J Neural Transm (2006) [Suppl] 70: 17–20

Synchronizing activity of basal ganglia and pathophysiology of Parkinson's disease

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Summary. Early physiological studies emphasized changes in the discharge rate of basal ganglia in the pathophysiology of Parkinson's disease (PD), whereas recent studies stressed the role of the abnormal oscillatory activity and neuronal synchronization of pallidal cells. However, human observations cast doubt on the synchronization hypothesis since increased synchronization may be an epi-phenomenon of the tremor or of independent oscillators with similar frequency. Here, we show that modern actor/critic models of the basal ganglia predict the emergence of synchronized activity in PD and that significant non-oscillatory and oscillatory correlations are found in MPTP primates. We conclude that the normal fluctuation of basal ganglia dopamine levels combined with local cortico-striatal learning rules lead to non-correlated activity in the pallidum. Dopamine depletion, as in PD, results in correlated pallidal activity, and reduced information capacity. We therefore suggest that future deep brain stimulation (DBS) algorithms may be improved by desynchronizing pallidal activity.

Introduction: The computational roles of the basal ganglia and dopamine

Modeling of the basal ganglia has played a major role in our understanding of the physiology and pathophysiology of this elusive group of nuclei. These models have undergone evolutionary and revolutionary changes over the last twenty years, as ongoing research in the fields of anatomy, physiology and biochemistry of these nuclei has yielded new information. Early models dealt with a single pathway through the basal ganglia nuclei (cortex-striatum-internal segment of the globus pallidus; GPi) and focused on the nature of the processing performed within it, convergence of information vs. parallel processing of information. Later, the dual (direct and indirect) pathway model (Albin et al., 1989) characterized the inter-nuclei interaction as multiple pathways while maintaining a simplistic scalar representation of the nuclei themselves. The dual pathway of the basal ganglia networks emphasized changes in the discharge rates of basal ganglia neurons. The model predicts that in the dopamine depleted Parkinsonian state firing rates in the external segment of the globus pallidus (GPe) are reduced, whereas cells in the internal segment (GPi) and the subthalamic nucleus (STN) display increased firing rates (Miller and DeLong, 1987; Bergman et al., 1994). This model resulted in a clinical breakthrough by providing key insights into the behavior of these nuclei in hypo- and hyper-kinetic movement disorders, and lead

to subsequent findings showing that inactivation of STN and GPi can improve the motor symptoms in Parkinsonian animals (Bergman et al., 1990) and human patients. Finally, in line with the model predictions many studies have demonstrated reversed trends of pallidal discharge rates in response to dopamine replacement therapy (DRT) in both human patients and primates (e.g. Heimer et al., 2002). The next generation of models elaborated the intra-nuclei interactions and focused on the role of the basal ganglia in action selection and sequence generation which form the most current consensus regarding basal ganglia function in both normal and pathological conditions (Mink, 1996).

The dual pathway rate and the action-selection models represent the most common delineation of the basal ganglia functional anatomy and physiology. Nevertheless, new findings challenge these models. Thus, several primate studies have failed to find the expected significant changes of firing rates in MPTP monkeys. Similarly, biochemical and metabolic studies indicate that GPe activity does not change in Parkinsonism. Whereas the rate model strongly predicts that the enhanced GPi inhibitory output in Parkinsonism should reduce thalamic and motor cortex firing rates, several studies in dopamine-depleted primates have shown no change in spontaneous thalamic and motor cortical firing rates (e.g. Goldberg et al., 2002). Finally, both the dual-pathway rate and the action-selection model predict strong (positive or negative) correlations between pallidal neurons. However, all correlations studies (e.g. Raz et al., 2000; Bar-Gad et al., 2003a) of pallidal neurons in the normal monkey revealed lack of correlation between the spiking activity of these neurons.

The complex anatomy of the basal ganglia and the physiological correlation studies point to a different neural network approach to information processing in the basal ganglia. One example is the *Reinforcement Driven Dimensionality Reduction (RDDR)* model (Bar-Gad et al., 2003b). The RDDR model postulates that the basal ganglia can be modeled as an actor/critic reinforcement learning neuronal network whereas the goal of the system is to maximize the (discount) expectation of all future reinforcements by dynamic modification of behavior. The reinforcement signal is provided by the midbrain dopaminergic (the critic) projections to the striatum, i.e., to the actor networks of the basal ganglia. The dopamine-reinforcement signal represents the mismatch between expectations and reality or the temporal difference (TD) error. In the normal primate the background dopamine activity (5–10 spikes/s) represents a match between the animal's prediction and reality, whereas elevation or suppression of dopaminergic activity represents a situation where reality is better or worse than predictions, respectively (Morris et al., 2004). The actor part of the basal ganglia network (cortex; striatum and STN; GPe and GPi) compress cortical information using reinforcement controlled cellular (Hebbian and anti-Hebbian) learning rules. The ultimate goal of basal ganglia actor is to achieve optimal behavior or policy, e.g., optimal state-action (stimulus-response) associations, by modification of the efficacies of the gigantic matrix of $>10^{13}$ cortico-striatal synapses. This setting of the cortico-striatal functional efficacy leads to optimal connectivity between the sensory and the frontal cortices and optimal behavior which maximize expected future reward. Optimal representation of the state-action matrix in the actor part of the basal ganglia networks is achieved by decorrelation of the spiking activity of the pallidal neurons (output stage of the basal ganglia). The model suggests that the chronic dopamine depletion in the striatum of PD patients is perceived as encoding a continuous state whereas reality is worse than predictions. This lead to modifications in the delicate high-dimensional matrix of efficacies of the cortico-striatal synapses and abnormal synchronization of

the basal ganglia networks (in additions to changes in firing rate and pattern). Furthermore, inappropriate dopamine levels – as, for example during pulsatile dopamine replacement therapy – will cause abnormal random organization of the cortico-striatal network, and eventually would lead to dyskinesia (inappropriate state-action pairing).

Results: Synchronized activity in the basal ganglia

Multiple electrode studies analyzing for correlations of pallidal neurons in the normal monkey revealed lack of correlation between the spiking activity of these neurons (e.g. Raz et al., 2000; Bar-Gad et al., 2003a). These studies have shown an increase in both oscillatory activity and in neuronal correlation of pallidal cells in MPTP primates (Raz et al., 2000; Heimer et al., 2002). This increase in pallidal synchronization has been shown to decrease in response to dopamine replacement treatment (Heimer et al., 2002).

However recent human studies have found oscillatory neuronal correlation only in tremulous patients and raised the hypothesis that the increased neuronal synchronization in Parkinsonism is an epi-phenomenon of the tremor or of independent oscillators with similar frequency (Levy et al., 2000). Human studies are limited by constraints related to recording duration, selected anatomical targets and clinical state of the patients (e.g., most surgical patients have undergone many years of dopamine replacement therapy (DRT) and have already developed dyskinesia). We therefore investigated the role of oscillatory activity and of neuronal correlation throughout the different clinical states of PD in the MPTP primate models of this disease. The tremulous vervet monkey and the rigid-akinetic rhesus monkey were selected to imitate tremulous and non-tremulous subtypes of human patients. We combined multi-electrode recordings with a newly improved tool for spectral analysis of both single cells discharge and interneuron relations (Rivlin et al., 2006) and distinguished between neuronal correlations of oscillatory nature and non-oscillatory correlations. We found that a major fraction of the primate pallidal cells develop both oscillatory and non-oscillatory pair-wise synchronization, following the induction of dopamine depletion and PD clinical signs. Non-oscillatory burst oscillations were mainly found in the GPe, whereas 10 Hz synchronous oscillations were dominant in the GPi. In contrast with the study of human patients, we found oscillatory activity in both the tremulous and the non-tremulous monkey. Clearly, non-oscillatory synchronized burst cannot be the result of a common tremor drive or of independent oscillators with similar frequencies. Moreover, our theoretical analysis of coherence functions revealed that small changes – such as of 0.1% of the basic oscillatory frequency – between the oscillation frequencies of two simulated neurons would result in non-significant coherence value if the recording duration is equal or longer than 10 minutes. Therefore, we can rule out the possibility of false detection of significant coherence in the typical recording duration applied in our primate recordings.

Discussion

The basal ganglia networks can be modeled as an actor/critic reinforcement learning network. The actor networks connect all cortical areas through the basal ganglia with the executive areas of the frontal cortex. The midbrain dopaminergic neurons (the critic) provide a temporal-difference error message to the striatum controlling the efficacies of the cortico-striatal synapses. The distribution of the cortico-striatal efficacies represent the state-action matrix (policy) implanted by basal ganglia. Under normal dopamine influence, the basal ganglia provide an optimal representation of state-action matrix, resulting in non-correlated activity of neurons in

the output structures of the basal ganglia. However, in dopamine depleted subjects the striatum faces an unremitting message of ''reality worse than predictions'' leading to modification of the efficacies of the cortico-striatal synapses and abnormal synchronization of basal ganglia activity. Current DBS methods overcome this probably by imposing a null spatio-temporal firing in the basal ganglia enabling the thalamo-cortical circuits to ignore and compensate for the missing basal ganglia. We therefore suggest that future DBS methods should be directed towards manipulation of the abnormal synchronization of the basal ganglia in PD. This may be achieved by multiple micro-contacts within the DBS targets, rather than the single macro-contact used today.

Acknowledgments

This research was supported in part by a Center of Excellence grant from the Israel Science Foundation (ISF), by the German–Israel BiNational Research Program (GIF) and by the ''Fighting against Parkinson'' foundation of the Netherlands friends of the Hebrew University (HUNA).

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