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REVIEW

COMPUTATIONAL PHYSIOLOGY OF THE NEURAL NETWORKS OF THE PRIMATE GLOBUS PALLIDUS: FUNCTION AND DYSFUNCTION

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Abstract—The dorsal pallidal complex is made up of the external and internal segments of the globus pallidus (GPe and GPi respectively). It is part of the main axis of the basal ganglia (BG) that connects the thalamo-cortical networks to the BG input stages (striatum and subthalamic nucleus) and continues directly, and indirectly through the GPe, to the BG output stages (GPi and substantia nigra reticulata). Here we review the unique anatomical and physiological features of the pallidal complex and argue that they support the main computational goal of the BG main axis (actor); namely, a behavioral policy that maximizes future cumulative gains and minimizes costs. The three mono-layer competitive networks of the BG main axis flexibly extract relevant features from the current state of the thalamo-cortical activity to control current (ongoing) and future actions. We hypothesize that the striatal and the subthalamic projections neurons act as mono-stable integrators (class I excitability) and the *in-vivo* pallidal neurons act as bi-stable resonators (class II excitability). GPe neurons exhibit pausing behavior because their membrane potential lingers in the vicinity of an unstable equilibrium point and bi-stability, and these pauses enable a less-greedy exploratory behavioral policy. Finally, degeneration of midbrain dopaminergic neurons and striatal dopamine depletion (as in Parkinson's disease) lead to augmentation of striatal excitability and competitive dynamics. As a consequence the pallidal network, whose elements tend to synchronize as a result of their bi-stable resonance behavior, shifts from a Poissonian-like non-correlated to synchronous oscillatory discharge mode.

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Key words: basal ganglia, primate, neurons, correlations, oscillations, Parkinson's disease.

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Abbreviations: BG, basal ganglia; CV, coefficient of variance; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; HCN, hyperpolarization and cyclic nucleotide-gated; ISI, inter-spike-interval; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSNs, medium spiny neurons; SNr, substantia nigra pars reticulate; STN, subthalamic nucleus.

The neural networks of the globus pallidus are part of the main axis of the basal ganglia (BG) that connects the cortical and thalamic networks, hippocampus and amygdala with the cortical and brainstem motor centers. The input structures of the basal ganglia—the striatum and the subthalamic nucleus (STN)—are reciprocally connected to the external segment of the globus pallidus (GPe) and these three structures (striatum, STN, and GPe) innervate the output structures of the

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basal ganglia—the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr). The rodent homologue nuclei of the primate GPe and GPi are the globus pallidus (GP) and the entopeduncular nucleus (EP), respectively. To simplify this review we will use the primate terminology also for the rodent pallidum.

Current computational models of the basal ganglia treat them as an actor/critic reinforcement learning network. The main axis or the actor part implements the behavioral policy or the mapping between states and actions. The neuromodulators of the basal ganglia, which include the midbrain dopaminergic neurons, striatal cholinergic interneurons and others, provide the main axis with a temporal prediction error. We recently hypothesized (Parush et al., 2011) that the computational goal of the basal ganglia is to optimize the tradeoff between the orthogonal goals of maximizing future cumulative gain and minimizing the behavioral cost. This multi-dimensional or multi-objective optimization goal naturally leads to a soft-max like behavioral policy where dopamine plays a dual role. First, and as in previous models, dopamine affects the efficacy of the cortico-striatal synapses (Schultz et al., 1997). But, dopamine also acts as a pseudo-temperature soft-max parameter that controls the tradeoff between gain and cost and the continuum between exploratory (gambling) and greedy (akinetic) behavioral policies (the motor vigor, Cools et al., 2011; Niv et al., 2007).

In this manuscript, we limit ourselves to the main axis of the basal ganglia. In the first section we provide a brief historical review of the evolvement of models of basal ganglia connectivity. We end up with current views of the basal ganglia that connect the thalamic and cortical networks with the cortical and brainstem motor system. In these models the GPe is the central nucleus of the basal ganglia and affects all other basal ganglia structures (Kita, 1994b, 2007). The second section is devoted to a description of the unique cellular anatomy of the pallidal neurons. Here, we emphasize the structural specificities of the long and sparsely branched dendrites of pallidal neurons that are oriented perpendicular to the afferent striatal axons (Percheron et al., 1984), and covered by 30,000 to 40,000 synapses, ~90% of which are GABAergic from the striatum, and only 5–10% glutamatergic from the STN (Shink and Smith, 1995a). In the third section we briefly review the field of the intracellular physiology of pallidal neurons. We confine our review to the neuronal class that probably corresponds to the *in-vivo* high-frequency discharge pallidal neuron. In the fourth section we summarize the main results of extracellular recording studies of single and multiple neurons (units) in awake and behaving primates. Next, we describe the changes in the discharge properties (rate, pattern and synchronization) in the pallidum following dopamine depletion and the development of Parkinsonian symptoms. These two sections correspond to the experimental paradigm of our research group, and therefore are more detailed than the previous sections. The sixth section is devoted to a dynamical system analysis of the high-frequency discharge neurons in the pallidum. Here we present our working hypothesis that pallidal neurons behave *in-vivo* like bi-stable resonators (class II excitability). We claim that the linear I–f curve reported in *in-vitro* studies can be attributed to recordings in the soma and the lack of tonic synaptic inputs to the pallidal neurons in the anaesthetized animal and in *in-vitro* conditions. Finally, in the concluding section we show how the intrinsic (i.e. mono-stable integrators and bi-stable resonators) and the network properties of the basal ganglia enable the basal ganglia to achieve their computational goal—efficient and flexible feature extraction of the thalamo-cortical state.

INPUT/OUTPUT ORGANIZATION OF THE BASAL GANGLIA AND THE PALLIDAL NETWORK

Perspectives on basal ganglia connectivity have evolved considerably over the years. A comprehensive historical review of this magnificent “relay race” of knowledge is far beyond the scope of this manuscript. Below, we briefly summarize our view of three generations of basal ganglia models.

The first generation—pyramidal vs. extra pyramidal subsystems

The motor system was classically described as consisting of two parts: the pyramidal and the extra-pyramidal subsystems. The pyramidal system starts at the motor cortices (upper motor neurons), and through the brainstem pyramids projects to spinal alpha (lower) motor neurons, innervating the distal parts of the limbs. In contrast, the extra-pyramidal system originates in the basal ganglia and the cerebellum, descends parallel to the pyramidal system, and innervates the spinal circuits involved in control of automatic and postural movements. Neurology textbooks thus taught that the pyramidal system controls the execution of distal (e.g. fingers) accurate, voluntary movements whereas the extra-pyramidal system controls more axial (postural), automatic non-voluntary movements.

The second generation—the basal ganglia is part of a cortical closed loop

The revolution in anatomical methods during the second half of the 20th century led to changes in the way the motor system and the basal ganglia were perceived. The basal ganglia were redefined as the feed-forward part of a closed loop connecting all cortical areas sequentially through the striatum, pallidum, and thalamus back to the frontal cortex. The frontal cortex projects downstream through the cortico-spinal and cortico-brainstem pathways to the spinal level. This revised view of the basal ganglia networks assumed that there are two segregated internal basal ganglia pathways that start in the striatum and converge on the output structures of the basal ganglia (the GPi and the SNr). The so-called “direct pathway” is a direct GABAergic inhibitory pathway, whereas the “indirect pathway” is a polysynaptic dis-inhibitory pathway through the GPe and the glutamatergic (excitatory) STN. The reciprocal connections between the GPe and the STN (Carpenter et al., 1981a; Kim et al., 1976) tended to be ignored in these models, and the GPe was depicted as a relay nucleus