Neurophysiological characteristics of apathy in Parkinson’s disease

by

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Abstract

Apathy in Parkinson’s disease (PD) is often resistant to therapy, difficult to quantify and poorly understood. It is commonly characterized by a lack of motivation and emotional blunting. Neural responses recorded using electroencephalography (EEG), such as neural oscillations and event-related potentials (ERPs), are often associated with motivated behaviour and emotion processing, but few studies have examined how these characteristics are affected in apathetic PD patients.

To examine the behavioural and neural oscillatory characteristics of motivated movement in apathetic PD patients, we used an incentivized motor task, in which subjects could win money based on the amount of effort they produced on a hand grip. We demonstrated that PD patients with lower apathy scores could modulate their effort production to increasing rewards, whereas patients with more severe apathy could not. EEG results showed that apathetic PD patients exhibited a higher resting power in the alpha and theta frequency bands compared to non-apathetic PD subjects and healthy subjects. Furthermore, there was a significant correlation between absolute resting alpha power and relative alpha power during squeezing. These two factors were able to predict patient apathy scores, irrespective of age or disease severity. The same was true for absolute resting theta power and relative theta power during squeezing.

To explore emotion processing in PD, we investigated ERPs from EEG recordings as subjects viewed emotionally evocative visual stimuli. We employed a data-driven approach to separate unique ERP time courses from one another called multiset canonical correlation analysis (MCCA). Results showed that the late positive potential (LPP), an ERP that responds to emotional stimuli, had a blunted amplitude in response to negative visual stimuli compared to healthy
subjects. Interestingly, there was also a greater centro-parietal topographical representation of the LPP in PD subjects compared to healthy subjects, suggesting the presence of potential compensatory mechanisms for blunted neural reactivity to emotional stimuli in PD patients. This work lays the foundation for further understanding apathy and provides a quantitative test to measure apathy in people living with Parkinson’s.
Lay Summary

Apathy is a common symptom of Parkinson’s disease (PD) and often involves low motivation and reduced emotions. To determine how the brain changes in apathetic PD patients, we used electrical brain recordings called electroencephalography (EEG) to observe brain wave patterns during two experiments exploring motivational and emotional aspects of apathy. In the motivation experiment, subjects earned money by squeezing a grip force device. We found that highly apathetic PD subjects exerted similar effort, regardless of how much money could be won. Additionally, these subjects had altered brain wave characteristics that predicted their apathy scores. In the emotion experiment, subjects viewed emotionally-stimulating pictures. PD subjects showed a reduced brain response to negative pictures compared to healthy subjects, but stronger brain activation, suggesting that there are tools to compensate for defects in emotion processing in PD. This work provides a measure for apathy in PD, while furthering our understanding of the condition.
Preface

The work in this thesis was designed, conducted, analyzed, and written by Maria Zhu under the supervision of Dr. Martin McKeown and Dr. Silke Cresswell. Dr. Martin McKeown was additionally involved in the development of the study design, data analysis, and data interpretation. Dr. Azadeh HajiHosseini contributed to the study design, EEG training, and data analysis. Christina Jones played a main role in patient recruitment. Custom-written scripts in MATLAB involved Saurabh Garg, who helped write experimental task and EEG preprocessing scripts, and Robert Baumeister, who helped with regression analyses and MCCA. The MCCA code was written by Jessie Fu, based on open source code available from Prof. Adali, University of Maryland.

Dr. Martin McKeown, Robert Baumeister, Christina Jones, Dr. Azadeh HajiHosseini, and Stephanie Tran assisted with the editing of the current manuscript.

The University of British Columbia’s Clinical Research Ethics Board (Certificate # H16-00817) and the Vancouver Coastal Health Ethics Committee (Certificate # V16-00817) approved all research included in this thesis.
Table of Contents

Abstract ........................................................................................................................................ iii
Lay Summary .................................................................................................................................. v
Preface .......................................................................................................................................... vi
Table of Contents ......................................................................................................................... vii
List of Tables ................................................................................................................................ xi
List of Figures .............................................................................................................................. xii
List of Abbreviations .................................................................................................................. xiii
Acknowledgements ..................................................................................................................... xv
Dedication ...................................................................................................................................... xvi

Chapter 1: Introduction .................................................................................................................. 1
  1.1 Parkinson’s disease .................................................................................................................. 1
  1.1.1 Pathophysiology ................................................................................................................ 1
  1.1.2 Etiology ................................................................................................................................ 4
  1.1.3 Pathological synchronicity of beta and alpha frequency oscillations ....................... 5
  1.1.4 The role of alpha and beta desynchronization and its modulation in PD ................ 7
  1.1.5 Treatments for PD .............................................................................................................. 8
  1.2 Apathy in Parkinson’s disease ............................................................................................. 9
  1.2.1 The impact of apathy on quality of life ........................................................................... 9
  1.2.2 Measuring apathy ............................................................................................................. 10
  1.2.3 Apathy and depression ..................................................................................................... 11
Chapter 2: Apathy in Parkinson’s disease is associated with abnormal alpha and theta oscillatory activity during incentivized movement

2.1 Introduction

2.2 Materials and Methods

2.2.1 Subjects

2.2.2 Experimental Setup

2.2.3 Behavioral Analysis

2.2.4 EEG recording

2.2.5 Preprocessing

2.2.6 EEG spectral analyses

2.2.7 Determining channels of interest

2.2.8 Spectral statistics over the centro-parietal area

2.2.9 Spectral comparisons between $1 and $50 conditions

2.3 Results

2.3.1 Behavioural results

2.3.2 Channels of interest
<table>
<thead>
<tr>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3.3</td>
</tr>
<tr>
<td>2.3.4</td>
</tr>
<tr>
<td>2.3.5</td>
</tr>
<tr>
<td>2.3.6</td>
</tr>
<tr>
<td>2.3.7</td>
</tr>
<tr>
<td>2.3.8</td>
</tr>
<tr>
<td>2.4</td>
</tr>
<tr>
<td>2.4.1</td>
</tr>
<tr>
<td>2.4.2</td>
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<tr>
<td>2.4.3</td>
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</tr>
<tr>
<td>2.4.5</td>
</tr>
<tr>
<td>2.4.6</td>
</tr>
<tr>
<td>2.5</td>
</tr>
</tbody>
</table>

Chapter 3: Altered emotional processing in PD event-related potentials ........................................... 63

<table>
<thead>
<tr>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
</tr>
<tr>
<td>3.2</td>
</tr>
<tr>
<td>3.2.1</td>
</tr>
<tr>
<td>3.2.2</td>
</tr>
<tr>
<td>3.2.3</td>
</tr>
<tr>
<td>3.2.4</td>
</tr>
</tbody>
</table>
List of Tables

Table 2.1. Subject demographic and clinical characteristics .......................................................... 28
Table 2.2. High and low apathy PD subject demographic and clinical characteristics ...................... 32
Table 2.3. Theta band: Tukey HSD test results after MANOVA .......................................................... 43
Table 2.4. Alpha band: Tukey HSD test results after MANOVA .......................................................... 44
Table 2.5. Group means and one-way ANOVA results for theta, alpha, and beta frequency bands ....... 51
Table 2.6. Tukey HSD test $p$-values for group differences in relative theta, alpha, and beta power ....... 52
Table 2.7. Tukey HSD test $p$-values for group differences absolute theta, alpha, and beta power ........ 52
Table 3.1. Subject demographics and clinical scores ........................................................................ 66
List of Figures

Figure 1.1. Schematic diagram of the basal ganglia network in the healthy and parkinsonian states……..3
Figure 1.2. Synchronized 10 Hz oscillations of a GPi neuron in an MPTP-treated primate model ...........6
Figure 1.3. Brain regions associated with different apathy subcategories........................................21
Figure 2.1. Behavioural task ............................................................................................................30
Figure 2.2. Time-frequency analysis and scalp distributions ...............................................................36
Figure 2.3. Schematic diagram of time frames used in spectral data analysis .....................................37
Figure 2.4. Principal component regression .......................................................................................39
Figure 2.5. Behavioural results ........................................................................................................41
Figure 2.6. Relative and absolute theta power over time.....................................................................47
Figure 2.7. Relative and absolute theta power over time.....................................................................49
Figure 2.8. Relative and absolute beta power over time ....................................................................50
Figure 2.9. Correlation between resting absolute oscillatory power and relative oscillatory power during squeezing .................................................................................................................53
Figure 2.10. Scatter plots of normalized predicted vs. actual apathy scores using principal component regression squeezing .................................................................................................................55
Figure 3.1. Experimental stimuli and design .......................................................................................67
Figure 3.2. Multiset canonical correlation analysis ............................................................................69
Figure 3.3. LPP topographic distributions and waveforms from Component 1 of the MCCA output .....72
Figure 3.4. N200 topographic distributions and waveforms from Component 4 of the MCCA output ....74
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>Anterior cingulate cortex</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<td>BDI</td>
<td>Beck’s Depression Inventory</td>
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<td>DBS</td>
<td>Deep brain stimulation</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<tr>
<td>ERP</td>
<td>Event-related potential</td>
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<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<tr>
<td>GPe</td>
<td>Globus pallidus externus</td>
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<tr>
<td>GPi</td>
<td>Globus pallidus internus</td>
</tr>
<tr>
<td>ICA</td>
<td>Independent component analysis</td>
</tr>
<tr>
<td>LARS</td>
<td>Lille Apathy Rating Scale</td>
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<td>LFP</td>
<td>Local field potential</td>
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<td>LPP</td>
<td>Late positive potential</td>
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<td>MCCA</td>
<td>Multiset canonical correlation analyses</td>
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<td>MEG</td>
<td>Magnetoencephalography</td>
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<td>MoCA</td>
<td>Montreal Cognitive Assessment</td>
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<td>MRBD</td>
<td>Movement-related beta desynchronization</td>
</tr>
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<td>MVC</td>
<td>Maximum voluntary contraction</td>
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<td>NAcc</td>
<td>Nucleus accumbens</td>
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<td>NMS</td>
<td>Non-motor symptoms</td>
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<td>PCA</td>
<td>Principal component analysis</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PCR</td>
<td>Principal component regression</td>
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<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
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<td>PET</td>
<td>Positron emission tomography</td>
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<td>PFC</td>
<td>Prefrontal cortex</td>
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<td>PMBR</td>
<td>Post-movement beta rebound</td>
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<td>QoL</td>
<td>Quality of life</td>
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<tr>
<td>rOFC</td>
<td>Right orbitofrontal cortex</td>
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<tr>
<td>SAS</td>
<td>Starkstein Apathy Rating Scale</td>
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<td>SMA</td>
<td>Supplementary motor area</td>
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<tr>
<td>SNC</td>
<td>Substantia nigra pars compacta</td>
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<tr>
<td>SNr</td>
<td>Substantia nigra pars reticulata</td>
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<tr>
<td>STN</td>
<td>Subthalamic nucleus</td>
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<tr>
<td>UPDRS</td>
<td>Unified Parkinson’s Disease Rating Scale</td>
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<tr>
<td>VTA</td>
<td>Ventral tegmental area</td>
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<tr>
<td>α-synuclein</td>
<td>Alpha-synuclein</td>
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To Jamie, for being my rock.

Finally, to my mom and my aunt, thank you for being my greatest sources of inspiration and support. You both have shown me what it means to work hard while staying honest and humble. I am so grateful and love you both so much.
Dedication

To Mom
Chapter 1: Introduction

1.1 Parkinson’s disease

Parkinson’s disease (PD) is a progressive neurodegenerative disease of the central nervous system that was first characterized by James Parkinson in 1817 [1]. It is the second most common neurodegenerative disorder after Alzheimer’s disease, occurring in approximately 1% of people over the age of 60 and 0.3% of the global population [2]. The mean age of onset is around 55 years old [3], although 5 to 10% of patients are diagnosed before the age of 40 and are considered to have “early-onset Parkinson’s disease” [4]. The mortality rate of individuals with PD is two to five times higher than that of people in the same age range [5] and the progression of PD symptoms is highly correlated with increased caregiver burden and decreased quality of life outcomes [6].

The disease is most recognized for its motor symptoms, which can include a resting tremor, bradykinesia (slowness of movement), akinesia (loss of voluntary movement), hypokinesia (reduction in movement amplitude), and rigidity. Although PD is most recognized for its motor symptoms, there are a number of non-motor symptoms associated with the disease that can be just as debilitating. In particular, several studies have shown that neuropsychiatric symptoms, such as apathy, depression, and psychosis have a significant negative impact on quality-of-life measures, caregiver burden, institutionalisation rates, or health economics for people with PD [7], [8].

1.1.1 Pathophysiology

Degeneration of dopaminergic neurons

The main pathological feature of PD is the gradual degeneration of dopaminergic neurons in the basal ganglia, a group of subcortical neuronal clusters called nuclei. These nuclei include...
the putamen and caudate nucleus which form the striatum, the internal and external globus pallidus (GPi and GPe, respectively), subthalamic nucleus (STN) and the substantia nigra pars compacta and reticulata (SNc and SNr, respectively) [9]. Connections between these nuclei and associated areas play a crucial role in regulating voluntary movements and, together, form the cortico-basal ganglia network [10]. Two major motor control pathways can be identified from this network: the direct pathway, which promotes motor output, and the indirect pathway, which inhibits motor output. At rest, the indirect pathway exerts a constant inhibitory effect on the motor cortex [11], [12].

Dopaminergic projections from the SNc to the striatum, which form the nigrostriatal dopaminergic pathway, play a major role in both the direct and indirect pathways. During motor execution, dopamine binds to excitatory dopamine D1 receptors on post-synaptic neurons in the direct pathway. Conversely, the simultaneous binding of dopamine D2 receptors inhibits the indirect pathway, lifting its tonic inhibition of movement. The net effect of dopamine is movement initiation [11] (Figure 1.1A).

In Parkinson's disease (PD), progressive degeneration of dopaminergic neurons results in the characteristic motor symptoms of the disease. The most prominent loss of these neurons occurs in the SNc where 50-70% of neurons are lost before the onset of symptoms [13]. The loss of dopamine-producing neurons causes a decrease in dopamine binding to striatal neurons in the direct and indirect pathways, which reduces the facilitation of motor output by the direct pathway and increases motor inhibition by the indirect pathway [12], [14] (Figure 1.1B). Accordingly, loss
of dopaminergic neurons in PD results in a severe reduction in movement amplitude, speed, and
initiation.

Lewy bodies

In remaining dopaminergic neurons, the accumulation of the protein α-synuclein in the
form of inclusions called Lewy bodies, occurs in the majority of PD cases, and is often used as an
indicator of disease progression [15]. It is currently unknown whether the presence of Lewy bodies
is pertinent to the cause of neuronal death or the protection of neurons. Some studies suggest that
other forms of α-synuclein that do not aggregate into Lewy bodies, such as oligomers, may be the toxic forms of the protein [16].

1.1.2 Etiology

Genetics

PD is considered a multifactorial disease that stems from a combination of genetic and environmental factors. Most cases of PD occur sporadically. However, about 10 to 30% of people with PD report first-degree family members who also have PD [17]. Recently, strides have been made in the identification of genes responsible for monogenic forms of the PD, which have clear Mendelian, autosomal-dominant or autosomal-recessive, patterns of inheritance [18]. Currently, all known monogenic forms of PD combined explain only about 30% of familial and 3 to 5% of sporadic cases [19]. The causes in the rest of the cases are due to various combinations of factors.

A number of genes shown to contribute to PD are involved in two important biological processes present in most cases of the disease: the aggregation of the protein α-synuclein to form Lewy bodies and the impairment of the ubiquitin-proteasome system (UPS), which, under normal conditions, promotes protein degradation. These include mutations in the SNCA gene, which encodes α-synuclein [20], and the PRKN gene, which encodes parkin, a critical enzyme in ubiquitination [21]. Genes involved in mitochondrial metabolism (PINK1, PARK2) and lysosomal-autophagy (ATP13A2, GBA, LRRK2) have also been implicated in PD [22], [23], [24]. Notably, mutations in the LRRK2 gene tend to be the most common contributors to both familial and idiopathic PD [25].
Environment

In 1983, several people developed symptoms of PD after intravenous injection of a synthetic opioid drug contaminated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [26]. It was later found that MPTP causes dopaminergic neuron death in the substantia nigra.

Since then, many epidemiological studies have also examined effects of exposure of environmental toxins, such as pesticides and herbicides, living in rural areas, and drinking of well water, on the risk of developing PD [27]. Evidence suggests there is a positive association between pesticide exposure and PD risk [28]. Conversely, smoking cigarettes and drinking coffee have shown a negative association with the risk of PD [29], [30].

1.1.3 Pathological synchronicity of beta and alpha frequency oscillations

Neural oscillations are present at many levels in the basal ganglia as well as other neural structures and occur at a wide range of frequencies in both healthy and pathological states [9]. These oscillations, reflecting the synchronized activity of neuronal populations, are believed to play a major role in regulating behavior [31].

Electrophysiological studies in PD patients and in animal models of PD have suggested that neuronal activity patterns in the parkinsonian state show excessive synchronized oscillatory activity in cortico-basal ganglia pathways, specifically in the alpha (8-12 Hz) and beta frequency ranges (13-30 Hz), known as the alpha and beta bands, respectively [32], [33]. After MPTP treatment in primates, simultaneously recorded GPi neurons and striatal cholinergic tonically active interneurons (TANs) exhibit oscillatory firing that is synchronized in the 10-12 Hz frequency range [34].
Based on measurements of local field potential (LFP) recordings of neuron populations in basal ganglia structures of both animal models and PD patients, synchronization of neuronal activity occurs in the 8-35 Hz frequency range, and has been shown to directly correlate with the severity of PD motor symptoms [34], [35]. These oscillations have been hypothesized to occur as a result of the pathological synchronization across neuronal populations, as evidenced by intra-operative recordings that demonstrate that the firing of single neurons in the STN is time-locked to oscillatory LFP activity in the alpha and beta frequency bands [36]. Other studies have found excessive synchronization of beta and alpha frequency oscillations in the GPi and cortex, indicating that this is a characteristic common to the entire cortico-basal ganglia network. This abnormal oscillatory behaviour can typically be suppressed by dopaminergic medication and deep brain stimulation [35], [37]. Conversely, applying electrical stimulation to the primary motor
cortex at 20 Hz, in the beta band, has been shown to slow motor performance in healthy subjects[38], [39]. Given the extensive evidence supporting their pathological contributions to PD, alpha and beta frequency oscillations have become an area of interest for studying motor dysfunction in Parkinson’s disease.

1.1.4 The role of alpha and beta desynchronization and its modulation in PD

Excessive alpha and beta band synchrony is proposed to maintain the motor status quo, whereas a decrease in synchrony promotes motor output [39]. In healthy subjects, alpha and beta power decrease just prior to and during movement. The decrease in beta power during movement, which is more prominent and well-characterized, is known as Movement-Related Beta Desynchronization (MRBD). MRBD is followed by a transient post-movement beta power increase above pre-movement levels called Post-Movement Beta Rebound (PMBR) [40], [41].

In a magnetoencephalography (MEG) study investigating neural oscillatory responses during a motor task performed by unmedicated PD patients and healthy subjects, people with PD exhibited significantly reduced beta and alpha desynchronization over central and frontal regions compared with controls prior to and during movement. Patients also exhibited impaired suppression of cortical alpha and beta synchronization just before movement, indicating abnormalities in movement planning, which is hypothesized to contribute to diminished motor output [42].
1.1.5 **Treatments for PD**

The first line of treatment for managing the symptoms of PD is the drug, levodopa (L-3,4-dihydroxyphenylalanine), a precursor to dopamine. It is able to cross the blood brain barrier and be converted to dopamine, replenishing dopamine stores that are lost as a result of dopaminergic neurodegeneration [4]. Although levodopa is effective in alleviating PD symptoms, it does not slow disease progression, and with prolonged treatment, causes a side-effect characterized by involuntary, hyperkinetic movements, called levodopa-induced dyskinesia (LID). LIDs occur in up to 80% of PD patients after 5 to 10 years of levodopa treatment, with the percentage of those affected increasing with treatment duration [43]. Dyskinesias are often difficult to manage and significantly impair patient quality of life.

Other pharmacological treatments include dopamine agonists, such as pramipexole, apomorphine, and ropinirole, which may be used in place of levodopa or in combination with it. Dopamine agonists bind directly to dopamine receptors, mimicking the effects of endogenous dopamine. Unlike levodopa, dopamine agonists do not require enzyme activation and generally cause fewer motor fluctuations [44].

For more severe cases of PD, in which symptoms cannot be adequately controlled with pharmacological options, deep brain stimulation (DBS) is often a second line of treatment. DBS involves the surgical placement of stimulating electrodes in either the STN or the GPi of the basal ganglia [45]. Once the procedure is complete, a battery-operated device on the body is used to send electrical pulses to target areas. The mechanisms behind how DBS works are not completely understood. However, many experts believe that it disrupts the pathological oscillatory activity in the cortico-basal ganglia loop, thereby alleviating the inhibition of movement [46].
Although it is very effective in treating motor symptoms that respond to medication such as rigidity, bradykinesia, and tremor, DBS is a highly invasive procedure and is not suitable for many patients. Furthermore, it is less effective for medication-unresponsive symptoms such as imbalance, freezing of gait, and non-motor symptoms [47], [48]. Some studies have revealed that DBS may even exacerbate cognitive and neuropsychiatric symptoms such as memory loss and apathy[49], [50].

1.2 Apathy in Parkinson’s disease

Apathy is a common and debilitating non-motor symptom of PD, characterized by a lack of motivation, emotional indifference, and loss of interest. The incidence rate of apathy is about 20 to 36% in PD patients who are not medicated. In early-stage PD, apathy may decrease after the introduction of dopaminergic medications, but after 5 to 10 years, the frequency of apathy increases to 40% in patients without dementia and 60% in patients with dementia [51]. In terms of demographics, some studies report associations between age and apathy as well as sex and apathy, but the results are inconclusive [3], [52]. Apathy on its own can arise during early or advanced stages of PD, though the presence of apathy may be a risk factor for future cognitive decline and dementia [53].

1.2.1 The impact of apathy on quality of life

Apathy in PD can significantly reduce the quality of life (QoL) of patients and increase caregiver frustration. It is associated with decreased sociability, awareness of behavioral and cognitive decline, treatment compliance, clinical outcomes, and overall QoL [54]. Apathetic patients often undergo earlier institutionalization than similarly impaired non-apathetic patients [55].
A multicenter survey of 1,072 PD patients assessed the prevalence of non-motor symptoms and their impact on QoL [7]. QoL was assessed using the 39-item Parkinson's Disease Questionnaire (PDQ-39). The result of the survey reported that compared to all other non-motor symptoms of PD, apathy had the largest negative impact on patient QoL with a median PDQ-39 SI score of 36.0. Apart from the detrimental impacts on the individual, apathy also contributes to caregiver distress, dissatisfaction, and frustration [56], [57]. Nonetheless, despite the important clinical implications of apathy in PD, the mechanisms underlying the condition remain largely unknown.

1.2.2 Measuring apathy

The standard method of measuring apathy has been through questionnaire-based assessments. The Starkstein Apathy Scale (SAS) [58] and the Lille Apathy Rating Scale (LARS) [59] are classified as “recommended” by the Movement Disorders Society. The LARS has an advantage of providing an overall apathy score, as well as four subscores that assess subcategories of apathy, including intellectual curiosity, action initiation, emotion, and self-awareness. Other qualitative apathy measures include the Apathy Evaluation Scale [60] and the apathy item (item 7) on the Neuropsychiatric Inventory (NPI) [61].

Most studies use clinically validated cutoff scores in apathy scales to diagnose apathy. However, the various types of assessments, sources, and cutoff points used may contribute to subjectivity in apathy scores and are crucial limitations to qualitative apathy questionnaires. For example, studies using the LARS and the NPI reported nearly a 10% lower rate of apathy compared with studies using the SAS [51]. Because different apathy scales are scored by different sources (SAS: self-reported, LARS: clinician or researcher-based, NPI: caregiver-based), it is difficult to
determine whether a difference in apathy prevalence is caused by the assessments themselves or the source of the information. Ultimately, the scores derived from apathy scales are qualitative measures with variable diagnostic criteria, which can be subjective. The development of a more objective, quantitative biological marker of apathy is required to ensure diagnostic accuracy.

1.2.3 Apathy and depression

One of the main challenges in the diagnosis of apathy in PD is its overlap with depression and cognitive deficits. For instance, many symptoms of apathy are often confused with those of depression, such as anhedonia, so multiple scales measuring separate symptoms of apathy and depression are necessary when categorizing the two conditions.

Contrasting results regarding the rate of apathy without depression and dementia as comorbidities were reported in different studies. Kirsch-Darrow et al. [62] assessed 80 PD patients with the SAS and several depression scales, and found that 29% of the sample had apathy but no depression. Starkstein et al. [54] determined that out of 52 PD patients diagnosed with apathy in a 164 patient cohort, only 3% had apathy alone, whereas the rest had either comorbid depression or dementia, or both. Dujardin et al. [53] reported apathy in 56% of PD patients, but only 9% of apathy cases exhibited neither depression nor dementia. Taken together, findings suggest that the presence of apathy tends to overlap with the presence depression and dementia. However, it is important to recognize that, although apathy and depression are often comorbid, apathy can also exist as its own entity and have separate pathophysiological mechanisms that merit distinct targets for treatment.
1.2.4 **Pathophysiology of apathy**

*Dopamine*

Consistent with the characteristic loss of dopaminergic neurons in PD, apathy in PD has been associated with impairment in the mesolimbic dopamine reward system [63], which is crucial for the control and reinforcement of motivated behaviours. The system begins with excitatory dopaminergic projections from the ventral tegmental area (VTA) in the midbrain to the nucleus accumbens (NAcc), a part of the ventral striatum [64]. The release of dopamine into the NAcc regulates hedonic evaluation of rewarding stimuli and facilitates reward-based reinforcement learning of motor output [65], [66]. The degeneration of dopaminergic neurons in PD are hypothesized to cause a breakdown in this reward pathway and lead symptoms of apathy [67].

However, there is increasing evidence that dysfunction in other systems outside of the dopamine reward system may also contribute to the pathological features of apathy. Dujardin et al. [53] found a significant association between apathy and cognitive, but not motor deficits and suggested that non-dopaminergic circuits may be additionally related to the mechanism of apathy in PD. Furthermore, dopaminergic medications are not always effective in treating apathy. Starkstein et al. [68] hypothesized that levodopa may either only improve apathy in the early stages of PD, or that it will benefit a subgroup of patients with more severe dopamine deficits.

*Other neurotransmitters*

In addition to the neurodegeneration of dopaminergic neurons in the basal ganglia, the pathology of Parkinson’s disease involves multiple neurotransmitters and brain structures. Consequently, the underlying pathology of apathy in PD is multidimensional and can be caused by impairment of different neural pathways. Serotonergic, cholinergic, and noradrenergic
neurotransmitter systems, connecting key reward structures, such as the amygdala, ventral striatum, and prefrontal cortex (PFC), have also been found to play a role in apathy [51].

Maillet et al. [69] used positron emission tomography (PET) imaging of dopaminergic and serotonergic radioligands in de novo PD patients and found that apathetic patients had greater serotonergic abnormalities in the ventral striatum, the dorsal and subgenual areas of the anterior cingulate cortex (ACC), the right caudate nucleus, and the right orbitofrontal cortex (rOFC). They also found that the severity of apathy was mainly related to specific serotonergic lesions within the right anterior caudate nucleus and the OFC, without a prominent contribution from dopaminergic degeneration, highlighting the impact of serotonergic degeneration in apathy.

Pathology in the cholinergic system may also contribute to apathy in PD. After a 6 month multicenter trial of the effects of an acetylcholinesterase inhibitor, rivastigmine, on apathetic PD subjects, results reported that this treatment led to a significant improvement in apathy [70].

Atrophy of deep brain nuclei in dopamine-resistant apathy

Because it is linked to dopamine depletion, apathy may arise after dopaminergic medications are tapered after deep brain stimulation. However, even in the absence of tapering, some patients may develop apathy as PD progresses. This form of apathy, known as dopa-resistant apathy, responds poorly to dopaminergic medications and is often related to cognitive decline. An MRI study exploring striato-frontal morphological changes in apathetic PD patients found that dopa-resistant apathy was associated with atrophy of the left nucleus accumbens and the dorsolateral head of the left caudate [71].
Metabolism

Hypometabolism in the ventral striatum has been shown to be associated with the risk of apathy after STN stimulation in PD. In non-STN-DBS patients, apathy has been associated with hypometabolism in the left insula, the right frontal and occipital regions, and the cerebellum [72]. ACC dysfunction may underlie the cognitive and emotional aspects of apathy because of the structure’s role in problem solving, error detection, adaptive responses, and evaluating emotional salience.

Grey matter

A structural MRI study in non-demented apathetic PD patients showed grey matter decreases in the lateral prefrontal cortex, OFC, and left NAcc, regions involved in executive function and reward processing [57]. Reijnders et al. [73] assessed structural brain differences in 60 PD patients without dementia or depression and found that apathy severity was associated with grey matter density reduction in the premotor cortex, bilateral precentral gyrus, inferior parietal and frontal gyrus, insula, the posterior cingulate gyrus, and the right precuneus. They suggested that dysfunction in the premotor cortex and cingulate gyrus may constitute less motivation to initiate voluntary movements, that insular atrophy may be related to loss of emotional responsiveness, and that parietal and frontal lobe pathology may contribute to executive dysfunction.

Apathy subcategories

Levy proposed that apathy can be divided into three subcategories, each with its own characteristics and neural correlates: auto-activation, emotional-affective, and cognitive apathy [74].
1.2.5 **Auto-activation apathy**

Auto-activation apathy is characterized by the inability to self-initiate thoughts or actions. This results in a quantitative reduction of voluntary behaviour, which can typically be reversed through external prompting. Levy and Dubois suggested that this form of apathy is commonly characterized by bilateral lesions of the limbic system and associative areas of the basal ganglia as well as subcortical structures connected to the medial and lateral PFC and the supplementary motor area (SMA) through the caudate nucleus and the ACC [74]. The disruption of these connections may impair the selective appraisal of relevant actions, leading to difficulties in decision-making [75]. Notably, patients with auto-activation deficits will have difficulties associating reward with a given behavior, which can be interpreted as a lack of motivation.

1.2.6 **Modulating effort in response to reward**

In a study exploring differences between patients with auto-activation deficit disorder (AAD) due to bilateral striato-pallidal lesions and patients with PD, Schmidt et al. [76] used a behavioural paradigm involving an externally driven task, in which subjects were instructed to produce different levels of force by squeezing a hand grip, and an incentive-based task, in which subjects could win different amounts of money depending on how hard they squeezed. AAD patients did not differ from PD patients in their grip force response to external instructions. However, unlike PD patients, their grip force response remained consistent, regardless of the level of monetary incentives, suggesting that auto-activation apathy may arise from a disconnect between motor output and the affective evaluation of rewards. Although apathy is a common feature of PD, the study did not differentiate between apathetic and non-apathetic PD patients.
Chong et al. [77] examined the role of reward on effort production in PD patients who were not clinically apathetic as defined by the Lille Apathy Rating Scale (LARS). Even in the absence of clinical apathy, when subjects were off their dopamine medication, they showed deficits in incentivized effort production when rewards were low, whereas the addition of dopamine eliminated these deficits. Although dopamine was able to improve reward-response deficits in PD patients without apathy, the effects of apathy on motivation-based behaviour and whether dopamine is effective in treating apathetic symptoms in PD remains unclear.

*Beta band oscillations (13-30 Hz)*

Akinesia, the inability to execute movement, and hypokinesia, the reduction of movement, are characteristic symptoms of PD that are hypothesized to be related to motivational deficits [78], [79], especially considering the common role of dopamine in these conditions. Neural oscillations also play a role in modulating movement. For instance, the delay in voluntary movement initiation seen in PD is linked to insufficient reduction of beta synchrony in the subthalamic nucleus [80].

An MEG study tested healthy individuals exerting physical effort using a squeeze grip device to win monetary amounts proportional to the time spent above a target force [81]. Behavioral data indicated that rest periods were shorter when monetary incentives were high, while MEG data revealed that the magnitude of beta desynchronization over the motor cortex correlated with both incentive level and rest duration. Furthermore, the level of desynchronization was shown to modulate the effect of incentive level on rest duration, suggesting that motor beta desynchronization may act as a mechanism that quickens the initiation of effort production in the presence of greater rewards. Such a paradigm has not yet been explored in PD patients with apathy.
Alpha band oscillations (8-12 Hz)

In an EEG study exploring motivation in response to rewards, quick successions of images were presented to participants and they were asked to discriminate a target image from distractor images. Some trials were “motivational” (internally-driven using monetary rewards) while others were externally-driven [82]. Findings revealed a significant decrease in alpha band amplitude in the preparatory period for reward trials as well as better trial performance. This finding is consistent with fMRI findings from Engelmann et al. (2009) that motivation in response to reward improves behavioral performance in attention-demanding tasks by enhancing evoked responses in frontoparietal attentional brain networks [83].

Theta band oscillations (4-7 Hz)

4-7 Hz theta frequency oscillations around the human anterior cingulate cortex (ACC) and frontal cortex oscillations are known to be associated with attentional processes. More recent studies have shown that theta band oscillations increase in response to rewarding stimuli. Tsujimoto et al. [84] located the neural generators of frontal theta oscillations using a primate model involving monkeys that performed a self-initiated hand-movement task. Theta power in the medial PFC and the rostral ACC increased just prior to and immediately after movement. Interestingly, when the movement was rewarded, the theta power increased again, whereas it decreased in unrewarded trials, suggesting that theta activity during attentional processes may be associated with the assessment of reward.

An EEG study involving a gambling game in which participants chose either high-risk/high-reward or low-risk/low-reward bets, revealed a feedback-induced increase in theta band power the frontal cortical region that was higher in amplitude following high-risk bets [85].
Cohen et al. [86] recorded LFPs using deep brain stimulation electrodes implanted in the nucleus accumbens and the medial frontal cortex of major depression patients. Patients performed a reversal learning task in which they could alter decision strategies following monetary losses. Strategy switches following losses were preceded by enhanced theta (4-8 Hz) phase synchrony between the nuclei accumbens. These findings suggest that theta phase synchrony of the nuclei accumbens aid in adjusting reinforcement-guided behaviors.

1.2.7 Emotional-affective Apathy

Emotional-affective apathy is the inability to accurately interpret affective contexts that guide behavior and evaluate positive or negative outcomes [74]. This is often termed “emotional blunting,” whereby the individual reacts to emotional situations in a short-lived or reduced manner [51]. Patients with emotional-affective apathy may experience decreased drive to participate in activities such as social situations, sexual activity and personal hygiene [87] and show a reduced response to rewarding stimuli [88], [89]. Emotional-affective apathy is typically associated with dysfunction in the orbital, medial PFC, and limbic areas of the basal ganglia including the ventral striatum and ventral pallidum [87].

Event-related potentials

Scalp-recorded event-related potentials (ERPs) are well-suited to measuring rapid affective and cognitive processes associated with emotion regulation. ERPs are small voltage responses in the brain that are time-locked to specific events or stimuli and are thought to reflect the summed activity of postsynaptic potentials produced when a large number neurons fire in synchrony [90]. Early potentials in the first 100 ms are involved in stimulus detection, whereas later potentials
reflect information processing and interpretation [90]. They can serve as potential biological markers in pathological cases of emotional dysfunction or deficits [91].

Martinez-Horta et al. [92] used a gambling task to measure an ERP associated with the assessment of performance, the feedback-related negativity (FRN), in response to monetary gains and losses in non-demented, non-depressed patients with early- to late-stage PD and healthy controls. The amplitude of the FRN was significantly reduced in PD patients with apathy compared to those without apathy and healthy controls. These findings suggested an impairment in reward processing and hedonic evaluation in apathetic PD patients, which was proposed to be caused by the decrease in dopaminergic connections in the mesolimbic dopamine reward system, which disrupts connectivity among the ventral striatum, PFC, caudate, ACC, and VTA.

An ERP evoked by emotionally engaging stimuli is the late positive potential (LPP), which is characterized by an amplitude enhancement for pleasant and unpleasant stimuli, relative to neutral stimuli, over the centroparietal region. The LPP typically begins at around 300 to 400 ms after stimulus onset and is often sustained throughout the duration of stimulus presentation [93]. LPP amplitude has been shown to vary in relation to the experienced intensity of the affective picture content [94] and exhibit abnormal patterns in mood disorders and other psychiatric conditions.

Dietz et al. [91] investigated EEG emotional processing in non-demented patients with PD and healthy control participants while viewing pleasant, neutral, and unpleasant pictures. Highly apathetic PD patients showed reduced amplitude of the centro-parietal LPP specifically when viewing unpleasant compared to low apathy PD patients and healthy controls. These results suggest that apathy in PD may be related to a deficit in defensive activation.
1.2.8 **Cognitive apathy**

Cognitive apathy is characterized by the impairment in executive functions. These include deficiencies in planning and organizing goals, self-generating rules, creating strategies to retrieve information from episodic and semantic memory, and maintaining information in working memory [74], [95]. Voluntary actions associated with cognitive inertia become particularly impaired. A gradual decrease in cognitive performance has been observed in apathetic subjects, suggesting that apathy may be a predictive factor for dementia and cognitive decline [53]. Neuroimaging studies in cognitively apathetic PD patients without dementia show decreased activity in the dorsolateral PFC, lateral aspects of the caudate nucleus and putamen, the ACC, and the posterior parietal cortex [96], [74], [51].

Notably, dopamine depletion has been correlated with cognitive impairments in PD [97], [98]. Animal studies showed that dopamine receptor inhibition in the cortico-basal ganglia loop led to cognitive dysfunction [99], [100], [101], while a human study demonstrated that dopamine levels in caudate nucleus modulate glucose metabolism in fronto-striatal circuits that are crucial for executive function [102]. Together, the findings reveal a crucial role of dopamine in cognitive processes.
Figure 1.3 Brain regions associated with different apathy subcategories. Adapted from Pagonabarraga et al. (2015) [19].

1.2.9 Treatments for apathy in PD

Studies on the treatment of apathy in PD are limited. Management is difficult as patients are often indifferent to their own wellbeing and to caregivers. Often, their inactivity can be misconstrued as “laziness”. Non-pharmacologic strategies include prescribing a personalized daily schedule with social and stimulating activities that help to maintain a satisfactory activity level and enrichment [103], [104].

Pharmacological interventions such as dopaminergic drugs, cholinesterase inhibitors, and antidepressants show some benefit, although results vary between patients. Some studies report that the administration of levodopa and dopamine agonists are associated with lower apathy scores [105], [106]. Dopamine receptor agonists have been shown to be particularly effective in treating
apathy symptoms, including the piribedil, pramipexole, rotigotine, and ropinirole [105], [107], [15], [108], [109], [110]. However, there is conflicting evidence in regards to the effectiveness of levodopa as a treatment for apathy, as other studies found that higher levodopa dosage either had no effect on apathy improvement or even worsened apathy scores [111], [112]. In moderately to severely affected PD patients without dementia or depression, a significant improvement in the LARS score was reported after 6 months of treatment with the cholinergic drug, rivastigmine [70].

The use of antidepressants to treat apathy in PD is also controversial. Single cases of postoperative parkinsonian apathy after STN-DBS have reported to be resistant to depression medications such as selective serotonin reuptake inhibitors [113]. In patients who have not had DBS surgery, selective serotonin reuptake inhibitors have even been reported to increase apathy in Parkinson's disease [114].

1.3 Aims and hypotheses

Given the multifactorial nature of apathy in PD, further research into the exact neural mechanisms underlying apathy is crucial for the development of more precise and effective therapeutics to combat this debilitating condition. Additionally, because apathy is currently diagnosed using subjective questionnaire-based evaluation scales, determining potential neural markers of apathy in PD can be beneficial in increasing the reliability of its diagnosis.

As apathy can be associated with a disconnect between reward evaluation and a concomitant behavioural response, often related to a lack of motivation, we were interested in investigating the effects of apathy on motor output in response to reward and the accompanying neural oscillatory behavior. Previous studies have compared the relationship between reward and motor effort in healthy subjects and PD subjects as a whole, but have not made a distinction
between apathetic and non-apathetic PD subjects. Furthermore, a limited number of EEG studies investigating neural oscillatory characteristics of apathy in PD have been done.

We were also interested in characterizing emotional deficits in apathy using ERPs that have previously been implicated in processing and evaluating emotional stimuli, such as the late positive potential (LPP). Although one study found a blunted LPP response to unpleasant visual stimuli in PD patients with higher apathy [91], a more traditional method of ERP analysis was used, which failed to account for spatial and temporal differences in EEG signals that can confound ERP results. We attempt to validate this study using a method that takes these confounds into consideration.

In Chapter 2, we explore the behavioural and neural oscillatory characteristics of motivated movement in non-apathetic PD, apathetic PD, and healthy subjects. Specifically, we use an incentivized squeeze grip paradigm to examine the effects of winning different monetary values on effort production and oscillatory activity. We hypothesized that apathetic PD patients would exhibit abnormal neural oscillatory behavior in the beta, alpha, theta, and delta frequency bands during effort production in response to reward.

In Chapter 3, we investigate ERPs involved in processing emotionally evocative visual stimuli using a technique called Multiset Canonical Correlation Analysis (MCCA). In contrast to the conventional method of obtaining ERPs, MCCA has the advantage of accounting for mild spatial and temporal differences in EEG signals across tasks or subjects. We hypothesized that apathetic PD patients would exhibit a blunted LPP amplitude in response to emotionally arousing visual stimuli compared to non-apathetic PD patients and healthy individuals.
Chapter 2: Apathy in Parkinson’s disease is associated with abnormal alpha and theta oscillatory activity during incentivized movement

2.1 Introduction

Apathy in PD is often resistant to therapy, difficult to quantify and poorly understood. It is commonly characterized by a lack of motivation and reduced sensitivity to reward. Other characteristic motor symptoms of PD, including akinesia, the inability to execute movement, and hypokinesia, the reduction of movement, are hypothesized to be related to motivational deficits [78], [79].

The current method of diagnosing apathy in patients is to use qualitative questionnaire-based scales, but results are often subjective. Therefore, a biological marker that can be quantitatively measured can provide significant benefits to the diagnosis of apathy in PD. Prior studies have used incentivized motor tasks to measure apathy and have revealed a reduction in response to rewards in apathetic individuals in both healthy and pathological states[76], [77]. However, the underlying mechanisms of these neural abnormalities remain unclear. In particular, neural oscillations, which are widely known to play a vital role in modulating motor output and processing rewards, have not been closely explored in apathy.

Normally, alpha (8-12 Hz) and beta (12-30 Hz) oscillations in the motor cortex decrease in power, or desynchronize, just prior to and during movement [40], [41]. These oscillations are typically observed in both contralateral and ipsilateral sensorimotor cortices during movement and have been shown to have high inter-individual consistency [115]. On the other hand, electrophysiological studies in PD patients and in animal models of PD have suggested that neuronal activity patterns in the parkinsonian state show widespread excessive synchronized
oscillatory activity, specifically in the alpha and beta frequency ranges in cortico-basal ganglia pathways. Prior to and during movement, PD patients who are not on dopaminergic medication tend to exhibit significantly reduced beta and alpha desynchronization compared to healthy individuals, a characteristic that has been suggested to contribute to their diminished movement capacities [42]. As the reduction of motor output may be related to a lack of motivated behaviour in PD, these neural oscillations exhibit specific abnormalities related to apathy in PD.

In addition to being critical for movement, alpha and beta frequency oscillations have been shown to play a crucial role in motivation and reward processing. In an EEG study exploring motivation in response to rewards, quick successions of images were presented to participants and they were asked to discriminate a target image from distractor images. Some trials were internally-driven using monetary rewards, while others were externally-driven [82]. Findings revealed a significant decrease in alpha band amplitude in the preparatory period for reward trials as well as better trial performance.

In a magnetoencephalography (MEG) study, Meyniel et al. tested healthy individuals exerting physical effort using a squeeze grip device to win monetary amounts proportional to the time spent above a target force [81]. Behavioral data indicated that rest periods were shorter when monetary incentives were high, while MEG data revealed that the magnitude of beta desynchronization over the motor cortex correlated with both incentive level and rest duration. Furthermore, the level of desynchronization was shown to modulate the effect of incentive level on rest duration, suggesting that motor beta desynchronization may act as a mechanism that quickens the initiation of effort production in the presence of greater rewards. Such a paradigm has not yet been explored in PD patients with apathy.
More recent studies have shown that theta band oscillations (4-7 Hz) in the anterior cingulate cortex (ACC) and frontal cortex increase in response to rewarding stimuli. In a primate model, a self-initiated hand-movement task induced increased theta power in the medial prefrontal cortex and the rostral ACC just prior to and immediately after movement [84]. Theta power increased again when the movement was rewarded, whereas it decreased in unrewarded trials, suggesting that theta activity may be associated with the assessment of reward. An EEG study involving a gambling game in which participants chose either high-risk/high-reward or low-risk/low-reward bets, revealed a feedback-induced increase in theta band power the frontal cortical region that was higher in amplitude following high-risk bets [85]. Thus, theta band oscillations may also be a frequency band of interest when studying reward-processing abnormalities, as in the case of apathy.

One caveat to the study of neural oscillations is that oscillatory activity is almost always represented as a percent power change relative to a baseline prior to a stimulus. Although this accounts for inter-individual variability of baseline oscillations, resting oscillatory activity, that is either pathologically high or low, may explain various behavioural abnormalities. However, this aspect of neural oscillatory behaviour is often overlooked when, in fact, neural oscillatory changes such as event-related alpha or beta desynchronization, may be related to the absolute oscillatory power at rest. Despite the potential significance of resting oscillatory power in motor control in the case of PD, very few studies have examined absolute resting and relative movement-related oscillatory activity[116].

Given the potential role of neural oscillations in healthy and pathological behaviour, an investigation into the different aspects of oscillatory activity may provide insight into the
underlying mechanisms of apathy in PD, and may act as a potential apathy biomarker. In this chapter, we investigate behavioral and neural oscillatory characteristics associated with motivational deficits in apathetic people with PD. Specifically, we use EEG recordings to examine both absolute and relative neural oscillatory activity of apathetic PD, non-apathetic PD, and healthy subjects as they perform an incentivized motor task.

2.2 Materials and Methods

2.2.1 Subjects

We recruited 13 apathetic PD subjects, 14 non-apathetic PD subjects, and 13 healthy control subjects for the study. Subjects with PD were recruited from the UBC Movement Disorders Clinic while healthy subjects were either recruited from the community or were spouses of PD patients. One subject from the apathetic PD group and one subject from the non-apathetic PD group were excluded from the analysis due to excessive artifacts in the EEG data. An additional non-apathetic PD subject was excluded due to a device malfunction. The remaining analyses included 12 apathetic PD subjects (5 female, 70.1 ± 4.7 years), 12 non-apathetic PD subjects (6 female, 67.7 ± 5.3 years) and 13 healthy subjects (8 female, 69.9 ± 7.3 years). All subjects had normal or corrected-to-normal vision and all except one apathetic subject were right-handed. This was corrected for during subsequent analyses (see Methods). Informed written consent was obtained and the study was approved by the University of British Columbia’s Clinical Research Ethics Board and the Vancouver Coastal Health Ethics Committee.

Subjects were administered the following assessments prior the experiment: Starkstein Apathy Scale (SAS) and the Lille Apathy Rating Scale (LARS), Beck’s depression inventory (BDI), and the Montreal Cognitive Assessment (MoCA). PD subjects were additionally
administered the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS). The SAS was used for subsequent analyses. All demographic and clinical scores are summarized in Table 2.1. The apathetic PD group had significantly greater depression scores than the non-apathetic PD and healthy groups. Therefore, depression score was included as a covariate in subsequent statistical analyses. All subjects with PD had been prescribed a regularly monitored dosage of an antiparkinsonian medication for at least 2 months prior to study enrollment and had shown a satisfactory clinical response to the medication. During the experiment, subjects with PD were tested while on their usual dopaminergic medication.

Table 2.1. Subject demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Apathetic PD</th>
<th>Non-apathetic PD</th>
<th>Healthy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>(5/7)</td>
<td>(6/6)</td>
<td>(8/5)</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70.1 ± 4.7</td>
<td>67.7 ± 5.3</td>
<td>69.9 ± 7.3</td>
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<tr>
<td>MoCA</td>
<td>26.2 ± 0.8</td>
<td>26.4 ± 0.6</td>
<td>26.2 ± 0.7</td>
<td>0.938</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>27.8 ± 2.3</td>
<td>24.9 ± 2.4</td>
<td>-</td>
<td>0.645</td>
</tr>
<tr>
<td>BDI</td>
<td>13.3 ± 1.5</td>
<td>5.1 ± 1.3</td>
<td>4.9 ± 1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAS</td>
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<td>6.9 ± 1.5</td>
<td>6.8 ± 1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LARS</td>
<td>-20.7 ± 1.6</td>
<td>-28.9 ± 2.0</td>
<td>-30.8 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LEDD(^2)</td>
<td>877.7 ± 408.8</td>
<td>1015.1 ± 651.5</td>
<td>-</td>
<td>0.544</td>
</tr>
<tr>
<td>Antidepressant use</td>
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<td>5 (41.7)</td>
<td>-</td>
<td>1.000</td>
</tr>
<tr>
<td>Cholinesterase</td>
<td>1 (8.3)</td>
<td>0 (0)</td>
<td>-</td>
<td>0.339</td>
</tr>
<tr>
<td>inhibitor use (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 MoCA, Montreal Cognitive Assessment; UPDRS III, Unified Parkinson’s Disease Rating Scale; BDI, Beck’s Depression Inventory; SAS, Starkstein Apathy Scale; LARS, Lille Apathy Rating Scale

2 LEDD, levodopa equivalent daily dosage in milligrams

3 Three group comparisons are done using one-way ANOVA, while two group comparisons are done using Student’s t-tests.
2.2.2 Experimental Setup

Subjects were seated comfortably in front of a 19” computer screen in a noise-reduced room. They performed an incentivized squeeze grip task using a grip force transducer (Hand Dynamometer Logger Sensor NUL-237, NeuLog, USA).

Maximum Voluntary Contraction Calibration

Subjects were instructed to squeeze as hard as they could over three exertions using their dominant hand. The maximum force reached across the three exertions was recorded. Subjects were then instructed to squeeze the grip force transducer so as to reach a red line on a graduated scale displayed on the computer screen, with real-time visual feedback. The red line corresponded to a target level of force that was either 40, 80, or 120% of the maximum force recorded previously. Each force level was presented three times in a randomized order, for a total of 9 trials. The 120% level ensured that subjects were in fact squeezing to their maximum force. If this exceeded the maximum force recorded, the highest force reached over the three 120% trials was recorded as the new maximum force. If individuals reached or exceeded the red line indicating the 120% mark, subjects were required to repeat the procedure again. The final maximum force value that was obtained was termed the Maximum Voluntary Contraction (MVC).

Behavioral Task

At the start of each trial, subjects were presented with one of three monetary values ($1, $10, or $50) for 2 s, indicating the maximum amount they could earn for the trial (Figure 2.1A). Next, they were shown a graduated scale with the incentive at the top for 4 s. They were told that they would earn a monetary amount proportional to how hard they squeezed the grip force transducer (Figure 2.1B), with the maximum being the monetary value presented at the beginning
of the trial. At the end of each trial, feedback on the amount of money earned was displayed for 2 s, followed by 9 s of rest. Each subject’s MVC was set to 50% of the total monetary value on the scale. Therefore, when subjects attained their MVC, they reached the midline and won half of the monetary incentive. This was done to avoid ceiling effects. The task consisted of 45 trials, with 15 trials per monetary incentive presented in a mixed and randomized order.

![Figure 2.1. Behavioural Task. A) The screenshots were displayed in a successive order for each trial (shown from left to right). One the computer screen, subjects were first presented with either $1, $10 or $50 in a randomized order. Next, a graduate scale with the monetary value at the top appeared, which signaled subjects to squeeze a hand grip device and allowed them to view their performance in real-time. At the end of the trial, the amount of money earned in the present trial and cumulative money earned was presented as feedback. Each trial was followed by a 9 s rest period. B) Subjects were required to squeeze the corresponding grip force transducer to earn money.](image)
2.2.3 Behavioral Analysis

Grip force data

Grip force data, recorded at a sampling rate of 15 Hz, were digitized and fed into the computer running MATLAB (Mathworks, Natick, USA). The maximum force value reached over each trial of the behavioural task was taken to obtain each subject’s grip force response (GFR) per trial. The GFR was then averaged over trials for each money value.

To assess the modulation of grip force, we performed a two-way mixed analysis of variance (ANOVA) with groups (apathetic PD, non-apathetic PD, and healthy controls) as the between factor and money value ($1 and $50; we focused on these two money values as we expected the largest behavioural differences to come from this comparison) as the within factor. Subsequently, we performed post-hoc two-tailed $t$-tests for between-group comparisons and two-tailed paired $t$-tests for within-group comparisons.

To investigate whether the degree of apathy had an influence on GFR, all PD subjects were re-grouped based on higher and lower apathy scores. Due to the subjective nature of apathy scales, PD subjects who had borderline apathy scores that were either equal to or slightly above the clinical cutoff may not have necessarily been clinically apathetic. Additionally, the SAS was found to be more sensitive than other apathy scales, such as the LARS and NPI, in previous studies [51]. Therefore, we combined those patients that scored below 18 on the SAS, creating a group of nineteen “low apathy” PD subjects. Five subjects scored either 18 or above and were categorized as “high apathy” PD subjects (See Table 2.2). We performed a 2-way mixed ANOVA with the new PD groups as the between factor and money value ($1 and $50) as the within factor. We then performed post-hoc two-tailed paired $t$-tests comparing the $1 and $50 responses of the high
apathy and low apathy PD groups as well as separate two-tailed t-tests comparing the responses between the two PD groups towards the $1 and $50 conditions.

Table 2.2. High and low apathy PD subject demographic and clinical characteristics

<table>
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<th>Low Apathy PD</th>
<th>p-value&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
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<td>(3/2)</td>
<td>(8/11)</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70.8 ± 5.3</td>
<td>68.4 ± 5.0</td>
<td>0.392</td>
</tr>
<tr>
<td>MoCA</td>
<td>26.0 ± 3.4</td>
<td>26.4 ± 1.9</td>
<td>0.801</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>29.4 ± 5.0</td>
<td>26.3 ± 8.8</td>
<td>0.326</td>
</tr>
<tr>
<td>BDI</td>
<td>17.8 ± 3.1</td>
<td>7.1 ± 4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAS</td>
<td>20.0 ± 1.9</td>
<td>9.9 ± 4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LARS</td>
<td>-18.0 ± 4.5</td>
<td>-26.2 ± 6.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LEDD&lt;sup&gt;2&lt;/sup&gt;</td>
<td>856.4 ± 486.8</td>
<td>970.1 ± 558.8</td>
<td>0.666</td>
</tr>
<tr>
<td>Antidepressant use (n, %)</td>
<td>2 (40.0)</td>
<td>8 (42.1)</td>
<td>0.941</td>
</tr>
<tr>
<td>Cholinesterase inhibitor use (n, %)</td>
<td>1 (8.3)</td>
<td>0 (0)</td>
<td>0.374</td>
</tr>
</tbody>
</table>

<sup>1</sup> MoCA, Montreal Cognitive Assessment; UPDRS III, Unified Parkinson’s Disease Rating Scale; BDI, Beck’s Depression Inventory; SAS, Starkstein Apathy Scale; LARS, Lille Apathy Rating Scale

<sup>2</sup> LEDD, levodopa equivalent daily dosage in milligrams

2.2.4 EEG recording

Data were collected using a 64-channel EEG cap (Neuroscan Ltd.) and the high impedance amplifier Neuroscan SynAmps<sup>2</sup> (Compumedics Neuroscan Ltd., VA, USA) at a sampling rate of 500 Hz. Impedances were kept below 20 kΩ using Electro-Gel (Electrode-Cap International, OH, USA). From the original 64 electrodes, recordings were taken from 34 electrodes. Recording
electrodes were positioned according to the International 10-20 EEG System [117]. Two additional pairs of surface electromyographic electrodes were used to detect horizontal and vertical eye movements for subsequent artifact removal.

2.2.5 Preprocessing

EEG data were preprocessed offline using custom-written scripts in MATLAB, incorporating functions from the open-source MATLAB toolbox, EEGLAB [118]. Continuous EEG recordings were segmented into 8 s epochs, which included 1 s of rest before the start of the trial, 2 s of money presentation, 4 s of squeeze duration, and 1 s post-squeezing. Each epoch was linearly detrended and band-pass filtered between 1 and 50 Hz. Epochs were then concatenated and band-pass filtered again between 1 and 50 Hz. Using the EEGLAB plug-in, clean_rawdata, channels containing continuous artifacts were removed and interpolated using spherical spline interpolation. Data were then re-referenced to average reference and stereotypical artifacts, such as eye blinks, eye movements and muscle tension were separately removed using an automatic artifact rejection method based on the blind source separation algorithm [119] Independent Component Analysis (ICA). ICA separates a multivariate signal into statistically independent components representing linear combinations of the original variables [120]. Artifacts due to eye movements and muscle activity are temporally independent from neural activity, which allows them to be identified and removed. Finally, any trial containing data with an absolute amplitude exceeding 180 microvolts was removed. On average, 2% of the trials were removed, which did not differ between subject groups (one-way ANOVA: p>0.40). Electrodes designating the scalp distribution for the one left-handed subject were flipped over the sagittal plane to account for any lateralized differences.
2.2.6 **EEG spectral analyses**

Time-frequency analysis was performed on the preprocessed data using a seven-cycle complex Morlet wavelet for a frequency range of 1–50 Hz. Both absolute and relative time-frequency data were computed and averaged over trials for each subject, then averaged across subjects to create group time-frequency plots (Figure 2.2 A). Relative time frequency data was defined as the 10* log10 change in power relative to 1 second of average baseline power before the start of each trial.

To identify the sensors showing the strongest theta, alpha, and beta modulation, we plotted the grand average scalp distribution for each frequency range across all subjects, taken as an average relative power over the first 3 seconds of motor output for each of the theta (4-7 Hz), alpha (8-12 Hz), and beta (12-30 Hz) frequency ranges (Figure 2.2 B). Nine common centro-parietal electrodes were identified to have the highest theta, alpha, and beta modulation during squeezing based on grand-average scalp distributions: Cz, C4, CP5, CP1, CPz, CP2, CP6, Pz, and P4. These electrodes were also consistent with electrodes found in previous literature to show movement-related desynchronization [121], [122], [123], [124], [117].

2.2.7 **Determining channels of interest**

In order to determine the EEG channels with the greatest theta, alpha, and beta power differences between subject groups during different time periods, we performed separate one-way multivariate analysis of variance (MANOVA) tests with subject group (apathetic PD, non-apathetic PD, and healthy controls) as the independent variable and each of the nine centro-parietal channels (Cz, C4, CP5, CP1, CPz, CP2, CP6, Pz, P4) as a dependent variable. MANOVA is particularly useful in detecting differences when response variables are correlated, as in the case
of EEG channels. Specifically, we were interested in the rest period (1 s before the beginning of the next trial) and squeezing period (first 3 s of the squeeze period). For the rest period, one-way MANOVA was performed for absolute power in the beta, alpha and theta bands separately. For the squeezing period, one-way MANOVA was performed on the relative and absolute power for beta, alpha, and theta bands separately. Thus, a total of nine one-way MANOVA tests were performed to account for between-group comparisons involving absolute power during rest, absolute power during squeezing, and relative power during squeezing for each of the three frequency bands of interest. Subsequent one-way ANOVA tests were done to determine differences between groups for each channel and Tukey HSD post-hoc tests were done to determine differences between individual groups.

Once we found a common group of channels with significant differences specifically between the apathetic and non-apathetic PD groups (CPz, CP1, CP2, Pz; Figure 2.2C), we computed an average of these channels across each frequency band for all further analyses.
Using the averaged data, we performed separate two-way mixed ANOVAs for relative and absolute theta, alpha, and beta power, including group (healthy, non-apathetic PD, and apathetic...
PD) as a between group factor and time period as a within group factor. Time periods were defined as: ‘rest’ (1 s before the start of the next trial), ‘money presentation’ (2 s duration of monetary incentive presentation on the computer screen), and ‘squeezing’ (0.5-1 s following onset of squeezing, during which the greatest event-related theta, alpha, and beta modulation occurs). The rest period was not included in any relative power analyses because this was the baseline period that was normalized to 0. Additionally, due to the presence of a momentary increase in theta power during the start of the squeeze period, an additional time period was included for the analysis of the theta band and was denoted the ‘squeeze initiation’ (0-0.5 s during the onset of squeezing) period (Figure 2.3).

![Figure 2.3. Schematic diagram of time frames used in spectral data analysis. Rest: -3 to -2 s; Money Presentation: -2 to 0 s; Squeeze Initiation: 0 to 0.5 s; Squeezing: 0.5 to 1 s. Blue line indicates the power evolution over time averaged over the frequency band of interest (ie. theta, alpha, or beta).](image)

Ten separate one-way ANOVA analyses comparing absolute power in the different frequency bands between groups were performed for time periods averaged over rest, money presentation, and squeezing duration. Five one-way ANOVA tests were used to compare relative
power in the different frequency bands between groups during the money presentation and squeezing time periods. Tukey HSD post-hoc tests were subsequently performed to further investigate significant differences between individual groups and correct for multiple comparisons.

Correlation analysis using all subjects was performed between resting alpha power and relative alpha power during squeezing over the centro-parietal region (averaged over CPz, CP1, CP2, and Pz). The same analysis was done between resting theta power and relative theta power during squeezing over the centro-parietal region.

Principal component regression (PCR) was performed to predict apathy scores of all PD subjects based on power during particular time periods in the frequency bands of interest and other demographic and clinically relevant factors. PCR was used in place of multiple linear regression to correct for the presence of predictor variables that were highly correlated with one another. This regression method constructs new predictor variables, known as components, as linear combinations of the original predictor variables and creates components to explain the observed variability in the predictor variables. To do this, we first performed principal components analysis (PCA) on predictor variables to group highly correlated independent variables into independent principal components, then conducted a multiple linear regression of the response variable on the components (Figure 2.4). Each variable was normalized by its mean and standard deviation to account for differences in variance [125].
In order to compare spectral differences in response to different money values, we separated and grouped EEG trials based on the $1 and $50 conditions and performed paired t-tests on the $1 and $50 condition spectral data for each group separately. Specifically, we compared the average relative power over each time point of interest: rest, money presentation, and squeezing. Mean power was computed over the theta, alpha, and beta bands separately.

2.3 Results

2.3.1 Behavioural results

Two-way mixed ANOVA on GFR values, with subject groups (apathetic PD, non-apathetic PD, and healthy controls) as the between factor and money values ($1 and $50) as the within factor, revealed a significant main effect of group ($F(2,34) = 4.50, p = 0.018$), a significant main effect of money value ($F(1,34) = 21.60, p < 0.0001$), and no interaction between group and money value ($p > 0.05$). Post-hoc paired t-tests within each group showed that the GFR for the $50 condition was significantly higher than the GFR for the $1 condition (Figure 2.5.A). Independent post-hoc t-tests comparing GFR between groups showed that apathetic PD subjects had a significantly lower...
GFR than healthy controls for both the $1 and $50 conditions, but no other significant differences were found.

After reorganizing the PD subject groups into a “high apathy” PD group and a “low apathy” PD group, two-way mixed ANOVA on GFR between subject groups (apathetic and non-apathetic PD) and money values ($1 and $50) showed a significant main effect of money ($F(1,22) = 14.28, p = 0.001$) and a significant main effect of group ($F(1,22) = 4.38, p < 0.05$), but no significant interaction between money and group ($F(1,22) = 0.56, p > 0.4$). Two-tailed paired $t$-tests revealed that the responses to the $1 and $50 conditions of high apathy PD subjects did not differ significantly ($t(4) = -1.85, p = 0.138$), but differed significantly in the low apathy PD group ($t(18) = -4.63, p < 0.001$) (Figure 2.5.B). Comparisons between the two groups showed a marginally non-significant difference between the response to the $1 condition (two-tailed $t$-test; $t(22) = -1.95, p = 0.065$). However, the response to the $50 condition in the low apathy group was significantly higher than that of the high apathy group (two-tailed $t$-test; $t(22) = -2.44, p = 0.023$). Furthermore, there was no significant difference in UPDRS 3 scores between the two groups (two-tailed $t$-test; $p > 0.05$), suggesting that disease severity was not a main factor in observed behaviour.
Figure 2.5. **Behavioural results.** A) Mean grip force response (GFR) shown as a percentage of the total maximum voluntary contraction (MVC) for apathetic PD, non-apathetic PD, and healthy control subjects in response to $1, $10, and $50. Error bars are ±SEM. Asterisks indicate a significant difference (paired t-test) between $1 and $50 conditions. *p<0.05, **p < 0.005, ***p < 0.0005. B) Mean GFR for high apathy PD (n=5), low apathy PD (n=19), and healthy control subjects in response to $1, $10, and $50. Asterisks indicate a significant difference (paired t-test) between $1 and $50 conditions. *p<0.05, **p < 0.005, ***p < 0.0005, N.S. = non-significant.

### 2.3.2 Channels of interest

One-way MANOVA using the 9 selected centro-parietal channels showed a significant difference in theta band power between subject groups for absolute theta power during squeezing...
(F(2,34) = 1.82, \( p < 0.05 \); Pillai’s Trace = 0.754, partial \( \eta^2 = 0.38 \)). However, Tukey HSD post-hoc tests specifically comparing apathetic and non-apathetic PD groups showed no significant differences for any channels. Although one-way MANOVA showed no significant difference between groups for absolute resting theta power (F(2,34) = 1.71, \( p = 0.068 \); Pillai’s Trace = 0.724, partial \( \eta^2 = 0.36 \)) and relative theta power during squeezing (F(2,34) = 1.41, \( p = 0.167 \); Pillai’s Trace = 0.639, partial \( \eta^2 = 0.32 \)), individual comparisons using Tukey HSD post-hoc tests showed significant differences between the two PD groups in the CP1 and Pz electrodes for absolute resting theta power and in the CPz, CP1, and Pz electrodes for relative theta power during squeezing (Table 2.2).

One-way MANOVA also showed a significant difference between subject groups for absolute resting alpha power (F(2,34) = 1.80, \( p < 0.05 \); Pillai’s Trace = 0.751, partial \( \eta^2 = 0.38 \)), absolute alpha power during squeezing (F(2,34) = 2.23, \( p < 0.05 \); Pillai’s Trace=0.853, partial \( \eta^2 = 0.43 \)), and relative alpha power during squeezing (F(2,34) = 2.53, \( p = 0.005 \); Pillai’s Trace = 0.903, partial \( \eta^2 = 0.45 \)). After Tukey HSD post-hoc tests, only absolute resting alpha power in the CPz, CPz, CP2, and Pz electrodes was significantly greater in apathetic PD subjects compared to both non-apathetic PD subject and healthy subjects (Table 2.3).

For the beta frequency band, no comparisons showed significant differences between groups in any of the 9 selected EEG channels.
Table 2.3. Theta band: Tukey HSD test results after MANOVA. The table shows between-group comparisons for absolute resting theta power, absolute theta power during squeezing, and relative theta power during squeezing in four centro-parietal electrodes. The mean and standard deviations (SD) for each group and electrode are shown. Results are only presented for the four electrodes (CPz, CP1, CP2, Pz) that were used for subsequent analyses and had significant differences in power between apathetic and non-apathetic PD groups. Bolded p-values denote statistical significance (p < 0.05).
Table 2.4. Alpha band: Tukey HSD test results after MANOVA. The table shows between-group comparisons for absolute resting alpha power, absolute alpha power during squeezing, and relative alpha power during squeezing in four centro-parietal electrodes. The mean and standard deviations (SD) for each group and electrode are shown. Results are only presented for the four electrodes (CPz, CP1, CP2, Pz) that were used for subsequent analyses and had significant differences in power between apathetic and non-apathetic PD groups. Bolded $p$-values denote statistical significance ($p < 0.05$).

<table>
<thead>
<tr>
<th>Electrode</th>
<th>Groups</th>
<th>Mean ±SD</th>
<th>$p$-value</th>
<th>Mean ±SD</th>
<th>$p$-value</th>
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<tr>
<td></td>
<td>Absolute - Rest</td>
<td></td>
<td></td>
<td>Absolute - Squeezing</td>
<td></td>
<td>Relative - Squeezing</td>
<td></td>
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<tr>
<td>CPz</td>
<td>Apathy</td>
<td>182.80±131.46</td>
<td>0.016</td>
<td>89.62±59.95</td>
<td>0.105</td>
<td>-2.77±1.85</td>
<td>0.167</td>
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<td></td>
<td>No apathy</td>
<td>80.12±44.72</td>
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<td>56.03±26.69</td>
<td></td>
<td>-1.46±1.32</td>
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<tr>
<td></td>
<td>Healthy</td>
<td>182.80±131.46</td>
<td>0.001</td>
<td>89.62±59.95</td>
<td>0.001</td>
<td>-2.77±1.85</td>
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<td></td>
<td>No apathy</td>
<td>43.22±55.32</td>
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<td>25.07±20.17</td>
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<td>-1.40±1.94</td>
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<tr>
<td></td>
<td>Healthy</td>
<td>80.12±44.72</td>
<td>0.534</td>
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<td>-1.46±1.32</td>
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<td>43.22±55.32</td>
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<td>25.07±20.17</td>
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<tr>
<td>CP1</td>
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<td>185.64±128.69</td>
<td>0.020</td>
<td>94.31±73.36</td>
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<tr>
<td></td>
<td>No apathy</td>
<td>83.30±43.03</td>
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<td>61.11±33.16</td>
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<td>-1.54±1.23</td>
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<tr>
<td></td>
<td>Healthy</td>
<td>185.64±128.69</td>
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<td></td>
<td>Healthy</td>
<td>83.30±43.03</td>
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<td>50.11±70.70</td>
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<td>-1.71±2.06</td>
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<td>CP2</td>
<td>Apathy</td>
<td>214.64±172.98</td>
<td>0.026</td>
<td>92.54±68.97</td>
<td>0.104</td>
<td>-3.06±1.71</td>
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</tr>
<tr>
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<td>No apathy</td>
<td>98.15±52.81</td>
<td></td>
<td>55.45±30.15</td>
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<td>-2.38±1.58</td>
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<tr>
<td></td>
<td>Healthy</td>
<td>214.64±172.98</td>
<td>0.0003</td>
<td>92.54±68.97</td>
<td>0.001</td>
<td>-3.06±1.71</td>
<td>0.159</td>
</tr>
<tr>
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<td>No apathy</td>
<td>34.66±30.91</td>
<td>0.295</td>
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<td>0.115</td>
<td>-2.38±1.58</td>
<td>0.661</td>
</tr>
<tr>
<td></td>
<td>Healthy</td>
<td>98.15±52.81</td>
<td></td>
<td>34.66±30.91</td>
<td></td>
<td>-1.80±1.74</td>
<td></td>
</tr>
<tr>
<td>Pz</td>
<td>Apathy</td>
<td>246.63±178.83</td>
<td>0.034</td>
<td>113.88±72.02</td>
<td>0.309</td>
<td>-2.94±1.51</td>
<td>0.192</td>
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<td>126.26±54.81</td>
<td></td>
<td>85.17±35.77</td>
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<td>-1.84±0.79</td>
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<tr>
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<td>246.63±178.83</td>
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<td>113.88±72.02</td>
<td>0.001</td>
<td>-2.94±1.51</td>
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<td>No apathy</td>
<td>56.73±63.12</td>
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<td>-2.38±1.58</td>
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<td>246.63±178.83</td>
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<td>34.62±19.97</td>
<td></td>
<td>-1.38±1.96</td>
<td></td>
</tr>
</tbody>
</table>
2.3.3 Relative and absolute theta power

Relative theta power

A two-way ANOVA on relative theta power averaged across CPz, CP1, CP2, and Pz electrodes (Figure 2.6.C) with subject group as the between-subject factor (apathetic PD, non-apathetic PD, healthy controls) and time frame as the within subject factor (money presentation, squeeze initiation, squeezing) revealed a significant main effect of group \( (F(2,34) = 11.7, \ p = 0.0001) \), a significant interaction between group and time frame \( (F(2,34) = , \ p = 0.040) \), and no main effect of time frame. One-way ANOVA revealed significant differences between apathetic and non-apathetic PD subjects during money presentation \( (F(2,34) = 7.30, \ p < 0.002) \), squeeze initiation \( (F(2,34) = 7.97, \ p = 0.001) \), and squeezing \( (F(2,34) = 11.6, \ p < 0.001) \). For the money presentation period, apathetic PD subjects showed significantly lower relative theta power \( (M = -0.83, \ SD = 0.89) \) compared to both non-apathetic PD subjects \( (M = 0.09, \ SD = 0.75, \ p = 0.017) \) and healthy subjects \( (M = 0.29, \ SD = 0.67, \ p = 0.002) \). More specifically, during squeeze initiation, apathetic PD subjects had a significantly lower theta power compared to both non-apathetic PD subjects and healthy subjects. The same was true for the squeezing: apathetic PD subjects \( (M = -1.29, \ SD = 1.40) \) showed significantly lower theta power compared to both non-apathetic PD subjects \( (M = 0.16, \ SD = 0.99, \ p = 0.005) \) and healthy subjects \( (M = 0.72, \ SD = 0.77, \ p < 0.001) \) (Figure 2.6.B; top).

Absolute theta power

A two-way ANOVA on absolute theta power averaged across CPz, CP1, CP2, and Pz electrodes with subject group as the between-subject factor (apathetic PD, non-apathetic PD, healthy controls) and time frame as the within subject factor (rest, money presentation, squeeze
initiation, squeezing) showed a significant main effect of time frame ($F(2,34) = 3.86, p = 0.026$), consistent with previous knowledge of alpha behavior during motor output. There was also a significant main effect of group ($F(2,34) = 7.01, p = 0.003$). Additionally, there was a significant interaction between group and time frame ($F(2,68) = 2.12, p = 0.009$). One-way ANOVAs for each time frame revealed that there was a significant difference between groups for absolute theta power during rest ($F(2,34) = 6.67, p = 0.004$), money presentation ($F(2,34) = 7.43, p = 0.002$), squeeze initiation ($F(2,34) = 7.50, p = 0.002$), and squeezing ($F(2,34) = 3.72, p = 0.035$). Tukey HSD post-hoc comparisons revealed that only during rest, apathetic PD subjects had a significantly higher absolute theta power ($M = 207.36, SD = 210.84$) compared to both non-apathetic PD ($M = 79.59, SD = 50.87, p = 0.042$) and healthy subjects ($M = 31.24, SD = 15.25, p = 0.003$) (Figure 2.6.B; bottom).
Figure 2.6. Relative and absolute theta power over time. A) Relative (left) and absolute (right) theta power time courses were extracted by taking the average theta power over centro-parietal electrodes (CPz, CP1, CP2, and Pz). Values for relative theta power are shown in dB and values for absolute theta power are shown in $\mu V^2$. -2 s is the time of money presentation and 0 s is the time of squeeze onset. Shaded areas denote the SEM. B) Average relative (top) and absolute (bottom) theta power were computed for each subject group during rest (-2.8-2 s, absolute power only), money presentation (-2-0 s), and two periods of squeezing (0-0.5 s and 0.5-1 s). *p<0.05, **p < 0.005, ***p < 0.0005
2.3.4 Relative and absolute alpha power

Relative alpha power

For relative alpha power (Figure 2.7.A; left), two-way ANOVA showed a significant main effect of time frame \( F(1,34) = 68.14, \ p < 0.001 \) and a significant interaction between group and time frame \( F(2,34) = 7.68, \ p = 0.002 \). Though there was no significant main effect of group \( (p > 0.05) \), we were particularly interested in the squeezing periods of apathetic and non-apathetic PD subjects, so we continued with further analyses. One-way ANOVA showed that there was a significant difference between groups during the squeezing period \( F(2,34)=5.14, \ p = 0.011 \). Despite higher baseline values, apathetic PD subjects exhibited significantly lower relative alpha power during squeezing \( (M = -3.98, \ SD = 1.34) \) compared to both non-apathetic PD subjects \( (M = -2.28, \ SD = 1.38, \ p = 0.041) \) and healthy subjects \( (M = -2.02, \ SD = 2.06, \ p = 0.014) \) (Figure 2.7.B; left). This was the only significant difference observed for relative alpha power.

Absolute alpha power

A two-way mixed ANOVA comparing absolute alpha power (Figure 2.7.A; right) between groups and time frames showed a significant main effect of time frame \( F(2,33) = 17.21, \ p < 0.0001 \), consistent with previous knowledge of alpha behavior during motor output. There was also a significant main effect of group \( F(2,34) = 10.31, \ p < 0.0001 \) and a significant interaction between group and time frame \( F(2,68) = 7.14, \ p < 0.0001 \). Subsequent one-way ANOVAs for each of the rest, money presentation, and squeeze conditions showed a significant effect of group on absolute alpha power during rest \( F(2,34) = 9.61, \ p < 0.001 \), during money \( F(2,34) = 10.03, \ p < 0.001 \), but not during squeezing. Post-hoc analyses revealed that during rest, apathetic PD subjects had a significantly higher absolute power \( (M = 207.42, \ SD = 147.46, \ p = 0.018) \) than the
non-apathetic PD \((M=96.96, SD=45.56, p=0.018)\) and healthy subjects \((M=46.18, SD=54.23, p<0.001)\). During money presentation, absolute alpha power was also significantly higher in apathetic PD subjects \((M=158.32, SD=121.1, p=0.028)\) compared to non-apathetic PD \((M=77.80, SD=36.59, p=0.028)\) and healthy subjects \((M=28.66, SD=18.36, p<0.001)\) (Figure 2.7.B; right). No significant differences were observed between non-apathetic PD and healthy subjects.

Figure 2.7. Relative and absolute alpha power over time. A) Relative (left) and absolute (right) alpha power time courses were extracted by taking the average alpha power over centro-parietal electrodes (CPz, CP1, CP2, and Pz). Values for relative alpha power are shown in dB and values for absolute alpha power are shown in \(\mu V^2\). -2 s is the time of money presentation and 0 s is the time of squeeze onset. Shaded areas denote the SEM. B) Average relative (left) and absolute (right) alpha power were computed for each subject group during rest (-2.8-2 s, absolute power only), money presentation (-2-0s), and squeezing (0.5-1 s). *\(p<0.05\), **\(p < 0.005\), ***\(p < 0.0005\)
2.3.5 Absolute and relative beta power

Although overall one-way ANOVA showed significant differences between groups for absolute beta power during rest, money presentation, and squeezing, subsequent Tukey post hoc tests showed no differences between apathetic and non-apathetic PD groups, which was the main comparison of interest (Figure 2.8.).

**Figure 2.8. Relative and absolute beta power over time.** A) Relative (left) and absolute (right) beta power time courses were extracted by taking the average beta power over centro-parietal electrodes (CPz, CP1, CP2, and Pz). Values for relative beta power are shown in dB and values for absolute beta power are shown in $\mu V^2$. -2 s is the time of money presentation and 0 s is the time of squeeze onset. Shaded areas denote the SEM. B) Average relative (left) and absolute (right) beta power were computed for each subject group during rest (-2.8-2 s, absolute power only), money presentation (-2-0s), and squeezing (0.5-1 s). *$p<0.05$
Table 2.5. Group means and one-way ANOVA results for theta, alpha, and beta frequency bands. Each row represents a one-way ANOVA test. SD: standard deviation. Bolded p-values denote statistical significance ($p < 0.05$).
Table 2.6. Tukey HSD test \(p\)-values for group differences in relative theta, alpha, and beta power. Group 1 and Group 2 denote the groups that were compared using Tukey HSD. Bolded \(p\)-values denote statistical significance (\(p < 0.05\)).

<table>
<thead>
<tr>
<th>Time Frame</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Theta (p)-value</th>
<th>Alpha (p)-value</th>
<th>Beta (p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Money Presentation</td>
<td>Apathetic PD</td>
<td>Non-apathetic PD</td>
<td>0.0169</td>
<td>0.7126</td>
<td>0.7488</td>
</tr>
<tr>
<td></td>
<td>Apathetic PD</td>
<td>Healthy</td>
<td>0.0027</td>
<td>0.9785</td>
<td>0.0610</td>
</tr>
<tr>
<td></td>
<td>Non-apathetic PD</td>
<td>Healthy</td>
<td>0.7964</td>
<td>0.8183</td>
<td>0.0105</td>
</tr>
<tr>
<td></td>
<td>Apathetic PD</td>
<td>Non-apathetic PD</td>
<td>0.0319</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Squeeze Initiation</td>
<td>Apathetic PD</td>
<td>Healthy</td>
<td>0.0012</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Non-apathetic PD</td>
<td>Healthy</td>
<td>0.4493</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Apathetic PD</td>
<td>Non-apathetic PD</td>
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<td>0.0412</td>
<td>0.5448</td>
</tr>
<tr>
<td>Squeezing</td>
<td>Apathetic PD</td>
<td>Healthy</td>
<td>0.0001</td>
<td>0.0143</td>
<td>0.6336</td>
</tr>
<tr>
<td></td>
<td>Non-apathetic PD</td>
<td>Healthy</td>
<td>0.4416</td>
<td>0.9184</td>
<td>0.9852</td>
</tr>
</tbody>
</table>

Table 2.7. Tukey HSD test \(p\)-values for group differences absolute theta, alpha, and beta power. Group 1 and Group 2 denote the groups that were compared using Tukey HSD. Bolded \(p\)-values denote statistical significance (\(p < 0.05\)).

<table>
<thead>
<tr>
<th>Time Frame</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Theta (p)-value</th>
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<th>Beta (p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Money Presentation</td>
<td>Apathetic PD</td>
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<td>0.0169</td>
<td>0.7126</td>
<td>0.7488</td>
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<td></td>
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<td>0.0027</td>
<td>0.9785</td>
<td>0.0610</td>
</tr>
<tr>
<td></td>
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<td>Healthy</td>
<td>0.7964</td>
<td>0.8183</td>
<td>0.0105</td>
</tr>
<tr>
<td></td>
<td>Apathetic PD</td>
<td>Non-apathetic PD</td>
<td>0.0319</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Squeeze Initiation</td>
<td>Apathetic PD</td>
<td>Healthy</td>
<td>0.0012</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Non-apathetic PD</td>
<td>Healthy</td>
<td>0.4493</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Apathetic PD</td>
<td>Non-apathetic PD</td>
<td>0.0051</td>
<td>0.0412</td>
<td>0.5448</td>
</tr>
<tr>
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<td>Apathetic PD</td>
<td>Healthy</td>
<td>0.0001</td>
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<td>0.6336</td>
</tr>
<tr>
<td></td>
<td>Non-apathetic PD</td>
<td>Healthy</td>
<td>0.4416</td>
<td>0.9184</td>
<td>0.9852</td>
</tr>
</tbody>
</table>
2.3.6  Correlating absolute resting oscillatory power with relative power during squeezing

Using all subjects, there was a significant negative correlation between absolute resting theta power and relative theta power during squeezing over the centro-parietal area (Pearson’s correlation; $r = -0.640, p < 0.001$; Figure 2.9, left). The same was true between absolute resting alpha power and relative alpha power during squeezing (Pearson’s correlation; $r = -0.588, p < 0.001$; Figure 2.9, middle) and resting beta power and relative beta power during squeezing (Pearson’s correlation; $r = -0.5360, p < 0.001$; Figure 2.9, right). Taken together, the higher the resting power in these frequency bands, the greater the accompanying relative power reduction.

![Figure 2.9](image)

**Figure 2.9.** Correlation between resting absolute oscillatory power and relative oscillatory power during squeezing. The left panel shows absolute resting theta power plotted against relative theta power during squeezing. The middle panel shows absolute resting alpha power plotted against relative alpha power during squeezing. The right panel shows absolute resting beta power plotted against relative beta power during squeezing (0.5-1 s). Blue: apathetic PD; red: non-apathetic PD; black: healthy controls.

2.3.7  Predicting PD apathy scores using alpha and theta power at rest and during squeezing

Principal component regression (PCR) using absolute resting alpha power, relative alpha power during squeezing, UPDRS 3 scores, age, and depression scores as predictors found that a two component model was able to significantly predict patient apathy scores ($R^2 = 0.694$, $F(24,21)$
= 23.8, \( p < 0.0001 \)). The first principal component significantly contributed to the model (\( p < 0.0001 \)). Combined PCA and regression coefficients showed the greatest contribution from absolute resting alpha power (combined PCA and regression \( \beta \) coefficient = 0.357) and relative alpha power during squeezing (combined PCA and regression \( \beta \) coefficient = -0.360) to the component. Depression also had a high, but slightly lower contribution, with a combined PCA and regression \( \beta \) of 0.290. This is consistent with previous knowledge that depression and apathy are highly correlated conditions (Figure 2.10; right).

PCR using absolute resting theta power, relative theta power during squeezing, age, UPDRS 3 scores, and depression scores found that a two component model was able to significantly predict patient apathy scores (\( R^2 = 0.592, F(24,21) = 15.3, p < 0.0001 \)). Again, the first principal component significantly contributed to the model (\( p < 0.0001 \)). For theta power, absolute resting theta power (combined PCA and regression \( \beta \) coefficient = 0.297), relative theta power during squeezing (combined PCA and regression \( \beta \) coefficient = -0.234), and depression (combined PCA and regression \( \beta = 0.300 \) had the highest contribution to the component, with depression having the highest contribution in this model (Figure 2.10; left).
Figure 2.10. Scatter plots of normalized predicted vs. actual apathy scores using principal component regression. The left panel depicts normalized (z-score) predicted apathy score plotted against normalized (z-score) actual apathy score using absolute resting theta power, relative theta power during squeezing, age, UPDRS 3, and depression as predictors of apathy score ($R^2 = 0.694$, $F(24,21) = 23.8$, $p < 0.0001$). The right panel depicts normalized (z-score) predicted apathy score plotted against normalized (z-score) actual apathy score using absolute resting alpha power, relative alpha power during squeezing, age, UPDRS 3, and depression as predictors of apathy score ($R^2 = 0.592$, $F(24,21) = 15.3$, $p < 0.0001$).

2.3.8 Spectral comparison between $1 and $50

Paired $t$-tests on the $1 and $50 condition for theta, alpha, and beta, showed no significance was found between the two money value conditions for any of the groups.
2.4 Discussion

2.4.1 Grip force response

In the current study, we investigated the behavioural and neural oscillatory characteristics associated with apathetic patients with Parkinson’s disease using an incentivized squeeze grip paradigm. Although there was no significant difference between apathetic and non-apathetic PD subjects in GFR based on the recommended cutoff of 14 used for the Starkstein Apathy Scale to classify apathy, re-grouping patients into a “higher apathy” group and a “lower apathy” group, defined using a higher cut-off of 18, revealed that more severely apathetic individuals did not significantly differ in their GFR for high or low money values. Additionally, the higher apathy PD group had a significantly lower GFR to the highest money value condition ($50) compared to the lower apathy group. One caveat is that the sample size of our “higher apathy” PD group consisted of five subjects, which may have limited the strength of our observations.

Our results are in line with findings by Schmidt et al. [76] comparing patients with auto-activation deficit (AAD) disorder to patients with PD using a similar squeeze grip paradigm. They found that PD patients exerted greater motor effort in response to higher monetary rewards, whereas AAD patients did not differ in their effort expenditure, regardless of the monetary value at stake. Our results show that PD subjects with lower apathy scores are able to modulate their effort production to increasing rewards, whereas PD subjects with more severe apathy, and possibly auto-activation deficits, are not able to do so. Thus, it may be that only in more severe cases of apathy that PD subjects lose the ability to modulate their behaviour in response to rewards. This is the first study to demonstrate a blunted behavioural response to rewards in apathetic PD patients using an incentivized motor task.
2.4.2 **Distinct oscillatory characteristics of apathetic PD patients**

Our EEG results demonstrate that (1) apathetic PD subjects exhibit a higher baseline alpha and theta power compared to non-apathetic PD subjects and healthy subjects controlling for disease severity and age, and that (2) there is significant negative correlation between absolute resting alpha power and relative alpha power during squeezing. In other words, a higher baseline alpha power is followed by a greater alpha desynchronization. Furthermore, the combination of absolute resting alpha power with relative alpha power during squeezing was able to predict patient apathy scores, controlling for age or disease severity. The same was true for absolute resting theta power and relative theta power during squeezing. In these models, depression had a substantial contribution, which is in line with the previous understanding that apathy and depression are often comorbid symptoms of PD. Additional research should explore whether these oscillatory characteristics in apathy differ between apathy alone and apathy with comorbid depression.

Interestingly, apathetic people had a greater decrease in relative alpha power, but not beta power during incentivized motor execution, despite the conventional focus on beta frequency oscillations in the research on movement and motor dysfunction in PD. This may suggest that the beta band may be more specifically related to motor function, whereas the alpha and theta band activity may be associated with a combination of motor function and neuropsychiatric characteristics, such as apathy and depression.

2.4.3 **Alpha and theta oscillations at rest**

Previous studies have shown that theta and alpha oscillatory power are higher at rest in PD patients and exhibit abnormal coupling over cortical motor areas [126]. Their increase has related to disease severity as well as the presence of dementia [127]. Apathy has also been found to herald...
future cognitive decline and dementia and therefore, may be associated with abnormal increases in the alpha and theta bands. Recently-diagnosed, drug-naive patients also tend to have an overall increase in resting-state alpha power that is not strongly affected by disease progression or levodopa treatment, suggesting potential non-dopaminergic and non-motor correlates of parkinsonism [127]. Higher theta, alpha, and beta power was also an overall feature of the PD patients in our current study. To add to the literature, we were able to distinguish that the level of theta and alpha power present at rest was associated with apathy in PD.

The level of alpha power at rest may regulate cortical excitability [128]. Using EEG combined with TMS applied to the primary motor cortex, Sauseng et al. demonstrated that a motor evoked potential was elicited more easily when alpha power immediately preceding the TMS was low, whereas it was more difficult to elicit when alpha power was high. [129] Thus, EEG alpha band synchronization may be a sign of deactivated cortical areas that are in an idling state [130].

In concordance with the cortical excitability hypothesis, an increase in frontal theta and frontal and occipital alpha activity has been associated with mental fatigue and decreased levels of arousal [131], [132]. This relationship may be further linked to motivational mechanisms, as mental fatigue is suggested to be an incongruity between the amount of effort invested into a task and potential rewards [133]. The anterior cingulate cortex (ACC) evaluates rewarding stimuli and promotes behavioural changes to obtain the maximal reward with the least aversive consequences [134]. According to Sarter et al. [135] this system is capable of maintaining stable cognitive functioning even under suboptimal conditions, given that motivation is high. However, the loss of motivation may, in turn, influence mental fatigue. Mental fatigue is a very common symptom of apathy in Parkinson’s disease and those with apathy tend to become more fatigued compared to
non-apatheic individuals. In our study, more severely apathetic PD patients exhibit a significantly lower GFR compared to non-apatheic individual for the highest reward, and generally do not differentiate their grip force as well in response to varying monetary values, which may be a behavioural consequence of a combination of fatigue and lack of motivation. Concurrently, the heightened resting alpha and theta power in apathetic patients may be due to fatigue and lack of motivation in apathetic individuals.

Using simultaneous EEG recordings and MRI, Laufs et al. [136] reported a negative correlation between EEG alpha power and regional cerebral blood flow (rCBF) in parietal and frontal cortical regions associated with attentional processes. They suggested that high alpha activity is associated with low brain metabolism and may be linked to inattention. In PD subjects with apathy, metabolic alterations in these brain areas have also been reported [72]. Apathy in other neurological diseases, such as Alzheimer’s disease has been correlated with decreased regional cerebral blood flow in frontal, temporal, and parietal regions [137].

2.4.4 Relative alpha and theta changes during movement

In addition to higher levels of resting alpha and theta activity in centro-parietal motor cortical regions in apathetic PD patients, there also seems to be a direct relationship between resting alpha and theta oscillations and the magnitude of alpha and theta modulation during reward-related movement in these frequency bands. During movement, there is a characteristic desynchronization in the alpha and beta bands over the motor cortex. Heinrichs-Graham et al. [116] explored beta power differences between younger and older adults during movement and found that older individuals exhibited higher baseline beta power levels. Accompanying a higher baseline power was a greater beta desynchronization. They suggested that the motor cortex may have an absolute
threshold that must be reached in order to execute proper movements. Greater resting levels of beta in the motor cortex may require stronger suppression to reach that threshold. Furthermore, they conjectured that a greater reduction in beta power required for movement may be a sign of a less efficient motor system. In our current study, the presence of apathy in PD seems to be associated with a similar pattern presented by Heinrichs-Graham and colleagues in the theta and alpha frequency bands in addition to the beta band. Due to the increase in resting alpha, theta, and beta power in the motor cortex with apathy, these frequency bands may require greater modulation in order to reach a threshold required for movement execution.

The larger desynchronization seen in individuals with higher apathy scores, and in turn, higher baseline alpha and theta power, may be evidence of a neural compensatory effect to counteract the higher baseline power in apathetic individuals with PD. It is unclear whether this effect is associated with apathy alone or in combination with the effects of dopaminergic medications, as all PD patients were on their daily dose of medication during the study. Oswal et al. [138] found that movement associated with a suppression of local alpha power in the temporal cortex and STNr is independent of dopaminergic status. Nonetheless, it would be interesting to investigate this oscillatory behaviour further in apathetic PD patients who are both on and off their normal dopaminergic medication.

2.4.5 Relative theta increase during movement initiation

Relative theta power increases as a result of rewarding or attention-demanding processes and preceding movement onset [84], [85], [139], [140]. In our study, we observed that theta increases during motor initiation in response to rewarding stimuli and that apathetic PD subjects exhibited significantly lower relative theta power compared to both non-apathetic PD subjects and
healthy subjects. Thus, relative increases in theta power may be a potential neural marker for a blunted reward response in apathetic PD patients.

2.4.6 Relationship between behavioural results to oscillatory activity

Despite a significant effect of money value on GFR in all subjects groups in this study, our present results did not reveal significant differences in any of the frequency bands between the highest and lowest money values. This is in contrast to the findings of Zénon and colleagues, in which PD patients on medication showed an increase in power of frequencies of 10 Hz and lower in response to larger rewards and corresponded with increased effort production [141]. However, similar to our current study, they found large inter-individual discrepancies in response to varying rewards. To tackle this problem, they used cluster-based permutation analysis to distinguish significantly difference portions of spectral data subject-by-subject, which was not performed in our study.

2.5 Conclusion

This is the first study to demonstrate a blunted behavioural response to reward in severely apathetic PD patients using an incentivized motor task and to identify distinct neural oscillatory activity associated with apathy in PD. Our results show that PD subjects with lower apathy scores are able to modulate their effort production to increasing rewards, whereas PD subjects with more severe apathy, and possibly auto-activation deficits, are not able to do so. We also demonstrate that apathetic PD subjects exhibit a higher resting EEG alpha and theta power compared to non-apathetic PD subjects and healthy subjects and that there is significant correlation between absolute resting alpha power and relative alpha power during squeezing. Furthermore, the combination of absolute resting alpha power with relative alpha power during squeezing was able to predict patient
apathy scores, while controlling for age or disease severity. The same was true for absolute resting theta power and relative theta power during squeezing. In the future, absolute resting alpha and theta power and the degree of alpha and theta power reduction may serve as potential biomarkers for apathy severity in PD.
Chapter 3: Altered emotional processing in PD event-related potentials

3.1 Introduction

A subcategory of apathy in PD is emotional-affective apathy which is characterized by the inability to accurately interpret affective contexts that guide behavior and evaluate positive or negative outcomes [74]. Patients with emotional-affective apathy may experience decreased drive to participate in activities such as social situations, sexual activity and personal hygiene [87] and show a reduced response to rewarding stimuli [88], [89]. Emotional-affective apathy is typically associated with dysfunction in the orbital, medial prefrontal cortex (PFC), and limbic areas of the basal ganglia including the ventral striatum and ventral pallidum [87].

Scalp-recorded event-related potentials (ERPs) of EEG signals are well-suited to measuring rapid affective and cognitive processes associated with emotion regulation. ERPs are small voltage responses in the brain that are time-locked to specific events or stimuli and are thought to reflect the summed activity of postsynaptic potentials produced when a large number neurons fire in synchrony [90]. They can serve as potential biological markers in pathological cases of emotional dysfunction or deficits [91].

An ERP evoked by emotionally engaging stimuli is the late positive potential (LPP), which occurs in the centro-parietal region of the cortex. It has a latency that typically begins at around 300 to 400 ms after stimulus onset and is often sustained throughout the duration of stimulus presentation [93]. The LPP amplitude has been shown to vary in relation to the experienced intensity of the affective picture content [94] and exhibit abnormal patterns in mood disorders and other psychiatric conditions.
A widely-used approach to investigating affective information processing in the brain involves the employment of emotionally evocative pictures taken from the International Affective Pictures System (IAPS) [142] in combination with ERPs. In studies employing this approach, the amplitude of the LPP in healthy individuals typically increases in response to pleasant and unpleasant stimuli, relative to neutral stimuli [94]. Dietz et al. [91] investigated EEG emotional processing in non-demented patients with PD and healthy control participants while viewing pleasant, neutral, and unpleasant pictures. Highly apathetic PD patients showed reduced amplitude of the centro-parietal LPP specifically when viewing unpleasant pictures compared to low apathy PD patients and healthy controls, suggesting that apathy induces a blunted response to aversive stimuli. A more traditional method of ERP analysis was used in their study, which involves averaging multiple trials of EEG data to reduce the poor signal-to-noise ratio of EEG signals. This approach introduces a number of challenges that may confound ERP results.

The experimenter frequently pre-selects EEG electrodes or time courses of interest based on *a priori* hypotheses or after visual inspection of the ERP data. Both methods can lead to experimenter biases [143]. Additionally, although ERPs have very high temporal resolution, they have relatively poor spatial resolution. Voltage fields from one brain structure may volume conduct across the scalp and be detectable in most electrodes [144], [145], [146]. This causes EEG signals to overlap as they become weighted sums of underlying brain sources [120], making it difficult to distinguish one ERP from another [147]. Finally, there may also be inter-subject variability in the spatial distribution of ERPs due to differences in electrode placement over the scalp, head shapes, and the structure of the brain itself [148]. We attempt to validate the study by Dietz et al. [91] using a method which takes these confounds into consideration, known as multiset canonical correlation analysis (MCCA).
MCCA is based off of a multivariate statistical method called canonical correlation analysis (CCA) that was originally developed by Hotelling [149] in 1936 to identify the linear combination of two datasets that maximized the Pearson’s correlation coefficient between them. Eventually, a CCA approach for more than two data sets was developed. The method was summarized by Kettenring [150], and is now referred to as multi-set CCA, or MCCA. MCCA provides a data-driven method of finding unique ERP time courses across subjects that that are maximally correlated with one another. It has the advantage of objectively separating ERPs from one another while taking into account differences in spatial locations [151].

In this chapter, we investigate event-related potentials involved in processing emotionally evocative visual stimuli using MCCA.

3.2 Materials & Methods

3.2.1 Subjects

The same subjects from the motivation experiment were used in the present experiment. They tested on the same day with a 5-minute break in between. Study order was randomly counterbalanced to control for potential effects of fatigue. 13 apathetic PD subjects, 14 non-apathetic PD subjects, and 13 healthy control subjects without PD were recruited for the study. Subjects with PD were recruited from the UBC Movement Disorder Clinic while healthy subjects were either recruited from the community or were spouses of PD patients. Two healthy subjects were excluded from the analysis due to excessive artifacts in the EEG data. The remaining subjects included 13 apathetic PD subjects, 14 non-apathetic PD subjects, and 11 healthy subjects. All subjects were age-matched and had normal or corrected-to-normal vision. Informed written
consent was obtained and the study was approved by the University of British Columbia’s Clinical Research Ethics Board and the Vancouver Coastal Health Ethics Committee.

All subjects with PD had been prescribed a regularly monitored dosage of an antiparkinsonian medication for at least 2 months prior to study enrollment (Table 1) and had shown a satisfactory clinical response to the particular antiparkinsonian medication(s). During the experiment, subjects with PD were tested while on their usual dopaminergic medication.

Table 3.1. Subject demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Apathetic PD</th>
<th>Non-apathetic PD</th>
<th>Healthy</th>
<th>p-value$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Gender (F/M)</td>
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<td>(7/7)</td>
<td>(6/5)</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.8 ± 4.6</td>
<td>67.4 ± 4.9</td>
<td>70.7 ± 7.5</td>
<td>0.315</td>
</tr>
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<td>MoCA</td>
<td>26.4 ± 2.6</td>
<td>26.2 ± 2.0</td>
<td>26.3 ± 2.6</td>
<td>0.983</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>27.3 ± 7.8</td>
<td>26.6 ± 8.3</td>
<td>-</td>
<td>0.832</td>
</tr>
<tr>
<td>BDI</td>
<td>12.8 ± 5.4</td>
<td>5.0 ± 3.8</td>
<td>3.6 ± 4.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAS</td>
<td>16.9 ± 2.9</td>
<td>6.9 ± 3.1</td>
<td>5.8 ± 4.9</td>
<td>&lt;0.001</td>
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<td>LARS</td>
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<td>-29.1 ± 5.2</td>
<td>-31.7 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LEDD$^2$</td>
<td>890.0 ± 393.9</td>
<td>1042.6 ± 734.7</td>
<td>-</td>
<td>0.519</td>
</tr>
<tr>
<td>Antidepressant use (n, %)</td>
<td>6 (46.2)</td>
<td>6 (42.9)</td>
<td>-</td>
<td>0.870</td>
</tr>
<tr>
<td>Cholinesterase inhibitor use (n, %)</td>
<td>1 (7.7)</td>
<td>0 (0)</td>
<td>-</td>
<td>0.337</td>
</tr>
</tbody>
</table>

$^1$ MoCA, Montreal Cognitive Assessment; UPDRS III, Unified Parkinson’s Disease Rating Scale; BDI, Beck’s Depression Inventory; SAS, Starkstein Apathy Scale; LARS, Lille Apathy Rating Scale

$^2$ LEDD, levodopa equivalent daily dosage in milligrams

$^3$ Three group comparisons are done using one-way ANOVA, while two group comparisons are done using Student’s t-tests.
3.2.2 **Stimuli**

60 pictures were selected from the International Affective Picture System [142] that included pictures of different valence types: 20 pleasant pictures (erota, romantic couples, food, vacation destinations), 20 unpleasant pictures (mutilations, threatening animals, human violence), and 20 neutral pictures (household items).

3.2.3 **Experimental setup**

The pictures were displayed using a custom script written in MATLAB to participants on a 19 inch computer screen. Participants were told to focus on each picture that was presented. IAPS pictures were displayed for 6 s each, in a random order, followed by a variable inter-trial interval (ITI) of 3, 4, or 5 s. A fixation point featuring a white cross on a black screen was presented during the ITI to allow subjects to focus on the screen (Figure 3.1).

![Figure 3.1. Experimental stimuli and design.](image)
3.2.4 EEG recording

Continuous EEG recordings were done on the same 64-channel EEG cap at a sampling rate of 500 Hz using the high impedance amplifier Neuroscan SynAmps² (Compumedics Neuroscan Ltd., VA, USA). Impedances were kept below 20 kΩ using Electro-Gel (Electrode-Cap International, OH, USA). From the original 64 electrodes, recordings were taken from 38 electrodes. Recording electrodes were positioned according to the International 10-20 EEG System [117]. Two pairs of surface electromyographic electrodes were used to detect horizontal and vertical eye movements for subsequent artifact removal during analysis [161].

3.2.5 EEG preprocessing

EEG data was preprocessed offline using custom-written scripts in MATLAB, incorporating functions from the open-source MATLAB toolbox, EEGLAB [118]. Each epoch was band-pass filtered between 0.1 and 30 Hz. Using the EEGLAB plug-in clean_rawdata, channels containing continuous artifacts were removed, but not yet interpolated. EEG recorded during motor performance was segmented into 2.5 s epochs, which included 1 s of baseline before stimulus presentation and the first 1.5 s of stimulus presentation. Any trial containing data exceeding ±75 µV was removed and overall, an average of 2% of trials were removed per subject. The number of trials removed did not differ significantly between groups (one-way ANOVA; p>0.2). Data were then re-referenced to the average of all channels. Epochs were concatenated and stereotypical artifacts, such as eye blinks, eye movements and muscle tension were separately removed using an automatic artifact rejection method [152] based on Independent Component Analysis (ICA) [120]. ICA uses linear combinations of electrodes to derive temporally independent waveforms from a mixed signal. Artifacts due to eye movements and muscle activity
are statistically independent from ongoing brain rhythms in the time domain, allowing them to be identified and removed [162]. After ICA, bad channels were interpolated using spherical spline interpolation. Finally, epochs were re-segmented and ordered into their respective stimulus conditions (positive, negative, and neutral pictures). 1 s prior to stimulus presentation served as the baseline period. The mean over this period was then subtracted from each data point of the ERP epochs.

3.2.6 **Multiset canonical correlation analysis**

MCCA was used to find and combine highly correlated temporal features across all subjects in each group separately. The mean positive, negative, and neutral time courses for each subject were then concatenated across time. The final input to MCCA was a 3-dimensional matrix, $X_{k \times m \times n}$, with $k$ number of EEG channels, $m$ number of concatenated time points, and $n$ number of subjects (see Figure 3.2 for a schematic illustration). Using MCCA, we were able to find the most common patterns across subjects, summarized into 10 components. Each component consisted of

![Figure 3.2. Multiset canonical correlation analysis.](image-url)
a pair of weights, $W$, and a transformed time series, $P$. $P$ represents a unique combined temporal pattern across all subjects and can be understood as a linear combination of channel time courses, $P = X^*W$, with $W$ determining the contribution of each channel. In order for more robust interpretations, we used the canonical loadings, which are the Pearson correlations between original channels and the transformed data.

### 3.2.7 Statistical Analysis

After obtaining the ERP components of interest from the MCCA output (see results), the responses to different stimuli were quantified by measuring the mean peak amplitude of each ERP of interest. These ERPs included the LPP, for which we analyzed the amplitude from 400-700 ms and the N200, for which we analyzed amplitudes between 250-400 ms. Separate one-way repeated-measures ANOVA tests were performed for each group with stimulus valence (positive, negative, neutral) as the within-subject factor. Bonferroni-corrected post-hoc tests were conducted to determine differences between individual stimuli in each group. Due the nature of the MCCA output, we were not able to make direct comparisons of the component time courses between groups. Topographical distributions of the ERPs were determined based on the raw loadings from the MCCA output.

Because the LPP topographical distributions between the two PD groups were very similar, we averaged raw loadings across all PD subjects over centro-parietal electrodes that had the greatest LPP representation (CP1, CP2, CPz, Pz, P3, P4). We then performed a two-tailed $t$-test comparing the magnitude of the raw loadings of all PD subjects with healthy subjects (averaged across the same centro-parietal electrodes). For the N200 component, we averaged raw loadings over frontal electrodes that had the greatest N200 representation (Fz, FC1, FCz, FC2, FC5, FC6,
F3, F4) over each of the healthy, non-apathetic PD, and apathetic PD groups. We subsequently performed a one-way ANOVA to compare the magnitude of averaged frontal electrode raw loadings across groups.

3.3 Results

3.3.1 MCCA

MCCA was able to find common patterns (components) across subjects, while accounting for spatial differences in the EEG recordings. Furthermore, it allowed us to separate different types of ERPs into components, based on their spatial and temporal characteristics.

3.3.2 LPP

Based on the transformed data, MCCA was able to separate the LPP into the first component (Figure 3.3B). Its centro-parietal topographical distribution based on raw loadings from the MCCA output (Figure 3.3A) and 400-700 ms peak amplitude was characteristic of the LPP in previous literature and confirmed its identity [91], [94]. Separate one-way repeated measures ANOVA tests comparing the average LPP peak amplitudes (from 400-700 ms) showed that there were significant differences between stimulus valences for healthy ($F(2,20) =531.32, p <0.0001$), non-apathetic PD ($F(2,26) =39.78, p <0.0001$), and apathetic PD groups ($F(2,24) =29.58, p <0.0001$). For healthy controls, post-hoc Bonferroni tests revealed that all three stimulus types had responses that significantly differed from one another in LPP amplitude (all corrected $p$-values < 0.0001). Negative pictures induced the highest LPP amplitude ($M = 1.84, SD = 0.10$), followed by positive pictures ($M = 1.10, SD = 0.13$), while neutral pictures induced the lowest LPP amplitude ($M = 0.06, SD = 0.14$). On the other hand, neither apathetic nor non-apathetic PD patients showed significant differences in LPP amplitude between positive and negative pictures. However, the
LPP amplitudes in response to the positive and negative images were significantly greater than the responses to neutral pictures for both apathetic and non-apathetic PD subjects (corrected $p$-values $< 0.0001$).

After combining all PD subjects, a two-tailed $t$-test comparing the raw loadings of all PD subjects with healthy subjects (averaged across CP1, CP2, CPz, Pz, P3, P4) showed that PD subjects ($M = 0.64$, $SD = 0.21$) had a significantly greater LPP topographical representation compared to healthy controls ($M = 0.39$, $SD = 0.26$); $t(36) = 2.99$, $p = 0.005$.

![Figure 3.3. LPP topographic distributions and waveforms from Component 1 of the MCCA output. A) Topographic distributions of the raw loadings pertaining to the N200 component, averaged across subjects and stimulus types for each group. B) The late positive potential was separated from the original EEG signal into Component 1 from the MCCA output. The transformed times series were averaged across subjects for each group and stimulus type. The grey box denotes the time period that was averaged and compared across stimulus types.](image)

### 3.3.3 N200

In addition to the LPP, MCCA separated the N200 into the fourth component (Figure 3.4B). Its identity was confirmed based on its frontal spatial distribution (Figure 3.4A) and peak
amplitude between 200-350 ms after stimulus presentation, characteristic of the N200 in previous literature [153], [154]. Separate one-way repeated measures ANOVA tests showed that there were significant differences between stimulus valences for healthy ($F(2,20) = 9.25, p = 0.001$), non-apathetic PD ($F(2,26) = 12.16, p < 0.001$), and apathetic PD groups ($F(2,24) = 34.25, p < 0.0001$). For healthy controls, the N200 amplitude in response to both positive ($M = 1.83, SD = 0.34$) and negative ($M = 1.85, SD = 0.29$) stimuli was significantly greater than that of neutral stimuli ($M = 1.34, SD = 0.42$, Bonferroni corrected $p$-values $< 0.05$). The N200 amplitudes in response to positive and negative stimuli did not significantly differ from one another.

In contrast, non-apathetic PD subject showed that both positive ($M = 2.28, SD = 0.35$) and negative ($M = 2.05, SD = 0.48$) stimuli elicited significantly smaller N200 amplitudes compared to neutral stimuli ($M = 2.53, SD = 0.47$, corrected $p$-values $< 0.05$). The amplitude differences between positive and negative stimuli did not differ significantly.

Finally, for apathetic PD subjects, the N200 amplitudes in response to all three stimulus types significantly differed from one another (corrected $p$-values $< 0.05$). Negative pictures induced the largest N200 amplitude ($M = 2.37, SD = 0.65$), followed by positive pictures ($M = 2.00, SD = 0.49$), while neutral pictures induced the smallest amplitude ($M = 1.06, SD = 0.29$). However, the baseline values before stimulus presentation for apathetic PD subjects differed slightly between subjects, which may have contributed to the differences observed.

One-way ANOVA showed no significant differences between the raw loadings (averaged across Fz, FC1, FCz, FC2, FC5, FC6, F3, and F4) across the three subject groups.
3.4 Discussion

In the currently study, MCCA was able to separate unique ERP time courses from one another and allowed us to accurately compare the affective ERP responses between apathetic PD, non-apathetic PD, and healthy subjects. Because MCCA is a data-driven method of finding common features in different datasets, there was no need to pre-select EEG electrodes for analysis, which reduced experimenter bias.

MCCA results showed that PD subjects, regardless of the presence of apathy, had a blunted LPP amplitude in response to negative visual stimuli compared to healthy subjects. However, the
LPP response to positive and negative stimuli was still higher than the response to neutral stimuli. Interestingly, based on the raw loadings, we found a greater topographical representation of the LPP over the centro-parietal area in PD subjects compared to healthy subjects.

We also observed differences in the frontal N200 component, which has previously been shown to increase in amplitude in response to arousing, novel, or emotional stimuli [155], [156], [157], [158]. In the current study, apathetic PD subjects showed a similar pattern of N200 responses compared to healthy subjects, in which both the negative and positive stimuli elicited greater N200 amplitudes compared to neutral stimuli. However, we present these findings cautiously, as baseline values before stimulus presentation for apathetic individuals differed slightly between stimulus types, which may have contributed to the observed differences. Non-apathetic PD subjects, on the other hand, showed a reduced response to positive and negative pictures. Comparing just the non-apathetic PD subjects and healthy controls, the reduction in N200 amplitude in response to emotionally evocative stimuli in PD subjects may reflect dysfunctional processing of novel, more arousing stimuli.

We were particularly interested in the LPP, as it is most commonly modulated by emotionally evocative stimuli [159], [160]. Our findings regarding the LPP in PD subjects contrast with those of Dietz et al. [91], in which only highly apathetic PD patients showed a blunted response to viewing negative visual stimuli. This discrepancy may be due to the difference in methods that were used. We employed MCCA, which accounted for experimenter biases, ERP overlaps, and spatial differences in ERP distribution. We also had a slightly larger sample size of 13 apathetic subjects (≥14 on the SAS), compared to their sample size of 8 apathetic patients (≥14 on the SAS), which may have increased the statistical power of our results.
The blunted LPP response to negative visual stimuli in PD patients observed in our study is supported by a study conducted by Bowers et al. [161] exploring startle eyeblink responses in non-demented, non-depressed PD patients on dopaminergic medication. They found that, when viewing IAPS pictures, startle eyeblink responses elicited from white noise bursts during aversive picture viewing was reduced in PD patients compared to healthy controls. This reduced response was related to disease severity and lower arousal ratings of aversive pictures. The researchers suggested that this blunted startle response may involve a translational defect whereby emotional arousal is not appropriately relayed from the amygdala into a somato-motor response. They ventured that the mechanism involved dysfunctional gating of the amygdala due to loss of dopamine in PD, resulting in increased amygdala inhibition [162].

Interestingly, despite a blunted response to negative stimuli, PD subjects showed a greater topographical representation of the LPP over the centro-parietal region compared to healthy controls. These observed characteristics may be a result of compensatory responses during emotional processing in PD patients, which has previously been described by Moonen and colleagues [163]. Using blood oxygen level-dependent (BOLD) fMRI to explore emotional processing in PD, the researchers found that when passively viewing positive, negative, and neutral pictures, individual valence and arousal ratings of the pictures provided by PD subjects on dopaminergic medication did not differ from healthy subjects. Although emotional processing seemed unaffected at the behavioural level in PD subjects, fMRI results showed that PD patients had decreased bilateral activation in the putamen, but increased activation in the right dorsomedial PFC, which was most evident for highly arousing pictures. They reasoned that increased medial PFC activity may be a top-down compensatory response in PD to overcome striatal dysfunction. LPP activity has previously been correlated with increased BOLD activity in emotion-processing
areas, such as the amygdala and PFC [164]. Taken together, the greater spatial representation of the LPP may also be a compensatory effect for emotion-processing deficits associated with PD.
Chapter 4: Conclusion

4.1 Summary of findings

In Chapter 2, we demonstrated that PD patients with lower apathy scores were able to modulate their effort production to increasing rewards during an incentivized motor task, whereas patients with more severe apathy, and possibly auto-activation deficits, were not able to do so. EEG results showed that apathetic PD patients exhibited a higher resting alpha and theta power compared to non-apathetic PD subjects and healthy subjects. Furthermore, there was a significant correlation between absolute resting alpha power and relative alpha power during squeezing. These two factors were able to predict patient apathy scores, controlling for age or disease severity. The same was true for absolute resting theta power and relative theta power during squeezing.

In Chapter 3, we explored differences in ERP responses of PD patients to emotionally evocative visual stimuli. We employed a data-driven approach to separate unique ERP time courses from one another called multiset canonical correlation analysis (MCCA). Results showed that although the LPP response to positive and negative stimuli was higher than the response to neutral stimuli, PD subjects, regardless of the presence of apathy, had a blunted LPP amplitude in response to negative visual stimuli compared to healthy subjects. Interestingly, there was also a greater centro-parietal topographical representation of the LPP in PD subjects compared to healthy subjects, suggesting the presence of potential compensatory mechanisms for blunted neural reactivity to emotional stimuli in PD patients. On the other hand, there was reduction in frontal N200 amplitude in response to emotionally evocative stimuli in PD subjects, which may reflect dysfunctional processing of novel, more arousing stimuli.
4.2 Significance

Because apathy in PD is often resistant to therapy, difficult to quantify and poorly understood, further research into its exact neural mechanisms is crucial for the development of more precise and effective therapies to combat this debilitating condition.

Previous studies have compared the relationship between reward and motor effort in healthy subjects and PD subjects as a whole, but no distinction have been made between apathetic and non-apathetic PD subjects. Furthermore, no EEG study to date has investigated neural oscillatory characteristics of apathy in PD. The study in Chapter 2 is the first to characterize abnormal oscillatory behaviour of apathy in PD, providing insight into the underlying mechanisms behind this debilitating condition. Because absolute resting alpha and theta power and relative alpha and theta power during movement was able to predict apathy scores, these characteristics may also act as potential apathy biomarkers. As apathy is currently diagnosed using subjective questionnaire-based evaluation scales, determining potential neural markers of apathy in PD can be beneficial in increasing the reliability of its diagnosis.

The use of MCCA in Chapter 3 as way of finding and separating common ERPs across subjects is also a novel approach that has not previously been done. This sets the basis for future studies to use a similar ERP analysis method that reduces experimenter biases, accurately distinguishes unique ERPs from one another, and accounts for inter-subject variability in ERP topographical distributions. Furthermore, the study’s findings support previous literature suggesting that PD subjects on dopaminergic medication who have blunted neural responses to emotionally evocative stimuli, may have compensatory mechanisms to counteract these effects.
4.3 Limitations

One of our main challenges during the recruitment process was to find PD patients who were more severely apathetic. A number of the subjects in our studies had borderline apathy scores on the SAS, which were at or slightly above the cutoff of 14. Some crucial behavioural and neurophysiological differences we observed between apathetic and non-apathetic PD subjects may have been more pronounced with a larger number of subjects who had higher apathy scores.

Crucially, the subjectivity of the any qualitative apathy scale may lead to inaccuracies in categorizing patients as apathetic or non-apathetic. Some individuals who scored 14 and above on the SAS may not have necessarily been clinically apathetic. Additionally, while some apathetic patients may exhibit emotional-affective deficits, others may exhibit different deficits related to apathy, such as auto-activation or cognitive dysfunction.

Finally, higher depression scores in apathetic PD subjects was a confounding variable in our results that made it difficult to differentiate whether the effects were driven by apathy or depression. Because apathy and depression are often comorbid symptoms, the effects we observed may have been a characteristic of both conditions. We did, however, include depression as a covariate in our regression analyses in Chapter 2.

4.4 Future research directions

Based on our findings, a number of future research directions can be explored. These include:

(1) An investigation of neural oscillatory behaviour or ERPs in more severe cases of apathy in PD.
(2) A comparison of the effects of being on and off dopaminergic medication on neural oscillatory activity in apathy.

(3) Determining whether depression contributes to the abnormal neural oscillatory behaviour exhibited by apathetic PD patients, or whether the behaviour is a characteristic of apathy alone.
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