PARKINSON'S DISEASE AND OSCILLATORY BRAIN RHYTHMS: EXPLORING THE PREDICTIVE PROPERTIES OF ALPHA BAND OSCILLATIONS IN MOTOR AND COGNITIVE PROCESSES.

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder linked to the neurophysiological changes in dopaminergic neurons of basal ganglia (BG). Multiple studies have shown the integrative role of BG in sensory and motor processes and confirmed the involvement of these nuclei in cognitive domains such as processing multisensory information, habit learning, coordination, balance, posture and gait. These studies also took advantage of the frequency-specific oscillatory brain rhythms (OBRs) detected on the electroencephalogram (EEG) as potential biomarkers, signaling change in various neural networks. The periodicity and temporal nature of the OBRs are well-known phenomena that are thought to govern time-dependent processes in BG, Cerebellum and the frontal cortices. EEG studies have shown that neural oscillations are not only generated in the absence of external influence but could change their synchronicity as the exogenous cues change. This bidirectional property is a vital feature of our day to day interaction with the environment which helps us change behaviour accordingly and plays an important role in inter/intra neural network communication, motor and cognitive processes. Here we examined the oscillatory changes before and after amelioration of motor and non-motor symptoms, after pharmacotherapy and neurorehabilitation interventions and provided evidence for the putative role of these frequency-specific OBRs as the potential biomarkers in order to quantify network-dependent cognitive and motor changes in PD, and to utilize these biomarkers to develop targeted treatment options for this patient population.

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Abbreviations

Ach: Acetylcholine
BG: Basal Ganglia
CNS: central Nervous System
CSF: Cerebral Spinal Fluid
DA: Dopamine
DBS: Deep Brain Stimulation
DWP: Dance With Parkinson's
EEG: Electroencephalogram
EMG: Electromyogram
EOG: Electro-Oculography
EPSP: Excitatory Postsynaptic Potentials
FPM: Firing Pattern Model of basal ganglia
FRM: Firing Rate Model of basal ganglia
GABA: Gamma-Aminobutyric Acid
Glu: Glutamate
GPe: Globus Pallidus Externa
GPi: Globus Pallidus Interna
Hz: Hertz
IPSP: Inhibitory Postsynaptic Potentials
L-dopa: L-3,4-dihydroxyphenylalanine
LC: Locus Coeruleus
LFP: Local Field Potential
MDS: Movement Disorder Society
MPTP: N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine
MSQ: Mayo Sleep Questionnaire
OBR: Oscillatory Brain Rhythm
PD: Parkinson's Disease
PET: Positron Emission Tomography
PNS: Peripheral Nervous System
PPN: pedunculopontine nucleus
PSG: Polysomnography
PwPD: Patients with Parkinson's Disease
RBD: Rapid Eye Movement Sleep Behaviour Disorder
SMA: Supplementary Motor Cortex
SN: Substantia Nigra
SNc: Substantia Nigra Pars Compacta
SNr: Substantia Nigra Pars Reticulata
TMT: Trail Making Test

UPDRS-III: Unified Parkinson's Diseases Rating Scale part three (motor)
VTA: Ventral Tegmental Area
WCST: Wisconsin Card Sorting Test
WF: Word Fluency

1.1 Overview and Objectives

Parkinson's disease (PD) is a neurodegenerative disorder that is caused by disruption in the dopaminergic pathways of basal ganglia (BG) (Bergman & Deuschl, 2002). PD is the second most common neurodegenerative disorder after Alzheimer's disease, and there are over 10 million patients with PD (PwPD) worldwide. In the united states alone 60,000 new cases are diagnosed each year, and 6600 new cases of PD are diagnosed yearly in Canada (Tysnes & Storstein, 2017).

Since the mid 1950's pharmacotherapeutic agents such as L-dopa have shown promising results to improve the motor symptoms and the quality of lives of PwPD, but the prevalence of the disease has increased as the aging population live longer (Goetz, 2011). This disease not only threatens the independence of PwPD but also negatively affects caregivers and exhausts healthcare dollars. According to statistics Canada only in 2016 the total out-of-pocket cost from caregivers of PwPD was estimated to be around $249.0 million dollars, and tax-payers funded over $ 10.4 billion for the care of neurodegenerative disorders where PD comprised 40% of this population, and despite advancements in medical sciences and research, PD remains incurable.

In the past few decades multiple explanatory models have been proposed and rejected (Tysnes & Storstein, 2017). Although there is little doubt that the dopaminergic neurons of the substantia nigra (SN) are the main culprit in the pathophysiology of PD, the exact mechanism of multi-network failure in PD, and the progressive nature of the disease remain unexplored. This project focuses on providing a multifaceted review of literature and explores the current research in PD, while examining the potential biomarker properties of alpha frequency in this patient population.

Objectives:

1) To provide a multidisciplinary review from basic pathophysiology to the current research in PD.
2) To explore and review the current models of the BG dysfunction in PD (firing rate model vs. firing pattern model).
3) To examine the role of dopamine replacement therapy and amelioration of motor symptoms followed by changes in the frequency-dependent OBRs.
4) To propose a model to study and validate the link between motor behaviour and cognition using the OBRs as the biomarkers of change in the sound-induced flash illusion paradigm.

1.2 BASAL GANGLIA

The name "basal ganglia" is a misnomer, because ganglia are the cell bodies in the peripheral nervous system (PNS), but nuclei are the cell bodies in the central nervous system (CNS) (Bergman & Deuschl, 2002). These nuclei are located subcortically within each hemisphere in telencephalon at the base of the forebrain, highly specialized to function as a system to integrate motor and sensory in/outputs (Nambu, Tachibana, & Chiken, 2015). BG comprise 4 main components as shown in figure 1: 1) The striatum: the ventral striatum which has shown to be involved in reward and behaviour, the dorsal aspect of striatum consists of caudate nucleus and putamen that are separated by the internal capsule, and the ventral striatum which in recent studies include nucleus accumbens as well as the olfactory tubercle. 2) The pallidum: the medial or internus globus pallidus (GPi) and the lateral or externus globus pallidus (GPe). 3) The subthalamic nucleus (STN) which is the only nucleus in the BG that has an excitatory role, utilizing glutamate in order to stimulate the GPi. 4) The substantia nigra pars

compacta (SNc) and pars reticulata (SNr) that have shown to play a role in the production of dopamine (DA), and work in conjunction with the GPi in order to inhibit the thalamus (Rivlin-Etzion et al., 2006).

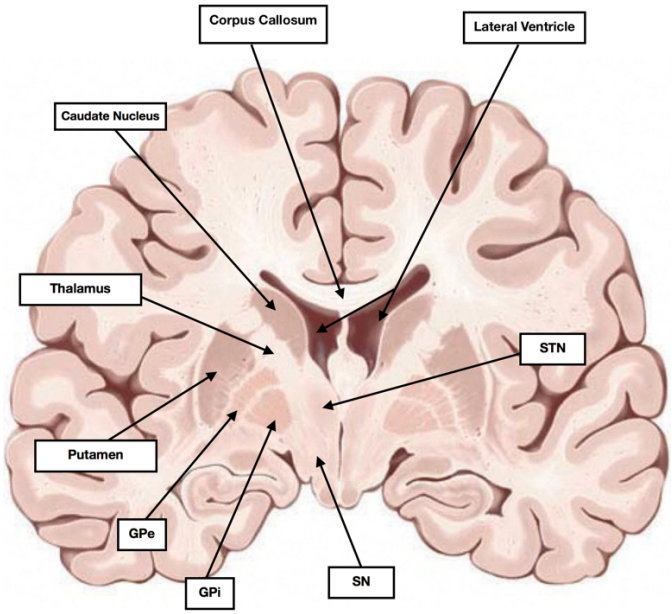

***Figure 1.1*:** A coronal view of the brain and the approximate locations of multi components of the BG. (picture credit: www.strokesciences.com)

The BG also consist of 4 main circuits that begin in the cerebral cortex and loop through the BG via thalamus. The motor, cognitive, limbic and oculomotor loops, each contribute to multiple aspects of motor behaviour. The motor loop begins in the sensory and motor cortices and loops through the striatum, thalamus and the supplementary motor cortex (SMA), and contributes to the motor control, motor learning, habit learning, postural balance and coordination of movement. There are two important pathways involved in this circuitry, the direct and indirect pathways. These pathways modulate the volitional control of movement and control the strength and intensity of movement production via excitation or inhibition of the motor cortex through the striatum (Figure 2). Both direct and indirect pathways utilize neurotransmitters such as dopamine

(DA) via D1 receptors and glutamate (Glu) to activate the excitatory clusters of neurons in the striatum, and neurotransmitters such as gamma-Aminobutyric acid (GABA) and DA via D2 receptors to inhibit or dampen the excitation of the motor cortex, mainly the SMA (Avanzino et al., 2016). During movement, a healthy SNr remains active and is in favor of the direct pathway (abnormal SNr causes PD). The activation of the direct pathway is specifically important for the SMA, because the excitatory neural signals pass through this area milliseconds prior to the production of a movement by the motor cortex, activation of the SMA is necessary in motor planning and the coordination of movement (Figure 2-a). In contrast, the indirect pathway reduces the GABAergic inhibition of the thalamus which in turn dampens or halts the excitation of the SMA and the motor cortex, leading to reduced motor production (Figure 2-b). This intricate excitatory/inhibitory mechanism is the key reason for the production of smooth and coordinated movements and is the main culprit in the pathogenesis of PD and other movement disorders (Caligiore et al., 2016).

The cognitive loop of the BG plays an important role in motor learning, neuroimaging studies have shown the increased activity of the caudate nucleus, putamen, globus pallidus externus (GPe), and the thalamus while performing a novel motor task with the contralateral hand. The projections of this loop begin in the prefrontal cortex, premotor cortex, and loops through the basal ganglia and the thalamus while integrating sensory and motor information from both peripheral and the central nervous systems. After multiple trials and practice, when mastery level is achieved, the cognitive loop is offline, and the motor loop is responsible for the automation of the previously learned motor tasks. Dysfunction in this circuitry or its components is the main reason for impairment in executive dysfunction, motor learning, motor planning and carryover of the benefits of neurorehabilitation in patients with neurodegenerative disorders (Liu, Chan, & Stoessl, 2017).

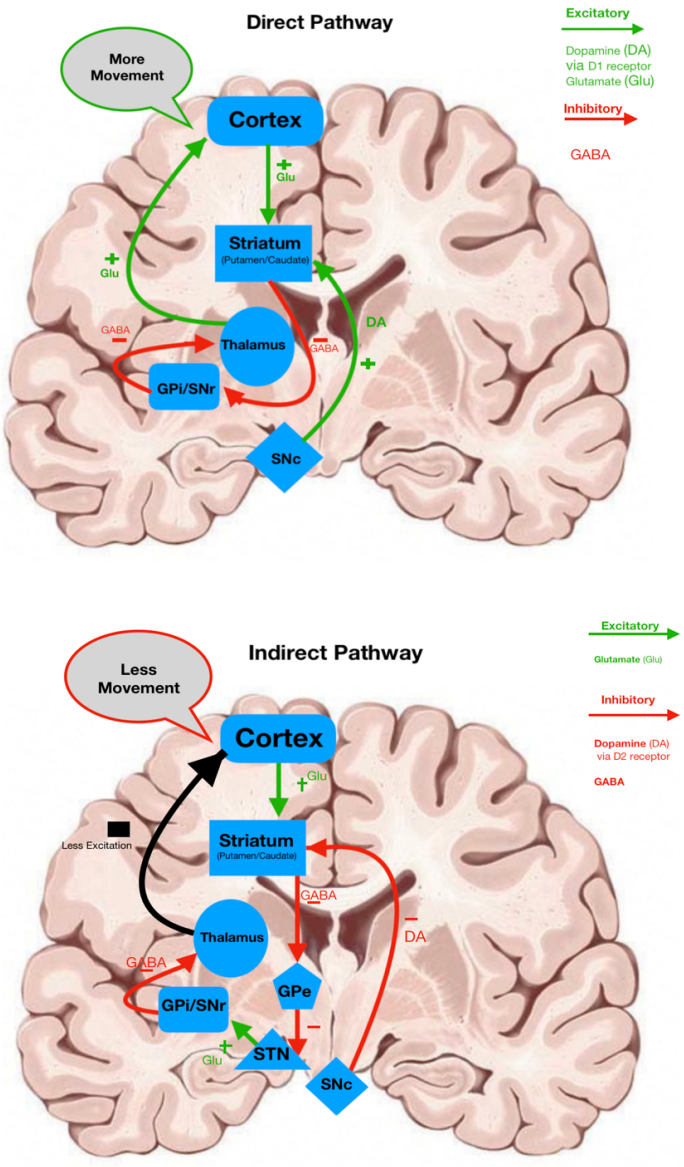

***Figure 1.2*:** The circuitry of BG A) Direct pathway (mainly excitatory): Promotes movement by increasing excitation of the SMA and the motor cortex. B) Indirect pathway (mainly inhibitory): for suppression of unwanted movement GPe and STN become involved and dampen the GABAergic pathways from the GPi/SNr to thalamus and reduce the excitation of the SMA and motor cortex. (picture credit: www.strokesciences.com)

The third main circuitry of the BG is the limbic loop, where nucleus accumbens (NA) located ventrally on the striatum (neighboring the olfactory tubercle), and inferior

prefrontal cortex, loops through the thalamus. It has been speculated that motor involvement of the expression of emotions is processed within this loop, hence the mask-like faces and lack of spontaneous gesture in PwPD. It is also important to note that one of the prodromal features of PD is olfactory dysfunction (Anosmia), which perhaps is due to the disruptions in the olfactory tubercle adjacent to NA (Caligiore et al., 2016).

And the fourth, the oculomotor loop, starts its projections in the frontal eye field and posterior parietal cortex, loops through the caudate, SNr, and back to the frontal eye field through the thalamus. In this loop SNr plays an inhibitory role, where the GABAergic projections to the superior colliculus responsible for controlling volitional saccadic eye movements. Deliberate saccadic movements activate the oculomotor loop and disinhibits the superior colliculus, and eyeballs can reach a speed up to 80 km/h while flicking toward the target. Due to the SN dysfunction, and lack of disinhibition in the superior colliculus, oculomotor hypokinesia is observed in PwPD in experiments involving voluntary eye movements toward a target in the peripheral visual filed (Caligiore et al., 2016).

Motor Loop	**Cognitive Loop**	**Limbic Loop**	**Oculomotor Loop**
- Sensorimotor Cortex - Striatum - Thalamus - SMA	- Caudate - Prefrontal Cortex - GPe - Thalamus	- Inferior prefrontal cortex - NA - GPi - Thalamus	- Frontal eye field - Posterior parietal cortex - Caudate - SNr - Thalamus
Function: coordination of movement, and scaling the strength of muscle contractions.	**Function:** Novel motor actions, and motor learning.	**Function:** Motor expression of emotions, reward-based motor learning.	**Function:** Eyeballs flick to the target at maximum speed. Normal anti saccade
Dysfunction: Hypokinesia and lack of coordinated movements due to weakened SMA.	**Dysfunction:** Inability in motor error correction, lack of carryover in neurorehabilitation.	**Dysfunction:** Mask facies, lack of spontaneous gestures. *The olfactory tubercles adjacent to NA may cause anosmia (a prodromal symptom of PD)	**Dysfunction:** Ocular hypokinesia, slow prosaccade, and impaired antisaccade.

Table 1: The 4 loops of BG.

1.3 A BRIEF HISTORY AND THE PATHOPHYSIOLOGY OF PD

Although James Parkinson is accounted to be the first who described paralysis agitans or shaking palsy as a neurological syndrome, this disease was described centuries earlier in ancient Indian and Chinese texts around 1000 BC. PD is thought to be an irreversible and progressive neurodegenerative disorder that affects approximately 18 per 100,000 individuals worldwide. It has long been proposed that the degeneration of dopaminergic neurons in substantia nigra (SN) is the main cause of PD, and despite advancements in medical and surgical management of PD, the progressive nature of this neurodegenerative disorder remains incurable. Until 1959 supportive care was the sole treatment option for patients with PD (PwPD) and it was Hornykiewicz who discovered the application of L-dopa for managing the symptoms of PD (Goetz, 2011).

Amongst causes of PD, environmental toxins, hereditary genetic mutations, vascular diseases, and trauma have been attributed to the initial onset of the disease, but up to 80% of the PD cases are caused by an unknown origin or idiopathic parkinsonism (Bergman & Deuschl, 2002).

1.4 NIGROSTRIATAL PATHWAY IN PD

As mentioned earlier, dysfunctions in the BG can produce a wide array of neurological signs and symptoms. In hypokinetic disorders such as PD, faulty dopaminergic nigrostriatal pathways in SNc where modulation of the direct and indirect pathways occurs, causes a failure in maintenance of an adequate balance between the excitatory and inhibitory processes, leading to motor and non-motor symptoms in PwPD (Nambu, Tachibana, & Chiken, 2015).

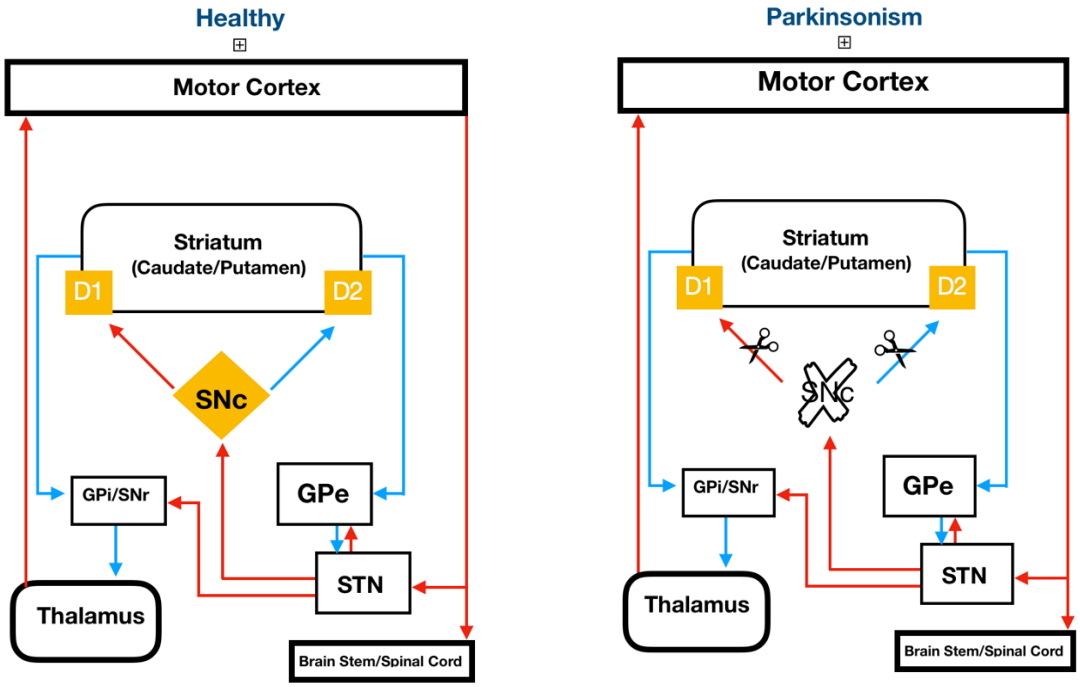

Figure 1.3: Changes in the BG pathways of healthy individuals leading to PD.

The mechanism of neurodegeneration in the dopaminergic neurons of the SNc has shown to be caused by the toxin effects of a mutant protein that signals the activation of the programmed cell death (Apoptosis) and oxidative stress (Liu, Chan, & Stoessl, 2017). Alpha-synuclein (α-synuclein) is the main mutant protein with neurotoxin properties involved in the pathogenesis of PD, which is detectable in post-mortem microscopy of the brain tissue of PwPD. This mutation is thought to occur due to genetic, environmental toxin exposure, or cerebrovascular diseases such as stroke or trauma, though lack of general consensus on how this mutation is triggered is the main reason most PD cases are called idiopathic. It is important to note, that although α-synuclein remains the usual suspect, in the recent years, multiple hypotheses such as Braak's staging of PD have emerged and proven inadequate to explain the root cause of formation and accumulation of this protein in the brain (Braak & Del Tredici, 2017).

1.5 NEUROCHEMICAL IMBALANCE IN PD

Neural signaling is mainly achieved through the synthesis of neurotransmitters that are released in the synaptic cleft via presynaptic axonal terminals, where they act on the postsynaptic target neurons or other cells such as gland and muscle cells. The total number of neurotransmitters are not known, but it is estimated that there are over 100 neurotransmitters in the CNS and the peripheral nervous system (PNS) (Avery & Krichmar, 2017). Neurotransmitters play a pivotal role in modulation of neural assemblies and behaviour, and imbalances in their levels could radically influence the equilibrium of the nervous system leading to pathology (Bergman & Deuschl, 2002).

As mentioned earlier the dysfunction of the dopaminergic nigrostriatal pathways in the SNc depletes the levels of DA, and therefore impedes DA-dependent processes in the CNS. Although lack of consensus among experimental studies makes it difficult to determine the primary location of DA synthesis, literature suggests that both the SNc and the ventral tegmental area (VTA) are highly involved in the production of DA. It is known that each neurotransmitter signals a different process in a different network, and imbalances in the levels of one neurotransmitter can affect the functions of the rest, this is especially evident in neurodegenerative disorders such as PD, where a wide range of neurochemical imbalances is detected in the CNS of PwPD (Kenemans & Kähkönen, 2011).

Studies in PD suggest, that depletions in DA levels in the dopaminergic pathways, and serotonin in the serotonergic pathways originating from the raphe nucleus in the brainstem projecting into the forebrain (striatum, hippocampus, amygdala and cortex),

noradrenaline in the noradrenergic pathways originating both from the locus coeruleus (LC), and the acetylcholine (Ach) in the cholinergic pathways originating from the basal forebrain , are the main causes of multi-system failure observed in PwPD, and could explain the long list of motor and non-motor symptoms of PD (Avery & Krichmar, 2017).

1.6 PRODROMAL AND CLINICAL MOTOR AND NON-MOTOR SYMPTOMS

According to the latest movement disorder society (MDS) guidelines, PD symptoms could be divided in prodromal (up to a decade before the emergence of the motor symptoms), early clinical symptoms (0-2 years as the symptoms progress), and late clinical symptoms (2-10 years or more). In clinical neurology, most prodromal symptoms of PD are deemed to be non-specific, epidemiological studies have developed a statistical repository of likelihood ratios that can improve the specificity and the predictive value of these early signs and symptoms (Goldman & Postuma, 2014).

Looking at the signs and symptoms of PD, it is evident that dysfunction in the dopaminergic nigrostriatal pathways could not explain all the symptoms. The current evidence suggests that PD is a multi-system failure, where noradrenergic and serotonergic pathways in the brainstem regions as well as cholinergic pathways of the frontal lobe also are involved as the disease progresses (Dickson, 2018).

Polysomnography studies (PSG) - a form of multi-parametric sleep study- have demonstrated, that years before the diagnosis of PD, around 58% of PwPD were diagnosed with the rapid eye movement sleep behaviour disorder (RBD). Olfactory dysfunctions such as anosmia (loss of sense of smell) or hyposmia (decreased sense of

smell), autonomic dysfunctions such as orthostatic hypotension, and constipation (parasympathetic nervous system and the vagus nerve) years before the definitive diagnosis of clinical PD. It is the constellation of these non-specific (but sensitive) prodromal symptoms that contributes to their predicative power (Goldman & Postuma, 2014).

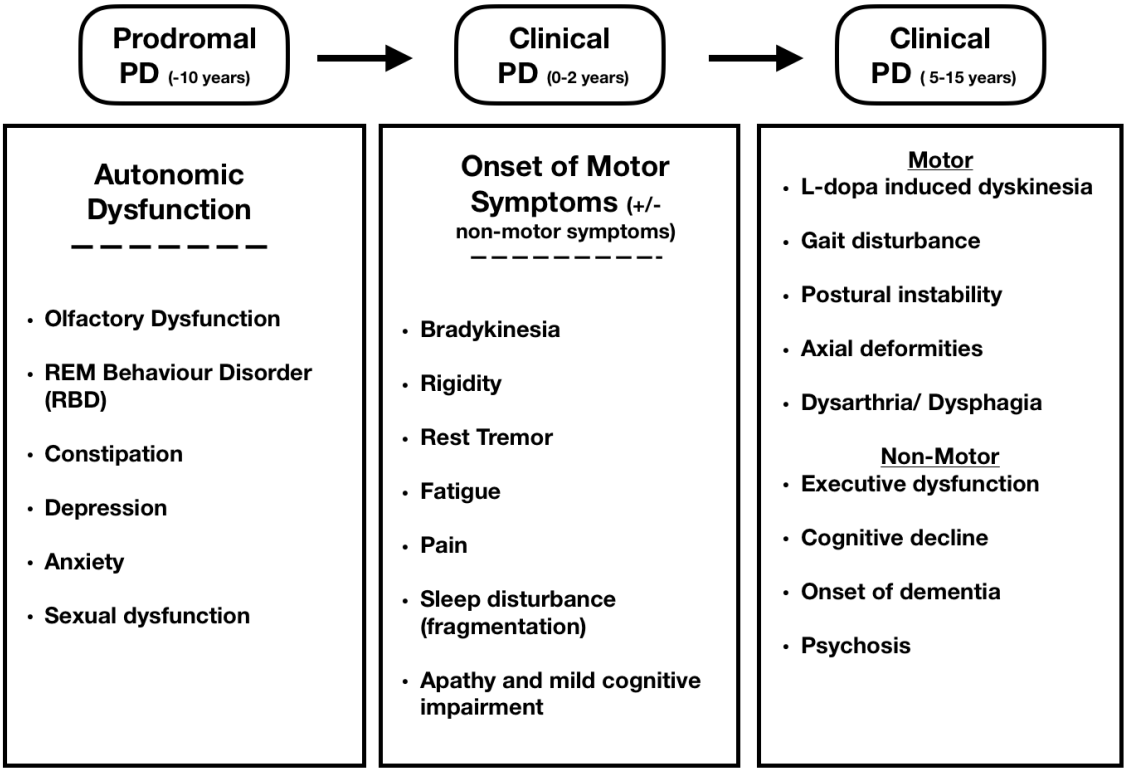

Table 2: Symptoms of PD: Signs and symptoms of PD appears years before the onset of the disease.

1.7 DIOGNOSIS

In order to diagnose PD in the clinical setting, routine laboratory tests and usual neuroimaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) have shown to be of no use, because in the absence of cerebrovascular disease and neoplasm these studies are generally normal. History and physical examination on the other hand, have proven to be of high diagnostic values. In the research setting, researchers take advantage of the properties of the radiopharmaceutical 6-[^{18}F]- fluorodopamine (F-dopa) which is taken up by dopaminergic neurons in the SN and metabolized to 6-[^{18}F]- fluorodopamine (Brittain & Brown, 2014). Using positron emission tomography (PET) scans, the reduced F-dopa uptake in dopaminergic axonal terminals in the striatum (putamen and caudate) signals the presence of pathology. In PD research the use of single-photon emission CT (SPECT) is also a common approach to study the underlying dopamine pathways using radioligands that label the DA transporter on the striatal nerve terminals. It is important to note that these technologies are not usually available in clinical setting and their use is mainly limited to research (Gaetz, MacDonald, Cheyne, & Snead, 2010).

1.8 TREATMENT AND MANAGEMENT OF PD

Due to the incurability of PD, medical and surgical treatments of this disease focus mainly on symptom management and neuroprotective strategies in order to delay the progression. Pharmacotherapeutic approaches in symptom management of PD include: DA replacement therapy, DA agonists, dopa decarboxylase inhibitors, catechol-O-methyl transferase (COMT) inhibitors, and monoamine oxidase (MAO) inhibitors,

which are usually used in conjunction with each other to increase bioavailability, inhibit re-uptake and the breakdown of DA in the CNS (Salavati et al., 2018).

Drug	Mechanism of Action	Indication	Starting Dose	Dosing[1]
Carbidopa/Levodopa	DA Replacement	Troublesome motor symptoms	25/100 mg tablets	TID- QID
Pramipexole	DA Agonist	Early stages, add-on	0.25mg-1 mg tablets	TID with meals
Selegiline (or selegiline)	MAO Inhibitor	Add-on to prolong carbidopa/levodopa effects	5 mg tablets	Once Daily
Entacapone	COMT Inhibitor	Add-on to prolong carbidopa/levodopa effects	200 mg tablets	1 tablet with carbidopa/ levodopa
Amantadine	DA Agonist/ NMDA antagonist	Add-on, antidyskinetic. Reduces side-effects of levodopa	100 mg tablets	Various dosing

Table 3: Commonly used antiparkinsonian drugs

Levodopa (also known as L-dopa) is a precursor which crosses the blood-brain-barrier, increases the synthesis of DA in the CNS and has a half-life of 30 to 60 minutes. unfortunately, over time, and as the disease progresses, PwPD experience a faster wear-off time, and require dose adjustment. Motor fluctuations and complications such as levodopa-induced dyskinesia appear only after a few years, which negatively affects the

[1] BID = twice a day (bis in die), TID = 3 time a day (ter in die), and QID = 4 time a day (quater in die).

quality of life of this patient population leaving surgical interventions as the last resort (Brittain & Brown, 2014).

1.8.a Surgery and DBS

Levodopa-induced dyskinesia is one of the debilitating side effects of dopamine replacement therapy that affects the quality of life of PwPD. Initially, during the "honeymoon phase", levodopa administration resolves most of the signs and symptoms of the disease, but as the disease progresses, side effects such as dyskinesia will emerge, and after a few years, pharmacotherapy becomes ineffective (Wagle Shukla & Okun, 2014). Although dose adjustment and add-on medications are the first corrective measures in such cases, neurosurgical interventions have proven to be valuable when managing side effects fails.

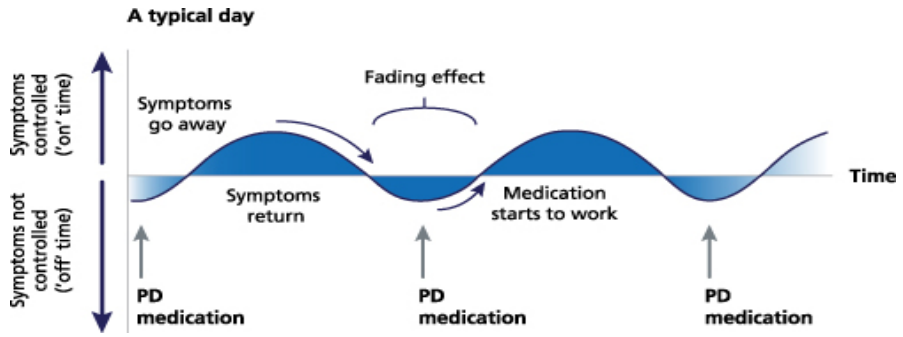

Figure 1.4: L-dopa and fluctuations in the effectiveness of the medication due to a relatively short half-life (rationale behind the on/off state) (Martinu, Degroot, Madjar, Strafella, & Monchi, 2012).

Between 1940 to 1960, surgical interventions for movement disorders were performed routinely. Despite lack of advanced neuroimaging technologies, and solely based on

anatomical and observational studies, clinicians realized that ablation in the thalamic or the pallidum projections could alleviate the motor symptoms of movement disorders. In the early 1960's, due to major side effects and the discovery of levodopa, thalamotomy and pallidotomy were abandoned (Goetz, 2011). It was in 1994 that deep brain stimulation (DBS) was first introduced for the treatment of PD. DBS takes advantage of the inhibitory properties of electrical stimulation to disrupt the excitatory function of STN, and therefore decreases excitation in motor cortex. (Sironi, 2011). As mentioned earlier, the progressive nature of PD, and lack of long-term benefits of the current medical and surgical techniques leave neurorehabilitation a feasible approach as an adjunct therapy to improve the efficacy of medications and decrease the rate of disease progression.

1.8.b Neurorehabilitation and Multisensory training

Originally, neurorehabilitation interventions failed to show effectiveness in managing PD. Such approaches were mainly limited to supportive therapies such as stretching to reduce rigidity, and assisted ambulation in order to keep PwPD mobile. But in the past couple of decades interventions such as metronome therapy, neurofeedback therapy and dance therapy have proven to be the most effective non-invasive therapeutic approach in conjunction with pharmacotherapy. Taking advantage of external cues, metronome therapy could improve the quality and speed of gait in PwPD, neurofeedback therapies promote error correction techniques using electromyogram (EMG) in order to improve the timing of muscle contractions combined with EEG feedback, where the information on rhythms of the brain could be used for optimal motor re-learning.

Dance with Parkinson's (DwP) is another neurorehabilitation approach, where rhythmic multisensory cues such as music, coordination of movement with a partner, copying instructors, and performing rhythmic movements improve motor and non-motor symptoms of PD (Bar & DeSouza, 2016).

2- PARKINSON'S DISEASE AND THE OSCILLATORY BRAIN RHYTHMMS

2.1 PERDIODICITY AND CYCLIC NATURE OF THE WORLD

The cyclic nature of the universe governs almost everything; day and night cycles, seasons, planetary motion, locomotion, cell division, heartbeat, respiration, ovulation, and many more. The continuous reoccurrence of these cycles is referred to as periodicity, which is the fundamental element of cyclic processes and is the main reason for the existence of time (Buzsáki & Watson, 2012). Biological organisms and physiological processes are all governed by the law of periodicity and have evolved sophisticated mechanisms to process temporal information and thus be able to predict the future patterns of recurrence. They are able to use the cyclic external cues (such as day/night cycles) and coordinate the endogenous physiological processes such as sleep-wake cycle, release of hormones, etc... Neurons are not an exception to this law. Excitatory and inhibitory processes work harmoniously as the voltage-gated ion channels change the neural membrane potentials, where electrical impulses create a synchronous rhythmic pattern of oscillations. Measuring devices such as clock, electrocardiogram (ECG), blood pressure cuff, and EEG all take advantage of the rate of change in the periodicity of rhythmic cycles and provide valuable information on the nature of temporal processing of information (Buzsáki & Mizuseki, 2014). Since the advent of electrophysiology, it has

been speculated that the rhythmic property of the neuron activities observed on the EEG recording is no exception to this law. Researchers have shown that the OBRs may play an important role in neural communication, and changes in synchronous rhythmicity of these oscillations could signal pathophysiological changes in the CNS of the mammalian brain (Brittain & Brown, 2014).

2.2 PHYSIOLOGICAL BASIS OF EEG

EEG detects and measures the summation electrical activity of a group of cortical neurons with large projections and similar orientation (pyramidal cells). The excitatory postsynaptic potentials (EPSPs) are inputs coming from a presynaptic neuron causing an action potential in a postsynaptic target neuron, and the inhibitory postsynaptic potentials (IPSPs) reverses the membrane potential of the presynaptic cell to the resting state and inhibits actions potentials (Androulidakis et al., 2008). The source and the sink caused by these fluctuations in membrane potential are the main reason behind the positive and negative deflections on the EEG recordings picked up by the scalp electrodes (figure 2.2) As depicted in figure 2.1 deflections on the EEG waveforms represent the electrical currents (charge) closest to the scalp at the time of recording (Pfurtscheller & Lopes da Silva, 1999).

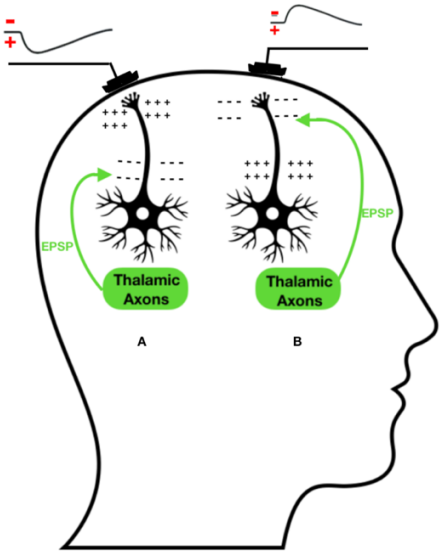

Figure 2.1: Electrical currents recorded by EEG electrodes: Axonal projections from thalamus causing EPSP in neuron A, proximal to the cell body (away from the scalp), leaving the distal axonal region more negatively charged or excited, leading to a negative deflection (sink) wave pattern picked up by the scalp electrode. Neuron B shows the opposite pattern with a positive deflection (source).

The rhythmic oscillations observed on EEG recordings have three important features: frequency (speed of oscillations) or number of cycles per second measured in Hertz (Hz), amplitude or power is the amount of energy in a frequency band, and phase is the time that an oscillation occurred. EEG oscillations are mainly recognized based on their patterns and frequency bands. By convention frequencies between 0.5-4 Hz are labeled as delta, 4-7 Hz theta, 8-12 Hz alpha, 12-Hz, and 30-100 Hz gamma. These frequency bands have commonly been used in neuroimaging studies, both in awake and sleep states, in order to study the neurophysiological changes linked to cognitive, motor, sensation and perception. In clinical medicine brain activities are monitored using the

properties of these frequencies and diagnoses such as epilepsy is based on EEG studies (Rana, Ghouse, & Govindarajan, 2017).

2.2.a The Bayesian brain, frequency-specific oscillations and behaviour

Blood-oxygen-level-dependent imaging (BOLD) technique used in fMRI studies have demonstrated that decreases in EEG power (desynchronization) are consistent with hypoperfusion of the same regions, and local hyperfusion is consistent with EEG increased power (synchronization) in the same location of interest (O'Gorman et al., 2013). A simplified version of the observed behaviour matched with specific frequency bands and their approximate anatomical locations are provided in table 4.

Type	Frequency (Hz)	Location	Normally
Delta	up to 4	frontally in adults, posteriorly in children; high amplitude waves	• adults slow wave sleep • in babies • Has been found during some continuous attention tasks
Theta	4 – 8	Found in locations not related to task at hand	• young children • drowsiness or arousal in older children and adults • idling • Associated with inhibition of elicited responses (has been found to spike in situations where a person is actively trying to repress a response or action).
Alpha	8 – 13	posterior regions of head, both sides, higher in amplitude on non-dominant side. Central sites (c3-c4) at rest	• relaxed/reflecting • closing the eyes • Also associated with inhibition control, seemingly with the purpose of timing inhibitory activity in different locations across the brain.
Beta	>13 – 30	both sides, symmetrical distribution, most evident frontally; low amplitude waves	• alert/working • active, busy or anxious thinking, active concentration
Gamma	30 – 100+	Somatosensory cortex	• Displays during cross-modal sensory processing (perception that combines two different senses, such as sound and sight) • Also is shown during short term memory matching of recognized objects, sounds, or tactile sensations

Table 4: A brief and simplified overview of the brain's dominant frequencies (Bellotti, De Carlo, Massafra, de Tommaso, & Sciruicchio, 2004).

Although sufficient empirical evidence supports the physiological basis of these oscillations, the circumstantial evidence has shown that these oscillations are not just a byproduct of the neuronal excitatory and inhibitory processes, but also, play a neuromodulatory role in intra and inter-neuronal communication and top-down predictive coding in mammalian brains (Buzsáki & Watson, 2012; Friston, Bastos, Pinotsis, & Litvak, 2015). The automaticity and the high processing speed of various cognitive, perceptual, sensory and motor information in the brain, leaves the saltatory model of signal propagation vulnerable to failure when used as an explanatory model to underlie the mechanisms involved in high speed communication and signal processing. The predictive coding model of the OBRs can adequately explain the feasibility of the OBR patterns used as syntax in neural communication lending support to the notion that the processing efficiency in the brain could only be achieved if a statistical predictive mechanism governs action, perception and sensory processes in the brain, especially in cases when previous exposure primes the CNS for dealing with reoccurring information, or learned tasks sing minimal neural resources (Buzsáki & Mizuseki, 2014).

Research has validated the efficient neural processing mechanism using the predictive coding model. Bastos et al (2012) demonstrated that during visual tasks gamma and theta appear when bottom-up registration of stimuli is in processes, but immediately replaced by the beta oscillations perhaps as a signature of past exposures, and act as an inter-network comparator in error correction processes, predicting the orderly activations of the networks involved in error correction or continuation of task. In an animal study the extrastriatal beta oscillations predicted the strength of the event potentials in V1 of the monkeys that were previously trained to perform a motor task (Richter et al., 2012).

Bauer and collogues (2014) also showed that the probability of a stimulus change could be measured and predicted by the alpha band frequency desynchronization involved in top-down task related attention, and the gamma frequency bands involved in the unfamiliar tasks where comparators do not have enough time to predict the outcome and compare the subjective bottom-up reception of sensory input with already coded previous exposures. This may very well be indicative of the role of alpha frequencies in communication and the gamma frequencies in prediction (O'Gorman et al., 2013).

2.3 ENDOGENOUS OSCILLATIONS AND EXOGENOUS INFLUENCE

It is well known that oscillation patterns change over time and in response to the environment. Brain functions as a receiver, almost like a radio that broadcasts different channels based on their frequencies (Cohen, 2017). Neural networks also appear to follow the same pattern, neurons or networks of neurons tuned to a specific frequency or pattern of oscillations respond only to the information at that frequency. Flexibility and change over time are fundamental adaptive features of these frequency-specific networks in the brain, which makes it possible for an organism to successfully change behaviour and function in varying environmental conditions (Jing et al., 2016).

Since the invention of the EEG by Hans Berger in 1924 the bidirectional property of the OBRs has encouraged scientists to explore the idea of bottom-up tuning of the OBRs using frequency-specific targets to improve function in the disease models. In the past few decades clinical experiments in neurodegenerative disorders such as Alzheimer's have shown that the OBRs could in fact be used to change the neurophysiological processes in the CNS of animals and humans.

Literature suggests that gamma oscillations (30-100 Hz) could predict an increased focused attention, and imbalances in gamma synchronization is indicative of neuropsychiatric pathologies. Cardin et al. (2009) in a seminal paper published in Nature, provided causal evidence that distinct network activities could be induced. Their optogenetic manipulation model in barrel cortex of mice showed that stimulation between 8- 200 Hz change the neural oscillatory patterns proportionately to the amplitude of the frequencies. They observed that fast oscillations regenerate gamma frequencies in frontal and hippocampal regions, whereas lower frequencies entrained the oscillations in subcortical thalamic and pyramidal neurons. A few years later, another Nature publication by Iaccarino and colleagues (2016) clearly showed that using the gamma oscillation properties by having an LED monitor that flickers at 40 Hz can reduce the amyloid plaques in the visual cortex of their Alzheimer's mice model, improving their neuronal and glial mechanisms involved in attenuation of plaque buildup. This study not only shows that oscillations could be entrained to an external force, but also confirms the role of OBRs in modification of biochemical and neurophysiological processes in the brain.

2.4 RHYTHMICITY FILURE AND OSCILLATORY BRAIN RHYTHMS IN PD

Multiple experimental and observational studies have shown the role of external rhythmic cues and amelioration of symptoms in PwPD. Over a century ago Jean-Martin Charcot, one of the founding fathers of modern neurology, observed that after a train or horseback ride, PwPD experience an amelioration of symptoms, including less tremors and better gait. Although he successfully built a replication device called "fauteuil

trépidant" (shaking chair) which moderately alleviated the motor symptoms of PD for a short period of time, his observations remained abandoned until the past couple of decades (Goetz, 2011). In 1997 Enzensberger and colleagues studied the effects of rhythmic entrainment of PwPD in gait re-training using a metronome, and successfully showed improvements in the speed and quality of gait in this patient population.

Given the bidirectional property of the OBRs, neurophysiological influence of exogenous tuning on the oscillatory patterns of the brain, and the pathological changes in the BG of PwPD, it is not far-fetched to speculate that the BG play a role in modulation of rhythmic movements, interval recognition, and the temporal processing of information.

2.4a Firing rate model of BG

In the early primate models of PD, decreased activity in GPe and increased STN activities were observed. Also, DA tracing studies demonstrated a reduction in excitatory striatal inputs to direct and indirect pathways of BG. These two mechanisms have shown to increase mean firing rate in GPi and the SNr through inhibition of the direct pathway and excitation of the indirect pathway (Lobb, 2014). Such increased firing rate and activity is thought to create an imbalance between inhibitory and excitatory mechanisms producing conflicting motor symptoms such as bradykinesia and tremors. observations led to formulation of the firing rate model (FRM). This model has been criticized, because invasive electrode recordings directly from the GPe and GPi have not been able to detect significant changes in these nuclei. Also, lesion studies suggest that ablation in GPe does not induce severe motor symptoms or involuntary movements (Nambu, Tachibana, & Chiken, 2015). As a matter of fact, pallidotomy has shown to improve PD symptoms, therefore the increased firing rate in the pallidum could not explain the

symptoms in hyperkinetic movement disorders, especially PD. On the other hand, recent studies demonstrated the role of OBRs and the patterns of oscillations as one of the secondary causes of disease progression after the initial stage of PD (Bergman & Deuschl, 2002).

Firing pattern model of BG 2.4.b

As mentioned earlier, the predicative coding property of the OBRs make them a reasonable candidate to explain the mechanism of information processing. The firing pattern model (FPM) takes advantage of the OBRs and irregular firing patterns in multiple BG nuclei in order to explain the motor symptoms of PD (Li, Zhuang, & Li, 2015). Local filed potentials (LFPs) recorded via invasive electrodes in PwPD undergoing DBS surgery have shown burst activities (series of firings at short time intervals) in the GPi, GPe, and the STN. Normal synchronous neural oscillations are the hallmark of the firing pattern in these nuclei, and the existence of such powerful desynchronus oscillations is thought to play an important role in worsening of symptoms. Animal studies demonstrated that inducing PD using N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), changes the OBRs from a synchronous manner, into a burst like desynchronized pattern. In humans, alleviation of motor symptoms after administration of L-dopa has been linked to the return of synchronous OBRs, especially beta (13-30 Hz). Given that the FPM successfully explains tremors, and bradykinesia in hypokinetic disorders such as hemiballismus and PD, and the evidence provided earlier on the role of the OBRs in modulation of the thalamo-cortical and the BG activities, the FPM seems to be able to accurately explain the oscillatory changes in the Parkinsonian brain (Friston, Bastos, Pinotsis, & Litvak, 2015).

3 – CURRENT REASERCH IN PD

3.1 THE SEARCH FOR BIOMARKERS

Despite advanced neuroimaging and biomolecular technologies, the multifactorial nature of PD has made it almost impossible to develop a repository of biomarkers predicting the onset of the disease. At the moment, genetic testing may predict the long-term risk of familial or genetic parkinsonism (usually occurs before the age of 50), but as shown in figure 3.1, the prodromal symptoms are the only sensitive predictors of the onset of the disease, and technologies such f-DOPA PET scan play a confirmatory role in the diagnosis of the idiopathic PD (Delenclos, Jones, McLean, & Uitti, 2016). And as the disease progresses, research specific biomarkers such as catecholamine metabolites, α-synuclein and peripheral inflammatory factors in the blood or the cerebral spinal fluid (CSF) are also observed (Perlmutter & Norris, 2014).

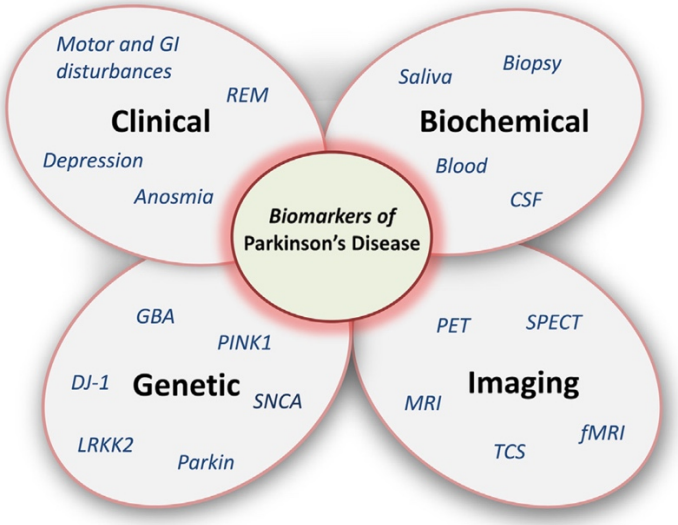

Figure 3.1: Biomarkers of PD (Delenclos, Jones, McLean, & Uitti, 2016)

Although the search for a sensitive biomarker is still ongoing, many researchers have shifted their focus on identifying biomarkers with predictive values in efficacy of disease modifying treatments and neurorehabilitation. EEG studies suggest that alpha (8-12 Hz) and beta (13-30 Hz) oscillations could signal the effectiveness of dose-dependent motor improvements after the acute administration of L-dopa (Melgari et al., 2014). A longitudinal study by Klassen et al (2011) also demonstrated that the risk of developing dementia is 13 times higher in PD patients with diminished background rhythm frequencies (lower than 8.5 Hz). In this study theta band power (4-8 Hz) was also a predictive factor for the onset of dementia in PwPD. In our lab, Levkov et al (2014) demonstrated that multisensory training could induce a higher frontal alpha power in a PD cohort enrolled in DwP (as discussed in section 1), a 4 year longitudinal study following the same cohort also showed that the rate of progression in this cohort attending weekly DwP classes were near zero (Bearss et al., 2018). Although speculative, correlation between alpha power and the rate of disease progression may indeed play a predictive role. Given that research has already demonstrated the changes in the OBRs in response to the external rhythmic cues, alpha, beta and gamma powers could be utilized as biomarkers in order to measure the effectiveness of the rehabilitation interventions such as multisensory training.

3.2- EXECUTIVE DYSFUNCTION IN PD

Executive function refers to a set of cognitive processes that control goal-directed behaviours from intention and planning to successful execution and processing of the outcome of an action. PwPD have shown to struggle with mild cognitive dysfunction

(MCI) or dementia at various stages of their disease. As discussed in section 1.2, the cognitive loop of BG plays an important role in cognitive processes involved in day to day activities. In a newly diagnosed untreated PwPD, cognitive impairment has been reported in 36% of cohorts in two multicenter studies in the UK (Dirnberger & Jahanshahi, 2013). Using tests including: The Wisconsin Card Sorting Test (WCST), Stroop, Trail Making Test (TMT), Word fluency (WF), digit span backwards, and Tower of London test, researchers have observed the following cognitive dysfunctions in PwPD: response inhibition, rules deduction and generation, maintenance and shifting of sets, information generation (fluency tasks), planning, response initiation and sustained alertness coordination of dual task, and episodic memory strategic processes (Parker, Lamichhane, Caetano, & Narayanan, 2013).

3.3 – PD AND VISION RESEARCH

Once again, looking at the BG dysfunction and PD, it is clear that the oculomotor loop of the BG should induce visual disturbances in PwPD. Since the early 1900's scientists have explored multiple aspects of oculomotor changes in PD. Visual acuity, saccadic and antisaccadic eye movements, smooth pursuit, reduced reaction response to visual stimuli, and hypometria are some of the observed oculomotor signs in PwPD (Mathewson, Gratton, Fabiani, Beck, & Ro, 2009).

Clinical studies using electro-oculography (EOG) have reported abnormal saccade and smooth pursuit eye movements in about 75% of PwPD, as well as abnormal pupil reactivity (significantly larger diameter in PD) due to autonomic dysfunction.

Probably one of the most important visuomotor experiments done in PD, is the antisaccade paradigm, where the participant is instructed to fixate on a stationary target, avoid reflexive saccades towards a peripheral visual stimulus and instead make a saccadic movement towards the opposite direction (Weil et al., 2016). PET scan studies have shown that during an antisaccade task, SMA, putamen, and the frontal eye filed in the frontal lobe are highly active (the same regions involved in the oculomotor loop of the BG).

In an fMRI study, Ewnczyk et al. (2017) enrolled 30 PwPD and age-matched healthy controls, in whom they demonstrated the role of impaired antisaccadic latencies as an indirect marker of postural instability. They also showed a decreased functional connectivity between the pedunculopontine nucleus (PPN), SMA and the frontal eye fields in the PD group, lending support to the idea that lack of anticipatory mechanisms in reflexive movements and impaired voluntary movements are the main cause of postural instability and falls in PwPD, mainly arising from dysfunctions in the SMA, and the PPN circuitries (Hood et al., 2007).

Interestingly, antisaccadic behaviour in PwPD has shown to improve markedly with administration of levodopa, consistent with previous studies corelating improvements in motor symptoms coupled with better synchronicity of the OBRs while being on L-dopa. The correlation between dopamine replacement therapy, amelioration of motor symptoms, and improved executive function is an important interaction that is discussed in more detail in section 5.

3.4 – DISTORTIONS IN TIME AND BEAT PERCEPTION IN PD

Time perception is a fundamental element in processing temporal information. Given the cyclic and rhythmic nature of our world, a successful interaction with the environment requires an accurate time estimation. From hours to minutes, seconds to milliseconds, we process information at different rates, and the voluntary and involuntary motor and cognitive processes in our body are time dependenat (Bellinger, Altenmüller, & Volkmann, 2017). Given that the BG are highly involved in the integration of multisensory information, and their role in comparing incoming temporal information with the endogenous comparators for time estimation, it would be fair to speculate that the etiology of PD may cause distortions in time perception (Avanzino et al., 2016).

The current literature in PD supports this idea by exploring the auditory beat perception, musical rhythm perception, and interval counting, using the "scalar expectancy theory" where an endogenous clock (pacemaker), a working memory and decision-making influence the processing of temporal information and time-dependent actions (Cope, Grube, Singh, Burn, & Griffiths, 2014).

Honma et al. (2016) demonstrated that PwPD underestimate time on time production tasks especially in intervals greater than 10 seconds.

In a beat perception study, Bellinger et al. (2017) showed the PD cohort underperformed significantly in detection of time intervals between 220-300 ms on a temporal discrimination task, using a short melody with clear beat-based rhythms, compared with the age-matched healthy controls. This temporal deficit has also been linked to the etiology of tremors and lack of coordination in PD, which underlies the imbalance in the

temporal order of muscle contractility in muscle activation/deactivation in agonist and antagonists muscle groups (Lucas et al., 2013).

3.5 - BIOLOGICAL MOTION PERCEPTION IN PD

Biological motion perception is a bottom-up integration of incoming visual, and motion information combined with top-down influence when perceiving or interpreting movements and actions of other individuals. Kloeters et al. (2017) tested 20 PwPD and 23 healthy controls while presenting two-dimensional point-light animations of human, animal, and object motion, and were able to demonstrate that PwPD are impaired in the perception of human movements, interestingly the impaired perception was most pronounced when human motion animations presented a transitive, goal-directed movements. In another study, 26 PwPD were recruited and presented with human point-light walker videos in a noise mask. Compared with 24 healthy controls enrolled in the study, PwPD showed a significantly lower sensitivity for detecting human motion (Jaywant, Shiffrar, Roy, & Cronin-Golomb, 2016). Although there is no general consensus on how or why this deficit is observed in PwPD, Liu et al. (2017) tested their PD participants during on and off states of the medication effectiveness (dopamine replacement therapy) and found that the PD group indeed have deficits perceiving biological motions but performed significantly better during the on state of medication, suggesting the involvement of dopamine-dependent processes in motion perception.

3.6 – SLEEP STUDIES IN PD

Sleep disturbances antedate motor symptoms in PD. reduction in sleep time, deep sleep, and REM sleep duration as well as RBD, makes sleep a special topic of research, especially because sleep disturbances are considered as prodromal markers of PD. The sleep/wake cycle has two important features: 1) the endogenous biological clock and 2) biochemical homeostasis (Selvaraj & Keshavamurthy, 2016).

As mentioned, early experimental data has already suggested that the endogenous clock (on millisecond scale) is impaired in PwPD, whether such conclusions apply to the hour and day time scale is a question that has not been settled, though the DA-melatonin interaction in the hypothalamus and the striatum has shown to play a role in sleep/wake dysfunctions (Mack et al., 2016).

It is important to note that melatonin regulates the expression of neutrophins that are involved in the survival of dopaminergic neurons and by protecting the dopaminergic system reduces α-synuclein aggregation in the CNS. Although many researchers identify melatonin as the first culprit in the pathogenesis of PD, conflicting evidence has complicated this hypothesis (Mack et al., 2016; Zisapel, 2001).

PSG studies in PD have demonstrated that the altered sleep spindles in stage 2, where theta frequency bands are observed is one of the hallmarks of the preclinical stages of the disease (Christensen et al., 2015), but prior to the oscillation changes during sleep, RBD is usually reported by PwPD on the Mayo Sleep Questionnaire (MSQ). MSQ is a 16-question scale, which is one of the most sensitive questionnaires (100% sensitivity) for detecting RBD and is filled by a bed partner (Boeve et al., 2011) (see appendix).

Although the etiology of RBD remains unclear, like many other symptoms of PD, a dose-

adjusted administration of L-dopa has shown to improve RBD, sleep fragmentation and the quality of sleep in PwPD (Belaid et al., 2014).

4 - L-DOPA, MOTOR BEHAVIOUR AND RHYTHMICITY

4.1 INTRODUCTION

A mounting body of evidence suggests that DA replacement therapy not only improves motor symptoms, but also affects non-motor symptoms. In the past few years multiple studies have reported the effects of on-medication performance of PwPD in dual task performance, task-set switching, probabilistic reversal, auditory beat perception, and the visual reaction time experiments (Melgari et al., 2014). Given the anatomy of the BG as a sensorimotor integrator, and the fact that imbalances in the DA levels impact the equilibrium and balance of other neurotransmitters and related neural networks, theoretically it is safe to speculate, that the amelioration of motor symptoms after the administration of L-dopa should be coupled with other cross-domain improvements. Clinical studies have already confirmed the role of acute administration of L-dopa and a better motor score on the Unified Parkinson's Disease Rating Scale- Part 3 (UPDRS III) in PwPD, and the current EEG literature suggests that lower alpha (8-12 Hz) and beta (13-30 Hz) frequency bands (higher alpha and beta power) are often observed before the effects of medication wears off. Understanding this phenomenon could be beneficial in two important ways 1) better understanding of the role of oscillations and the underlying neural networks 2) using these oscillations as biomarkers to evaluate the effectiveness of therapies and the rate of disease progression (Alexander et al., 2006).

In this section the effects of L-dopa on motor scores and EEG oscillations were examined before and after multisensory training (DwP project).

4.2 METHOD

Design 4.2.a

After obtaining informed consent, 18 volunteer participants with PD and a total of 36 data sets were collected as a subgroup of an ongoing DwP research project before and after dance classes. Clinical assessments including a medication questionnaire and a motor scale (UPDRS-III) were administered before and after dance classes and the scores were recorded. In addition, a non-invasive scalp EEG headset recorded electrical brain activities before and after dance classes.

Participants 4.2.b

18 participants ($M_{age}=71.73, SD=7.14$) including 10 females and 8 males with mild to moderate PD ($M_{H\&Y}=1.32, SD=0.53$) and an average disease duration of 6.06 years ($SD=5.077$) volunteered to take part in this study. Inclusion criteria were based on a definite diagnosis of PD, the type, dose, and subjective effectiveness of medication.

In order to homogenize the cohort only 15 participants who took their medication 30 to 150 minutes prior to the testing session in the "pre" condition and reported to be off medication during the testing session after the dance class (post) were included in the motor score statistical analysis. The 3 excluded participants reported the exact opposite (off medication during the pre-test and on medication during post-test), and their data were included only in the EEG analysis as the control group.

Procedure 4.2.c

Each participant underwent a motor examination using the UPDRS-III. This 14-item test, assesses speech, facial expression, tremor, rigidity, bradykinesia, gait and postural instability on a scale of 0-56. In the absence of other comorbidities, a higher score indicates worse motor symptoms (Bergman & Deuschl, 2002). A medication questionnaire was also completed by each participant, where questions such as the name, dose, and frequency of PD medications, as well as effectiveness and wear-off time of the medications were answered. Using the medication effectiveness and wear-off time reported by the participants and taking into consideration that the half-life of metabolism of carbidopa/levodopa 25/100 mg in humans with normal liver and kidney functions range about 120-150 minutes, ON or OFF states were assigned to each pre and post motor scores. Although medication on/off state is a question included in the UPDRS-III, due to having participants answering "neither" to the question, it was necessary to use a dichotomous scale in order to stratify participants based on the medication effectiveness. Therefore, the on and off medication state were determined based on the mechanism of action, metabolism and half-life determined by previous research (Salavati et al., 2018).

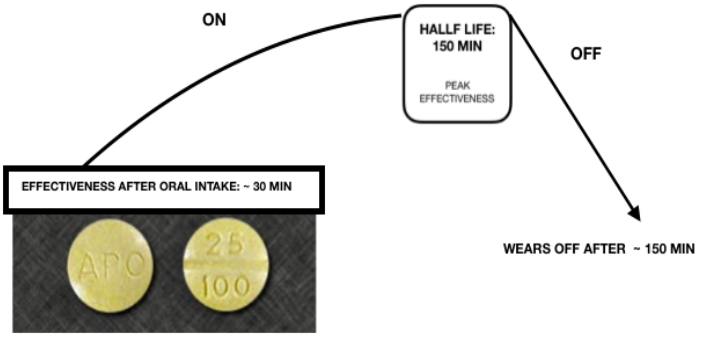

Figure 4.1: Stratifying participants based on the half-life metabolism of L-dopa and subjective on/off medication effectiveness state.

After re-stratification of participants, a 14 channel EMOTIV EPOC^{+} headset with a sampling rate of 128 samples per second was used for EEG recordings of eyes closed (EC) and eyes opened (EO) conditions, before and after dance classes. Headset placement was performed according to the 10-20 international system.

Statistical Analyses and Signal Processing 4.2.d

Pre and post UPDRS-III scores were dichotomized based on medication effectiveness (on/off), and in SPSS V.25 (IBM, Inc. Armonk, NY, USA) an independent-samples t-test with a $p < 0.05$ significance level was conducted for comparisons between pre and post data.

EEG data were preprocessed in MATLAB 2018a (Mathworks, Inc. Natick, MA, USA) and the EEGLAB tools box V. 14_1_2b (Delorme & Makeig, 2004).

Prior to independent components analysis (ICA), channel locations were loaded and defined, re-referencing was performed using the averaging technique, data was then inspected by eye and artifacts were rejected (except eye blinks which are removed by ICA), signals from faulty channels were removed and ICA was performed (Figure 4.3).

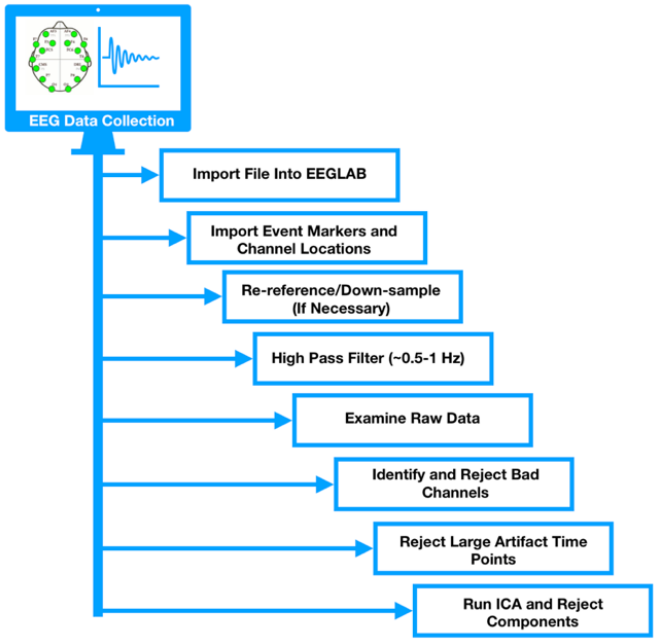

Figure 4.2: EEG preprocessing pipeline.

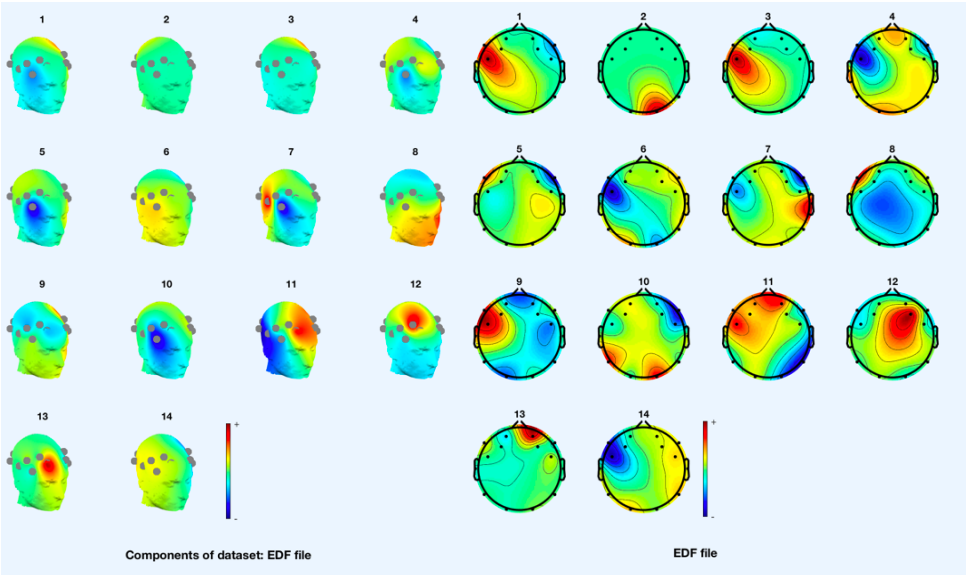

Figure 4.3: 3-D and 2-D EEG components head maps after performing ICA.

After preprocessing, the data is extracted, saved, and re-transferred into MATLAB in order to obtain the mean frequencies of interest (in this case 8-12 Hz), and perform the

spectral analysis using the discrete Fourier transform (FT) function (provided below) and calculate the log frequency and log power (Jing et al., 2016).

$$X_f = \sum_{k=0}^{n} x_k e^{-i2\pi f(k-1)n^{-1}}$$

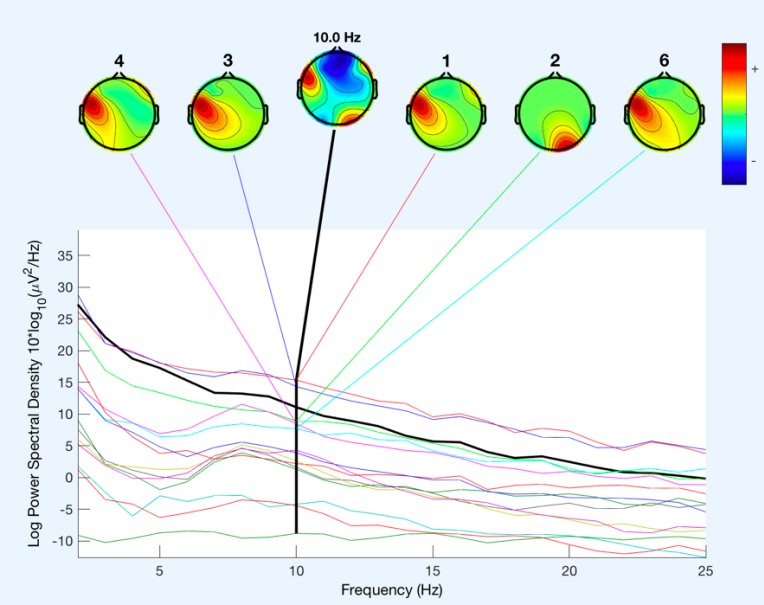

Figure 4.4: *Head maps showing the locations and electrodes of the frequency of interest in spectral analysis using the neural network tool box on MATLAB.*

4.3- RESULTS

L-dopa and Motor scores 4.3.a

An independent sample *t* test reported a significant difference in motor scores while on and off medication, t (28) = -2.50, $p < 0.01$, 95% *C.I.* The subjects who were on medication, showed on average a lower motor score or less motor disturbances (*M= 20.46, SD = 10.4*) tested before the dance class (pre), and the subjects who were off medication, performed sub-optimally on the UPDRS-III with higher motor scores (*M= 26.35, SD = 10.34*) tested after the class (post).

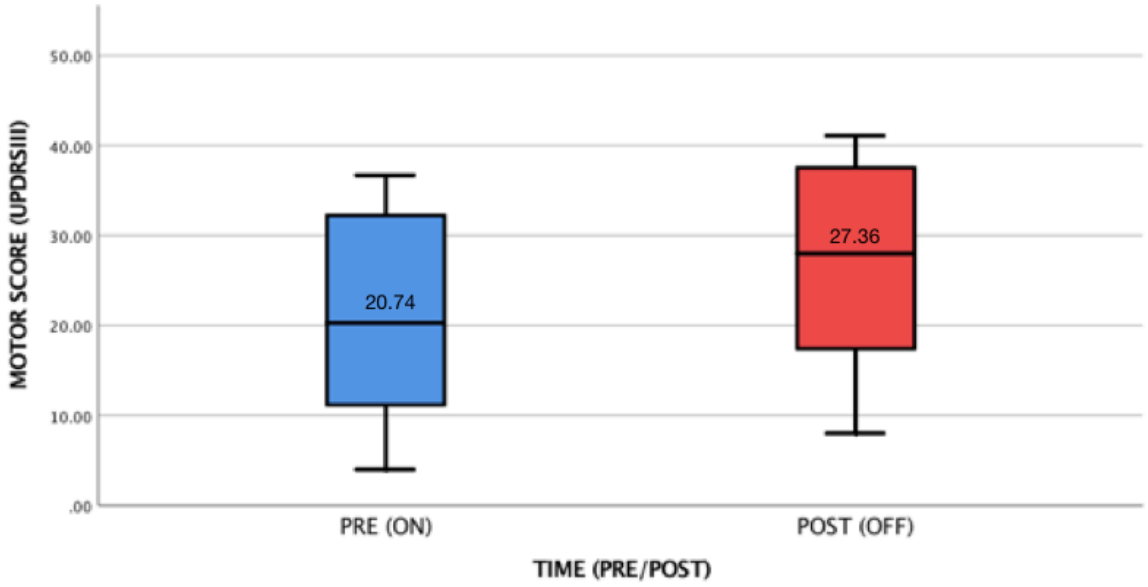

***Figure 4.5**:* Mean differences in motor scores (UPDRS-III) between the pre-class data while participants were on medication (blue) versus post-class data while participants were off medication (red).

EEG Results 4.3.b

The EEG recordings of three participants with an average change of – 6 points on the UPDRS-III (pre to post) who were on medication during the eyes-closed, pre-class testing session, and off medication during the post-class testing were selected and labelled as group B (declined). Their mean change scores per electrode were then compared with the mean frequency changes of the three excluded participants who were on medication during the pre-class testing session and had an average change score of +6 on the UPDRS-III. As shown in figure 4.6 in the EC condition there is a substantial difference in frequency changes in F7, FC5 and FC6 between two groups almost in the

opposite direction. And in the EO condition in figure 4.7, this difference in frequency changes is observable in F3, F8, FC5, FC6, O2 and O1.

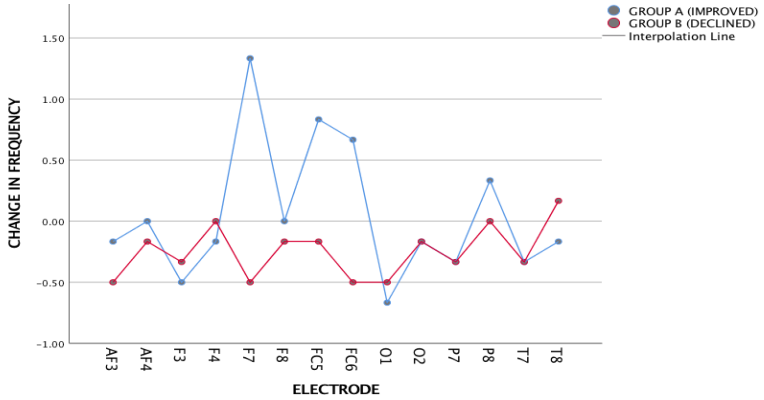

Figure 4.6: Mean frequency changes in alpha band from pre to post testing in each electrode in the EC condition. The blue data points and line or group A (lower motor scores while being on medication during post class testing), represents the change scores from the eyes closed condition. The red data points and line or group B (higher motor scores while being off medication during post class testing).

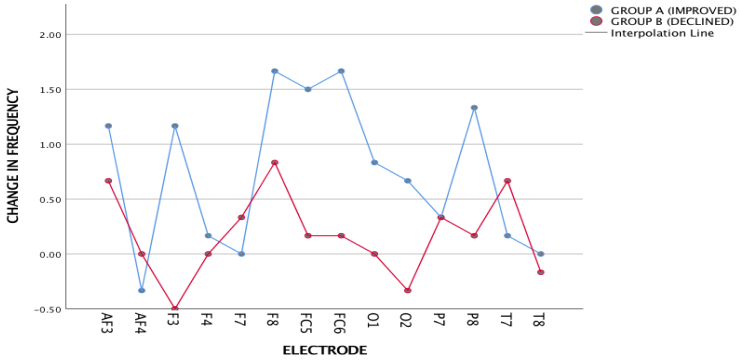

Figure 4.7: Mean frequency changes in alpha band from pre to post testing in each electrode in the EO condition.

During the spectral analysis of alpha band frequencies a global increase in lower alpha (8-10 Hz) was observed in group A during in EEG recording before the class (Pre) ($M_{groupA(EC)}$= 0.35, *SD*= 0.21), ($M_{groupA(EO)}$= 0.085, *SD*= 0.61), ($M_{groupB(EC)}$= 0.68, *SD*= 0.58)($M_{groupB(EO)}$= 0.46, *SD*= 0.31) and in the post recording ($M_{groupA(EC)}$= 0.41, *SD*= 0.29), ($M_{groupA(EO)}$= 0.43, *SD*= 0.32), ($M_{groupB(EC)}$= - 0.71, *SD*= 0.58) and ($M_{groupB(EO)}$= - 0.47, *SD*= 0.31).

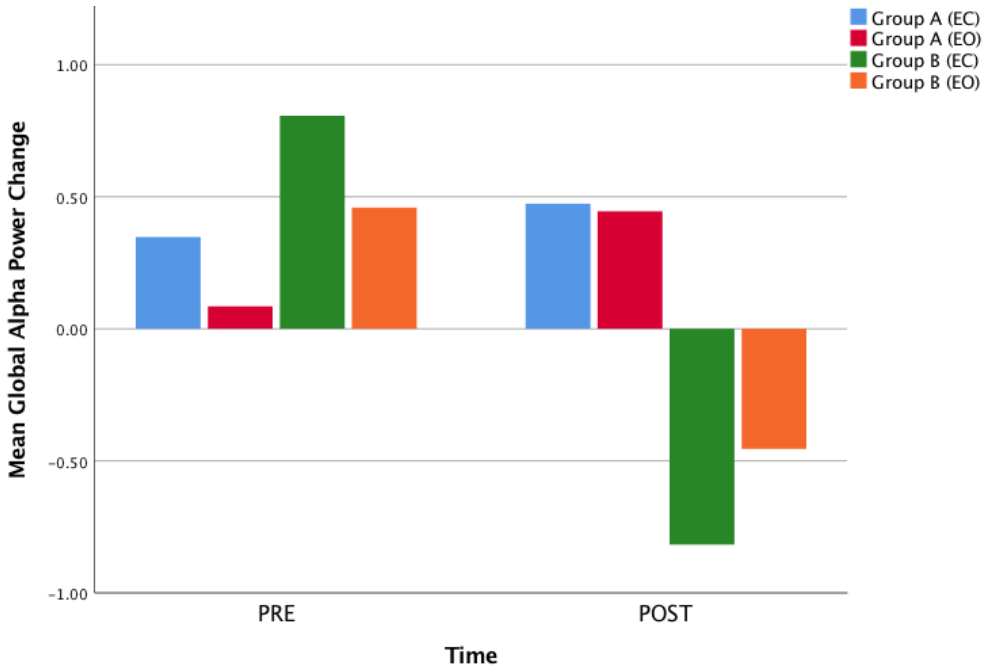

Figure 4.8: Global alpha power changes from pre to post between groups A (lower motor scores while being on medication during post class testing) and B (higher motor scores while being off medication during post class testing).

4.4 DISCUSSION

The objective of this study was to examine the role of dopamine replacement therapy in motor scores and the EEG activity changes. As mentioned earlier, almost

every study in PD literature, from executive function tasks to motor and perception studies, reported a change of outcome when PwPD are on L-dopa. Our data also appears to follow the same trend. In both EO and EC conditions (figures 4.6 and 4.7) subjects who were on medication had lower alpha frequencies (alpha synchrony) in multiple electrodes, compared with the subjects in the off-state who had desynchronus or higher alpha frequencies on the EEG. As shown in figure 4.8 there is an inverse relationship between frequency and power of oscillations, lower frequencies lead to a higher spectral power, and higher frequencies lead to a lower spectral power.

Based on the data provided, the alpha power changes, and the motor performance observed in the UPDRS-III scores in both groups have the same direction of change. When subjects were in on-medication state, they had lower motor scores (better motor performance) and higher alpha powers, but when the same participants were in off-medication state their alpha power and motor performance dropped (higher UPDRS-II scores), which may confirm the involvement of dopamine replacement therapy on changes in both motor performance and the frequency-specific oscillations, mainly in alpha frequency band.

4.5 CONCLUSION

The data provided in this study demonstrated that the behaviour of the dopamine-dependent alpha frequency bands change in the same direction as the changes in L-dopa effectiveness and the motor performance. This co-emergence may reflect the putative biomarker property of the alpha frequency and its ability to detect dopamine-dependent cortical processes involved in motor performance.

4.6 LIMITAIONS AND FUTURE DIRECTIONS

This study was originally designed to measure changes before and after multisensory training. Lack of control over the timing of medication intake and relying heavily on subjective self-report time of intake may have reduced the validity of the results. Also, the small sample size of this study makes it difficult to deduce a statistically sound conclusion based on the collected data, therefore the results should be treated as observational. A larger sample size with age-matched controls (PD) are required for better validity a specificity of the results. Also, testing participants early in the morning during the withdrawal time can give us a better baseline on how L-dopa affects the motor performance and the EEG oscillations.

5 – EXECUTIVE FUNCTION AND THE SOUND-INDUCED DOUBLE FLASH ILLUSION.

5.1 INTRODUCTION

Evidence provided in section 3 indicates the importance of rhythmicity in pathophysiology of PD. Given the nature of this disease and the involvement of the BG, we now know that in PD, both motor and cognitive processes are affected, and DA is the cornerstone of the underlying mechanism of various motor and non-motor symptoms of PD. The external tuning of the endogenous oscillators (i.e. thalamocortical oscillations) observed after rhythmic entrainment of the gait and movements to the music, or to the beats of a metronome in gait training, and multisensory training are all indicative of an

internal mechanism that has remained unexplored. The main purpose of this proposal is to identify the faulty endogenous oscillatory rhythms, and to explore the potential underlying mechanisms of the effects of exogenous cues on cognitive, motor and perceptual processes in PD.

Objectives

- To investigate the correlation between motor behaviour and cognition.
- To identify a reliable neurophysiological biomarker as both a measure of the progression of the disease and the treatment efficacy.
- To investigate the temporal window of sensory integration, and its role in cognition and temporal processing of the incoming information.

5.2 –SOUND-INDUCED FLASH ILLUSION, OBRs AND MOTOR PERFORMANCE

In order to quantify and validate these observations mentioned in section 3, measuring cortical oscillatory rhythms via electroencephalography (EEG) would be the ideal neuroimaging method of choice. These brain waves oscillating at currents of 20-100μV can be detected via scalp electrodes, measured in microvolts and are thought to be generated by reciprocal excitatory and inhibitory interactions of neighboring cortical cell columns which are directly and indirectly are in contact with subcortical regions (i.e., thalamus and basal ganglia) (Buzsáki & Watson, 2012). In the past few years, numerous studies observed and quantified an increase of spectral

powers in the slow frequency bands <8 Hz (delta and theta) and a decrease in the fast frequency bands >8 Hz (alpha, beta, and, less significantly, gamma) as spectral markers of PD-related physical and cognitive decline (Cozac et al., 2016).

These electrophysiological changes are not only a potential explanation for motor and non-motor symptoms but could also provide an explanation for an altered temporal discrimination threshold of paired sensory stimuli (tactile, auditory and visual) in PwPD (Lange, Keil, Schnitzler, van Dijk, & Weisz, 2014). Given this background, looking at the oscillatory brain waves and the ability to percept auditory and visual cues in PwPD may provide a valuable window in order to understand the underlying causes of the defective endogenous time-interval generators.

The evidence provided in section 4 and multiple other studies indicating the effects of L-dopa on the OBRs, specifically the dopamine-dependent oscillatory frequencies such as alpha and beta makes L-dopa a feasible target to manipulate in order to measure changes in the OBRs and the performance on cognitive, motor and perceptual tasks.

As Levkov et al. (2014) previously demonstrated the increased alpha power after multisensory training is coupled with better balance and subjective reports of improved motor symptoms, these results match the alpha changes after administration of L-dopa and amelioration of motor symptoms, which warrants the use of alpha as a target frequency band for the purpose of this study.

In order to measure and evaluate the cross-domain effects pharmaceutical or neurorehabilitation interventions (both in motor and cognitive domains) in PD, incorporating a sensory and perceptual paradigm in pre and post conditions would be an

ideal route to measure changes in motor symptoms and the temporal window of integration in audiovisual tasks, where speed of processing is the main dependent variable. Using the sound-induced flash illusion (SIFI) paradigm, Cecere et al (2015) demonstrated that the window of integration could be entrained using the transcranial magnetic stimulation. The SIFI paradigm takes advantage of two important features: the fission illusion, where a single flash accompanied by two auditory tones perceived as two flashes, and fusion illusion with two visual flashes and a single auditory tone that is perceived as one flash. This paradigm measures the temporal window of integration and can provide valuable insight into the changes in temporal processing with aging or the presence of pathology.

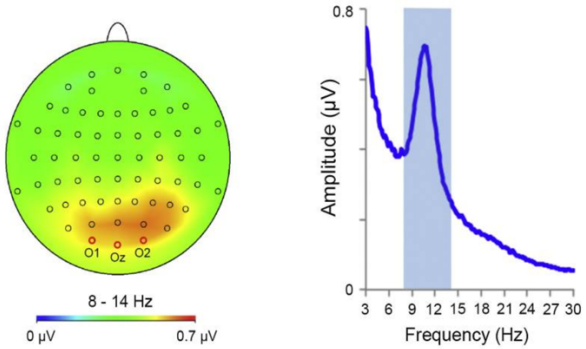

Figure 5.1: Cecere et al. (2015) showed that the temporal window of integration ~ 100 ms falls within the range of occipital alpha frequencies

5.3 DESIGN AND APPARATUS

Based on the population variance found in similar studies a sample size of 26 (α = 0.05 and β = 0.2) at a 0.8 power, paired with age-matched controls is required to detect a significant effect size.

A 14 channel EMOTIV EPOC+ EEG headset is the possible EEG recording device to measure brain rhythms while participants perform a sound-induced double flash illusion

(SIDF) task as the stimulus of choice. Stimuli created in MATLAB using the Psych toolbox will be presented to participants at various speeds and time intervals (50- 300 ms) coupled with auditory stimuli. The widely accepted temporal window of integration in healthy adults is approximately around ~100-120 ms (Shams, Kamitani, & Shimojo, 2000; Cecere, Rees, & Romei, 2015), and previous studies in aging population have shown a marked difference between younger adults and the aging population. Therefore, it is recommended to add a baseline step to measure individual thresholds for each testing session. (McGovern, Roudaia, Stapleton, McGinnity, & Newell, 2014).

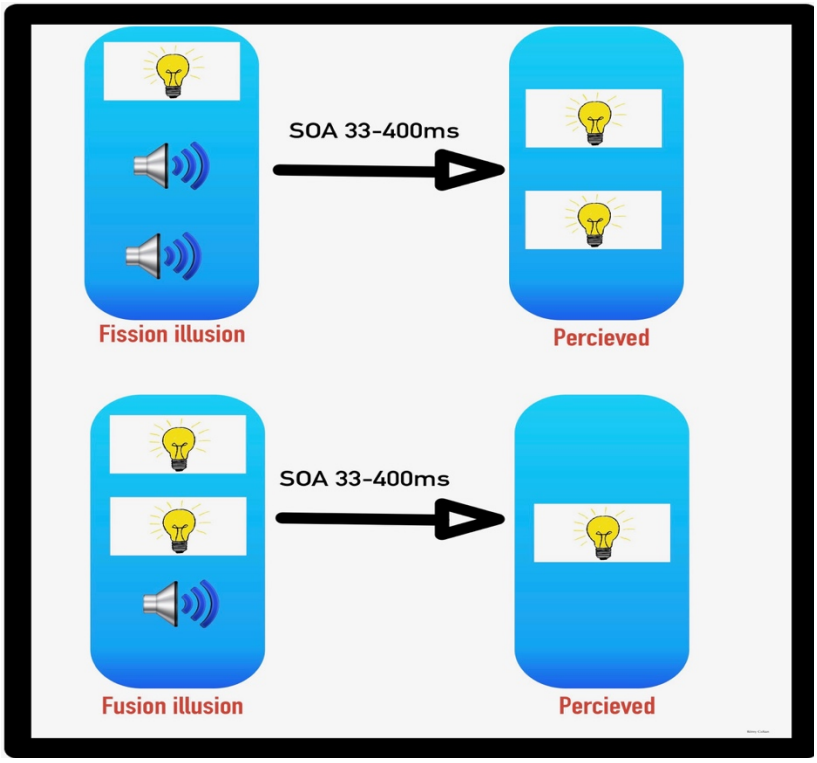

Figure 5.2: SIFI paradigm: Tested before and after multisensory training, or conducted once during the L-dopa effectiveness (on medication) and after the medication wears off to measure the changes in temporal widow of integration.

5.4 FUTURE DIRECTIONS

The main goal of this experiment would be to measure the effects of both L-dopa and multisensory training on the temporal window of integration, and to correlate the results with the putative changes in motor scores. If the results show a significant change in pre to post conditions, it would be safe to accept the biomarker properties of the alpha frequency bands in motor and cognitive processes, specifically in the PD population, which also implies a close collaboration between these two domains, raising doubt in the current model of separation between motor and cognitive neural networks.

6 – REFRENCES AND APPENDIX

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DATA SUMMARY

						UPDRS III
TIME OF TESTING	PRE	MEDICATION	ON	1		31.76
				2		36.70
				3		33.50
				4		8.00
				5		21.00
				6		27.33
				7		11.34
				8		20.30
				9		12.80
				10		4.00
				11		11.00
				12		11.00
				13		14.00
				14		35.70
				15		32.70
				Total	N	15
					Mean	20.7420
					Std. Error of Mean	2.91026
					Std. Deviation	11.27137
			OFF	1		24.60
				2		15.70
				3		23.70
				Total	N	3
					Mean	21.3333
					Std. Error of Mean	2.82862
					Std. Deviation	4.89932
			Total	N		18
				Mean		20.8406
				Std. Error of Mean		2.44381
				Std. Deviation		10.36821

	POST	ON/OFF STATE	ON	1		21.60
				2		13.20
				3		22.30
				Total	N	3
					Mean	19.0333
					Std. Error of Mean	2.92366
					Std. Deviation	5.06392
			OFF	1		37.74
				2		41.10
				3		40.50
				4		12.38
				5		31.00
				6		38.15
				7		23.30
				8		26.74
				9		17.83
				10		8.00
				11		17.00
				12		16.70
				13		28.00
				14		37.33
				15		34.60
				Total	N	15
					Mean	27.3580
					Std. Error of Mean	2.82755
					Std. Deviation	10.95105
			Total	N		18
				Mean		25.9706
				Std. Error of Mean		2.49411
				Std. Deviation		10.58160
	Total	N				36
		Mean				23.4056
		Std. Error of Mean				1.77456
		Std. Deviation				10.64739