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Review

Firing dynamics and LFP oscillatory patterns in the dopamine-depleted striatum during maze learning

Ledia F. Hernandez [a,b,*]

[a] McGovern Institute for Brain Research and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[b] Movement Disorders Group, Neurosciences Division, Center for Applied Medical Research and Center for Networked Biomedical Research on Neurodegenerative Diseases (CIBERNED), 31008 Pamplona, Spain

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ABSTRACT

Dopamine loss in Parkinson's disease (PD) is most severe initially in the dorsolateral part of the striatum (DLS) and spread over time to other striatal regions. The DLS is thought to play a critical role for the acquisition of habitual motor behaviors and procedural tasks. During such habit-like, procedural learning, a subset of medium spiny neurons (MSNs) in the DLS develops pronounced activity around the beginning and the end of a T-maze task. Dopaminergic input to the DLS may be required for habit formation in instrumental conditioning tasks, such as the T-maze task. Here I review data characterizing the effects of focal dopamine depletion, mimicking early stages of PD, and L-DOPA therapy on the firing activity of different subpopulations of striatal neurons and on oscillatory patterns in local field potential (LFP) activity during the learning and performance of a conditional maze task.

Contents

Introduction

Parkinson's disease (PD) is characterized by the loss of dopamine-containing neurons in the midbrain, particularly in the ventral tier of the substantia nigra pars compacta (SNpc) that provides dopaminergic innervation to the dorsal striatum [1]. Motor problems, including tremor, bradykinesia, rigidity, postural instability and difficulties with gait, have long been considered as hallmark symptoms of PD [2,3]. Increasingly recognized, however, are the cognitive difficulties that PD patients suffer including an increased risk of depression and cognitive impairments, such as difficulty in learning sequential movements and memory disturbances [4–7].

Experimental work on animal models of PD and clinical studies have identified changes in the physiology of striatal neurons that occur as a result of dopamine depletion [8–10]. Many of the neuronal cell types in the striatum are affected, on one hand, the medium spiny projection neurons (MSNs) that give rise to the direct and indirect pathways of the basal ganglia [11,12]. Among the striatal interneurons affected are the tonically active neurons

* Correspondence to: Movement Disorders Group, Neurosciences Division, Center for Applied Medical Research (CIMA), Avenida Pio XII 55, Pamplona 31008, Spain.
E-mail address: lediafh@unav.es

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(TANs) largely corresponding to the cholinergic interneurons whose learning-dependent activity is altered after dopamine depletion [13], and the fast-spiking parvalbumin-containing interneurons (FSIs) whose synaptic pattern is changed drastically after dopamine removal [14,15].

These population changes have consequences on the overall neuronal activity, and key changes in LFP activity have been identified across the cortico-basal ganglia circuits, both clinically and experimentally. Landmark features in PD are the alterations in the brain oscillations. Increased beta-band activity and diminished gamma-band activity [16,17] have been described in association with this pathology, and these changes may be critical to both motor and cognitive deficits that occur in Parkinsonian patients [16,17].

Dopamine loss in PD occurs first in the dorsolateral striatum (DLS) before other striatal and extrastriatal regions are gradually affected. The DLS is implicated in the acquisition and performance of habits and procedural behaviors [18–20], and dopamine may be required for these learning- and motor-related functions of the DLS [21]. I will review here studies in which the consequences of dopamine depletion and L-DOPA therapy on task-related striatal network activity have been identified. Both the firing activity of the different subclasses of striatal neurons and oscillatory field activity were affected in a very specific manner in an animal model of early PD during the performance and acquisition of a procedural task [22,23].

T-maze task and dopamine depletion

A procedural T-maze task was used in these studies (Fig. 1). The rat was placed at the start of the long arm of the maze where a click will signal the start of the trial and subsequent opening of a start gate. Half-way into the long arm, a photobeam triggered a tone (1 or 8 kHz) to indicate the availability of reward (chocolate sprinkles) at one of the two goal sites. The rats were trained once daily for 40 trials. This task is designed to study the neural basis of procedural learning that starts out as a goal-directed behavior and develops to a habitual/automatic behavior. As this transition happens, the individual actions that together lead to obtaining a reward are "chunked" into an automatically executable set of motor acts, and the behavior becomes independent of outcomes and insensitive to devaluation of reward [24].

Previous findings demonstrated that as rodents learn these conditional maze tasks, the neural activity in the sensorimotor striatum (i.e., DLS) undergoes remarkable changes in patterning

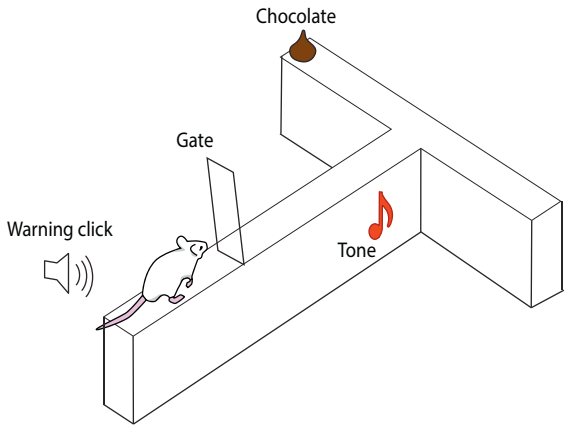

Fig. 1. T-maze task diagram. Rat waits for warning "click" that indicates trial start, followed by gate opening. Half-way through the run an auditory tone (1 or 8 kHz) signals the location of the reward (chocolate sprinkles) at the end of the right or left arm.

[25,26]. At the beginning of training, during the "goal-directed" phase of the task acquisition, moderate population activity of MSNs in the DLS is present throughout the maze run, but, as training progresses, the activity is organized and becomes more predominant at the beginning and end of the maze, and in some cases, also at the maze turns [25–28]. It has also been shown that, in normal rats, LFP oscillatory patterns in the dorsal striatum change during maze learning [29]. These findings served as a basis for detecting changes in neural activity observed in dopamine-depleted rats.

An early stage of PD was mimicked by local infusion of 6-hydroxydopamine (6-OHDA) that induced unilateral dopamine depletion restricted in the DLS. Thus, effects of dopamine depletion were tested by recording neural activity simultaneously in the depleted and non-depleted DLS as rats learned and performed the T-maze task. Subsequently, L-DOPA, the most accepted and widely used medication for PD, was administered daily to well-trained animals in order to assess the effects of this therapy on neuronal firing and LFP activity.

Striatal projection neurons are strongly affected by dopamine depletion and show different learning-related dynamics

The findings reported by Hernandez et al. [23] support the division of MSNs in the sensorimotor striatum into a subpopulation of neurons that fire during the task time and show marked plasticity in their task-related responses (task-activated units), and a second subpopulation that reduce their firing during the active task time relative to their pre-task activity (task-suppressed units) [26]. Such a division of striatal MSNs has been confirmed and extended in a number of studies [27,28,30,31]. The fact that the two subpopulations are intermingled and found in relatively similar proportions (43% and 38%, respectively, in the control striatum) has raised the suggestion that these neuronal groups could correspond to the direct and indirect pathway neurons of the striatum [28,30–32]. In fact, changes in learning-related plasticity could occur specifically in the striatopallidal (indirect) pathway [32], suggesting the possibility that the indirect pathway is involved preferentially in the performance of a task as it becomes habitual. However, this claim remains to be studied in more detail since the "simplistic" dual hypothesis of basal ganglia function should be revisited in the light of new work that reports the co-activation of both striatal pathways during initiation of an action [33].

In the dopamine-depleted striatum, the firing rates of task-activated MSNs were increased, relative to the control striatum, during both pre- and in-task periods throughout training, whereas the firing rates of the task-suppressed units were significantly different from the control side only during certain task periods and/or learning phases. Previous studies reported that striatal MSNs classified as types I and II respond differently to dopamine depletion: neurons in one group (type II) recover their pre-lesion firing rates, whereas neurons in the second population (type I) maintain high spontaneous firing rates [34]. These previous results suggest that the direct and indirect pathway neurons could be affected differentially by dopamine depletion and that the differences that we found between task-activated and task-suppressed MSNs could, themselves, be part of these two main projection subtypes.

Regarding the task-suppressed population, the authors showed that this neuronal group could be divided further into subgroups [23]. In the control striatum, task-suppressed units were classified on the basis of their activity during the runs: they were either tonically suppressed throughout the task (approximately 24% of units) or dynamically suppressed during particular task events (approximately 14% of units). The relative numbers of units in