Predicting Impulsivity in Parkinson's Disease Based Upon Medication Responsiveness

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This thesis is submitted in partial fulfilment of the Honours Degree of Bachelor of Psychological Science (Honours)

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University of Adelaide

September, 2023

Word count: 6697

Table of Contents

List of Figures

List of Tables

Abstract

Parkinson's Disease (PD) is a common neurodegenerative disease characterised by dopamine loss and associated motor symptoms including bradykinesia (slowness of movement), resting tremor, rigidity, and postural instability. Dopaminergic replacement therapies aim to alleviate motor symptoms but can significantly increase the risk of developing an impulse control disorder (ICD), a behavioural disorder associated with failure to resist and control impulse desires and behaviours. However, medication dosage is not entirely predictive of the amount of dopamine that reaches the brain and is a poor predictor of ICD risk. We sought to capture a more accurate representation of dopamine medication efficacy by measuring the medication-induced change in motor symptom severity and testing whether it could predict ICD risk better than dopamine medication dosage. Evidence also suggests the severity of dyskinesias (abnormal involuntary movements) predicts ICD risk, and therefore was included in this study to compare against our alternative predictors. We tested 26 PD patients' motor performance 'on' and 'off' dopamine medication using five precise motor measures. Impulsivity and dyskinesia were captured using self-rated questionnaires, The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale and Unified Dyskinesia Rating Scale. We found that whilst the change in motor function accounted for a larger amount of variance than medication dosage or dyskinesia scores, no predictor had a statistically significant relationship with impulsivity scores. The variance explained by our predictor is promising, but replication studies with a larger sample size are warranted to investigate a true relationship. Further implications for research and clinicians are discussed.

Keywords: Parkinson's Disease, impulse control disorder, medication efficacy, objective motor measures

Declaration

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Contributor Roles Table

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CONCEPTUALIZATION	Ideas; formulation or evolution of overarching research goals and aims.	X	X	
METHODOLOGY	Development or design of methodology; creation of models.	X	X	X
PROJECT ADMINISTRATION	Management and coordination responsibility for the research activity planning and execution.		X	X
SUPERVISION	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team.		X	
RESOURCES	Provision of study materials, laboratory samples, instrumentation, computing resources, or other analysis tools.		X	X
SOFTWARE	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code.		X	X
INVESTIGATION	Conducting research - specifically performing experiments, or data/evidence collection.	X		X
VALIDATION	Verification of the overall replication/reproducibility of results/experiments.	X	X	
DATA CURATION	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later re-use.	X	X	X
FORMAL ANALYSIS	Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data.	X	X	X
VISUALIZATION	Visualization/data presentation of the results.	X		
WRITING – ORIGINAL DRAFT	Specifically writing the initial draft.	X		
WRITING – REVIEW & EDITING	Critical review, commentary or revision of original draft	X	X	

The research conducted in this thesis was funded by the James and Diana Ramsay Foundation and the Australian Research Council.

Chapter 1

Introduction

1.1 Parkinson's Disease and Dopaminergic Replacement Therapy

Parkinson's Disease (PD) is a common neurodegenerative disease characterised by its cardinal motor symptoms including bradykinesia (slowness of movement), resting tremor, rigidity, and postural instability (Kalia & Lang, 2015). Although PD is considered a motor disorder, it has a significant impact on cognition and mood; the symptoms experienced by different individuals with PD vary widely, making it difficult to manage (Fereshtehnejad & Postuma, 2017). The prevalence of this disease was reported to be approximately 8.5 million worldwide in 2019, this number is suspected to significantly increase over the coming years (Ou et al., 2021), mainly due to the ageing population (Elbaz et al., 2016). Therefore, an understanding of both motor and cognitive function in the disease could have widespread benefits for our ageing population.

PD impairments are a direct result of the death of dopaminergic neurons, resulting in significantly decreased dopamine levels in the basal ganglia (Lotharius & Brundin, 2002). Dopamine plays a key role in the basal ganglia, which is responsible for motor control, and the depleted levels of this neurotransmitter in PD lead to circuit-level changes contributing to the commonly observed motor symptoms (McGregor & Nelson, 2019). According to the classical model of basal ganglia function, a lack of dopamine in the striatum inhibits thalamic output to the motor cortex, therefore reducing motor activation and suppressing movement (McGregor & Nelson, 2019). The striatum and basal ganglia circuits are also found to communicate with key cortical and subcortical areas such as the prefrontal cortex, ventral tegmental area and amygdala via the dopaminergic mesolimbic and mesocortical pathways (Latella et al., 2019). The mesolimbic pathway is responsible for reward learning while the mesocortical pathway is involved in executive functions and decision-making (Jimenez-Urbieta et al., 2015). Therefore, depleted striatal dopamine levels also consequently lead to

diminished cognitive ability and altered reward-based learning (Latella et al., 2019). The widespread function and impact of dopamine among different circuitry demonstrates that PD is more complex than just its motor symptoms, yet cognitive function in PD is still relatively understudied. Furthermore, in addition to the effects of the disease, cognitive side effects are commonly reported related to medications used to alleviate PD motor symptoms, but it is not clear which individuals are most susceptible to these effects.

Dopaminergic replacement therapy is usually administered to improve motor function in patients by replacing dopamine in the depleted striatum (Zahoor et al., 2018). Levodopa is the most common type of PD medication (Rao et al., 2006). Whilst dopamine itself cannot cross the blood-brain barrier, the dopamine precursor levodopa can and therefore is effective in being administered as therapy (Samii et al., 2004; Zahoor et al., 2018). Dopamine agonists are another common type of dopaminergic medication and can be used either in isolation or adjunct to levodopa (Schapira, 2005). Dopamine agonists are typically used during earlier stages of PD; however, most individuals are eventually prescribed levodopa therapy (Kondo, 2002). For PD individuals who take multiple types of antiparkinsonian medications, calculating the levodopa equivalent daily dose (LEDD) from their various medications is a common method in the literature to capture an artificial but uniform measure of medication regimen across different medication types (Schade et al., 2020). Overall, dopaminergic replacement therapy has shown to be an effective treatment for the control of PD motor complications. However, while dopaminergic replacement therapies may alleviate motor symptoms, they can also influence and overstimulate the dopamine-mediated reward circuits in the striatum, therefore increasing the potential for reward-seeking behaviours, and potentially leading to the development of impulse control disorders (Kelly et al., 2020; Voon et al., 2011a).

1.2 Impulse Control Disorders

Impulse control disorders (ICDs) are an increasingly common behavioural disorder in individuals with PD and have a prevalence ranging from 3.53% to 35.9% across international PD populations (e.g., Antonini et al., 2017; Baig et al., 2019; Callesen et al., 2014; Fan et al., 2009; Weintraub et al., 2010). Individuals with ICDs and other compulsive behaviours fail to resist impulse desires and are unsuccessful in attempting to control certain behaviours (Evans et al., 2009). These impulsive behaviours significantly interfere with life functioning as they are typically performed excessively and repetitively (Evans et al., 2009). The most common ICD types are pathological gambling, hypersexuality, compulsive shopping and binge eating (Weintraub et al., 2010). Other impulse control behaviours have also been reported in individuals with PD, including punding (repetitive, non-goal-oriented behaviours) hobbyism (e.g., writing, handiwork, computer use) and compulsive PD medication overuse (Antonini et al., 2017).

Extensive literature suggests that dopaminergic replacement therapies are the main risk factor for the development of ICDs in PD. A significant body of research supports the idea that dopamine agonists at higher dosages pose the greatest risk of developing an ICD compared to other types of dopaminergic treatments (e.g., Bastiaens et al., 2013; Mamikonyan et al., 2008; El Otmani et al., 2019). For example, a longitudinal study by Corvol et al. (2018) demonstrated that the frequency of ICDs was strongly associated with increased duration and dose of dopamine agonists. Further, the authors showed that ICD behaviours progressively reduced after the discontinuation of DA.

In addition to dopamine agonists, levodopa, in high doses, has also been suggested to be associated with ICDs (Weintraub et al., 2010). Furthermore, levodopa treatment concurrent with dopamine agonists was reported to increase the risk of ICDs by ~50% (Weintraub et al., 2010). One multicentre case-control study indicated that there was no

association between dopamine agonist treatment and ICDs in comparison with a significant association between levodopa and ICDs (Voon et al., 2011b). Further, Simoni et al. (2020) showed that PD patients treated with levodopa presented with ICDs more frequently and suffered from more severe symptoms than patients who did not undergo levodopa treatment.

Nevertheless, some research suggests that there is no significant difference between dopamine agonists and levodopa in their association with ICD risk (Antonini et al., 2017; Isaias et al., 2008; Poletti et al., 2013). Other studies suggest that dopaminergic treatment is only associated with the onset of ICDs rather than the severity of symptoms (Bentivoglio et al., 2013; Marin-Lahoz et al., 2018).

Taken together, this evidence suggests that dopaminergic replacement therapy plays a role in the development of ICDs, however, the existence of a true medication dose-effect relationship is still unclear. This makes using medication dosage (e.g., LEDD) an unreliable predictor of which patients might be at risk of developing an ICD. It is important clinically to be able to predict which PD individuals are more likely to develop an ICD to prevent the onset of these complications, however, the conflicting evidence reviewed above suggests that other factors need to be considered to achieve this.

1.3 Limitations to Using Medication Dosage to Predict ICD Onset

A significant issue identified in the studies that have investigated a medication dose-effect relationship with ICDs is the fact that medication dosage is not entirely predictive of the amount of dopamine that reaches the brain (e.g., Hauser et al., 2009; van Vliet et al., 2023; Nutt et al., 1984). The effectiveness of dopaminergic drugs in alleviating motor symptoms and inducing other behavioural symptoms can vary depending on disease progression as a greater loss of dopaminergic neurons means a decreased ability for the brain to metabolise, store and release dopamine (Schapira, 2005). Further, the metabolism of levodopa in the gastrointestinal tract before travelling to the brain is susceptible to several

interfering processes, for example, altered absorption due to competing proteins using the same amino acid transporters (Poewe et al., 2010). Additionally, the combination of the short half-life of levodopa (36-96 minutes) and the multiple daily doses patients are usually administered is associated with significant fluctuations in levodopa plasma levels, which has been found to correlate directly with the development of additional motor and behavioural complications (Poewe et al., 2010). Therefore, measuring one's dosage of oral antiparkinsonian medications is not always an accurate measure of the effect it has on the brain and PD symptoms.

Considering the heterogeneity and complexity of PD (Bloem et al., 2021) and the factors contributing to gut-brain interactions (Tan et al., 2022), it is evident that prescribing an optimal dosage for PD patients is complicated, and as such, there can be a notable gap between the amount of oral levodopa intake and how much levodopa reaches the brain. It is therefore an aim of this study to further investigate the viability of this predictor, as well as alternative methods that may capture a more accurate representation of dopamine efficacy on PD symptoms as predictors of ICD risk.

1.4 Dyskinesia and PD

Long-term levodopa therapy can induce additional motor complications, including dyskinesias (abnormal involuntary movements) (Pahwa & Lyons, 2009), which affect up to 80% of PD patients (Voon et al., 2017). A significant area of research has investigated the relationship between dyskinesia and impulse control behaviours in PD individuals due to their common associations with dopaminergic replacement therapy. Studies have shown that both ICDs and dyskinesia may be associated, so perhaps the presence of dyskinesias might predict an exacerbated effect of dopaminergic medication on the brain and the resultant risk of developing ICDs. Biundo et al. (2017) found that more than half of their PD participants with dyskinesia had ICDs and related behaviours, 36% of patients had clinically significant

symptoms. Indeed, several recent studies present similar findings (Picazio et al., 2018; Simoni et al., 2020; Solla et al., 2011). Furthermore, studies have found that punding (Silveira-Moriyama et al., 2006) and the presence of multiple ICDs (Voon et al., 2011a) are associated with more severe dyskinesias. Therefore, the presence and severity of dyskinesias in PD may be a better predictor of the likelihood of developing an ICD than medication dosage.

However, some studies suggest that PD patients can be partially to completely unaware of the presence of dyskinesias (Amanzio et al., 2010; Seltzer et al., 2001; Vitale et al., 2001). Therefore, studies commonly utilising self-report as a measure of dyskinesias may not be entirely accurate. One study by Pietracupa et al. (2013) demonstrated that 23.3% of PD patients were subjectively unaware of the presence of dyskinesias. Patients were only aware of their dyskinesias after observing a video recording of themselves. Whilst a relatively small percentage, these findings still implicate a potential inaccuracy in self-report measures of dyskinesia, which limits the utility of this potential predictor of ICDs.

Whilst a key predictor identified in the literature, dyskinesias are but one motor symptom affected by dopaminergic medication. The research surrounding other motor symptoms, especially objectively measured, and their potential usefulness for predicting ICDs, is limited. It may therefore be valuable to investigate the effects of medication on other PD motor symptoms and their potential usefulness for predicting the development of ICDs.

1.5 The Current Study

This study aims to further elucidate the role of dopaminergic replacement therapy in ICD development by investigating whether the change in motor function induced by medication could better predict the presence of ICDs compared to previously identified predictors, i.e., dopamine medication dosage and the presence of dyskinesias. As previously noted, there are significant limitations to using dopamine dosage or dyskinesias as accurate

predictors of the development of ICDs. We, therefore, propose that measuring the medication-induced change in motor symptom severity might more accurately reflect the effect of the medication on the brain and may prove to be a more accurate predictor of ICDs. This will be achieved by measuring the cardinal motor symptoms of individuals with PD both on and off medication, and therefore, the difference between the two measurements will provide a proxy for medication efficacy. This measurement avoids the issues associated with dopaminergic metabolism in the gut, as the medication-induced change represents the effectiveness of dopamine in the brain. Thus, we hypothesise that the medication-induced change in motor symptom severity (the difference between on- and off- medication states, which reflects the extent to which the medication has an effect) will correlate with the frequency of impulse control behaviours.

As well as using these predictors to compare against our proposed measure, we aim to add to the research surrounding the relationship between LEDD and ICDs, and the severity of dyskinesias and ICDs. Considering the inconsistent evidence from the literature, we aim to investigate the role of LEDD (i.e., as an overall measure of the strength of the dopaminergic replacement therapies) in predicting the frequency of impulse control behaviours to further research in this area. Further, we predict that an increase in the severity of dyskinesias (often induced by high doses of levodopa) will directly correlate with an increase in the frequency of impulse control behaviours.

Chapter 2

Method

2.1 Participants

Twenty-six PD patients (*16 male, 10 female; mean age = 72 years, range = 49-88 years; mean levodopa equivalent daily dose = 682.67mg, range = 300-1620mg*) were recruited from Facebook advertisements, magazine articles, Parkinson's SA newsletters, conferences, support group meetings and word-of-mouth.

Inclusion criteria for participants were a prior diagnosis of Parkinson's Disease, permission from a doctor to withhold PD-related medication for 'off' medication testing, fluent in English and no prior diagnosis of a learning disability. Informed consent was given in the pre-testing questionnaires and before in-person testing. Ethical approval was granted by the University of Adelaide Human Research Ethics Committee.

2.2 Procedure

The current study was part of a larger study, using specifically selected components from that study.

Participants who expressed interest in participating were sent information documents pertaining to the study and participation details. Participants then completed a 30-minute online questionnaire before in-person testing. The questionnaire collected information including demographics, lifestyle behaviours, disease history, mood, and personality. The questionnaire also included the Unified Dyskinesia Rating Scale (UDysRS) and the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS). Upon completion, participants scheduled two testing appointments, one 'on' medication and one 'off' medication on separate days; both appointments were scheduled in the morning and the order of these appointments was randomised for each participant. For the 'off' medication session, participants were asked to withhold dopamine agonist medication for 24 hours and levodopa for 12 hours before testing. Participants were given the option to

complete participation in the testing lab at the University of Adelaide or home with two visiting researchers. On testing days, participants were screened for COVID-19, informed of the test proceedings, asked to fill out a consent form, and informed of their right to withdraw from the study at any time. Participants then completed a series of motor tasks (i.e., tapping task, two-choice reaction task, balance task, tremor task and walking task). All motor tasks were completed both in the 'on' and 'off' sessions. After completion of each testing session, participants were compensated with a $20 gift card.

2.3 Measures

2.3.1 Motor Measures

The motor tests assessed six functions or symptoms: dyskinesia (involuntary, jerky, movements), motor speed as captured by a tapping test (which should reflect bradykinesia, or slowness of movement) and motor processing speed, balance, tremor, and gait. The tapping test and motor processing speed scores were averaged together to represent motor speed. Dyskinesia was assessed only once via self-report, whereas the other functions were assessed via automated tests administered both 'on' and 'off' medication. The difference in scores was calculated by subtracting 'off' medication scores from 'on' medication scores for all motor measures. The difference in scores for each motor measure was then averaged and combined to represent overall motor function change due to medication.

2.3.1.1 Unified Dyskinesia Rating Scale (UDysRS)

Dyskinesia was assessed using the UDysRS (Goetz et al., 2008) to evaluate involuntary movements associated with PD. We used the first two parts of the scale assessing the following aspects via self-report: on-dyskinesia (involuntary movements associated with medication) and off-dystonia (involuntary movements associated with no medication or medication no longer having an effect). The first questionnaire pertaining to on-dyskinesia contained 11 questions enquiring about multiple aspects of the participant's experiences with

dyskinesia over the past week (see Appendix E). The second questionnaire pertaining to off-dystonia contained four questions enquiring about multiple aspects of the participant's experiences with dystonia (see Appendix E). For most questions, participants rated their experience on a five-point Likert scale ranging from 0 (normal) to 4 (severe), with the exception of questions 1 and 12 (see Appendix E). The authors of the scale recognised both choreic dyskinesia and dystonia to be important elements of 'dyskinesia' as they are both classified as 'involuntary movements' (Goetz et al., 2008). Therefore, the total score across all items from Parts I and II indicated the level of severity of the dyskinesia.

The UDysRS has been used in previous studies assessing the prevalence of ICDs in PD individuals with varying degrees of dyskinesia (Biundo et al., 2017). The scale is recognised in the literature to possess strong psychometric properties; high inter- (kappa 0.89) and intra-reliability (kappa 0.90) for total score, and high internal consistency for its self-report sections – the first two parts that we used (Cronbach's alpha = 0.92) (Colosimo et al., 2010).

2.3.1.2 Bradykinesia

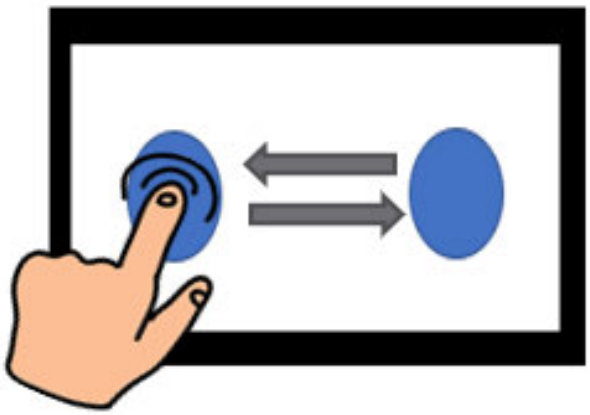
Bradykinesia was assessed using a tapping test on an iPad. The test records the speed at which an individual can move their hand to tap two dots displayed horizontally back and forth for 30 seconds. The first 5 seconds of the recording are omitted due to the tendency for participants to exhibit a delayed start after commencing the task. Bradykinesia is quantified as the number of taps completed in the remaining 25-second recording period, with a higher number of taps indicating less bradykinesia. Both hands are tested, beginning with the participant's dominant hand. The number of taps for both hands was averaged together to allow for a single measure of bradykinesia.

Kinesia scores from tablet-based tapping tests have shown to have good reliability (ICC = 0.836, $p < 0.001$) (Hasan et al., 2019). Furthermore, tablet-based tapping tests have

shown to possess a fair to excellent ability to discriminate PD participants from healthy participants (AUC = 0.77-0.94) (Schallert et al., 2022).

Figure 1

Tapping Test Sequence



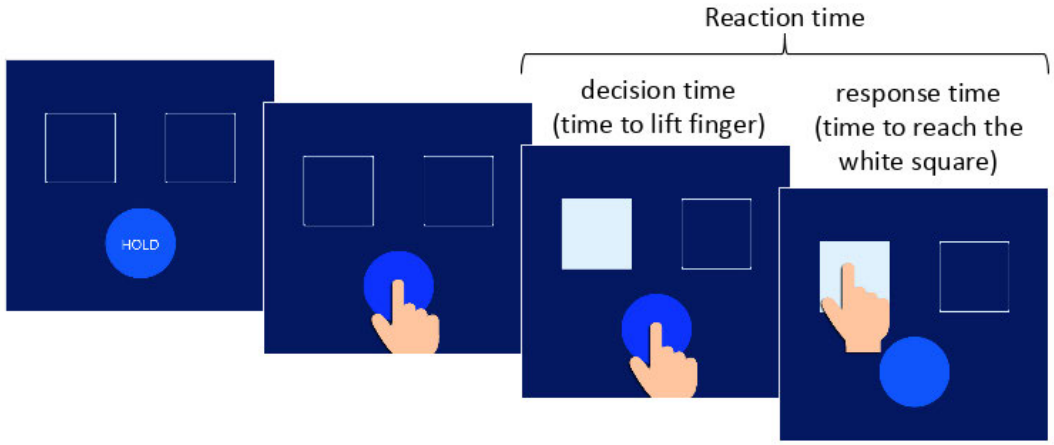
Note. The participant is required to tap one dot after the other repeatedly.

2.3.1.3 Motor Processing Speed

Motor processing speed was assessed using a two-choice reaction time task on an iPad. Participants were asked to hold a single finger on a circle button and when one of the two above blue squares turned white, they had to move their finger to tap that square as fast as possible. They then returned their finger to the circle button and waited for either of the squares to turn white again. Participants completed 40 trials of this task, the interval time between the response and the next stimulus varied from two to six seconds. Reaction time encapsulates two different aspects, decision time (time to lift finger) and response time (time to reach the square). Reaction time is therefore the time of these two aspects in total, of which a faster total time indicates better motor processing speed and subsequent coordinated peripheral movement response. The scores from this measure were reversed to reflect an improvement in motor speed.

Figure 2

Two-choice Reaction Time Task Sequence Example



Note. Participant holds the circle button with their index finger and reacts to the square that turns white by moving their finger to touch the white square.

2.3.1.4 Balance

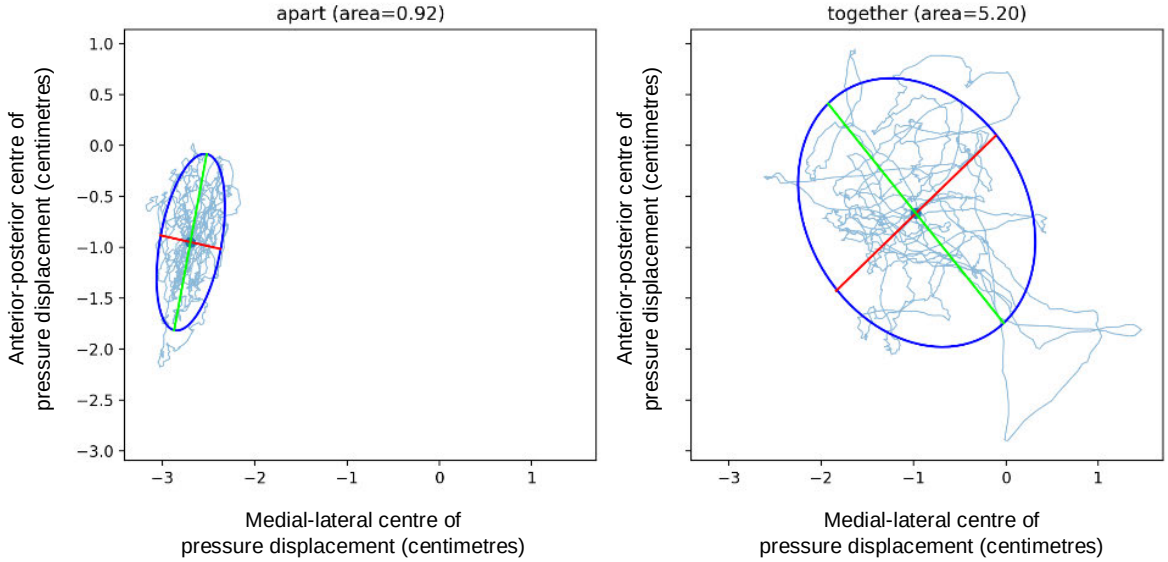
A Nintendo® Wii Balance Board and custom recording software (Wowii) were used for assessing balance. Participants were asked to stand on the board for 30 seconds while staring at a red dot placed on a wall two metres away at a height of 1.75 metres. Participants completed this task twice, once with feet together and once with feet apart; this order was randomised for all individuals.

The Wowii program connected to the balance board's four pressure sensors measures the individual's movements to determine their centre of pressure. Based on the movements made by the participant, a sway area was computed. This sway area captured the space traversed by the path length of the centre of pressure during the 30-second interval. A 95% confidence ellipse was later calculated around the data points to capture 95% of the participant's pressure path length (Duarte & Zatsiorsky, 2002; Tahayori et al., 2012). Postural stability was represented by the size of the ellipse; such that shorter path lengths and smaller

ellipse sizes represent better balance (see Figure 3). The path length and ellipse scores were averaged together to represent balance; scores were also reversed so that higher scores would reflect better balance. The Wii Balance Board has been shown to be a valid and reliable method of measuring balance, showcasing excellent concurrent validity with a force plate (ICC = 0.77-0.89) and test-retest reliability for multiple standing positions for healthy participants (Clark et al., 2010). This measure has also been shown to have excellent concurrent validity with a force platform (ICC = 0.92-0.98) for PD participants (Holmes et al., 2013).

Figure 3

Balance Measures Examples for One Participant



Note. The path length is shown in light blue and the 95% confidence ellipse around the path is shown in dark blue. Examples are shown for the feet apart condition, where balance is easier to maintain (left panel) and feet together condition, where balance is more difficult to maintain (right panel). Note that path length and ellipse are larger when balance is more difficult to maintain.

2.3.1.5 Tremor

Tremor was measured using a Nintendo® Wii Controller and the Wowii software. Participants were asked to sit still in an armchair and lay their arm across the arm of the chair and their wrist over the edge, whilst holding the controller limply for 60 seconds. During this period, Wowii recorded accelerometer data reflecting the remote's movement in 3D space. This test was completed twice, once for each hand, the order randomly determined. Results for both hands were averaged together to allow for a single measure of tremor. As PD tremor correlates highly with theta band change (Asch et al., 2020), tremor was quantified as the proportion of total power in the theta band, with 3-7 Hz being the representative frequency for PD. Therefore, a higher theta power proportion indicated a more severe resting tremor.

Resting tremors as measured by the Wii controller have been shown to be consistent with the Hoehn and Yahr clinical-rating scale of PD symptoms (internal reliability = 0.89) (Koçer & Oktay, 2016). Further, one study has reported that the Wii controller measurements can discriminate between PD participants and a control group (Synnott et al., 2012).

2.3.1.6 Gait

Gait was measured using the G-Walk (BTS Bioengineering, Milan, Italy), a wearable inertial sensor that captures several spatiotemporal parameters of gait, including speed, cadence, and stride length relative to height (Vítečková et al., 2020). Participants successively completed two trials of a 16-metre total walk whilst wearing the G-Sensor, which was attached to them at the lumbar region of the lower back using a Velcro-attached belt. The walking course was created by placing markers eight metres apart in a straight line on a strip of ground. For each trial, the participant was asked to stand at the beginning of the course, and when instructed to, they walked the length of the course, made a 180-degree turn around the further mark and walked back to the spot where they began. The stride length relative to height, speed and cadence scores were averaged together to represent gait quality. The G-

Walk is a portable and more affordable alternative to the GAITRite (CIR Systems Inc., Franklin, NJ, USA), a state-of-the-art system that allows measurement of gait, and yet the two systems have shown a high level of agreement across the measured gait parameters (ICC > 0.81) (Vítečková et al., 2020). Further, the G-Walk has demonstrated excellent reliability (rho > 0.75) across the cadence, speed and stride length gait parameters for PD participants (Vítečková et al., 2020).

2.3.2 Impulsivity measures

2.3.2.1 The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale

The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS) (Weintraub et al., 2009) is a 28-item self-report scale used to detect ICDs and their severity in individuals with PD. Each item pertains to the frequency of impulsivity symptoms and is rated on a five-point Likert scale ranging from 0 (never) to 4 (very often). Each question addresses seven ICD types, for example, pathological gambling and hypersexuality (see Appendix D). Customised follow-up questions were included enquiring about the participant's general medication use, and if they believed their ICDs changed because of taking their PD medication (see Appendix D), note, however that the answers to these additional questions were not analysed here. The level of overall impulsivity was captured by the total score of all items, with higher scores representing a higher level of impulsivity.

The QUIP-RS has been found to be a consistent tool used in the literature to analyse the severity of impulse control behaviours in PD (e.g., Biundo et al., 2017; Morgante et al., 2016). Furthermore, a study by Evans et al. (2019) critically analysed over 50 impulsivity scales and their appropriateness for PD populations and found the QUIP-RS to be the most appropriate scale to capture multiple aspects of impulsivity. The authors reported the

reliability of patient-rating and test-retest reliability for all disorders to be >0.60 and the scale has been validated against other similar neuropsychiatric measures (Martinez-Martin & Catalan, 2018).

Chapter 3

Results

3.1 Principal Components Analysis (PCA): Motor Function

We first computed difference scores for each motor measure that reflect the change induced by medication, i.e., the difference between each motor measure collected in the 'on' medication and 'off' medication sessions. Although each motor measure assesses a different motor function, we expected that medication might similarly influence at least some of the motor assessments. We therefore attempted to obtain a composite score from these measures via PCA (Jolliffe, 2002). Table 1 summarises the results of this analysis, with the first unrotated component having an eigenvalue of 1.54 and accounting for 39% of the variance in the four measures' difference scores.

The first unrotated component was associated with better motor speed, balance and reduced motor tremor. However, the gait loading was very close to zero, therefore the first component did not reflect the change in gait. For this reason, we decided to analyse gait changes separately and re-ran the PCA on only the first three motor changes. Table 2 summarises the PCA solution without gait, with the first unrotated component having an eigenvalue of 1.54 and accounting for 51% of the variance with the remaining three measures. The loadings of the three measures suggest that this component captured an improvement in motor function on medication (note that the loadings are almost identical to those in Table 1 since gait did not seem to contribute to the first component).

Table 1

Principal Components Analysis for Motor Functioning

Motor Measure	Loading
Motor Speed	0.82
Balance	0.73
Tremor	-0.58
Gait	-0.02

Note. Positive scores for Motor Speed and Balance and negative scores for Tremor indicate better motor functioning.

Table 2

Principal Components Analysis for Motor Functioning Without Gait

Motor Measure	Loading
Motor Speed	0.82
Balance	0.73
Tremor	-0.58

Note. Positive scores for Motor Speed and Balance and negative scores for Tremor indicate better motor functioning.

3.2 Regression Analyses

3.2.1 Motor Function

Regression analyses were performed to predict whether LEDD, medication-induced motor changes and dyskinesia increase the risk for an ICD. In all models, the QUIP-RS scores were used as the outcome variable.

We elected to run multiple regression models and incrementally investigate the increase in variance explained by the addition of each of our predictor variables. We started with simpler models that included easier-to-measure predictor variables (e.g., LEDD) and then tested whether the harder-to-measure predictor variables (e.g., motor function) increased the model's explained variance in impulsivity scores. Further, comparing the models would indicate whether the harder-to-measure predictors increase the variance explained and are worth implementing into clinical testing.

To control for the potential confounding effects of age and gender, a regression model was performed first with impulsivity scores as our outcome variable and age and gender as predictors. Subsequent models added our predictors of interest and we tested whether the addition of these variables significantly increased the variance explained by the model. That is, in the intermediate model we added LEDD, and in the complex models we further added motor performance and dyskinesia to the list of predictors. Neither the simple nor the intermediate model (see Table 3) were significant, simple model: $R^2 = 0.011$, $F(2, 22) = 0.121$, $p = .887$; intermediate model: $R^2 = 0.012$, $F(3, 21) = 0.083$, $p = .969$. These results address our aim of investigating the role of LEDD in predicting impulsivity scores suggesting the lack of a relationship.

In a more complex model, we added the scores for the first unrotated component reflecting an improvement in motor speed, balance and tremor (referred to as 'motor function') and the gait difference scores (see Table 3). Whilst the complex model was not

significant, note that the proportion of explained variance was much higher compared to the intermediate model, $R^2 = 0.250$, $F(5, 18) = 1.19$, $p = .353$.

We further ran an ANOVA to compare the intermediate and complex models. Although the complex model explained approximately 24% more variance in the impulsivity scores compared to the intermediate model, this increase in explained variance was not significant ($F(2, 18) = 2.20$, $p = .140$). Based on these results, we reject our hypothesis that there will be an association between the medication-induced change in motor symptom severity and impulsivity scores.

Table 3

Multiple Linear Regression Models Predicting Impulsivity Scores – Motor Function

	R^2	*B*	*SE B*	*p*
Simple Model	0.011			
Age		-0.141	0.337	0.680
Gender		-1.69	5.71	0.770
Intermediate Model	0.012			
Age		-0.153	0.357	0.672
Gender		-1.99	6.27	0.754
LEDD		0.001	0.009	0.896
Complex Model	0.250			
Age		-0.031	0.370	0.934
Gender		-1.80	5.97	0.766
LEDD		0.002	0.009	0.812
Motor Function		4.79	2.69	0.092
Gait		5.16	4.48	0.156

Note. R^2 = explained variance. *B* = regression coefficient. *SE B* = standard error of regression coefficient.

3.2.2 Severity of Dyskinesias

Regression analyses were run separately from motor function due to the small number of participants who filled out the dyskinesia questionnaire (N = 18). We repeated the intermediate model with this subset of participants who had complete dyskinesia data so that

we could compare it to the two complex models that included the dyskinesia predictors (see Table 4).

We first regressed age and gender alongside LEDD but omitted any participant's data who did not have complete dyskinesia data. The intermediate model was not significant, R^2 = 0.025, $F(3, 15) = 0.129$, $p = .941$. The addition of the total UDysRS scores whilst increased the proportion of explained variance, was also not significant, $R^2 = 0.136$, $F(4, 14) = 0.549$, $p = .703$. We also regressed age, gender and LEDD alongside the separate subscales of the UDysRS, the on-dyskinesia scores and off-dystonia scores, to determine if there was a change in variance explained compared with the total scores. This complex model 2 was also not significant and did not change significantly from the results of complex model 1, R^2 = 0.151, $F(5, 13) = 0.462$, $p = .798$. Based on these results, we reject our hypothesis that an increase in the severity of dyskinesias will correlate with an increase in impulsivity scores.

Table 4

Multiple Linear Regression Models Predicting Impulsivity Scores – Severity of Dyskinesias

	R^2	*B*	*SE B*	*p*
Intermediate Model	0.025			
Age		-0.355	0.631	0.582
Gender		-0.484	8.81	0.957
LEDD		0.004	0.012	0.730
Complex Model 1	0.136			
Age		-0.259	0.670	0.683
Gender		-5.85	9.48	0.547
LEDD		0.009	0.012	0.479
UDysRS Total		0.845	0.632	0.202
Complex Model 2	0.151			
Age		-0.269	0.638	0.680
Gender		-9.31	12.1	0.455
LEDD		0.009	0.012	0.459
On-Dyskinesia Scores		1.64	1.77	0.371
Off-Dystonia Scores		-0.475	2.80	0.868

Note. R^2 = explained variance. *B* = regression coefficient. *SE B* = standard error of regression coefficient.

Chapter 4

Discussion

4.1 Current Study Findings

In the present study, we aimed to investigate the role of dopaminergic replacement therapy in ICD development by investigating whether the change in motor function induced by medication could predict the likelihood of developing ICDs. The role of LEDD and dyskinesia severity as comparable predictors was also considered.

4.1.1 Effect of LEDD on Impulsivity

As presented in the results, we commenced our regression models by analysing LEDD alongside age and gender. LEDD did not show a significant relationship with impulsivity scores; evidently, it explained very little variance. These results addressed our aim to investigate the role of LEDD in predicting ICD behaviours. Our findings are not entirely surprising given the inconsistency in the literature regarding the role of total medication dosage in the development of ICDs (e.g., Mamikonyan et al., 2008; Weintraub et al., 2006). However, the very little variance explained by LEDD can be partially attributed to our small sample size and therefore should be further investigated in future research with a larger sample size to determine if there is a true relationship. There is also a possibility that no consistent relationship will be found given the arguments introduced earlier (i.e., differences in levodopa metabolism in the gut, etc., would influence the medication's efficacy in the brain, so dosage may not be a strong enough predictor given the influencing factors).

4.1.2 Effect of Medication-Induced Motor Function on Impulsivity

Interestingly, the medication-induced change in gait did not fit within the motor function factor and therefore was analysed as a separate predictor. We propose that this can perhaps be attributed to our underpowered study, but no other evident explanation could be proposed. However, the regression model including both motor function and gait together as separate predictors presented the highest degree of variance explained.

Our results revealed that the medication-induced change in motor function and gait explained a quarter of the variance in impulsivity scores. However, the model itself was not significant, and so was the ANOVA comparing it to a simpler model, showing that our motor predictors were not statistically significant. Despite the non-significance of the models and analyses, the high proportion of variance explained by the motor predictors is note-worthy. The unavoidable issues in this study (i.e., small sample size), meant that we were unable to determine a true relationship in our research. The medication-induced change in motor function as a predictor for the likelihood of developing an ICD is still a promising relationship to research, however, more data is needed to investigate this relationship. Again, considering our earlier arguments, it appears that ICD risk may be better captured by medication efficacy rather than just medication dosage.

4.1.3 Effect of Dyskinesia Severity on Impulsivity

Dyskinesia severity did not have a significant relationship with participant ICD scores. This was demonstrated by considering both UDysRS total scores, and the separation of on-dyskinesia and off-dystonia scores, which together also explained a relatively low proportion of the variance. Considering the literature surrounding this relationship, these results are surprising and contrary to our hypothesis. However, a low sample of participants reported having dyskinesia, therefore our study was significantly underpowered and can explain why our results were not aligned with previous research findings (e.g., Biundo et al., 2017; Voon et al., 2011b).

4.2 Practical Implications

Whilst this study could not infer dopaminergic replacement therapy's role in the risk of developing an ICD, the high variance explained means that investigating the changes in motor function as a proxy for medication effect rather than the dosage itself can be considered further. Given this, clinicians should question the viability of medication dosages

as a sole, reliable predictor of impulsivity and potentially consider employing techniques to assess the medication-induced change in motor function as well. However, clinicians should be aware that more research should be conducted before implementing any changes. Understanding a clearer relationship between medication effect and the likelihood of developing an ICD will allow clinicians to consider early interventions and potentially prevent the negative side effects of dopaminergic replacement therapies. Further, health professionals could consider implementing precise motor measures in clinics in conjunction with or in place of subjective measures, such as the Unified Parkinson's Disease Rating Scale, and specifically, its motor subscale (UPDRS-III). Such measurements might better identify patients at risk of developing ICDs and allow for medication dosage adjustments.

4.3 Strengths and Limitations

We chose to employ objective measures to assess motor function contrary to past literature (e.g., Antonini et al., 2017; Mamikonyan et al., 2008; Voon et al., 2011b), which frequently used the UPDRS-III, a PD clinical diagnostic tool (Goetz et al., 2008). The UPDRS-III is often used in research as a quick and easy-to-use tool for measuring motor function, however, it cannot discern between subtle individual differences in motor performance. This imprecision can be attributed to the subjective nature of the tool as clinicians use a four-point Likert scale to evaluate motor performance via visual inspection. Past literature has found that where precise motor measures identify significant tremor, gait and balance differences on and off levodopa, such changes were not detected with the UPDRS-III (Nova et al., 2004; Schaafsma et al., 2003). Further, recent literature suggests that the measurement of motor signs through the UPDRS-III in the early stages of PD may not be optimal as the scale items identify only more advanced PD features and lacks precision (Regnault et al., 2019). This further suggests the inaccuracy of the scale to discriminate between subtle differences of severity in motor signs. The objective measures employed in

this study can measure individual differences in motor severity and therefore provide a more accurate representation of such.

The short period available to complete this study meant that we were constrained to a cross-sectional study design and limited recruitment time, hence a small sample size. This meant that a longitudinal investigation was not able to be conducted. Further, we did not capture previously resolved impulse control disorders, nor were we able to track the development of impulsivity over time. Given that the levels of impulsive behaviour as well as the effects of levodopa evolve over time, a longitudinal design may be useful in future. Patients often increase their levodopa dosage over time to maintain mobility (Marsden & Parkes, 1977), so the effect of medication should be tracked longitudinally. Additionally, as stated previously, this study was significantly underpowered as a result of the small sample size. Therefore, any implications from the results are to be taken with caution, and replication studies should provide a larger sample size.

The performance from the two motor speed tasks reflected rigidity, a cardinal motor symptom of PD; however, these tasks are not a direct measure of rigidity. Rigidity can be measured accurately using electromyography (EMG) to record muscle contractions directly (Ferreira-Sánchez et al., 2020). However, due to the short period of this study and the invasive nature of this technique, an EMG was unable to be conducted but should be considered in future research as a recommended method. This would allow the measurement of all cardinal motor symptoms of PD and complete our battery of tests.

4.4 Future Directions

Further understanding of the relationship between dopaminergic replacement therapy and impulsivity in PD patients was established in this study, whilst also considering the role of dyskinesia. Future research into this relationship should investigate the role of different types of dopaminergic medications (levodopa versus dopamine agonists), as it is evident in

the literature that they can differ in their effect (e.g., Bastiaens et al., 2013; Voon et al., 2017). Moreover, PD patients often take different dopaminergic replacement therapies together, therefore it is difficult to determine which medication is eliciting a greater effect (Zahoor et al., 2018). Given this, it would prove valuable for researchers to complete 'on' and 'off' testing with PD patients who solely take a certain type of dopaminergic treatment and compare this with patients with differing treatments.

One variable we did not explicitly consider was the effect of psychiatric medications on our predictor and outcome variables. Comorbidity with different psychiatric conditions (e.g., mood and anxiety disorders) is frequently seen in PD patients and therefore many individuals may take additional medications to mediate these symptoms (Kulisevsky et al., 2008; Nuti et al., 2004). Psychiatric medications have been shown to influence motor symptoms, for example, patients can be simultaneously influenced by dopaminergic medication, which can induce psychosis, and antipsychotic medication, which worsens parkinsonism (Weintraub & Stern, 2005). Further, psychiatric co-morbidity can occur with ICDs. However, the evidence surrounding the effect of psychiatric medications on ICD symptoms is controversial and speculative (Samuel et al., 2015). We recommend that further research focusing on the relationship between dopaminergic replacement therapies and impulsivity should test both PD patients who take different types of psychiatric medication and those who do not and compare the results of these different groups to determine if these medications affect motor severity.

Observations made of our participants' questionnaire answers on the UDysRS showed that often participants rated on-dyskinesia or off-dystonia highly on one but not the other, suggesting that they were different factors. Indeed, our results revealed that whilst on-dyskinesia and off-dystonia were positively correlated, some participants reported experiencing significant dystonia without dyskinesia (see Appendix G). We therefore tested

whether dyskinesia and dystonia were differentially associated with the impulsivity scores in complex model 2 (Table 4), though this analysis might have been underpowered. The very few studies that used the UDysRS and discussed the role of dyskinesia in impulsivity include dystonia as part of dyskinesia, rather than as a separate entity (Biundo et al., 2017). However, it is evident that whilst related, dystonia is a different form of involuntary movement compared to dyskinesia and, in future research, should be investigated separately rather than combining the two subscales.

4.5 Conclusion

The current thesis presents new research on the role of dopaminergic replacement therapy in the risk of developing an ICD, focused on considering whether the medication-induced change in motor function as a proxy for medication efficacy could predict impulsivity scores. Our study enhanced this area of literature by utilising thorough and accurate measures to investigate the relationship between impulsivity and our predictor variables, medication-induced change in motor function, LEDD and dyskinesia severity. Results showed our introduced predictor to explain the greatest degree of variance in impulsivity scores, compared to LEDD and dyskinesia severity, but no predictor variable was statistically significant. These findings warrant further research from higher-powered studies to determine a true relationship between dopaminergic replacement therapy and the development of ICDs. This study also implicates the need for new methods of investigating the relationship between medication and impulsivity, as the majority of this research has used only self-rated measures. Employing objective techniques assessing the medication-induced change in motor function could be implemented by clinicians during patient evaluation if they can predict negative behavioural effects such as impulsivity, which could be prevented or ameliorated.

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Appendix A

Participant Information Sheet

WESTERN SYDNEY UNIVERSITY Flinders UNIVERSITY THE UNIVERSITY of ADELAIDE

Cognitive function in patients with different subtypes of Parkinson's disease

Participant Information Sheet

Investigators	Dr [redacted] A/Prof [redacted], Prof [redacted], A/Prof [redacted], Dr [redacted] A/Prof [redacted]
Human Research Ethics Committee Approval Number	H-2020-017
Location	The University of Adelaide, North Terrace Campus

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have Parkinson's disease. You will be asked to donate a sample of saliva which will be used for genetic research.

Please read the information contained in this document carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
- Understand what you have read
- Consent to take part in the research project

- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

This project will examine how general cognitive function (reasoning ability, working memory, processing speed, etc.) differs in two different subtypes of Parkinson's disease: tremor-dominant and akinetic-rigid. It has been shown that the two Parkinson's disease subtypes are associated with different cognitive outcomes, yet the reasons for this are unclear. This project will try to understand patterns of cognitive performance that may help to predict the development of cognitive problems in people with Parkinson's disease. In addition, we will investigate whether genetic information, in particular variation that is related to brain function, could be used to predict particular patterns of cognitive performance. This understanding may lead to more targeted and effective treatment recommendations for cognitive dysfunction in Parkinson's disease.

3 What does participation in this research involve?

For this study, we are seeking participants who:

1. have a prior diagnosis of Parkinson's disease
2. are a fluent English speaker
3. have no prior diagnosed learning disability.

There will be **two testing sessions**, and each will take approximately 2.5-3 hours in total, with breaks given as required. Refreshments will be available during needed breaks. We encourage you to attend the sessions accompanied by a member of your family, or a friend.

Before one of the testing sessions, you will be asked to **stop taking dopamine agonist medication 24 hours prior to testing** (for example, Pramipexole (Mirapex), Ropinirole (ReQuip), Rotigotine (Neupro), Apomorphine (Apokyn), Bromocriptine (Parlodel), etc.), **and levodopa 12 hours prior to testing** (for example, Duodopa, Kinson, Madopar, Sinemet, Stalevo). To minimise any potential risks associated with this procedure, we will require your treating health professional (e.g. GP or neurologist) to provide written consent that it is safe for you to withdraw your medication for this period of time using the form attached at the end of this information sheet. If you are eligible for this study, **we recommend that you bring your medication so that it can be taken following this testing session**.

Prior to the other testing session, there is no need to stop taking your normal Parkinson's medication. Please take all of your medications, as per normal, and as directed by your health professional.

You will be informed of the order of the two testing sessions at the time of booking your appointments, that is, whether you will be asked to withhold your medication before the first or the second testing session.

Please note however, that **if you cannot obtain medical consent to withdraw your medication or prefer not to withdraw your medication for one of the testing sessions, you can nevertheless participate in our study**. In this case, we will only book the testing session that requires you to take your medication as usual. Furthermore, **if you do not take any medication for Parkinson's disease, you can also participate in our study** by completing only one testing session.

Each testing session will take approximately 2.5-3 hours to complete. If you book two sessions, they will be scheduled on different days, and there are no follow up requirements. The testing sessions will take place at the University of Adelaide, North Terrace Campus, but if traveling to and from campus is difficult, we also provide the option of sending a research assistant to complete the in-person tests in your home. You will also be asked to complete a series of surveys using an online link that will be sent to you via email or text message. If you are having difficulty accessing or completing the surveys online, please let us know and we will organise for you to complete them in person during one of the testing sessions.

To thank you for your participation in the study, you will receive a $20 Coles/Myer gift card at the end of each testing session.

Questions and tests will include:

1. Questions regarding demographic and health information (age, gender, disease history, education, work and leisure activities)
2. Questions regarding current medications
3. Questions regarding vascular risk factors (high blood pressure, tobacco use, weight, history of diabetes, physical inactivity, poor diet, history of high cholesterol/lipids, food preferences)
4. The Unified Parkinson's Disease Rating Scale
5. Short tests that assess motor function (for example, tremor and muscle rigidity).

6. The Montreal Cognitive Assessment
7. Short questionnaires that assess history of adverse life events, mood and personality (depression, anxiety, stress, impulsivity, schizotypal personality)
8. A series of tests that assess your reasoning ability, processing speed, working memory, executive function, and general vocabulary.
9. Tests that assess your ability to learn to select correct actions and inhibit incorrect actions.

In order to investigate whether there is a relationship between target genotypes and cognitive performance, we will ask you to provide a saliva sample from which your DNA will be analysed. The genetic code of our DNA varies between people, with these changes called a variant, or a mutation. This variation exists for a number of reasons, and can contribute to the many things that make us different from one another. In addition to physical factors such as hair, and eye colour, they can contribute to behaviour and how we learn and make decisions. We know that different DNA variants affect learning, and we would like to compare your DNA with that of other participants, to identify potential genetic pathways that are related to differences in learning. The genetic variation we will investigate is likely to have small effects on cognitive performance. This could, nevertheless, be useful for more accurate diagnosis and treatment choice in the future, along with other pieces of information, such as motor, cognitive and mood assessments.

We wish to store your DNA and collected data in a biobank, a database that contains your de-identified information (preserving your anonymity) so that other researchers could use this data to answer other research questions. Please see the attached Biobank Information Sheet and Consent Form.

4 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form, as well as the Biobank Information Sheet and Consent Form, to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you, your relationship with The University of Adelaide, or your opportunity to take part in other studies.

5 What are the possible benefits of taking part?

The results of this research project will not provide you with any direct benefit. However, it may provide valuable information to improve the diagnosis, treatment or care of people with Parkinson's disease in the future. The current study will advance our understanding of brain functions, which has potential implications for treatment of cognitive impairment in Parkinson's disease. The treatment of this common symptom of Parkinson's disease is currently a major, unmet clinical need.

6 What are the possible risks and disadvantages of taking part?

<u>Cognitive testing and medication</u>
You may experience fatigue from the cognitive testing, or some discomfort from withholding medication for 12-24h. If this occurs, we will monitor you via follow-up calls and may instruct you to contact your primary care physician if symptoms persist.

<u>Mood questionnaires</u>
You will be asked to complete questionnaires that assess levels of depression, anxiety and stress. The questionnaires are not diagnostic tools and cannot be used to diagnose depression

or anxiety. However, you may be contacted (via e-mail and telephone) for follow-up based on your scores. The purpose of this follow-up is to provide you with information about available resources for coping with psychological problems should you need them.

Montreal Cognitive Assessment

We will use the Montreal Cognitive Assessment to screen for possible cognitive impairment. Scores below 23/30 are considered abnormal, and we may contact you if your score is below 23 to inform you of the outcome of the test, as an early diagnosis of cognitive impairment could help planning treatment. Please note that this is not a diagnostic test. Mild cognitive impairment is not dementia, and it does not always lead to dementia. It is defined as a noted problem with cognition or brain processing that is unusual for a person's age or education. Mild cognitive impairment does not usually cause any interference with the person's daily level of activities. Although the cause of the syndrome is not fully known, it is possible that it could be triggered by stress or illness. So someone can score below the cutoff score of 23 on the Montreal Cognitive Assessment because of temporary illness, fatigue, or other reasons. Furthermore, a good number of people who score below the cutoff at some point seem to recover their cognitive function and score in the normal range when retested. For these reasons, this test cannot be used to diagnose an illness such as dementia. Such a diagnosis would require further testing.

Genetic analyses

Finally, even though results do not have clinical utility at this stage and individual results will not be returned, statutory or contractual duties may require us or you to disclose the results of genetic tests or analysis to third parties (for example, insurance companies, employers, financial and educational institutions), particularly where results provide information about health prospects.

7 Will I be given the results of the research project?

If you wish to find out the aggregate results of the study as they might appear in professional publications, please feel free to follow A/Prof. Cohen-Woods' laboratory's official facebook page linked below. Please note that these publications will not include any information that can identify any individual.

Behavioural GEMs Facebook page: https://www.facebook.com/bGEMslab/

We have developed new cognitive tests to assess cognitive performance more precisely. However, because these tests are novel, they have not been standardised. This means although one can compare scores of different individuals, it is difficult to interpret these differences in a meaningful way (for example, a given score on a test does not necessarily indicate cognitive decline). For this reason, we will not give you feedback on your results on the cognitive tests. We can only give you feedback on the Montreal Cognitive Assessment and the mood questionnaires, which are standardised tests.

Part 2 How is the research project being conducted?

8 What will happen to information about me?

All genetic and other biological samples and data will be de-identified; a unique ID number will be given to all your samples in place of your name, in order to prevent anyone from identifying you from your samples or data. These ID numbers **will not** correspond to any names, emails, addresses or phone numbers that may be used to identify you. A document linking your name to your unique ID will be kept by the Principal Investigator, Dr Irina Baetu, who will store this securely on a computer at the University of Adelaide. She will be the only one able to access this information. This information will only be accessed in the case that a) we find medically significant information, and b) you have requested that we inform you of said information. In general, your samples and data will not be released for any use without your prior

consent, unless required by law or by the ethics committee that approved this project. It may also be used to re-contact you in the future to ask for your participation in a follow up study if you have consented to be re-contacted for that purpose, or to convey the results of mood questionnaires and the Montreal Cognitive Assessment, as explained in Section 6.

Only average results from all participants will be reported in future publications and presentations. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, maintaining your confidentiality.

Please note that publication and funding requirements may require submission of data or information to controlled access repositories that meet international security and safety standards for sharing with researchers globally. Any data (including genetic and cognitive testing data) shared via such repositories will be de-identified, protecting your anonymity.

In accordance with relevant Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the study team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

9 Who is organising and funding the research?

This project is funded by the [redacted] and [redacted] Foundation and the Australian Research Council, and is being conducted by Dr [redacted], A/Prof [redacted] and Professor [redacted] of the University of Adelaide, A/Prof. [redacted] and Dr [redacted] of Flinders University, and A/Prof [redacted] of Western Sydney University.

Please note that you will not benefit financially from your involvement in this research project even if, for example, knowledge acquired from analysis of your saliva sample and other information collected from you prove to be of commercial value to the institutions with which the investigators are affiliated.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

10 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of the University of Adelaide.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2018)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

11 Further information and who to contact

The person you may need to contact will depend on the nature of your query.
If you want any further information concerning this project, you can contact the principal investigator, D[redacted] or any of the following people:

D[redacted]
Phone: (08) [redacted]
Email: [redacted]@adelaide.edu.au

A/Prof [redacted]
Phone: (08) [redacted]
Email: [redacted]@adelaide.edu.au

Prof [redacted]
Phone: (08) [redacted]
Email: [redacted]@adelaide.edu.au

Dr [redacted]
Phone: (08) [redacted]
Email: [redacted]@flinders.edu.au

A/Prof [redacted]
Phone: (08) [redacted] / (08) [redacted] Email: [redacted]@flinders.edu.au

A/Prof [redacted]
Phone: (02) [redacted]
Email: [redacted]@westernsydney.edu.au

The study has been approved by the Human Research Ethics Committee at the University of Adelaide (approval number H-2016-219). Please contact the Human Research Ethics Committee's Secretariat on phone +61 8 [redacted] or by email to [redacted]@adelaide.edu.au if you wish to speak with an independent person regarding concerns or a complaint, the University's policy on research involving human participants, or your rights as a participant. Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

12 If I want to participate, what do I do?

Following your reading of this Participant Information sheet, if you wish to participate, please contact [redacted]**@adelaide.edu.au** or **(08)** [redacted] If you wish to participate in both sessions, you will be asked to contact your treatment health professional to determine whether it is safe for you to withdraw your medication before one of the testing sessions. Your treating health professional will be required to read this information sheet and consent form and complete and sign the attached medical consent form. If you are eligible for the study, you will be asked to sign the consent form on the day of your first appointment.

Appendix B

Participant Consent Form

Cognitive function in patients with different subtypes of Parkinson's disease
Participant Consent Form

Investigators	[redacted]
Human Research Ethics Committee Approval Number	H-2020-017
Location	The University of Adelaide, North Terrace Campus

Declaration by Participant

I have read the Participant Information Sheet.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with any answers I have received.

I understand that I will be given a signed copy of this document to keep.

I give permission for the use of my data and DNA and/or tissue for the purposes of **(choose one)**:

The research project associated with this study only ☐

The research project associated with this study, and any future research projects that may or may not be related to the aims of this research project ☐

I consent to being recontacted in the future if I am eligible to participate in other studies and/or to provide further biological samples: **Yes** ☐ **No** ☐

I wish my treating health professional to be notified if my scores on the mood questionnaires indicate that I may be suffering from depression, anxiety, or stress, or if my score on the Montreal Cognitive Assessment is below 23/30. If you tick yes, please provide his or her name and contact information: **Yes** ☐ **No** ☐

Name_____ Contact Information: _____

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project by contacting the researchers listed in the information sheet, and that withdrawal will not affect my future health care.

I understand that should I choose to withdraw, I can request for my data (including questionnaire answers and genetic information) be omitted from research, and my biological samples destroyed.

Name of Participant (please print): _____

Signature: _____ Date: _____

Declaration by Researcher

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood all the necessary information contained in the information sheet required for their informed consent.

Name of Researcher (please print): _____

Signature: _____ Date: _____

Note: All parties signing the consent section must date their own signatures.

Appendix C

Neurologist Consent Form for Associated Parkison's Disease Patients

Cognitive function in patients with different subtypes of Parkinson's disease

Medical Consent Form

(to be filled out by treating health professional)

Investigators	[redacted]
Human Research Ethics Committee Approval Number	H-2016-219
Location	The University of Adelaide, North Terrace Campus

Name of the health professional: .....

Contact information:.....

Name of the patient: .....

I confirm that this patient is diagnosed with idiopathic Parkinson's disease **Yes** ☐ **No** ☐

Disease duration: .....years and .....months

Hoehn & Yahr stage:.....

Medication:..... Dose:.....

Medication:..... Dose:.....

Medication:..... Dose:.....

Medication:..... Dose:.....

Medication:..... Dose:.....

Please endorse one of the following:

☐ I have read the study information sheet and consent form and, to my knowledge, it is safe for this patient to withhold dopamine agonist medication 24 hours prior to the experiment and to withhold levodopa overnight 12 hours prior to the experiment.

☐ I have read the study information sheet and consent form and, to my knowledge, it is NOT safe for this patient to withhold dopamine agonist medication 24 hours prior to the experiment and to withhold levodopa overnight 12 hours prior to the experiment.

Signature:..... Date:.....

Appendix D

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (Modified)

Survey Page 1

Date _____

Name _____

Questions about impulsive behaviours

How much do you think about the following behaviors (such as having trouble keeping thoughts out of your mind or feeling guilty)?	Never	Rarely	Sometimes	Often	Very often
Gambling?	○	○	○	○	○
Sex?	○	○	○	○	○
Buying?	○	○	○	○	○
Eating?	○	○	○	○	○
Drinking alcohol?	○	○	○	○	○
Performing tasks or hobbies?	○	○	○	○	○
Repeating simple activities?	○	○	○	○	○
Taking your PD medications?	○	○	○	○	○
Taking non-PD medications?	○	○	○	○	○
Taking drugs for non-medicinal purposes?	○	○	○	○	○
Other (1)	○	○	○	○	○
Other (2)	○	○	○	○	○

Please specify for "Other (1)" _____

Please specify for "Other (2)" _____

Do you have urges or desires for the following behaviors that you feel are excessive or cause you distress (including becoming restless or irritable when unable to participate in them)?	Never	Rarely	Sometimes	Often	Very often
Gambling?	○	○	○	○	○
Sex?	○	○	○	○	○
Buying?	○	○	○	○	○
Eating?	○	○	○	○	○
Drinking alcohol?	○	○	○	○	○
Performing tasks or hobbies?	○	○	○	○	○
Repeating simple activities?	○	○	○	○	○
Taking your PD medications?	○	○	○	○	○
Taking non-PD medications?	○	○	○	○	○
Taking drugs for non-medicinal purposes?	○	○	○	○	○
Other (1)	○	○	○	○	○
Other (2)	○	○	○	○	○

Survey Page 2

Do you have difficulty controlling the following behaviors (such as increasing them over time, or having trouble cutting down or stopping them)?

	Never	Rarely	Sometimes	Often	Very often
Gambling?	○	○	○	○	○
Sex?	○	○	○	○	○
Buying?	○	○	○	○	○
Eating?	○	○	○	○	○
Drinking alcohol?	○	○	○	○	○
Performing tasks or hobbies?	○	○	○	○	○
Repeating simple activities?	○	○	○	○	○
Taking your PD medications?	○	○	○	○	○
Taking non-PD medications?	○	○	○	○	○
Taking drugs for non-medicinal purposes?	○	○	○	○	○
Other (1)	○	○	○	○	○
Other (2)	○	○	○	○	○

Do you engage in activities specifically to continue the following behaviors (such as hiding what you are doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts)?

	Never	Rarely	Sometimes	Often	Very often
Gambling?	○	○	○	○	○
Sex?	○	○	○	○	○
Buying?	○	○	○	○	○
Eating?	○	○	○	○	○
Drinking alcohol?	○	○	○	○	○
Performing tasks or hobbies?	○	○	○	○	○
Repeating simple activities?	○	○	○	○	○
Taking your PD medications?	○	○	○	○	○
Taking non-PD medications?	○	○	○	○	○
Taking drugs for non-medicinal purposes?	○	○	○	○	○
Other (1)	○	○	○	○	○
Other (2)	○	○	○	○	○

Survey Page 3

If you answered 'Rarely', 'Sometimes', 'Often' or 'Very often' to any of the questions on the two previous pages and you currently take medication for Parkinson's disease, could you please answer a few more questions about each of these behaviours below. If you answered 'Never' to the previous questions or you do not take medication for Parkinson's disease, please leave the following two pages blank.

Gambling

When did this behaviour (or thoughts about this behaviour) first become problematic?

Approximate date: _____

Do you believe this behaviour has changed as a result of taking your Parkinson's Disease associated medication (i.e. do you feel your symptoms have improved/worsened after starting your medication?)

Worsened significantly	Worsened slightly	No change	Improved slightly	Improved significantly
○	○	○	○	○

Sex

When did this behaviour (or thoughts about this behaviour) first become problematic?

Approximate date: _____

Do you believe this behaviour has changed as a result of taking your Parkinson's Disease associated medication (i.e. do you feel your symptoms have improved/worsened after starting your medication?)

Worsened significantly	Worsened slightly	No change	Improved slightly	Improved significantly
○	○	○	○	○

Buying

When did this behaviour (or thoughts about this behaviour) first become problematic?

Approximate date: _____

Do you believe this behaviour has changed as a result of taking your Parkinson's Disease associated medication (i.e. do you feel your symptoms have improved/worsened after starting your medication?)

Worsened significantly	Worsened slightly	No change	Improved slightly	Improved significantly
○	○	○	○	○

Eating

When did this behaviour (or thoughts about this behaviour) first become problematic?

Approximate date: _____

Do you believe this behaviour has changed as a result of taking your Parkinson's Disease associated medication (i.e. do you feel your symptoms have improved/worsened after starting your medication?)

Worsened significantly	Worsened slightly	No change	Improved slightly	Improved significantly
○	○	○	○	○

Alcohol

When did this behaviour (or thoughts about this behaviour) first become problematic?

Approximate date: _____

Do you believe this behaviour has changed as a result of taking your Parkinson's Disease associated medication (i.e. do you feel your symptoms have improved/worsened after starting your medication?)

Worsened significantly	Worsened slightly	No change	Improved slightly	Improved significantly
○	○	○	○	○

Survey Page 4

Performing tasks or hobbies

When did this behaviour (or thoughts about this behaviour) first become problematic?

Approximate date: _____

Do you believe this behaviour has changed as a result of taking your Parkinson's Disease associated medication (i.e. do you feel your symptoms have improved/worsened after starting your medication?)

Worsened significantly	Worsened slightly	No change	Improved slightly	Improved significantly
○	○	○	○	○

Repeating simple activities

When did this behaviour (or thoughts about this behaviour) first become problematic?

Approximate date: _____

Do you believe this behaviour has changed as a result of taking your Parkinson's Disease associated medication (i.e. do you feel your symptoms have improved/worsened after starting your medication?)

Worsened significantly	Worsened slightly	No change	Improved slightly	Improved significantly
○	○	○	○	○

Taking your PD medications

When did this behaviour (or thoughts about this behaviour) first become problematic?

Approximate date: _____

Do you believe this behaviour has changed as a result of taking your Parkinson's Disease associated medication (i.e. do you feel your symptoms have improved/worsened after starting your medication?)

Worsened significantly	Worsened slightly	No change	Improved slightly	Improved significantly
○	○	○	○	○

Taking your non-PD medications

When did this behaviour (or thoughts about this behaviour) first become problematic?

Approximate date: _____

Do you believe this behaviour has changed as a result of taking your Parkinson's Disease associated medication (i.e. do you feel your symptoms have improved/worsened after starting your medication?)

Worsened significantly	Worsened slightly	No change	Improved slightly	Improved significantly
○	○	○	○	○

Other (1)

When did this behaviour (or thoughts about this behaviour) first become problematic?

Approximate date: _____

Do you believe this behaviour has changed as a result of taking your Parkinson's Disease associated medication (i.e. do you feel your symptoms have improved/worsened after starting your medication?)

Worsened significantly	Worsened slightly	No change	Improved slightly	Improved significantly
○	○	○	○	○

Other (2)

When did this behaviour (or thoughts about this behaviour) first become problematic?

Approximate date: _____

Do you believe this behaviour has changed as a result of taking your Parkinson's Disease associated medication (i.e. do you feel your symptoms have improved/worsened after starting your medication?)

Worsened significantly	Worsened slightly	No change	Improved slightly	Improved significantly
○	○	○	○	○

Survey Page 5

Medication Questions

Medication

Do you take medication for Parkinson's disease (for example, levodopa)?
- ○ Yes
- ○ No

If you answered 'Yes' above, please answer the following questions.

PD MEDICATION

When did you start taking your Parkinson's Disease associated medication? Please provide an approximate date.

_____ (approximate date)

Do you believe your medication usually alleviates any of the following symptoms or improves any of the following abilities? Tick all that apply.

- ☐ tremor
- ☐ bradykinesia (slowness of movement)
- ☐ balance
- ☐ muscle stiffness
- ☐ walking ability
- ☐ gait changes
- ☐ initiating movement (for example, getting up from a chair, or reaching for an object)
- ☐ attention and focus
- ☐ judgement and planning
- ☐ memory
- ☐ anxiety
- ☐ depression
- ☐ other

Please specify for "other"

_____

Do you believe your medication worsens any of the following symptoms or hinders any of the following abilities? Tick all that apply.

- ☐ tremor
- ☐ bradykinesia (slowness of movement)
- ☐ balance
- ☐ muscle stiffness
- ☐ walking ability
- ☐ gait changes
- ☐ initiating movement (for example, getting up from a chair, or reaching for an object)
- ☐ attention and focus
- ☐ judgement and planning
- ☐ memory
- ☐ anxiety
- ☐ depression
- ☐ other

Please specify for "other"

_____

Appendix E

Unified Dyskinesia Rating Scale (Modified)

Survey Page 6

Dyskinesia questions

If you medication for Parkinson's disease, please answer the following questions about dyskinesias. If you do not take medications, please skip this section and answer the subsequent dystonia questions.

Patient On-Dyskinesia Questionnaire

This questionnaire will ask you about the effect of movements called "on-dyskinesias" on your usual activities. On-dyskinesias are jerking or twisting movements that occur in patients with Parkinson's disease when their medicines are working.

Please answer questions about how dyskinesia affects your activities.

Do not answer these questions based on how other problems affect your activities.

Do not base your answers on tremor, which is a regular back and forth shaking and part of the Parkinson's disease itself. Do not base your answers on slowness or stiffness that is part of Parkinson's disease itself Do not base your answers on spasms or cramps that can be painful and occur when your medicines are not working. You will answer questions about this problem later. Concentrate only on jerking or twisting movements when your Parkinson's medicine is working. There are 11 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in the average or usual impact of on-dyskinesia over the past week including today. Only one answer is allowed for each question, so please mark the answer that best describes how on-dyskinesia, if present, affects these activities most of the time.

SLEEP

Over the past week, how many hours do you usually sleep on a daily basis, including nighttime sleep and daytime napping?	_____
Considering your previous answer, calculate the number of hours you are awake for (by subtracting your previous answer from 24).	_____
Out of those awake hours, how many hours in total are your medications working to control your Parkinson's disease (hours on)?	_____ (Record 0 if you do not take Parkinson's disease medication)
During the hours that your medications are working, do you have jerking or twisting movements? (do not count tremor)	◯ Yes ◯ No
Add up all the time during the waking day when your medications are working and you have these jerking or twisting movements, how many hours?	_____

Survey Page 7

SPEECH

Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems with your speech? Consider only effects of dyskinesias, not problems caused by Parkinson's disease.

- ◯ Normal: Not at all, no problems.
- ◯ Slight: Dyskinesias were present, but they did not interfere with my speech.
- ◯ Mild: Dyskinesias caused a few problems with my speech and people asked me to repeat myself occasionally.
- ◯ Moderate: Dyskinesias caused enough problems that I tried to avoid talking when I had on-dyskinesias.
- ◯ Severe: When I had dyskinesias, most or all of my speech could not be understood.

CHEWING AND SWALLOWING

Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems swallowing pills or eating meals? Did you need your pills cut or crushed or your meals to be made soft, chopped or blended to avoid choking? Consider only effects of dyskinesias, not problems caused by Parkinson's disease.

- ◯ Normal: Not at all, no problems.
- ◯ Slight: Dyskinesias were present, but they did not interfere with my chewing or swallowing.
- ◯ Mild: Dyskinesias caused a few problems with chewing and swallowing and it took me longer to chew or swallow because of on-dyskinesias.
- ◯ Moderate: Dyskinesias caused enough problems that I tried to avoid chewing and swallowing when I had on-dyskinesias.
- ◯ Severe: When I had dyskinesias, I was unable to chew or swallow at all.

EATING TASKS

Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause trouble handling your food and using eating utensils? For example, did you have trouble handling finger foods or using forks, knives, spoons, chopsticks? Consider only effects of dyskinesias, not problems caused by Parkinson's disease.

- ◯ Normal: Not at all, no problems.
- ◯ Slight: Dyskinesias were present, but they did not interfere with my eating.
- ◯ Mild: Dyskinesias caused a few problems with eating and it took me longer to eat because of on-dyskinesias.
- ◯ Moderate: Dyskinesias caused enough problems that I tried to avoid eating when I had on- dyskinesias.
- ◯ Severe: When I had dyskinesias, I needed help for most or all eating tasks.

DRESSING

Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems with your dressing? For example, did you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry? Consider only effects of dyskinesias, not problems caused by Parkinson's disease.

- ◯ Normal: Not at all, no problems.
- ◯ Slight: Dyskinesias were present but they did not interfere with dressing tasks.
- ◯ Mild: Dyskinesias caused a few problems with dressing and it took me longer to get dressed because of on-dyskinesias.
- ◯ Moderate: Dyskinesias caused enough problems that I tried to avoid getting dressed when I had on-dyskinesias.
- ◯ Severe: When I had dyskinesias, I needed help for most or all dressing tasks.

Survey Page 8

HYGIENE

Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems with your personal hygiene? For example, did you need help with washing, bathing, shaving, brushing teeth, or combing your hair? Consider only effects of dyskinesias, not problems caused by Parkinson's disease.

- ◯ Normal: Not at all, no problems.
- ◯ Slight: Dyskinesias were present but they did not interfere with hygiene tasks.
- ◯ Mild: Dyskinesias caused a few problems with hygiene tasks and it took me longer to do these activities because of on-dyskinesias.
- ◯ Moderate: Dyskinesias caused enough problems that I tried to avoid doing hygiene tasks when I had on-dyskinesias.
- ◯ Severe: When I had dyskinesias, I needed help for most or all of my hygiene tasks.

HANDWRITING

Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause trouble with your handwriting? Consider only effects of dyskinesias, not problems caused by Parkinson's disease.

- ◯ Normal: Not at all, no problems.
- ◯ Slight: Dyskinesias were present, but they did not interfere with my handwriting.
- ◯ Mild: Dyskinesias caused a few problems with writing and it took me longer to write because of on-dyskinesias.
- ◯ Moderate: Dyskinesias caused enough problems that I tried to avoid writing when I had on- dyskinesias.
- ◯ Severe: When I had dyskinesias, most or all words could not be read.

DOING HOBBIES AND OTHER ACTIVITIES

Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on- dyskinesias usually cause trouble doing your hobbies or other things that you like to do? Consider only effects of dyskinesias, not problems caused by Parkinson's disease.

- ◯ Normal: Not at all, no problems.
- ◯ Slight: Dyskinesias were present but they did not interfere with these activities.
- ◯ Mild: Dyskinesias caused a few problems with these activities and it took me longer to do them because of on-dyskinesias.
- ◯ Moderate: Dyskinesias caused enough problems that I tried to avoid doing hobbies or other activities when I had on-dyskinesias.
- ◯ Severe: When I had dyskinesias, I was unable to do most or all of these activities.

WALKING AND BALANCE

Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems with balance and walking? Consider only effects of dyskinesias, not problems caused by Parkinson's disease.

- ◯ Normal: Not at all, no problems.
- ◯ Slight: Dyskinesias were present but they did not interfere with walking or balance.
- ◯ Mild: Dyskinesias caused a few problems with walking. It took me longer to walk because of on-dyskinesias and I occasionally bumped into things.
- ◯ Moderate: Dyskinesias caused enough problems that I usually used a walking aid (cane, walker) to walk safely without falling. However, I did not usually need the support of another person. I tried to avoid walking when I had on-dyskinesias.
- ◯ Severe: When I had dyskinesias, I could not walk safely without falling.

Survey Page 9

PUBLIC AND SOCIAL SETTINGS

Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems when you were dealing with other people or in public? Consider only effects of dyskinesias, not problems caused by Parkinson's disease.

- ◯ Normal: Not at all, no problem.
- ◯ Slight: Dyskinesias were present but they did not interfere with these activities.
- ◯ Mild: Dyskinesias caused a few problems and I was self-conscious in public but I did not avoid social situations.
- ◯ Moderate: Dyskinesias caused enough problems that I tried to avoid some social situations when I had on-dyskinesias.
- ◯ Severe: When I had dyskinesias, I could not be with people, even friends or family.

EXCITING OR EMOTIONAL SETTINGS

Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on- dyskinesias usually cause problems during emotional conversations, exciting movies, or other highly stimulating situations? Consider only effects of dyskinesias, not problems caused by Parkinson's disease.

- ◯ Normal: Not at all, no problem.
- ◯ Slight: Dyskinesias were present, but they did not interfere with these activities.
- ◯ Mild: Dyskinesias caused few problems.
- ◯ Moderate: Dyskinesias caused enough problems that I tried to avoid some exciting situations when I had on-dyskinesias.
- ◯ Severe: When I had dyskinesias, I could not stay in exciting situations.

Survey Page 10

Dystonia questions

Please answer the following questions regardless of whether you take medication for Parkinson's disease.

Patient Off-Dystonia Questionnaire

This questionnaire asks you questions about spasms or cramps that occur when Parkinson's disease medications are not taken or when they are not working well. We call that time OFF. Off-dystonia movements are sometimes painful and often occur in the early morning or nighttime, but occasionally at other times when Parkinson's disease medications are not working.

Do not answer these questions based on how other problem affect your activities.

Do not base your answers on tremor, which is a regular back and forth shaking and part of the Parkinson's disease itself. Do not base your answers on slowness or stiffness that is part of Parkinson's disease itself. Do not base your answers on jerking, twisting movements which occur when you have taken Parkinson's disease medication and it is working. Concentrate only on spasms or cramps, called off-dystonia. In general, these movements develop in the early morning, nighttime or when you have not taken medication or the good effects of medicines have worn off. Sometimes, there is pain along with the spasms.

There are 4 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in the average or usual impact of off-dystonia over the past week including today. Only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

TIME SPENT WITH OFF-DYSTONIA

Over the past week, on a typical day, think about the number of hours of the day when you are stiff and slow, whether this is before you take morning medications, perhaps late in the evening, or during the day when the good effects of medication have worn out. Within these "OFF" times, how many hours or minutes do you have spasms or cramps that we call OFF-dystonia?

- ◯ Never
- ◯ Less than 30 minutes a day
- ◯ Less than 60 minutes a day.
- ◯ Less than 2 hours a day.
- ◯ Greater than 2 hours a day.

EFFECTS OF SPASMS OR CRAMPS CALLED OFF-DYSTONIA SEPARATE FROM PAIN ON ACTIVITIES

During the past week, separate from pain, have spasms or cramps called OFF-dystonia occurred?

- ◯ Normal: Not at all.
- ◯ Slight: Off-dystonia occurred but it did not interfere with my daily activities.
- ◯ Mild: Off-dystonia caused a few problems and it took me longer to do activities because of off-dystonia.
- ◯ Moderate: Off-dystonia caused enough problems that I avoided doing these activities when I had off-dystonia.
- ◯ Severe: When off-dystonia occurred, I could not do many activities.

EFFECTS OF PAIN FROM OFF-DYSTONIA ON DAILY ACTIVITIES

On average during this past week, if spasms or cramps called off-dystonia occurred, did pain limit your activities?

- ◯ Normal: Not at all, no pain from off-dystonia.
- ◯ Slight: I had pain from off-dystonia, but it did not limit my activities
- ◯ Mild: Pain from off-dystonia caused a few problems and it took me longer to do activities because of pain from off-dystonia.
- ◯ Moderate: Pain from off-dystonia caused enough problems that I avoided doing these activities when I had pain from off-dystonia.
- ◯ Severe: Because of pain from dystonia, I could not do many activities.

DYSTONIA PAIN

On average during the past week, how severe was the pain from the spasms or cramps of off-dystonia?

- ◯ Normal: Not painful
- ◯ Slight: Mild ache or discomfort.
- ◯ Mild: Moderate ache and discomfort.
- ◯ Moderate: Severe discomfort.
- ◯ Severe: Excruciating pain

Appendix F

Ethics Approval

RESEARCH SERVICES
OFFICE OF RESEARCH ETHICS, COMPLIANCE AND INTEGRITY
THE UNIVERSITY OF ADELAIDE
[redacted]
CRICOS Provider Numbe[redacted]

Our reference [redacted]

09 June 2023

D[redacted]
Psychology

Dear Dr Baetu

ETHICS APPROVAL No: H-2016-219
PROJECT TITLE: Cognitive function in patients with different subtypes of Parkinson's disease

Thank you for the amended ethics application provided on 12/05/2023 requesting an amendment to add the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease and the Unified Diskinesia Rating Scale, as well as questions on traumatic brain injury or concussions, as survey instruments; to contact people who have previously completed the already approved tests and consented to being recontacted for future studies to complete these new questionnaires; and to add [redacted] an Honours student to the project. The amendment has been approved.

The ethics amendment for the above project has been reviewed by the Executive, Human Research Ethics Committee and is deemed to meet the requirements of the *National Statement on Ethical Conduct in Human Research 2007 (Updated 2018)*.

You are authorised to commence your research on: 29/03/2017
The ethics expiry date for this project is: 31/03/2026

NAMED INVESTIGATORS:

Chief Investigator:	Dr [redacted]
Associate Investigator:	Associate Professor [redacted]
Associate Investigator:	Professor [redacted]
Associate Investigator:	Dr [redacted]
Associate Investigator:	D[redacted]
Associate Investigator:	Dr [redacted]
Student - Postgraduate Doctorate by Research (PhD):	Miss [redacted]
Student - Postgraduate Doctorate by Research (PhD):	Ms [redacted]
Student - Postgraduate Doctorate by Research (PhD):	Mr [redacted]
Student - Postgraduate Doctorate by Research (PhD):	Mr [redacted]
Student - Postgraduate Doctorate by Research (PhD):	[redacted]

Student - Postgraduate Doctorate by Research (PhD):	[redacted]
Student - Postgraduate Doctorate by Research (PhD):	[redacted]
Associate Investigator:	Dr [redacted]
Associate Investigator:	Professor [redacted]
Associate Investigator:	Associate Professor [redacted]
Student - Postgraduate Doctorate by Research (PhD):	Mr [redacted]
Student - Postgraduate Doctorate by Research (PhD):	Mr [redacted]
Student - Postgraduate Doctorate by Research (PhD):	Mr [redacted]
Student - Undergraduate Bachelors Honours:	[redacted]

Ethics approval is granted for three years and is subject to satisfactory annual reporting. The form titled Annual Report on Project Status is to be used when reporting annual progress and project completion and can be downloaded at http://www.adelaide.edu.au/research-services/oreci/human/reporting/. Prior to expiry, ethics approval may be extended for a further period.

Participants in the study are to be given a copy of the information sheet and the signed consent form to retain. It is also a condition of approval that you immediately report anything which might warrant review of ethical approval including:

- serious or unexpected adverse effects on participants,
- previously unforeseen events which might affect continued ethical acceptability of the project,
- proposed changes to the protocol or project investigators; and
- the project is discontinued before the expected date of completion.

Yours sincerely,

Dr [redacted]
Acting Chair

The University of Adelaide

Appendix G

Correlation for Dyskinesia Scores and Dystonia Scores