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**“Cortical Asymmetry in Parkinson's Disease: Investigation of
Cognitive and Motor Event-Related Potentials”**

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Abstract

The human central nervous system presents a generally symmetric structure. Each side of a person's body is primarily controlled in its sensory and motor functions by the contralateral cerebral hemisphere. However, there are a number of cognitive functions that appear to be distributed in asymmetric networks across the brain. The goal of the present research was to investigate hemispheric (a)symmetry of two well-known event-related potentials (ERP) in Parkinson's disease (PD). PD is a neurodegenerative disease affecting not only motor but also cognitive functions. It is characterized by a clinically asymmetric onset and therefore serves as an excellent model for studying lateralized brain functions. The rationale behind this research was to explore changes in EEG patterns between hemispheres in PD and their relation to dopaminergic medication. We first investigated differences in the amplitude of Readiness Potential (BP), related to motor preparation and execution. Specifically, we compared more and less affected hemispheres in PD patients. Second, we studied how PD affected the cognitive P3 amplitude, which is normally asymmetric and related to attention and working memory functions. Our results show that both the disease and its dopaminergic medication may affect hemispheric (a)symmetry of ERPs. We found that BP was not only generally lower in PD compared to healthy controls, but also asymmetric, being more pronounced on the more affected side. The BP potential was restored by dopaminergic medication. Furthermore, the usual asymmetry of P3 amplitude was less pronounced when PD patients were tested on dopaminergic medication. These results suggest that, while medication may improve motor function, it may also have negative effects on some cognitive functions.

Keywords: *Hemispheric asymmetry, attention, motor preparation, EEG, ERP, Parkinson's disease, Readiness potential, oddball task.*

Abstrakt (Deutsch)

Das menschliche Zentralnervensystem weist eine im Allgemeinen symmetrische Struktur auf. Die sensorischen und motorischen Funktionen jeder Körperseite werden primär durch die jeweils kontralaterale Hemisphäre gesteuert. Es gibt jedoch eine Reihe von kognitiven Funktionen die auf asymmetrische Netzwerke verteilt sind. Ziel der vorliegenden Arbeit war es, die hemisphärische (α) Symmetrie von zwei bekannten ereigniskorrelierten Potentialen (ERP) bei der Parkinson-Krankheit (PD) zu untersuchen. PD ist eine neurodegenerative Erkrankung, die nicht nur motorische sondern auch kognitive Funktionen beeinträchtigt. Sie zeichnet sich durch einen klinisch asymmetrischen Krankheitseinbruch aus und ist daher ein hervorragendes Modell für die Erforschung lateralisierter Gehirnfunktionen. In der vorliegenden Forschung wurden Veränderungen in EEG-Mustern zwischen Hemisphären bei PD und deren Beziehung zu dopaminergen Medikamenten betrachtet. Dazu untersuchten wir zunächst Unterschiede in der Amplitude des Bereitschaftspotentials (BP), welche mit Bewegungsvorbereitung und -ausführung assoziiert sind. Insbesondere verglichen wir stark und weniger stark betroffene Hemisphären bei PD-Patienten. In einem zweiten Schritt untersuchten wir wie sich PD auf die, normalerweise asymmetrische und mit Aufmerksamkeits- und Arbeitsgedächtnisfunktionen verbundene, P3-Amplitude auswirkt. Wir fanden heraus, dass sowohl die Krankheit als auch die mit ihr verbundene dopaminerge Medikation die hemisphärische (α) Symmetrie von ERPs beeinflussen können. Das BP war bei PD im Vergleich zu gesunden Kontrollen nicht nur allgemein niedriger, sondern auch asymmetrisch, mit höherer Ausprägung auf der stärker betroffenen Seite. Das BP-Potential wurde durch dopaminerge Medikation wiederhergestellt. Darüber hinaus war die übliche Asymmetrie der P3-Amplitude weniger ausgeprägt, wenn PD-Patienten mit dopaminergen Medikamenten getestet wurden. Diese Ergebnisse deuten darauf hin, dass, während Medikamente die motorische Funktion verbessern mögen, sie möglicherweise auch negative Auswirkungen auf einige kognitive Funktionen haben können.

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1. Introduction

One of the most apparent physical features of the human central nervous system is that its structure is divided into two symmetrical hemispheres (Hugdhal, 2005). Research of hemispheric asymmetry has a very long history, as scientists have long been studying functional differences. Early studies suggested that the two hemispheres could be specialized in processing different sorts of information. The historical development of the idea that the hemispheres of the brain perform separate activities is an example of how very old concepts may survive, evolve, and merge on the basis of accumulating evidence. The current state of research suggests that the two halves of the brain have developed through evolution into separate but highly interconnected structures (Toga & Thompson, 2003; Salvador et al., 2005). Each hemisphere is responsible for sensory and motor functions of the contralateral body side in a symmetrical fashion (Bear, Connors, & Paradiso, 2007). However, there is a number of cognitive functions that appear to be predominantly reliant on one hemisphere (Ocklenburg & Güntürkün, 2012). Therefore, the control of different brain functions may be symmetric or asymmetric, depending on the specific task. It is worth noting that hemispheric differences are often oversimplified in neuromarketing purposes or in popular science (Hellige, 1993). The relationship between hemispheres deserves a function-specific and evidence-based analysis (Harrison, 2015).

Different methods of investigation, such as neuroimaging and

electrophysiological techniques, have contributed significantly to our understanding of specialized hemispheric functions. In this respect, structural brain lesions represent a traditional model to study functional brain anatomy. Deficits in a specific function may be correlated with the anatomical localization of the lesion (Bear et al., 2007). Notably, asymmetric neurodegenerative diseases may differentially affect motor and cognitive functions and may serve as a model to study functional asymmetries (Gordon, 2016). In our research we used Parkinson's disease (PD) as a model of disruption of the normal balance between hemispheres. PD is a neurodegenerative disorder characterized by a strong lateralization of motor symptoms, caused by the asymmetric degeneration of dopaminergic neurons (Thenganatt & Jankovic, 2014). In PD, the clinically more affected side of the body corresponds to a contralateral “more affected” hemisphere (Tomer, Levin, & Weiner, 1993; Cronin-Golomb, 2010). We used the electroencephalogram (EEG) to test two well-known electrophysiological paradigms for motor and cognitive functions. The Readiness Potential (BP) precedes the execution of a movement, and relates to motor preparation (Jahanshahi & Hallett, 2003). Using perceptual stimuli, the visual and auditory oddball task generates a P3 potential, which is related to cognitive functions such as attention and working memory (Polich & Criado, 2006). These two potentials are respectively symmetric and asymmetric in healthy subjects. We collected and analyzed neurophysiological and clinical data from 14 Parkinson's patients “on” and “off” dopaminergic medication and compared them to the data from 13 healthy participants. The research had two main goals. First, to test whether asymmetry of motor symptoms in PD is reflected in an asymmetry of BP. Second, to test whether a

normal physiological asymmetry of cognitive event-related potential is disrupted by the asymmetrical neurodegeneration that characterizes PD.

1.1 Structure of the thesis

At the beginning of section 2 the theoretical framework relevant for the study is presented. This includes concepts of symmetrical and asymmetrical brain functionality, the description of PD as a prototype of asymmetric brain disorder caused by dopaminergic deficit, and a review of the effects of dopaminergic medication on cognitive functioning. Then, the theoretical background of event-related EEG potentials is introduced. Section 3 contains the study methods. Results are presented in section 4. Section 5 discusses the significance of the findings, including study limitations.

2. Background

2.1 The Architecture of the Brain

In a Neuroscience perspective, the concepts of symmetry and asymmetry are closely tied to the two hemispheres of the human brain, and the mirror symmetrical organization of the body along the vertical body axis, producing two mirror body halves. (Hugdahl, 2005, p. 119)

Symmetry in structure does not necessarily imply symmetry in function and, in this regard, the external structure of the brain might be to some extent misleading. Despite their macroscopic appearance, the two halves of the human brain are not completely equivalent, as they present a number of functional asymmetries (Hugdahl, 2005). The relation between the hemispheres is not only a subject of scientific research, but it has been a fashionable topic also outside of the academic community. A widespread misrepresentation of the functional difference between the hemispheres, often used for marketing purposes, states that the “left brain” is rational whereas the “right brain” is creative (Hellige, 1993). The goal of this section is to illustrate the scientific aspects of symmetry and asymmetry in brain functionality and to present the framework of our research.

2.1.1 Symmetry

One of the fundamental properties of most biological systems is a rough bilaterally symmetrical organization. In general, this applies to the human brain as well,

structurally and functionally (Duboc, Duforcq, Blader, & Roussigné 2015). In fact, its neurophysiological architecture appears to be strongly symmetrical (Figure 1). Evidence from functional Magnetic Resonance Imaging (fMRI) research suggests that, during resting state, homologous regions process information bilaterally (Salvador et al., 2005). The left and the right side of the body are predominately controlled by the sensorimotor systems in the contralateral hemisphere (Harrison, 2015). The motor network is a clear model of this mirror symmetrical control. When a person moves a limb, the execution of the movement is primarily processed by the contralateral motor cortex (Bear et al., 2007). This characteristic of the brain was observed very early in history. In ancient Greece, doctors from the Hippocratic school realized that wounds on one side of the head could be associated with convulsions on the opposite side of the body. Evidence for this can be found in the so-called “Hippocratic Corpus”, written around 400 B.C. (Prins, 2006).

Although the final execution of movement depends on the contralateral hemisphere, planning of the movement occurs bilaterally instead (Jahanshahi & Hallett, 2003). Furthermore, evidence shows that humans have a natural tendency towards symmetrical contraction of homologous muscles. Bilateral movements are associated with proportionally less cortical activation, compared to alternated bimanual movements or unilateral movements (Cincotta & Ziemann, 2008). The execution of strictly unilateral movement requires complex interhemispheric interactions between a wide range of cortical areas. The two hemispheres of the brain communicate continuously through a thick tract of white matter known as the Corpus Callosum (CC) (Harrison, 2015). During the performance of unilateral movement, the

CC inhibits the motor output from the primary motor area (M1) in the hemisphere ipsilateral to the movement (Beaulé, Tremblay, & Théoret, 2012). Mirror movements (i.e. involuntary movement of corresponding muscles from the contralateral side that accompany the intended movement) appear in fatiguing tasks or are a sign of motor dysfunction (Espay, Li, Johnston, Chen, & Lang, 2005).

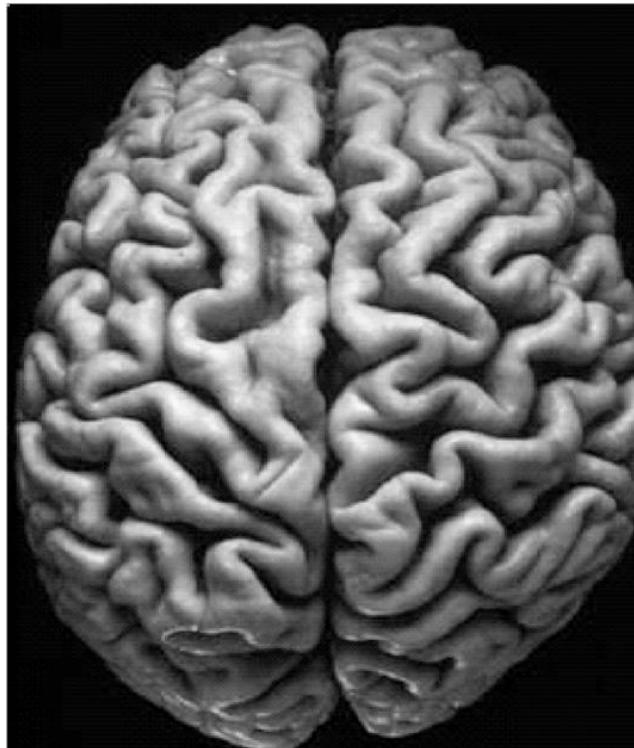


Figure 1 This superior view of a human brain highlights the symmetry that characterizes its structure. The two hemispheres, physically separated by the longitudinal fissure in the middle, are strongly interconnected through the CC underneath. (Source: Hugdhal, 2005, p. 120)

However, there is at least one clear preference for motor functions in human behavior that is handedness, i.e. the preference for using one hand (the 'dominant')

with respect to the other. Despite the left hemisphere being dominant for handedness in 90% of individuals (Bear et al., 2007), the anatomic asymmetries inside the motor network are negligible (Toga & Thompson, 2003). For instance, it has been suggested that there is a larger neural mapping of the dominant hand in M1 as a consequence of practice and brain plasticity (Hammond, 2002). However, the general structure of the motor network is not affected.

2.1.2 Asymmetry

Symmetry, and especially bilateral symmetry, has generally been associated with harmony and perfection, but also with a form of boring rigidity. Instead, asymmetry is often associated with chaos, but at a subjective dose, its unpredictable nature makes it attractive. (Duboc et al., 2015, p. 648)

Despite anatomic symmetry, many relevant functional asymmetries have been observed in relation to a number of cognitive functions. The exploration of hemispheric asymmetries in neuroscience can be tracked back to Broca's famous paper dated 1861 (Broca, 1861/2011). The paper describes a case study of a patient who presented a massive speech impairment. This was connected to a lesion in the region of the left frontal cortex now known as Broca's area. It was the first piece of evidence that the left hemisphere had a dominant role in language processing (Ocklenburg & Güntürkün, 2012). Following Broca's study, the concept of cerebral dominance for specific functions became widely accepted (Galaburda, Lemay, & Kemper, 1978). The idea that the two hemispheres of the brain would be specialized

for different functions became central in research. Although language is one of the most straightforward examples of hemispheric asymmetry, several other cognitive functions showed similar lateralization. During times in which neuroimaging did not yet exist, this theory was backed-up by evidence from lesion studies producing specific dysfunctions. In the 1960s-70s, reports on the behavior of the so-called “split brain” patients suggested asymmetrical aspects of cognition that impressed researchers as well as the general public (Hellige, 1993). For instance, the following is a report on the behavior of a patient after surgery. The patient’s CC was cut, so that his hemispheres were no longer connected:

For a considerable period after the operation the left side of the body rarely showed spontaneous activity, and the patient generally did not respond to stimulation of that side: when he brushed against something with his left side he did not notice that he had done so, and when an object was placed in his left hand he generally denied its presence. (Gazzaniga, 1967, p. 24)

This report illustrates an attentional deficit affecting the left side of the body and indicating vulnerability of the right hemisphere. Evidence suggests that the right hemisphere would be more specialized for attention than the left one (Stevens, Calhoun, & Kiehl, 2005). Attention can be defined as the ability to selectively process different sources of information (Bear et al., 2007). It enables focused processing of relevant data out of a larger amount of incoming information (Dreo, Attia, Pirtošek, & Repovš 2016). Evidence of right hemispheric dominance was observed in relation to several attention-related tasks, especially in frontal areas (Corbetta & Shulman, 2002).

It has been suggested that a network reliant on right hemispheric regions could be prominently involved in sustained attention, stimulus evaluation, target detection, and working memory (Gilmore, Clementz, & Berg, 2009). Working memory can be defined as “an active system for temporarily storing and manipulating information needed for the execution of complex cognitive tasks” (Frank, Loughry, & O’Reilly, 2001, p. 138).

In summary, motor execution is represented by a network mainly relying on the contralateral hemisphere, without hemispheric dominance. Both right and left limb movements activate contralateral areas of the cortex (with a contribution from ipsilateral ones), in a mirroring fashion. At the same time, several cognitive functions rely on asymmetric networks, in which regions located either in the right or in the left hemisphere are primarily involved, so that one hemisphere may be dominant for a specific function. The relation between hemispheres is complicated, specific to functions and networks. Different tasks could rely on either symmetrical or asymmetrical forms of processing. These ideas emerged very early from observed lesion studies, evolving and refining in the course of time thanks to the use of modern neurophysiological techniques.

2.2 Parkinson’s Disease

Several neurological diseases are characterized by a prominent clinical asymmetry from disease onset (Gordon, 2016), with Parkinson's disease (PD) being one of the most common (Bear et al., 2007; Connolly & Lang, 2014). PD is a chronic

neurodegenerative disease caused by a loss of dopaminergic neurons in the substantia nigra pars compacta (SN) (Thenganatt & Jankovic, 2014). Its onset is typically asymmetric, with one side of the body presenting more evident motor symptoms (Barrett, Wylie, Harrison, & Wooten, 2011). This indicates that the contralateral hemisphere is significantly more affected (Blesa, Juri, & Adanez, 2011). Symptoms of PD arise as a consequence of midbrain and basal ganglia (BG) dysfunction, which are connected to cortical areas through motor, associative, and limbic circuits (Rinne et al., 2000). The disease eventually affects widespread brain networks in addition to motor circuits. Thus, although PD is primarily known as a motor disease, patients also manifest cognitive and psychiatric symptoms. The lateralized onset and progression of PD generates a hemispheric imbalance that makes PD an excellent model to investigate functional changes affecting the interaction between hemispheres (Cronin-Golomb, 2010).

Motor symptoms of PD include resting tremor, bradykinesia (i.e. slowness of movement), and rigidity, with postural instability appearing later in the disease course (Jankovic, 2008). The severity of the motor symptoms and their asymmetric distribution can be quantified by clinical rating scales (Goetz et al., 2007; 2008). At its onset, PD shows the most straightforward lateralized pattern of motor symptoms. Although asymmetry becomes less pronounced as the disease progresses, it can still be detected even in advanced stages (Melamed & Poewe, 2012). There is no clear explanation for the characteristic asymmetric neurodegeneration in PD (Djaletti, Ziv, & Melamed, 2006; Hobson, 2012). Handedness might be an important factor determining the side of PD onset (Uitti, Baba, Whaley, Wszolek, & Putzke, 2005), since

in approximately 60% of the cases the symptoms begins on the dominant hand side (Van der Hoorn, Burger, Leenders & De Jong, 2012).

2.2.1 Non-motor Symptoms

PD is also characterized by a variety of non-motor symptoms. This includes a wide range of cognitive and neuropsychiatric disturbances (Pellicano et al., 2015). PD patients generally experience cognitive decline with disease progression (Aarsland, Bronnick, Larsen, Tysnes, & Alves, 2009), but its nature and severity varies widely (Katzen, Levin, & Weiner, 2006). Additionally, the range of cognitive symptoms is heterogeneous (Kehagia, Barker, & Robbins, 2010). It includes impairment of attention and working memory. Other common cognitive symptoms of PD include impairment of learning, verbal fluency, and executive functions (Moustafa, Sherman, & Frank, 2008; Muslimović, Post, Speelman, & Schmand, 2005; Rinne et al., 2000; Teramoto et al., 2016). During the advanced stages of the disease, PD may result in dementia, a risk increasing with disease progression (Braak, Rüb, Jansen Steur, Del Tredici, & de Vos, 2005).

The role of the side of onset on the pattern of cognitive decline in PD is unclear. Some studies suggest little or no interaction, stating that the most affected side influences motor functions but not cognitive ones (Cubo, Martin, Martin-Gonzalez, Rodriguez-Blazquez, & Kulisevsky, 2010; Pellicano et al., 2015). However, other studies have proposed complex relationships between motor and cognitive symptoms (Katzen et al., 2006). It has been suggested that left-sided onset of motor symptoms could be related to a decreased performance in a number of cognitive measurements

and a higher degree of cognitive decline (Riederer & Sian-Hulsmann, 2012; Tomer et al., 1993). This indicates a more important role of the right hemisphere in the development of PD's cognitive symptoms. This topic has also been recently reviewed by Verreyt, Nys, Santens, & Vingerhoets (2011), with the conclusion that right-sided onset correlates with problems in language-related tasks, while left-sided onset of motor symptoms correlates with problems in spatial attention, mental imagery and memory tasks.

2.2.2 Dopaminergic Medication

The initial cause of PD is dopamine depletion. Dopamine is a neurotransmitter playing an important role in regulating and integrating different aspects of brain functionality (Nieoullon & Coquerel, 2003) (Figure 2). It has been shown to be involved in movement control, motivation, and cognition (Arias-carrion & Pöppel, 2007). Rather than a single system, dopaminergic neurons are involved in different task-specific pathways (Alexander, De Long, & Strick, 1986). PD patients are administered dopaminergic medication as a replacement therapy, to compensate for the loss of dopamine-producing cells and reduce motor symptoms (Connolly & Lang, 2014; Kehagia et al., 2010; Nieoullon & Coquerel, 2003). In PD patients, a decrease in cognitive performance correlates with a lower uptake of dopamine (Rinne et al., 2000).

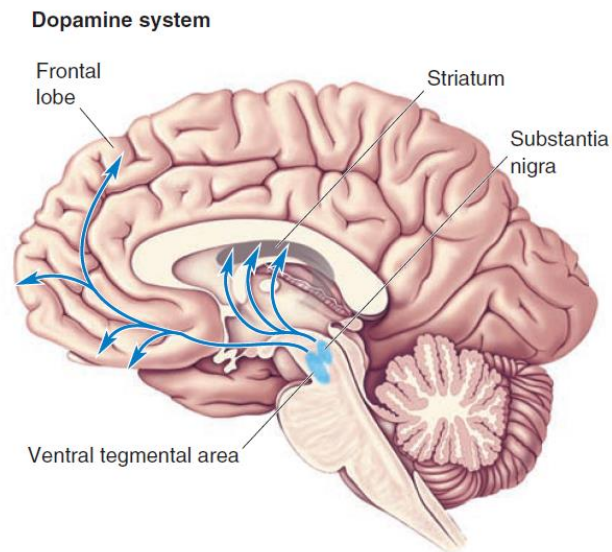


Figure 2 Representation of the dopaminergic pathways that extend from the midbrain towards the cortex. The network of dopamine projections has been mapped in detail previously (Bjorklund & Dunnett, 2007). In the figure, two main pathways are represented: the nigrostriatal system (starting from SN, reaching cortical areas of the motor network) and the corticolimbic system, projecting towards PFC and primarily involved in cognitive functions (Alexander et al., 1986). They are differentially affected by PD (Cools et al., 2001). (Source: Bear et al., 2007, p. 503)

Variability in the response to dopaminergic drugs in PD patients can be observed across different tasks and behaviors, as well as between different individuals (Cools & Esposito, 2011). Initially, the loss of dopaminergic functionality affects mainly the motor control, while there is still a sufficient level of dopamine to support cognitive functioning. Consequently, replacement therapy may result in an “excess” of dopamine, thus having negative effects on the performance of specific

cognitive tasks (Slagter et al., 2016). The dopamine overdose hypothesis states that dopaminergic medication effects follow an inverted U-shaped function. Both too little and too much dopamine impairs performance (Cools & Esposito, 2011). It has also been suggested that medication would restore some cognitive functions while impairing others, in a task-dependent manner (Cools, Barker, Sahakian, & Robbins, 2001; Evens, Hoefler, Biber, & Lueken, 2016). Deleterious effects of medication have been documented in relation to learning, attention, and decision making (Evens et al., 2016; Slagter et al., 2016; Swainson et al., 2000). The different effects of therapy on different cognitive functions probably depends on variability in dopamine depletion in separate pathways (Kish, Shannak, & Hornykiewicz, 1988).

In conclusion, PD is a valuable model to investigate the functional relation between hemispheres. First, because the motor network is differentially affected between sides because of asymmetric dopamine depletion. Second, because it is possible to examine how this depletion, as well as medication, modulates cognitive dysfunctions in PD.

2.3 EEG and ERP

We collected neurophysiological data using electroencephalography (EEG). This technique allows us to record the electrical activity from a participant's brain (Figure 3). Largely used for research and clinical purposes, the EEG procedure is non-invasive and has been employed to study very diverse cognitive and motor phenomena (Picton, 2000). EEG is characterized by a great temporal but poor spatial resolution. The raw

EEG data represents a conglomerate of different neural activities and noise. By applying the right processing steps, it is possible to extract responses associated with specific cognitive functions (Luck, 2014). The first EEG recording was performed in 1929, when Hans Berger showed that electrical signal could be recorded by use of an electrode placed on the scalp (Berger, 1929). While at first the resulting output was believed by many researchers to be just an artifact, it was soon acknowledged that it represented actual electrical activity from the brain (Luck, 2014).

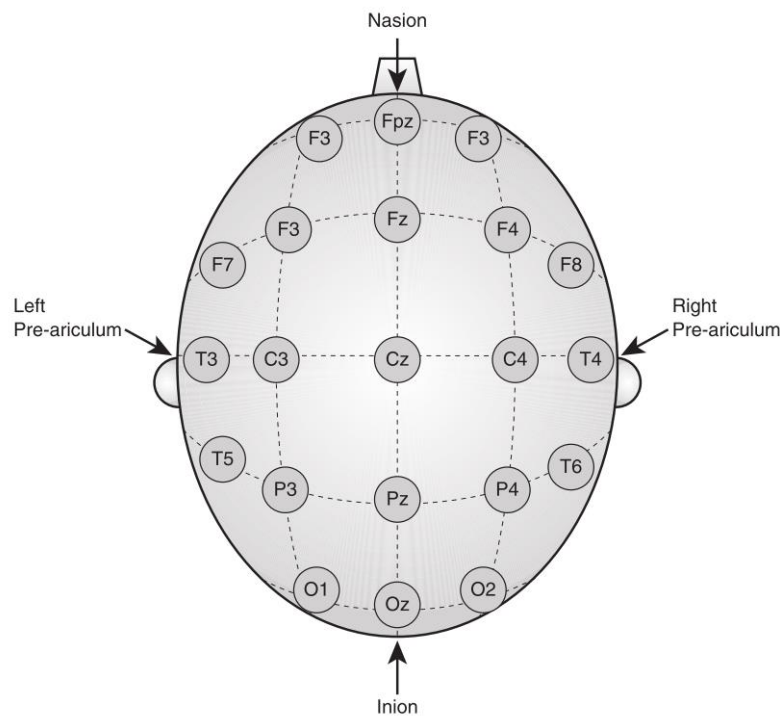


Figure 3 A depiction of EEG electrode locations ordered according to the international 10/20 system of electrode placement. This well-known system is agreed upon by the research community and aids reproducibility in the field (Luck, 2014). More complex EEG setups are available, including higher numbers of electrodes. (Source: Dickter & Kieffaber, 2014, p. 40)

There are many approaches analyzing EEG data, including the event-related potential (ERP) technique (Dickter & Kieffaber, 2014). ERPs are usually evoked by the perception of an external stimulus or by the preparation and execution of a response. In the ongoing EEG activity, they appear as amplitudes averaged after many repetitions of the stimuli that are time-locked to certain sensory, motor or cognitive events (Georgiev, Lange, Seer, Kopp, & Jahanshahi, 2016). ERPs are small with respect to the level of noise, and therefore many repetitions of a task are necessary so that an average value can be taken. This data can be analyzed in many ways, but it is usually described in terms of amplitude (i.e., the dimension of the evoked waveform) or latency (i.e., the delay of the waveform with respect to the event). Both motor and cognitive ERP responses can be detected using different paradigms of this technique. This allows for evaluation of the brain's processing of relevant events that precede behavioral responses. Limitations of the ERP technique include the difficulty to clearly locate the neural generators, and to distinguish the underlying activities of the brain during a task when several are simultaneously possible (Luck, 2014).

2.3.1 Readiness Potential and Related Motor Functions

PD affects motor functions in an asymmetrical way. In order to explore the EEG correlates of this motor asymmetry, we tested an ERP that is connected to the preparation and execution of self-timed movements. It is known as Readiness potential, or by its German name *Bereitschaftspotential* (thus BP). It was first reported by Kornhuber & Deecke (1964). BP is a movement-related potential – i.e. an ERP that is associated in different paradigms with processes of voluntary movement

preparation, initiation, and execution (Georgiev et al., 2016). It is time-locked to the subject's action, e.g., pressing a button. In the EEG signal filtered from noise, BP appears as a negative slope preceding the movement. To experimentally measure BP, participants are asked to voluntarily perform a predefined number of identical movements and to vary the interval between them (Verleger, Haake, Baur, & Smigasiewicz, 2016). The subject moves on their self-timed decision, without following any external clue. BP's reputation is especially related to the experiments of Libet, Gleason, Wright, & Pearl (1983), which connect it to the philosophical concept of free will. This famous study suggested that the neural processing related to the preparation of a movement begins before the awareness of the decision to move. Therefore, BP may relate to cognitive concepts such as awareness, decision making, and movement planning. While Libet's research and the consequent debate is fascinating and inspiring, it is not relevant in our study and, therefore, will not be discussed further. From a more direct point of view, BP is simply a measure related to motor preparation and execution (Shakeel et al., 2015).

Different terminologies have been used to identify components of BP. We focused on two components: early BP and late BP. Early BP is a slowly decreasing section, more pronounced at scalp midline. It begins roughly two seconds before movement. The current state of research converges towards the idea that early BP represents activation of the supplementary motor area (SMA). This component does not indicate the side of movement in healthy subjects. Late BP is a steeper section closer to movement time (starting ca. 650ms). It reaches a peak amplitude just before the movement. The late BP component has been shown to represent activation of M1.

It is larger on the central electrode contralateral to the side of movement. Therefore, it reveals which side is going to be moved. The late BP is maximal over the contralateral central area (approximately C1/C2 of the International 10–20 EEG system) for the hand movement (Jahanshahi & Hallett, 2003). BP's shape and components are depicted in Figure 4.

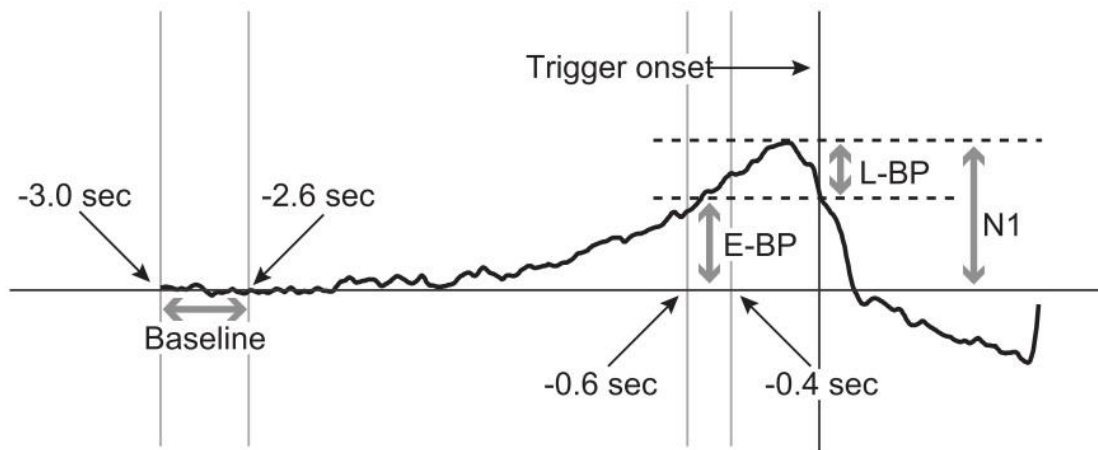


Figure 4 Shape of the BP potential and its subcomponents. The negative value is plotted upwards and the positive downwards, following a widespread convention in ERP research (Luck, 2014). From the baseline, the slope grows and peaks before the movement (marked as “trigger onset”). In our study we analyzed early BP (marked as “E-BP”) and late BP (marked as “L-BP”). (Source: Fumuro et al., 2013, p. 1400)

BP is particularly relevant in relation to motor impairment of PD. It is known that PD involves impaired activation of frontal cortical areas, including the SMA and prefrontal cortex (PFC) (Jahanshahi & Hallett, 2003; Macdonald & Halliday, 2002).

Early BP, but not late BP, was observed to be reduced in PD (Dick et al., 1989; Shibasaki & Hallett, 2006), although this was not confirmed by all studies (Georgiev et al., 2016). Another seminal study reported that dopaminergic medication causes an increase in early BP in both PD patients and healthy controls. On the other hand, late BP was observed to be unaffected by the disease (Dick et al., 1987). This suggests that early BP is related to the level of dopamine present in the system more directly than late BP. One study investigated the changes of BP potentials in relation to PD asymmetric onset in completely unilateral cases of PD. It was found that electrodes contralateral to the affected side show a reduction in the amplitude of late BP with respect to the unaffected side (Simpson & Khuraibet, 1987). This result suggests that BP could be differentially affected by side of onset of motor symptoms and by dopaminergic medication.

2.3.2 Oddball Task and Related Cognitive Functions

To investigate neurophysiological correlates of cognitive deficit in PD, we chose to test P3, an ERP time-locked to a perceptual stimulus, related to attention processing and working memory. Morphologically, it appears after the stimulus as a large positive component. It is highest near the midline, at electrodes Fz, Cz, and Pz (Polich, 2007). Although the neural generators of P3 components are still not entirely clear, evidence from different imagining studies converge towards highlighting a frontal to parietal activation pattern (Huang, Chen, & Zhang, 2015).

P3 appears to be specifically enhanced as a response to rare stimuli. In fact, it has been consistently observed that an infrequent stimulus elicits a larger P3

amplitude than a frequent one (Ritter, Vaughan, & Costa, 1968; Luck 2014). P3 was first described in 1965, in connection to visual and auditory stimuli, peaking at around 300 ms after the stimulus (Sutton, Braren, Zubin, & John, 1965). For this reason it was at first called P300. However, its latency has been usually found to be longer and it is affected by a large number of variables. Therefore, it is now commonly reported in literature as P3 (i.e., the third positive peak on EEG after stimulus). The most common task to study P3 is the oddball paradigm. An oddball paradigm consists of a series of repeated perceptual stimuli, of two or three different kinds, that is presented to the subject of the experiment (Figure 5). Several paradigms of the oddball task exist, including different sensory modalities and stimulus types. Visual and auditory modalities are the more commonly used (Luck, 2014).

The three-stimulus oddball elicits two major sub-components of the P3 amplitude. Target and distractor stimuli are embedded in a series of frequent standard stimuli. Usually, the participants are required to keep track of the targets while ignoring the distractors (Polich, 2007). With respect to the task, distractor stimuli elicit a 'p3a' and target stimuli elicit a 'p3b' amplitude (Courchesne, Hillyard, & Galambos, 1975). These two ERP subcomponents reflect different cognitive processes. Peaking at frontocentral EEG electrode locations near midline, P3a is related to redirection of attention. It is evoked by a distractor stimulus and is primarily modulated by dopaminergic pathways. On the other hand, P3b is believed to underlie a more conscious response involving working memory processing. It has been suggested that it is produced when attention resources are allocated for memory updating. On the scalp, it appears more posteriorly, peaking at centroparietal

electrode locations near the midline. It is associated to target stimuli and is probably mediated primarily by locus-coeruleus–norepinephrinergic (LC-NE) pathways (Polich & Criado, 2006). P3a peaks earlier than p3b (Courchesne et al., 1975; Polich, 2007).

Normally, P3b amplitude is asymmetric in both visual and auditory modality. It was reported as larger at right than left electrode locations (Alexander et al., 1995; 1996). The visual P3a is also asymmetric, to a minor extent, while less is known about asymmetry of auditory P3a. Studies using fMRI highlighted a role of right PFC areas in this task (Bledowsky, Prvulovic, Goebel, Zanella, & Linden, 2004; Brazdil, Mikl, Marecek, Krupa, & Rektor, 2006; Strobel et al., 2008). This evidence reinforces the hypothesis of right hemispheric dominance for attention.

P3 has long been known to be affected by PD (Lagopoulos et al., 1998; Tsuchiya, Yamaguchi, & Kobayashi, 2000), but variability is very high in the reported results. This is probably due to uncontrolled factors related to PD's biology, or use of different methodologies. A recent review suggested that, while P3b is clearly affected in demented PD patients, there is less evidence that this would hold for non-demented PD patients (Seer, Lange, Georgiev, Jahashahi, & Kopp, 2016). P3a has recently been proposed as a potential biomarker of PD, since it was observed to be reduced in PD patients with respect to controls (Solis-Vivanco et al., 2015; Kaufman, Bowers, Okun, Van Patten, & Perlstein, 2016). Additionally, auditory P3a is affected by dopaminergic medication. An increase in amplitude was observed in PD patients on medication, with respect to the same group off medication (Georgiev et al., 2015). In the reviewed

literature no published study was found on the topic of P3's asymmetry in PD.

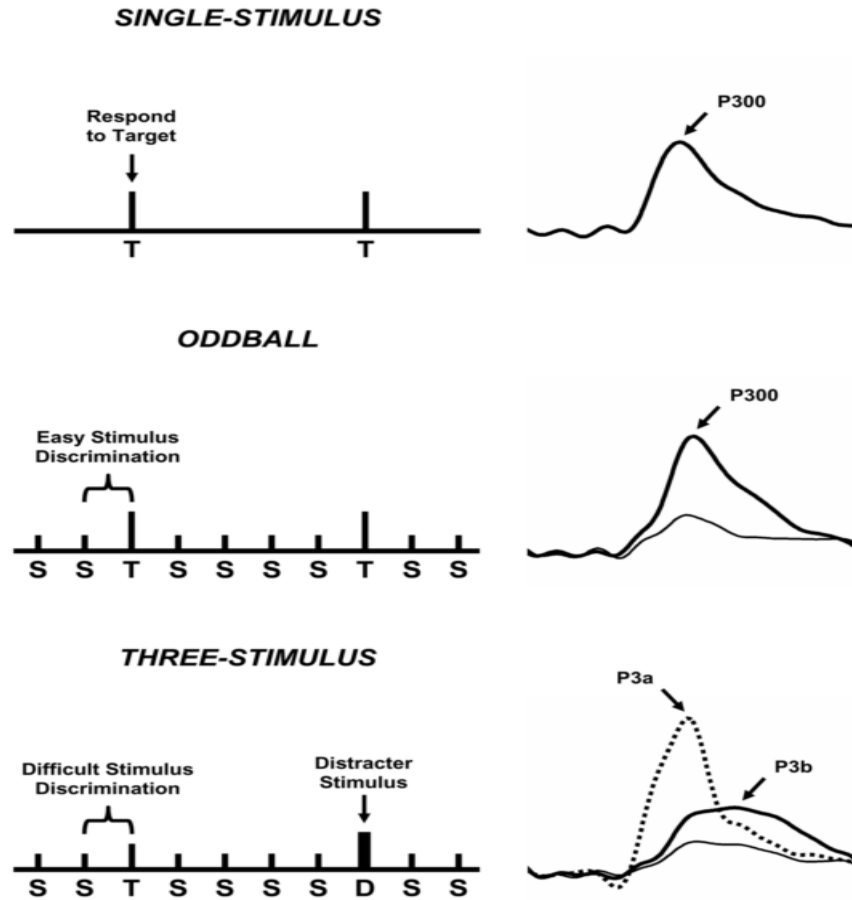


Figure 5 A representation of different paradigms to elicit P3 responses. In general, P3 is enhanced in relation to rare stimuli (top). For this reason, a paradigm was developed in which rare target stimuli are embedded in a sequence of frequent standard ones known as oddball task (middle). In our experiment, we employed a more complex paradigm called three-stimulus or three-way oddball. In the sequence there is an additional rare distractor stimulus, unrelated to the task performance. Target and distractor stimuli enhance two different sub-components of P3, known as P3b and P3a respectively. (Source: Polich & Criado, 2006, p. 173)

2.4 Our study

The present research is composed by two experiments, involving one motor and one cognitive task respectively. We used models of tasks that involve processing information in a way that is either symmetrical (early BP), contralaterally symmetrical without hemispheric dominance (late BP), or asymmetrical with right hemisphere dominance (auditory and visual P3). We investigated how lateralized diseases such as PD may affect these tasks. For this purpose, we collected and analyzed neurophysiological data from PD patients on and off medication as well as healthy controls. The recordings were performed in the context of another experiment and partial data from the oddball task, not including analysis of asymmetry (focus of the present study), has been published (Georgiev et al., 2015). BP data has not been previously analyzed. My main contributions to this project include literature review, data analysis, the description of results and their discussion. I have practical experience in the experimental tasks employed as well as experience in EEG recording. I have carried out several experiments at the laboratory using the same paradigms and technique.

2.4.1 Motivation

Our main experimental goal is to investigate changes in the normal hemispheric balance underlying motor and cognitive functions in PD, and its relation to dopaminergic medication. The first goal is to reach a better understanding of interhemispheric differences in PD that can be detected at the level of the cerebral cortex. Recently, several studies focused on the identification of potential biomarkers

of PD; as a result, several variations in EEG patterns have been proposed as possible candidates for early PD detection (Klassen et al., 2011; Mostile et al., 2015; Solis-Vivanco et al., 2015). To our knowledge, none of these studies considered hemispheric differences in EEG patterns. Additionally, by testing PD patients on and off replacement therapy, we can assess how these parameters are modulated by dopamine.

EEG is a relatively inexpensive research method, widely used in clinical environments. ERP components may offer an insight of which stage of neural processing is affected in the examined tasks. Both BP and P3 are relatively well-known ERPs (Georgiev et al., 2016; Luck, 2014). Even though the literature around them is abundant, little attention has been paid to hemispheric asymmetries of cognitive ERPs (Gilmore et al., 2009).

2.4.2 Interdisciplinary Aspects of the Research

The present project can primarily be framed in the field of cognitive neuroscience. Carrying out research in cognitive neuroscience is an intrinsically interdisciplinary endeavor. It requires knowledge from disciplines as diverse as biology, physics, computer science, and psychology. This reinforces the relevance of developing interdisciplinary team-working and communication skills.

In the present study, the literature research included the historical development of the topic of brain symmetry and asymmetry. This involved a review of different hypotheses of hemispheric functionality from the early days to the contemporary understanding (philosophy, history of science). The subject pool

included neurological patients and research on all aspects of PD was central to the present study (neuroscience, medicine). The oddball paradigm was used to test some aspects of their cognitive functionality (cognitive psychology). Further, EEG data was collected and processed (neuroscience, electrical engineering). Technical software and different programming languages were used for data and statistical analysis (computer science, statistics). For all these reasons, the current project may be regarded as interdisciplinary work.

Furthermore, the findings of this study are relevant for other areas related to cognitive science research. BP and its components find application in the development of Brain-Computer interfaces (Shakeel et al., 2015), while studying the neural processing connected to attention and memory can inform disciplines such as psychology, human-computer interaction, and artificial intelligence.

2.4.3 Research Questions

The goal of our research was to test differences between hemispheres in BP and P3 potentials in an asymmetric disease such as PD and the relation of ERPs to dopaminergic medication. We framed the following null (H0) and alternative (H1) hypotheses.

Motor task

BP and PD asymmetry

(H0) There is no difference in BP between more affected and less affected body side in PD patients, nor compared to controls.

(H1) There are differences in BP between more affected and less affected body side in PD patients, and compared to controls.

BP and medication

(H0) There is no effect of dopaminergic medication on BP in PD patients.

(H1) There are effects of dopaminergic medication on BP in PD patients.

UPDRS and BP

(H0) There is no correlation between lateralized UPDRS scores and corresponding BP.

(H1) There is a correlation between lateralized UPDRS scores and corresponding BP.

Cognitive task

P3 and PD asymmetry

(H0) There is no difference in hemispheric asymmetry of P3 between PD patients and controls.

(H1) There are differences in the hemispheric asymmetry of P3 between PD patients and controls.

P3 and medication

(H0) There is no effect of medication on hemispheric asymmetry of P3.

(H1) There are effects of medication on hemispheric asymmetry of P3.

P3 and side of PD onset

(H0) There is no difference in hemispheric asymmetry of P3 between PD patients with right-sided onset vs. left-sided onset.

(H1) There are differences in hemispheric asymmetry of P3 between PD patients with right-sided onset vs. left-sided onset.

3. Methods

3.1 Participants

A total of 28 subjects participated in the study. Due to technical error during EEG recordings, one PD patient was excluded from the experiment. The effective subject pool included 14 PD patients (6 females, 8 males; 10 right-handed) and 13 healthy participants (6 females, 7 males; 12 right-handed). The two groups were matched by age (PD patients group = $60,39 \pm 12,25$ years old; control group = $57 \pm 8,58$ years old), education, and handedness. All participants reported normal or corrected to normal vision and hearing. All of them signed an informed consent. The study was reviewed and approved by the medical ethical committee at the University of Ljubljana. All subjects performed an active three-stimulus oddball task, consisting in visual and auditory blocks. Additionally, 10 of the PD patients and all healthy participants performed the motor task. Four PD patients did not perform the motor task due to fatigue.

3.2 Experimental Procedure

Cognitive and motor tasks were recorded from each subject during the same session. PD patients underwent two different sessions, on and off dopaminergic medication, separated by at least one week. For the “off” condition, medication was withdrawn for a time of at least 12 hours before recording (range: 12–17 h), in line with previous research (Dick et al., 1987). The recordings were performed in a randomized,

counterbalanced fashion, in order to prevent learning and habituation effects that could arguably modulate their neurophysiological and behavioral responses to the oddball task. Thus, half of the patients performed the task first off and later on medication and vice versa (Georgiev et al., 2015). The healthy controls performed the task only once. The motor symptoms of PD patients were rated according to the Unified Parkinson's Disease Rating Scale (UPDRS) III both in the on and off condition.

3.2.1 The UPDRS test

The UPDRS III is a clinical test to evaluate and quantify motor symptoms of PD. Performed by a clinician, the test gives a reliable value of the current state of the motor symptoms (Goetz et al., 2008). Using UPDRS scores off medication, we defined a more affected (MA) and a less affected (LA) body side for each patient. A lateralized UPDRS score was calculated for each body side as the sum of the items that are related to upper and lower limbs' bradykinesia, tremor, and rigidity. Using as a criterion the difference of at least one point between the two values, the higher value obtained was defined as the MA side and vice versa. This method of analysis was previously used by Gomez-Esteban et al. (2010). Relevant scores and data for each PD patient are given in Table 1.

Table 1: UPDRS scores

	More Affected		Less Affected		MA Side ¹	Total ²		L-DOPA equivalent dose ³
<u>Subj.</u>	<u>OFF</u>	<u>ON</u>	<u>OFF</u>	<u>ON</u>		<u>OFF</u>	<u>ON</u>	
s01	17	15	8	2	L	35	23	340
s02*	21	14	14	10	L	48	35	1065
s03	23	13	10	5	R	42	27	480
s04	11	9	8	2	R	27	19	715
s05	19	19	10	13	L	41	41	880
s06	17	12	7	3	L	37	22	260
s07	15	12	6	1	R	29	20	300
s08	25	18	16	6	L	53	35	992
s09*	16	12	13	11	R	43	34	360
s10*	17	18	10	11	L	37	37	300
s11	23	18	15	10	R	51	35	240
s12	17	11	10	10	R	39	32	600
s13	18	11	7	3	R	34	20	240
s14*	23	13	13	5	R	45	29	120
MEAN	18.71	13.93	10.5	6.57		40.07	29.21	492.28
STDEV	3.85	3.17	3.2	4.11		7.66	7.34	306.83

Subjects marked with * participated to the oddball but not to the BP task.

¹ More affected side of the body in terms of left (L) vs. right (R) asymmetry.

² The total UPDRS score is not simply the total of the affected sides because some of the UPDRS entries are side-independent.

³ Medication dosage described as the equivalent amount of dopamine.

Side-specific and total UPDRS scores of the PD patients. Both scores on and off medication are included, as well as medication dosages for each subject.

3.2.2 Recording conditions

The experiment was conducted in the Laboratory for Cognitive Neuroscience (Medical University Center Ljubljana, Slovenia). EEG recordings were performed in a sound-proof and electrically shielded room. During the experiment, the participants were sitting comfortably on a chair in front of a 27-inch computer monitor. The distance between their head and the monitor was one meter. The head was not fixed and minor movements to adjust position were allowed, as is normal in this setup. In order to prevent the formation of excessive artifacts in the EEG recordings, however, the participants were instructed to sit still. Neurophysiological data was collected using an EEG cap with a chinstrap (ActiCap, Brain Products). The cap consisted of an arrangement of 34 active electrodes (including ground and reference) placed according to the 10/20 standard system. Abrasive gel was used to scrub the participants' scalp at the ground and reference electrodes. Conductivity between the electrodes and the scalp was obtained through the application of a small quantity of conductive gel beneath the electrodes by mean of a syringe. This procedure was aimed to keep the impedance below 10 k Ω . The syringe was then used to move the subjects' hairs away from the center of the electrode, an additional measure to facilitate the conductivity between the electrodes and the skin. This was achieved by performing a rotatory movement. Data was recorded using a BrainAmp (Brain Products) amplifier with a sampling frequency of 512 Hz and a cutoff of 0.01 Hz.



Figure 6 Picture taken during a pilot study, showing the subject station and one of the 32 electrodes EEG setup in use at our laboratory (Picture courtesy of Maja Kapitler and Filip Agatić).

3.2.3 Tasks

Motor task

In the motor experiment participants were asked to perform a self-paced hand movement. This task is a typical paradigm meant to elicit a BP potential. The movement consisted of clicking the button of a computer mouse using their index fingers. Participants were instructed to press it at self-paced intervals of more than five and less than ten seconds. No additional external stimuli or hints were presented during this task. Participants were asked not to follow any rhythm or to count the seconds but to keep the movements to a random timing. The experiment was composed of two separate blocks, in which participants performed the task once using their right and once using their left hand. Each block lasted for four minutes. The order of the right-left hand movement was randomized to exclude effects of

habituation. During the experiment, participants were asked to look at a fixation point in the center of the computer monitor. The fixation point appeared as a white cross of 1x1cm. The reason for including a fixation point in this task was to prevent large EEG artifacts related to eye movement.

Oddball task

In the cognitive experiment, the participants underwent an oddball task. The task described in this section was also reported in Georgiev et al. (2015). We employed a three-way oddball paradigm. The task included a number of rare “target” stimuli and rare “distractor” stimuli scattered amongst a series of frequent standard stimuli (Polich & Criado, 2006). The oddball task was composed of two sensory modalities, i.e., separate blocks of either visual or auditory stimuli. Subjects were instructed to mentally count the target stimuli in the series and to report their number at the end of each block. All other stimuli could be ignored.

A complete session consisted of four blocks of each sensory modality. Every session started with a block of one sensory modality, which was then followed by a block of the other. The order of visual and auditory blocks was randomized from participant to participant. The series was composed of rare targets (15%), rare distractors (15%), and standard stimuli (70% of the total). During the task, the participants were asked to fixate on a red dot that was presented on a black computer display. The display was placed at 0.69° of the participant’s visual field. This setup was constant between all the blocks and in both sensory modalities. All the stimuli (visual and auditory) were presented to the participants for a duration of 200ms. Stimulus

presentation was followed by 2500ms of inter-trial interval.

In the **auditory blocks**, the target stimuli were sinusoid, monochromatic 1000 Hz sounds. The sound of distractor stimuli was in the form of white noise. Choosing white noise over novel stimuli for distractor has been shown to enhance a robust p3a with reduced inter-trial variability (Frank, Yee, & Polich, 2012). Targets and distractors were scattered in a series of frequent standard stimuli. These stimuli were 500 Hz frequency sounds. Stimuli were presented using a system of loudspeakers set to an intensity of 60 dB.

In the **visual blocks**, the target stimuli were large blue circles (subtending 5.72° of the visual field), whereas frequent standard stimuli were smaller blue circles subtending 4.36° of the visual field. Distractor stimuli were chessboard patterns ($5.72^\circ \times 5.72^\circ$, one black or white square subtending $0.57^\circ \times 0.57^\circ$ of the visual field). All the visual stimuli were presented on the black background of the display and centered on the always-present red fixation dot. In the course of a whole experimental procedure, 85 target and 85 distractor stimuli were displayed for each sensory modality, scattered amongst 387 standard stimuli. The general design of the oddball task is depicted in Figure 7.

As is typical in ERP research, participants were accustomed to the task by an initial block of practice for each modality. The practice block was two minutes long. It included 40 stimuli for each modality (composed of eight target, eight distractor, and 24 standard stimuli). E-Prime® 2.0 Professional software was used to program and display the task on a Windows OS.

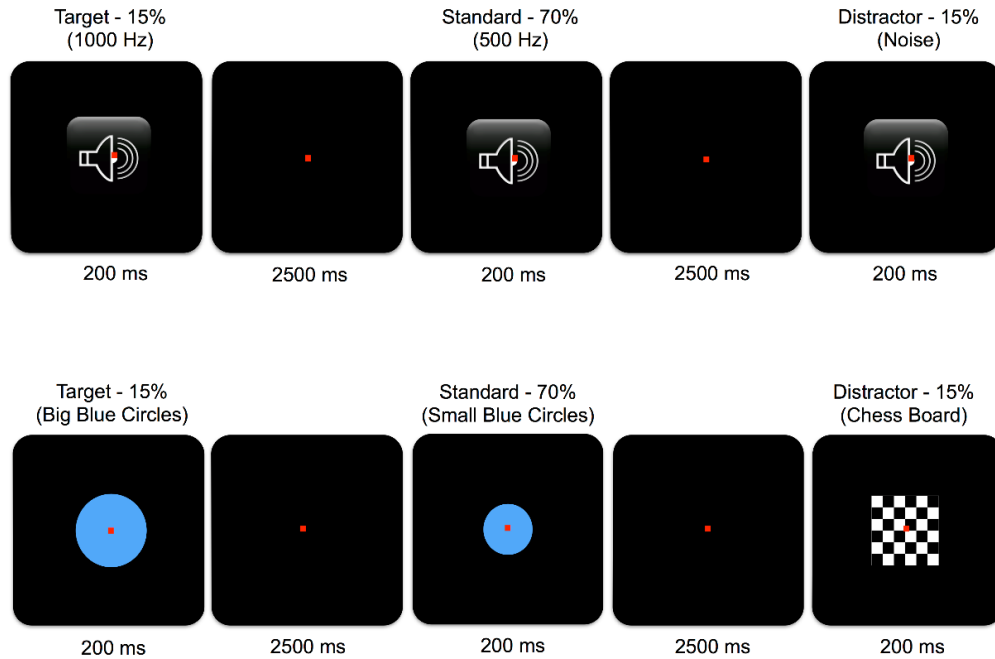


Figure 7 Description of the oddball task that was used in the experimental procedure. The task is divided in auditory (top) and visual (bottom) sensory modalities. Of the total number of stimuli presented, 15% are respectively targets and distractors, the remaining 70% are standard ones. Targets are similar to standards, while distractors are distinct from both. The fixation dot in the center of the monitor is displayed for the whole duration of the block. Stimuli are displayed for 200 ms and they are separated by a 2500ms interval. (Source: Georgiev et al., 2015, p. 48)

3.3 Data Analysis

Processing of the raw EEG data was performed in EEGLAB and ERPLAB, two open-source toolboxes of MATLAB. MATLAB (The Mathworks, Inc., Natick, MA, USA) is a full-featured programming language widely used in science and engineering (Lopez-Calderon & Luck, 2014). EEGLAB is a toolbox and graphic user interface for processing

collections of single-trial and averaged EEG data from any number of channels (Delorme & Makeig, 2004). An ERPLAB toolbox can be used to process and analyze ERP data in the MATLAB environment (Lopez-Calderon & Luck, 2014).

The early steps of our method of pre-processing EEG data, described in Georgiev et al. (2015), are here commented on more detail and with reference to the literature (Luck, 2014). First, the data was re-referenced offline to a linked earlobe that was calculated as the difference between T7 and T8. This approach takes into account two mirror electrodes and should not be biased towards a single hemisphere. Next, epochs with visible artifacts (e.g., muscle artifacts, environmental noise) were identified and manually rejected. The manual procedure is equivalent to the application of a well-designed algorithm. It presents the advantage of training the researcher's eye in the task and familiarize them with the data. On the other hand, it is more time-consuming (Figure 8). Bad channels were identified, excluded from independent component analysis decomposition, and interpolated using spherical spline interpolation after removal of components capturing noise and artifacts. The independent components reflecting eye blinks, eye movements and muscle activity were identified by visual inspection of the topographical distribution of the components, signal to noise ratio and the frequency spectrum of each independent component.

For the **motor task**, the data was time-locked to the moment of the movement (marked on the data by the mouse click). Epochs were generated starting 2500ms before and ending 1000ms after the event. Baseline correction was performed between 2500ms and 2000ms before movement.

For the **oddball task**, the data was time-locked to the presentation of the stimuli. Epochs were generated, starting 500 ms before and ending 2000 ms after stimulus presentation. Baseline correction was performed between 500 ms and 0 ms before presentation.

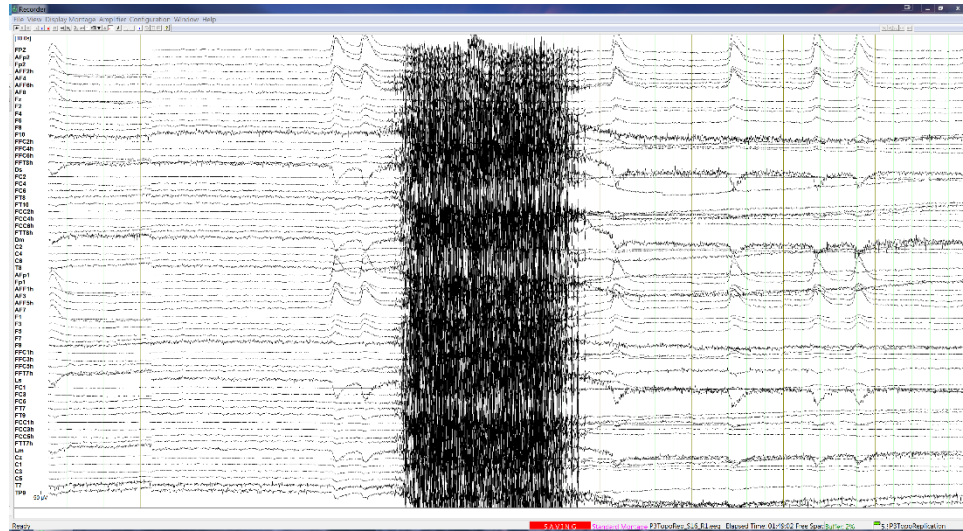


Figure 8 Noise in the EEG signal that must be rejected, presumably from a movement artifact. (Picture courtesy of Maja Kapitler and Filip Agatić)

For both ERPs, the mean amplitudes were extracted and analyzed in both sensory modalities. This value is formulated as a mean amplitude between two selected latencies. Thus, it is necessary to define the right time window that would include the ERP. The mean P3 amplitude presents some advantages that makes it preferable with respect to the classical peak amplitude (Georgiev et al., 2015). Mean amplitudes are less sensitive to noise with respect to peak amplitudes. Furthermore, peaks and components are not the same thing. Mean amplitudes describe ERP components in their extension over time. It facilitates comparisons between

electrodes, whereas amplitude can peak at different times. We did not consider P3 latencies because it did not suit the analysis method that we planned to perform. In ERPs, a single component propagates almost instantly and thus it is not expected to see differences in latencies between hemispheres (Luck, 2014).

3.3.1 BP Data

To measure the mean amplitude from the data, the start and end point of the BP slope was defined by visual inspection of data from the electrodes surrounding the area C1/C2. According to the literature, at these electrode locations BP amplitude is supposed to be most pronounced. The time windows were defined for late BP (time window -800ms to 0ms prior to movement) and early BP (from -1500ms to -650ms prior to movement). They were defined from visual inspection and with consideration to the literature (Filipovic et al., 2001; Shakeel et al., 2015). Electrodes C3, C4, Cz were extracted for further analysis.

We tested electrodes contralateral to movement side (C3 for right-finger button pressing and C4 for left-finger button pressing) for late BP and midline (Cz for both right- and left-finger button pressing) for early BP, in line with previous research (Filipovic et al., 2001). For each PD patient movement side and affection were matched (i.e., PD patients with right side onset were assigned right side movement as MA and left side movement as LA and vice versa for the PD patients with left side onset). This resulted in the formation of two variables for each medication factor (on and off): MA and LA side of movement. This factor is independent from a distinction in terms of right and left side of the body, and it is only characterized by the magnitude

of the PD-related affection.

3.3.2 P3 Data

The mean P3 amplitude was separately measured for distractor (P3a) and target (P3b) stimuli in auditory and visual oddball tasks. For every component and modality, the start and the end point of the time windows were defined by visual inspection of the grand average of the midline electrodes Cz/Pz. Determination of the waveforms through visual inspection was performed according to the method described in Wall, Davidson, & Dalebout (1991). Additionally, the method described in previous studies was used for comparison (Georgiev et al., 2015; Frank et al., 2012; Patel & Azzam., 2005; Polich & Comerchero, 2003; Wronka, Kaiser, & Coenen, 2013). Specific time windows were set for auditory distractor (200 to 500ms after stimulus presentation), auditory target (250 to 700ms), visual distractor (250 to 700ms) and visual target (300 to 800ms). These time windows were to best suite the observed shape of ERPs in the data.

Values from electrodes F3, Fz, F4, C3, Cz, C4, P3, Pz, P4 were extracted for further analysis. For our purpose of investigating the relation between hemispheres, we decided to compute the difference in amplitude between contralateral electrodes for each task. This presented one major advantage with respect to the comparison of the raw amplitudes at a single location: the number of factors included in the statistical analysis was lowered. Given the limited sample size, this preserved statistical power. The difference was computed as (Right – Left) between contralateral electrodes at each location (F, C, and P). The difference was computed so that the

resulting positive values represented an asymmetry higher on the right half of the scalp, while negative values represented an asymmetry higher on the left half. The electrodes included in the analysis were F3 and F4, C3 and C4, P3 and P4. These electrodes were chosen because of their location, clearly lateralized yet not too far from the midline. Previous studies have shown that P3 amplitude decreases on more lateral electrodes (Alexander et al., 1995, 1996). On the other hand, electrodes closer to the midline would be more likely to catch any spurious signals originating from either hemisphere.

3.3.3 Statistical Analysis

Mixed between-group (PD patients vs. healthy controls) and within-group (PD patients on and off medication) designs were employed. Statistical analysis, all calculations and plots were performed using the following software packages: SPSS (version 23.0), R (version 3.3.2), and Microsoft Excel (version 2016). Data was analyzed using mixed-design and repeated measures ANOVAs, t-tests, and regression analysis. Greenhouse–Geisser correction was used in case that the assumption of sphericity was violated (according to Mauchly's test).

4. Results

4.1 Readiness Potential

Data from MA and LA hemispheres of PD patients was compared to left and right hemispheres in healthy participants. Additionally, we compared data from PD patients on and off dopaminergic medication.

4.1.1 Side Differences in BP Amplitude

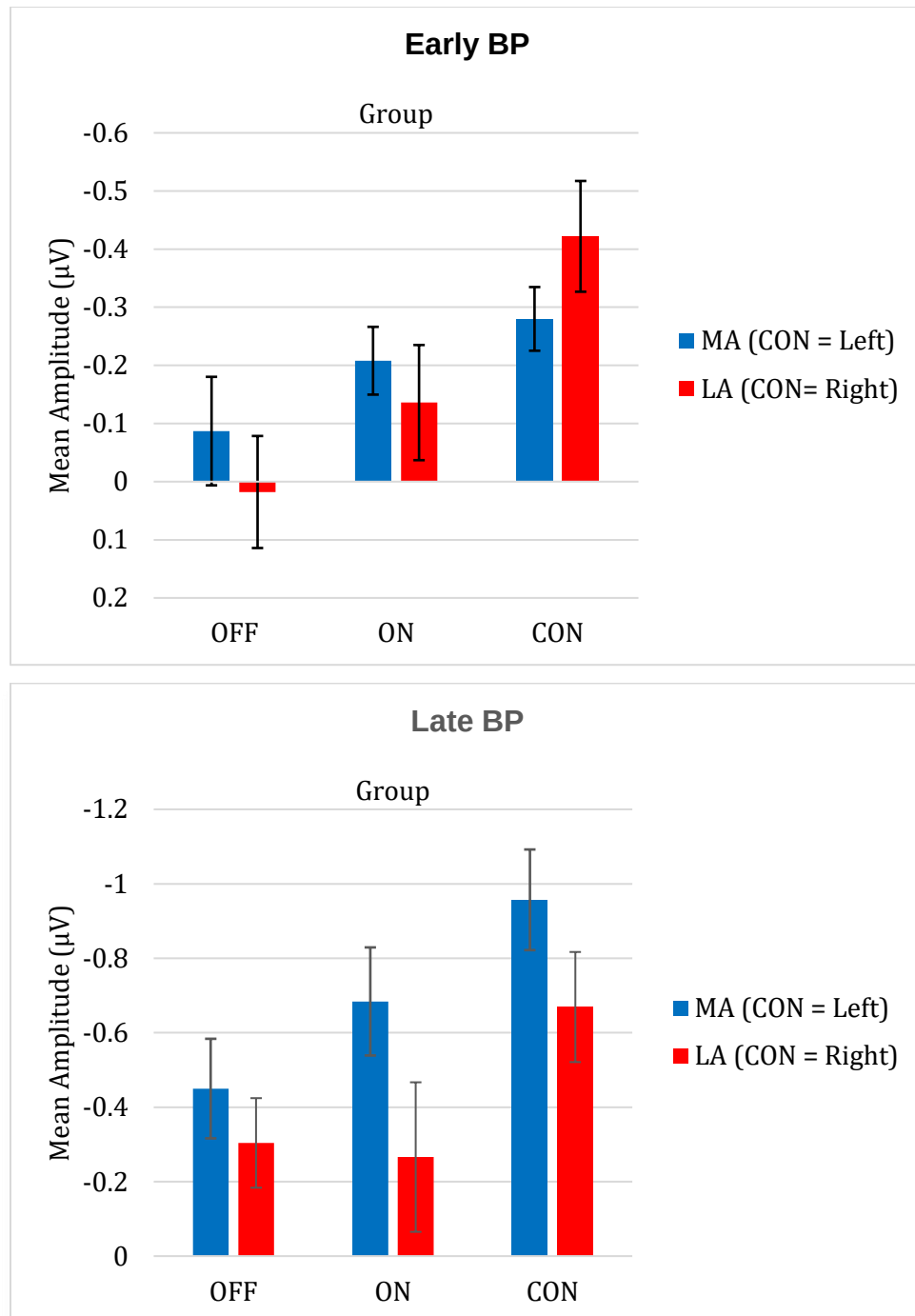
We performed a mixed-design ANOVA with between-subjects factor GROUP (PD patients off medication vs. healthy controls) and within-subject factors BP COMPONENT (early vs. late BP) and MOVEMENT SIDE (MA/left vs. LA/right). MA and LA were factor levels for the PD patients' group while right and left were the factor levels for the healthy controls' group. As expected, there was a significant main effect of the factor COMPONENT ($F(1, 21) = 29.263$; $p < .001$), due to the larger amplitude of late BP compared to the amplitude of early BP. Additionally, there was a significant main effect for the factor GROUP ($F(1, 21) = 6.864$ and $p = .016$). This was due to PD patients having overall smaller BP with respect to controls. This main effect was component-independent, since it was observed in early BP and late BP combined. No interactions between factors were significant (all $ps > .118$).

4.1.2 Effects of Medication

Next, we compared the effects of dopaminergic medication on BP in PD patients. Repeated measures ANOVA with main factors MEDICATION (on vs. off), COMPONENT (early BP vs. late BP), and MOVEMENT SIDE (MA vs. LA) revealed that factor MEDICATION was significant ($F(1, 9) = 11.655$; $p = .008$). This was due to BP amplitude of PD patients on medication being overall larger with respect to the off medication condition. Factor COMPONENT was also significant ($F(1, 9) = 9.860$; $p = .012$), because of the typical shape of BP's slope (late BP is larger than early BP). Factor SIDE was also significant ($F(1, 9) = 6.027$; $p = .036$). This was due to BP being more pronounced in MA with respect to LA. This result was independent from the medication status and component as no interactions between main factors were observed. As expected, the score of the UPDRS III was significantly higher in PD patients off medication rather than on medication ($p < .05$), indicating a reduction of motor impairment due to medication (Plot 1).

4.1.3 Correlation between UPDRS Scores and BP

Finally, we wanted to test the relationship between motor impairment and early and late BP amplitude. We ran two linear regression analyses for early and late BP to explore its relationship with lateralized UPDRS (off medication). No significant correlation was observed (all $ps > .522$).



Plot 1 the BP elicited in PD patients appears to be less pronounced in terms of amplitude for both on and off medication condition. Medication enhanced the amplitude of both components. Data from healthy controls is plotted by right and left sided movement.

4.2 Oddball Task

4.2.1 PD Patients vs. Controls

To test differences in hemispheric asymmetry between PD patients and healthy participants, we ran two separate mixed-design ANOVAs for P3a and P3b. P3a and P3b rely to a certain extent on separate receptors and pathways (Polich & Criado, 2006) that may be differentially affected by PD. ANOVAs included one between-subject factor, i.e. GROUP (PD patients off medication vs. healthy controls), and two within-subjects factors, i.e., SENSORY MODALITY (auditory vs. visual) and ELECTRODE LOCATION (frontal, central, and parietal areas). No significant main effect or interaction were found (all p s > .18).

To explore the effects of dopaminergic medication, we ran two separate repeated measures ANOVAs (one for P3a and one for P3b). Three within-subject factors were included: MEDICATION (on vs. off), SENSORY MODALITY (auditory vs. visual), and ELECTRODE LOCATION (frontal, central, and parietal). No significant main effects were observed. For P3b, a MEDICATION $\times$ ELECTRODE LOCATION interaction was significant ($F(2, 26) = 6.602$ and $p = .005$). Since three locations were included in the model, post hoc analysis was performed by running three two-by-two repeated measures ANOVAs. Interaction between medication and frontal/central locations was found to be significant after Bonferroni-Holm correction ($F(1,13) = 4.055$ and $p = .0011$). This interaction was due to the fact that medication induced a prominent left-sided asymmetry at the central location, whilst for off medication a right-sided asymmetry was observed (P3b amplitude was decreased at location C4 for PD patients on medication). A difference in hemispheric asymmetry persisted,

albeit strongly reduced, at parietal location, whereas at frontal location the hemispherical asymmetry was very similar (i.e., slightly right-sided) for both on and off medication conditions. This result is modality-independent, as no differences were found between the visual and the auditory sensory modalities (Plot 2).

We then compared PD on medication to healthy controls in mixed-design ANOVA, with between-subject factor GROUP (PD on medication vs. healthy controls) and two within-subject factors, SENSORY MODALITY (auditory vs. visual) and ELECTRODE LOCATION (frontal, central, parietal). From this analysis, the interaction between group and location appeared to be near significance ($F(2,50) = 2.853$; $p = .85$). This result reinforces the idea that dopaminergic medication affects a normally present asymmetry. In summary, we observed that the asymmetry of P3b amplitude in PD patients off medication was similar to healthy controls (with P3b amplitude being larger over the right hemisphere), while this trend was reversed in PD patients on medication.

Regarding P3a, repeated-measures ANOVA revealed a significant MEDICATION x MODALITY interaction ($F(1,13) = 5.844$; $p = .031$). This was due to the fact that PD patients on medication showed no right-sided asymmetry for visual stimuli (which is present off medication).

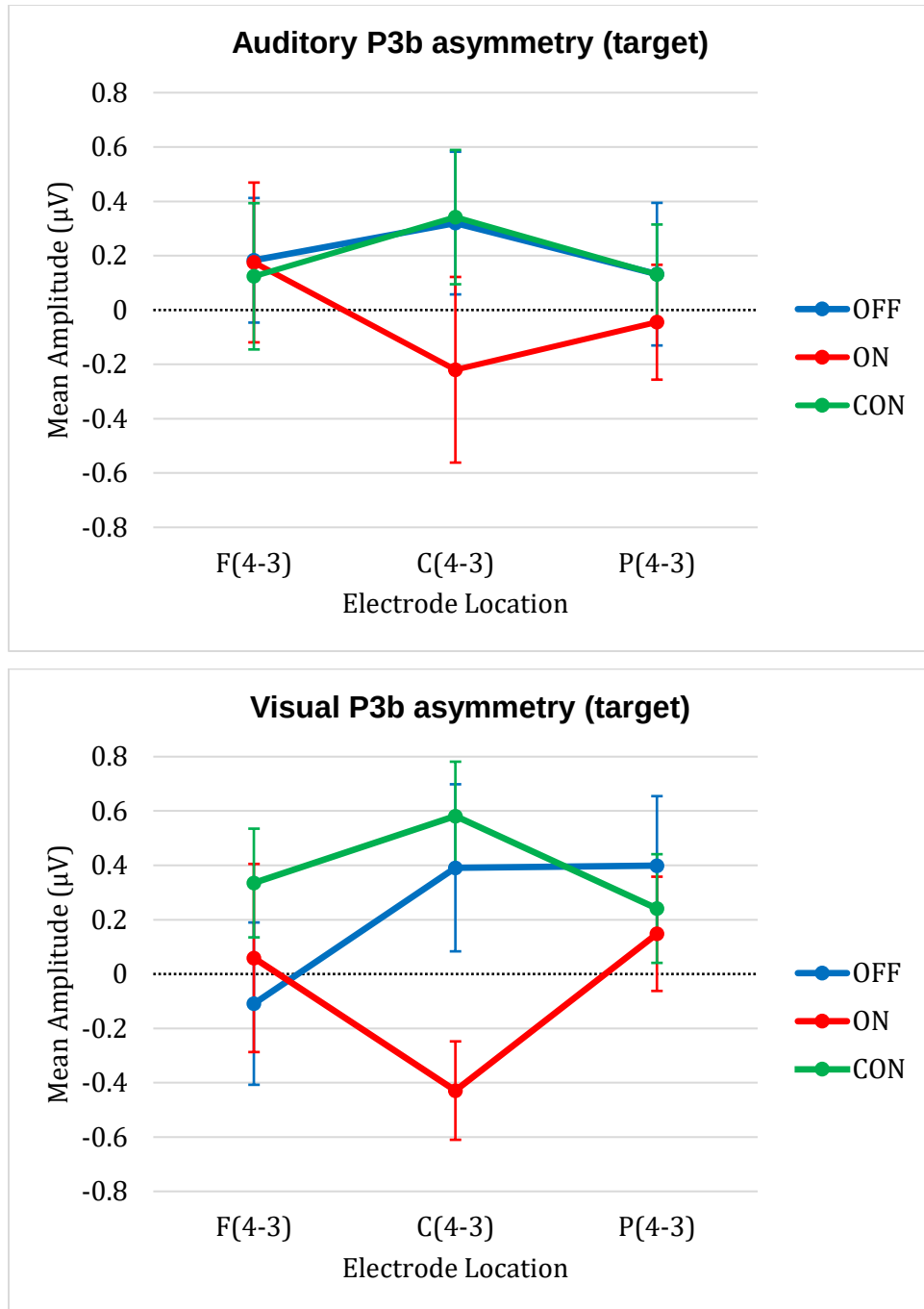
PD patients on medication have larger right-sided asymmetry in the auditory modality than off medication, and is conversely reduced in the visual modality. This result was location-independent, i.e., it came from data from all three locations. However, by visualizing the data, it is clear that the result depends primarily on

differences in asymmetry at frontal electrode locations (Plot 3).

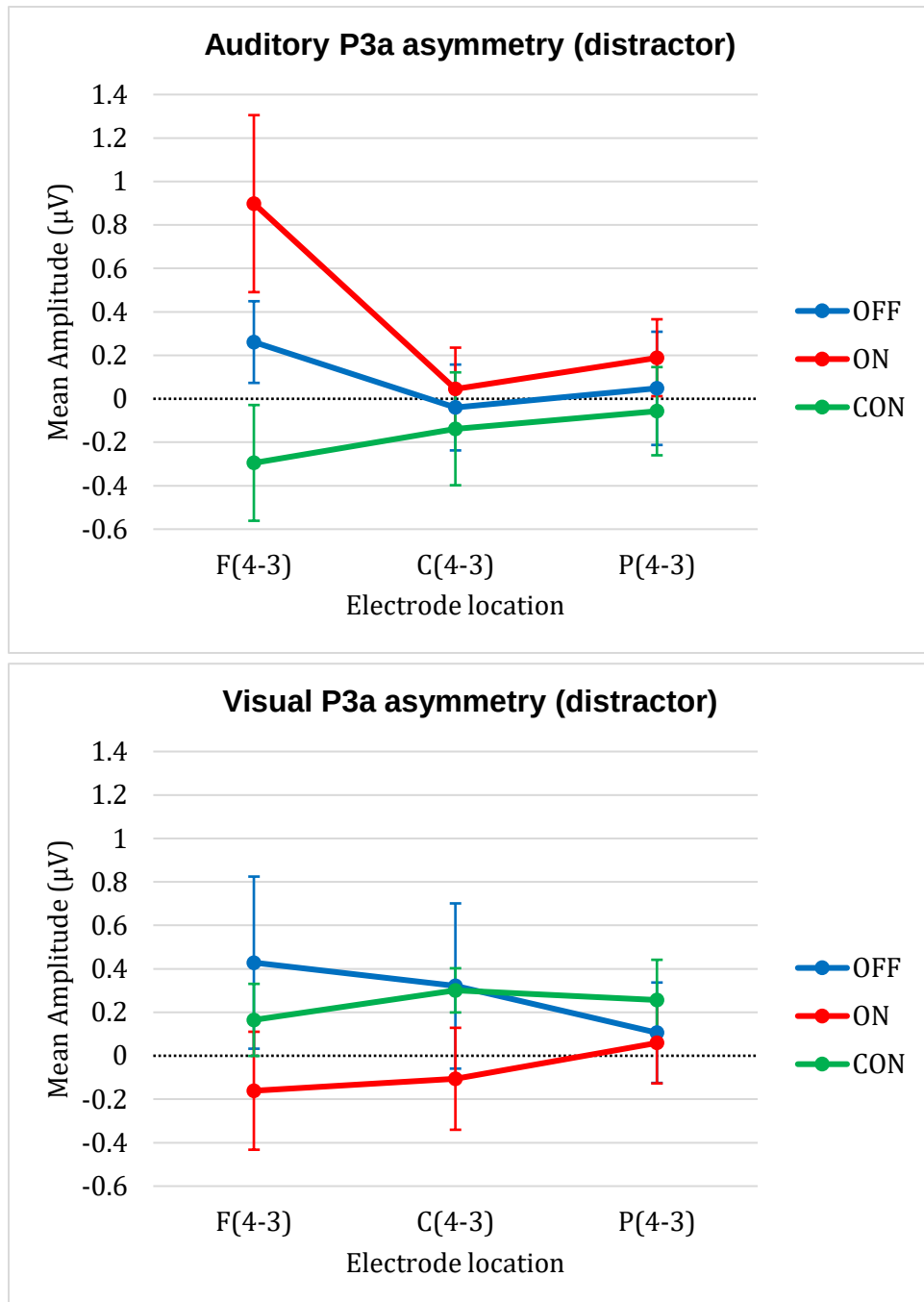
We then compared PD patients on medication to healthy controls. The same group-modality interaction was found to be significant ($F(1,25) = 7.675$; $p = .010$). In summary, interactions were significant between both factors MEDICATION and GROUP separately.

4.2.2 Side of Onset of PD Symptoms and P3 Asymmetry

Additionally, we tested if the side of PD symptoms' onset (right vs. left onset) affected P3 asymmetry. We ran a series of independent sample t-tests, including as a between-subject factor the side of affection (right vs. left), for each of the 12 combinations of location (F, C, and P) and sensory modality (auditory and visual) of the PD off medication group. These comparisons revealed no significant differences ($ps > .159$).



Plot 2 P3b asymmetry between groups (PD patients on/off medication and controls). Values are the difference between mirroring electrodes. Positive values represent an asymmetry larger on the right side, negative on the left side. The difference of asymmetry in PD patients on medication appears with respect to controls and PD patients off medication.



Plot 3 P3a between groups (PD patients on/off medication and controls) and sensory modality (visual and auditory). Positive values represent an asymmetry larger on the right side, negative values on the left side. The statistical significance of the result depends on all the electrodes, that here are plotted separately, clarifying the contribution of data from frontal electrodes.

5. Discussion

5.1 Study Design

In the present study, we explored whether motor asymmetry of PD is reflected in asymmetry of electrophysiological measures related to motor preparation and attentional processing, and how these measures are affected by dopaminergic medication. In particular, in our first experiment we tested whether asymmetry of motor symptoms of PD is reflected in asymmetry of BP components – motor related potentials that show no significant asymmetry in healthy controls. A similar approach has been previously used to study the relationship between asymmetry of motor symptoms and measures of cortical excitability and plasticity using TMS (Kojović et al., 2012; Derejko, Rakowicz, Antczak, Inglot, & Niewiadomska, 2013). Only one previous study explored the relation between asymmetry of motor symptoms and motor preparation using BP (Simpson & Khuraibet, 1987) involving PD patients with strictly unilateral symptoms. On the other hand, the P3 attentional task is processed asymmetrically in healthy participants (Bledowski et al., 2004; Polich & Criado, 2006). Few studies in healthy participants analyzed P3 in terms of amplitude difference between hemispheres using EEG (Alexander et al., 1995; 1996). A recent paper from Vafaii, Mazhari, Pourrahipi, & Nakhee (2016) suggests its importance for the study of neurological conditions. Thus, in our second experiment we tested whether P3 physiological asymmetry is disturbed in PD. We compared the difference between mirroring electrodes to test how PD and its medication would affect the normal

asymmetric pattern of P3 observed in healthy participants. From both experiments we are able to report several significant results, particularly in relation to dopaminergic medication. Results suggest that the dopamine replacement therapy, while improving motor symptoms, may have some negative effects on cognitive functions.

5.2 Key Findings

5.2.1 Readiness Potential

We found that, in PD, patients' off medication BP amplitude was overall reduced (i.e., in both its early and late components) with respect to healthy participants. This result was expected for early BP, as SMA, the region of the motor cortex primarily responsible for its generation, receives strong projections from the BG that are functionally impaired in PD (Colebatch, 2007). Further, we found that in PD patients' late BP was also reduced. The current understanding of the topic suggests that late BP is, in general, not significantly affected by PD (Filipovic et al., 2001; Jahanshahi & Hallett, 2003; Shibasaki & Hallett, 2006), although some previous studies have found this component to be either reduced or increased in PD patients. This discrepancy may be explained by differences in patients' characteristics and differences in the methodology used (Georgiev et al., 2016). However, it should be noted that most previous studies measured BP contralateral to movement on one side only (usually the dominant) without considering the laterality of the symptoms or comparing it to the less affected side. Our results suggest that in PD the late BP's amplitude is decreased in both the more and the less affected side. As in the case of early BP

reduction, this could represent a physiological dysfunction in motor preparation.

Additionally, we tested the effect of PD treatment on early and late BP and found that dopaminergic medication partially recovered BP amplitude, as patients on medication presented overall larger BP than PD patients off medication. This result is in line with previous research and adds to the already existing body of literature on the topic (Dick et al., 1987; Colebatch, 2007).

The third result is more relevant to asymmetry in PD. We found that the MA side presented overall larger amplitudes than the LA side. Since in PD patients BP amplitudes are generally reduced in comparison to healthy controls, one may expect that the more affected hemisphere would show even greater reduction. Instead, the results contradicted this expectation. Only one previous study compared BP amplitudes between sides in PD (Simpson & Khuraibet, 1987) and found that PD patients had lower BP in the affected hemisphere. However, the patients included had strictly unilateral parkinsonian symptoms and a comparison between more and less affected sides could not be made. We have also observed smaller BP amplitudes in the more affected side compared to healthy participants.

Studies have shown that the performance of unilateral movements is compromised in PD (Espay et al., 2005), so that bilateral activation of M1 is observed when PD patients perform an action with their more affected limb (Thobois et al., 2000). Thus, PD patients show deficient lateralization of brain activity when performing a movement with the MA side, resulting in activations of not only contralateral but also ipsilateral hemisphere (Wu, Hou, Hallett, Zhang, & Chan, 2015).

It is, therefore, difficult to evaluate the specific contribution of each hemisphere. Early BP was measured from the electrode Cz, at the scalp midline. This location captures signals of neural activity from both hemispheres. Our observation of increased early BP amplitude may reflect a change in cortical activation, due to the impact of PD on network efficiency, that can affect either hemisphere. However, late BP, being measured at more lateral locations (C3/4), should mainly represent signals from a single hemisphere.

Another possible explanation would be a difference in the effort necessary to perform the task. BP amplitude is generally increased by more difficult tasks in healthy subjects (Jahanshahi & Hallett, 2003). In the case of PD patients, it could be argued that movements are more effortful when performed with the MA than with the LA side. This could also explain the increase of late BP, captured by electrodes contralateral to movement of the more affected side (and therefore not affected by bilateral activation). The hypothesis of a compensatory mechanism is often proposed to explain counterintuitive results in PD experiments. For example, occasional observations of an increase of late BP in PD patients have been interpreted as a compensatory mechanism for reduced SMA activity resulting in overactivation of the M1 area (Dick et al., 1989).

Finally, we found no correlation between UPDRS scores and BP amplitudes. Different symptoms of PD could rely on diverse mechanisms, involving uncontrolled variables. For instance, a potential role of the ipsilateral hemisphere was suggested for resting tremor generation (Erro, Barone, Vicidomini, Picillo, & Pappatà, 2013).

Thus, a promising approach of investigation would be to compare motor ERPs with specific clusters of motor symptoms separately (e.g., symptoms related to bradykinesia alone).

5.2.2 Oddball Task

We found that the cortical asymmetry of P3b was differentially affected in PD patients on dopaminergic medication compared to off medication status and healthy participants. In fact, PD patients off medication did not differ from healthy participants, showing right-sided asymmetry of P3, i.e., ERP amplitudes generally larger at right EEG locations. PD patients on medication showed a reversed pattern, with amplitude larger at left central locations of the EEG. These results suggest that dopaminergic medication influences an interhemispheric balance relevant in attentional processing. Arguably, this result may hint at negative side effects of medication on attention and working memory processing.

The other significant finding concerns P3a amplitude and how it is affected by medication. We observed that the normally right-sided P3a asymmetry decreased in PD patients on medication in the visual modality, while it increased in the auditory modality. The difference was prominent at frontal locations, especially in the auditory condition. This was probably related to the physiological distribution of P3a on the scalp, which is more frontal than P3b (Polich & Criado, 2006). The differences between sensory modalities in attentional tasks and its relation to our findings reinforces the hypothesis that, in the oddball paradigm, visual and auditory modalities rely on partially different neural sources (Dreo et al., 2016) and thus they

might be differentially affected by dopaminergic medication.

Finally, we did not find any correlation between P3 asymmetry and side of onset in PD motor symptoms. As the number of subjects in our study was probably too small to detect possible associations, we believe that this issue deserves further investigations on larger PD cohorts.

There are a number of cognitive side effects related to dopaminergic medication. PD patients on medication present impulse control disorders (Connolly & Lang, 2014) and a recent review concluded that they show significant impairment in the Iowa Gambling Task, a well-known paradigm related to decision making, while on replacement therapy (Evens et al., 2016). Interestingly, a study found that dopaminergic medication leads to abnormalities in PD patients' attentional and emotional decision making (impulsivity) while it reduced their attentional inflexibility. This suggests that dopamine can improve or impair the performance depending on the nature of the task, with too little or too much dopamine having detrimental effects (Cools, Barker, Sahakian, & Robbins, 2003). Another study found that medication modulated performance in a temporal attention task. The effect of medication on this task depended on the subject's baseline performance. This corroborates the thesis that there is an optimal level of dopamine in cognitive functioning (Slagter et al., 2016). The general picture that emerges from these studies is that dopaminergic medication has diverse effects on different cognitive tasks. Some effects are dysfunctional, and this might depend on the baseline level of dopamine.

In summary, the present study is the first work focusing on hemispheric asymmetry of P3 in relation to PD. The design of our experiment is an example of a research approach for studying cortical asymmetries in PD. Dopaminergic medication improved the motor-related BP affected by PD as it was significantly increased. On the other hand, it had the opposite effect on the cognitive P3 since dopaminergic replacement affected the normal physiological asymmetry in attentional processing. This opposite effect is explained by a differential influence of replacement therapy on the separate dopaminergic pathways through which motor and attentional functions are mediated.

Degeneration of the nigrostriatal system is the main cause leading to the typical motor symptoms of PD. This pathway is involved in the cortico-striato-thalamo-cortical motor loop that involves SMA and the premotor cortex – structures that are responsible for internally driven motor planning and preparation. Thus, a deficit of dopamine in PD will cause under-functioning of the motor loop, while its replacement as dopaminergic therapy may reverse the deficit. On the other hand, attentional processing is under the influence of mesocorticolimbic pathways (Nieoullon & Coquerel, 2003) that are probably asymmetrically distributed (Molochnikov & Cohen, 2014). In PD patients, the loss of dopaminergic neurons is greater in the motor loop, while pathways related to higher cognitive functions are only partially affected (Kish et al., 1988). Thus, dopaminergic replacement therapy may be enough to reduce motor symptoms, while at the same time it is overwhelming for less affected pathways with relatively well-preserved dopaminergic functionality.

5.2.3 Limitations

EEG has poor spatial resolution, allowing only a rough estimate of neural sources (Luck, 2014). We tried to overcome this limitation by choosing relatively distant electrodes that would carry less risk of co-registering the same source. Nevertheless, the different locations that we tested in the P3 study could hardly be linked to specific areas as ERP generators without considering additional evidence. This is a general problem in EEG studies. With its focus on “hemispheric origins”, our approach should not significantly suffer from poor spatial resolution. Additionally, we were able to provide further support for our results in light of evidence from different techniques (e.g., fMRI and other imaging studies).

It should be noted that previous analysis of behavioral data from our cognitive experiment did not reveal any differences in task performance (Georgiev et al., 2015). This may be because behavioral data from our oddball paradigm is not sensitive enough to capture subtle differences in performance. Therefore, we cannot state with certainty that the neurophysiological alterations related to medication are signs of dysfunction. Evidence of that is the difference of PD patients on medication with respect to healthy controls and the previous literature on the effects of dopamine replacement on cognitive functions.

In our study, the sample size was relatively small. Thus, the study was underpowered to reveal possible associations between the side of onset of PD symptoms (i.e., right vs. left) and asymmetry of EEG findings. Furthermore, it has been reported that the hemisphere contralateral to the MA side is not always the more damaged in PD patients. It has been suggested that damage to the ipsilateral

hemisphere could occur in as many as 10-15% of PD patients (Kaasinen, 2015) and a small sample size would be sensitive to this variability. We encourage replication of our experimental approach on larger cohorts to study side-specific changes of ERPs in relation to PD. Furthermore, the PD subjects we included were not in the very early stages of disease, which is the time at which the lateralization of symptoms is most evident.

Another limitation of our work was that it was impossible for us to control for handedness without excluding too many subjects. Although it is unclear whether handedness affects BP, an improved experimental design should include a larger sample of right-handed subjects only. On the other hand, previous studies found that P3 asymmetry was not affected by handedness in its asymmetric traits (Alexander & Polich, 1997; Eskikurt, Yücesir, & Isoglu-Alkac, 2013).

6. Conclusion

Two ERP paradigms were recorded from PD patients (on and off dopaminergic medication) and healthy controls in order to assess hemispheric (a)symmetry in their amplitudes. We performed between-group (PD patients vs. healthy participants) as well as within-group (PD patients on vs. off dopaminergic medication and more vs. less affected side in PD patients) comparisons.

In the motor ERP experiment, the amplitude of early and late BP components was reduced in PD patients and recovered relatively well with dopaminergic medication. This result suggests that dopamine replacement may restore normal processing of motor planning and execution. Furthermore, the analysis revealed that in PD patients, BP was larger on the MA hemisphere with respect to the LA. This trend was consistently observed regardless of medication status, and it could be related to compensatory mechanisms of the affected motor network that deserve further investigations.

In the cognitive ERP experiment, we found that the normal asymmetry of P3 was not directly affected by the disease. However, it was affected by dopamine therapy, suggesting that medication, although helpful for motor symptoms, may have unwanted effects on the patients' cognitive functions. This probably depends on the effect of medication on separate neural pathways that are differentially affected by loss of dopamine-producing cells. These effects should be further investigated, along with their impact on patients' functioning in daily life.

Often ERP data is analyzed following customary procedures that take only a few standard electrodes into account. In the present study we point out the advantages of investigating other traits of these potentials, as we did by exploring aspects of ERP asymmetry.

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Appendices

A.1 List of figures

Figure 1: Superior view of a human brain.

Figure 2: Representation of the dopamine system in the human brain.

Figure 3: EEG electrode locations on the 10/20 system.

Figure 4: BP potential and its components.

Figure 5: Different paradigms of the oddball task and P3 subcomponents.

Figure 6: Subject station and EEG cap.

Figure 7: Experimental design of the oddball task.

Figure 8: Artifact in the EEG data.

A.2 List of Tables

Table 1: UPDRS scores of PD patients

A.3 List of Plots

Plot 1: BP results

Plot 2: P3b results

Plot 3: P3a results

A.4 List of Abbreviations

BG: Basal Ganglia

BP: *Bereitschaftspotential*, or Readiness Potential

CC: Corpus Callosum

EEG: Electroencephalogram

ERP: event-related potential

fMRI: functional Magnetic Resonance Imaging

LA: Less affected

LC-NE: locus-coeruleus–norepinephrinergic pathways

MA: More affected

M1: Primary motor area

PD: Parkinson's disease

PFC: Prefrontal cortex

SMA: Supplementary motor cortex

SN: Substantia Nigra

TMS: Transcranial Magnetic Stimulation

UPDRS: Unified Parkinson's disease rating scale