slow wave oscillations (Mallet et al., 2008): some fired preferentially during the surface-negative component of the cortical oscillation (inactive, hence named GP-TI); others during the surface-positive phase of the cortical oscillation (active phase, GP-TA). In this study, Mallet et al. (2012) used juxtacellular labeling of in vivo recorded cells to establish that these two types of neurons, identified based on their firing dynamics, constitute indeed different cell types within GPe, with quite distinct molecular profiles, neuronal structures, and projection patterns.

The authors observed that all GP-TA neurons expressed the neuropeptide precursor preproenkephalin (PPE), while none of the GP-TI neurons did. Other markers, like parvalbumin, were more expressed in GP-TI neurons, but were also found in GP-TA neurons. Therefore, PPE could be used as a specific marker for GP-TA neurons. Using this marker, the authors showed that GP-TA and GP-TI neuronal populations are spatially intermingled in GPe, and that they are both GABAergic neurons. Next, they characterized the structure and projection specificity of individual neurons from both populations. They observed that while GP-TI neurons have the projection profile expected for GPe neurons—descending projections to downstream BG nuclei

such as STN, which sometimes sent collaterals to striatum—GP-TA neurons had an unanticipated projection pattern. All GP-TA neurons analyzed presented one projecting axon that extensively innervated the striatum, but not the STN (Figure 1). Furthermore, a detailed analysis of the striatal innervation of reconstructed GP-TA neurons revealed that each axon could split into several axonal collaterals, and form thousands of axonal boutons in the striatum, constituting the largest extrinsic GABAergic input to the striatum. Additional observations revealed that GP-TA neurons target all main populations of neurons in the striatum, i.e., projection neurons and the major classes of interneurons. Lastly, the authors also show that axon collaterals from GP-TI and GP-TA neurons can form local connections with both GP-TI and GP-TA neurons, i.e., these two populations can communicate directly within and between each other. These observations indicate yet another potential degree of regulation in GPe networks.

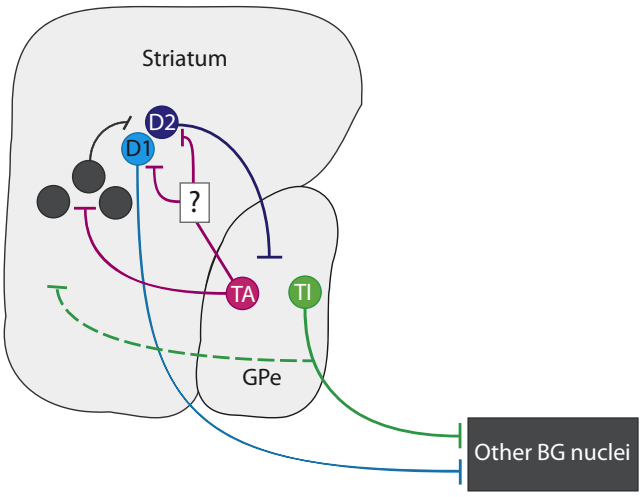

Figure 1. Scheme of GPe Projection Neurons from the Two Populations Identified

All GP-TI neurons (represented in green) have the prototypical projection pattern of GPe neurons, i.e., they project to downstream basal ganglia areas such as subthalamic nucleus (STN) with some collaterals sparsely innervating the striatum. Arkypallidal, or GP-TA neurons (magenta), however, present an unexpected projection pattern, not targeting the STN but instead projecting to the striatum with extensive axonal arborization. GP-TA neurons can target both interneurons and projections neurons.

This new population of striatal projecting pallidal neurons (arkypallidal) adds to an increasingly complex picture of basal ganglia connectivity that challenges the basic feedforward view of corticobasal ganglia loops. In particular, it presents a new way of looking at GPe, not simply as a relay area that forwards information from the striatum to downstream structures like the STN, but as a region with different circuits that can differentially target specific points of a larger network. Because of the large projection of the GP-TA neurons to the striatum, this population can potentially have a major impact on the dynamics of this structure.

For example, it may shape models about the balance between direct and indirect pathways, and how these pathways dynamically influence each other. This will depend largely on a more extensive characterization of the projections of GP-TA neurons. Are they synapsing preferentially into direct or indirect neurons? If they target neurons from the indirect pathway, is this a complete feedback loop where they are projecting back to same neurons from which they receive input? These and other questions can entirely change the predictions of what these neurons do in basal ganglia circuits, with different potential combinations resulting in the emergence of rather different network dynamics. Also, since ventral, medial and lateral networks in corticobasal ganglia loops have been implicated in different aspects of behavior (Balleine et al., 2007), it would be interesting to investigate if the projections of arkypallidal neurons are topographically structured or not, as this could constitute yet another level of organization. Another pending question relates to input to both populations of GPe neurons, that is, which cells project to GP-TI neurons and which project to GP-TA neurons. One can consider situations where both cell types receive projections from the same neurons, or a sort of functional organization of the inputs, which could be at least partially responsible for the diverse firing pattern of the two populations. The observation that GP-TI and GP-TA can form connections between each other is critical. Lateral inhibition can be another way, by itself or in coordination with other inputs, of controlling the activity of the two GPe populations, and maintain asynchrony between them.

The identification of this new pallidal cell type may be important to understand the pathophysiology of PD, and also shed light into why deep brain stimulation in the STN and lesions of the GPe are effective treatments for PD symptoms. Still, one important next step will be the analysis of the activity and role of this pathway in nonlesioned, freely behaving animals. It is necessary to confirm that the differences in population dynamics and molecular profiles are a constitutive characteristic of the system, and not mainly observed in PD lesioned animals. In this respect, the authors showed that GP-TA neurons and GP-TI neurons also behaved differently from each other during cortical activation states, which suggests that they may indeed play an important role in a variety of brain states, and in awake behaving animals. It would be interesting, for instance, to investigate if activity of these neurons is related to the emergence of normal beta oscillations in behaving animals (Howe et al., 2011; Leventhal et al., 2012). Given that these neurons express specific molecular markers (e.g., PPE), they can be genetically targeted using simple or combinatorial approaches to express recombinases and/or viral vectors. This can also expedite the use of optogenetics and the exploration of the functional connectivity of these neurons.

In summary, this finding opens a new realm of possibilities to investigate the function of a structure that was so far considered relatively homogenous. One can go one step further and question how many more populations can there be in GPe. As an example, some neurons recorded had high tonic firing rates not in synchrony with SWA. Could they represent a third population of neurons in GPe? Even the GP-TI population presents some heterogeneity, which could be

explained by the existence of subpopulations within these neurons. Hopefully, these and future studies will help shed light on the operations of this complex network, not only in healthy conditions, but also in diseases that deregulate its normal balance.

REFERENCES

Albin, R.L., Young, A.B., and Penney, J.B. (1989). Trends Neurosci. *12*, 366–375.

Balleine, B.W., Delgado, M.R., and Hikosaka, O. (2007). J. Neurosci. *27*, 8161–8165.

Gerfen, C.R., Engber, T.M., Mahan, L.C., Susel, Z., Chase, T.N., Monsma, F.J., Jr., and Sibley, D.R. (1990). Science *250*, 1429–1432.

Graybiel, A.M. (2005). Curr. Opin. Neurobiol. *15*, 638–644.

Groenewegen, H.J., Berendse, H.W., Wolters, J.G., and Lohman, A.H. (1990). Prog. Brain Res. *85*, 95–116, discussion 116–118.

Howe, M.W., Atallah, H.E., McCool, A., Gibson, D.J., and Graybiel, A.M. (2011). Proc. Natl. Acad. Sci. USA *108*, 16801–16806.

Kravitz, A.V., Freeze, B.S., Parker, P.R., Kay, K., Thwin, M.T., Deisseroth, K., and Kreitzer, A.C. (2010). Nature *466*, 622–626.

Leventhal, D.K., Gage, G.J., Schmidt, R., Pettibone, J.R., Case, A.C., and Berke, J.D. (2012). Neuron *73*, 523–536.

Mallet, N., Pogosyan, A., Márton, L.F., Bolam, J.P., Brown, P., and Magill, P.J. (2008). J. Neurosci. *28*, 14245–14258.

Mallet, N., Micklem, B.R., Henny, P., Brown, M.T., Williams, C., Bolam, J.P., Nakamura, K.C., and Magill, P.J. (2012). Neuron *74*, this issue, 1075–1086.

Nini, A., Feingold, A., Slovin, H., and Bergman, H. (1995). J. Neurophysiol. *74*, 1800–1805.

Plenz, D., and Kital, S.T. (1999). Nature *400*, 677–682.

Yin, H.H., and Knowlton, B.J. (2006). Nat. Rev. Neurosci. *7*, 464–476.