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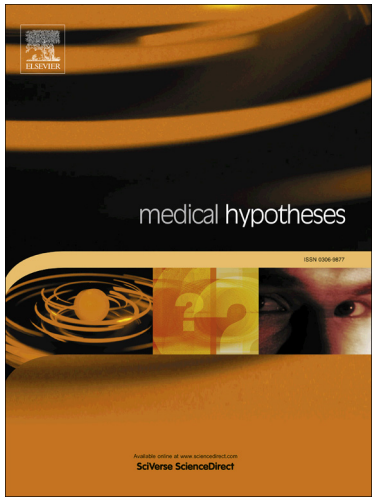

EEG Coherence as a diagnostic tool to measure the initial stages of Parkinson Disease

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Abstract

Although Parkinson Disease was described a long time ago by James Parkinson and several biomarkers were used to predict the symptoms of PD, there is no accepted tool to distinguish the initial stages of this pathology. The present hypothesis discusses the Coherence Function, an Electroencephalography measure which could be used as a simple, and low-cost tool to describe the onset of cardinal signals of PD. Our hypothesis is based on three factors: beta frequency related to movement, motor action over particular

cortical regions, and cortical coupling between cortical areas involved in the execution of voluntary movement. We believe that these factors support our hypothesis pointing out coherence function as an interesting measure to detect initial stages of PD.

Keywords: Parkinson's Disease, Beta Coherence, Cortico-cortical Coupling

INTRODUCTION

Parkinson's Disease (PD) was first discovered in 1817 by a British physician named James Parkinson member of the royal college of surgeons (1). Parkinson published an essay describing, for the first time, the symptoms of PD as "paralysis agitans"(2). Nowadays, it is known that PD is a chronic, degenerative and progressive pathology with an average onset of individuals older than 60 years. However, in rare cases the symptoms can appear much earlier in younger adults. The major cardinal symptoms of PD are akinesia, bradykinesia, rigidity (stiffness of the muscles), tremor, postural and balance instability (3). At the present moment, the PD etiology is not well established, however, some hypothesis and findings support several explanations about the cause of the disease (4). The loss of dopaminergic neurons in the substantia nigra has been point out as the most significant outcomes (5,6). This reduction of the neurotransmitter dopamine produces the primary motors symptoms of PD. This dopamine dysregulation induces a hyperactivity of the indirect tract which is responsible for the nerve impulses flow from the thalamus to the cerebral cortex (7). Even though we

have acquired a variety of knowledge from PD experiments, the parameters to establish a precise diagnosis still remain controversial (8,9). The most effective current method remains to use subsequent follows ups with reassessment of the physical and neurological symptoms in during the initial phase of PD or when Levodopa has less effect, have shown controversial results. In this context, our hypothesis aims to fill a methodologic gap exploring techniques that could give support to detect the initial phase of Parkinson Disease. In particular, our hypothesis is based on three previous neural aspects (beta frequency, neural population region distribution, and coupling between regions) that together would help early diagnoses of Parkinson Disease.

HYPOTHESIS

Among several diagnostic approaches utilized for the management of PD, the electroencephalography (EEG) has been considered less often despite EEG studies performed to patients during the initial phase of this disease (10). EEG was developed in 1924 by Hans Berg and since then, a large amount of knowledge and several EEG variants were discovered correlating mental stages and plastic changes in the cerebral cortex (11). Typically, EEG is a non-invasive electrophysiological monitoring technique to record electrical activity from superficial layers through multiples electrodes distributed across the scalp for a certain period of time (12,13). Due to its excellent temporal resolution, the EEG allows to better assess data related to cortical processing and activity when comparing it to other techniques, such as Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET) scan and Magnetic Resonance Imaging (MRI) (14,15). However, EEG still shows significant limitations associated with its spatial resolution. In order to cope with this disadvantage, contemporary EEG systems were increased to hold more channels i.e., caps built with 512 channels (16).

A variety of parameters can be extracted from EEG signals. One of these parameters, Coherence Function (CF), has been used to assess the relationship among distinct cortical areas. Since CF quantifies cortico-cortical functional connectivity, it can be used during neurophysiological investigations to understand the coupling or the flow of information between these cortical areas observed on a specific frequency range (17). Specifically, CF provides a measure of linear dependence through the frequency domain between a pair of electrodes placed on the scalp (18). In this context, we introduce the

hypothesis that CF can be used to evaluate and distinguish PD patients in the initial phase of the disease. Coherence is such a sensitive measure it can detect changes in the functional and effective cortical interconnections which have occurred in the initial onset of PD (19). In detail, CF mathematically quantifies frequency of synchronized neural pattern resulting from the oscillatory activity of the brain (20). In addition, CF can be interpreted as an estimate of the amplitude and phase between a pair of electrodes through a wide range of frequencies (e.g. delta, theta, alpha, beta and gamma). When this consistency is maintained we can observe an increase in the values of coherence, in the opposite, the lack of this consistency will produce a reduction in the CF value. Our hypothesis focuses on three important factors which would allow CF to distinguish between healthy individuals and PD patients. The first factor is related to beta frequency, which responds to several stimuli, such as: alertness, attention, problem solving, judgment, and decision making essentially located on primary motor cortex and supplementary motor areas (21). In addition, beta frequency has been associated with sensory information, muscle contraction and several changes in movement patterns. The second fact is correlated to distribution regions (i.e., cortical and subcortical areas) involved with motor action, particularly, during volitional or voluntary movements (22). The last factor would explore the possible cortical interconnections during real-time functional motor tasks and observe the coupling between cortical areas through the Coherence Frequency.

EVALUATION OF THE HYPOTHESIS

Even though it is described as a simple motor action, the ability to execute a motor task, such as grasping an object is an extremely complex task for the Central Nervous System (CNS) and the Peripheral Nervous System (PNS). The coordination of

this simple action involves several CNS structures which regulate the fine control of this motor action. This complexity is very obvious when motor tasks are observed in PD cases, the disease impact is seen when the motor system is activated. This motor coordination includes different stages of integration. Some examples of these stages are to identify, to perceive, to size an object, to estimate the trajectory of the movement and to perform the action (23). PD causes a considerable decrease of the neurotransmitter dopamine this occurs on basal ganglia, specifically at substantia nigra (6). This dysregulation produces an instability of communication between several neuroanatomic centers which participate during motor action. We look forward to arguing that CF would be an interesting methodological tool to evaluate and distinguish the coupling between cortical areas in PD patients during initial stages when compared to healthy individuals. Therefore, our hypothesis believing CF will show this unstable communication between several neuroanatomic centers for PD will be present in 3 factors: i) beta frequency; ii) cortical and subcortical distribution; iii) coupling between regions.

First factor- for more than four decades, beta frequency has been associated with a state of engagement evaluated during motor actions. This beta frequency has a range between 12.5 to 30 Hz or can be decomposed into sub-bands, such as: beta 1 (12.5-18.0 Hz); beta 2 (18.5- 25Hz); beta 3 (25.5-30Hz). The beta frequency was chosen due to findings associating the increase of this band on the subthalamic nucleus and its relation with the beginning of akinesia, which is one of the cardinal signals of PD (24). Increased beta activity is observed in motor regions during isotonic muscle contractions, and simultaneously, beta activity suppression is observed before initiating and during a motor action (25). In addition, beta activity increase during an isometric muscle contraction or a movement suppression. Pfurtscheller & Neuper (26) demonstrated an

event-related desynchronization (ERD) which is a power beta decrease in relation to the baseline. This power reduction occurred around 10 Hz, 2 seconds before the beginning of the movement, and following the movement in a continuous form. At the same time, a peak beta activity around 30Hz was observed and correlated with the beginning of the movement. Pfurtscheller & Neuper (26) suggested that the motor planning is followed by an ERD over central regions, which is characterized by a mu activity, i.e., beta showing on motor regions, and also by a 30Hz oscillation onset with a 0.5 seconds duration.

Second factor- Control, regulation, and orientation of a movement involve a complex brain network composed of cortical and subcortical regions, which seems to be not working correctly in PD cases. Each structure of this complex network contributes in a distinct way to the motor execution. Subcortical structures, such as hippocampus, cerebellum, basal ganglia, amygdala, and brainstem play an important role in motor action, however, we won't be discussing them in this paper since their activity cannot be directly recorded by EEG (27,28). The Frontal and Parietal lobe are the most important brain regions involved in motor function. The Primary Motor Cortex (M1) is located immediately anterior to the central sulcus and lies along the precentral gyrys. The M1 is the main cortical area involved in motor function (29). The neural impulses coming from M1 control and regulate muscles of the contralateral sides of the body. All parts of the body are represented in the motor strip and are somatotopically arranged in relation to the body part use and sensibility (30). The clinical evolution of PD produces alterations of several structures, particularly alteration of connection between Putamen and Motor Cortex. In parallel, functional changes are presented on dopaminergic cell projections from midbrain directly to motor regions (31). The motor cortex also includes the Brodmann area 6. This area is located anterior to the M1 and it is divided

into the Premotor Cortex (PMC) and the Supplementary Motor Area (SMA). The PMC assists in posture and is a key cortical area for movement guided by cutaneous and proprioceptive feedback (32,33). The SMA, however, is located anterior to M1 and medial to the PMC. Studies suggested that SMA is involved in motor planning and movement initiation based on previous experiences (34,35). A movement anticipation is one of example where it is possible to observe the engagement of the SMA. In addition, this area is also involved in the planning of complex movements and bilateral coordination activities (36,37). Both SMA and PMC send inputs to M1 and to several brainstem regions (38,39). Besides the Frontal cortex, the Posterior Parietal Cortex also plays an important role in voluntary movements. This region receives several inputs, such as: somatic, proprioceptive, and visual which are used to determine the localization of the body and a target-object in space. The integration of these stimulus creates an internal representation, an internal model of the external environment that can predict motor commands before the engagement of motor areas. PD patients when compared to control demonstrated a diminished functional connectivity between anterior cingulate cortex and parietal cortex, in particular, between the precuneus and the inferior parietal lobule. Changes in the default-mode network (DMN) have been highlighted in PD patients with primary akinetic-rigidity. The Inferior parietal cortex and left posterior cingulate cortex showed decrease activity with DMN when PD patients primary akinetic-rigidity when compared to the control group and the PD with tremor-predominant symptoms (40).

The **third factor** refers to the possibility of exploring the interconnections or coupling between cortical areas through CF during real-time functional motor tasks. The CF allows to obtain an overall notion about how cortical areas are coupling to detect environment parameters and tasks features. For example, grasping an object

recruits several cortical regions to deal with a very complex series of tasks (23,41). The complexity of this action involves not only the M1 role, but the engagement of other motor regions, and parietal regions (42). In this context, instead of analyzing each region separately, it is much more interesting observe the coupling between them. In this way, it would allow us to understand the dynamic interaction of the essential regions engaged during a motor action. In particular, CF would show us the coupling between nearby regions directly involved in the motor action. A simple task, flexion/extension of the index finger is a good example to illustrate how the adjacent regions of the motor cortex participate, increasing or decreasing their coupling during a motor execution (43). When trying to understand the dynamic of a particular patient population it is possible to investigate between brain regions by using CF.

DISCUSSION

Parkinson Disease is a progressive neurodegenerative disorder which affects the mobility of the patient. The progressive loss of the dopaminergic neurons over substantia nigra cause a deeper imbalance of the nigrostriatal pathway which is the efferent connection between the substantia nigra and the corpus striatum (44). The corpus striatum contains high level of acetylcholine and dopamine (45). The cardinal symptoms of PD are attributed to the progressive loss of striatal dopaminergic neurons (46). Our proposed hypothesis is based on the assumption that Beta Coherence will be able to detect under the cerebral cortex supposed alterations that occurred in synapses and neurons over subcortical structures and changes on communication between deep nuclei and superficial sensory and motor regions. Distinct models have had been proposed in order to better understand the PD, such models represent diverse aspect at

several levels: Behavioral, Neurophysiological, Molecular and Cellular (47). CF gives the possibility to explore the linear relation between two signals. This relation expresses the functional connectivity between regions assessed through a frequency range, for example, beta frequency. A higher coherence value demonstrates a higher coupling between regions (48–50). A coupling between cortical areas using CF reflects a compensatory mechanism. This dynamic suggests neuroplasticity modulation associated with progressive and chronic loss of dopamine, in particular, over basal ganglia (51). The evidence pointed out the hypothesis evaluation section supported the idea that EEG technique could be used to evaluate and distinguish PD patients in the initial phase of the disease. For this reason, CF can be an interesting tool to detect changes in scalp activity coming from deeper unstable structures during the initial phase of PD. In addition, the CF was showed to be able to measure the coupling between distinct regions based on the International 10-20 system EEG placement (52). Lastly, this EEG derivation allowed the possibility to explore the degrees of connection between distinct areas that have a main or secondary role in the motor action (53).

CONCLUSION

The present hypothesis points out that Coherence Function is an interesting tool to help diagnose initial stages of Parkinson Disease. In particular, the possibility to detect, through non-invasive scalp electrodes, cortical dynamic imbalances make the CF a relevant tool to study PD. Furthermore, beta frequency sensibility in relation to movement/action provide a supplementary feature to CF. Additionally, the design of a detailed database built on specific statistical principles for confirmation of the pathology

(stage of PD), age range, and sample would be the basic criteria for the use of the measure as a low cost and simple means of diagnosing PD.

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Conflict of Interest Statement:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Captions to illustrations

Figure 1: Schematic illustration of the three study-hypothesis: 1.A) Beta Frequency; 1.B) Cortical areas related to motor action; 1.C) Cortical coupling between regions

Figure 2: Hypothesis basis diagram: Fast Oscillation - Increased beta activity is observed in motor regions during isotonic muscle contractions, and simultaneously, beta activity suppression is observed before initiating and during a motor action; Distributed Cortical Network in Parkinson's Disease – cortical and subcortical areas associated with motor control; Cortico-cortical Coupling – exploring the interconnections or coupling between cortical areas through Coherence Frequency during real-time functional motor actions.

Fig. 1A: Beta Frequency: 13-35 Hz

Fig. 1B: Distributed cortical network for sensorimotor integration

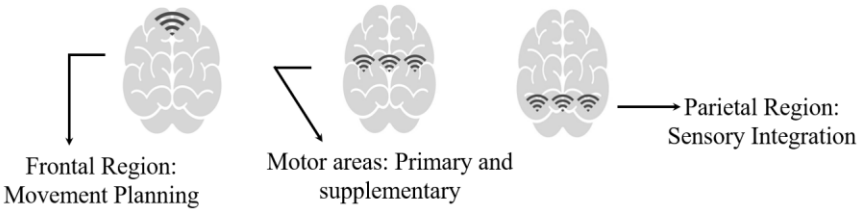

Fig. 1C: Coherence Measure: Coupling between cortical regions