Exploring the Role of Cognitive Reserve in Parkinson's Disease Patient's Responsiveness to Levodopa Treatment

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List of Abbreviations

Cognitive Reserve ..... CR

Cognitive Reserve Index questionnaire ..... CRIq

Levodopa Equivalent Dose..... LED

Lifetime Experiences Questionnaire ..... LEQ

Parkinson's Disease ..... PD

Principal Components Analysis..... PCA

Stop Signal Delay ..... SSD

Unified Parkinson's Disease Rating Scale–Motor Subscale ..... UPDRS-III

Variance Inflation Factor..... VIF

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disease characterised by dopamine loss. Dopamine medication as levodopa has been established to reduce PD motor symptoms and seemingly has erratic consequences for cognition. Cognitive reserve (CR), the mind's resistance to brain damage, has been proposed to justify PD patients experiencing different impairments despite no significant neuropathological differences. Given the interaction between CR and levodopa state change is unexplored for PD, we sought to determine if CR predicts levodopa responsiveness and the role of other possible predictors. We tested six PD patient's motor and fluid intelligence performance ON and OFF levodopa, to determine any variations in levodopa responsiveness. CR was measured with the comprehensive Cognitive Reserve Index questionnaire and a premorbid intelligence test. Motor and fluid intelligence performance was assessed with five precise measures of different abilities in ON and OFF levodopa states. Time limited data collection, meaning 80 PD patients were simulated from the six PD patients to meet regression conditions. We found CR did not significantly predict how PD patients responded to levodopa when controlling for age and levodopa equivalent dose (LED). However, LED was a significant predictor of change in motor and fluid intelligence performance, therefore acting as the most important contributing variable towards levodopa responsiveness. Age displayed a significant relationship with change in fluid intelligence performance. These findings suggest CR's protective ability for PD was negligible when considering change in levodopa states and LED was the predominant levodopa responsiveness predictor. Implications for PD treating clinicians and patients are explored.

Declaration

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Isaac Saywell

27th September 2021

Contribution Statement

In writing this thesis, my supervisor and I collaborated to generate research questions of interest and design appropriate methodology. I conducted literature search, while the ethics application, project registration, and uploading of all relevant information onto the Open Science Framework were completed by my supervisor as part of the larger study that my thesis was constructed from. My supervisor, other research assistants, and I collaborated in participant testing, while recruitment was largely run by research assistants as part of a larger study and my supervisor provided all participation incentives. My supervisor and I collaborated to code all analyses in R. I wrote up all aspects of the thesis.

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Chapter 1

Introduction

1.1 Parkinson's Disease and Treatment

Parkinson's Disease (PD) is a progressive neurodegenerative disease associated with motor dysfunction and has a prevalence of 315 per 100,000 (Ascherio & Schwarzschild, 2016; Pringsheim et al., 2014). Diagnosis is made according to four cardinal symptoms, requiring bradykinesia plus one of tremor (4-6 Hz), rigidity, or postural instability (Hughes et al., 1992). Symptoms can present unilaterally or bilaterally, and as different subtypes determined by symptom type or disease onset (Fereshtehnejad & Postuma, 2017). Since 1999 PD prevalence has doubled (Schapira, 1999), and is set to double again by 2030 (Dorsey et al., 2005) mostly due to our ageing population (Elbaz et al., 2016).

PD impairments are characterised by dopamine loss in the basal ganglia, decreasing dopamine striatum levels (Schapira, 1999). Dopaminergic neurotransmission is critical for functioning of basal ganglia circuits, which communicate with the prefrontal and motor cortexes (McGregor & Nelson, 2019). This means these circuits are involved in motor functions like voluntary movement, but also in cognitive functions like fluid intelligence abilities and learning (Alexander et al., 1990; Elhalal et al., 2014; Kimberg et al., 1998; Petrides, 1994). In PD lack of striatal dopamine inhibits the thalamus, reducing motor and prefrontal cortex activation (McGregor & Nelson, 2019). Impairment of these dopamine-dependent circuits triggers the manifestation of parkinsonian symptoms (Wichmann, 2019), diminishing motor and cognitive ability (Berridge & Robinson, 1998; Bodden et al., 2010; Jones et al., 2008). This demonstrates the reliance basal ganglia influenced functions have on dopamine (Leisman et al., 2014) and indicates PD is more than just a motor neurodegenerative disease.

Dopamine medication, as dopamine precursor levodopa, is the most common PD treatment (Rao et al., 2006). It was designed to alleviate motor impairments by converting into dopamine that brain cells cannot generate (Schapira, 2005). However, given the involvement of dopamine and basal

ganglia in cognitive performance, levodopa can influence cognitive abilities (Lange et al., 1992). Levodopa dosage differs depending on the extent of dopamine degeneration (Leroi et al., 2013), where greater benefits usually arise with more severe impairments or subtypes that often present with greater dopamine loss (Hershey et al., 2003; Mohl et al., 2017). Incorrect dosage level, however, can introduce harmful side effects and extended use can cause a 'wearing-off' of benefits as patients develop tolerance (Obeso et al., 2000). Prescribing optimal dosage is further complicated by some patients presenting different levels of impairment without a neuropathological reason (Stern, 2009). In other words, level of neurodegeneration does not always match the symptom severity. Our aim was therefore to explore a factor that might explain this phenomenon, namely cognitive reserve (CR).

1.2 Introduction to Cognitive Reserve

Mismatches between neuropathological changes and clinical outcomes in dementia have prompted applying CR to other neurodegenerative diseases (Bettcher et al., 2019; Guzzetti et al., 2019; Suemoto et al., 2017). It was originally used when examining dementia residents post-mortem, revealing unaccountable differences in brain weight and neuronal degenerations (Katzman et al., 1988). Less deteriorated patient brains were not representative of dementia severity, leading to Katzman et al. (1988) suggesting CR as a protective factor. CR is the brain's ability to resist damage, through developing flexible neural compensatory circuits formed by life-long mental engagement (Imbimbo et al., 2021). Commonly proxies of CR like education, social activities, and occupation are used as measurements, along with recently developed CR assessment tools like the Cognitive Reserve Index questionnaire (CRIq) (Nucci et al., 2012; Stern, 2009). Some view CR as similar to intelligence, although it differs as CR explains resilience to neural damage rather than acquiring and applying higher level abilities.

The reserve hypothesis states individuals with higher CR may better handle brain damage (Fratiglioni & Wang, 2007; Lee et al., 2019). That is, CR may protect cognitive performance from neurodegeneration by allowing the brain to engage compensatory mechanisms. Several studies

(Ciccarelli et al., 2018; Guzzetti et al., 2019; Herman et al., 2018; Hindle et al., 2017; Koerts et al., 2013; Roldán-Tapia et al., 2012; Souza et al., 2013) have found CR predicts motor and fluid intelligence impairments among neuropathologically similar PD patients. CR may delay or slow down the symptom onset and is more effective for patients with more severe symptoms (Guzzetti et al., 2019; Stern, 2009), but it does not seem to slow the rate of progression into the stages of the disease with more severe symptoms (Zahodne et al., 2011). If the reserve hypothesis is true then it could account for neuropathologically unexplainable differences in the effect of levodopa has on PD motor functioning and fluid intelligence. Limited PD research has been concentrated on assessing the effect of CR and levodopa independently, never previously considering an interaction effect between these variables. The current study therefore aims to test whether PD patient CR disparities can account for differences in levodopa responsiveness by assessing unexplainable differences in motor and fluid intelligence outcomes. Considering lack of research, the following sections will review studies that have investigated the independent effects of CR and levodopa on motor and fluid intelligence functions.

1.3 Relationship between CR and Motor Function

Eight studies investigating CR's influence on PD motor functioning were reviewed, finding positive correlations between CR and most motor abilities, with a few null results (see Table 1). This is consistent with the idea that CR may compensate for dopamine loss by recruiting basal ganglia resources to resist motor deterioration (Stern, 2009). CR is positively associated with gait parameters speed and stride length, measured in a six minute walk test (Imbimbo et al., 2021; Wegrzyk et al., 2019) and better postural stability (Imbimbo et al., 2021; Souza et al., 2013) (see Table 1). Furthermore, Herman et al. (2018) found that PD patients with a lower CR were more likely to convert into PD subtypes that cause severe postural instability. However, a lower CR and converting into these worse subtypes does not seem to affect early-stage PD symptom tremor (Herman et al., 2018). This implies that CR may be a late-stage protective factor for PD motor functioning, supporting the notion that protective importance increases over time (Guzzetti et al., 2019; Stern,

2009). Furthermore, motor processing speed appears to be faster in patients who have a higher premorbid intelligence and greater educational attainment, preserving their ability to process and respond to stimuli (Koerts et al., 2013; Lee et al., 2019). Supportive of these findings multiple studies (Guzzetti et al., 2019; Herman et al., 2018; Lee et al., 2019) identified that researcher ratings of impairment, using the Unified Parkinson's Disease Rating Scale–Motor Subscale (UPDRS-III), were lower for higher CR patients. These findings suggest CR can help resist developing worse PD motor impairments.

Table 1

Reviewed Studies Investigating Cognitive Reserve's Influence on Parkinson's Disease Patient Motor Functioning

Study	CR Measure(s)	Measured Motor Ability Effect	Sample Size (Gender)	Mean Age (Years)	Mean Year Disease Duration
Guzzetti et al. (2019)	CRIq	U (+)	50 (36 M 14 F)	70	N/A
Herman et al. (2018)	E	U (+) Ba (+) T (*) G (+)	26 (22 M 4 F)	66	10
Imbimbo et al. (2021)	CRIq	Ba (+) G (+)	26 (22 M 4 F)	73	5
Koerts et al. (2013)	PMI, E	MPS (+)	48 (28 M 20 F)	63	5.5
Lee et al. (2019)	E	U (+) G (+)	415 (245 M 170 F)	62	2.5
Rouillard et al. (2017)	E, LT, SOS	MPS (+)	49 (27 M 22 F)	66	6.5
Souza et al. (2013)	E	U (*) MPS (+) Ba (+)	28 (N/A)	67	N/A
Wegrzyk et al. (2019)	E	U (*) G (+)	34 (19 M 15 F)	61	11

*Note. CRIq = Cognitive Reserve Index questionnaire, E = Education, PMI = Premorbid Intelligence, LT = Leisure Time, SOS = Socio-occupational Status, U = Unified Parkinson's Disease Rating Scale-Third Subscale, Br = Bradykinesia, MPS = Motor Processing Speed, Ba = Balance, T = Tremor, G = Gait, + = denotes a positive relationship with cognitive reserve, - = denotes a negative relationship with cognitive reserve, * = denotes no significant relationship with cognitive reserve, M = Male, F = Female.*

1.4 Relationship between CR and Fluid Intelligence

CR may also explain neuropathologically unaccountable differences in PD fluid intelligence impairments. Preservation of fluid intelligence is more likely in younger and short disease duration patients (Guzzetti et al., 2019; Venezia et al., 2018). CR acts as a strong precursor for prefrontal cortex function, enabling some older patients with a longer disease duration to have preserved fluid intelligence (Hindle et al., 2014; Marioni et al., 2012). The reviewed literature generally found higher CR scores are associated with better fluid intelligence, however, most studies only assessed working memory (see Table 2). Better PD patient performance on verbal working memory tasks like the forward/backwards digit span are significantly correlated with higher CRIq scores (Ciccarelli et al., 2018; Guzzetti et al., 2019). While CR proxies, such as education, social engagement, and socio-occupational level, also predict better verbal and visual working memory performance (Koerts et al., 2013; Roldán-Tapia et al., 2012; Rouillard et al., 2017). Premorbid intelligence as a CR proxy also has a positive relationship with working memory (Ciccarelli et al., 2018; Koerts et al., 2013). However, Hindle et al. (2017) found no significant relationship between working memory and CR, measured by the Lifetime Experiences Questionnaire (LEQ). The authors argue this could be attributed to the extended LEQ length that makes it difficult for PD patients to complete or the preserved executive functioning of their convenience sample.

Since mostly working memory has been compared to CR in PD research (see Table 2), it is difficult to generalise results to other cognitive functions. However limited research still found PD patient reasoning ability, assessed by Raven's Progressive Matrices, differs significantly depending on CRIq or premorbid intelligence scores (Ciccarelli et al., 2018; Guzzetti et al., 2019). Although Ciccarelli et al. (2018) found that the relationship was approaching significance ($p=0.06$). Despite this, when both measured with different tests, CR displays a significant positive relationship with reasoning ability (Roldán-Tapia et al., 2012). CR as indexed by educational attainment has the strongest relationship with reasoning ability (Muslimović et al., 2009; Roldán-Tapia et al., 2012).

Additionally, premorbid intelligence and education predict a greater PD response inhibition ability (Koerts et al., 2013; Roldán-Tapia et al., 2012). There is currently limited research on the effect CR has on response inhibition, but the positive relationship it has for healthy individuals may indicate a direction of effect for PD patients (Rouillard et al., 2017). Like response inhibition, visual processing speed PD research, in relation to CR, is lacking. A similar construct, perceptual speed (symbol comparison speed) that is measured by a symbol digit modality test, is slower for patients with a lower CR (Rouillard et al., 2017). This may indicate CR could positively influence PD visual processing speed, but the symbol digit modality test does also assess confounding variables motor, memory, and learning.

Table 2

Reviewed Studies Investigating Cognitive Reserve's Influence on Parkinson's Disease Patient Fluid Intelligence

Study	CR Measure(s)	Measured Fluid Ability Effect	Sample Size (Gender)	Mean Age (Years)	Mean Year Disease Duration
Ciccarelli et al. (2018)	CRIq, PMI	WM (+) RA (*)	35 (27 M 8 F)	76	6
Guzzetti et al. (2019)	CRIq	WM (+) RA (*)	50 (36 M 14 F)	70	N/A
Hindle et al. (2014)	E	WM (+)	MA	MA	MA
Hindle et al. (2016)	E, SE, SOS	WM (+)	323 (212 M 118 F)	66	N/A
Hindle et al. (2017)	LEQ	WM (*)	69 (N/A)	73	6
Koerts et al. (2013)	PMI, E	WM (+) RI (+)	48 (28 M 20 F)	63	5.5
Lee et al. (2019)	E	WM (+)	415 (245 M 170 F)	62	2.5
Rouillard et al. (2017)	E, LT, SOS	VPS (+) WM (+)	49 (27 M 22 F)	66	6.5

*Note. CRIq = Cognitive Reserve Index questionnaire, E = Education, PMI = Premorbid Intelligence, LT = Leisure Time, SOS = Socio-occupational Status, SE = Social Engagement, LEQ = Lifetime Experiences Questionnaire, VT = Vocabulary Test, RA = Reasoning Ability, RI = Response Inhibition, VPS = Visual Processing Speed (assessed using a proxy that may have confounded with learning and motor speed), WM = Working Memory, + = denotes a positive relationship with cognitive reserve, - = denotes a negative relationship with cognitive reserve, * = denotes no significant relationship with cognitive reserve, M = Male, F = Female. MA = Meta Analysis.*

1.5 Relationship between Levodopa and Motor Function

As explained previously, levodopa has a known positive effect on PD motor functioning given it is administered to improve movement (Rao et al., 2006). Most studies use the easy to administer UPDRS-III to examine motor performance and very few used specific motor assessments (see Table 3). Bradykinesia, assessed by finger tapping frequency, is less severe following levodopa treatment ('ON' state), but still more impaired than in healthy individuals (Michely et al., 2012). Levodopa also allows faster movement, reducing rigidity, and therefore decreasing the intensity of bradykinesia (Mancici et al., 2007). Consistent improvements for patient sway and reduced centre of pressure area in dynamic settings, assessed by the BBS and laboratory-grade force platforms, also occurs ON levodopa (Mancici et al., 2007; Palmisano et al., 2020; Workman et al., 2019). Static balance, however, does not appear to be significantly influenced (Workman et al., 2019). Accelerometry and surface electromyography devices have been used to measure tremor amplitude, regularity and coherence, which are greater in the 'OFF' state, after levodopa withdrawal (Blahak et al., 2007; Sturman et al., 2004).

Gait analyses revealed levodopa improves gait parameters stride length, step velocity and step time asymmetry (Galna et al., 2015; Palmisano et al., 2020). Levodopa also helps patients maintain control over freezing of gait, if this symptom occurs (Zibetti et al., 2017). Motor processing speed can be preserved with levodopa, although first time intake does not provide significant benefits (Müller et al., 2000). It is suggested that a lack of neurodegeneration in early-stages of PD causes this, only providing a beneficial effect over time for patient motor processing speed. Levodopa also improves motor processing speed by reducing impairment of readiness to respond (Jahanshahi et al., 1992), suggesting improvement with levodopa may occur by heightening alertness.

UPDRS-III scores ON and OFF levodopa seem dependent on disease duration, levodopa dosage amount and length of levodopa usage. Later-stage patients ON levodopa perform 15-30% better on the UPDRS-III but experience more motor fluctuations and dyskinesias (Rosqvist et al.,

2018). Dyskinesias also occur more frequently for patients on a high levodopa dosage, indicating the presence of the wearing-off effect (Obeso et al., 2000; Schapira, 2005). Studies using the UPDRS-III also found that levodopa appears to drastically reduce motor impairment especially for first time users of the drug (Cilia et al., 2020; Müller et al., 2000). These beneficial effects become less pronounced with extended years of levodopa use (Cilia et al., 2020).

Table 3

Reviewed Studies Investigating Levodopa's Influence on Parkinson's Disease Patient Motor Functioning

Study	Patient First Time Levodopa Intake	Measured Motor Ability (Relationship with Levodopa)	Sample Size (Gender)	Mean Age (Years)	Mean Year Disease Duration
Blahak et al. (2007)	No	U (+) T (+)	9 (6 M 3 F)	70	13
Cilia et al. (2020)	Yes	U (+)	30 (19 M 11 F)	64	7
Galna et al. (2015)	No	U (+) T (+) G (+)	121 (81 M F 40)	67	N/A
Jahanshahi et al. (1992)	No	MPS (+)	8 (5 M 3 F)	61	8
Mancici et al. (2007)	No	U (+) Br (+) Ba (+) G (+)	14 (N/A)	66	13
Michely et al. (2012)	No	U (+) Br (+) MPS (*)	17 (12 M 5 F)	62	8
Müller et al. (2000)	Yes	U (+) MPS (+)	31 (24 M 7 F)	58	N/A
Palmisano et al. (2020)	No	U (+) Ba (+) G (+)	13 (8 M 5 F)	62	N/A
Rosqvist et al. (2018)	No	U (+)	30 (N/A)	N/A	N/A
Sturman et al. (2004)	No	U (*) T (+)	10 (5 M 5 F)	53	N/A
Workman et al. (2019)	No	U (+) Ba (+)	16 (12 M 4 F)	67	N/A
Zibetti et al. (2017)	No	U (+)	32 (22 M 10 F)	68	14

*Note. U = Unified Parkinson's Disease Rating Scale-Third Subscale, Br = Bradykinesia, MPS = Motor Processing Speed, Ba = Balance, T = Tremor, G = Gait, + = denotes a positive relationship with levodopa, - = denotes a negative relationship with levodopa, * = denotes no significant relationship with levodopa, M = Male, F = Female.*

1.6 Relationship between Levodopa and Fluid Intelligence

Recently dopamine has been suggested to influence fluid intelligence in addition to motor control and learning (Cohen et al., 2002). The most commonly assessed fluid intelligence component, working memory, is provenly manipulated by dopamine (Arnsten, 2015; Howes et al. 2017; Perlstein et al. 2001). This occurs indirectly as the prefrontal cortex, which controls some fluid abilities, interacts with basal ganglia dopamine (Klaus & Pennington, 2019). Considering this relationship, fluid abilities associated with working memory, are also likely to be dopamine-dependent. Working memory has a capacity limit relevant to complex tasks and contributes to reasoning ability, a construct highly related to intelligence (Cools & D'Esposito, 2011). Further, reasoning ability has a strong positive correlation with verbal and spatial working memory tasks (Süß et al., 2002), along with three visual processing speed tests (Deary et al., 1989). This shows the interconnectedness between fluid components and implies all are affected by dopamine similarly to working memory.

However, levodopa's effectiveness for reducing PD fluid intelligence impairments is inconsistent and reviewed research mostly focused on working memory (see Table 4). It is hypothesised that PD patient's impaired working memory improves ON levodopa through greater dopamine levels increasing connectivity between the caudate nucleus and right parietal cortex (Simioni et al., 2017). This successively reflects changes on prefrontal cortex neural circuits (Cooper et al., 1992). Levodopa withdrawal after extended use causes working memory impairments to worsen, while first time levodopa users experience a rapid working memory performance boost (Fournet et al., 2000; Lange et al., 1992; Cooper et al., 1992). Nevertheless, there is evidence suggesting negative effects of levodopa on working memory for trials with a greater delay (Fallon et al., 2019). PD patients ON levodopa are more likely to make misbinding errors when working memory task delay is longer, causing excessive hippocampus activity and recall corruption (Fallon et al., 2018; Pertzov et al., 2012). Cools et al. (2010) also found that patients taken OFF levodopa were less susceptible to working memory task distractions, although levodopa improved backwards digit

span performance. This likely reflects low striatum dopamine levels and possible upregulated frontal dopamine levels, causing enhanced distractor resistance but weaker backwards digit recall OFF levodopa (Cools et al., 2010). Levodopa may therefore impact distinct aspects of working memory differently. Further null effects of levodopa on working memory also occurred (see Table 4).

PD patients generally have impaired visual processing speed that does not change while ON levodopa, requiring a long stimulus presentation time (Johnson et al., 2004). In reasoning ability tasks PD patients OFF levodopa perform significantly worse, experiencing time and accuracy deficits (Lange et al., 1992). This is consistent with the idea that similar levodopa effects should present for working memory and reasoning ability considering their relationship (Cools & D'Esposito, 2011). Furthermore, no significant differences in stop signal reaction time scores ON and OFF levodopa in Go/NoGo tasks were present for PD patients (Leroi et al., 2013; Obeso et al., 2011). Although Manza et al. (2017) did find better response inhibition ON levodopa, but with very early stage patients who likely had less severe impairments. This indicates a possible interaction between disease duration, levodopa and fluid intelligence. Furthermore, studies that investigated impulsivity using Go/NoGo response inhibition tasks found that first time intake patients with a shorter disease duration experienced greater performance benefits on the task in the ON state (Kübler et al., 2019; Leroi et al., 2013). It is possible that these benefits are not seen in patients with longer disease duration because they are experiencing the levodopa wearing-off effect. Ultimately, levodopa's effect on PD patient fluid intelligence is unclear, likely because of limited research and lack of consistent findings.

Table 4

Reviewed Studies Investigating Levodopa's Influence on Parkinson's Disease Patient Fluid Intelligence

Study	Patient First Time Levodopa Intake	Measured Fluid Ability (Relationship with Levodopa)	Sample Size (Gender)	Mean Age (Years)	Mean Year Disease Duration
Cools et al. (2010)	No	WM (*)	15 (7 M 8 F)	65	8
Cooper et al. (1992)	Yes	WM (+)	25 (13 M 12 F)	58	2
Fallon et al. (2019)	No	WM (-)	20 (12 M 8 F)	71	N/A
Fournet et al. (2000)	No	WM (+)	12 (4 M 8 F)	64	9
Johnson et al. (2004)	No	VPS (*)	20 (13 M 7 F)	65	N/A
Kubler et al. (2019)	No	RI (-)	27 (15 M 12 F)	61	5
Lange et al. (1992)	No	WM (+) RA (+)	10 (8 M 2 F)	59	10
Leroi et al. (2013)	No	RI (*)	55 (39 M 16 F)	63	8
Manza et al. (2017)	No	RI (+)	20 (12 M 8 F)	64	3
Obeso et al. (2011)	No	RI (*)	17 (12 M 5 F)	69	10
Simioni et al. (2017)	No	WM (+)	19 (N/A)	66	7

*Note. RA = Reasoning Ability, RI = Response Inhibition, VPS = Visual Processing Speed, WM = Working Memory, + = denotes a positive relationship with levodopa, - = denotes a negative relationship with levodopa, * = denotes no significant relationship with levodopa, M = Male, F = Female.*

1.7 Past Study Issues and Relevance of Current Study

Despite being insightful previous CR and levodopa PD research contain multiple measurement issues. Since CR is a relatively new concept specifically designed CR measures have only been recently developed (Hindle et al., 2014; Nucci et al., 2012). Early CR research used independent proxies, like education or occupation, allowing assessment of a somewhat indiscernible construct (Lewis-Beck et al., 2004). Such proxies have been proven to not fully capture CR, lacking reliability and accuracy compared to newer comprehensive measures (Guzzetti et al., 2019; Hindle et al., 2017; Nucci et al., 2012). For example, proxy 'years of education' usually only captures early-life CR, not across the lifespan (Malik-Ahmadi et al., 2017). Psychometrically validated measures like the CRIq can capture CR across the lifespan and assess multiple CR dimensions (Ciccarelli et al., 2018; Hindle et al., 2017; Nucci et al., 2012). Further, common proxy education yields no additional insights above and beyond the CRIq (Guzzetti et al., 2019).

Furthermore, motor functioning was most frequently assessed using the UPDRS-III, a PD clinical diagnostic tool (Goetz et al., 2008). Despite being a clinical tool it is used often in research as it is cheap and quick to administer, although it cannot discern subtle motor differences. UPDRS-III imprecision occurs as ratings with the scale are completed with a subjective, four-point Likert scale. Past literature identified significant tremor, stride length, and balance differences ON and OFF levodopa when using precise motor measures where the UPDRS-III revealed none (Nova et al., 2004; Schaafsma et al., 2003). Goetz et al. (2002) also proved that the subjectiveness of the UPDRS-III causes significant variability in ratings depending on interpreter ability. Raters would classify PD patients as less impaired when ON placebo medication compared to OFF, despite no real motor change. Finally, fluid intelligence comprises of a range of abilities (Horn & Cattell, 1966) but frequently only working memory is used, meaning fluid intelligence is rarely captured completely. The current study aims to investigate whether CR moderates levodopa's effect on PD motor and fluid intelligence performance. This variable interaction is lacking research in PD, meaning the present study may help decipher whether CR is a protective factor that may associate with varying

outcomes for different levodopa conditions. Additionally, the study will aim to identify whether other potentially confounding variables like age, levodopa dosage, and disease duration also influence PD levodopa responsiveness, as well using more precise measurement tools than in previous research.

Chapter 2

Method

2.1 Participants

Six PD patients (*4 male, 2 female; mean age = 72 years, range = 49-86 years; mean disease duration = 8 years; mean levodopa equivalent dose = 787.17mg, range = 200-1873mg*) who never experienced deep brain stimulation were recruited from Parkinson's SA advertisements. Data collection period was limited, meaning obtaining a large enough sample for run statistical analyses was not possible. Thus, 30 age-matched healthy controls (*12 males, 18 females; mean age = 65 years*) who underwent same protocols were also only used to compute PD patient composite scores for CR, motor and fluid abilities using principal components analysis (PCA).

Once we estimated the six patients' CR, motor and fluid abilities, composite scores and demographics were applied to produce 80 simulated PD patients. Simulated data used the 'fakeData' R function to produce this new dataset resembling, but not identical to, the existing six PD patients (see Appendix A; Bates & Estabrook, 2016). That is, the algorithm artificially expanded the original dataset while maintaining the existing correlations between variables.

Participation eligibility included having a prior PD diagnosis (PD patients only), permission from neurologist to go OFF levodopa (PD patients only) (Appendix B), being fluent in English and having no diagnosed learning disability. Informed consent was provided in the pre-testing questionnaire and in the testing lab. Ethical approval was granted by the Human Research Ethics Committee, of the University of Adelaide, under approval number H-2016-219 (see Appendix I).

2.2 Procedure

First it should be noted that the current study was a small portion of a much larger study, using select larger study components. Participants completed a 30 minute online questionnaire prior to testing of motor and cognitive function. Before the questionnaire participants were sent study details (see Appendix C), notified of voluntary participation, and asked for informed consent (see

Appendix D). For the current study demographics, age, disease information (PD patient only), levodopa dosage (PD patient only), and CRIq scores were obtained from the questionnaire. After completion of the questionnaire, PD patients scheduled two testing appointments, one ON levodopa and one OFF on another day, in random order, while healthy controls scheduled one session. Testing occurred in the morning for both PD patient sessions, maintaining consistency and minimising time OFF levodopa. Before testing participants were screened for COVID-19, told study proceedings, asked to give written consent, and given right to withdraw. Participants then self-sufficiently completed four fluid intelligence tests and one motor assessment on an iPad, before completing four motor measures and one fluid intelligence evaluation with a researcher. Participants were thanked and compensated with a gift card.

2.3 Measures

2.3.1 Cognitive Reserve Measures

CR was assessed through the CRIq and a vocabulary test. For PD patients the CRIq was completed online before their appointments (presumably ON levodopa) while the vocabulary test was completed in the laboratory ON and OFF levodopa.

2.3.1.1 Cognitive Reserve Index questionnaire

The CRIq assesses three subscales (CRI-Education, CRI-Working Activity, and CRI-Leisure Time) related to lifetime mental engagement, creating a total score ranging from 70 (low CR) to 130 (high CR). The CRIq is one of few standardised and psychometrically controlled measures of CR (Nucci et al., 2012; Guzzetti et al., 2019). It is proven to measure CR efficiently and as intended, displaying significant positive correlations with age and differs as a construct from intelligence, only exhibiting a moderate correlation (Nucci et al., 2012).

2.3.1.2 Crystallised Intelligence

The Spot-the-Word vocabulary test (Baddeley et al., 1993) assessed crystallised intelligence as a premorbid intelligence CR proxy. Participants are tasked with identifying which of two words are real and the test comprises 60 pairs total. PD patients completed either the odd or even items ON

and OFF levodopa, where the items change in the second testing period to avoiding learning possibly confounding scores. Correctly identified words were scored with one point and incorrect zero, meaning scores ranged from 0 to 30. Healthy controls also completed a random 30 items. A crystallised intelligence measure was a reasonable CR proxy as it is proven to not significantly change over the duration of PD or with the onset of PD (Bašić et al., 2014), and is not significantly impacted by levodopa (Cooper et al., 1992).

2.3.2 Motor Measures

Motor ability was assessed with five motor functions: bradykinesia, motor processing speed, balance, tremor and gait. PD patients completed all motor measures ON and OFF levodopa, healthy controls completed measures once.

2.3.2.1 Bradykinesia

Bradykinesia was measured using a Tapping Test on an iPad that records how fast an individual can move their index finger to repeatedly tap two dots within a period of 30 seconds, where more taps indicate less bradykinesia (see Figure 1). Both hands are tested, starting with the participants dominant hand. The Tapping Test also indexes rigidity.

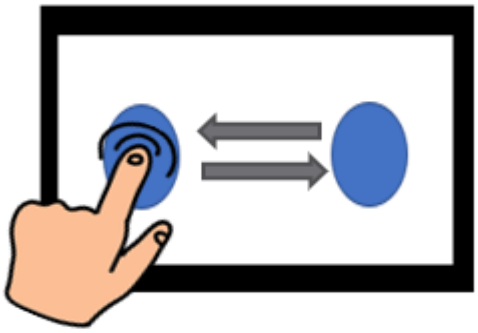

Figure 1. Tapping Test sequence: index finger taps one blue dot before tapping the opposing one, process is completed repeatedly.

2.3.2.2 Motor Processing Speed

A two-choice reaction time task was used to calculate motor processing speed (see Figure 2). Participants completed a total of 40 trials on the iPad with pre-determined sequence of intervals between response and next stimulus varying from two to six seconds. This test is slightly different than a basic reaction time task as it includes both reacting to the stimulus and moving to it. Quicker times indicate better motor processing speed.

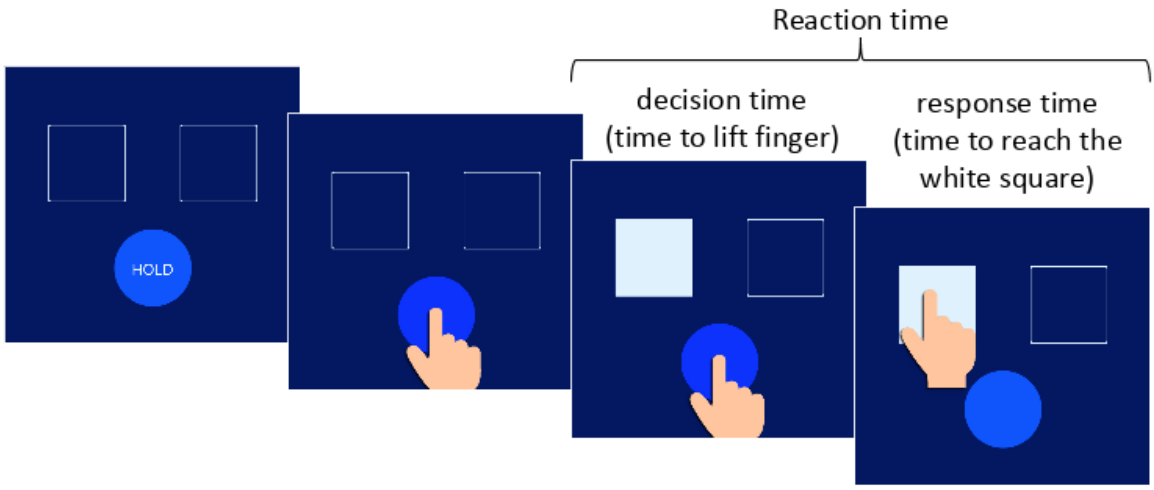

Figure 2. Two-choice Reaction Time task sequence example: displaying participant holding a blue button with their index finger and reacting to the specific white square that lights up white by removing their index finger and touching the select white square.

2.3.2.3 Balance

Balance was assessed using a Nintendo® Wii Balance Board and custom recording software Wowii, which was previously developed in the laboratory. Participants stand on the board for 30 seconds while staring at a red dot two metres away and 1.75 metres high. Two versions of the test are completely separately, feet-together and feet-apart, and conducted in random order. The Wowii program measures weight distribution and movement using the board's four pressure sensors to determine centre of pressure. This allows tracking of changes in position over time, developing a unique participant path length. A 95% ellipse area around the path was calculated, such that the size of the ellipse captured 95% of the centre of pressure path length for the participant across the 30-second period. The size of the ellipse was used to index postural stability, with smaller ellipse sizes

indicating better balance. This study only used the data from the feet-together test, which is more difficult and generates larger individual variability. The Wii Balance Board performs almost identically to laboratory-grade force platforms among many standing balance parameters (Negus et al., 2019), displaying excellent concurrent validity and between-device test-retest reliability (0.77-0.89) (Clark et al., 2010). This has been further corroborated by Huurnink et al. (2013) for healthy individuals and by Holmes et al. (2013) for PD patients.

2.3.2.4 Tremor

Tremor was measured using a Nintendo® Wii Controller and Wowii. Participants sit, remain still and hold the controller limply for 60 seconds while Wowii records accelerometer data reflecting remote movement. This assessment occurs separately, twice, in 60 second periods per hand (order is randomly determined). Since PD tremor correlates highly with theta band change (Asch et al., 2020) level of tremor was measured by theta power proportion. This parameter represents activity in the theta band frequency (3-7 Hz) for hand oscillations, where higher theta power proportions indicate more severe tremor. Correlations between Wii controller tremor amplitude scores, as residual magnitude, and self-rating tremor scores have been found (Synnott et al., 2012). Additionally, resting tremor scores measured using the Wii controller and the Hoehn and Yahr PD scale are consistent (0.89 internal-reliability) (Koçer & Oktay, 2015), further suggesting this measure accurately captures tremor.

2.3.2.5 Gait

Gait was measured using the most widely used gait sensor tool G-walk (Vítečková et al., 2020), an inertial sensor that can capture different gait parameters for PD patients (Zago et al., 2018). Compared to the 'gold standard' gait measurement, GAITRite, G-walk produces near identical results when assessing PD patients (Vítečková et al., 2020). This makes G-walk almost as accurate and reliable as GAITRite while being cheaper and not requiring a large testing area (Vítečková et al., 2020). In the current study participants complete an eight metre walk twice, before doing the same

task a second time. Parameter stride length relative to height was assessed as this factor seems to consistently elicit significant differences between healthy controls and PD patients with G-walk (Vítečková et al., 2020).

2.3.3 Fluid Intelligence Measures

Fluid intelligence was tested across four different abilities: working memory (two tests), visual processing speed, reasoning ability, and response inhibition. PD patients completed these tests ON and OFF levodopa, excluding one patient who did not finish the response inhibition task and another patient who did not complete the reasoning ability assessment. Healthy controls completed tests once.

2.3.3.1 Visual Working Memory

The dot matrix task is a visual working memory assessment that identifies storage capacity of working memory and resistance to interference (Law et al., 1995). The task requires participants to recall the location of a series of dots on a 5x5 grid, while indicating whether a basic math problem (interference) is 'TRUE' or 'FALSE' (see Figure 3). Two versions of the task with similar difficulty items allow task completion twice ON and OFF levodopa without learning confounding performance. Each version includes 16 unique items with four items per level, where a level increase requires participants to recall an increasing number of dots (from 2 to 5). The test ended if participants were less than 75% correct in identifying dot locations, per level. One point was awarded per correct dot recall.

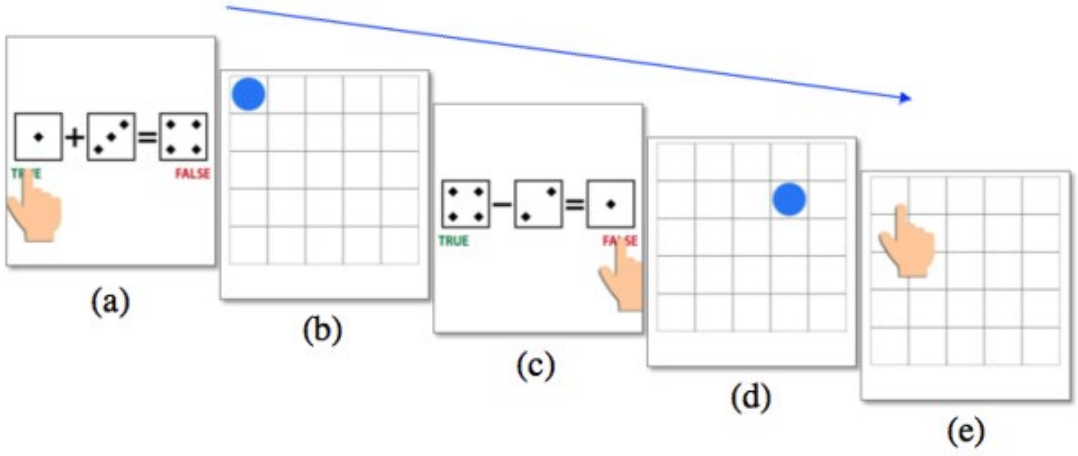

Figure 3. Example of the sequence of the Dot Matrix task for level 2 dots: (a) Basic math problem (b) First dot location presented (c) Second basic math problem (d) Second dot location presented (e) Recall of dot locations from (b) and (d) by selecting points on empty grid.

2.3.3.2 Verbal Working Memory

The digit span task is a verbal working memory task measuring storage capacity and influence of information manipulation. It is administered forwards (recalling number sequences as presented) and then backwards (recalling number sequences in backwards order). The forward digit span consists of 16 items varying from two, to nine digits per sequence, and the backwards digit span comprises of 14 items, from two to eight digits in each sequence. Each level (number of digits per sequence) has two items, and testing discontinues if both items are incorrectly recalled. To maintain testing consistency, digits are read out by a recording that kept a steady pitch and pronounced one digit per second. One point is awarded per correctly recalled sequence.

2.3.3.3 Visual Processing Speed

Visual processing speed was assessed via inspection time, the shortest exposure duration required to input information and identify stimulus direction (Nettlebeck, 2001). Participants indicate the direction of an arrow (stimulus) presented before it is covered by a pattern backward mask arrow (see Figure 4). Participants underwent 90 trials, half of which showed a left arrow and the other half, a right arrow. A Bayesian algorithm adjusts the duration of the stimulus required for 75% correct

response rate: lengthening the duration if there are too many incorrect responses and shortening it if there are too many correct responses. 30 easy trials (stimulus duration of 450ms) were included to ease frustration. This task can measure processing speed without motor or learning confounding results. Scores are given in milliseconds, where smaller values indicate a faster visual processing speed.

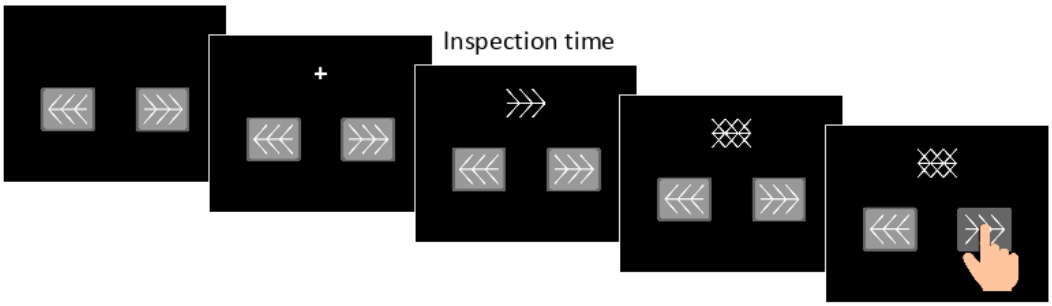

Figure 4. Inspection Time sequence example: display the onset of the stimulus before the mask covers the original stimulus direction and the two pressable keys used to indicate the direction of the stimulus presented.

2.3.3.4 Reasoning Ability

Reasoning ability was assessed using Raven's Progressive Matrices (Raven et al., 2003), a non-verbal intelligence test. It contains 36 items, where 18 items are administered per session, allowing patients to be tested ON and OFF levodopa with different items. Difficulty of the two 18-item sets are matched. In this test participants identify the missing item that completes the presented pattern (see Figure 5). One point is awarded per correct item selection.

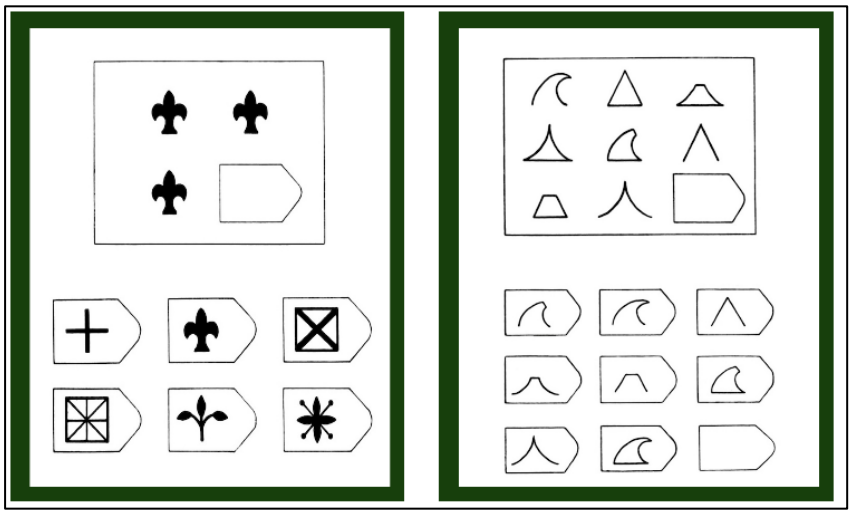

Figure 5. Two example items from Raven's Progressive Matrices: the top square of each item displays the incomplete pattern, while the six or nine shapes below are the selectable options, one of which completes the pattern above.

2.3.3.5 Response Inhibition

Response inhibition was measured with a Stop Signal Task. Participants were shown two arrow buttons, and on each trial were shown a singular arrow (Go signal) that would remain the same (Go signal) or another arrow cover it (Stop signal) (see Figure 4). The participant's task is to press the button corresponding to the Go signal quickly, but to inhibit this response when the Stop signal is shown. There are 120 Go trials and 60 Stop trials randomly intermixed. The duration of the interval between Go and Stop signals on Stop trials is adjusted by a Bayesian algorithm that finds the interval that results in 50% successful inhibitions (the critical Stop Signal Delay, SSD). This delay interval can vary between 50ms and 550ms, and each trial begins with an inter-trial interval of one second. A participant's Stop Signal Reaction Time, which is the difference between the average Go reaction time on Go trials and the critical SSD, determines response inhibition ability (see Figure 6).

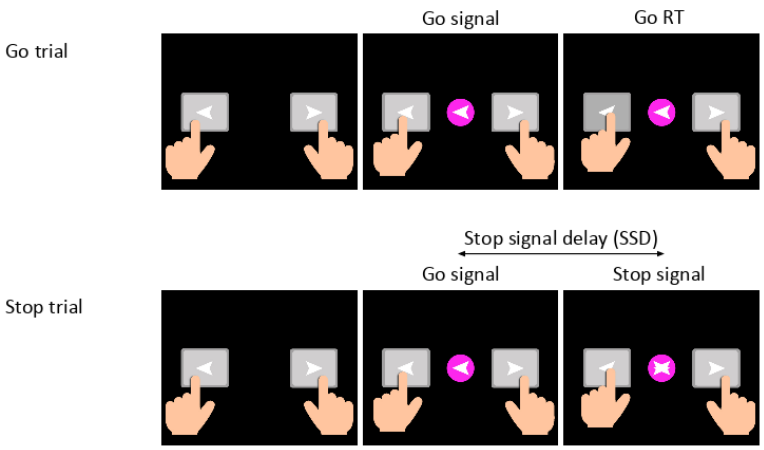

Figure 6. Stop Signal Task trials (Go and Stop trials): the go trial demonstrates a participant having to select a direction while the stop trial displays having to inhibit one's response due to another arrow appearing.

Chapter 3

Results

3.1 Principal Components Analysis: Cognitive Reserve, Motor Functioning, and Fluid Intelligence

PCA (Jollife, 2002) was chosen to develop composite scores for CR and motor and fluid intelligence difference scores ON and OFF levodopa. Hatcher (1994) recommended a PCA needs a sample size five times larger than the number of variables. Since we only had six PD patients and up to five variables per PCA, a minimum sample of 25 was required. Therefore, the 30 age-matched healthy controls were used to help anchor composite score development for the six PD patients. These healthy controls were purposefully selected as they had similar age distribution as the six PD patients (see Appendix E, Figure E1) and they completed the same testing. The PD patients (*M = 72, SD = 12.47)* and the healthy controls (*M = 65.2, SD = 8.75)* did not significantly differ in age, $t(6) = -1.27$, $p = 0.25$. One PCA was conducted for CR, while two (ON and OFF levodopa) were performed for both motor and fluid intelligence performance so composite difference scores could be calculated. That is, the data from the 6 patients tested ON levodopa were combined with that of the healthy controls in one set of PCAs, and their data OFF levodopa were again combined with that of the healthy controls in another set of PCAs. This allowed us to estimate their cognitive and motor performance in the ON and OFF states relative to the healthy controls.

3.1.1 Cognitive Reserve PCA

CR measures CRIq and Spot the Word displayed a positive correlation of 0.29, justifying derivation of a single CR estimate. Only ON scores for CR measures were used as the CRIq was only ON for patients and patient Spot the Word scores did not change with levodopa (ON: *M = 27.42, SD = 1.76,* OFF: *M = 27.37, SD = 1.77)*[1]. This is consistent with Cooper et al. (1992), who found no significant difference in PD patient crystallised intelligence tests relating to levodopa state.

[1] Significant difference testing was not possible here as the PD patient sample size was too small, and perhaps unnecessary considering the almost equivalent group means.

Therefore, scores ON levodopa for CR measures were used in the PCA. Table 5 summarises the CR PCA solutions for the first unrotated component, possessing eigen value of 1.32 and accounted for 66% of variance between CR assessments. From this point onwards, participant's CR composite scores are referred to as 'CR-scores'.

Table 5

Principal Components Analysis for Cognitive Reserve

Cognitive Reserve Measure	Loading
Cognitive Reserve Index questionnaire	0.81
Spot the Word	0.81

3.1.2 Motor PCAs

Scores on the five motor abilities correlated with one another in the expected directions (see Appendix F, Tables F1 and F2). Table 6 summarises the motor PCA solution ON levodopa, with the first unrotated component having an eigen value of 2.00 and accounting for 40% of the variance in the five measures. Table 7 summarises the motor PCA solutions OFF levodopa, with the first unrotated component having an eigen value of 2.13 and accounting for 43% of the variance in the five measures. Hereafter participant motor component scores, identified as 'MotorON-scores' and 'MotorOFF-scores', were used to estimate motor functioning (see Appendix G, Figure G1), for the distribution of scores for patients and healthy controls).

Table 6

Principal Components Analysis for Motor Functioning ON levodopa

Motor Measure	Loading
Tapping Frequency	0.80
MPS	-0.67
Balance (Ellipse)	-0.32
Tremor (TPP)	-0.57
Gait (SLRH)	0.70

Note. MPS = Motor Processing Speed. *TPP* = Theta Power Proportion. *SLRH* = Stride Length Relative to Height. Lower scores for Motor Processing Speed, Balance, and Tremor indicate better motor functioning.

Table 7

Principal Components Analysis for Motor Functioning OFF levodopa

Motor Measure	Loading
Tapping Frequency	0.74
MPS	-0.80
Balance (Ellipse)	-0.34
Tremor (TPP)	-0.67
Gait (SLRH)	0.62

Note. MPS = Motor Processing Speed. *TPP* = Theta Power Proportion. *SLRH* = Stride Length Relative to Height. Lower scores for Motor Processing Speed, Balance, and Tremor indicate better motor functioning.

3.1.3 Fluid Intelligence PCAs

The fluid intelligence measures correlated with each other in the expected direction (see Appendix F, Tables F3 and F4), justifying the use of PCA to combine them. Table 8 summarises fluid intelligence PCA solution ON levodopa for the first unrotated component, possessing an eigen value of 2.05 and accounting for 41% of measure variance. Table 9 summarises the fluid intelligence PCA solution OFF levodopa for the first unrotated component, displaying an eigen value of 2.15, and accounting for 43% of measure variance. Henceforth participant fluid intelligence scores for the first unrotated component in each PCA are referred to as 'GfON-scores' and GfOFF-scores' (see Appendix G, Figure G2), for the distribution of scores for patients and healthy controls).

Table 8

Principal Components Analysis for Fluid Intelligence ON levodopa

Gf Measure	Loading
Dot Matrix	0.77
Digit Span	0.58
Inspection Time	-0.45
RPM	0.64
SST	-0.71

Note. RPM = Raven's Progressive Matrices. *SST* = Stop Signal Task. Lower scores for Inspection Time and the Stop Signal Task indicate better fluid intelligence.

Table 9

Principal Components Analysis for Fluid Intelligence OFF levodopa

Gf Measure	Loading
Dot Matrix	0.66
Digit Span	0.53
Inspection Time	-0.65
RPM	0.71
SST	-0.71

Note. RPM = Raven's Progressive Matrices. *SST* = Stop Signal Task. Lower scores for Inspection Time and the Stop Signal Task indicate better fluid intelligence.

3.2 Generating the Final Dataset

3.2.1 Difference Score Development and Creation of the Dataset to be Simulated

Since current study aimed to investigate whether CR is associated with levodopa responsiveness, difference scores for motor and fluid intelligence were calculated. The difference between MotorON-scores and MotorOFF-scores is referred to as 'MotorDiff-scores', while the difference between GfON-scores and GfOFF-scores was labelled 'GfDiff-scores'. Disease duration and levodopa equivalent dose (LED) for the six PD patients were also included in the dataset, meaning four (age, CR, LED, disease duration) predictor variables were selected for data simulation alongside the outcome variables MotorDiff-scores and GfDiff-scores. Note, however, that disease duration was later removed from the set of predictors as it generated large variance inflation factor values (see section 3.4), and gender was not used in the simulation as the function used can only simulate continuous variables.

3.2.2 Data Simulation Process

In order to perform regression analyses to test the relationship between CR and motor and fluid intelligence change with levodopa a sample larger than six was required. An appropriate sample for regression analyses avoids confusion and low reproducibility of findings (Jenkins & Quintana-Ascencio, 2020), while reducing margin of error (Campbell, 2019). According to Jenkins & Quintana-Ascencio (2020), there should be a minimum of eight observations per variable but ideally a sample of 25 per variable. Furthermore, a power analysis using the software G*Power was also used to justify the size of the simulated sample. To detect an effect size (f^2) of 0.15 at an alpha (significance) level of 0.05, and accounting for three predictors, a simulated sample of 77 participants would be required to maintain an adequate power of 0.8. To simulate a larger dataset based on the smaller real dataset, a data simulation code, called 'fakeData' (Bates & Estabrook, 2016), was utilised in R. This code used the original data from the six patients and to simulate a greater number of participants that maintained resemblance of the original dataset (Bates & Estabrook, 2016). To meet the requirements of Jenkins & Quintana-Ascencio (2020) and G*Power without generating an unreasonably large sample, a dataset with 80 simulated PD patients was produced.

3.2.3 Correlation Similarities between Original and Simulated Data

Correlations between all predictors and outcome variables for the six PD patients from the original dataset are displayed in Table 10. The same relationships for the 80 simulated PD patients can be viewed in Table 11. The correlations in the simulated dataset maintained relationship direction and were of similar strength, fittingly resembling the original six patient dataset. Visualisation of the relationships of interest (correlation between predictor CR-score and dependent variables MotorDiff-score and GfDiff-score) further support similarity of the simulated dataset (see Figures 7 and 8).

3.3 Correlations between Predicting Variables and Difference Scores

Considering the simulated data as representative, we henceforth analysed the simulated data. Age displayed a significant positive relationship with MotorDiff-score, but a significant negative correlation with GfDiff-score (see Table 11). This indicates a greater age results in a larger difference in motor performance ON and OFF levodopa. CR-score presented a non-significant positive relationship with MotorDiff-score, but a significant negative correlation with GfDiff-score (see Figures 7 and 8). Consequently, a better CR appears to result in less fluid intelligence change ON versus OFF levodopa, where lower CR PD patients were more likely to have their fluid intelligence performance altered more by levodopa than higher CR PD patients. LED showed a significant positive correlation with MotorDiff-scores, and a significant negative correlation with GfDiff-scores (see Table 11). A higher LED therefore appears to cause a greater difference in motor performance according to levodopa intake, while alternatively a higher LED causes less change in fluid intelligence performance between levodopa states.

Table 10

Correlations between Regression Predictors, Motor Differences, and Fluid Intelligence Differences for the Original Dataset (n = 6)

	Age	CR-score	LED	Disease Duration	MotorDiff-score	GfDiff-score
Age	-					
CR-score	0.55	-				
LED	0.65	0.54	-			
Disease Duration	0.31	0.68	0.84	-		
MotorDiff-score	0.05	0.09	0.47	0.37	-	
GfDiff-score	-0.56	-0.31	-0.56	-0.50	-0.07	-

Note. No significant correlations between variables for the original dataset given the small sample size. *LED* = Levodopa Equivalent Dose.

Table 11

Correlations between Regression Predictors, Motor Differences, and Fluid Intelligence Differences for the Simulated Dataset (n = 80)

	Age	CR-score	LED	Disease Duration	MotorDiff-score	GfDiff-score
Age	-					
CR-score	0.53	-				
LED	0.73	0.44	-			
Disease Duration	0.41	0.61	0.84	-		
MotorDiff-score	0.32	0.10	0.64	0.49	-	
GfDiff-score	-0.60	-0.35	-0.59	-0.57	-0.29	-

Note. For the simulated dataset all correlations above 0.2 are significant at an alpha level of 0.05. *LED* = Levodopa Equivalent Dose.

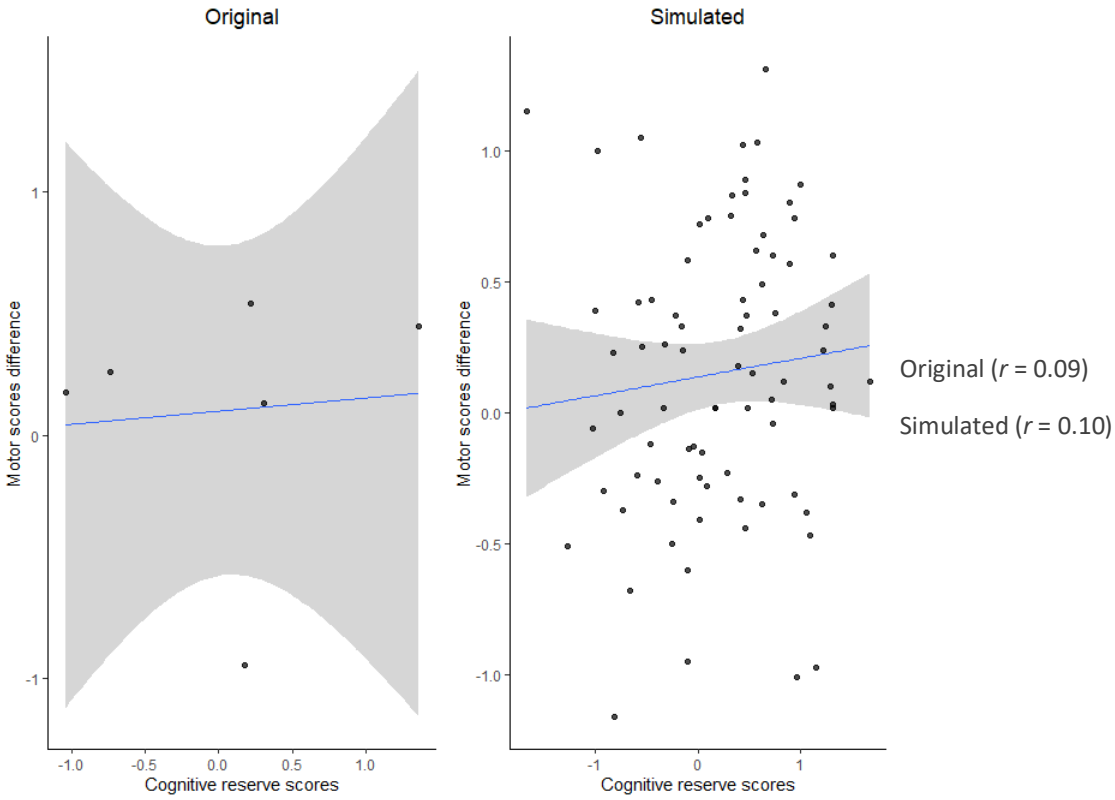

Figure 7. Scatter plots showing the correlations between cognitive reserve scores and motor difference scores for the original (*n = 6*) and the simulated patient (*n = 80*) samples.

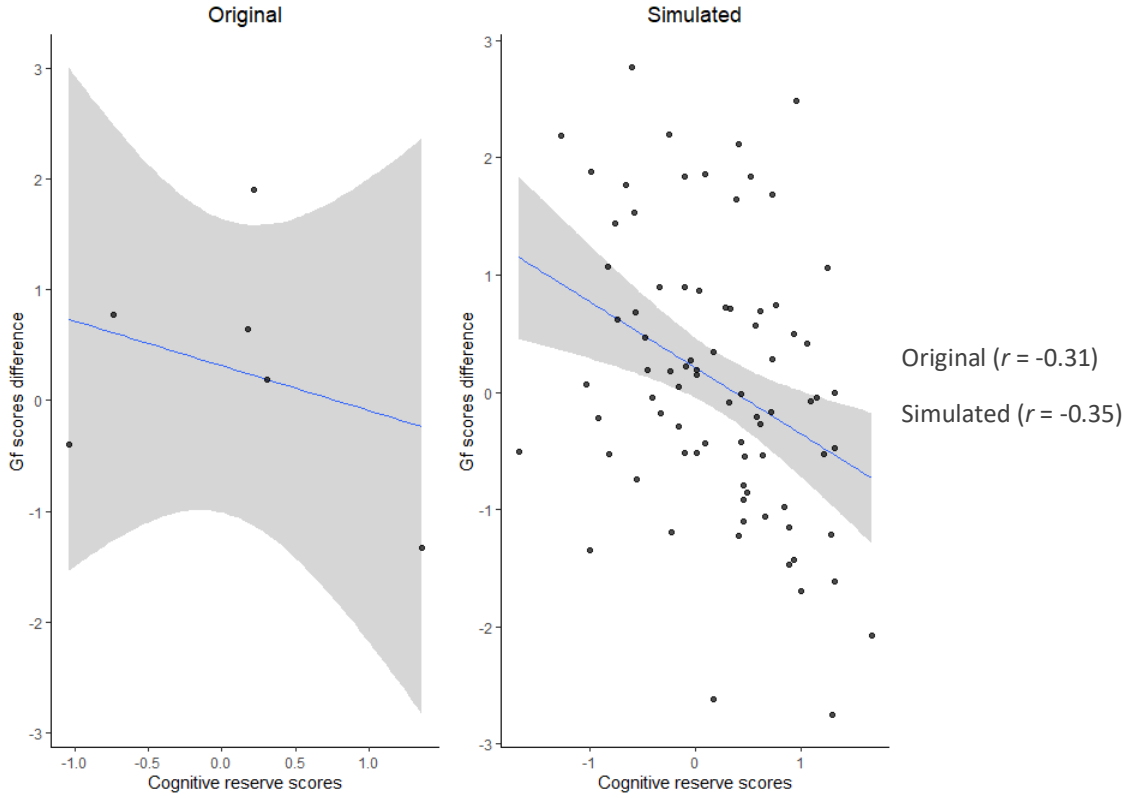

Figure 8. Gf = fluid intelligence. Scatter plots showing the correlations between cognitive reserve scores and fluid intelligence difference scores for the original (*n = 80*) and the simulated (*n = 80*) patient samples.

3.4 Regression Analyses

3.4.1 Removal of Variable Disease Duration

It should be noted that in both the original and simulated dataset disease duration and LED displayed high multicollinearity (0.84; see Tables F1 and F2). This extremely large correlation caused problems for identifying significant predictors in the simulated regression models. Predictor variables should be independent and not strongly correlate as it becomes difficult to identify predictor significance. Therefore, disease duration was removed in the conducted regression models, where related predictor LED acted as a disease duration proxy (Parkinson Study Group, 2000; Rascol et al., 2000). A variance inflation factor (VIF) assessment was performed in R using the package 'car' (Fox & Weisberg, 2019). This tests if multicollinearity is too high to conduct regression with certain predictors, where VIFs greater than 5 imply the model will have problems estimating relative predictor coefficients. Table 12 shows that, when disease duration is present,

predictor VIFs are all above five, but were less than five when disease duration is removed. This classifies predictors age, CR-score, and LED suitable for regression analyses.

Table 12

Variance Inflation Factors for Predictors Age, CR-score, LED, and Disease Duration for both Motor and Fluid Intelligence Regression Models

	Age	CR-score	LED	Disease Duration
VIF (with Disease Duration)	12.64	6.47	31.57	23.42
VIF (without Disease Duration)	2.43	1.40	2.17	-

Note. VIF = Variance Inflation Factor. VIF values larger than 5 indicate the regression model is not appropriate.

3.4.2 Motor and Fluid Intelligence Difference Regression Models

Regression analyses were utilised to predict whether a PD patient's CR moderates responsiveness to levodopa, two regression models were performed on MotorDiff-scores and GfDiff-scores. Along with CR-score being used to measure possible predictor CR in these models, the potentially confounding predictors age and LED were included. The model predicting the MotorDiff-scores was significant, $R^2 = 0.352$, $F(3, 76) = 23.13$, $p < 0.001$. However, only LED significantly predicted patient MotorDiff-scores, with higher medication doses (LED) predicting more motor improvement ON levodopa (see Table 13). Neither age or CR-score were significant predictors, though younger age was marginally associated with more motor improvement ON levodopa. The fluid intelligence (Gf) model was also significant, $R^2 = 0.4056$, $F(3, 76) = 17.29$, $p < 0.001$. Both age and LED significantly predicted performance change (see Table 13), with younger age predicting more cognitive improvement ON levodopa, but larger LED predicting worse cognitive performance ON levodopa. However, despite the significant correlation, CR-score did not

significantly influence change in fluid intelligence ON levodopa after controlling for age and LED (see Table 13).

Table 13

Multiple Linear Regression Models Predicting Confounding Variable Influence on Levodopa Responsiveness

	R^2	*B*	*SE B*	*p*
Motor model	0.3974*			
Constant		0.269	0.355	0.451
Age		-0.011	0.006	0.057
LED		0.0007	0.00009	< 0.001
CR-score		-0.123	0.073	0.099
Gf model	0.4056*			
Constant		3.091	0.822	< 0.001
Age		-0.032	0.013	0.013
LED		-0.0006	0.0002	0.016
CR-score		-0.035	0.170	0.838

Note. R^2 = change in explained variance. *B* = regression coefficient. *SE B* = standard error of regression coefficient. *Gf* = Fluid Intelligence. *CR-score* = PCA cognitive reserve composite score.

* = $p < 0.001$.

3.5 Relative Importance of Significantly Confounding Variables

Considering both regression models displayed statistical significance, tests of relative importance were conducted to distinguish which predictors contribute the most to the proportion of variance explained by the models. To conduct a relative importance test in R, the package 'relaimpo' was used (Groemping, 2006).

3.5.1 Relative Importance of Motor Model Predictors

Out of the total 39.74% of variance in motor difference scores that the motor model explains, LED accounts for the most variance. LED accounts for 39.3% of variance in motor difference scores, while other non-significant predictors age and CR-score account for 6.7% and 1.8% of variance, respectively. In terms of relative importance, LED is the main variable predicting change in motor difference scores, explaining 82% of the explained variance (see Figure 9).

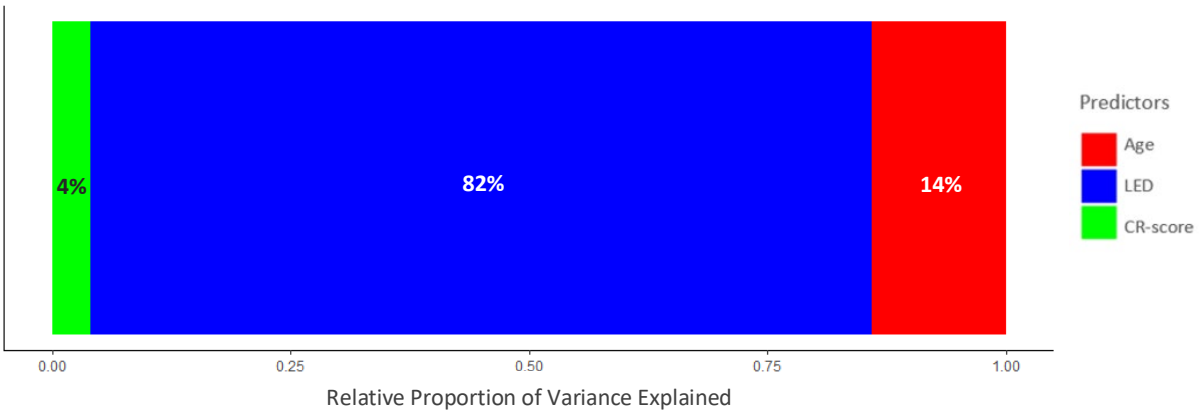

Figure 9. Relative Proportion of Variance Explained by Predictors Age, Levodopa Equivalent Dose (LED), and CR-score for change in PD patient motor functioning (Motor Model).

3.5.2 Relative Importance of Fluid Intelligence Model Predictors

Of the 40.56% of variance in fluid intelligence difference scores that the fluid intelligence model explains, age and LED are the most significant contributors. Age accounts for 18.5% and LED 17.8% of variance, while the non-significant predictor CR-score accounts for 4.2% of variance in fluid intelligence difference scores. In terms of relative proportion of explained variance, age accounted for 46%, LED 44% and CR-score 10% of the explained variance (see Figure 10).

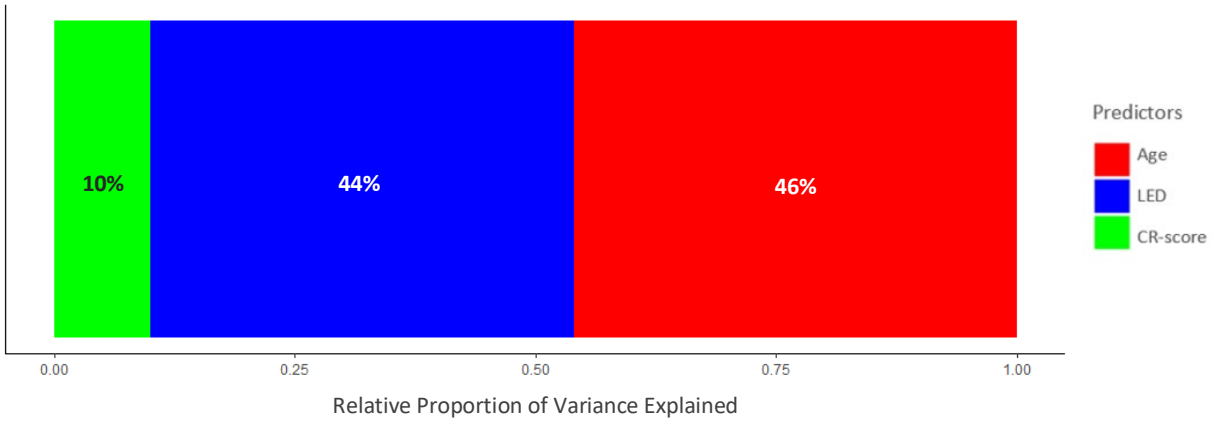

Figure 10. Relative Proportion of Variance Explained by Predictors Age, Levodopa Equivalent Dose (LED), and CR-scores for change in PD patient fluid intelligence (Gf Model).

Chapter 4
Discussion

4.1 Current Study Findings

The current study explored the role of CR on PD patient levodopa responsiveness, an interaction previously unconsidered. Possible predictive factor age and LED were also considered. Amendment for our small sample materialised through simulated data analysis that preserved original dataset relationships.

4.1.1 Effect of CR on Levodopa Responsiveness

Results revealed CR did not significantly influence motor functioning change with levodopa withdrawal. Previous research investigating CR's impact on motor functioning, without considering the change in performance with levodopa states, reported that higher CR patients had less impaired movement (see section 1.3, Table 1). Patients with more severe impairments usually encounter greater dopamine loss (Hershey et al., 2003; Mohl et al., 2017). Knowledge of this indicated higher CR patients should not respond to levodopa as efficiently, where levodopa benefits may be greater for lower CR patients with more severe impairments. Although this correlation did not occur and was not justified by our regression model (see section 3.4.2, Table 13). Therefore, by introducing levodopa, CR's effect on motor ability becomes non-existent. Perhaps then, CR's utility as a motor protective factor may only remain significant when levodopa is omitted.

Alternatively, CR showed a significant negative relationship of moderate strength with difference in fluid intelligence scores ON and OFF levodopa. Past research consistently suggested higher CR patients experience less fluid intelligence impairments (see section 1.4, Table 2). Our results support the assumption of the reserve hypothesis (Fratiglioni & Wang, 2007; Lee et al., 2019), as PD patients with a higher CR experienced less of a change in fluid intelligence performance with levodopa (see section 3.3, Figure 8). This relationship functions as expected, supported by previous findings that found higher CR results in greater resistance to neurodegeneration and preserved cognition (Guzzetti et al., 2019; Koerts et al., 2013; Lee et al.,

2019). However, when age and LED are controlled in a regression model, CR's predictive strength for fluid intelligence performance change with levodopa withdrawal becomes non-significant. As mentioned (see section 3.5.2), age and LED remained almost equal significant predictors of change in fluid intelligence performance. Considering age's contribution to fluid intelligence deterioration, especially with PD, (Jahanshahi et al., 1992; Venezia et al., 2018) and levodopa's varying influence on fluid intelligence (see Table 4), it explains CR's insignificant predictiveness. Age's influence over CR is further supported as CR does not impact fluid intelligence outcomes for older patients (see section 1.4, Table 2). Therefore, CR is unable to explain unattributable differences in levodopa responsiveness, where predictors age and LED seem more important.

4.1.2 Effect of Age on Levodopa Responsiveness

Age had a significant, but moderate positive relationship with differences in motor functioning ON and OFF levodopa. Older age patients experienced a greater levodopa benefit, where motor performance was mostly better ON levodopa. According to past research this was expected as ageing causes motor deterioration, where PD accelerates this decline (Michely et al., 2012). Greater older age patient motor differences could be attributed to levodopa's singular focus on alleviating declining motor impairments (Jahanshahi et al., 1992). Interestingly though, age cannot significantly predict differences in motor performance, when controlling for LED, likely due to LED's strong relationship with movement.

As expected, age displayed a strong negative relationship with change in fluid intelligence ON and OFF levodopa. Older PD patients experienced a significant reduction in fluid intelligence performance from levodopa, while younger PD patients experienced a considerable benefit (see Appendix H, Figure H1). Previous research identified that younger patients experience a strong initial fluid intelligence benefit from levodopa (Poletti et al., 2013). Although as patients age, levodopa's effect on fluid intelligence becomes undesirable, likely as it was not exclusively designed to treat cognitive dysfunction and PD quickens cognitive decline (Venezia et al., 2018). Furthermore, older patients could be experiencing levodopa wearing-off (Obeso et al., 2000), where negative fluid

intelligence effects may present with extended levodopa use. When CR and LED are controlled age maintains significance as a fluid intelligence change predictor, demonstrating age's strong connection with fluid intelligence and that levodopa was not designed for treating cognitive impairments. It appears fluid intelligence impairments that change with levodopa state are similarly dependent on age and LED (see Figure 10), where age only partially explains levodopa responsiveness (see section 4.2.3).

4.1.3 Effect of LED on Levodopa Responsiveness

Like age, LED displayed a significant positive relationship with change in motor functioning ON and OFF levodopa, but the correlation was far stronger. In other words, motor functioning was better improved using a higher LED. Higher LED benefits could be attributed to having PD for longer, leading to more severe symptoms (Leroi et al., 2013), and consequently resulting in enhanced levodopa benefits (Hershey et al., 2003; Mohl et al., 2017). Previous literature found motor performance is significantly enhanced by levodopa (see Table 3) and an increased LED can result in better motor outcomes (Pandey & Srivanitchapoom, 2017). Although it should be noted that LED cannot be infinitely increased to improve motor outcomes, where excess dopamine can trigger poor motor outcomes like dyskinesias as levodopa benefits plateau (Pandey & Srivanitchapoom, 2017). Therefore, identification of optimal LED for unique patients is critical for best motor outcomes (Meder et al., 2019). These results may also indicate that PD patients develop a greater levodopa reliance as disease duration increases. When controlling for variables CR and age, LED maintains its predictiveness of change in motor performance with levodopa withdrawal. This demonstrates levodopa's powerful relationship with PD cardinal symptoms, further supporting current study findings (see section 3.3) and previous research (see Table 3).

Interestingly LED showed a strong negative relationship with change in fluid intelligence ON and OFF levodopa. This indicates patients using a higher LED experienced worse fluid intelligence outcomes from levodopa, while a lower LED caused little or a slightly positive change (see Appendix H, Figure H2). These results could imply that the wearing-off effect of levodopa was

occurring (Obeso et al., 2000), but since levodopa was not intended to treat cognitive deficits an increase in LED may have caused poor fluid intelligence outcomes. Regression analyses provide clarification, where LED still predicted fluid intelligence difference performance when age was controlled. Consequently, it is unlikely the levodopa wearing-off effect occurred as it heavily relies on and is predicted by age (Obeso et al., 2000). LED's effect in the current study is consistent with Fallon et al. (2019) and Kubler et al. (2019), who found increasing LED had a negative effect on fluid abilities working memory and response inhibition. LED's significant predictiveness for both impairment outcomes suggests that of the three considered predictors, LED most significantly influences levodopa responsiveness. However, it should also be noted that LED strongly correlated with disease duration (see section 3.4.1), meaning it may be difficult to disentangle LED effects from disease duration.

4.2 Implications for Parkinson's Disease Treatment

While the current study could not identify CR as an influential predictor of levodopa responsiveness, it highlighted levodopa's positive effect on motor functioning and negative consequence for cognition. PD has been, and still is, primarily considered a motor disorder, meaning treatments like levodopa have been designed to address motor impairments (Schapira, 2005). However, PD patients present with cognitive deficits and, as discussed, increasing LED can cause adverse changes in fluid intelligence, especially for older patients. Additionally, increasing levodopa excessively to relieve motor problems can potentially prompt dopamine overdose, leading to unfavourable side effects like impulsiveness that further impair cognition (Meder et al., 2019; Obeso et al., 2000). Considering this, clinicians should be concerned with the cognitive consequences of levodopa and conduct assessments of their PD patients that evaluate motor and cognitive ability, instead of focusing on motor symptoms alone to prescribe a LED. Furthermore, for patients who appear to be experiencing amplified cognitive deficits from levodopa, different therapies should be utilised wherever possible.

Several alternative therapies could be considered to alleviate both motor and cognitive PD symptoms. PD surgery has rapidly evolved, now including destructive lesions and deep brain stimulation. These methods can offer an important therapeutic substitute to levodopa, although they are invasive, expensive, can present surgical side effects and do not benefit patient's with unique PD subtypes (Schapira, 2007). If neither surgery or levodopa are suitable, then replacement interventions like other medications, physical activity, and physiotherapy could be considered (Mak et al., 2017; Lees, 2005). Treatments other than levodopa may be more suitable for older patients already on a high LED, where a higher LED puts patients at a greater risk of developing severe cognitive impairments and may cause levodopa wearing-off (see section 4.1). Therefore, clinicians should take a holistic approach to treating PD that never prioritises only treating motor symptoms and patients may benefit from considering treatment options relative to their age. These implications, however, need to be considered with caution given study limitations, where further research is imperative.

4.3 Strengths and Limitations

4.3.1 Approaches to Analyses

The use of PCA was a strength that simplified regression analyses of broad constructs CR, motor functioning and fluid intelligence. Compared to previous research that relied on single variable measures to assess a complex factor (see chapter 1, Tables 1, 2, 3, & 4), the current study's multivariate approach could draw more expansive conclusions at a lower risk of overgeneralisation by a single measure. It could be disputed that with a multivariate approach, PCA should be dismissed in favour of multiple regression models. Although, by adding more predictors, irrespective of theoretical significance, explained variance can be infinitely raised due to regression model complexity (Keith, 2015). This can cause variance inflation of factors, where PCA helps correct this in the presence of high multicollinearity between components (Lafi & Kaneene, 1992). PCA avoids multicollinearity by introducing new uncorrelated variables to minimise information loss and improve model predictability (Jolliffe & Cadima, 2016), which proved valuable in the current study.

However, time constraints limited our sample size to six, restricting PCA usability, meaning healthy controls were needed to meet PCA requirements (Hatcher, 1994; Jenkins & Quintana-Ascencio, 2020). If our patient sample size were sufficiently large, difference scores for change in levodopa states could have been directly calculated and used in PCAs. Also, only having composite scores for six patients was too small for regression analyses with three predictors (see section 3.2.2; Jenkins & Quintana-Ascencio, 2020), meaning data simulation was required. A strength of the data simulation tool used was that it created new data that resembles, and does not deviate severely, from the original dataset (Bates & Estabrook, 2016). Although, simulation cannot guarantee the representativeness that real PD patients would, especially considering the tool was originally designed for sharing error diagnostic data, meaning speed of simulation is favoured over precision (Bates & Estabrook, 2016). Additionally, binary data could not be simulated with this algorithm (Bates & Estabrook, 2016), meaning gender as a predictor was not analysed.

4.3.2 Missing Levodopa Responsiveness Evaluations

Our study utilised more diverse and precise measures to assess CR, motor functioning, and fluid intelligence compared to previous research (see chapter 1, Tables 1, 2, 3 & 4). Despite this being a strength, we did not directly measure PD cardinal symptom rigidity. To properly assess rigidity, electromyography is required (Perlmutter, 2009; Trager et al., 2020), which was not available as it is too time-consuming and expensive (di Biase et al., 2018; Trager et al., 2020). It could be argued that rating scales can assess rigidity, but we did not consider these to maintain consistency of measurement precision and to avoid subjectivity. Instead, our bradykinesia measure, the tapping test, indexed rigidity, where fewer taps implied greater rigidity. This index is justified as bradykinesia and rigidity display a strong negative correlation (-0.94) when measured by inertial sensors (Teshuva, 2019). Nevertheless, this is not a direct rigidity evaluation, meaning motor composite scores may have not accounted for as much variance as they could have. Whenever possible objective assessments, like electromyography, should be used.

Additionally, learning, an ability commonly impaired by PD, was not analysed in the study as it was beyond the study's scope. Considering learning's reliance on dopamine-dependent circuits in the basal ganglia (Alexander et al., 1990; Petrides, 1994), it could have possibly been another levodopa responsiveness indicator. Future research should investigate learning as a levodopa responsiveness outcome variable, where it may reveal CR as a predictor.

4.3.3 Choice of Study Design and Sample Characteristics

Investigation of the relationship between PD, CR and levodopa over time (Guzzetti et al., 2019; Hindle et al., 2016; Obeso et al., 2020) were constrained by the cross-sectional study design and PD patients being a limited population (Ascherio & Schwarzschild, 2016; Pringsheim et al., 2014). The short time available to complete this study meant a longitudinal investigation could not occur. Given that Hindle et al. (2016) found CR influences cognitive performance over time and levodopa's effect is also influenced by time (Schapira, 2005), a longitudinal focus may prove valuable.

Past studies found that PD patients taking levodopa for the first time experienced different effects compared to those previously exposed to levodopa (Cooper et al., 1992; Cilia et al., 2020; Muller et al., 2000). First time levodopa intake patients commonly experience a rapid boost in motor performance and even unexpected cognitive benefits (Kübler et al., 2019; Leroi et al., 2013). With the current study time limited and selecting participants from a limited population, a newly diagnosed PD patient sample was impractical to recruit. To best assess levodopa responsiveness, a patient sample never exposed to levodopa would be ideal. Patients with extended levodopa use have previously had their opportunity to respond to the medication, meaning they are prone to the wearing-off effect and side effects (Obeso et al., 2000; Rosqvist et al., 2018). This makes it difficult to interpret the current study findings as the way patients respond to levodopa depends on treatment length.

4.4 Future Directions

A foundation for research investigating the interaction between CR and levodopa in PD patients was established by this study, while also considering the roles of age and LED. To deepen the literature pool on this subject matter, future research should first look to verify the current study findings with real, not simulated, PD patients. After validating our findings, it could prove valuable to test PD patients who are taking levodopa for the first time under the same conditions. This type of PD sample would allow investigating levodopa responsiveness without the confounds of extended use, potentially eliciting different predictor effects. Furthermore, additional variables that could not be considered in this study, like gender, rigidity and learning, should be included in future analyses. Moreover, given CR is strongly related to time, a longitudinally designed study may help identify CR effects that a cross-sectional study could not. Future research could also validate if CR has significance in influencing responsiveness to other PD interventions, like deep brain stimulation, exercise and other medications.

4.5 Conclusion

The current study introduced new research in the rapidly expanding CR, levodopa and PD literature, focused on identifying PD patient levodopa responsiveness predictors. Our study improved upon previous research by using comprehensive and precise measures to investigate the interaction between CR, age, LED and levodopa responsiveness. Results could not support CR as having a significant role in levodopa responsiveness, when controlling predictors. Although, LED was a significant predictor for both motor and fluid intelligence performance change with levodopa withdrawal, suggesting a patient's LED is critical towards determining levodopa responsiveness. This finding should be thought of in terms of implications regarding the neglect of PD cognitive dysfunction and treatment for these impairments. Considerations of cognitive impairments should be at the forefront of patient evaluation and discussion along with motor impairments to stimulate a balanced treatment approach.

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Appendix A

R code used to generate a 'fakeData' function in R that allowed simulation of the six patient dataset

```
#Generating Simulated Data from 6 Patients

require(OpenMx)

# from https://openmx.ssri.psu.edu/wiki/generating-simulated-data
fakeData <- function(dataset, digits=2, n=NA,
                     use.names=TRUE, use.levels=TRUE, use.miss=TRUE,
                     mvt.method="eigen", het.ML=FALSE, het.suppress=TRUE){

  # This function takes as argument an existing dataset, which
  # must be either a matrix or a data frame. Each column of the
  # dataset must consist either of numeric variables or ordered
  # factors. When one or more ordered factors are included,
  # then a heterogeneous correlation matrix is computed using
  # John Fox' polycor package. Pairwise complete observations
  # are used for all covariances, and the exact pattern of
  # missing data present in the input is placed in the output,
  # provided a new sample size is not requested. Warnings from
  # the hetcor function are suppressed.

  # Author:   Ryne Estabrook
  # Created:  17 Aug 2010

  require(mvtnorm)
  require(polycor)

  # requires data frame or matrix
  if((is.data.frame(dataset)+is.matrix(dataset))==0){
    warning("Data must be a data frame or matrix")
  }

  # organization
  row <- dim(dataset)[1] # number of rows
  if(is.na(n))(n <- row) # sets unspecified sample size to num rows
  col <- dim(dataset)[2] # number of columns
  del <- is.na(dataset)  # records position of NAs in dataset
  if(n!=row){
    select <- round(runif(n, 0.5, row+.49),0)
    del <- del[select,]
  }
  num <- rep(NA, col)    # see what's not a factor
  ord <- rep(NA, col)    # see what's an ordered factor

  # which columns are numeric (the others are factors)?
  for (i in 1:col){
    num[i] <- is.numeric(dataset[,i])
    ord[i] <- is.ordered(dataset[,i])
  }

  # check for unordered factors
  location <- !(num|ord)
  unorder <- sum(location)

 if(unorder>0)warning(
   paste("Unordered factor detected in variable(s):",
         names(dataset)[location]
   )
 )

 # if everything is numeric, don't invoke polycor
 if(sum(!num)==0){
   # generate data with rmvnorm
   fake <- rmvnorm(n,
                   apply(dataset, 2, mean, na.rm=TRUE),
                   cov(dataset, use="pairwise.complete.obs"),
                   mvt.method)

   # round the data to the requested digits
   fake <- round(fake, digits)

   # insert the missing data, if so requested
   if(use.miss==TRUE)(fake[del] <- NA)

   # give the variables names, if so requested
   if(use.names==TRUE)(names(fake) <- names(dataset))

   # return the new data
   return(fake)
 }

 # if there are factors, we start here

 # find the variable means (constrain to zero for factors)
 mixedMeans <- rep(0, col)
 mixedMeans[num] <- apply(dataset[,num], 2, mean, na.rm=TRUE)

 # estimate a heterogeneous correlation matrix
 if (het.suppress==TRUE){
   suppresswarnings(het <- hetcor(dataset, ML=het.ML))
 } else (het <- hetcor(dataset, ML=het.ML))
 mixedCov <- het$correlations

 # make a diagonal matrix of standard deviations to turn the
 # correlation matrix into a covariance matrix
 stand <- matrix(0, col, col)
 diag(stand) <- rep(1, col)
 diag(stand)[num] <- apply(dataset[,num], 2, sd, na.rm=TRUE)
 # pre and post multiply hetero cor matrix by diagonal sd matrix
 mixedCov <- stand %*% mixedCov %*% stand

 # generate the data
 fake <- as.data.frame(rmvnorm(row, mixedMeans, mixedCov, mvt.method))

 # insert the missing data, if so requested
 if(use.miss==TRUE)(fake[del] <- NA)

 # turn the required continuous variables into factors
 for (i in (1:col)[!num]){
   # the original data for this column
   old <- dataset[,i]

   # the new data for this column, omiting NAs
   new <- fake[!is.na(fake[,i]),i]

   # what are the levels of the original factor?
   lev <- levels(old)

   # establish cutpoints in new variable from cdf of old factor
   cut <- cumsum(table(old))/(sum(!is.na(old)))

   # put continuous variable into a matrix, repeating value across columns
   wide <- matrix(new, length(new), length(lev))

   # put the cutpoints in a matrix, repeating the cut point values across rows
   crit <- matrix(quantile(new, cut), length(new), length(lev), byrow=TRUE)

   # for each value (row of the wide matrix),
   # how many cutpoints is the value greater than?
   # number of cutpoints surpassed=category
   fake[!is.na(fake[,i]),i] <- apply(wide>crit, 1, sum)

   # make it a factor
   fake[,i] <- factor(fake[,i], ordered=TRUE)

   # give the new factor the same levels as the old variable
   if(length(levels(fake[,i]))!=length(lev))message(
     paste("Fewer categories in simulated variable",
           names(fake)[i], "than in input variable", names(dataset)[i]))
   if(use.levels==TRUE&(length(levels(fake[,i]))==length(lev))){
     levels(fake[,i]) <- lev} else (levels(fake[,i]) <- 1:length(lev))
 }

 # round the data to the requested digits
 fake[,num] <- round(fake[,num], digits)

 # give the variables names, if so requested
 if(use.names==TRUE)(names(fake) <- names(dataset))

 # return the new data
 return(fake)
}
```

Appendix B

Neurologist Consent Form for Associated Parkinson'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	Dr Irina Baetu, A/Prof Lyndsey Collins-Praino, Prof Nicholas Burns, A/Prof Sarah Cohen-Woods, Dr Oren Griffiths, A/Prof Ahmed Moustafa
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 forthis 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 experimentand to withhold levodopa overnight 12 hours prior to the experiment.

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

Appendix C

Participant Information Sheet

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

Participant Information Sheet

Investigators	Dr Irina Baetu, A/Prof Lyndsey Collins-Praino, Prof Nicholas Burns, A/Prof Sarah Cohen-Woods, Dr Oren Griffiths, A/Prof Ahmed Moustafa
Human Research Ethics Committee Approval Number	H-2016-219
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 thisinformation 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.

Each testing session will take approximately 2.5-3 hours to complete. Each session will take place over one day, and there are no follow up requirements. The testing sessions will take place at the University of Adelaide, North Terrace Campus. 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, foodpreferences)
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 26/30 are considered abnormal, and we may contact you if your score is below 26 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 26 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 James and Diana Ramsay Foundation and the Australian Research Council, and is being conducted by Dr Irina Baetu, A/Prof Lyndsey Collins-Praino and Professor Nicholas Burns of the University of Adelaide, A/Prof. Sarah Cohen-Woods and Dr Oren Griffiths of Flinders University, and A/Prof Ahmed Moustafa 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 peoplewho 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, Dr Irina Baetu, or any of the following people:

Dr Irina Baetu
Email: irina.baetu@adelaide.edu.au

A/Prof Sarah Cohen-Woods
Email: sarah.cohenwoods@flinders.edu.au

Prof Nicholas Burns
Email: nicholas.burns@adelaide.edu.au

Dr Oren Griffiths
Email:
oren.griffiths@flinders.edu.au

A/Prof Lyndsey Collins-Praino
Email: lyndsey.collins-praino@adelaide.edu.au

A/Prof Ahmed MoustafaPhone
Email: A.Moustafa@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 8313 6028 or by email to hrec@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 **cns_laboratory@adelaide.edu.au** or **(08) 8313 0012**. You will be asked to contact your treatment health professional to determine whether it is safe for you to withdraw your medication before testing. 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, we will schedule two appointments and you will be asked to sign the consent form on the day of your first appointment

Appendix D

Participant Consent Form

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

Participant Consent Form

Investigators	Dr Irina Baetu, A/Prof Lyndsey Collins-Praino, Prof Nicholas Burns, A/Prof Sarah Cohen-Woods, Dr Oren Griffiths, A/Prof Ahmed Moustafa
Human Research Ethics Committee Approval Number	H-2016-219
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 **(chooseone)**:

The research project associated with this study only ☐

This 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 otherstudies 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 26/30. 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 E

Spread of Age and Cognitive Reserve PCA scores

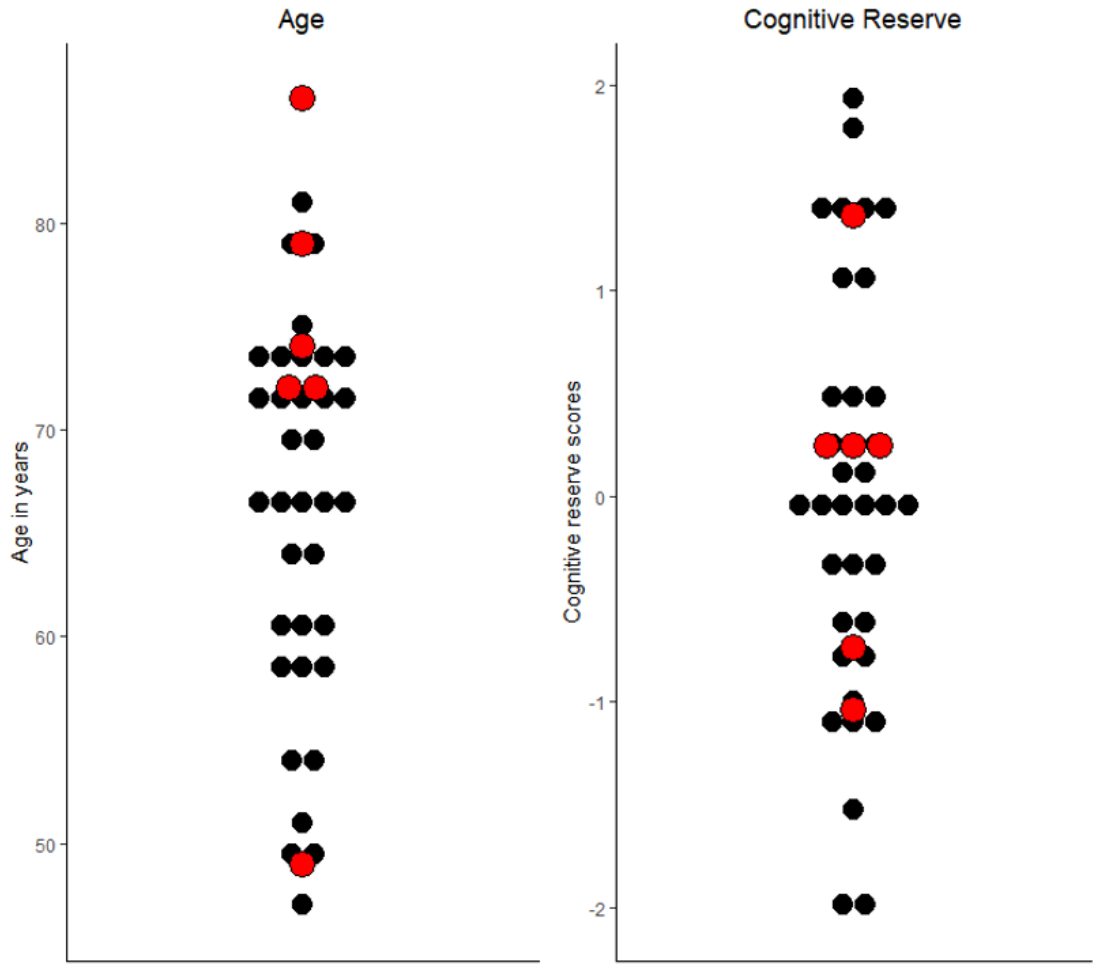

Figure E1. Age and cognitive reserve composite scores for the healthy controls (black) and patients (red).

Appendix F

Correlation Matrices for Motor and Fluid Intelligence Measures

Table F1

Correlations between Motor Measures (Patients ON Levodopa)

	Tapping Frequency	MPS	Balance (Ellipse)	Tremor (TPP)	Gait (SLRH)
Tapping Frequency	-				
MPS	-0.48**	-			
Balance (Ellipse)	-0.09	0.07	-		
Tremor (TPP)	-0.32	0.05	0.30	-	
Gait (SLRH)	0.39*	-0.34*	-0.05	-0.26	-

Note. MPS = Motor Processing Speed. TPP = Theta Power Proportion. SLRH = Stride Length Relative to Height. Correlations are calculated from 36 observations (6 PD patients ON levodopa, 30 age-matched healthy controls).

* = $p < 0.05$. ** = $p < 0.01$.

Table F2

Correlations between Motor Measures (Patients OFF Levodopa)

	Tapping Frequency	MPS	Balance (Ellipse)	Tremor (TPP)	Gait (SLRH)
Tapping Frequency	-				
MPS	-0.49**	-			
Balance (Ellipse)	-0.10	0.19	-		
Tremor (TPP)	-0.33*	0.34*	0.28	-	
Gait (SLRH)	0.30	-0.42*	0.05	-0.25	-

Note. MPS = Motor Processing Speed. TPP = Theta Power Proportion. SLRH = Stride Length Relative to Height. Correlations are calculated from 36 observations (6 PD patients OFF levodopa, 30 age-matched healthy controls).

* = $p < 0.05$. ** = $p < 0.01$.

Table F3

Correlations for Fluid Intelligence Measures (Patients ON Levodopa)

	Dot Matrix	Digit Span	Inspection Time	RPM	SST
Dot Matrix	-				
Digit Span	0.43*	-			
Inspection Time	-0.13	-0.07	-		
RPM	0.16	0.38*	-0.23	-	
SST	-0.56**	0.01	0.26	-0.32	-

Note. RPM = Raven's Progressive Matrices. SST = Stop Signal Task. These correlations are calculated from 42 observations of 36 participants (6 PD patients ON levodopa, 30 age-matched healthy controls).

* = $p < 0.05$. ** = $p < 0.01$.

Table F4

Correlations for Fluid Intelligence Measures (Patients OFF Levodopa)

	Dot Matrix	Digit Span	Inspection Time	RPM	SST
Dot Matrix	-				
Digit Span	0.37*	-			
Inspection Time	-0.21	-0.16	-		
RPM	0.15	0.38*	-0.35*	-	
SST	-0.41*	0.02	0.37*	-0.41*	-

Note. RPM = Raven's Progressive Matrices. SST = Stop Signal Task. These correlations are calculated from 42 observations of 36 participants (6 PD patients OFF levodopa, 30 age-matched healthy controls).

* = $p < 0.05$. ** = $p < 0.01$.

Appendix G

Spread of Motor and Fluid Intelligence PCA scores ON and OFF Levodopa

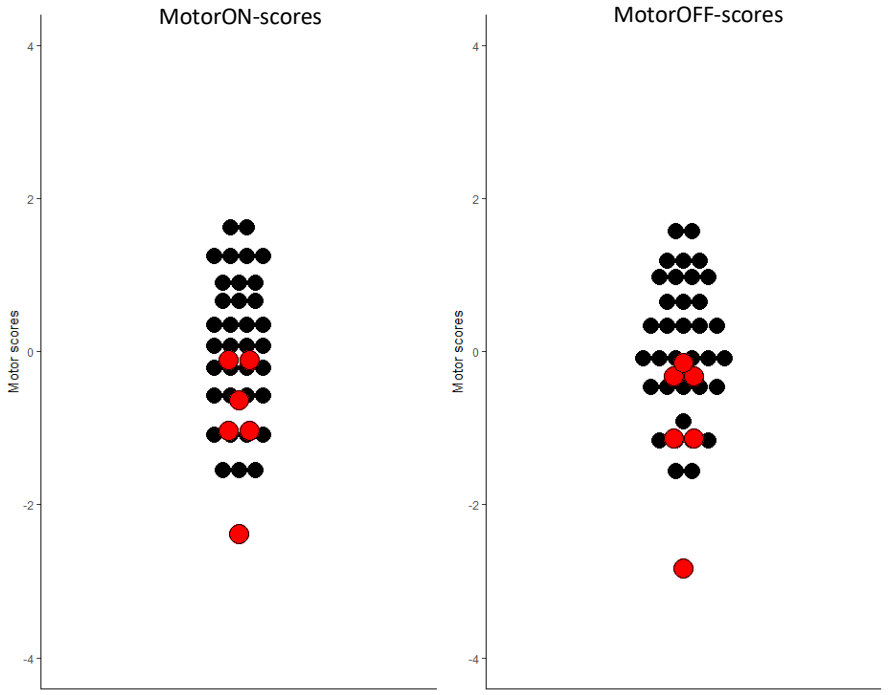

Figure G1. Motor composite scores for the healthy controls (black) and patients (red) ON and OFF levodopa.

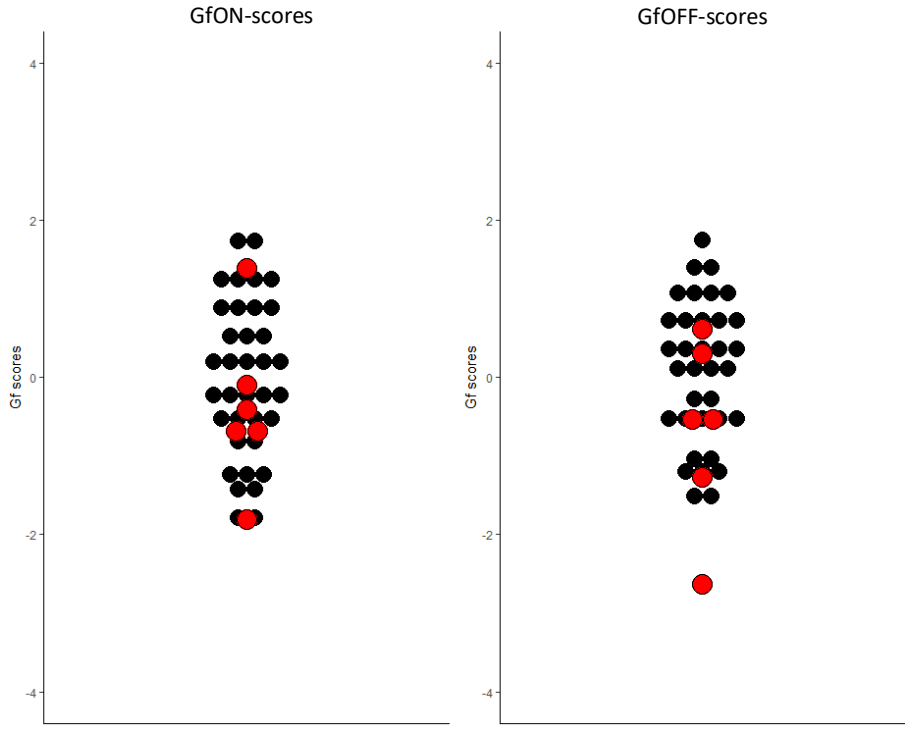

Figure G2. *Gf* = Fluid Intelligence. Fluid Intelligence composite scores for the healthy controls (black) and patients (red) ON and OFF levodopa.

Appendix H

Relationships between Predictors Age and LED and Outcome Variable Differences in Fluid Intelligence ON and OFF levodopa

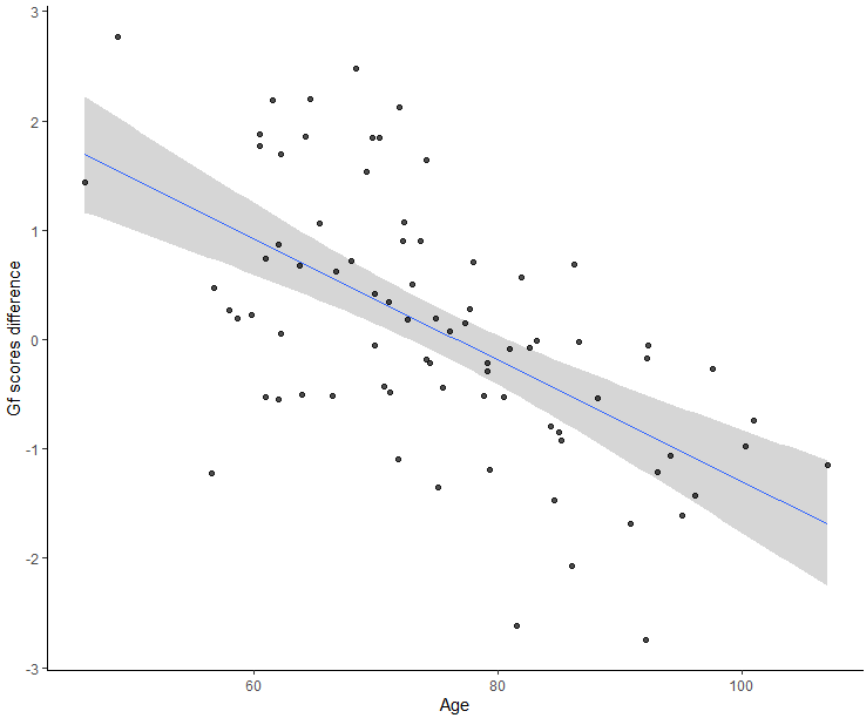

Figure H1. Gf = Fluid Intelligence. Scatter plot showing the correlation between age and fluid intelligence difference scores for the simulated PD patients (*n = 80*).

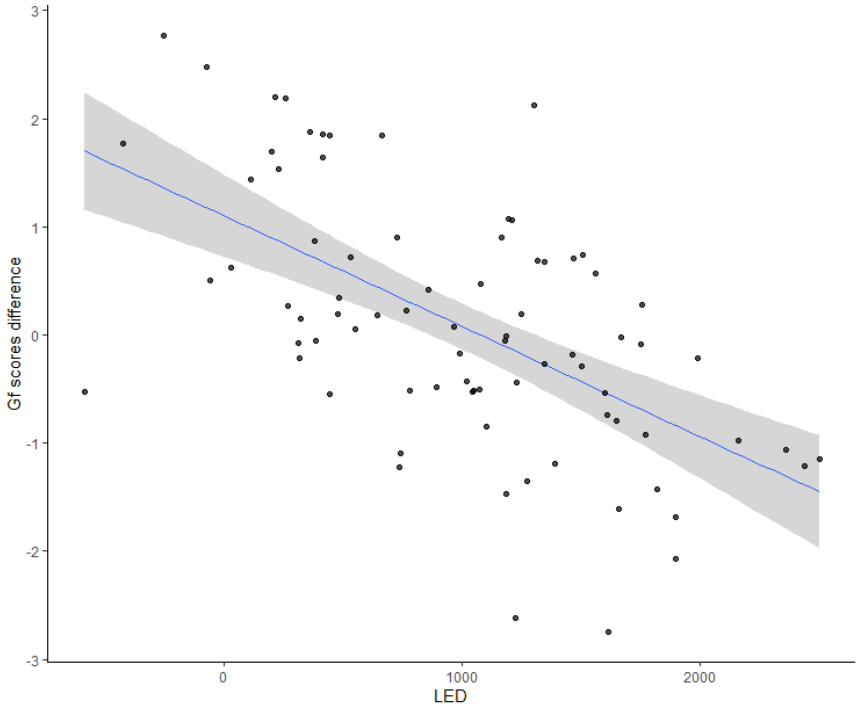

Figure H2. Gf = Fluid Intelligence. Scatter plot showing the correlation between LED and fluid intelligence difference scores for the simulated PD patients (*n = 80*).

Appendix I

Ethics Approval

Our reference 0000022030

THE UNIVERSITY of ADELAIDE

RESEARCH SERVICES
OFFICE OF RESEARCH ETHICS, COMPLIANCE AND INTEGRITY
THE UNIVERSITY OF ADELAIDE

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CRICOS Provider Number 00123M

07 February 2020

Dr Irina Baetu
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 annual report requesting time extension and the amendment request to amend the protocol as submit on the 7th of February 2020. The amendment and extension are approved.

The ethics amendment for the above project has been reviewed by the 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: 31/03/2023

NAMED INVESTIGATORS:

Chief Investigator: Dr Irina Baetu

Associate Investigator: Associate Professor Lyndsey Collins-Praino

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,

Professor Paul Delfabbro
Convenor

The University of Adelaide