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

Mariana Gongora[a,*], Bruna Velasques[b], Mauricio Cagy[c], Silmar Teixeira[d], Pedro Ribeiro[a]

[a] Brain Mapping and Sensorimotor Integration Laboratory, Institute of Psychiatry of the Federal University of Rio de Janeiro (IPUB/UFRJ), Rio de Janeiro, RJ, Brazil
[b] Neurophysiology and Neuropsychology of Attention, Institute of Psychiatry of the Federal University of Rio de Janeiro (IPUB/UFRJ), Rio de Janeiro e, RJ, Brazil
[c] Biomedical Engineering Program, COPPE, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
[d] Brain Mapping and Functionality Laboratory, Federal University of Piauí, Piauí, Brazil

A B S T R A C T

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.

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

* Corresponding author at: Rua Presidente Pedreira, 153 Apt 901, Ingá, Niterói, Rio de Janeiro CEP 24210-470, Brazil.
E-mail addresses: marianagongora@gmail.com, marianabgongora@gmail.com (M. Gongora).

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 (See Fig. 1).

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 and 30 Hz or can be decomposed into sub-bands, such as: beta 1 (12.5–18.0 Hz); beta 2 (18.5–25 Hz); beta 3 (25.5–30 Hz). 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
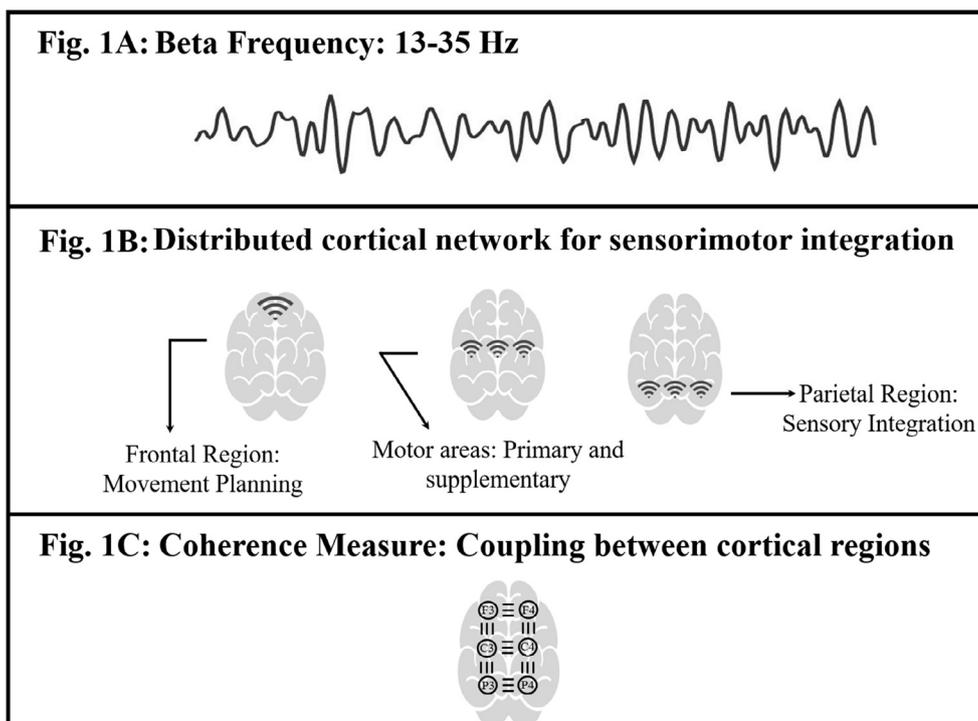

Fig. 1A: Beta Frequency: 13-35 Hz

Fig. 1B: Distributed cortical network for sensorimotor integration

Frontal Region:
Movement Planning

Motor areas: Primary and supplementary

Parietal Region:
Sensory Integration

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

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

reduction occurred around 10 Hz, 2 s before the beginning of the movement, and following the movement in a continuous form. At the same time, a peak beta activity around 30 Hz 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 30 Hz oscillation onset with a 0.5 s 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] (See Fig. 2).

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
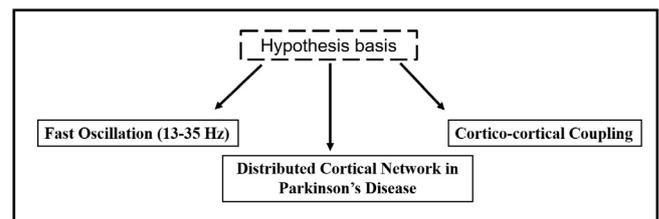
Fig. 2. Hypothesis basis diagram: Fast Oscillation – Increased beta activity is observed in motor regions during isotonic muscle contractions, and simultaneously, beta activity suppression is observed before initiating and during a motor action; Distributed Cortical Network in Parkinson's Disease – cortical 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.

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.

Acknowledgements

Nothing to report.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2018.12.014.

References

[1] Goetz CG. The history of Parkinson's disease: early clinical descriptions and neurological therapies. Cold Spring Harb Perspect Med 2011;1(1).
[2] Lees AJ. Unresolved issues relating to the Shaking Palsy on the celebration of James Parkinson's 250th birthday. Mov Disord 2007;22(SUPPL. 17).
[3] Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. J Neurochem. 2016;139:318–24.
[4] Samii A, Nutt JG, Ransom BR. Parkinson's disease. Lancet 2004;363(9423):1783–93.
[5] Surmeier DJ, Guzman JN, Sanchez-Padilla J, Goldberg JA. What Causes the death of Dopaminergic Neurons in Parkinson's Disease? [Internet]. Progress in Brain Research. Elsevier B.V.; 2010. p. 59–77. 10.1016/S0079-6123(10)83004-3.
[6] Kinoshita KI, Tada Y, Muroi Y, Unno T, Ishii T. Selective loss of dopaminergic neurons in the substantia nigra pars compacta after systemic administration of MPTP facilitates extinction learning. Life Sci [Internet]. Elsevier Inc. 2015;137:28–33. https://doi.org/10.1016/j.lfs.2015.07.017.
[7] Merims D, Giladi N. Dopamine dysregulation syndrome, addiction and behavioral changes in Parkinson's disease. Park Relat Disord. 2008;14(4):273–80.
[8] Tolosa E, Wenning G, Poewe W. The diagnosis of Parkinson's disease. Lancet Neurol. 2006;5(1):75–86.
[9] Obeso JA, Stamelou M, Goetz CG, Poewe W, Lang AE, Weintraub D, et al. Past, present, and future of Parkinson's disease: a special essay on the 200th Anniversary of the Shaking Palsy. Mov Disord. 2017;32(9):1264–310.
[10] B.T. K, J.G. H, H.A. S, E. D-D, V.G.H. E, M.N. S, et al. Quantitative EEG as a predictive biomarker for Parkinson disease dementia. Neurology [Internet]. 2011;77(2):118–24. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L51463123%5Cnhttp://dx.doi.org/10.1212/WNL.0b013e318224af8d.
[11] Cozac VV, Gschwandtner U, Hatz F, Hardmeier M, Rüegg S, Fuhr P. Quantitative EEG and cognitive decline in Parkinson's disease. Parkinsons Dis. 2016;2016(d).
[12] Caviness JN, Hentz JG, Belden CM, Shill HA, Driver-Dunckley ED, Sabbagh MN, et al. Longitudinal EEG changes correlate with cognitive measure deterioration in Parkinson's disease. J Parkinsons Dis. 2015;5(1):117–24.
[13] Gongora M, Bittencourt J, Teixeira S, Basile LF, Pompeu F, Droguett EL, et al. Low-frequency rTMS over the Parieto-frontal network during a sensorimotor task: the role of absolute beta power in the sensorimotor integration. Neurosci Lett. Elsevier Ireland Ltd 2016;611:1–5.
[14] Lopes da Silva F. EEG and MEG: Relevance to Neuroscience. Neuron [Internet]. Elsevier Inc.; 2013. p. 1112–28. 10.1016/j.neuron.2013.10.017.
[15] Burle B, Spieser L, Roger C, Casini L, Hasbroucq T, Vidal F. Spatial and temporal resolutions of EEG: is it really black and white? A scalp current density view. Int J Psychophysiol [Internet]. Elsevier BV 2015;97(3):210–20. https://doi.org/10.1016/j.ijpsycho.2015.05.004.
[16] Srinivasan R. Spatial structure of the human alpha rhythm: global correlation in adults and local correlation in children. Clin Neurophysiol. 1999;110(8):1351–62.
[17] Andres FG, Mima T, Schulman AE, Dichgans J, Hallett M, Gerloff C. Functional coupling of human cortical sensorimotor areas during bimanual skill acquisition [In Process Citation]. Brain 1999;122(Pt 5):855–70.
[18] Bowyer SM. Coherence a measure of the brain networks: past and present. Neuropsychiatr Electrophysiol [Internet]. Neuropsychiatric. Electrophysiology 2016;2(1). https://doi.org/10.1186/s40810-015-0015-7.
[19] de Solages C, Hill BC, Koop MM, Henderson JM. Bronte-Stewart H. Bilateral symmetry and coherence of subthalamic nuclei beta band activity in Parkinson's disease. Exp Neurol [Internet]. Elsevier Inc. 2010;221(1):260–6. https://doi.org/10.1016/j.expneurol.2009.11.012.

[20] Srinivasan R, Nunez PL, Silberstein RB. Spatial filtering and neocortical dynamics: estimates of EEG coherence. IEEE Trans Biomed Eng 1998;45(7):814–26.
[21] Gola M, Magnuski M, Szumska I, Wróbel A. EEG beta band activity is related to attention and attentional deficits in the visual performance of elderly subjects. Int J Psychophysiol. 2013;89(3):334–41.
[22] Matsuzaka Y, Aizawa H, Tanji J. A motor area rostral to the supplementary motor area (presupplementary motor area) in the monkey: neuronal activity during a learned motor task. J Neurophysiol 1992;68(3):653–62.
[23] Nelissen K, Fiave PA, Vanduffel W. Decoding grasping movements from the parieto-frontal reaching circuit in the nonhuman primate. Cereb Cortex [Internet] 2017:1–15. https://academic.oup.com/cercor/article/3003198/Decoding.
[24] Kuhn AA, Doyle L, Pogosyan A, Yarrow K, Kupsch A, Schneider G-H, et al. Modulation of beta oscillations in the subthalamic area during motor imagery in Parkinson's disease. Brain England 2006 Mar;129(Pt 3):695–706.
[25] Alegre M, Labarga A, Gurtubay IG, Iriarte J, Malanda A, Artieda J. Beta electro-encephalograph changes during passive movements: sensory afferences contribute to beta event-related desynchronization in humans. Neurosci Lett Ireland 2002;331(1):29–32.
[26] Pfurtscheller G, Neuper C. Simultaneous EEG 10 Hz desynchronization and 40 Hz synchronization during finger movements. Neuroreport England 1992;3(12):1057–60.
[27] Bimbi M, Festante F, Coudé G, Vanderwert RE, Fox NA, Ferrari PF. Simultaneous scalp recorded EEG and local field potentials from monkey ventral premotor cortex during action observation and execution reveals the contribution of mirror and motor neurons to the mu-rhythm. Neuroimage 2018;175(March):22–31.
[28] Seo R, Stocco A, Prat CS. The bilingual language network: differential involvement of anterior cingulate, basal ganglia and prefrontal cortex in preparation, monitoring, and execution. Neuroimage [Internet]. Elsevier Ltd 2018;174:44–56. https://doi.org/10.1016/j.neuroimage.2018.02.010.
[29] Kumru H, Albu S, Pelayo R, Rothwell J, Opisso E, Leon D, et al. Motor cortex plasticity during unilateral finger movement with mirror visual feedback. Neural Plast 2016;2016:1–9.
[30] Di Pino G, Maravita A, Zollo L, Guglielmelli E, Di Lazzaro V. Augmentation-related brain plasticity Available from Front Syst Neurosci [Internet] 2014;8(June):1–22http://journal.frontiersin.org/article/10.3389/fnsys.2014.00109/abstract.
[31] Obeso JA, Rodríguez-Oroz MC, Benitez-Temino B, Blesa FJ, Guridi J, Marin C, et al. Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease. Mov Disord 2008;23(SUPPL. 3):548–59.
[32] Biagi L, Cioni G, Fogassi L, Guzzetta A, Sgandurra G, Tosetti M. Action observation network in childhood: a comparative fMRI study with adults. Dev Sci 2016;19(6):1075–86.
[33] Kantak SS, Stinear JW, Buch ER, Cohen LG. Rewiring the brain: Potential role of the premotor cortex in motor control, learning, and recovery of function following brain injury. Neurorehabil Neural Repair 2012;26(3):282–92.
[34] Alves-Pinto A, Turova V, Blumenstein T, Hantuschke C, Lampe R. Implicit learning of a finger motor sequence by patients with cerebral palsy after neurofeedback. Appl Psychophysiol Biofeedback Springer, US 2017;42(1):27–37.
[35] Caligiore D, Mustile M, Spalletta G, Baldassarre G. Action observation and motor imagery for rehabilitation in Parkinson's disease: a systematic review and an integrative hypothesis. Neurosci Biobehav Rev [Internet]. Elsevier Ltd 2017;72:210–22. https://doi.org/10.1016/j.neubiorev.2016.11.005.
[36] Eaves DL, Riach M, Holmes PS, Wright DJ. Motor imagery during action observation: a brief review of evidence, theory and future research opportunities. Front Neurosci 2016;10:1–10.
[37] Butler JS, Fearon C, Killane I, Waechter SM, Reilly RB, Lynch T. Motor preparation rather than decision-making differentiates Parkinson's disease patients with and without freezing of gait. Clin Neurophysiol Int Federation Clin Neurophysiol 2017;128(3):463–71.
[38] Shadmehr R. Learning to predict and control the physics of our movements Available from J Neurosci [Internet]. 2017;37(7):1663–71http://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.1675-16.2016.
[39] Sébille SB, Belaid H, Philippe AC, André A, Lau B, François C, et al. Anatomical evidence for functional diversity in the mesencephalic locomotor region of primates. Neuroimage. Elsevier 2017(September 2016):14766–78.
[40] Karunanayaka PR, Lee EY, Lewis MM, Sen S, Eslinger PJ, Yang QX, et al. Default mode network differences between rigidity- and tremor-predominant Parkinson's disease. Cortex [Internet]. Elsevier Ltd 2016;81:239–50. https://doi.org/10.1016/j.cortex.2016.04.021.
[41] Gerbella M, Rozzi S, Rizzolatti G. The extended object-grasping network. Exp Brain Res. Springer, Berlin Heidelberg 2017;235(10):2903–16.
[42] Säfström D, Domellöf E. Brain activations supporting linking of action phases in a sequential manual task. Neuroimage [Internet]. Elsevier Inc. 2018;172:608–19. https://doi.org/10.1016/j.neuroimage.2018.02.014.
[43] Brauns I, Teixeira S, Velasques B, Bittencourt J, Machado S, Cagy M, et al. Changes in the theta band coherence during motor task after hand immobilization. Int Arch Med [Internet] 2014;7(1):51. http://www.intarchmed.com/content/7/1/51.
[44] Rodriguez-Oroz MC, Jahanshahi M, Krack P, Litvan I, Macias R, Bezard E, et al. Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms. Lancet Neurol [Internet]. Elsevier Ltd 2009;8(12):1128–39. https://doi.org/10.1016/S1474-4422(09)70293-5.
[45] Aosaki T, Miura M, Suzuki T, Nishimura K, Masuda M. Acetylcholine-dopamine balance hypothesis in the striatum: an update. Geriatr Gerontol Int 2010;10(SUPPL. 1).
[46] DeMaagd G, Philip A. Parkinson's disease and its management: part 1: disease entity, risk factors, pathophysiology, clinical presentation, and diagnosis Available

from P T [Internet] 2015;40(8):504–32http://www.ncbi.nlm.nih.gov/pubmed/26236139%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4517533.

[47] Falkenburger BH, Saridaki T, Dinter E. Cellular models for Parkinson's disease. J Neurochem. England 2016;139(Suppl):121–30.

[48] Andrew C, Pfurtscheller G. Event-related coherence as a tool for studying dynamic interaction of brain regions. Electroencephalogr Clin Neurophysiol 1996;98(2):144–8.

[49] Gerloff C, Andres FG. Bimanual coordination and interhemispheric interaction. Acta Psychol (Amst) [Internet] 2002;110(2–3):161–86. http://linkinghub.elsevier.com/retrieve/pii/S000169180200032X.

[50] Weiss S, Mueller HM. The contribution of EEG coherence to the investigation of language. Brain Lang 2003;85(2):325–43.

[51] Silberstein P, Pogosyan A, Kuhn AA, Hotton G, Tisch S, Kupsch A, et al. Cortico-cortical coupling in Parkinson's disease and its modulation by therapy. Brain England 2005 Jun;128(Pt 6):1277–91.

[52] Teramoto H, Morita A, Ninomiya S, Akimoto T, Shiota H, Kamei S. Relation between resting state front-parietal EEG coherence and executive function in Parkinson's disease. Biomed Res Int Hindawi Publ Corp 2016;2016.

[53] Rosenberg-Katz K, Herman T, Jacob Y, Kliper E, Giladi N, Hausdorff JM. Subcortical volumes differ in Parkinson's Disease motor subtypes: new insights into the pathophysiology of disparate symptoms Available from Front Hum Neurosci [Internet] 2016;10(July):1–9http://journal.frontiersin.org/Article/10.3389/fnhum.2016.00356/abstract.