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Proposal for using time estimation training for the treatment of Parkinson's disease

Silmar Teixeira [a], Francisco Magalhães [a,*], Victor Marinho [a], Bruna Velasques [b], Pedro Ribeiro [a,b]

[a] Brain Mapping and Plasticity Laboratory, Federal University of Piauí (UFPI), Parnaíba, Brazil
[b] Brain Mapping and Sensorimotor Integration, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil

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ABSTRACT

Studies have shown an association between time perception and the basal ganglia and cortical areas, suggesting a role for these regions in the perception of seconds, minutes, and hours. We present the hypothesis that time estimation training tasks may change the modulatory activity of dopamine in the basal ganglia and the cortical areas related to temporal perception. Through this mechanism, the estimated training time interval can promote a compensatory effect on motor and cognitive performance via a dynamic neural adaptation process. We believe that the training will develop a competition between neural pathways involved in the process of time perception, positively affecting the brain pathways related to Parkinson's disease, and thereby minimizing the cognitive and motor deficits caused by the disease.

Introduction

Significant advances have been made in recent decades in rehabilitation strategies for treatment of Parkinson's disease (PD) [1]. The use of tools such as gene therapy, stem cells, intracerebral transplantation of fetal cells associated with neurological rehabilitation [2], swimming exercise (mouse model) [3], pharmacological models and transcranial magnetic stimulation has led to new understanding of central nervous system (CNS) behavior, and subsequently, of patients' treatment [4–8]. These advances stemmed from hypotheses that evolved along with experiments and provided new treatment resources with consequent benefits to patients. Thus, new approaches are extremely viable and must evolve with intense scientific research. In this light, we present the possibility of using time estimation training as a resource to relieve disease signs and symptoms in patients with PD [9] through cortical adaptation and compensatory dopaminergic effects. Our hypothesis is founded on the results of studies that used time estimation tasks in patients with PD to reveal a relationship between the accuracy of time interval estimation and central nervous system structures, particularly dopaminergic regions [10].

Our hypothesis proposes that CNS reorganization depends on the task and timing of the training, enabling learning from experience and recurrence [9,11,12]. Thus, the proposed training will encode changes in neuronal connections distributed in small neural networks [13,14]. This would point to a temporal integration mechanism, resulting from the dynamics of loops and synchronization of neural impulses depending on the timing of temporal events [15]. Therefore, our hypothesis includes a dynamic representation of a biologically plausible framework for neural adaptation, proposing an integrative role of neural networks in the discrimination of time intervals.

Hypothesis

We introduce the hypothesis that time estimation training can decrease the signs, symptoms, and use of medication in patients with PD. The hypothesis is based on three attributes of the CNS (see Fig. 1). The first refers to the ability of the CNS to respond to stimuli with different time interval oscillations in a synchronized and integrated manner, allowing the performance of tasks that require attention, memory, and decision-making [14,16,12]. We believe this occurs even when time lapse is not perceived because the CNS is designed to calculate the time required for motor gestures. For example, in the simple act of reaching for a cup to bring to the mouth, the CNS has already estimated the timing required before the motor gesture is performed, though the CNS can adjust the timing on the basis of the gesture-dependent motor external stimulus received. This is because of an understanding of the role of sensory receptors that interact with the external environment

* Corresponding author at: Av. São Sebastião, 2819, CEP-64202-020, Parnaíba PI, Brazil.
E-mail address: fisiofranciscoxavier@gmail.com (F. Magalhães).

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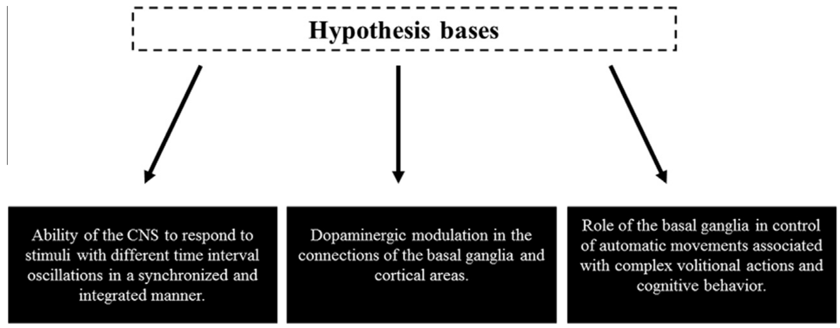

Fig. 1. Diagram: base of the hypothesis.

and with the CNS in interpreting the estimate of time [17]. We believe that this is directly related to the servo-control of parietal cortical function. In other words, in processing motor output, a copy of the motor cortex signals is sent to the parietal lobes, where it is compared with multimodal sensory feedback. If there is any difference between the desired and actual movement, the parietal lobes make corrective adjustments in the next sequence of movements [18]. This servo-driven system may provide a means to understand the influence of the parietal cortex in temporal perception; in addition to relate our hypothesis with CNS structures that are involved in the perception of time.

We relate the second attribute to the effects of dopaminergic modulation in the connections of the basal ganglia and cortical areas, which are important structures in the process timing and speed regulation of the "internal clock" [19]. As seen in rats with lesions in the pars compacta of the substantia nigra in the midbrain [20], the coding deficiencies in time intervals can be improved with the administration of the dopamine (DA) precursor, L-dopa, or by DA agonists [21]. Studies with mice that received prolonged time estimation training tasks observed a typical effect in timing accuracy and synchronization time. On the other hand, untrained mice exhibited disturbances in time control and were dependent on the administration of DA agonists to complete the task more accurately [22]. Thus, the hypothesis of a compensatory effect of dopaminergic transmission through conditioning by time estimation training is feasible because levels of DA inducers may be decreased, thereby assisting in the reestablishment of normal dopamine levels. Furthermore, the training promotes changes in cortical activity due to the increased firing rate of dopaminergic neurons resulting from the repetitive learning. Thus, training facilitates adaptation in the circuits between the cerebral cortex and the basal ganglia, triggering a compensatory dopamine signal that reduces the signs and symptoms of PD.

The third attribute involves the role of the basal ganglia in control of automatic movements associated with complex volitional actions [23] and cognitive behavior [24]. In addition to facilitative and inhibitory actions that the basal ganglia exert on the prefrontal cortex (PFC) premotor and motor areas through the direct and indirect pathways, the basal ganglia are also involved with essential subcortical components for motor and cognitive behavior [25]. Specifically, an imbalance caused by depletion of dopamine D1 and D2 receptors in the putamen can result in undesirable motor behavior in patients with PD [5,7]. Furthermore, the known relationship between the basal ganglia and limbic system contributes to the understanding of emotional behaviors, learning, memory, and motivation in patients with PD [26]. In particular, the amygdaloid complex has been associated with impulsive and emotional responses, in addition to modulating synaptic actions of time synchronization [27]. In this context, the proposed training will influence the activity of the circuits involving the basal ganglia and increase the likelihood of better motor response and cognitive behavior in patients with PD (see Fig. 2).

Hypothesis evaluation

We hypothesize that the neural adaptation caused by time estimation repetitive training will increase the processing of sensory information to the timed responses during training, in addition to increasing the ability to adapt and to maintain and enhance the stability of neural functions. This occurs when there is preferential recruitment of synaptic activity and compensatory dopaminergic modulation [28,29,27]. Dopamine, among many neuromodulators that assist brain activity, integrates neural circuits and induces neural plasticity via its neurotransmitter action. In addition, DA levels have a strong effect on the behavioral phenotype in humans [30–32], as they influence the mechanisms of electrical and biochemical regulation of neuronal function, synaptic transmission, integration and plasticity [33]. Thus, DA is closely associated with time estimation tasks and is related to changes in memory, attention, and decision-making in patients with PD [34–38]. This supports our hypothesis in relation to other treatments performed for the rehabilitation of patients with PD.

This proposal promotes a noninvasive rehabilitation alternative in order to reduce the symptoms of PD by performance of simple time estimation tasks for a certain period of treatment. In addition, time estimation tasks have not yet been used for the purpose described in our proposal; they have only been used to determine how patients with PD estimate time and how their perceptive capacities influence attention, memory, and decision-making. The typical analysis is directed toward measuring cognitive behavior, while our proposal aims to increase neural adaptation to positively affect patients by alleviating the signs and symptoms of PD.

Discussion

The role of DA in time estimation tasks is evidenced by studies that show that stimulation of neuronal firing in dopaminergic cells greatly influences the integration of cortical areas for the interpretation of the time interval [38–40]. This evidence is related to the ability of DA to modulate different cognitive functions, including learning and memory, via three neuronal pathways: nigrostriatal, mesolimbic, and mesocortical [41–43]. In particular, the mesolimbic pathway relates to the reward system [44], and, together with the mesocortical pathway, operates in emotional situations and behavioral states, including those that involve estimating time [43]. On the other hand, the nigrostriatal pathway is involved with motor activity [45]. The compensatory effect of these DA-activated neural pathways is stimulated by cognitive tasks that promote