A systematic, cross-sectional, and patient-informed approach to examining impulsivity and inhibitory control in Parkinson's

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Abstract

Parkinson's is primarily a movement disorder but can lead to many non-motor symptoms either directly, due to the loss of dopamine cells through degeneration in the substantia nigra, or indirectly due to the medication which aims to alleviate the motor symptoms of Parkinson's. Impulse control behaviours (ICBs) can include gambling, hypersexuality, compulsive shopping, binge eating, hobbyism, and punding, and are thought to occur primarily as a result of dopamine agonist medications. However, it is unclear how impulsivity (which covers a range of tasks and processes) and inhibitory control (withholding from an action) are affected in Parkinson's without ICBs, to what extent this is affected in ICBs, and what other aspects related to Parkinson's may affect it.

Firstly, I used a task of response inhibition (Stop Signal task) and response inhibition under conflict (Simon task) in a group of people with Parkinson's (PwPs) and a group of healthy controls (HCs), as the literature contained mixed results as to whether PwP showed reduced response inhibition or not. Response force placed upon the response keys was recorded as an additional sensitive measure of inhibitory cognitive control, and I found no significant group differences on either task for both traditional button-press measures and for response force.

To more thoroughly explore group differences in the literature so far, I conducted a systematic review of 246 studies examining impulsivity and inhibitory control, across a broad range of measures, in PwP, PwP with additional ICBs (PwP+ICBs), and HCs. The review uncovered largely mixed results with unclear conclusions as to whether PwP showed any impairment among different measures of impulsivity compared to HCs, and additionally whether PwP+ICBs showed any impairment compared to PwP. Exceptions where a clearer picture emerged included an impairment in PwP for response conflict and decision making under ambiguous risk, and both higher trait impulsivity and reduced ability to delay gratification for PwP+ICBs compared to PwP.

Next, I conducted a cross-sectional study using many of the tasks identified through the review with three groups of participants: PwP+ICBs, PwP without ICBs, and HCs. The study revealed largely null results; PwP+ICBs showed no significantly greater impulsivity than PwP on these behavioural measures, and PwP showed no greater impulsivity than HCs except on a Go/No-Go task where PwP showed significantly reduced action restraint compared to both PwP+ICBs and HCs.

Taken together, the evidence from these three studies suggests that there is no clear impairment for PwP and/or PwP+ICBs in terms of reduced inhibitory control or increased impulsivity as measured with behavioural and cognitive tasks. This may be due to the heterogeneity of Parkinson's, the types of ICBs that PwP experience, and issues with methodological quality.

Finally, in parallel with the preceding chapters, I developed a proof-of-concept behavioural intervention aimed at reducing the impact of ICBs in PwP. The protocol was developed with considerable input from patient and public involvement volunteers and demonstrates the importance of taking a patient-centred approach. Overall, this approach confirmed that research into ICBs and how impulsivity in general affects PwP is an important avenue for further inquiry for PwP, and better methodological rigour will greatly help to meet patient needs.

Lay abstract

Parkinson's is usually associated mostly with symptoms related to movement, such as slowed movements, tremor, and difficulty walking. These symptoms are caused by the loss of cells in a small area of the brain called the substantia nigra. The substantia nigra is responsible for producing the neurotransmitter dopamine, but in Parkinson's it no longer produces as much as it should. There are also many symptoms that are not related to movement, but which occur due to the lack of dopamine. For example, emotional and cognitive symptoms. Dopamine is important for lots of behaviours, but particularly reward and motivation.

The medication used to treat Parkinson's helps to restore dopamine to the affected brain areas but can also cause some changes in behaviour for some patients, such as an increased interest in risky behaviours such as gambling. These changes in behaviour can be distressing for patients and their families and currently the best method of treatment is to withdraw from the medication. However, if this medication works well to treat the movement symptoms of Parkinson's then it can cause a dilemma for patients.

We don't know whether it is just the medication that causes changes in behaviour, or whether Parkinson's itself causes changes in behaviour. Chapter 2 of this thesis aimed to see whether Parkinson's changes the ability to stop yourself from performing an action that you shouldn't ("inhibitory control"). I found that it does not seem to do this. In Chapter 3, I looked at previous work done by other researchers using a broad range of methods to see how much Parkinson's or medication contributes to changes in behaviour. The results were unclear, and I made some recommendations for ways that this could be made clearer in future, for example by improving research quality.

To try and get a clearer picture, I did a study in Chapter 4 where I looked at many different types of behaviours in people with Parkinson's who experienced problems with behaviour change, and people with Parkinson's who hadn't experienced these problems. I found that neither Parkinson's nor medication seemed to contribute much to the types of behaviour that we measured here. It might be that the medication only changes very specific behaviours.

Lastly, in Chapter 5, I developed a home-based training task that aims to reduce the impact caused by changes in behaviours. This may provide an alternative or complementary intervention to withdrawing from the problematic medication and keep the behaviour changes in check to a more manageable level. It was developed with the help of patients and their family members, who were very positive about the idea and provided a great deal of input to design the final training tool. The next step is to try the training tool out with a few patients who experience problematic changes in behaviour, and to see whether they find it easy to use and if they have any further feedback. After this, it can be tested in a bigger study to see if it meets its goal of reducing the behaviours.

Overall, in my research I did not find evidence that Parkinson's nor the medication seem to affect the sorts of behaviours that we were interested in experimentally, but that the behaviour changes that people with Parkinson's experience are still an important line of research. Patients are keen to see more research conducted to understand why they experience these behaviours and how we can reduce them.

Declaration

Due to the nature of the 1+3 Economic and Social Research Council funded Masters and PhD programme, parts of section 3 "Continuous force measurements reveal no inhibitory control deficits in Parkinson's disease" were submitted for partial fulfilment of the author's Master of Research (MRes) dissertation. The chapter includes data that were collected as part of the author's MRes degree; specifically 16 participants with Parkinson's (1 of which was excluded from analyses) and 12 healthy control participants were recruited during the MRes with the a-priori aim of adding to the sample during the PhD for an end total of 25 participants in each group. Additionally, all analyses pertaining to the continuous measure of force were completed solely for the purposes of the PhD and comprise the main theoretical focus of the paper in its final form as presented here.

Chapter 4 was completed in collaboration with a University of Manchester MRes student, Marta Majewska. A report written independently by Marta Majewska was submitted in partial fulfilment of her MRes award, but the report written within this thesis is the author's own work. Each empirical chapter within this thesis begins with a preface explaining the contribution of each author for clarity.

No other portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or institute of learning.

Copyright statement

Acknowledgements

The last few years have been an absolute rollercoaster! I was under no illusions that a PhD would be plain sailing, but there were some very unexpected events along the way. Broken limbs, global pandemics…that sort of thing. I am a very different person to the one I was when I started, which is in large part due to the supportive community that I've had around me, lifting me back up when things went wrong and celebrating when things went well.

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Book contributions

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Chapter 1 - General introduction

1.1. Parkinson's disease

Parkinson's disease was first comprehensively described by James Parkinson in "An Essay on the Shaking Palsy" (Parkinson, 1817) and is a neurodegenerative disease characterised by a range of symptoms largely related to the motor system; common symptoms include a resting tremor, rigidity in the joints, bradykinesia (slowness of movement), and postural instability which may involve balance problems and a shuffling gait (Jankovic, 2008).

Parkinson's is caused by the loss of dopamine producing cells in the substantia nigra pars compacta, part of the basal ganglia, due to the abnormal aggregation of the alpha-synuclein protein which forms Lewy bodies. As is evident by the most prominent symptoms of Parkinson's disease, one of the basal ganglia's primary functions is motor control (Mink, 1996). By the time the motor symptoms of Parkinson's are apparent, it is estimated that between 30 to 50% of substantia nigra neurons have already been lost (Armstrong & Okun, 2020; Cheng, Ulane, & Burke, 2010). The symptoms of Parkinson's are most often treated with dopaminergic medication, such as levodopa and dopamine agonists. The basal ganglia are heavily connected to cortical areas of the brain, and the loss of dopamine producing cells has knock-on effects on cortical loops that are implicated in aspects of cognition, emotion, and motivation (Vanderah & Gould, 2015). After 200 years of awareness and research, Parkinson's disease is still difficult to diagnose and there is no definitive way of testing for the disorder ante-mortem; misdiagnosis estimates range from 10-15% (Schrag, Ben-Shlomo, & Quinn, 2002) to as high as 25% (Tolosa, Wenning, & Poewe, 2006).

Attempts to provide a more consistent method of diagnosis and monitoring have resulted in the Unified Parkinson's Disease Rating Scale (UPDRS), the most recent revision of which is sponsored by the Movement Disorder Society (the MDS-UPDRS), which aims to assess the broad range of symptoms that a person with Parkinson's or suspected Parkinson's may experience (Goetz et al., 2008). The MDS-UPDRS includes both the motor symptoms and non-motor symptoms which are common in Parkinson's and can be administered by clinicians. It consists of four parts; non-motor experiences of daily living, motor experiences of daily living, motor examination, and motor complications.

Part 1, non-motor experiences of daily living, comprises a questionnaire in the form of an interview and assesses symptoms such as cognitive impairment, psychiatric problems (e.g. depression, anxiety, psychosis), sleep disturbance, pain, and digestion. Part 2 is, again, a questionnaire-based interview and examines patient-reported problems such as speech difficulties, mastication, swallowing, dressing, writing, hobbies, tremor, walking, and freezing of gait. Part 3, the motor examination, is a clinical assessment where the patient performs a series of movements and the clinician rates the severity of the associated symptom. For example,

simple finger and toe tapping exercises can reveal a deficit in movement amplitude and speed, and tremor can be observed under different conditions such as at rest, when engaged in reaching movements, and when holding the arms stationary in an extended position. The motor examination is also used to examine rigidity in the joints and observe gait problems such as shuffling and freezing whilst the patient walks. The observations from part 3 are used to provide an overall rating of motor symptom severity on the Hoehn & Yahr (1967) scale, which range from no symptoms (a score of 0), through to more mild unilateral (stage 1), bilateral (stage 2), or moderate symptoms (stage 3), and then through to a severe disability (stage 4), or wheelchair bound/bedridden unless aided (the final stage 5). Finally, part 4 of the MDS-UPDRS examines fluctuations in symptom severity as a result of dopamine medication; people with Parkinson's (PwP) are usually described as either being in the ON state, where medication is optimally controlling their symptoms, or the OFF state, where patients are responding poorly despite having taken medication or are not on medication at all.

The comprehensiveness of the MDS-UPDRS reveals the breadth of symptoms that PwP may experience and provides a way to track the severity of the motor components on the Hoehn and Yahr scale. However, the broad definition of Parkinson's as one coherent disease may be limited; many PwP do not experience the full range of defining symptoms, for example some patients may have problems with tremor whereas others may have difficulty with freezing of gait but never experience tremor through the course of the disease (Jankovic, 2008). To address this, attempts have been made to categorise the symptoms of Parkinson's into more narrowly defined subtypes.

There were previously suggestions that Parkinson's could be split into two subtypes; tremor dominant symptoms, or postural instability and gait dominant symptoms (Jankovic et al., 1990). However, the participants in this sample were from a clinical trial and were therefore selected with very stringent inclusion criteria due to the original aims of the study, and so have a limited scope for generalisability. A more recent systematic review suggested there were four subtypes; tremor dominant, postural instability and gait dominant, later onset with rapid progression, and early onset with slow progression (Van Rooden et al., 2010). More recently still a large cohort of Parkinson's participants exhibited four subtypes with slightly different variable clustering; fast motor progression, mild motor and non-motor disease, severe motor disease with poor psychological wellbeing and sleep, and slow motor progression with tremor dominant symptoms (Lawton et al., 2018). There are still no definitive classifications of subtypes, and biomarkers for these are lacking (Thenganatt & Jankovic, 2014), but Parkinson's is evidently a heterogenous disease with diverse presentations of disease onset, progression, motor symptoms, and non-motor symptoms (Armstrong & Okun, 2020).

The non-motor comorbidities of Parkinson's are far-reaching and can include problems such as depression, anxiety, sleep disturbance, olfactory impairment (anosmia), gastrointestinal

problems, pain, and hallucinations. The onset of non-motor symptoms can occur for many years before the motor symptoms become apparent, due to the Lewy pathology in the brainstem and autonomic nervous system which leads to symptoms such as anosmia early in the course of the disease (Jellinger, 2015). As the pathology progresses, other non-motor symptoms can occur in early Parkinson's, but this is confounded by the contribution of Parkinson's medications which is also a (non-exclusive) causal factor in many non-motor symptoms (Jellinger, 2015).

It was recently estimated that up to 50% of PwP additionally go on to develop impulse control behaviours (ICBs) at some point during the disease (Corvol et al., 2018; Voon, 2015; Weintraub et al., 2010). Impulse control disorders do exist in the general population, although at a lower prevalence and with different classifications to those seen in Parkinson's (Gatto & Aldinio, 2019). As of the DSM-5, typical ICDs in the general population consist of oppositional defiant disorder (3.3% prevalence), intermittent explosive disorder (2.7%), conduct disorder (4%), kleptomania (0.6%), and pyromania (only 3% of those imprisoned for arson; Fariba & Gokarakonda, 2021).

In Parkinson's they present uniquely and are commonly classified via the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP; Weintraub et al., 2012). In Parkinson's, the four main impulse control disorders are pathological gambling, hypersexuality, binge eating, and compulsive buying, whereas additional related behaviours comprise hobbyism, punding, walkabout, hoarding, and dopamine dysregulation syndrome (Gatto & Aldinio, 2019). All behaviours are collectively referred to as impulse control behaviours (ICBs) throughout this thesis. There is still some debate as to the underlying cause of ICBs, however the prevalent theory is that it is caused primarily by dopaminergic medication.

The dopamine overdose hypothesis, discussed in more detail particularly in Chapter 4, posits that whilst dopamine agonist medication is effective at treating the motor symptoms of Parkinson's by restoring dopamine levels along the dopamine-depleted nigrostriatal pathway, it effectively "overdoses" dopamine levels along the mesocortical and mesolimbic pathways that project from the relatively unaffected ventral tegmental area (Cools et al., 2001; Vaillancourt et al., 2013). These mesocorticolimbic pathways are associated with reward and motivation, and the increase of dopamine leads to poor regulation of these behaviours (Cools et al., 2001). Importantly, these remediation and overdosing effects interact with the severity of the Parkinson's pathology. A recent meta-analysis supports the notion that Parkinson's medication is primarily associated with the development of ICBs, as well as disease severity (Molde et al., 2018).

Whilst rat models of ICBs in Parkinson's are difficult to acquire (see Cenci et al, 2015 for further discussions), existing rat models do support the position that these ICBs are due to an interaction of medication and disease pathology. In rats, bilateral dopaminergic lesions that

simulate the earlier stages of Parkinson's alongside administration of pramipexole (a dopamine agonist medication) contributed to increased waiting impulsivity (Jiménez-Urbieta et al., 2019). Dopamine agonist administration also appears to contribute to impulsive behaviour in terms of motor impulsivity and probability-discounting in rodents (Engeln et al., 2016; Rokosik & Napier, 2012).

Whilst the effect of the dopamine overdose hypothesis is understood to be the main risk factor for the development of ICBs, it is not responsible in isolation. Being medicinally treated for Parkinson's with dopamine agonists appears to interact with other factors such as the dosage, other medications, pathology of Parkinson's itself (De Micco, Russo, Tedeschi, & Tessitore, 2018), or pre-existing characteristics of the individual themselves such as age, gender, and personality traits (Voon, 2015). Additionally, there may be a genetic component to ICB risk; 57% of the variance of ICB incidence in Parkinson's was explained by genetic variants, most notably the *OPRK1, HTR2A,* and *DDC* genotypes (Kraemmer et al., 2016).

Neuroimaging research also supports the dopamine overdose hypothesis more generally; PwP ON medication show impaired sequence learning compared to when OFF medication (Kwak et al., 2012), which was associated with reduced activity in the dopamine-depleted ventral striatum. Overdose effects in medication ON/OFF studies have also been found with regards to reward-learning which is associated with the ventromedial prefrontal cortex (Argyelan et al., 2018), and reward prediction errors in a probabilistic reward learning task which was associated with the ventral striatum (van Eimeren et al., 2009). Additionally, whilst dopamine is considered to be the main neurotransmitter involved in the development of ICBs, it is not the only neurotransmitter that contributes to impulsive behaviour more generally in Parkinson's, such as both increasing and decreasing serotonergic function (Evenden, 1999).

Overall, the dopamine overdose hypothesis is widely accepted as the main driver behind the development of ICBs, in context of other risk factors such as genetic influences, personal characteristics, and family history. There are a lack of treatment options for PwP who develop ICBs, and the current best-practice method is to fully withdraw from the dopamine agonists to gain at least a partial, if not full, remission from the ICB(s) (MacPhee et al., 2013). Whilst the far-reaching implications of Parkinson's are apparent, this PhD project focuses particularly on the effect of Parkinson's and related ICBs on inhibitory action control and impulsive behaviour.

1.2. Impulsivity and inhibitory control

Impulsivity is a multi-faceted and often poorly defined mechanism, or set of mechanisms, that guide behaviours. All individuals exhibit impulsivity to some extent along a continuum of low to high impulsivity; higher levels of impulsivity can result in the failure to inhibit particular behaviours which may result in reward but are considered to have an element of risk, whereas lower levels of impulsivity are associated with greater inhibition of such behaviours (Bari &

Robbins, 2013). Impulsivity and inhibitory control can comprise a wide range of behaviours, but this thesis seeks to focus particularly on the key areas that have already been examined in Parkinson's including response inhibition (Chapters 2-5), risky decision making, delay discounting, and trait impulsivity (Chapters 3-4).

Response inhibition relates particularly to the successful inhibition of impulsive (motor) actions. Higher impulsive action is associated with reduced response inhibition and may be related to increased action without forethought (Hamilton et al., 2015). Response inhibition is often tested experimentally with tasks such as the Go/No-Go and Stop Signal tasks. The Go/No-Go task requires participants to respond to a series of targets on screen with a button press, but to withhold this response if an infrequent No-Go target appears. The Stop Signal task is similar but, instead of No-Go trials, some Go trials are followed by a Stop Signal, after a variable delay (Logan, 1994). Therefore, whilst the Go/No-Go task measures action restraint the Stop Signal task measures the ability to stop an ongoing action.

The race model of inhibitory control posits that the Go process and Stop process are engaged in a race to completion, and whichever process finishes first dictates whether a response will be executed or not (Logan, 1994; Verbruggen & Logan, 2008). In the Stop Signal task, the stop signal reaction time can be calculated as an estimate of the time taken for the Stop process to overtake the Go process and is used as an individual measure of response inhibition. A shorter stop signal reaction time is indicative of greater inhibitory control compared to a longer stop signal reaction time, which is evidenced by patient groups that have particular difficulties with action impulsivity such as Tourette syndrome, obsessive compulsive disorder, and attention deficit hyperactivity disorder and who tend to exhibit longer stop signal reaction times (Verbruggen and Logan, 2008). Successfully inhibiting a movement is associated with activity in the right inferior frontal cortex, the subthalamic nucleus, and other areas of the basal ganglia (Aron, Robbins, & Poldrack, 2014; Kohl et al, 2015; Wessel et al., 2016). The Stop Signal task is used in Chapter 2, the Go/No-Go task is used in the development of an intervention in Chapter 5, and both tasks are used in Chapter 4.

Inhibition can also be selective; tasks such as the Simon, Eriksen, and Stroop tasks (Eriksen & Eriksen, 1974; Simon, 1969; Stroop, 1935) are designed to induce response conflict where one prepotent response must be inhibited in favour of the goal-directed response. In the Stroop task, for example, participants are asked to name the colour that the words are written in and to ignore the words themselves. Crucially, these words spell out the names of colours themselves, and sometimes they are congruent with task instructions (the word "BLUE" written in blue ink) or incongruent (the word "BLUE" written in red ink). The automatically elicited (and prepotent) response is to read the word despite task instructions, and this automatic response must be selectively inhibited in order to name, instead, the colour of the ink that it is written in. This interference effect generally results in slowed response times and reduced accuracy when

stimuli are incongruent compared to congruent. The Simon task is used in Chapter 2 and the Stroop and Eriksen tasks are used in Chapter 4.

Risky decision making can occur under ambiguous or objective risk. In decisions under ambiguous risk, the information required to make an informed choice is lacking, but the outcome can either be advantageous or disadvantageous. For example, in the Iowa Gambling Task (Bechara, Damasio, Damasio, & Anderson, 1994), two out of four decks of cards are advantageous (they result in a net gain) and two decks are disadvantageous (they result in a net loss) but this is not immediately obvious to participants. Participants must draw cards from the decks, and follow their own intuition to determine the best selection to make on each trial (see the somatic marker hypothesis for more detail; Damasio, Tranel, & Damasio, 1994; Dunn, Dalgleish, & Lawrence, 2006). Decisions made under objective risk differ in that the relevant information needed to make an informed decision is available to the participants. For example, in the Cambridge Gambling Task (Rogers, Everitt, et al., 1999), participants must guess whether a yellow token is hidden inside a red box or a blue box, and they are provided with ten boxes visually on the screen. The ratio of red boxes to blue boxes enables the participant to calculate the probability of the token being under each colour box, for example a ratio of nine red boxes and one blue box represents a 90% probability that the token will be under a red box, and a 10% probability that it will be under a blue box. Whereas decision making under ambiguous risk relies more on somatic markers, decision making under objective risk relies more on executive functioning processes (Brand, Labudda, & Markowitsch, 2006). Both tasks are examined in more detail in the systematic review in Chapter 3 and used in the study in Chapter 4.

Delay discounting encompasses the tendency to prefer smaller rewards sooner, rather than larger rewards later. For example, in the Kirby Monetary Choice Questionnaire (Kirby & Marakovic, 1996) participants are presented with a series of choices such as "Would you rather have $54 now or $55 in 117 days?" or "$31 now or $85 in 7 days?". The combined responses result in an index, *k*, of an individual's delay discounting rate which represents the point of equivalence at which there is no "best" choice (Al-Khaled, Heldmann, Bolstorff, Hagenha, & Münte, 2015; Kirby & Marakovic, 1996). A greater tendency for immediate gratification and choosing smaller rewards sooner (a higher *k* value) is thought to be associated with particular clinical populations such as those with attention deficit hyperactivity disorder and people with pathological gambling disorders (Alessi & Petry, 2003; Winstanley, Eagle, & Robbins, 2006).

1.3. Overview of the thesis

It is important to examine impulsivity and inhibitory control in Parkinson's to discover whether Parkinson's itself can lead to changes in behaviour, whether the development of ICBs can lead to other changes in behaviour, or whether these changes are limited to the clinical behaviours

associated with ICBs and specifically due to the dopaminergic medication as posited by the dopamine overdose hypothesis.

Whilst it is still unknown whether Parkinson's pathology directly contributes to changes in impulsivity, many studies to date have examined impulsivity and inhibitory control in Parkinson's and related ICBs (see Chapter 3). The literature is not always clear, and so empirical Chapter 2 aimed to look at two main tasks of inhibitory motor control that have produced mixed results so far, the Stop Signal task and the Simon task. The study sought to use a sensitive and novel measure of response force to capture "partial errors" in responding that may be missed by traditional button press measures; if significant differences in the ability to withhold impulsive motor responses between PwP and healthy controls (HCs) exist, it should be easier to detect with this measure.

As the response force measure still revealed non-significant group differences, Chapter 3 presents a broad systematic review of the literature into impulsivity and inhibitory control in PwP, HCs, and PwP with additional ICBs (PwP+ICBs) to further investigate the literature to date. The review aimed to capture the breadth of research available into a range of impulsivity including, but not limited to, response inhibition (impulsive action), response conflict, oculomotor inhibition, delayed gratification, decision making under ambiguous and objective risk, personality traits, and cognitive inflexibility. The review aims to be a starting point for future meta-analyses and includes a comprehensive and interactive resource of 246 studies' key features and results. The review made it clear that results were inconclusive as to whether PwP or PwP+ICBs were impaired for different types of impulsivity, and that this may be due to methodological differences between studies as well as the heterogeneity of participants between studies (see Table 16). This lack of clarity naturally led to the need for a more controlled experimental approach to asking a similar question; again, taking a broad perspective but with a more narrowly constrained methodology.

Chapter 4 contains a cross-sectional study examining some of the main types of impulsivity that were highlighted in the systematic review across three different participant groups; PwP without any ICBs, PwP+ICBs, and HCs. By using a range of tasks in the same participants, I aimed to remove the between-study participant heterogeneity that made it difficult to compare results in the systematic review. The tasks were carefully designed to conform to the highest methodological rigour, and the methods, exclusion criteria, and statistical analyses were pre-registered to ensure reduced researcher degrees of freedom. Very few significant group differences were found in this study, indicating that perhaps PwP and PwP+ICBs do not show impairment for different types of impulsivity and inhibitory control, contrary to the existing narrative in the literature that there are significant group differences. Various common biases may contribute to the narrative that exists in contrast to the evidence presented here, for

example publication bias, confirmation bias, and the availability heuristic. The implications are discussed further in Chapter 6.

Finally, Chapter 5 constitutes work completed in parallel to Chapters 2-4 over the course of the PhD, rather than as a direct follow-on. Here I propose a behavioural intervention for PwP+ICBs, which builds on the work by Verbruggen et al. (2012) who showed that practicing a task of response inhibition leads to a reduction in gambling behaviours, and the work of the FoodT intervention (https://www.exeter.ac.uk/foodt/) which has demonstrated that performing a Go/No-Go task can help reduce unhealthy eating behaviours. Here I propose a trailing tool consisting of a Go/No-Go task, to be practiced over several weeks, where the stimuli consist of ICB-relevant pictures that are selected by, and personalised to, the participant. The hope is that the ICB behaviours and severity can be reduced behaviourally whilst still allowing the patient to remain on the dopamine agonist medication that is successfully treating the motor symptoms of Parkinson's. Chapter 5 also acts as an exemplary case study of Patient and Public Involvement.

1.4. References

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Preface to Chapter 2

This chapter has been adapted from the following published paper:

Pickering, J.S., Leroi, I., McBride, J., & Poliakoff, E. (2020). Continuous force measurements reveal no inhibitory control deficits in Parkinson's disease. *Experimental Brain Research, 238*, 1119-1132. https://doi.org/10.1007/s00221-020-05768-0

Which is also available as a pre-print on bioRxiv:

Pickering, J.S., McBride, J., Leroi, I., & Poliakoff, E. (2020). Continuous force measurements reveal no inhibitory control deficits in Parkinson's disease. *bioRxiv*, https://doi.org/10.1101/809780

As mentioned in the *Declaration* section of this thesis, some of this data was submitted in partial fulfilment of an MRes degree.

Author Contributions: Jennifer McBride programmed the original version of the Stop Signal task and created the hardware for recording the force data and the original algorithm to process the data. Ellen Poliakoff programmed some of the data pre-processing materials for the button-press data. Jade Pickering adapted the Stop Signal task, force processing algorithm, and button-press pre-processing materials for the purposes of this project. All other materials including tasks, analyses, figures, and tables were created by Jade Pickering. Jade Pickering independently wrote the initial draft of this paper, which was then collaboratively re-written and edited for the purposes of publication by Jennifer McBride, Ellen Poliakoff, and Iracema Leroi.

Chapter 2 - Continuous force measurements reveal no inhibitory control deficits in Parkinson's disease

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2.1. Abstract

Suppression of unwanted motor responses can be disrupted by Parkinson's disease. People with Parkinson's (PwP) can show maladaptive reward-driven behaviours in the form of impulse control behaviours, which are associated with use of the dopaminergic treatments used to alleviate the motor symptoms of the disease. However, the effects of Parkinson's itself on impulsive behaviour and control are unclear – empirical studies have yielded mixed findings, and some imaging studies have shown a functional deficit in the absence of a measurable change in behaviour. Here, we investigated the effects of Parkinson's on response activation and control by studying the dynamics of response in standard inhibitory control tasks – the Stop Signal and Simon tasks – using a continuous measure of response force. Our results are largely in favour of the conclusion that response inhibition appears to be intact in PwP, even when using a more sensitive measure of behavioural control relative to traditional button-press measures. Our findings provide some clarity as to the effects of Parkinson's on response inhibition and show continuous response force measurement can provide a sensitive means of detecting erroneous response activity in PwP, which could also be generalised to studying related processes in other populations.

2.2. Introduction

Parkinson's disease is a neurodegenerative disorder affecting around 1% of all adults over the age of 60 (Tysnes & Storstein, 2017). Parkinson's is associated with significant loss of dopaminergic cells in the substantia nigra pars compacta, which in turn supplies dopamine to the dorsal striatum of the basal ganglia (Dauer & Przedborski, 2003) and frontal regions (Jahanshahi et al., 2015). This neural loss in Parkinson's has a profound effect on the motor system: people with Parkinson's (PwP) can experience muscle rigidity, tremor, freezing of gait, and slowness of movement (bradykinesia; Jankovic, 2008). In addition to PwP being slow to initiate and execute movements, they can also have difficulty with the *inhibition* of pre-potent responses (e.g., Gauggel, Rieger, & Feghoff, 2004; Nombela, Rittman, Robbins, & Rowe, 2014). Sometimes, deficits in inhibition and control can manifest as impulse control behaviours (ICBs), including pathological gambling, hypersexuality, binge eating, and compulsive shopping (Voon, 2015). Recent estimates suggest that up to 50% of PwP develop an ICB (Corvol et al., 2018), which can negatively impact on quality of life (Leroi et al., 2011; Phu et al., 2014).

However, "impulsivity" is a complex and multifaceted construct; Antonelli et al. (2011) distinguished between cognitive impulsivity – which is characterized by altered decision-making (e.g. risk-taking, altered time-perception, and avoidance of waiting), and motor impulsivity – which is associated with a relative inability to inhibit prepotent responses. Response conflict and inhibition have been widely studied experimentally using a variety of tasks, including the Go/No-Go (e.g. Gomez et al., 2007), Stop Signal (Verbruggen & Logan, 2008), and Simon tasks (Simon, 1967, 1990). In the Go/No-Go task participants must respond to the presence of a Go signal on most trials ("Go" trials) but withhold their response when presented with the No-Go signal on a small number of trials. Commission errors are the primary measure of interest; instances where participants fail to withhold their response on No-Go trials. In the related Stop Signal task, participants must respond as quickly as possible to a Go stimulus on each trial but withhold that response when this Go signal is followed by a Stop signal (presented on a minority of trials). Researchers typically calculate the stop signal reaction time (SSRT) – an estimate of the time needed to successfully inhibit a response which has already been initiated. Thus, the Stop Signal task requires *cancellation* of an in-progress response, whereas the Go/No-go task requires participants to *withhold* a prepotent response.

In contrast, the Simon task (Simon, 1967, 1990) measures inhibitory control over competing motor responses. For example, a typical set-up might include instructions to the participant to respond with the left button when they see a yellow stimulus, and the right button when they see a blue stimulus. Crucially, the stimulus may appear on the left or the right of the screen, but the location of the stimulus is not relevant to the participant's task (which is to respond according to stimulus colour). Therefore, the stimulus's location might prime a response that is congruent (same side) or incongruent (opposite side) with the response required by the task instructions. On incongruent trials, the automatically activated response elicited by the location of the stimulus must be inhibited in favour of the goal-directed response according to stimulus colour (or another visual feature), which results in longer response times (RTs) and reduced accuracy for incongruent compared to congruent trials. Therefore, the Simon task measures resolution of conflict between competing motor responses which have been simultaneously activated by different aspects of the stimulus.

Although Parkinson's has been associated with disrupted inhibitory control and a high incidence of ICBs, empirical studies investigating the effects of Parkinson's on response conflict and inhibition have produced mixed findings. For example, some studies using the Simon task have found that PwP show greater interference between competing responses (the difference in RTs for incongruent versus congruent trials e.g., Houvenaghel et al., 2016; van Wouwe et al., 2016) compared to healthy controls (HCs), whereas others have found no significant group differences (Wylie, Ridderinkhof, Bashore et al., 2010; Wylie, Ridderinkhof, Elias et al., 2010). Moreover, whilst some studies have shown that PwP produce more commission errors on the Go/No-Go

task compared to HCs (Geffe et al., 2016; Nombela et al., 2014), others have reported no group differences (de Rezende Costa et al., 2016; Georgiev, Dirnberger, Wilkinson, Limousin, & Jahanshahi, 2016). A hybrid Go/No-Go task that incorporated congruent and incongruent conditions (as in a Simon task) showed a larger interference effect for PwP relative to healthy controls in some conditions (Beste, Dziobek, Hielscher, Willemssen, & Falkenstein, 2009). Similarly, there is some evidence to suggest that PwP have longer SSRTs compared to HCs (and therefore reduced inhibitory control e.g., Gauggel et al., 2004; Nombela et al., 2014), whereas others have found no difference (Bissett et al., 2015). Still further studies have shown a functional deficit in PwP (e.g. differences in the blood oxygenation level-dependent (BOLD) signal in the fronto-striatal-thalamic loop during the Go/No-Go task, and the inferior frontal gyrus in the Stop Signal task) relative to HCs, even in the absence of an observable behavioural deficit (e.g. Baglio et al., 2011; Vriend et al., 2015).

Thus, it remains unclear whether or how Parkinson's may affect control over actions. However, there are substantial differences between studies – in terms of task, methods, analysis, and participants – which make it difficult to draw clear conclusions. For example, most studies investigating motor activation and/or control compare the time taken to respond in different conditions and report an overall central tendency for each condition. However, such a measure of central tendency does not elucidate differences in higher-order characteristics of the RT distribution and can be skewed by variability between participants (Ratcliff, 1993). More recently, some researchers have been comparing performance on tasks or conditions across the whole RT distribution. When applied to tasks measuring inhibition or conflict, these distributional analyses aim to temporally dissociate impulsive errors at the fast end of the RT distribution from failed inhibition at the slow end. According to the activation-suppression model (Ridderinkhof, 2002a, 2002b; van den Wildenberg et al., 2010) slower RTs allow more time for selective suppression of the automatic response to build up, whereas faster RTs do not allow sufficient time for inhibition and can result in fast, impulsive errors. This is visible by plotting accuracy (in conditional accuracy functions) or the RT interference effect (in delta plots) as a function of RT (see van den Wildenberg et al., 2010 for a review). Using these methods, studies have consistently revealed that PwP show deficits in successful inhibition of responses at the slow end of the RT distribution (van Wouwe et al., 2016; Wylie, Ridderinkhof, Bashore et al., 2010; Wylie, Ridderinkhof, Elias et al., 2010), but are no more susceptible to fast impulsive errors than HCs on the Simon task.

Moreover, many studies infer response inhibition and conflict by comparing the time it takes participants to press a button in response to different stimuli. However, button-press measures do not capture the process of response preparation, competition, and control. The binary nature of button press measures means that either a button press is detected, or it is not, and small amounts of force which are applied to a button (and reflect ongoing cognitive control)

might escape detection. The tools that have been used to measure these processes are not ideally suited to the task, and thus might contribute to the unclear nature of the effects of Parkinson's disease on inhibitory control. The findings of Baglio et al. (2011) and Vriend et al. (2015) suggest that there is a need for a more sensitive behavioural measure to examine response inhibition in Parkinson's. An alternative method of response measurement, therefore, is to directly measure response force. Indeed, such measures have been used successfully to measure simultaneous activation of competing motor plans, inhibition, and control in healthy adult participants (McBride, Sumner, & Husain, 2012, 2018) as well as neurological patients (McBride, Sumner, Jackson, Bajaj, & Husain, 2013), and similar measures have provided important constraints on computational models of human behaviour (Servant, White, Montagnini, & Burle, 2015).

In the present study we sought to examine the effects of Parkinson's disease on response inhibition and control by having the *same* participants complete two different tasks measuring different kinds of inhibitory control (the Stop Signal Task and the Simon task), while using a sensitive measure of continuous response force. Together, this provides an opportunity to elucidate the effects of Parkinson's disease on the dynamics of response inhibition and control.

The study firstly acts as a proof-of-concept. The force measurements (as opposed to binary measures) have been used successfully in healthy adult participants and other neurological populations, but not yet in Parkinson's. Using such a measure with Parkinson's presents unique challenges given the motor symptoms such as tremor and rigidity, and so we aim to demonstrate that force measures can be used with a unique algorithm to account for noise in the data generated by symptoms such as tremor.

If our results show that PwP generally show reduced inhibitory control in the Stop Signal Task (i.e., they have a longer SSRT) and/or Simon task (i.e. higher interference effects) than HCs, these group differences should *additionally* be evident in a more sensitive and continuous measure of response force. Crucially, the research is also driven by the mixed results for button-press response analyses in the previous literature but where there has been some indication of a functional deficit even when a behavioural deficit is not apparent (e.g. Baglio et al., 2011; Vriend et al., 2015). If PwP have reduced inhibitory control that is not evident from the traditional button-press measures for these two tasks, we may still be able to detect group differences with this sensitive measure of response force.

2.3. Materials and Methods

2.3.1. Participants

25 participants[1] (17 males, mean age 63.84 ± 5.35) with mild to moderate idiopathic Parkinson's[2] (Hoehn & Yahr stages 1-3) and 23 healthy control participants (12 males, mean age 68.91 ± 5.62) took part in the study (

Table 1). No participants reported a history of neurological conditions (except Parkinson's).

Two patients were not receiving dopaminergic treatment during the study, 21 were taking levodopa medication, 12 were taking dopamine agonists[3], and 18 were taking monoamine oxidase inhibitors. No patients had received deep brain stimulation. PwP were tested ON medication and had a mean score of 26.64 (± 12.61) on the Movement Disorders Society Unified Parkinson's Disease Rating Scale Motor Section III (Goetz et al., 2008) and 2 (± .65) on the Hoehn and Yahr (1967) staging of symptom severity.

All participants completed the Addenbrooke's Cognitive Examination (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) to exclude significant cognitive impairment (none were excluded on this basis), the Test of Pre-morbid Functioning (Wechsler, 2011), Edinburgh Handedness Inventory (Oldfield, 1971), Geriatric Depression Scale (Yesavage et al., 1983), and the Barratt Impulsiveness Scale[4] (Barratt, 1959). Missing data on the Geriatric Depression Scale were replaced with the total mean score for that participant.

The study was approved by an NHS Research Ethics Committee (NRES Committee North West – Liverpool Central) and was conducted in accordance with the Declaration of Helsinki[5].

[1] Sample size was determined by the availability of participants and funding and was therefore necessarily constrained by resources.
[2] Data were collected from one additional participant with Parkinson's, but the severity of their tremor meant they were not able to satisfactorily complete the tasks. Their data were not analysed.
[3] An anonymous reviewer suggested we check there were no differences in impulsivity on all main variables in the experimental analyses for patients on dopamine agonists medication vs those without. For all analyses (including BIS scores), there were no differences between these patient groups.
[4] During data collection, we discovered that two items from the Barratt Impulsiveness Scale ("I plan for job security", non-planning impulsivity; "I change jobs", motor impulsivity) were often irrelevant for this largely retired demographic, and after data collection we confirmed that this comprised the majority of the missing data. These items were therefore removed from analysis for all participants and any remaining missing data were replaced with the mean score for that sub-scale for that participant.
[5] Ethical documentation can be found in Appendix A.

Table 1. Characteristics of the Parkinson's and control groups[6]. Data represent ratios or means and standard deviations

	PwP (*n* = 25)	HCs (*n* = 25)	Statistical test
Age (years)	63.84 (5.35)	68.91 (5.62)	$t(46) = 3.20$, $p = .002$*
Education (years)	15.72 (3.16)	16.57 (3.34)	$t(46) = .90$, $p = .37$
Male:Female	17:8	12:11	$X^2(1, N = 48) = 1.26$, $p = .27$
Addenbrooke's Cognitive Examination	95.04 (3.81)	97 (2.20)	$t(38.9) = 2.20$, $p = .03$*
Barratt Impulsiveness Scale (total score)	57.89 (9.54)	51.24 (7.17)	$t(46) = 2.71$, $p = .009$*
BIS (attentional)	16.42 (3.01)	14.85 (2.90)	$t(46) = 1.83$, $p = .07$
BIS (motor)	21.23 (3.78)	18.50 (2.39)	$t(46) = 2.97$, $p = .004$*
BIS (non-planning)	20.52 (4.84)	18.45 (4.20)	$t(46) = 1.57$, $p = .12$
Handedness (L:R)	2:23	2:21	$X^2(1, N = 46) = .008$, $p = .93$
Test of Premorbid Functioning	57.56 (11.23)	61.87 (8.23)	$t(43.88) = 1.53$, $p = .13$
Geriatric Depression Scale	7.37 (5.91)	4.13 (4.09)	$t(42.83) = 2.22$, $p = .03$*
Disease duration (years)	8.08 (4.53)		
Symptom laterality (L:R)	16:9		
MDS-UPDRS III	26.64 (12.61)		
H&Y Stage	2 (.65)		
Subtype (TD:PIGD)[7]	8:17		

*Note: MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale, H&Y Stage = Hoehn & Yahr Stage, TD = Tremor dominant symptoms, PIGD = Postural instability/gait dominant symptoms. * denotes significant differences between groups with a two-tailed alpha level of .05*

2.3.2. Tasks and Procedures

Participants performed both tasks in a darkened room and provided button press responses using a standard QWERTY keyboard that had force sensing resistors (FSRs; Interlink Electronics FSRTM 400) placed upon the A and L keys. Force data were recorded at 1000Hz and digitized using a LabJack U3 HC data acquisition device with DAQFactory Express software (version 16.2, Azeo Tech Inc.). Participants were instructed to keep the index fingers of each hand on the FSRs throughout each task so that a continuous force measurement could be recorded. Voltage change from the FSRs provided a continuous measure of response force, simultaneously and independently from the left and right hands.

[6] As suggested by an anonymous reviewer, we repeated the main analyses in an exploratory manner with age and GDS scores as covariates to check that the significant group differences on these measures did not affect the pattern of results. We found that our conclusions remained the same.

[7] The MDS-UPDRS was used to identify tremor dominant and postural instability and gait dominant patients using the same method reported by Stebbins et al. (2013).

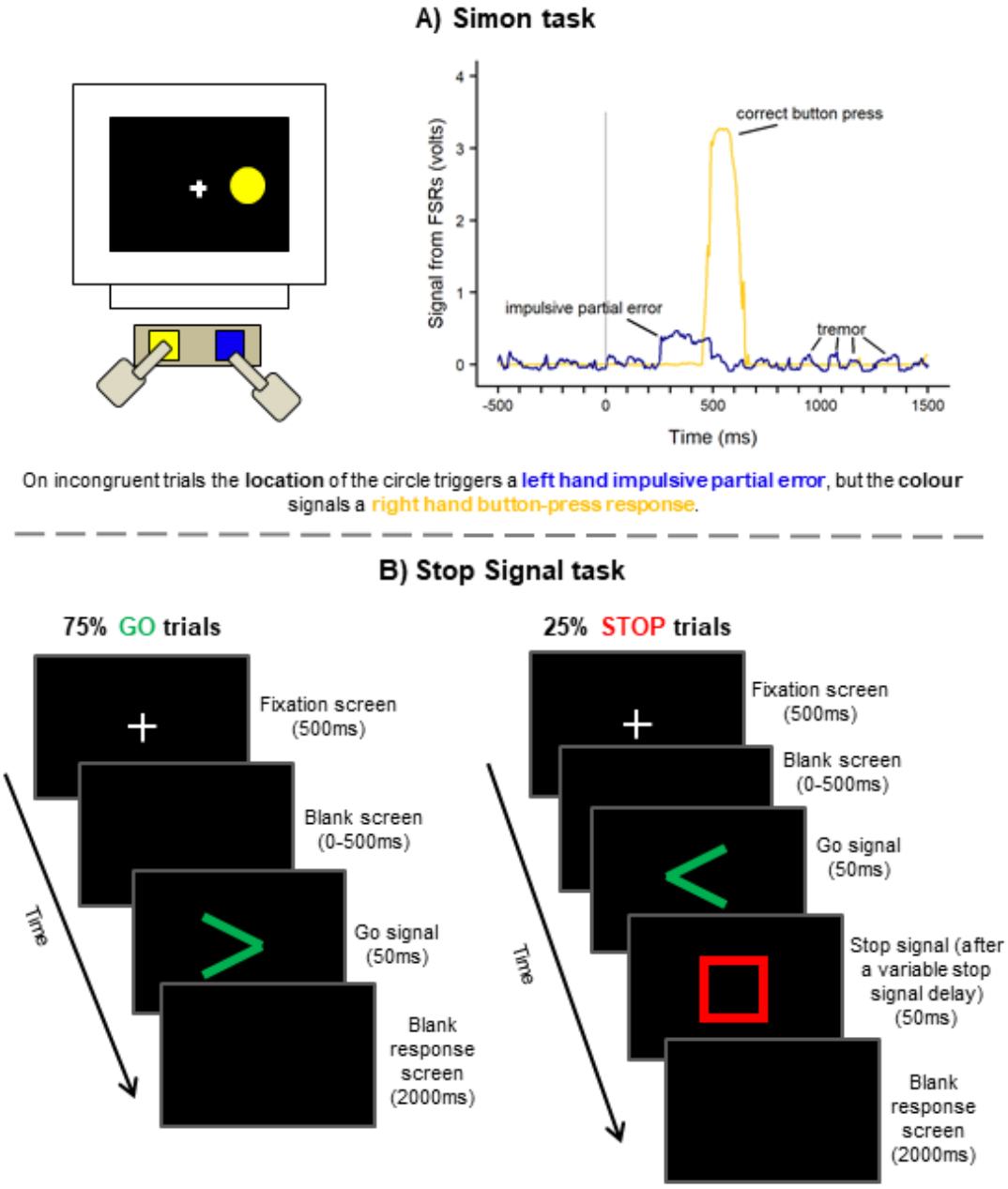

*Figure 1. Trial procedure for the Simon task and Stop Signal task. A) In the Simon task, we show an example incongruent trial and the resulting voltage over the course of that trial in a participant with Parkinson's. The stimulus location (at 0ms) triggered an impulsive right-hand force response (blue line) that was not detected by the button-press measure. The stimulus colour signalled a left-hand response (yellow) which **was** recorded as a button-press. Data have been smoothed using a 5-point moving average and baseline corrected. In B) Stop Signal task, participants responded according to the direction of the green arrow, and on 25% of trials attempt to withhold that response upon seeing a red Stop signal after a variable stop signal delay. This delay increases or decreases by 40ms in two 1-up-1-down staircase tracking procedures (independently for each hand) following a successful or unsuccessful Stop trial respectively.*

2.3.2.1. Simon task

The Simon task was programmed in E-Prime (version 1.2, www.pstnet.com) and run on a computer with a flat 20inch screen (resolution of 1024x768 pixels, 75Hz refresh rate). Although actual timings were dependent on the refresh rate, the timings reported here were as programmed in E-Prime. Each trial began with a centrally presented white fixation cross (77px) on a black screen for 500-1000ms (drawn from a rectangular distribution randomly and independently on each trial). A blue or yellow circle (176px diameter) was presented at one of three locations (left, right, or centrally; that is, horizontally centred at 25%, 50%, or 75% of the screen width) (Figure 1A). Participants were instructed to respond according to the colour of the circle as quickly and as accurately as possible, and to ignore its location on the screen.

Half of the participants in each group were instructed to press the left key for a blue circle and the right key for a yellow circle, whereas the other half of participants were given the opposite instructions in a counterbalanced design. The stimulus remained on the screen until the participant had made a response, and the next trial began after a 500ms blank inter-trial interval. The experiment consisted of 6 conditions: congruent blue, congruent yellow, incongruent blue, incongruent yellow, neutral blue, and neutral yellow. A trial was said to be "congruent" if the stimulus appeared on the same side of the screen as the side of the response, and "incongruent" if it appeared on the opposite side. In neutral trials the circle was presented centrally. Participants began with a short practice block containing 12 trials (2 trials x 6 conditions). During the practice block, participants were provided with on-screen feedback after each trial ("Correct!" or "Incorrect. Remember, blue = left, and yellow = right" according to counterbalancing) which was not present during the main experiment. The experiment itself consisted of two sessions, approximately an hour apart, each containing four blocks. The first block in each session contained 30 neutral trials (15 of each colour), and the remaining three blocks each contained 80 trials equally split amongst the remaining four conditions. The second session was identical to the first, which resulted in a total of 480 congruent and incongruent trials and 60 neutral trials. Trial order was shuffled randomly and independently for each block and participants were encouraged to rest between blocks.

2.3.2.2. Stop Signal task

The Stop Signal task was programmed in Presentation (version 16, www.neurobs.com) on the same computer as the Simon task, and using the same method of responding (the left and right keys covered by the FSRs). A white fixation cross (48px) was presented in the centre of a black screen for 500ms, followed by a blank screen for a random duration of 1-500ms to reduce anticipatory responses. The Go signal, a green arrowhead (200 x 200px), was presented in the centre of the screen for 50ms, and participants were instructed to respond with their left or right hand according to the direction of the arrow. On 25% of trials the Stop signal, a hollow red square (250 x 250px), appeared for 50ms after a variable stop signal delay (SSD) which

indicated that participants must withhold their pre-potent response to the Go signal (Figure 1B). The SSD began at 200ms for all participants and was adjusted according to a 1-up-1-down staircase (separately for left and right hands) with a fixed-step of 40ms. Therefore, following a successful Stop (where no button press was recorded) the SSD increased by 40ms on the next stop trial for that hand, and for an incorrect Stop the SSD decreased by 40ms. This procedure helped to ensure that participants were successfully inhibiting their responses on approximately 50% of left and 50% of right-hand Stop trials. Participants were instructed to respond as quickly and accurately as possible and were encouraged not to "wait" to see if a Stop signal would appear (as recommended by Logan, 1994). In both Go and Stop trials, a blank screen was presented after the stimuli for either 2000ms or until a response was recorded.

Participants first completed a practice block consisting of 12 trials during which on-screen feedback was supplied according to the participant's response ("Correct go", "Missed button", "Correct stop", "Incorrect stop"); this was not present in the main experiment. Participants could repeat the practice until they were comfortable with the task instructions. There were two sessions, approximately an hour apart, each containing 3 blocks. Each block had a total of 120 trials (45 right Go, 45 left Go, 15 right Stop, and 15 left Stop) shuffled randomly and independently for each block. Therefore, there were a total of 720 trials of which 180 were Stop trials.

2.3.3. Data analysis

Group data were subject to Tukey's (1977) box plot outlier removal procedure. This removes participants who produced a data point beyond the upper or lower boundaries (3 times the difference between the 25th and 75th percentiles) on any variable within each statistical test.

All data were tested for normality using the Shapiro-Wilk test and then arcsine or log10 transformed (for accuracy and RT data, respectively) if they violated the assumptions of normality. If transformed data still violated the assumptions of normality, then the equivalent non-parametric test was used on the untransformed data. We initially checked to see whether there were differences in performance on both tasks when split by handedness (dominant and non-dominant) but found no significant differences and so collapsed all responses across hands for the remaining analyses.

Alongside null hypothesis significance testing, we additionally calculated Bayes Factors (BF_{10}) due to the small sample size using default priors in JASP (https://jasp-stats.org/) which demonstrates the likelihood that a particular hypothesis is true given the data. Generally, a BF_{10} below .30 indicates substantial support for the null hypothesis, and a BF_{10} above 3 indicates substantial evidence in favour of the alternative hypothesis (Dienes, 2014; Wagenmakers et al., 2018).

2.3.3.1. Force measurements

Force data were processed using similar methods to those reported in McBride et al. (2012, 2018). In MATLAB R2012a, for each participant and separately for left and right hands, we first smoothed the data using a 5-point moving average; for each data point, an average was taken from that point and the two points either side of it to smooth high frequency noise. The data for each trial were then epoched into 2000ms periods with target onset at 500ms. The first 500ms of the epoch provided baseline activity in the pre-stimulus period which was then used to baseline-correct the following 1500ms on a trial-by-trial basis.

A response was said to have occurred at the first time point in the epoch where the following criteria were satisfied: a recorded amplitude greater than .2 volts[8] plus 3 standard deviations above the baseline activity, where 17 out of 20 of the following data points also satisfy this criterion, and where another measurement within 70-130% of its amplitude was not detected in the surrounding 250ms. These criteria were chosen[9] to remain sensitive enough to identify sub-threshold responses that were not forceful enough to produce a button press, whilst remaining conservative enough so as not to erroneously identify instances of tremor from PwP which usually occurs at a frequency of 4-6Hz (Lees, Hardy, & Revesz, 2009). Figure 1A illustrates a partial, sub-threshold, response in the Simon task from a participant with Parkinson's who had visible tremor, but where a button-press was recorded in the opposite hand only.

We checked that the force measurement was recording actual button-press responses as expected; full details of this can be found in the supplementary materials.

2.4. Results

We found no reliable interactions between our effects of interest and symptom laterality in PwP (see supplementary materials for full analyses) so the effects of symptom laterality are not reported any further.

2.4.1. Simon task

2.4.1.1. Button-press data

Accuracy on the Simon task was very high for both groups and in both trial types (accuracy over 96%), so accuracy analyses will not be reported further. Anticipatory RT errors that were likely to have been initiated before stimulus onset (< 150ms) and slow RTs (> 1500ms) were removed first and any remaining outliers removed using Van Selst and Jolicoeur's (1994) method[10]. One person with Parkinson's was identified as having very slow overall RTs using

[8] As in McBride et al. (2018) we used a constant in addition to a standard deviation threshold in order to reject noise and more reliably detect responses.
[9] The researchers were blind to the condition and group when making decisions as to how to process the data.
[10] This method trims outliers with a per condition and per participant moving standard deviation, where the standard deviation is adapted depending on the number of trials.

Tukey's (1977) box-plot outlier procedure and was excluded from analysis of such RTs. Summary data and results can be found in Table 2.

Table 2. Mean (SD) and statistical tests for the main button-press and response force variables associated with the Simon and Stop Signal tasks in both participant groups.

	PwP	HCs	Statistical test
Congruent RT (ms)	547 (65)	543 (58)	$t(45) = .26$, $p = .80$, $BF_{10} = .30$
Incongruent RT (ms)	586 (68)	583 (63)	$t(45) = .17$, $p = .86$, $BF_{10} = .29$
Simon effect for RT (ms)	39 (23)	40 (21)	$t(45) = .21$, $p = .84$, $BF_{10} = .30$
Congruent partial errors (%)	9 (5)	9 (5)	$t(43) = .38$, $p = .71$, $BF_{10} = 31$
Incongruent partial errors (%)	12 (5)	10 (6)	$t(43) = .84$, $p = .41$, $BF_{10} = .39$
Stop accuracy (%)	55 (4)	55 (4)	$t(41) = .22$, $p = .83$, $BF_{10} = .31$
Go-RT (ms)	716 (150)	699 (150)	$t(41) = .36$, $p = .72$, $BF_{10} = .32$
SSRT (ms)	290 (59)	272 (41)	$t(39.32) = 1.14$, $p = .26$, $BF_{10} = .49$
Go partial errors (%)	10 (5)	11 (7)	$U = 207$, $p = .43$, $BF_{10} = .34$
Stop partial errors (%)	28 (12)	27 (14)	$U = 211$, $p = .38$, $BF_{10} = .32$

A two-way mixed ANOVA showed that for RTs there was a significant main effect of congruency ($F(1,45) = 153.76$, $p < .001$, $BF_{10} = 1.084*10^{13}$) but no significant main effect of group ($F(1,45) = .05$, $p = .83$, $BF_{10} = .49$) nor an interaction between the effects of congruency and group ($F(1,45) = .04$, $p = .84$, $BF_{10} = .28$). A raincloud plot of the raw data, median, and interquartile range for RTs can be seen in Figure 2A.

2.4.1.2. Distributional analyses

To investigate how the Simon effect changed across the RT distribution, we plotted the Simon effect as a function of the overall correct RT in a delta plot (see e.g. Ridderinkhof, 2002a). Outliers (defined as responses faster than 150ms and slower than 1500ms) and incorrect responses were replaced with the median correct RT for that hand, for that participant, for that condition, within that block (to maintain equal bin-sizes). For each participant, RTs were then rank ordered separately for congruent and incongruent trials and divided into 6 equal sized bins (40 trials per bin per condition). The mean RT for each bin in each condition was calculated and then used to calculate the Simon effect (Incongruent RT minus Congruent RT on all correct trials) per bin. The mean Simon effect for each bin was plotted against the mean RT for that bin. The slope between the two bins in the slowest portion of the delta plot is considered the most sensitive measure of response inhibition where a steeper and more negative slope is indicative of greater inhibitory control (Ridderinkhof, 2002a; van den Wildenberg et al., 2010).

Figure 2C shows the RT distribution for PwP and HCs. A two-way mixed ANOVA showed a significant main effect of slope ($F(2.78,125.24) = 7.24$, $p < .001$, $BF_{10} = 1396$) but no significant main effect of group ($F(1,45) = 1.12$, $p = .30$, $BF_{10} = .30$) nor an interaction effect between slope and group ($F(2.78,125.24) = .33$, $p = .79$, $BF_{10} = .05$). This suggests that whilst susceptibility to the Simon effect does change as a function of RT, as evidenced by a main

effect of the gradient of the slopes, this does not differ between PwP and HCs. A planned independent t-test on the gradient of the slope between the slowest two bins additionally revealed that HCs did not have a significantly more negative going final slope compared to PwP ($t(45) = .65$, $p = .26$, $BF_{10} = .50$, one-tailed).

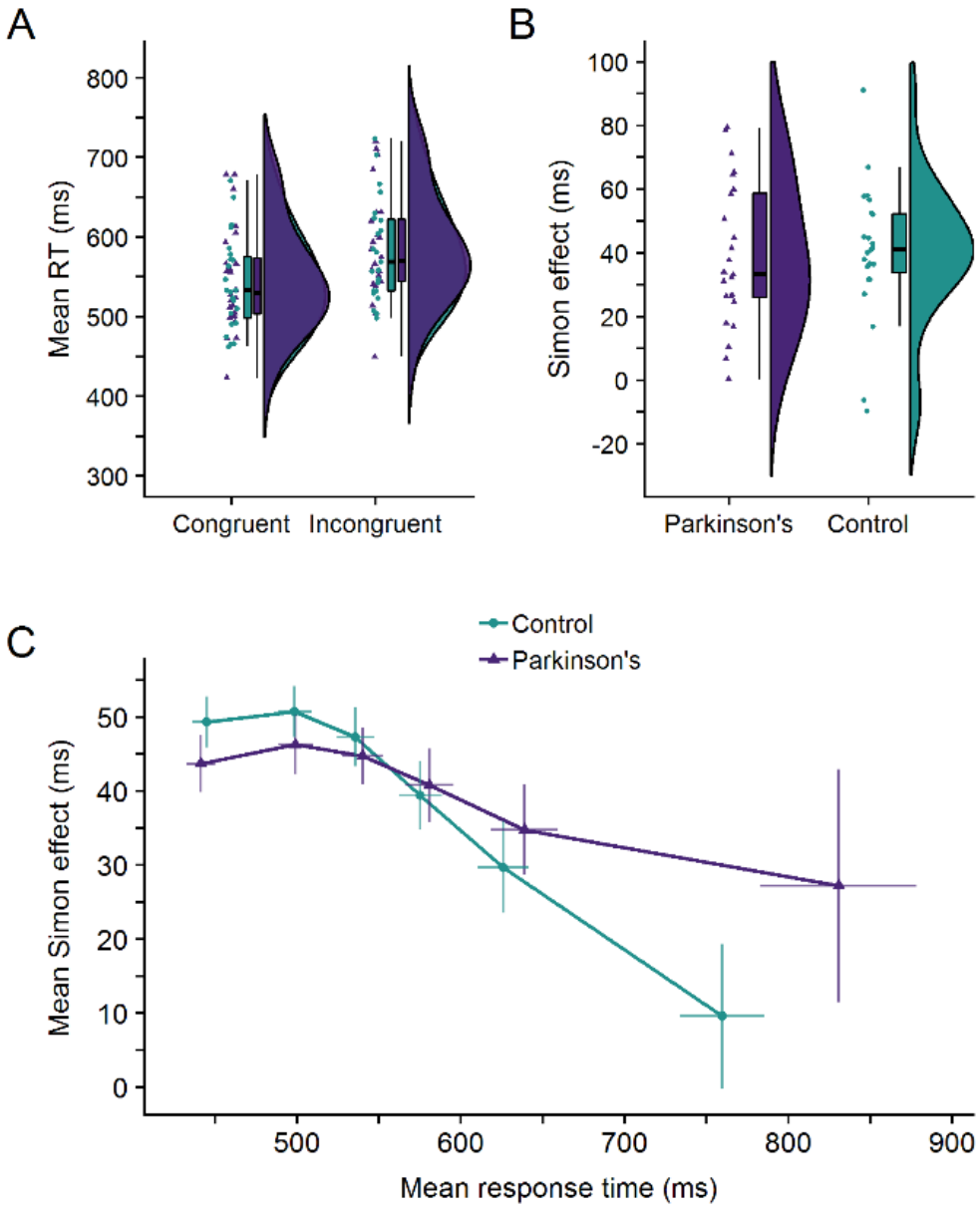

Figure 2. A) A raincloud plot for the response times (RT) in the Simon task on congruent and incongruent trials for both participant groups. The plot displays each participant's mean correct RT (horizontally jittered), a boxplot, and a split half violin plot of the density (Allen, Poggiali, Whitaker, Marshall, & Kievit, 2018). B) A raincloud plot for the Simon effect (incongruent RT minus congruent RT) for both participant groups. C) Delta plot for the Parkinson's and healthy control groups. The Simon effect is plotted as a function of RT. Error bars show the standard error of the mean.

2.4.1.3. Partial errors in response force

One participant with Parkinson's and one HC participant were not included in the force analysis for both tasks due to equipment failure on the day of their visit. One further person with Parkinson's was excluded as an outlier. The data from the FSRs were used to calculate partial errors in response force, that is the percentage of trials containing above-threshold force responses on the incorrect hand where no incorrect button-press was detected. A two-way mixed ANOVA on the percentage of partial errors in response force showed a significant main effect of congruency ($F(1,43) = 8.07$, $p = .007$, $BF_{10} = 6.17$) where more partial errors were detected on incongruent trials compared to congruent trials, but no significant main effect of group ($F(1,43) = .46$, $p = .50$, $BF_{10} = .45$) nor an interaction between the effects of congruency and group ($F(1,43) = .37$, $p = .55$, $BF_{10} = .33$). There were significantly more partial errors on incongruent trials compared to congruent trials for PwP ($t(22) = 2.18$, $p = .02$, $BF_{10} = 6.78$, one-tailed) and HCs ($t(21) = 1.86$, $p = .04$, $BF_{10} = 1.82$, one-tailed), but the Bayes factors suggest the alternative hypothesis is more likely than the null in PwP only. Figure 3A shows the raw data, median, and interquartile range for partial errors in response force.

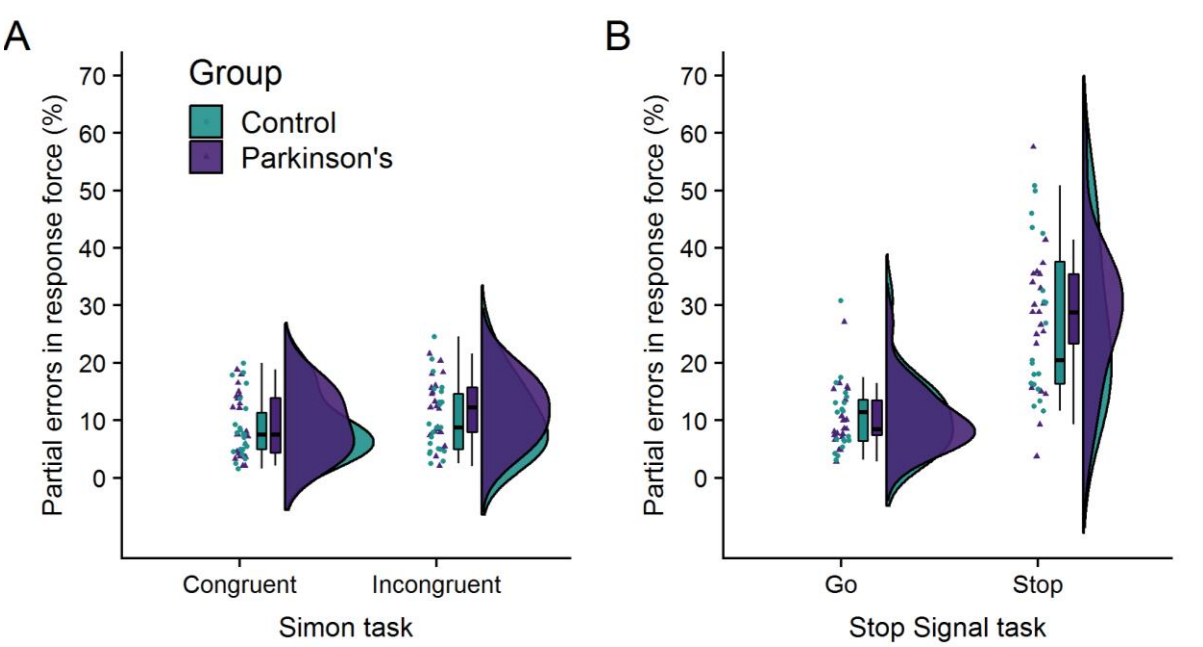

Figure 3. Raincloud plots for partial errors in response force for each group on A) congruent and incongruent trials in the Simon task, and B) Go and Stop trials in the Stop Signal task.

2.4.2. Stop Signal task

Five participants were excluded from analysis (2 PwP, 3 HCs) for using a waiting strategy against task instructions. This caused a plateau in the stop signal delays at the maximum

available value instead of continually adjusting throughout the task; this left a total of 23 PwP and 20 HCs[11].

2.4.2.1. Button-press data

Accuracy for Stop trials was expected to be approximately 50% due to the staircase tracking procedure. Go accuracy was very high for both groups (>97%) so was not analysed further. Anticipatory errors (<150ms) and slow RTs (>1500ms) were removed as outliers, and then any remaining values that were more than 2.5SD away from the mean for each block were also removed. Go-RT was defined as the RT on correct Go trials. There were no significant group differences for any of the above measures (see Table 2).

The SSRT was calculated separately for each hand following the procedure outlined by Verbruggen and Logan (2009): we subtracted the mean SSD from the *N*th percentile of the Go-RT distribution, where *N* is the percentage of failed stops. Although SSRTs were generally longer in PwP (mean = 290ms, SD = 59ms) relative to HCs (mean = 272ms, SD = 41ms), this difference was not significant: $t(39.32) = 1.14$, $p = .26$, $BF_{10} = .49$. Figure 4 shows the raw data, median, and interquartile range for SSRT.

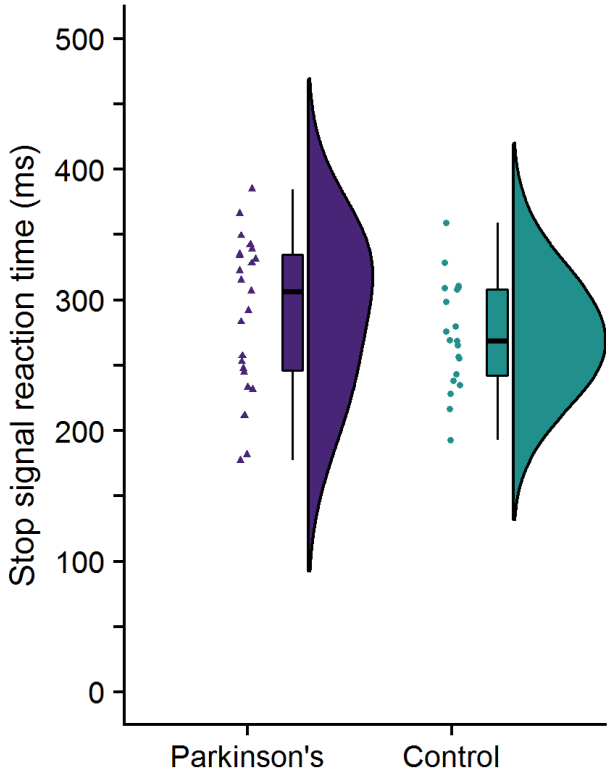

Figure 4. Raincloud plot for the stop signal reaction time (SSRT) for both the Parkinson's and healthy control groups. The SSRT is an estimation for how long it takes the "Stop" process to overtake the "Go" process for an individual participant.

[11] After removal of these participants' data there were no other meaningful changes to group differences on demographic or neuropsychological measures.

2.4.2.2. Partial errors in response force

One participant with Parkinson's was excluded as an outlier. The data from the FSRs were used to calculate partial errors in response force. For Go trials, that is the percentage of trials containing an above-threshold force response on the *incorrect* hand, where a correct button press response had been recorded in the *correct* hand. For Stop trials, this is the percentage of trials that were successfully inhibited according to the button-press data (i.e. no button-press detected), but where an above-threshold force response was detected in the hand *primed to respond* by the direction of the Go signal. Two Mann-Whitney U tests showed that PwP did not produce a significantly higher proportion of partial errors on Go trials compared to HCs (U = 207, p = .43, BF_{10} = .34, one-tailed) nor on Stop trials (U = 211, p = .38, BF_{10} = .32, one-tailed). There were significantly more partial errors on Stop trials compared to Go trials for PwP ($t(20)$ = 6.15, p < .001, BF_{10} = 7932, one-tailed) and HCs ($t(18)$ = 5.72, p < .001, BF_{10} = 2344, one-tailed). Figure 3B shows the raw data, median, and interquartile range for partial errors in response force.

2.5. Discussion

The present study used a continuous measure of response force alongside traditional button-press responses to provide a sensitive behavioural measure of cognitive control in people with Parkinson's compared to healthy adults in the Simon task and the Stop Signal task. Our button-press data show no significant differences between PwP (at least, with mild-to-moderate symptoms) and HCs with regards to the Simon effect or SSRT, although previous work in this area reports mixed findings. Moreover, and contrary to previous findings reported elsewhere (e.g., van Wouwe et al., 2016; Wylie et al., 2009a, 2009b; Wylie, Ridderinkhof, Bashore et al., 2010; Wylie, Ridderinkhof, Elias et al., 2010), distributional analyses of the time course of our Simon effect showed no significant differences in how well PwP and HCs were able to successfully inhibit responses at the slower end of the RT distribution. As shown in Fig. 2C, the RTs at the slow end of the RT distribution are very variable, particularly for PwP, which may account for the variable findings reported in this field previously. Such variance may be a feature of any sample of PwP which could suggest that other individual and variable factors of Parkinson's itself may differentially influence response inhibition.

2.5.1. Inconclusive group differences in SSRT

According to the race model of inhibitory control, the SSRT is an estimation of the time it takes the Stop process to overtake the Go process for each participant. Again, previous research has produced mixed findings. Whilst we found no significant group differences for SSRT, and although our study used a similar number of participants to studies reported elsewhere, our Bayes factors show that we do not have enough evidence to convincingly accept or reject the null hypothesis. Potentially, this explains the mixed findings in the literature thus far; many studies are underpowered (Dumas-Mallet, Button, Boraud, Gonon, & Munafò, 2017) and there

may not yet be enough evidence in the literature to conclude whether PwP have difficulties with response inhibition.

2.5.2. Both groups show more partial errors in response force for trials requiring response inhibition

Partial errors in response force on incongruent trials may reflect the cognitive process of suppressing an automatically activated response in favour of the goal directed response (Ridderinkhof, 2002a, 2002b; van den Wildenberg et al., 2010). We sought to use this measure to complement previous research that detected a functional deficit in PwP even where no behavioural deficit was present (Baglio et al, 2011; Vriend et al., 2015). We used these data to detect partial errors in response force; that is, where an increase in response force is detected either in the absence of a button-press (on Stop trials in the Stop Signal task), or where a button-press was detected in the *opposite* hand (in the Simon task, and on Go trials for the Stop Signal task). On the Simon task, both groups made significantly more partial errors in response force for incongruent trials compared to congruent trials. There were no group differences which may suggest that there is no functional deficit present in Parkinson's if our response force measure is sensitive enough to pick up more subtle differences in response conflict. Interestingly, the Bayes factors suggest that there is more evidence for the conclusion that PwP produce more partial errors on incongruent than congruent trials, but that in HC participants there is insufficient evidence to support the statistically significant difference and to confidently reject the null hypothesis. This could be tentatively interpreted in opposing ways. Firstly, this may reflect *better* response inhibition in PwP as they may be better able to suppress the response before it produces an incorrect button-press, whereas in HCs these partial responses may be more likely to result in an incorrect button-press. Alternatively, it could reflect *worse* response inhibition in PwP. HCs may be able to suppress their responses faster and produce fewer partial errors in response force for this reason, as the suppression successfully occurs earlier in the potential motor movement.

On the Stop Signal task, partial errors (where there was above-threshold force applied to the response button, but this force was not sufficient for a button-press to be detected) were recorded on up to 30% of Stop trials which demonstrates that our measure provides a sensitive means of detecting sub-threshold erroneous response activity in the effectors that would otherwise be missed by conventional button-press measures alone. Moreover, there was no significant difference in the number of partial errors recorded for PwP compared to healthy controls, and indeed our Bayes factors indicate that partial error rate was perhaps equivalent for the two groups (BF_{10} = .32).

Our results complement those of Vriend et al. (2015), who also found that the stop signal reaction time did not differ between PwP and HCs, which indicates no behavioural deficit.

However, they also found that a successful "Stop" was uniquely tied to the inferior frontal gyrus compared to "Go", and that a functional deficit in this region was observed in PwP. In the present study, we found an adjacent discovery; no behavioural deficit with the stop signal reaction time measure but a unique pattern of results with increased partial errors in successful "Stops" during ongoing cognitive control. Whilst the use of FSRs cannot directly support the theory that PwP experience functional deficits in the inferior frontal gyrus whilst engaged in the Stop Signal task, it may be that when a functional deficit does occur the response force data can also support this, more so than the traditional behavioural measure of stop signal reaction time. FSRs are an inexpensive and easy method to detect group differences more thoroughly, even if they alone cannot provide an explanation for those group differences as in neuroimaging studies.

2.5.3. Does performance on tasks correlate?

The Simon effect was significantly and positively correlated with the total Barratt Impulsiveness Score, but not the motor score (see supplementary materials). Therefore, a higher score of trait impulsivity is correlated with a larger Simon effect. This finding is consistent with previous research from Duprez et al. (2017); they found significant correlations between total impulsivity score and increased impulsive errors. However, they also found that total impulsivity is also correlated with *better* inhibitory control at the slow end of the RT distribution; they suggest the subthalamic nucleus, part of the basal ganglia circuitry affected in Parkinson's, has a temporally dissociated role in both poor conflict resolution and successful response suppression, as well as involvement in trait impulsivity (Duprez et al., 2017) which may help explain our correlation here.

The SSRT did not correlate significantly with the Barratt Impulsiveness Scale total or motor scores which suggests that trait impulsivity, especially when related to motor impulsivity (BF_{10} = .45), is unrelated to the ability to withhold a response, contrary to previous findings (Caswell, Bond, Duka, & Morgan, 2015; Gorlyn, Keilp, Tryon, & Mann, 2005; Nolan, D'Angelo, & Hoptman, 2011). Previous work has also suggested that the factor structure of the Barratt Impulsiveness Scale might be different in PwP compared to the general population, as there is low internal consistency (Smulders, Esselink, Cools, & Bloem, 2014), and indeed a different factor structure does appear to exist in PwP (Ahearn, McDonald, Barraclough, & Leroi, 2012).

We also found no significant correlation between the Simon effect and SSRT for PwP. Although previous research has suggested that there is an overlap in the brain networks required to perform successfully in both tasks (Jahfari et al., 2011; Sebastian et al., 2013), our data may suggest that the tasks load different mechanisms of inhibition and control.

2.5.4. Limitations of the current study

Parkinson's is a heterogeneous disease and, as such, it is difficult to compare samples across studies. Generally, participants with Parkinson's tend to have more mild symptoms, owing to the practicalities of needing to be able to perform the task(s) (e.g. make a response using a button-box) which limits the generalisability of any findings to more advanced Parkinson's cases. PwP across studies often exhibit a mix of confounding characteristics, some of which have been shown to affect response inhibition and response conflict in other studies, such as subthalamic nucleus deep brain stimulation and the presence of additional ICBs (Mirabella et al., 2012; Ray et al., 2009; Swann et al., 2011; van Wouwe et al., 2016; van den Wildenberg et al., 2006; Wylie, Ridderinkhof, Bashore et al., 2010; Wylie, Ridderinkhof, Elias et al., 2010; Wylie et al., 2012). Whilst there were no participants with deep brain stimulation in our present sample, much of the literature - including this study where we did not collect such information - do not specifically exclude or account for PwP who have additional ICBs, which may well be up to 50% of any sample (Corvol et al., 2018). It is therefore likely that an unknown proportion of any sample of participants with Parkinson's also have ICBs, which will affect any conclusions made about the effects of Parkinson's (relative to dopaminergic medication) on response inhibition.

It is also possible that the published literature may overestimate group differences. As noted above, we have used similar tasks with a similar number of participants to many of the studies reported in the literature, and yet our Bayes factors indicate that we do not always have enough evidence to accept or reject the null hypothesis. In those cases where we did have enough evidence, it was largely in favour of the null hypothesis that there are no significant differences in response inhibition between PwP and HCs.

The force response analysis used here was built upon previous work by McBride et al. (2012, 2013, 2018), and specifically adapted to be suitable for PwP. The data from the PwP had a lower signal-to-noise ratio than data from the HCs due to many PwP exhibiting the tremor that is often associated with their disease. We attempted to account for this during data analysis by filtering out above-threshold responses that occurred at a frequency of a typical Parkinsonian tremor (4-6Hz, Lees et al., 2009). It is therefore possible we are missing some genuine responses or mistakenly categorising tremor or random noise as a genuine response. Despite these possible imperfections, this measure still provides a more sensitive measure than button-presses, as shown by our ability to capture partial errors in response force that were not detected in the button-presses.

It is additionally possible that we may be mistakenly categorising mirror movements as partial errors in response force. Mirror movements are simultaneous movements of a lesser amplitude that can occur in the opposite hand to the one performing an action and were observed here visually early in the analysis process. They tend to be pathological in nature after childhood and

are particularly prominent in the earlier stages of Parkinson's (Beaulé et al., 2012; Espay, Li, Johnston, Chen, & Lang, 2005). We cannot assume that mirror movements occur independently of response inhibition and may therefore be unequally distributed across trials requiring, or not requiring, an inhibitory process. With our current method it is difficult to define and distinguish mirror movements from partial errors of inhibitory control.

Our algorithm was designed to remove the effects of Parkinson's tremor from the force data (so tremors were not mistaken for partial responses), and this necessarily means that we have not analysed any effects of tremor phase on participants' performance on the tasks presented here. It is possible that errors may have been elicited more commonly during different phases of the participants' tremor – such as when the stimulus onset as the tremor was in the same direction as the response. We would expect any such effect of stimulus presentation coinciding with tremor phase to be equally distributed across conditions and so is unlikely to account for any effects reported here, but this might be a fruitful avenue for further investigation.

2.5.5. Conclusions

Overall, we provide evidence that PwP and HCs do not significantly differ on their susceptibility to the Simon effect using button-press measures, but insufficient evidence regarding group differences for the percentage of partial errors on incongruent trials in this task. Conversely, we found insufficient evidence to support the null hypothesis that SSRTs do not differ between groups, but evidence in favour of the null hypothesis that the groups produce a similar percentage of partial errors in response force on Stop trials. In summary, we show that it is more likely that people with mild-to-moderate Parkinson's do not show an impairment in response inhibition or response conflict relative to healthy controls, but that more evidence is needed to make even stronger conclusions in favour of the null.

Additionally, we demonstrated the utility of a more sensitive method of measuring the cognitive process of response inhibition and response conflict using force sensing resistors; this allowed us to identify partial responses that would have gone undetected by conventional button-press measures (including up to 30% of trials in the Stop Signal task). This may be a useful tool to detect more subtle group differences in tasks of ongoing cognitive control that are usually measured with button-press responses.

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2.7. Supplementary materials

2.7.1. Correspondence between PwP and HC's button-presses and response force measures

As with any threshold, it is possible that we are missing some genuine responses in the force measurement and/or erroneously categorising some random noise as genuine response – the same would be true of any measure. To determine whether there are any systematic effects of the threshold we have chosen we examined what percentage of button press responses were also detected as being above force threshold, i.e. the "correspondence" between the two measures.

Overall, and reassuringly, correspondence was high for both tasks (see Table 3). This means that in most trials where a binary button-press was detected, there was also an identifiable response detected by the algorithm for the force sensing resistors (FSRs) data. There was a significantly higher correspondence for the HCs relative to the PwP (a mean of 98-99% correspondence compared to a mean of 95-96% correspondence), which most likely reflects the Parkinsonian tremor making it more difficult for our algorithm to discriminate tremor from response with 100% accuracy. Although this is a small difference in real terms, it might mean that our response force measure may miss more responses in PwP than in the HC group. Despite this, response force is still more sensitive than the standard button press measurement.

Table 3. The correspondence is the percentage of trials with a button-press where a response was also detected by the algorithm on the data from the FSRs

	PwP	HCs	Statistical test
Simon – Congruent	95 (8)	99 (1)	$U = 126$, $p = .004$, $BF_{10} = 7.97$
Simon – Incongruent	95 (6)	98 (1)	$U = 158$, $p = .03$, $BF_{10} = 1.85$
Stop Signal Task – Go	96 (4)	98 (2)	$U = 120$, $p = .03$, $BF_{10} = 1.38$

2.7.2. Symptom laterality

2.7.2.1. Simon task

A two-way within-subjects ANOVA with a factor of congruency (congruent, incongruent) and laterality (more-affected hand, less-affected hand) on RT showed a main effect of congruency ($F(1,23) = 72$, $p < .001$, $BF_{10} = .16$), but no main effect of laterality ($F(1,23) = 4.18$, $p = 0.05$, $BF_{10} = 0$) nor an interaction effect between laterality and congruency ($F(1,23) = 0$, $p > 0.99$, $BF_{10} = 0$).

A two-way within-subjects ANOVA on the percentage of partial errors in response force in the Parkinson's participants showed a significant main effect of congruency ($F(1,22) = 4.75$, $p = .04$, $BF_{10} = 2.71$) but no main effect of symptom laterality ($F(1,22) = .03$, $p = .88$, $BF_{10} = 0.22$), and no interaction effect between congruency and symptom laterality ($F(1,22) = 1.44$, $p = .24$, $BF_{10} = .32$).

2.7.2.1. Stop Signal task

Table 4. Data for the Stop Signal task by more-affected and less-affected hand in people with Parkinson's

	More-affected hand	Less-affected hand	Statistical test
Go RT	727ms ± 155ms	705ms ± 147ms	$t(22) = 3.08$, $p = .006$, $BF_{10} = 8.13$
SSRT	292ms ± 60ms	287ms ± 64ms	$t(22) = .78$, $p = .45$, $BF_{10} = .29$
Partial errors - Go	12% ± 6%	9% ± 6%	$t(20) = 1.89$, $p = .07$, $BF_{10} = 1.01$
Partial errors - Stop	29% ± 15%	27% ± 13%	$t(20) = .54$, $p = .60$, $BF_{10} = .26$

2.7.3. Correlations between response inhibition, response conflict, and trait impulsivity

As an exploratory addition, we also examined trait impulsivity with the Barratt Impulsiveness Scale (BIS; Barratt, 1959; Patton, Stanford, & Barratt, 1995), which has been shown to be generally higher in PwP compared to HCs (Isaias et al., 2008; Nombela et al., 2014).

We performed exploratory correlations to examine the relationship between SSRT (response inhibition), Simon effect (response conflict), and the Barratt Impulsiveness Scale's total and motor impulsivity scores (Patton et al., 1995). Exploratory Pearson's *r* correlations (Bonferroni corrected, $a = .01$) were performed in each group.

Table 5. Pearson's correlations for people with Parkinson's and the healthy control group

		Parkinson's			Healthy controls		
		Pearson's *r*	***p***	**BF_{10}**	**Pearson's *r***	***p***	**BF_{10}**
BIS (total)	SSRT	.26	.11	.90	-.24	.85	.15
BIS (total)	Simon effect	.50	.006*	9.86	.17	.22	.53
BIS (motor)	SSRT	.14	.27	.45	-.22	.83	.15
BIS (motor)	Simon effect	.27	.10	.98	.04	.42	.30
SSRT	Simon effect	.41	.03	2.80	.29	.11	.96

As shown in Table 5 and Figure 5, there was a significant positive correlation between the size of the Simon effect and the total impulsiveness score for people with Parkinson's at the adjusted *a* level ($r = 0.50$, $p = .006$, $BF_{10} = 9.86$), but not the healthy controls. This suggests some problems with impulsivity for PwP which may affect response conflict and trait impulsivity, but not response inhibition as measured with SSRT. There are higher impulsiveness scores and greater variability in scores for the Parkinson's group and not the HC group which may contribute to some findings; it could be that this applies to a subset of the patients such as those with undiagnosed/unreported impulse control disorders.

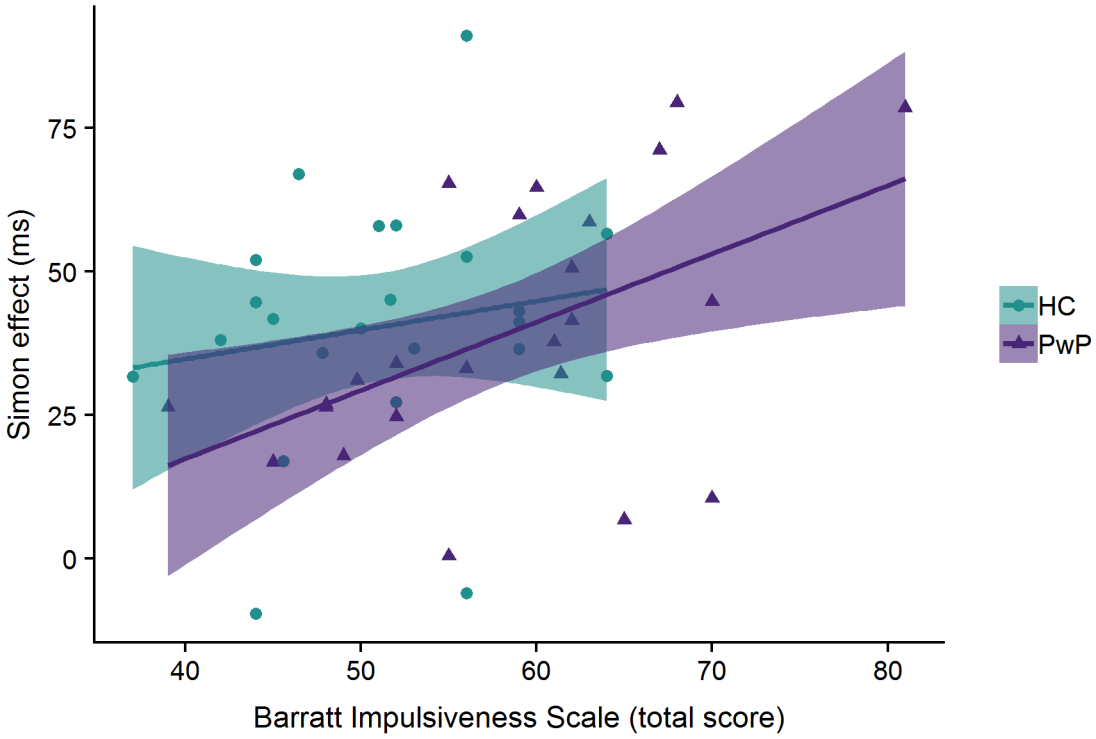

Figure 5. Scatterplot of the correlation between the Simon effect and total score on the Barratt Impulsiveness Scale for PwP and HCs. The data is shown with a linear regression line of best fit and shaded confidence intervals.

There were no other significant correlations between any of the measures taken for either participant group.

2.7.4. References

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Postscript to Chapter 2

One key question that remained from this study is whether the sensitive measure of response force was valid. We supervised a BSc Cognitive Neuroscience & Psychology student, Marta Majewska (MM), who used the same methodology with a group of younger control (YC) participants and used a version of the force algorithm that was more similar to that used originally by McBride et al. (2012; 2013; 2018) and that did not include the optimisation that we created in Chapter 2 for people with Parkinson's, which was designed to filter out the tremor cycle and reduce noise. MM compared the performance of YC participants with the older HC participants from Chapter 2 but reanalysed their force data with the new algorithm.

In the Simon task we discovered that the HC group showed significantly greater interference effects than YCs according to the button-press RT data, but there were no significant differences between groups on the percentage of partial errors in response force. However, we also discovered that the correspondence was low; whilst this did not differ significantly between groups or conditions, only 62-64% of correct congruent and incongruent trials (according to the button press) also showed a corresponding response in the force data as detected by the algorithm, so our force measure showed low sensitivity to responses (compared to Chapter 2 where correspondence was much higher).

In the Stop Signal task, HCs showed a significantly longer stop signal reaction time and a significantly lower percentage of partial errors in response force, compared to YCs, for otherwise correct Stop trials. Generally correspondence between the button-press and force data were higher (93% for HCs and 83% for YCs) than for the Simon task, so we can be more confident in our measure although it does differ between groups. However, given that HCs showed reduced response inhibition according to the button-press data and a lower percentage of partial errors *despite* having a higher correspondence between the button-press and force data compared to YCs, we can be more confident in our interpretation of this data. A lower percentage of partial errors may therefore signal worse inhibitory control, because any partial errors may be more likely to result in a full button press. An increased percentage of partial errors may therefore represent *better* inhibitory control because the YCs may have been more able to withhold the full response later on in the course of the cognitive control.

Further research into the time-course of partial responses will help to strengthen this conclusion, for example more partial errors later in the course of the trial (i.e. where the response was stopped at the last moment) may represent better inhibitory control. Overall, when correspondence between the button-press data and force data is high, the additional measure of response force appears to be sensitive to capturing ongoing inhibitory control. Therefore, we can be more confident that our null findings between PwP and HCs with both

measures really do represent a lack of group differences, particularly for the Stop Signal task where we have clear additional data with HCs and YCs to validate the measure.

Preface to Chapter 3

The study in Chapter 2 found little-to-no evidence that people with mild to moderate Parkinson's experience inhibitory control deficits in two commonly used tasks, even with a more sensitive measure of response force. The previous literature provided conflicting evidence as to whether people with Parkinson's experienced inhibitory control deficits generally, as well as in other areas of impulsivity such as motor impulsivity, risky decision-making, and trait impulsivity. Before proceeding with the original plans of developing a behavioural intervention targeted at people with Parkinson's who experience problems with impulse control, we first decided to perform a comprehensive systematic review with the aim of casting a wide net around the concept of "impulsivity" in people with Parkinson's who both do and do not experience impulse control behaviours, as well as compared to healthy controls.

We hoped that this would clarify the conflicting literature to date by performing a rigorous search for relevant literature, and to elucidate the mechanisms underlying the different results reported.

The review was pre-registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017051751) and a copy of the pre-registration is included in Appendix B.

Author contributions: Jade Pickering planned the study, including devising the search strategy, conducting the scoping searches, and conducting the final search. Ellen Poliakoff, Jennifer McBride, and Iracema Leroi supervised this process and provided intellectual input. Jade Pickering rated every study for inclusion/exclusion at each stage of the process. During the screening of the titles and abstracts, half of the October 2016 search results were additionally rated by two MRes students (Rachel Crone and Chloe Mann), and the results from October 2016-December 2018 were rated by PhD student Moudhi Al Twaijri. All three raters were conducting their own research into similar areas of inhibitory control and/or Parkinson's. During the screening of the full text, Ellen Poliakoff and Jennifer McBride each rated half of the results. Jade Pickering read, extracted the data, and synthesised the results from all the final studies, with input on thematic grouping from Ellen Poliakoff, Jennifer McBride, and Iracema Leroi. Jade Pickering independently wrote the initial draft of this chapter.

Chapter 3 - Impulsivity and inhibitory control in Parkinson's disease and related impulse control behaviours: A systematic review

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3.1. Abstract

There is some evidence to suggest that Parkinson's affects processes involved in impulsivity and inhibitory control, but that this may be particularly pronounced in people with Parkinson's (PwP) who additionally develop impulse control behaviours (ICBs), such as pathological gambling and binge eating, as a result of dopamine agonist medication according to the dopamine overdose hypothesis. However, it is unclear how much Parkinson's itself or additional ICBs contribute (or do not contribute) to trait, behavioural, and cognitive impulsivity.

In this systematic review, 246 studies were identified that examined impulsivity and inhibitory control in PwP both with and without additional ICBs. I firstly provide a resource bank of studies that compared PwP with healthy controls, PwP with PwP who have additional ICBs, within-subjects designs of impulsivity such as ON/OFF medication and deep brain stimulation, and between-subjects designs of PwP who differ on some other feature such as the presence of certain symptoms. This resource can provide a starting point for future meta-analyses or empirical investigations. Secondly, I provide a narrative synthesis of the studies that compared PwP to healthy controls, and PwP to PwP with additional ICBs.

Overall, for studies that compared PwP to HCs (N = 185) I found evidence that PwP are impaired at suppressing responses in tasks of response conflict (e.g., Simon task and Eriksen Flanker task) and decision making under ambiguous risk (e.g., Iowa Gambling Task) but show no differences in impulsivity for delayed gratification, set shifting, or personality traits compared to healthy controls. Studies that looked at PwP with additional ICBs compared to PwP without any ICBs were much fewer in number (N = 38), but generally show higher trait impulsivity and a reduced ability to delay gratification, with no differences in terms of response inhibition, response conflict, or set shifting. I discuss these results in the context of broader implications for the Parkinson's literature, as well as the way in which Parkinson's and dopamine medication may contribute to changes in impulsivity.

3.2. Introduction

3.2.1. Parkinson's disease

Parkinson's is a neurodegenerative motor disorder (Jankovic, 2008). Approximately 13-50% of people with Parkinson's (PwP) develop some form of clinically significant impulse control behaviour (ICB), which have been largely linked to dopaminergic medications used to treat the motor symptoms of Parkinson's (Corvol et al., 2018; Voon, 2015; Weintraub et al., 2010), and includes behaviours such as pathological gambling, hypersexuality, compulsive shopping/spending, binge eating, punding (repetitive behaviours such as collecting, sorting, and disassembling objects), and hobbyism (Voon, 2015).

3.2.2. Impulsivity and inhibitory control

Impulsivity is often thought of as a consequence of poor inhibitory control. Two main areas of impulsivity have been described in the general literature relating the inability to withhold from an impulsive action, or an impulsive choice (see Bari & Robbins, 2013, and Wang et al., 2016 for a more comprehensive overview). Motor inhibition is important for general motor control; it ensures we can act according to our current goals rather than only to the environment. Impulsive action usually refers to a failure in motor inhibition (Wang et al., 2016), where an action is prepared but a change of goal is not sufficient to stop the action from being performed, such as failing to apply the brakes in the car when a red stop light appears. This is usually measured experimentally through tasks that require actions to "go" and "stop" upon given cues, such as the Go/No-Go and Stop Signal tasks (Aron, Robbins, & Poldrack, 2014; Bari & Robbins, 2013; Verbruggen & Logan, 2009). Response inhibition can also occur under response conflict, such as when two competing responses are activated and the automatic response must be suppressed in favour of the goal directed response; i.e. a choice between two different "go" responses (rather than between a "go" and a "stop") such as in the Simon, Eriksen Flanker, and Stroop tasks (Eriksen & Eriksen, 1974; Simon, 1969; Stroop, 1935). For example, in the Stroop task the stimulus of the word "BLUE" written in red ink automatically evokes the response "BLUE", but the goal directed response should be to name the colour of the ink, "RED".

Impulsive choice, however, usually refers to a deficit in waiting, or delaying gratification, and is often measured experimentally with tasks that operationalise the ability to wait for a reward using a simple measure of delay discounting, k (Bari & Robbins, 2013; Kirby, 2009). Impulsivity also comprises risky decision making, especially when faced with the prospect of reward or loss. Experimentally this can be measured through paradigms where the risk is objective and the probability and value of the reward or loss is explicitly stated to the participant, as in the Game of Dice and Cambridge Gambling Tasks (Brand et al., 2002; Rogers et al., 1999), or where the risk is ambiguous such as in the Iowa Gambling Task (Bechara, Damasio, Damasio, & Anderson, 1994). Depending on the task, decisions are classified as impulsive or risky if they are made

quickly or skewed in favour of low probability, high value, outcomes. Trait impulsivity, usually measured through self-report questionnaires, encompasses characteristics such as novelty and sensation seeking, sensitivity to reward and punishment, and risk/harm avoidance.

There is a staggering amount of general literature on impulsivity and inhibitory control, and although this has been synthesised comprehensively by others (Bari & Robbins, 2013), there are still discrepancies between definitions, measures, and operationalisation of various aspects of cognitive and action control, and a lack of clarity in the relationships between them. This presents a challenge for understanding how these processes are affected in various conditions.

3.2.3. Impulsivity and inhibitory control in Parkinson's

There are several ways that inhibitory control and impulsivity may be affected in Parkinson's. Inhibitory action control is thought to be associated with prefrontal basal ganglia networks (Ridderinkhof, Forstmann, Wylie, Burle, & van den Wildenberg, 2011); these are significantly affected in Parkinson's through the gradual death of dopamine producing cells in the substantia nigra (Andersen & Chinta, 2016) which affects the nigrostriatal pathways. Other types of impulsivity, such as the motivation and desire for reward and pleasurable experiences, are associated particularly with the mesocorticolimbic pathways in the brain that project from the ventral tegmental area. The ventral tegmental area is relatively unaffected in Parkinson's, particularly in the earlier stages, and so those PwP that develop ICBs may be experiencing an increased level of dopamine along this pathway according to the dopamine overdose hypothesis (Cools, Barker, Sahakian, & Robbins, 2001; Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013).

Tasks that have been used with PwP cover many aspects of impulsivity such as response inhibition (e.g. Bissett et al., 2015; Gauggel, Rieger, & Feghoff, 2004; Leroi et al., 2013), response conflict (Praamstra & Plat, 2001; Wylie, Ridderinkhof, Bashore et al., 2010; Wylie, Ridderinkhof, Elias et al., 2010) delay discounting (de Rezende Costa et al., 2016; Milenkova et al., 2011; Nombela, Rittman, Robbins, & Rowe, 2014), risky decision making (Buelow, Frakey, Frace, & Friedman, 2014; Delazer et al., 2009), and trait impulsivity (Isaias, Siri, Cilia, De Gaspari, Pezzoli, & Antonini, 2008; Leroi et al., 2013). In most instances findings are mixed as to whether PwP demonstrate increased impulsivity or reduced inhibitory control compared to healthy controls (HCs), and whether people with Parkinson's and additional ICBs (PwP+ICBs) exhibit any differential deficits in impulsivity and inhibitory control compared to both HCs and PwP who do not have ICBs. This may be due to different tasks, methodological parameters, hypotheses, methods of measurement (i.e. the operationalisation of dependent variables), and/or variable samples (e.g. symptom severity) being used between studies.

This review therefore aims to systematically search and qualitatively synthesise the available literature on impulsivity and inhibitory control in Parkinson's in a systematic review, with a

particular focus on a) whether PwP show increased impulsivity (or reduced inhibitory control) on a variety of types of impulsivity compared to HCs, b) whether PwP+ICBs show increased impulsivity (or reduced inhibitory control) compared to both PwP and HCs, and c) any additional influences contributing to differences in impulsivity and inhibitory control in PwP such as medication and deep brain stimulation (DBS). A meta-analysis was not planned due to expected data heterogeneity, but by looking qualitatively across a breadth of tasks we hoped to draw inferences that may not be possible in more narrowly focused empirical papers and meta-analyses.

3.3. Method

3.3.1. Deviations from protocol

Following an iterative process of piloting search strategies and eligibility criteria, the protocol was preregistered publicly on PROSPERO (ID: CRD42017051751; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017051751) and includes the full search strategy and any revisions to the preregistration. Once the final search was completed according to the preregistration, the number of articles obtained was unexpectedly substantial in number. In order to make the review manageable, some deviations from the protocol were made.

Firstly, at the stage of screening full text articles for inclusion/exclusion, search results for conference proceedings, dissertations, and theses were checked against the publication lists of the authors (from personal websites, Google Scholar, ResearchGate, or a general internet search) to find full peer-reviewed manuscripts where available. If such a manuscript had been published, this replaced the original search item (unless the paper had already been included in the search results). If no manuscript was found to be published, the original search item was excluded from the review. Secondly, whilst the main findings were extracted from every study that was included in the review (Table 7) not all were included in the narrative synthesis presented in this manuscript. Studies were not included in narrative synthesis if they did not convincingly fit into one of the themes identified in the results section, for example if there was only one measure used in a small number of studies fitting one theme e.g. the Beads task was used in 4 studies to measure reflection impulsivity.

Finally, we initially made clear in the pre-registration that we were unaware of any existing scale that was appropriate to assess quality or risk of bias for the types of (non-interventional) experimental studies that we were to include here. We nevertheless suggested that we would attempt to modify an existing scale for our purposes. We attempted to modify the Newcastle-Ottawa and Downs and Black scales (Downs & Black, 1998; Wells et al., 2000) but this proved challenging. Such a bespoke scale not only has the potential to introduce more bias than it

resolves, but is generally recommended against (NHMRC, 2019), and so we discarded this element of the review.

3.3.2. Search strategy

In October 2016 the Web of Science, PubMed, PsycINFO (Ovid), SCOPUS, and Cochrane Library databases were searched for papers relating to Parkinson's, impulsivity, and inhibitory control, whilst excluding those that related to dementias, animal studies, and intervention studies as these were particularly prevalent in the original scoping searches [TITLE:(parkinson*) AND TOPIC: (inhibit* OR impuls*) NOT TOPIC: (*enzym* OR protein OR rat OR mouse OR mice OR rodent* OR primate* OR monkey* OR placebo OR dosage* OR inhibitor OR inhibitors) NOT TITLE: (dementia* OR alzheimer* OR depression OR schizophren*) NOT TOPIC: (randomi?ed NEAR/3 controlled)]. Additionally, OpenGrey and ProQuest Dissertations and Theses Global were searched to attempt to capture the grey literature. The search was then updated using the same search terms and databases in December 2018.

3.3.3. Inclusion/exclusion criteria

Full inclusion and exclusion criteria are given in Table 6, but in brief: To be eligible for inclusion the studies had to include an experimental/behavioural measure of impulsivity or inhibitory control, or a questionnaire measure of trait impulsivity, in PwP. Exclusion criteria included studies where brain imaging or genetic results were the main interest to the detriment of reporting any relevant behavioural results, studies where there were no adequate control group, or the study tested an intervention or validated a measure.

Table 6. Eligibility criteria for studies retrieved from the search

Inclusion criteria:
1. The study's main outcome included a measure of impulsivity or inhibitory control (whether experimental tasks, or self-report questionnaires)
2. One of the participant groups comprised PwP (whether with or without additional ICBs)
Exclusion criteria:
1. Review papers, case studies, case series studies, qualitative methods, prevalence studies, intervention or treatment studies such as randomised controlled trials.
2. Studies that do not use humans as active participants e.g. tissue samples, genetic testing
3. Studies with no adequate control group. Appropriate control groups are defined as: • A between-subjects design with PwP or PwP+ICB patients compared with each other, or an HC group, or both. • A between-subjects design with PwP or PwP+ICB patients compared with the same patient group who have a similar demographic background but who differ on one trait or sub-type that the authors believe is linked to impulsivity of inhibitory control • A within-subjects design of PwP or PwP+ICB patients, such as a medication or DBS ON/OFF study Comparison of PwP or PwP+ICB with another disease *alone* will not be included.
4. Studies where the only PwP sample have additional dementias
5. Questionnaires that act as diagnostic criteria
6. The study only sought to examine neurophysiological basis of impulsivity or inhibitory control, without reporting relevant behavioural results
7. The study aimed only to validate a particular measure of impulsivity or inhibitory control in PwP
8. Full text not available in English

3.4. Results

3.4.1. Study selection

The search yielded 6,772 results (3,218 after removing duplicates), and the titles and abstracts from each record were screened independently by 2-3 reviewers against the inclusion/exclusion criteria. Next, the full text of the remaining 423 results were screened independently by 2-3 reviewers, and a total of 246 papers remained for qualitative synthesis (see Figure 6). At both screening stages, all discrepancies were resolved through discussion between the reviewers.

A meta-analysis was not planned due to the expected heterogeneity of the studies included in the review. However, data were extracted pertaining to the participant groups (gender, age, disease severity, and disease duration where available). Additionally, the tasks used and the cognitive function that the study authors claimed to be measuring were extracted, as well as the main relevant behavioural findings. A detailed and interactive version of the data extracted from all 246 records is available as a Shiny app[12] (https://jspickering.shinyapps.io/sysreviewapp/), and a basic summary table is included in Table 7.

[12] Using the Shiny web application framework (version 1.3.2; Chang, Cheng, Allaire, Xie, & McPherson, 2017) for R (version 3.6.0; R Core Team, 2019) and the R-packages *janitor* (version 2.0.1; Firke, 2019), *shinydashboard* (version 0.7.1; Chang & Borges Ribeiro, 2018), and *tidyverse* (version 1.3.0; Wickham et al., 2019). Code and data available at: https://github.com/jspickering/sysreviewapp

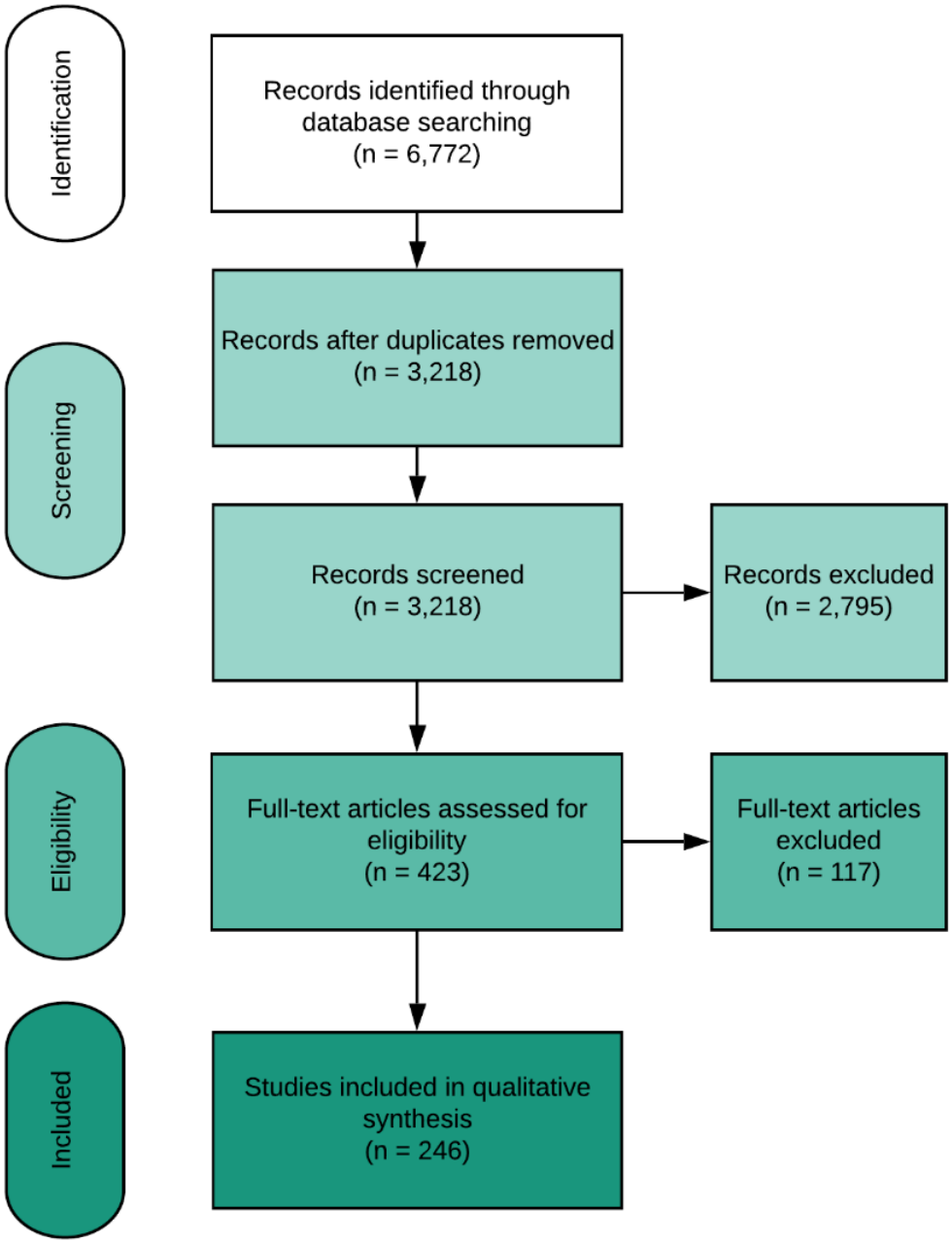

Figure 6. PRISMA flowchart (Moher et al., 2009) to illustrate the process of searching for the initial study records, screening (by title and abstract), screening the full text, and the final set of included papers. Criteria for exclusion can be found in Table 6.

Table 7. Results from the systematic search, including the participant groups and relevant comparisons as well as the measures used within the studies and the aspect of impulsivity or inhibitory control that the authors were measuring. Full information, including results extracted from each paper, can be found in the interactive online Shiny app (https://jspickering.shinyapps.io/sysreviewapp/).

Paper	Participant groups and comparisons				Measures
	PwP & HCs (N = 185)	PwP & PwP+ICBs (N = 38)	ON/OFF Medication (N = 38)	ON/OFF DBS (N = 32)	
Aarts et al. (2012)	✓				Behavioural Inhibition Systems/Behavioural Approach systems; Rewarded switching task
Aarts et al. (2014)	✓		✓		Rewarded task switching paradigm
Adam et al. (2011)	✓		✓	✓	Anti-cue keypress task
Ahearn et al. (2012)		✓			Barratt Impulsiveness Scale
Akamatsu et al. (2008)	✓				Trail Making Test; Distractor interference paper-rock-scissors
Al-Khaled et al. (2015)	✓				Intertemporal Choice Task; Go/No-Go Task; Stroop Task
Albani et al. (2010)	✓				Virtual Multiple Errand Test
Albert et al. (2010)	✓				Manual congruency task
Alegre et al. (2013)			✓		Stop Signal Task
Alonso-Recio et al. (2014)	✓				Emotional facial expression Stroop task
Amador et al. (2006)	✓				Anti-saccade task vs delayed anti-saccade task vs remembered anti-saccade task
Angwin et al (2017)	✓				Stroop
Antonelli et al. (2014)			✓		Delay discounting task; Go/No-Go task
Antoniades et al. (2015)	✓			✓	Anti-saccade task
Antonini et al. (2011)		✓			Barratt Impulsiveness Scale
Anzak et al. (2013)					Random number generation
Baglio et al. (2011)	✓				Go/No-Go
Balconi, Angioletti et al. (2018)		✓			Iowa Gambling Task
Balconi, Siri et al (2018)		✓			Iowa Gambling Task
Barbosa et al (2017)	✓				Trail Making Test; Verbal fluency
Barnes & Boubert (2008)	✓				Stroop; Go/No-Go; category fluency
Bayard et al. (2016)	✓	✓			UPPS Impulsive Behaviour Scale; Game of Dice task
Bentivoglio et al. (2013)		✓			Stroop task; Frontal Assessment Battery Go/No-Go; Barratt Impulsiveness Scale; Iowa Gambling Task
Benussi et al (2017)					Iowa Gambling task

Paper	Participant groups and comparisons				Measures
	PwP & HCs (N = 185)	PwP & PwP+ICBs (N = 38)	ON/OFF Medication (N = 38)	ON/OFF DBS (N = 32)	
Beratis et al (2018)	✓				Trail Making Test; Comprehensive Trail Making Test
Beste et al. (2009)	✓				Go/No-Go; Go/No-Go with S-R mapping reversed
Biars et al (2018)		✓			Iowa Gambling Task
Bissett et al. (2015)	✓				Stop Signal Task
Biundo et al. (2011)	✓	✓			Stroop; Trail Making Test
Bocquillon et al. (2015)	✓				Oddball paradigm; Stroop
Bódi et al. (2009)	✓		✓		Probabilistic classification task; Temperament and Character Inventory
Bokura et al. (2005)	✓				Go/No-Go
Boller et al. (2014)	✓		✓	✓	Game of Dice task
Boubert & Barnes (2015)					Category fluency; Stroop Task
Bouquet et al. (2003)	✓				Hayling test; Trail Making Test Part B
Brandt et al. (2015)	✓			✓	Game of Dice; Deal or No Deal; Framing Paradigm
Briand et al. (2001)	✓				Covert orienting task
Buelow et al. (2014)	✓				Iowa Gambling Task; Balloon Analogue Risk Task
Cagigas et al. (2007)	✓				Eriksen Flanker task
Cammisuli & Crowe (2018)	✓				FAB Go/No-Go
Cammisuli & Sportiello (2017)	✓				Stroop task
Campbell et al. (2008)				✓	Go/No-Go task
Campos-Sousa et al. (2010)	✓				Trail Making Test; Stroop task
Canesi et al. (2012)	✓				Barratt Impulsiveness Scale
Carriere et al. (2016)	✓	✓			Gambling task
Castner et al. (2007)	✓			✓	Hayling Test; Picture-Word Interference Task
Castrioto et al. (2015)	✓		✓	✓	Iowa Gambling Task
Centi et al (2017)	✓				Stroop task
Cerasa et al. (2015)			✓		Stop Signal Task; Stroop Task; Barratt Impulsiveness Scale
Chan et al. (2005)	✓				Pro-saccade task; anti-saccade task
Claassen et al. (2011)		✓			Balloon Analogue Risk Task
Cools et al. (2003)	✓		✓		Task switching; Cambridge Gambling Task
Cools et al. (2006)	✓				Stroop task; Behavioural Inhibition Systems/Behavioural Approach Systems; Reversal learning

Paper	Participant groups and comparisons				Measures
	PwP & HCs (N = 185)	PwP & PwP+ICBs (N = 38)	ON/OFF Medication (N = 38)	ON/OFF DBS (N = 32)	
Copland (2003)	✓				Semantic Priming Task
Crescentini et al. (2008)	✓				Verb/noun production task
Crescentini et al. (2012)	✓				Trail Making Test; Stroop task; Go/No-Go
Criaud et al. (2016)	✓				Simple RT task
Crucian et al. (2007)	✓			✓	Crossed Response Inhibition task; Anti-saccade task
D'Ostilio et al. (2013)	✓				Masked Prime Compatibility Task
de Rezende Costa et al. (2016)	✓				Beads task; Kirby temporal discounting questionnaire; Frontal Access Battery Go/No-Go
Delazer et al. (2009)	✓				Iowa Gambling Task; Probability-Associated Gambling Task; Trail Making Test B; Go/No-Go
Di Rosa et al. (2016)	✓				Working memory task
Disbrow et al. (2013)	✓				Cued activation/inhibition task
Djamshidian et al. (2010)	✓	✓	✓		Associative learning; Gambling task
Djamshidian et al. (2011)	✓	✓			Stroop task
Djamshidian et al. (2012)	✓	✓			Beads task
Djamshidian et al. (2013)	✓				Beads task
Dujardin et al. (1999)	✓				Stroop
Dunet et al. (2016)	✓				Stroop task
Duprez et al. (2017)	✓				Saccadic Simon task; Barratt Impulsiveness Scale
Duprez et al. (2018)					Oculomotor Simon task
Eddy et al. (2013)	✓				Stroop
Evens et al. (2015)	✓			✓	Delay discounting; incentive value task; Iowa gambling task; Barratt Impulsivity Scale
Fabbri et al (2018)	✓				Eriksen flanker
Fales et al. (2006)	✓				Task Switching; Stroop; Color Trails Test
Falkenstein et al. (2006)	✓				Eriksen flanker
Favre et al. (2013)	✓		✓	✓	Cue-target detection task
Fielding et al. (2005)	✓				Simon task
Filoteo et al. (1997)	✓				Orienting of Attention task
Filoteo et al. (1999)	✓				Dimensional Integration Task; Selective Attention task

Paper	Participant groups and comparisons				Measures
	PwP & HCs (N = 185)	PwP & PwP+ICBs (N = 38)	ON/OFF Medication (N = 38)	ON/OFF DBS (N = 32)	
Filoteo et al. (2002)	✓				Negative priming/ignored repetition task
Flannery et al. (2018)	✓				Pro/anti-saccade, Simon task, flanker task
Fleury et al. (2014)	✓		✓		Emotional Stroop task
Florin et al. (2013)	✓				Calculation task
Fluchère et al. (2015)			✓		Simon task
Fluchère et al. (2018)			✓	✓	Simon task
Foerde et al. (2016)	✓				Binary Choice Task, Valuation Rating Task, Choice Titration Task
Frank et al. (2007)	✓		✓	✓	Probabilistic selection task
Franz & Miller (2002)	✓				Cued Go/No-Go
Fumagalli et al. (2015)		✓			Economics task
Galpin et al. (2011)	✓				Affordance-based Simon task
Galtier et al. (2014)	✓				Stroop task
Gauggel et al. (2004)	✓				Stop Signal Task
Gawrys et al. (2014)	✓				Trail Making Test; Stroop; n-back task; Wisconsin Card Sorting Test
Geffe et al. (2016)	✓		✓		Go/No-Go
George et al. (2013)	✓		✓		Stop Signal Task
Georgiades et al. (2016)	✓				Virtual reality motor inhibition task
Georgiev et al. (2016)	✓				Go/No-Go task
Georgiev et al. (2015)	✓		✓		Oddball paradigm
Goelz et al (2017)	✓			✓	Prosaccade/antisaccade
Gorges et al. (2013)	✓				Visually guided reactive saccades; Smooth pursuit eye movements; Delayed saccade task; Rapidly alternating voluntary gaze shift
Gorges et al. (2017)	✓				Smooth pursuit; visual guided reactive saccades
Grande et al. (2006)	✓		✓		Inhibition of return; Negative Priming Task
Gurvich et al. (2007)	✓				Oddball task; Fixation-distractor task; Saccade-engagement-distractor task; Gap paradigm; Predictive paradigm
Hälbig et al. (2009)					Barratt Impulsiveness Scale
Harrington et al (2018)	✓				Stop Signal Task; Delis-Kaplan Stroop
Harris et al. (2015)	✓				Temperament and Character Inventory
Henderson et al. (2011)	✓				Saccadic smooth pursuit task

Paper	Participant groups and comparisons				Measures
	PwP & HCs (N = 185)	PwP & PwP+ICBs (N = 38)	ON/OFF Medication (N = 38)	ON/OFF DBS (N = 32)	
Henik et al. (1993)	✓				Stroop
Hiebert et al. (2014)	✓				Stimulus-response association learning
Housden et al. (2010)	✓	✓			Salience Attribution Test; Kirby delayed discounting questionnaire
Houvenaghel et al. (2016)	✓				Rewarded Simon task
Hsieh et al. (2008)	✓				Stroop task
Huang et al. (2015)	✓		✓		Moving Dots Task
Irmen et al. (2017)	✓			✓	Emotional Stroop
Irmen et al. (2018)	✓			✓	Barratt Impulsiveness Scale; decision-making task
Isaias et al. (2008)	✓	✓			Barratt Impulsiveness Scale
Jia et al. (2018)	✓				Stroop
Joti et al. (2007)	✓				Saccadic Redirect Task
Kingstone et al. (2002)	✓				Reflexive Covert Orienting; Saccadic Volitional Overt Orienting; Saccadic Reflexive Overt Orienting; Antisaccade/Volitional and Reflexive Overt Orienting
Kliegel et al. (2005)	✓				Stroop Task
Kobayashi et al. (2018)	✓	✓	✓		Economic choice task
Koerts et al. (2013)	✓				Temperament and Character Inventory; Stroop Task; Trail Making Test; Odd Man Out
Kohl et al. (2015)	✓			✓	Conditional Stop Signal task
Kojovic et al. (2016)	✓			✓	Rewarded Reaction Time
Kübler et al (2017)			✓		Stroop
Laurent et al (2018)	✓				Simon task; Delis-Kaplan Trail Making Test
Leroi et al. (2013)	✓	✓	✓		Stop Signal task; Delay Discounting task; Barratt Impulsiveness Scale
Machado et al. (2009)	✓				Distractor Interference Task
Manza et al. (2018)	✓		✓		Stop Signal Task
Mapelli et al. (2014)	✓				Iowa Gambling Task
Marí -Beffa et al. (2005)	✓				Semantic Priming Task; Repetition Priming Task
Marín-Lahoz et al. (2018)		✓			Barratt Impulsiveness Scale; PEBL Continuous Performance Test
Martini, Ellis et al. (2018)	✓	✓			Balloon Analogue Risk Task; Trail Making Test; Kirby delay discounting; Go/No-Go; Hayling Test; Barratt Impulsiveness Scale
Marzinzik et al. (2011)	✓		✓		Cued Go/No-Go

Paper	Participant groups and comparisons				Measures
	PwP & HCs (N = 185)	PwP & PwP+ICBs (N = 38)	ON/OFF Medication (N = 38)	ON/OFF DBS (N = 32)	
Marzinzik et al. (2015)	✓				Go/No-Go
Matar et al. (2013)	✓				VR Stroop task
Mathis et al. (2014)			✓		Stroop task
McDonell et al. (2018)			✓		Simon task
McKinlay et al. (2009)	✓				Delis-Kaplan Colour-Word Interference Test/Stroop task
Merola et al. (2017)		✓			Trail Making Test
Milenkova et al. (2011)	✓		✓		Intertemporal Choice task
Mirabella et al. (2012)	✓			✓	Countermanding Task
Mirabella et al. (2013)	✓			✓	Countermanding Task
Mirabella et al (2017)	✓				Countermanding Task
Nombela et al. (2011)	✓				Stroop
Nombela et al. (2014)	✓				Kirby Temporal Discounting task; Barratt Impulsiveness Scale; Behavioural Inhibitory System/Behavioural Approach System; Motor Go/No-Go task; Temporal Interval Estimation; Frontal Assessment Battery with Go/No-Go; Stop Signal Task; Cambridge Gambling Task; Hayling Sentence Completion; Stroop test, Saccade Go/No-Go
O'Callaghan et al. (2013)	✓				Excluded Letter Fluency test; Hayling test
Obeso, Wilkinson, Casabona et al. (2011)	✓				Conditional Stop Signal task; Stroop; Random number generation; Hayling sentence completion
Obeso, Wilkinson and Jahanshahi (2011)	✓		✓		Conditional Stop Signal task
Obeso et al. (2013)	✓			✓	Conditional Stop Signal task
Obeso et al. (2014)	✓				Conditional Stop Signal task
Obeso et al. (2017)					Hayling Test; Delis-Kaplan Stroop; Barratt Impulsiveness Scale; FAB Go/No-Go
Ouerfelli-Ethier et al (2018)	✓				Pro-/anti-saccade task
Pagonabarraga et al. (2007)	✓				Iowa Gambling Task; Stroop
Pan et al (2018)	✓			✓	Stop Signal Task
Pettorruso et al. (2014)		✓			Barratt Impulsiveness Scale; Snaith-Hamilton Pleasure Scale
Pettorruso et al. (2016)		✓			Snaith-Hamilton Pleasure Scale; Barratt Impulsiveness Scale
Picazio et al. (2018)	✓		✓		Barratt Impulsiveness Scale; Go/No-Go task; Stop Signal Task
Pineau et al. (2016)	✓	✓			Barratt Impulsiveness Scale; Conner's Performance Test; Trail Making Test; modified Iowa Gambling Task
Plessow et al. (2014)	✓			✓	Interference task

Paper	Participant groups and comparisons				Measures
	PwP & HCs (N = 185)	PwP & PwP+ICBs (N = 38)	ON/OFF Medication (N = 38)	ON/OFF DBS (N = 32)	
Poletti et al. (2010)	✓				Iowa Gambling Task
Poletti et al. (2011)					Iowa Gambling Task
Poliakoff et al. (2003)	✓				Tactile Inhibition of Return
Pollux & Robinson (2002)	✓				Alternating Stroop Switching Task
Possin et al. (2009)	✓				Inhibition of Return
Pote et al. (2016)	✓			✓	Moving Dots task
Praamstra & Plat (2001)	✓				Simon task
Price (2010)	✓				Anagram Task; Stroop task
Rajan et al. (2018)					Iowa Gambling Task
Ranchet et al. (2013)	✓				Stroop test; Trail Making Test
Rao et al. (2010)		✓			Balloon Analogue Risk Task
Ray et al. (2009)	✓			✓	Stop Signal task
Ray et al. (2012)		✓			Barratt Impulsiveness Scale
Ricciardi et al. (2017)	✓	✓			Intentional binding task; Stop Signal Task; Marble task; Balloon Analogue Risk Task; Trail Making Test
Richards et al. (1993)	✓				Stroop task; Odd Man Out test
Rivaud-Pechoux et al. (2007)	✓				Pro-saccade task; Anti-saccade task; Mixed pro-saccade and anti-saccade task
Rogers et al. (1998)	✓				Task switching paradigm
Rogers et al. (2011)				✓	Gambling task
Rosa et al. (2013)		✓			Economics task
Rossi et al. (2010)		✓			Stroop task; Zuckerman-Kuhlman Personality Questionnaire; Go/No-Go; Iowa Gambling Task; Game of Dice Task; Investment Task
Ruitenberg et al. (2018)		✓			Beads task; Barratt Impulsiveness Scale
Sáez-Francàs et al. (2014)					Trail Making Test; Stroop task; Iowa Gambling Task
Santangelo et al. (2018)					Trail Making Test; Stroop
Sauvaget et al. (2017)	✓				Temperament and Character Inventory; Barratt Impulsiveness Scale
Seinstra et al. (2016)					Intertemporal Choice task; Barratt Impulsiveness Scale; Quick Delay Questionnaire; Holt-Laury task
Seiss & Praamstra (2004)	✓				Masked Priming Compatibility task
Seiss & Praamstra (2006)	✓				Masked Priming Compatibility Task

Paper	Participant groups and comparisons				Measures
	PwP & HCs (N = 185)	PwP & PwP+ICBs (N = 38)	ON/OFF Medication (N = 38)	ON/OFF DBS (N = 32)	
Seymour et al. (2016)				✓	Instrumental Learning of Reward and Punishment; Inter-temporal choice task
Sharp et al. (2013)	✓		✓		Vancouver Gambling Task; Temperament and Character Inventory
Siegert et al. (2014)			✓		Speeded flanker task
Simioni et al. (2012)	✓		✓		Balloon Analogue Risk Task; Temporal Discounting Task
Smulders et al. (2014)					Barratt Impulsiveness Scale
Stefanova et al. (2014)	✓				Set Shifting; Stop Signal Task
Swann et al. (2011)	✓			✓	Stop Signal Task
Szamosi et al. (2013)	✓				Kirby Delayed Discounting Questionnaire
Terao et al. (2011)	✓				Visually guided saccades; Gap visually guided saccades; Memory guided saccades; Hand reaction time task
Terenzi et al. (2018)	✓	✓			Behavioural Inhibition System/Behavioural Activation Systems; Barratt Impulsiveness Scale; Trail Making Test
Tessitore et al. (2017)	✓	✓			Trail Making Test; Stroop task
Thota et al. (2017)					FAB conflicting instructions; FAB Go/No-Go
Tolleson et al. (2017)	✓				Stop Signal Task; Delis-Kaplan Trail Making Test
Torta et al. (2009)	✓				Cambridge Gamble Task
Torta et al. (2012)				✓	Cambridge Gambling task; Barratt Impulsiveness Scale; Sensitivity to Reward and Sensitivity to Punishment Questionnaire; Quick Delay Questionnaire
Trenado et al. (2018)	✓				Probabilistic Reversal Learning task
Troche et al. (2006)	✓				Identity Priming/Flanker Task; Location Priming Task
Troche et al. (2009)	✓				Identity Priming/Flanker Task; Location Priming Task
van den Wildenberg et al. (2006)				✓	Go/No-Go; Stop Signal task
van den Wildenberg et al. (2017)	✓				Stop-Change Paradigm
van Koningsbruggen et al. (2009)	✓				Prosaccade/antisaccade task
van Stockum et al. (2008)	✓				Prosaccade/antisaccade/delayed saccade
van Wouwe et al. (2016)	✓		✓		Simon task
van Wouwe et al. (2014)	✓				Simon task
Vandenbossche et al. (2011)	✓		✓		Attention Network Test
Vandenbossche et al. (2012)	✓				Attention Network Test; Stroop task
Verleger et al. (2010)	✓				Eriksen flanker task

Paper	Participant groups and comparisons				Measures
	PwP & HCs (N = 185)	PwP & PwP+ICBs (N = 38)	ON/OFF Medication (N = 38)	ON/OFF DBS (N = 32)	
Vintonyak et al. (2017)	✓				Smooth pursuit; Visually guided reactive saccades
Vitale et al. (2011)		✓			Trail Making Test; Stroop
Voon et al. (2007)		✓			Barratt Impulsiveness Scale; Temperament and Character Inventory
Voon, Gao et al. (2011)	✓	✓			Monetary decision making
Voon, Sohr et al. (2011)		✓			Temperament and Character Inventory; Delay discounting scale; Barratt Impulsiveness Scale
Vriend et al. (2015)	✓				Stop Signal Task
Walton, O'Callaghan et al. (2015)	✓				Step task/pro-saccade task; Peripheral conflict task/pro-anti-saccade task; Trail Making Test
Walton, Shine et al. (2015)					Delis-Kaplan colour-word interference test/Stroop
Wessel et al. (2016)					Verbal Stop Signal Task
Witt et al. (2004)				✓	Stroop task
Wu et al. (2018)	✓				Smooth pursuit
Wylie & Stout (2002)	✓				Ignored repetition task
Wylie et al. (2005)	✓				Eriksen flanker task
Wylie et al. (2009a)	✓				Eriksen flanker task
Wylie et al. (2009b)	✓				Eriksen flanker task
Wylie, Ridderinkhof, Bashore et al. (2010)	✓				Simon task
Wylie, Ridderinkhof, Elias et al. (2010)	✓			✓	Simon task
Wylie, Claassen et al. (2012)		✓	✓		Simon task
Wylie, van den Wildenberg et al. (2012)					Simon task
Wylie et al. (2018)			✓		Stop-Change Task
Yang et al (2018)			✓		Go/No-Go task
Yoo et al. (2015)	✓	✓			Stroop; Go/No-Go
York et al. (2008)					Trailing Making Test; Stroop task
Yugeta et al. (2010)	✓			✓	Visually guided saccade task; Gap saccade task; Memory guided saccade task; Anti-saccade task
Zhang, Rittman et al. (2016)	✓				Temporal bisection task; temporal trisection task
Zhang, Nombela et al. (2016)	✓				Saccadic Go/No-Go task

3.4.2. Study results: types of impulsivity, inhibitory control, and associated tasks

The search revealed that a wide variety of tasks have been used to examine inhibitory control and impulsivity in PwP, covering a range of domains of impulsivity from 1993-2018. The results were grouped into themes (see subheadings throughout results section) to allow for a coherent narrative synthesis. Themes were decided based on the type of impulsivity that study authors, collectively across studies, claimed to be measuring along with the systematic review authors' combined expertise. All results are reported with the PwP ON their usual medications and without undergoing deep brain stimulation (DBS) unless specified otherwise. For each type of impulsivity, we will report the number of relevant studies picked up by the search, briefly describe the task or measure, and provide a summary of differences in impulsivity between PwP, HCs, and PwP+ICB groups on that task. All additional comparisons such as ON/OFF medication or DBS, or patients experiencing different symptom types, were extracted and summarised in the online table (https://jspickering.shinyapps.io/sysreviewapp/).

3.4.2.1. Response inhibition

A total of 26 studies used the Go/No-Go task, 19 used the Stop Signal task, 3 used a Countermanding task, 2 used the Stop-Change task, and 5 used the Conditional Stop Signal task. An overview of the studies that compared PwP to HCs and PwP+ICBs can be found in Table 8.

Overall, results show a mixture of significant group differences between PwP and HCs (N = 4, Go/No-Go; N = 4, Stop Signal task; N = 1, Countermanding task, N = 1, Stop-Change task) and null results (N = 4, Go/No-Go; N = 5, Stop Signal task), whereas studies that examined the effect of ICBs have shown null results (N = 6).

3.4.2.2. Response conflict

To examine response conflict due to spatial incompatibility, 14 studies used the Simon task, 1 used an Interference task, and 1 used a Learned Stimulus-Response Association task. Target/distractor response conflict was assessed in 9 studies using the Eriksen Flanker task, and within-stimulus response conflict was measured in 51 studies with the Stroop task, and 1 study with the Picture-Word Interference task. 7 studies used the Hayling Sentence Completion Test to examine response initiation and suppression. An overview of the studies that compared PwP to HCs and PwP+ICBs can be found in Table 9.

Studies differed in the way in which they measured interference, particularly for the Simon, Eriksen, and Stroop tasks, and this seemed to contribute somewhat to the mixed results. Generally, studies reported mixed results when examining interference effects for accuracy and RT alone, and often studies reported an impairment on one measure (either accuracy or RT) and a null result for the remaining measure; this may be due to the effects of prioritising speed or accuracy (van Wouwe et al., 2014).

Many studies dissociated response capture (fast and impulsive errors that occur on trials with shorter RTs) from response suppression (a failure to inhibit responses on trials with longer RTs) which resulted in clearer results (van den Wildenberg et al., 2010). Generally, PwP and HCs are similarly susceptible to response capture in the Simon task (N = 6) and Eriksen Flanker task (N = 2), but PwP show a relative impairment with response suppression in both tasks (N = 6, and N = 2, respectively). Emphasising accuracy over speed seems to resolve this impairment, at least in the Simon task (N = 1). Studies that used the Stroop task also report various dependent variables, but results are mixed regardless of analytical choice. For the Hayling task, there does appear to be an impairment in PwP.

Although studies are few in number (N = 9), broadly there appears to be little difference between PwP and PwP+ICBs for performance on tasks of response conflict.

3.4.2.3. Oculomotor inhibition

Tasks of oculomotor inhibition usually involve either voluntary saccades where an eye movement is intentionally made to a target, or reactive/reflexive saccades where an eye movement automatically occurs in response to the onset of a peripheral target. To examine voluntary saccades, 13 used anti-, or combined pro-/anti-saccade tasks, and to examine reactive/reflexive saccades, 2 used a visually guided reactive saccade task. 6 used delayed visually guided reactive or delayed pro-/anti-saccade tasks. Five studies measured inhibitory control during smooth pursuit, and 3 studies used oculomotor versions of tasks described elsewhere in this review (2 used an oculomotor Go/No-Go task, 2 used an oculomotor Simon task, and 1 used a Saccadic Redirect task which is analogous to a Stop Signal task). An overview of the studies that compared PwP to HCs can be found in Table 10, but note that no studies compared PwP with PwP+ICBs.

For all measures of voluntary saccades, results are mixed for both errors on the pure anti-saccade task (N = 2 find a significant difference and N = 2 do not), however when task difficulty is increased by interleaving pro-saccade trials, studies slightly more often find increased errors from PwP (N = 3) than not (N = 1), with the opposite pattern occurring for saccadic latencies. For visually guided reactive saccades tasks both with and without delays, PwP show impairment for saccadic intrusions and overall errors (N = 2), disinhibition errors (N = 2, but N = 1 found no significant group differences), and saccadic latencies (N = 2). Smooth pursuit was largely shown to be impaired in PwP in terms of pursuit gain (N = 3, compared to N = 1 which found no group differences) and errors to distractor in a slightly different version of the task (N = 2).

PwP showed impairment on all oculomotor version of manual tasks which have been described elsewhere in the review. Specifically, in the oculomotor version of the Go/No-Go task (see section *3.4.2.1. Response inhibition* for the manual version of the task), PwP showed a greater

number of commission errors compared to HCs (N = 2), and in the oculomotor version of the Simon task (see section *3.4.2.2. Response conflict* for a manual version of the task) PwP showed greater interference effect for RTs (N = 1) and errors (N = 1). In the Saccadic Redirect task the target switch reaction time (analogous to the stop signal reaction time in the manual Stop Signal task described in section section *3.4.2.1. Response inhibition*) was impaired in PwP (N = 1).

3.4.2.4. Delayed gratification

15 studies used a Delay Discounting Task where a higher *k* (rate of discounting) indicates higher impulsivity. The studies that compared PwP, HCs, and PwP+ICBs are shown in Table 11. Overall, all studies that compared PwP and HCs demonstrated no significant group differences (N = 6) for overall *k* scores, and most (N = 3) studies that examined ICBs found that PwP+ICBs showed higher k scores than PwP without ICBs, although one study did not.

3.4.2.5. Decision making under ambiguous risk

Tasks of decision making under ambiguous risk do not provide participants with concrete probabilities to inform their decision making. Often the participant must learn the relative risk over the course of the task which may involve learning through gain and loss. 16 studies examined this type of decision making with the Iowa Gambling Task, 7 used the Balloon Analogue Risk Task, 3 used an economic learning task, 1 used a Deal or No Deal task, and 1 a reward processing gambling task. The studies that compared performance on these tasks across PwP, HCs, and PwP+ICBs can be found in Table 12.

Overall, PwP show impairment on the Iowa Gambling Task (N = 4) both in terms of the frequency of advantageous vs disadvantageous decisions as well as their ability to learn to avoid disadvantageous decisions, and PwP+ICBs seem to show more impairment still than PwP (N = 4). For both group comparisons there was one corresponding study showing null results. The opposite pattern was seen for the Balloon Analogue Risk Task, which showed no significant group differences between PwP and HCs for the main dependent variable of adjusted pumps (N=3) and no significant group differences between PwP and PwP+ICBs (N = 4).

In the economic learning task two studies showed that PwP+ICBs showed impairement in this task compared to PwP but one study showed null results.

3.4.2.6. Decision making under objective risk

Tasks of decision making under objective risk (unlike ambiguous risk) give the participants probabilistic and clear information about reward outcomes to facilitate informed choices. This was assessed in 4 studies with the Game of Dice task, 4 with the Cambridge Gambling task, 1 modified Iowa Gambling Task (to remove ambiguity), 1 Vancouver Gambling task, 1 Probability Associated Gambling task, 1 Framing Paradigm, 1 Investment task, 2 with a Monetary Decision

Making task, 1 Alternative Choice Gambles, 1 Dice Roll task, and 1 Loss Chasing Gambling task. A summary of the relevant studies is shown in Table 13.

Overall PwP appear to make riskier decisions on the Game of Dice task (N = 3) than HCs, but evidence is more mixed on the Cambridge Gambling Task. On a Monetary Decision Making task PwP showed no significant differences compared to HCs or PwP+ICBs in terms of risk aversion, but PwP+ICBs showed riskier choices in a gain condition compared to PwP and PwP showed riskier choices in a loss condition compared to PwP+ICBs.

Five studies which used the modified Iowa Gambling Task, Vancouver Gambling task, Probability Associated Gambling task, Framing paradigm, and Alternative Choice Gambles tasks all showed no significant group differences between PwP and HCs, and 1 study which used the Investment task showed no significant group differences between PwP+ICBs and PwP.

3.4.2.7. Personality traits

Of the studies that examined personality traits related to impulsivity, 28 used the Barratt Impulsiveness Scale (Barratt, 1959; Patton, Stanford, & Barratt; 1995), 7 used the Temperament and Character Inventory, 1 used the Tridimensional Personality Questionnaire, 5 used the Behavioural Inhibition System/Behavioural Approach System Questionnaire (Carver & White, 1994), 3 used the Snaith-Hamilton Pleasure Scale (Snaith et al., 1995), 1 used the UPPS Impulsive Behaviour Scale (Whitside & Lynam, 2001; Whiteside et al., 2005), and 1 used the Zuckerman-Kuhlman Personality Questionnaire. Relevant studies are shown in Table 14.

Largely, studies showed no significant differences on the total score for the Barratt Impulsiveness Scale for PwP compared to HCs (N = 4), however PwP+ICBs did shower higher scores for trait impulsivity on this task (N = 10) than PwP. Studies reporting analyses on the attentional, motor, and non-planning sub-scales of the Barratt Impulsiveness Scale present a less clear picture for group differences between PwP+ICB and PwP with some finding evidence for group differences (N = 2, N = 4, and N = 2 respectively for each sub-scale) and others finding no significant differences (N = 5, N = 3, and N = 5 respectively).

Whilst only a few studies have used the Temperament and Character Inventory, studies show largely no significant group difference between PwP and HCs for trait impulsivity on the Temperament and Character Inventory scales of novelty seeking (N = 2, though N = 1 did find group differences), reward dependence (N = 2), and persistence (N = 2), although for harm avoidance there was one study reporting significant group differences and one reporting null results. PwP+ICBs show higher novelty seeking scores compared to PwP, but no difference for harm avoidance.

Generally, PwP show no differences compared to HCs on the Behavioural Inhibition Systems (N = 2) and Behavioural Approach Systems (N = 4 questionnaires), and nor did this differ between PwP+ICBs and PwP.

3.4.2.8. Set shifting/cognitive flexibility

Although set shifting is often described as a task of selective attention, there is evidence that inhibitory control is an important component in reducing unwanted (or no longer needed) attention in order to redirect to the goal-directed task (Rogers et al., 1998). Set shifting, a measure of cognitive flexibility, is often used synonymously with task switching. There are likely to be other relevant findings in the literature where the authors did not refer to inhibition, and therefore were not captured in this review. In our literature search 23 studies used the Trail Making Test (one of which was the Colour Trails version), 2 used the Odd Man Out, and 3 used general Task Switching paradigms, 2 used Rewarded Task Switching paradigms, and 1 used an n-back task. Relevant studies are shown in Table 15.

In the Trail Making and Colour Trails tests results were mixed regarding the time it takes to complete Trail B (N = 7 found that PwP took significantly longer than HCs, whereas N = 6 found null results) however when subtracting the time it takes to complete Trail A from Trail B (and thus accounting for the potential for global slowing in PwP), most studies reported null results (N = 6, compared to N = 1 which found that PwP performed worse). There were largely null results when comparing PwP+ICBs and PwP on both the time for Trail B (N = 3, compared to N = 1) and for Trail B-A (N = 4, compared to N = 1). On the Odd Man Out task PwP showed more errors compared to HCs (N = 2), and on a general task switching paradigm there were no difference between PwP and HCs regardless of whether the task contained an element of reward (N = 2) or not (N = 3).

Table 8. Response inhibition: tasks and dependent variables of interest with corresponding studies that make direct comparisons between PwP and HCs and between PwP+ICBs and PwP.

Task	Variable	PwP and HCs: Significant results (impaired in PwP unless specified)	PwP and HCs: Null results	PwP+ICB and PwP: Significant results (impaired in PwP+ICBs unless specified)	PwP+ICB and PwP: Null results
Go/No-Go	**Commission errors**	Bokura et al. (2005) Geffe et al. (2016)	Al-Khaled et al. (2015) Crescentini et al. (2012) Martini, Ellis et al. (2018)		Martini, Ellis et al. (2018) Rossi et al. (2010)
	Overall errors	Cammisuli and Crowe (2018) Nombela et al. (2014)	de Rezende Costa et al. (2016)		Bentivoglio et al. (2013)
	Seoul Neuropsychological Screening Battery Go/No-Go score				Yoo et al. (2015)
Stop Signal task	**Stop signal reaction time**	Gauggel et al. (2004) George et al. (2013) Nombela et al. (2014) Ricciardi et al. (2017)	Bissett et al. (2015) Harrington et al. (2018) Manza et al. (2018) Stefanova et al. (2014)		Ricciardi et al. (2017)
	Commission errors		Leroi et al. (2013)		Leroi et al. (2013)
Countermanding task	**Stop signal reaction time**	Mirabella et al. (2017)			
Stop-Change task	**Stop signal reaction time**	van den Wildenberg et al. (2017)			
	Change reaction time	van den Wildenberg et al. (2017)			

Table 9. Response conflict: tasks and dependent variables of interest with corresponding studies that make direct comparisons between PwP and HCs and between PwP+ICBs and PwP

Task	Variable	PwP and HCs: Significant results (impaired in PwP unless specified)	PwP and HCs: Null results	PwP+ICB and PwP: Significant results (impaired in PwP+ICBs unless specified)	PwP+ICB and PwP: Null results
Simon task	**Interference (accuracy)**	Laurent et al. (2018) Praamstra and Plat (2001)	Houvenaghel et al. (2016) van Wouwe et al. (2014); *when accuracy was emphasised* van Wouwe et al. (2014); *when speed was emphasised* van Wouwe et al. (2016) Wylie, Ridderinkhof, Bashore et al. (2010) Wylie, Ridderinkhof, Elias et al. (2010)		Wylie, Claassen et al. (2012)
	Interference (RT)	Houvenaghel et al. (2016) van Wouwe et al. (2014); *when accuracy was emphasised* van Wouwe et al. (2016)	Laurent et al. (2018) Praamstra and Plat (2001) van Wouwe et al. (2014); *when speed was emphasised* Wylie, Ridderinkhof, Bashore et al. (2010) Wylie, Ridderinkhof, Elias et al. (2010)		Wylie, Claassen et al. (2012)
	Incongruent accuracy	Flannery et al. (2018			
	Incongruent RT		Flannery et al. (2018)		
	Response capture		Laurent et al. (2018) Houvenaghel et al. (2016) van Wouwe et al. (2014) van Wouwe et al. (2016) Wylie, Ridderinkhof, Bashore et al. (2010) Wylie, Ridderinkhof, Elias et al. (2010)	Wylie, Claassen et al. (2012); *PwP impaired*	
	Response suppression	Laurent et al. (2018) Houvenaghel et al. (2016) van Wouwe et al. (2014); *when speed was emphasised* van Wouwe et al. (2016) Wylie, Ridderinkhof, Bashore et al.	van Wouwe et al. (2014); *when accuracy was emphasised*		Wylie, Claassen et al. (2012)

Task	Variable	PwP and HCs: Significant results (impaired in PwP unless specified)	PwP and HCs: Null results	PwP+ICB and PwP: Significant results (impaired in PwP+ICBs unless specified)	PwP+ICB and PwP: Null results
		(2010) Wylie, Ridderinkhof, Elias et al. (2010)			
Interference task	**Interference (accuracy)**		Plessow et al. (2014)		
	Interference (RT)		Plessow et al. (2014)		
Learned Stimulus-Response Association task	**Interference effect**		Hiebert et al. (2014)		
Eriksen Flanker task	**Interference (accuracy)**	Falkenstein et al. (2006) Wylie et al. (2009a)	Fabbri et al. (2018) Wylie et al. (2005) Wylie et al. (2009b)		
	Interference (RT)	Falkenstein et al. (2006); *HCs worse* Verleger et al. (2010); *flanker and target presented simultaneously* Wylie et al. (2005) Wylie et al. (2009a)	Cagigas et al. (2007) Fabbri et al. (2018) Verleger et al. (2010); *target presented after flanker*		
	Incongruent accuracy	Flannery et al. (2018			
	Incongruent RT		Flannery et al. (2018		
	Response capture		Wylie et al. (2009a) Wylie et al. (2009b)		
	Response suppression	Wylie et al. (2009a) Wylie et al. (2009b)			
Stroop task	**Interference (accuracy)**	Barnes & Boubert (2008) Fales et al. (2006) Hsieh et al. (2008) Obeso et al. (2011)	Cools et al. (2006) Galtier et al. (2014) Richards et al. (1993)		Biundo et al. (2011)
	Interference (RT)	Gawrys et al. (2014) Kliegel et al. (2005) McKinlay et al. (2009) Obeso et al. (2011) Pollux & Robertson (2002)	Angwin et al. (2017) Eddy et al. (2013) Fleury et al. (2014) Henik et al. (1993) Koerts et al. (2013)		Biundo et al. (2011)

Task	Variable	PwP and HCs: Significant results (impaired in PwP unless specified)	PwP and HCs: Null results	PwP+ICB and PwP: Significant results (impaired in PwP+ICBs unless specified)	PwP+ICB and PwP: Null results
		Ranchet et al. (2013)	Price (2010) Vandenbossche et al. (2012)		
	Incongruent accuracy	Centi et al. (2017) Crescentini et al. (2012) Eddy et al. (2013) Henik et al. (1993) Jia et al. (2018) Nombela et al. (2014)	Alonso-Recio et al. (2014) Angwin et al. (2017) Bocquillon et al. (2015) Djamshidian et al. (2011) Nombela et al. (2011) Vandenbossche et al. (2012)	Vitale et al. (2011)	Djamshidian et al. (2011) Rossi et al. (2010) Vitale et al. (2011)
	Incongruent RT	Nombela et al. (2011)	Bocquillon et al. (2015) Djamshidian et al. (2011)	Yoo et al. (2015)	
	Response capture	Vandenbossche et al. (2012)			
	Response suppression		Vandenbossche et al. (2012)		
	Unspecified/unclear		Al-Khaled et al. (2015) Tessitore et al. (2017		Bentivoglio et al. (2013) Tessitore et al. (2017)
Picture-Word Interference task	**Interference (RT)**		Castner et al. (2007)		
Hayling Sentence Completion Test	**Scaled score**	Nombela et al. (2014) O'Callaghan et al. (2013) Obeso et al. (2011)			Martini, Ellis et al. (2018)
	B-A	Bouquet et al. (2003)	Castner et al. (2007)		

Table 10. Oculomotor inhibition: tasks and dependent variables of interest with corresponding studies that make direct comparisons between PwP and HCs and between PwP+ICBs and PwP.

Task	Variable	PwP and HCs: Significant results (impaired in PwP unless specified)	PwP and HCs: Null results	PwP+ICB and PwP: Significant results (impaired in PwP+ICBs unless specified)	PwP+ICB and PwP: Null results
Anti-saccade task	**Anti-saccade errors**	Amador et al. (2006) Chan et al. (2005)	Crucian et al. (2007) Rivaud-Pechoux et al. (2007)		
	Overall errors				
	Saccadic latencies	Chan et al. (2005) Flannery et al. (2018) van Stockum et al. (2008)	Rivaud-Pechoux et al. (2007)		
Mixed pro-/anti-saccade tasks	**Errors**	Rivaud-Pechoux et al. (2007) Flannery et al. (2018) van Koningsbruggen et al. (2009)	Ouerfelli-Ethier et al. (2018)		
	Saccadic latencies	Flannery et al. (2018)	Ouerfelli-Ethier et al. (2018) Rivaud-Pechoux et al. (2007) van Koningsbruggen et al. (2009)		
Delayed pro-/anti-saccade tasks	**Disinhibition errors**	Amador et al. (2006)	van Stockum et al. (2008)		
	Anti-saccade errors	Chan et al. (2005)			
	Saccadic latencies		Chan et al. (2005)		
Visually guided reactive saccades task	**Saccadic intrusions**	Gorges et al. (2017) Vintonyak et al. (2017)			
	Error rate	Gorges et al. (2013)			
Delayed visually guided reactive saccades	**Disinhibition errors**	Gorges et al. (2013) Terao et al. (2011)	Yugeta et al. (2010)		
	Saccadic latencies	Terao et al. (2011)			

Task	Variable	PwP and HCs: Significant results (impaired in PwP unless specified)	PwP and HCs: Null results	PwP+ICB and PwP: Significant results (impaired in PwP+ICBs unless specified)	PwP+ICB and PwP: Null results
		Yugeta et al. (2010)			
Smooth pursuit	**Pursuit gain**	Gorges et al. (2013) Gorges et al. (2017) Vintonyak et al. (2017)	Wu et al. (2018)		
	Errors to distractor	Henderson et al. (2011)			
Oculomotor Go/No-Go task	**Commission errors**	Nombela et al. (2014) Zhang, Nombela et al. (2016)			
Oculomotor Simon task	**RT interference effect**	Duprez et al. (2017)			
	Errors	Duprez et al. (2017) Fielding et al. (2005)			
	Response capture	Duprez et al. (2017)			
	Response suppression		Duprez et al. (2017)		
Oculomotor Stop Signal task (saccadic redirect task)	**Target switch reaction time**	Joti et al. (2007)			

Table 11. Delayed gratification: tasks and dependent variables of interest with corresponding studies that make direct comparisons between PwP and HCs and between PwP+ICBs and PwP.

Task	Variable	PwP and HCs: Significant results (impaired in PwP unless specified)	PwP and HCs: Null results	PwP+ICB and PwP: Significant results (impaired in PwP+ICBs unless specified)	PwP+ICB and PwP: Null results
Kirby Delay Discounting Questionnaire	***k***		Evens et al. (2015) Housden et al. (2010) Martini, Ellis et al. (2018) Nombela et al. (2014) Simioni et al. (2012)	Housden et al. (2010) Voon, Sohr, et al. (2011)	Martini, Ellis et al. (2018)
	***k* large**		Housden et al. (2010)	Housden et al. (2010) Voon, Sohr, et al. (2011)	
	***k* medium**		Housden et al. (2010)	Housden et al. (2010) Voon, Sohr, et al. (2011)	
	***k* small**		Housden et al. (2010)	Housden et al. (2010)	Voon, Sohr, et al. (2011)
Delay Discounting Task	K^+		Leroi et al. (2013)	Leroi et al. (2013)	

Table 12. Decision making under ambiguous risk: tasks and dependent variables of interest with corresponding studies that make direct comparisons between PwP and HCs and between PwP+ICBs and PwP.

Task	Variable	PwP and HCs: Significant results (impaired in PwP unless specified)	PwP and HCs: Null results	PwP+ICB and PwP: Significant results (impaired in PwP+ICBs unless specified)	PwP+ICB and PwP: Null results
Iowa Gambling Task	**Frequency of advantageous or disadvantageous decisions**	Delazer et al. (2009) Mapelli et al. (2014) Pagonabarraga et al. (2007)	Evens et al. (2015)	Balconi, Angioletti, et al. (2018) Balconi, Siri, et al. (2018)	Biars et al. (2018)
	Learning to avoid disadvantageous decks	Buelow et al. (2014) Delazer et al. (2009) Mapelli et al. (2014) Pagonabarraga et al. (2007)			Biars et al. (2018)
	Total points scored			Rossi et al. (2010)	
Balloon Analogue Risk Task	**Adjusted pumps**	Simioni et al. (2012)	Buelow et al. (2014) Martini, Ellis et al. (2018) Ricciardi et al. (2017)		Claassen et al. (2011) Martini, Ellis et al. (2018) Rao et al. (2010) Ricciardi et al. (2017)
Economic Learning task	**Risk aversion**	Djamshidian et al. (2010)			Djamshidian et al. (2010)
	Risk taking			Fumagalli et al. (2015) Rosa et al. (2013)	
Deal or No Deal task	**Largest offer rejected**	Brandt et al. (2015)			
Reward Processing Gambling Task	**Frequency of risky choices**		Carriere et al. (2016)		Carriere et al. (2016)

Table 13. Decision making under objective risk: tasks and dependent variables of interest with corresponding studies that make direct comparisons between PwP and HCs and between PwP+ICBs and PwP.

Task	Variable	PwP and HCs: Significant results (impaired in PwP unless specified)	PwP and HCs: Null results	PwP+ICB and PwP: Significant results (impaired in PwP+ICBs unless specified)	PwP+ICB and PwP: Null results
Game of Dice task	**Risky decision making**	Bayard et al. (2016) Boller et al. (2014) Brandt et al. (2015)			Rossi et al. (2010)
Cambridge Gambling Task	**Impulsive decisions**	Cools et al. (2003) Torta et al. (2009)	Nombela et al. (2014)		
	Quality of decision making	Torta et al. (2009)	Cools et al. (2003)		
Monetary Decision Making Task	**Risk aversion**		Kobayashi et al. (2018)		Kobayashi et al. (2018)
	Risky decisions (gains)			Voon, Gao et al. (2011a)	
	Risky decisions (losses)			Voon, Gao et al. (2011a); *PwP made riskier decisions*	
Modified Iowa Gambling Task	**Decision making**		Pineau et al. (2016)		Pineau et al. (2016)
	Subjective valuation		Pineau et al. (2016)	Pineau et al. (2016)	
Vancouver Gambling Task	**Choices made (gain condition)**		Sharp et al. (2013)		
	Choices made (loss condition)		Sharp et al. (2013)		
Probability Associated Gambling Task	**Frequency of advantageous decisions**		Delazer et al. (2009)		
Framing Paradigm	**Gain risk**		Brandt et al. (2015)		
	Loss risk		Brandt et al. (2015)		
Investment task	**Decision making**				Rossi et al. (2010)
Alternative Choice Gambles	**Risk aversion**		Djamshidian et al. (2010)		Djamshidian et al. (2010)

Table 14. Personality traits: tasks and dependent variables of interest with corresponding studies that make direct comparisons between PwP and HCs and between PwP+ICBs and PwP.

Task	Variable	PwP and HCs: Significant results (impaired in PwP unless specified)	PwP and HCs: Null results	PwP+ICB and PwP: Significant results (impaired in PwP+ICBs unless specified)	PwP+ICB and PwP: Null results
Barratt Impulsiveness Scale	**Total score**	Isaias et al. (2008) Nombela et al. (2014)	Canesi et al. (2012) Duprez et al. (2017) Martini, Ellis et al. (2018) Terenzi et al. (2018)	Ahearn et al. (2012) Bentivoglio et al. (2013) Isaias et al.(2008) Leroi et al. (2013) Pettorruso et al. (2014) Pineau et al. (2016) Ray et al. (2012) Ruitenberg et al. (2018) Voon et al. (2007) Voon, Sohr et al. (2011)	Antonini et al. (2011) Marín-Lahoz et al. (2018) Martini, Ellis et al. (2018) Terenzi et al. (2018)
	Attentional impulsivity		Terenzi et al. (2018)	Antonini et al. (2011) Voon, Sohr et al. (2011)	Bentivoglio et al. (2013) Marín-Lahoz et al. (2018) Ruitenberg et al. (2018) Terenzi et al. (2018) Voon et al. (2007)
	Motor impulsivity		Terenzi et al. (2018)	Bentivoglio et al. (2013) Ruitenberg et al. (2018) Voon et al. (2007) Voon, Sohr et al. (2011)	Antonini et al. (2011) Marín-Lahoz et al. (2018) Terenzi et al. (2018)
	Non-planning impulsivity		Terenzi et al. (2018)	Voon et al. (2007) Voon, Sohr et al. (2011)	Antonini et al. (2011) Bentivoglio et al. (2013) Marín-Lahoz et al. (2018) Ruitenberg et al. (2018) Terenzi et al. (2018)
Temperament and Character Inventory	**Novelty seeking**	Bodi et al. (2009)	Koerts et al. (2013) Sharp et al. (2013)	Voon et al. (2007) Voon, Sohr et al. (2011)	
	Harm Avoidance	Koerts et al. (2013)	Bodi et al. (2009)		Voon et al. (2007)
	Reward Dependency		Bodi et al. (2009) Koerts et al. (2013)		
	Persistence		Bodi et al. (2009) Koerts et al. (2013)		
Behavioural Inhibition	**BIS**		Aarts et al. (2012) Cools et al. (2006)		

Task	Variable	PwP and HCs: Significant results (impaired in PwP unless specified)	PwP and HCs: Null results	PwP+ICB and PwP: Significant results (impaired in PwP+ICBs unless specified)	PwP+ICB and PwP: Null results
System (BIS) & Behavioural Approach System (BAS) Questionnaire	**BAS overall**		Aarts et al. (2012) Cools et al. (2006) Nombela et al. (2014) Terenzi et al. (2018)		Terenzi et al. (2018)
	BAS Drive		Aarts et al. (2012) Terenzi et al. (2018)		Terenzi et al. (2018)
	BAS Fun Seeking		Aarts et al. (2012) Terenzi et al. (2018)		Terenzi et al. (2018)
	BAS Reward Responsiveness	Aarts et al. (2012)	Terenzi et al. (2018)		Terenzi et al. (2018)
Snaith-Hamilton Pleasure Scale	**Total score**			Pettorruso et al. (2014)	
UPPS Questionnaire	**Urgency**	Bayard et al. (2016)			Bayard et al. (2016)
	Lack of premeditation	Bayard et al. (2016)			Bayard et al. (2016)
	Lack of perseverance	Bayard et al. (2016)			Bayard et al. (2016)
	Sensation seeking		Bayard et al. (2016)	Bayard et al. (2016)	
Zuckerman-Kuhlman Personality Questionnaire	**Sensation seeking**				Rossi et al. (2010)

Table 15. Set shifting/cognitive flexibility: tasks and dependent variables of interest with corresponding studies that make direct comparisons between PwP and HCs and between PwP+ICBs and PwP.

Task	Variable	PwP and HCs: Significant results (impaired in PwP unless specified)	PwP and HCs: Null results	PwP+ICB and PwP: Significant results (impaired in PwP+ICBs unless specified)	PwP+ICB and PwP: Null results
Trail Making Test	**Trail B-A (time)**	Gawrys et al. (2014)	Barbosa et al. (2017) Bouquet et al. (2003) Ranchet et al. (2013) Terenzi et al. (2018) Walton, O'Callaghan et al. (2015)	Vitale et al. (2011)	Biundo et al. (2011) Pineau et al. (2016) Terenzi et al. (2018)
	Trail B (time)	Akamatsu et al. (2008) Barbosa et al. (2017) Beratis et al. (2018) Campos-Sousa et al. (2010) Crescentini et al. (2012) Gawrys et al. (2014)	Bouquet et al. (2003) Delazer et al. (2009) Koerts et al. (2013) Ranchet et al. (2013) Ricciardi et al. (2017 Terenzi et al. (2018)	Tessitore et al. (2017)	Biundo et al. (2011) Merola et al. (2017) Ricciardi et al. (2017) Terenzi et al. (2018)
	Trail B (errors)		Campos-Sousa et al. (2010) Martini, Ellis et al. (2018)		Martini, Ellis et al. (2018)
Colour Trails Test	**Trail B-A (time)**		Fales et al. (2006)		
	Trail Part B (time)		Fales et al. (2006)		
Odd Man Out	**Errors**	Koerts et al. (2013) Richards et al. (1993)			
Task Switching	**Switch cost**		Cools et al. (2003) Rogers (1998)		
	RT		Fales et al. (2006)		
	Accuracy	Fales et al. (2006)			
Rewarded Task Switching	**Reward-related performance**		Aarts et al. (2012) Aarts et al. (2014)		
n-back task	**Fewer responses and more false alarms**	Gawrys et al. (2014)			

3.5. Discussion

The review aimed to synthesise the relevant literature to date that examined impulsivity and inhibitory control in PwP with and without additional ICBs. The review focused on breadth rather than depth, and the search identified a total of 246 relevant papers on the topic that included over 100 different tasks and measures (Table 7, Figure 6).

All studies were included in a Shiny app, available online (https://jspickering.shinyapps.io/sysreviewapp/), which summarises all 246 studies including the authors, year, title, descriptions of the participant groups (age, gender, UPDRS, H&Y, and disease duration), the measures used and the aspect of impulsivity that the authors were aiming to measure, and whether the comparisons were made between PwP and HCs, PwP+ICBs and PwPs, other between-groups designs with PwP (e.g. groups with and without various symptoms), or within-groups designs with PwP (e.g. medication ON/OFF). Studies that made direct comparisons between PwP and HCs, and PwP+ICBs and PwP without ICBs were included in a narrative synthesis. We categorised the measures into common themes; response inhibition, response conflict, oculomotor inhibition, delayed gratification, decision making under ambiguous and objective risk, personality traits, and set shifting/cognitive flexibility. It is important to note that many studies that include a sample of PwP, and no explicit PwP+ICB group, do not usually screen for ICBs in their sample and so it is not possible to be confident on the proportion samples of PwP that do or do not contain a subset of patients with ICBs.

Overall, the literature does not reach a consensus for most domains in terms of whether PwP (whilst ON their normal dopaminergic therapy) are impaired compared to age-matched HC participants. However, PwP do seem to show a greater difficulty with response suppression and a similar susceptibility to fast impulsive errors in tasks of the distribution of response times in tasks of response conflict, and increased risk-taking for decision-making under ambiguous risk (particularly when learning is involved, such as in the Iowa Gambling task), but show no significant differences for personality traits, delayed gratification, and tasks of set shifting. Studies that have compared impulsivity in PwP compared to PwP+ICBs are much fewer in number (N = 38 compared to N= 185 that included PwP and HCs) and have been completed using fewer measures. Generally, there appear to be no differences between groups on tasks of response inhibition (e.g. Go/No-Go, Stop Signal), response conflict (particularly the Stroop task), and set shifting (Trail Making Test) which complements a recent meta-analysis (Martini, Dal Lago et al., 2018). PwP+ICBs show reduced ability to delay gratification and higher general trait impulsivity (i.e. Barratt Impulsiveness Scale total score). Results were much more mixed for decision making under both ambiguous and objective risk. Oculomotor inhibition has not yet been examined in these two groups of patients.

The basal ganglia and fronto-striatal pathways are important for effective response inhibition, and activity in the right inferior frontal gyrus and anterior cingulate cortex have been

particularly associated with performance in the Stop Signal task (Aron, Robbins, & Poldrack, 2004, 2014; Jahanshahi, Obeso, Rothwell, & Obeso, 2015). These networks are implicated in Parkinson's as the loss of dopamine in the substantia nigra has a wide-reaching impact throughout this circuitry. Response inhibition has been studied extensively in PwP, and despite these theoretical reasons to expect an impairment the overall picture is still unclear. A recent meta-analysis (that was not necessarily able to account for the potential existence of additional ICBs in the included samples) found that, statistically, PwP do show impairment compared to HCs for commission errors (Go/No-Go task) and stop signal reaction time (Stop Signal task), and that this is unaffected by medication which suggests an effect of disease (Manza, Amandola, Tatineni, Li, & Leung, 2017). However, many studies are still not amenable to meta-analytic techniques due to heterogeneity within tasks, and so it is difficult to build up a larger overall picture of studies missing from meta-analyses.

Some aspects of response inhibition show clearer effects than others. Although fewer studies have used the Conditional Stop Signal Task and Stop-Change Task, stop signal reaction time was generally slower in these tasks for PwP, which may suggest that response inhibition is more difficult when an element of response conflict is introduced into the task (Obeso et al., 2014; Obeso, Wilkinson, Casabona et al., 2011). Whilst the response conflict literature provided an unclear picture, dissociating fast errors of impulsivity from the failure to build up appropriate inhibition can help to disentangle these results further.

The activation-suppression model explains how longer RTs allow time for the selective suppression of the automatic response that is activated along a direct route so that the alternative response can be executed (Ridderinkhof, 2002; van den Wildernberg et al., 2010). Distributional analyses consistently show that, whilst PwP and healthy controls are similarly susceptible to fast impulsive errors, PwP have greater difficulty inhibiting their responses at the slow end of the response time distribution on both tasks i.e. when response times are slower the ability to suppress that response is lower in PwP. Generally, the response conflict literature suggests that PwP may have some difficulty with deliberate inhibitory control when given enough time to overcome fast impulsive errors, however we were unable to replicate this finding in Chapter 2.

Whilst most studies of response inhibition and response conflict require manual motor movements, there are also analogous oculomotor tasks. PwP showed impairment on the oculomotor versions of the Go/No-Go, Stop Signal, and Simon tasks compared to HCs. Saccadic inhibition is more strongly associated with the basal ganglia than manual inhibition, which may explain why there appears to be a clearer control/inhibitory deficit for saccadic inhibition compared to manual motor inhibition (Jahanshahi et al, 2015).

Risky decision making under ambiguous risk seems to be impaired in PwP compared to HCs. In particular, PwP show a failure to learn in response to reward or punishment in some tasks such as the Iowa Gambling Task; however, there seem to be no group differences between self-reported sensitivity to reward or punishment according to the Behavioural Inhibition/Behavioural Approach Scales so this is potentially due to some other aspect of the learning process.

A domain of impulsivity that was consistently found to not differ between PwP and HCs was delay discounting, or the ability to forgo a smaller, more immediate, reward in favour of a larger reward in the future. The subjective value of a decision appears to be related to the dopaminergic reward system that projects from the ventral tegmental area (Haber, 2011). As the ventral tegmental area is largely unaffected in early Parkinson's, it is perhaps not surprising that delay discounting would be unaffected by the disease itself, at least in mild to moderate samples of participants. Conversely, this was also a clear impairment for PwP+ICBs who, according to the dopamine overdose hypothesis (Cools et al., 2001; Vaillancourt et al., 2013), perhaps have more dopamine availability in these pathways and therefore further suggest that delay discounting is related to these reward systems.

3.5.1. General implications

This review can be a starting point for future meta-analyses or empirical investigations where the results are currently unclear, but it has also identified some general areas where the cohesiveness of the literature can be improved. Across the studies included in the review, there were a wide variety of differences in terms of the participant samples, the methodology employed even across the same tasks, the analysis techniques, and the dependent variables that were chosen to reflect various aspects of impulsivity which, taken together, have implications for the comparability of studies and the amenability to meta-analytic techniques which we elected not to do here to ensure that we still kept the breadth of research.

Parkinson's is heterogenous by nature, both between patients in terms of the symptoms they experience but also within an individual patient hour-by-hour or day-by-day. The importance of reporting all relevant patient information has been highlighted in a previous systematic review of executive functioning (Kudlicka et al., 2011), and it would greatly help with evidence synthesis and literature cohesiveness for these practices to be more commonplace. For example, based on current knowledge of impulsivity and ICBs in general, it would be useful to report participant information such as UPDRS scores, Hoehn and Yahr staging, disease duration, the presence or absence of ICBs (see Evans et al., 2019, for best practice recommendations), and any treatment including a levodopa equivalent daily dose (i.e. according to the recommendations of Tomlinson et al, 2010), types of medication (levodopa, dopamine agonists, etc), and whether they are undergoing deep brain stimulation as this has been shown to affect impulsivity (Mosley et al., 2020). Having such information available in all studies will make it

easier to disentangle the elements of Parkinson's and related treatments that do, or do not, contribute to an increase or change in impulsivity.

Additionally, the methodology in the included studies was not always presented in sufficient detail to be reproducible, and thus they were often difficult to compare across studies. Methodological differences may lead to data that does not accurately reflect what the authors sought to measure. As an example, the Stop Signal task is a complicated task to implement correctly to ensure that the resulting dependent variable of interest (stop signal reaction time) accurately reflects the time taken for the stop process to overtake the go process according to the race model of inhibitory control (see Logan, 1994; Matzke, Verbruggen, and Logan, 2008; 2009). Whilst full recommendations were only recently made more accessibly available (see Verbruggen et al., 2019), previous recommendations centred around the importance of certain methodological decisions such as the presentation of Stop trials on a minority of trials in order to elicit a prepotent "go" response, and the method of calculating the stop signal reaction time (Logan, 1994; Verbruggen & Logan, 2009), both of which contribute to the validity of the end data.

Of the Go/No-Go and Stop Signal tasks in this review, many of those that showed no significant group differences had a higher proportion of No-Go or Stop trials, whereas those with a lower percentage showed more impairment. It is therefore possible that where there are no group differences this is due to a ceiling effect, or the task is not sensitive enough to detect group differences. Similarly, where response times are measured, it would be appropriate to account for general slowing in terms of bradykinesia or speech problems for motor responses and verbal responses respectively. Although these are just examples, studies which use established tasks should make all efforts to conform to best practice.

Even established measures may not necessarily be valid for use in Parkinson's. For example, trait impulsivity as measured by the Barratt Impulsiveness Scale was generally higher for PwP+ICBs than for PwP, but for the sub-scales of attentional impulsivity, motor impulsivity, and non-planning impulsivity results were more mixed. Indeed, the original factor structure by Patton et al. (1995) has low to average internal consistency on all sub-scales when used with PwP (Smulders et al., 2014), and Ahearn et al. (2012) additionally found that the factor structure that emerges in a sample of PwP (with and without ICBs) is different to that from the general population. The five factors that emerged in PwP are inattention, impetuosity, personal security, planning, and future orientation and, moreover, PwP+ICBs show higher scores on all factors compared to PwP (Ahearn et al., 2012). Further research into the validity of not only the Barratt Impulsiveness Scale, but other measures of impulsivity, is warranted.

Many studies were excluded that used similar or identical tasks to those included in the review but where the authors purported to be measuring different domains; additionally, it was not

always clear whether the authors' intentions really were to measure impulsivity or inhibitory control. For example, the Wisconsin Card Sorting Test is not featured in this review despite being a classic measure of set shifting. This may seem counterintuitive given that the theme of set shifting and cognitive flexibility is included in this review. To keep the review manageable, we pre-registered our intention to only include papers where the study authors clearly state that they are measuring impulsivity or inhibitory control, or where the expertise of this review's authors deemed the study to be applicable during the independent screening process. Therefore, many studies that used the Wisconsin Card Sorting Test were focused on attention instead of inhibitory control and so were not included, unless the study authors suggested otherwise. There is a clear overlap between attention and inhibitory control (see the literature on ADHD, e.g. Barkley, 1997), and so in many cases it is not always clear which mechanisms are explored with certain tasks. This review aims to provide a starting point at bringing together a wide range of tasks that have been used to measure impulsivity and inhibitory control in Parkinson's to date to inform future, more focused, syntheses that systematically review literature on particular tasks such as in previous efforts by Manza et al. (2017) and Martini, Dal Lago et al. (2018).

It is also important to highlight that, most likely due to a rapid change in knowledge and understanding of ICBs, many of the studies beyond the last 5-10 years that focus on samples of PwP in general do not identify whether there were participants with ICBs present in their samples. There are likely to be underlying differences in these two groups, as additionally highlighted by this review, so researchers performing empirical research into these domains should now work to identify and account for any confounding effects of ICBs in their samples. There are now validated screening tools available to test for the presence of ICBs, such as the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's (Weintraub et al., 2012) and for a review of this scale and more see Evans et al. (2019).

The synthesis presented here must additionally be taken in context of probable publication bias, where statistically significant findings are more likely to be published than null (DeVito & Goldacre, 2019). Whilst we have not quantified publication bias here (for applicable methods see Carter, Schönbrodt, Gervais, & Hilgard, 2019), many null results *were* reported in the studies included in the synthesis. It is important to note that there are likely many more null results that were *not* featured in the published literature, and that those featured here are still likely to be an underrepresentation even though we have not been able to quantify it here. It is a limitation of this systematic review that data were not extracted to assess bias.

We also did not assess study quality as no appropriate scale to measure risk of bias or quality in studies such as these existed (see section *3.3.1. Deviations from protocol*). Therefore, we refrain from drawing stronger conclusions without an adequate quantification of study quality.

3.5.2. Conclusions

In this ambitious review, we believe we have captured the breadth, and a significant amount of depth, of the literature to date that examines inhibitory control or impulsivity in Parkinson's and Parkinson's and ICBs. This will provide the foundations for future, more focused, meta-analytic efforts into examining the topic further, to complement those that already exist. It is clear that this is an important field of Parkinson's research, particularly due to the implications that disease progression and dopaminergic treatment have on the pathways implicated in impulsivity and inhibitory control. Future research should seek to use a similar variety of measures of impulsivity and inhibitory control with the same participants to remove the problems of between-study heterogeneity on the ability to form clear conclusions and to further examine where group differences lie. Tasks and measures used should conform to best practices, and the tasks and dependent variables chosen should be appropriate and representative for the mechanism under investigation.

Overall, according to this review, people with Parkinson's appear to show higher impulsivity compared to healthy controls in tasks of response conflict, and decision making under ambiguous risk, but not delayed gratification, set shifting, or personality traits. People with Parkinson's who have additional impulse control behaviours show higher impulsivity than PwP without ICBs for delay discounting and personality traits, but no differences for response inhibition, response conflict, and set shifting.

3.6. References

Asterisks denote papers that were identified by the systematic search.

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Postscript to Chapter 3

One of the greatest challenges for Chapter 3 was that the review was written at a time where no appropriate guidelines existed for conducting a systematic review of this nature where the studies included were not of an applied clinical, healthcare, educational, or interventional nature. Since embarking on this project, I set up an international collaborative working group of over 50 expert researchers and librarians, co-led with University of Surrey PhD student Marta Topor and with supervisory input from Professor Dorothy Bishop (University of Oxford, UK) and Dr Katie Corker (Grand Valley State University, Michigan, USA). The group, Non-Interventional, Reproducible, and Open Evidence Synthesis (NIROES), aim to directly address the difficulties and limitations that were found through the process of performing this review, and the shared difficulties discovered by others (particularly early career researchers) performing reviews of similar types of studies.

We firstly established a set of guidelines that can be used to pre-register and conduct a systematic review with a focus on non-interventional research and issues of open research. These guidelines have been available on the Open Science Framework since May 2020 (Pickering et al., 2020) and are already being used by researchers internationally to write and pre-register systematic review protocols, and have been incorporated into undergraduate and master's syllabi at the University of Coventry, UK and the University of the Philippines Diliman. A pre-print will be available soon to accompany publication of the final guidelines.

A major omission in Chapter 3 was the lack of quality assessment or risk of bias, as discussed in section *3.3.1. Deviations from protocol*, due to a lack of existing scale that was appropriate for the non-interventional studies included in this review. The second major output of NIROES is to develop a quality assessment tool to fill this gap, and development of this has been underway throughout 2020. Although this work does not form part of the PhD work itself, it aims to address the limitations in this chapter.

Pickering, J. S., Topor, M., Barbosa Mendes, A., Bishop, D. V. M., Büttner, F., Evans, T. R., … Zaneva, M. (2020, August 13). NIRO Systematic Reviews. Retrieved from https://osf.io/erkwa

Preface to Chapter 4

The study was completed collaboratively with MRes student, Marta Majewska, who used the same methods (pre-registered on the Open Science Framework, under embargo) to examine differences in impulsivity and inhibitory control between two age groups: the same older control sample used here compared with an additional group of younger participants (aged 18-30). Data collection was halted suddenly due to the COVID-19 pandemic and therefore the thesis presents an incomplete analysis of a pre-registered study. Once face-to-face testing resumes, the final data will be collected, and the chapter rewritten into a publishable manuscript which aligns fully with the pre-registered protocol.

Author contributions: The pre-registration for this chapter (available in Appendix C) and for Marta Majewska's MRes dissertation were co-written by Jade Pickering and Marta Majewska and form the basis of the methods section in this chapter. Jade Pickering primarily wrote the code for the Go/No-Go, Stop Signal, and Cambridge Gambling Tasks, Marta Majewska primarily wrote the code for the Eriksen flanker task, and Jennifer McBride primarily wrote the code for the Balloon Analogue Risk Task. Code is available on GitHub: https://github.com/jspickering/Experiments. Jade Pickering primarily wrote the code for the analysis of the Go/No-Go, Stop Signal, and Cambridge Gambling tasks as well as the questionnaire data and demographic information. Marta Majewska primarily wrote the code for analyzing the Kirby Delay Discounting task and the Balloon Analogue Risk Task. Jade Pickering was responsible for data collection (assisted by Marta Majewska) and all clinical aspects associated with the Parkinson's participants. The chapter draft was written solely by Jade Pickering.

Chapter 4 - Cross-sectional study measuring impulsivity and inhibitory control in Parkinson's disease and impulse control disorders

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4.1. Abstract

Dopaminergic medications are used to alleviate the (primarily) motor symptoms of Parkinson's by restoring dopamine levels in the nigrostriatal pathway which projects from the main site of dopamine depletion in Parkinson's, the substantia nigra. However, according to the dopamine overdose hypothesis, this effectively overdoses the mesocorticolimbic pathways which project from the relatively unaffected ventral tegmental areas and can thus lead to the development of impulse control behaviours (ICBs) in Parkinson's. These behaviours can comprise gambling, hypersexuality, and binge eating, amongst others, but less is known about the specific aspects of impulsivity and inhibitory control that are affected when ICBs emerge.

A systematic review (Chapter 3) showed largely mixed and unclear findings for many domains of impulsivity and inhibitory control when making comparisons between people with Parkinson's (PwP) and HCs, and PwP without ICBs and PwP+ICBs. One aspect that makes it difficult to compare results across studies is the heterogeneity between samples of Parkinson's participants, and so the present study aimed to tackle this by using several tasks and measures highlighted by the systematic review in three groups of participants: PwP, PwP+ICBs, and HCs.

Overall, no significant group differences (between PwP and HCs, or between PwP+ICBs) were found on measures of response inhibition (Stop Signal task), response conflict (Stroop task), set switching (Trail Making Test), decision making under ambiguous or objective risk (Balloon Analogue Risk Task and Cambridge Gambling Task respectively), delay discounting (Kirby Monetary Choice Questionnaire), sensation seeking (UPPS-P questionnaire), or sensitivity to punishment and reward (Behavioural Inhibition Systems/Behavioural Approach Systems

questionnaire). However, PwP showed significantly less action restraint (Go/No-Go task) than both PwP+ICBs and HCs, and there was a main effect of group for trait impulsivity (Barratt Impulsiveness Scale) although no significant pairwise comparisons.

Although data collection was halted prematurely (and therefore a smaller sample size than that which was pre-registered is presented here), results reflect a trend towards null results when examining behavioural aspects of impulsivity and inhibitory control outside of the clinically significant behaviours themselves.

4.2. Introduction

Parkinson's is a neurodegenerative disorder primarily characterised by motor symptoms such as tremor, rigidity, postural instability, gait difficulties, speech difficulties, dysphagia, and bradykinesia, and is associated with the gradual loss of dopamine producing cells in the substantia nigra (Jankovic, 2008). Despite being largely recognisable for its motor symptoms, which can often be treated with levodopa or dopamine agonist medications, Parkinson's is also associated with many non-motor symptoms, and in the past decade there has been a particular increase in research interest into impulse control behaviours (ICBs) such as pathological gambling, hypersexuality, binge eating, compulsive shopping, punding, and hobbyism (Voon, 2015).

ICBS are primarily thought to occur due to dopamine agonist medication, which is administered to replace the loss of dopamine in the nigrostriatal pathway. Previous conservative estimates of the prevalence of ICBs in people with Parkinson's (PwP) stood at approximately 10-15% (Voon, 2015; Weintraub et al., 2010), but more recent evidence suggests that the cumulative incidence over a 5-year period in PwP taking dopamine agonists may be as high as 50% (Corvol et al., 2018). Research is rapidly updating our understanding of ICBs and, whilst this is very much still an ongoing avenue for investigation, they seem to be primarily caused by dopamine agonists although levodopa has also been shown to contribute to the development of these symptoms (Voon, Potenza, & Thomsen, 2007). Risk factors for medication-induced ICBs include being younger, unmarried, having a history of familial addiction problems, and possessing certain cognitive and personality traits such as high delay discounting (preferring smaller rewards sooner rather than larger rewards later) and novelty seeking (Voon, 2015; Weintraub et al., 2010).

The dopamine overdose hypothesis provides an account for the emergence of ICBs; it postulates that dopaminergic medication (particularly dopamine agonists) restore functionality along the nigrostriatal pathway from the substantia nigra, which results in an improvement for the symptoms of Parkinson's. In turn, this effectively overdoses the mesolimbic and mesocortical pathways that project from the (relatively) unaffected ventral tegmental area which then increases impulsive behaviour associated with this pathway (Cools et al., 2001;

Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013). Therefore, when a patient is OFF medication their performance on experimental tasks that rely on the nigrostriatal pathway may additionally be impaired, whilst their performance for tasks that rely on the mesolimbic and mesocortical pathways may be unimpaired. Conversely, the opposite effect may occur when ON medication; as dopaminergic medication increases performance along one pathway it may decrease performance in others (Cools et al., 2001; Vaillancourt et al., 2013). A summary of some of these differences, along with a summary of the results from the systematic review in Chapter 3, can be found in Table 16.

Table 16. Summary table of predictions that we might expect according to the dopamine overdose hypothesis as well as a summary of the results from the systematic review in Chapter 3

	PwP compared to HCs (dopamine overdose hypothesis)	**PwP compared to HCs (systematic review)**	**PwP+ICBs compared to PwP (dopamine overdose hypothesis)**	**PwP+ICBs compared to PwP (systematic review)**
Nigrostriatal pathway				
Set switching (Trail Making Test)	Reduced performance in PwP	Mixed results	Similar performance	Null results
Decision making under objective risk (Cambridge Gambling Task)		Mixed results		Not enough data
Sensitivity to punishment (Behavioural Inhibition Systems)		Null results		Not enough data
Mesocorticolimbic pathways				
Decision making under ambiguous risk (Balloon Analogue Risk Task)	Potentially reduced performance in PwP	Null results	Reduced performance in PwP+ICBs	Null results
Decision making under ambiguous risk (Iowa Gambling Task)		Impaired in PwP		Impaired in PwP+ICBs
Sensitivity to reward (Behavioural Approach Systems)		Null results		Not enough data
Delay discounting (Kirby Monetary Choice Questionnaire)		Null results		Impaired in PwP+ICBs
Fronto-basal-ganglia circuits				
Action restraint (Go/No-Go task)	Potentially reduced performance in PwP	Mixed results	Similar performance	Null results
Action cancellation (Stop Signal task)		Mixed results		Null results

The nigrostriatal pathway is associated with the processes required for set switching (also referred to as task switching) abilities, decision making under objective risk, and sensitivity to punishment. Set switching involves the ability to shift attention between two different tasks; for example the Trail Making Test requires the participant to draw a continuous line going from circles labelled 1-A-2-B and so on so that they are alternating between searching for letters and numbers by selectively inhibiting the irrelevant set (e.g. numbers) when switching to the

alternate set (letters) (Arbuthnott & Frank, 2000). In tasks of decision making under objective risk, the participant is given probabilistic information about potential wins and losses which helps to facilitate informed decision making e.g. the Cambridge Gambling task and Game of Dice task. Sensitivity to punishment can be measured in terms of traits e.g. the Behavioural Approach/Inhibition Systems questionnaire (which examines sensitivity to reward/punishment respectively; Carver & White, 1994), and refers specifically to the degree that inhibitory processes are applied in response to actual or potential negative outcomes.

According to the dopamine hypothesis, the nigrostriatal pathway would be depleted of dopamine when OFF medication, but improved when ON medication (Brand, Labudda, & Markowitsch, 2006; Cools, 2006; Delazer et al., 2009; Rossi et al., 2010; Vaillancourt et al., 2013). Therefore, we might expect reduced performance on tasks requiring this pathway in PwP (regardless of whether they have additional ICBs or not) compared to healthy control participants (HCs), unless patients are on optimal medication regimes that are able to more fully restore this pathway (for example, in the very early stages of Parkinson's).

As demonstrated by the systematic review in Chapter 3, the evidence suggests that PwP show increased impulsivity under objective risk on the Game of Dice and Cambridge Gambling tasks compared to HC participants (Bayard et al., 2016; Boller et al., 2014; Brandt et al., 2015; Cools et al., 2003; Torta et al., 2009) although this is not a unanimous result (Nombela et al., 2014) and indeed some other tasks of objective risk have found no significant group differences (Delazer et al., 2009; Djamshidian et al., 2010; Sharp et al., 2013). There is not yet much evidence on this type of decision making between PwP and PwP+ICBs. Results are less clear for set switching, although when global slowing is taken into account on the Trail Making Test there are largely no group differences found between PwP and HCs (Barbosa et al., 2017; Bouquet et al., 2003; Fales et al., 2006; Ranchet et al., 2013; Terenzi et al., 2018; Walton et al., 2015). Sensitivity to punishment has not yet been examined much in PwP although the studies that do have found no significant group differences between PwP and HCs (Aarts et al 2012; Cools et al 2006).

The mesocorticolimbic pathways, on the other hand, are associated with decision making under ambiguous risk, sensitivity to reward, and delay discounting. Decision making under ambiguous risk differs from decision making under objective risk in that the individual is not given concrete information regarding the probabilities of outcomes, and often this information needs to be learned through experience of the task. For example, in the Balloon Analogue Risk Task (Lejuez et al., 2002) participants must press a key to blow up a balloon on screen where each keypress gains more points but, crucially, the balloon may pop before participants bank their points; the goal is to maximise points gained by balancing number of keypresses with the unknown likelihood of the balloon exploding. In the Iowa Gambling Task (Bechara, Damasio, Damasio, & Anderson, 1994) participants must learn to pick cards from advantageous decks that yield more

gains than losses compared to the disadvantageous decks through a process of sampling and learning. This reinforcement learning also relies on sensitivity to punishment for optimum risk-averse behaviour (Kim, Yoon, Kim, & Hamann, 2015), which is a key aspect of succeeding in tasks of decision making under ambiguous risk. Conversely, being more sensitive to reward may lead to the opposite behaviour and result in more risky decision making. Sensitivity to reward can be measured with the Behavioural Approach/Inhibition Systems questionnaire and delay discounting, often measured using the Monetary Choice Questionnaire, refers to the rate at which a reward decreases in value as a function of time (Kirby, Petry, & Bickel, 1999).

The mesocorticolimbic pathway is likely to be relatively unaffected in PwP, but potentially overdosed when ON medication especially in PwP+ICBs (Brand et al., 2006; Rao et al., 2010; Rossi et al., 2010). Therefore, we would expect higher impulsivity on such tasks in PwP+ICBs compared to both PwP and HCs when ON medication, and potentially higher impulsivity in PwP compared to HCs. The systematic review in Chapter 3 suggests that PwP with gambling ICBs show higher impulsivity compared to PwP on the Iowa Gambling Task (Balconi, Angioletti, et al., 2018; Balconi, Siri, et al., 2018; Rossi et al., 2010) but this is unclear for general ICBs (Biars et al., 2019; Pineau et al., 2016). In general PwP seem to show higher impulsivity than HCs on the Iowa Gambling Task (Buelow et al., 2014; Delazer et al., 2009; Mapelli et al., 2014; Pagonabarraga et al., 2007), but there are no group differences on the Balloon Analogue Risk task for PwP, PwP+ICBs, or HCs (Buelow et al., 2014; Claassen et al., 2011; Martini et al., 2018; Rao et al., 2010; Ricciardi et al., 2017), which is reported to have high construct validity (Hunt et al., 2005; Lejuez et al., 2002). PwP don't appear to show greater sensitivity to reward (Cools et al., 2006; Nombela et al., 2014; Terenzi et al., 2018) nor greater delay discounting (Housden et al., 2010; Martini et al., 2018; Nombela et al., 2014; Simioni et al., 2012) compared to HCs, but PwP+ICBs show higher delay discounting compared to PwP without additional ICBs (Housden et al., 2010; Leroi et al., 2013; Voon et al., 2011).

Impulsive action is not as strongly related to these most affected pathways but is additionally of interest in Parkinson's due to the overlap between motor areas affected in Parkinson's and the mechanisms for response inhibition which prevent impulsive motor action. Effective response inhibition, or reduced impulsive action, is associated with activity in the inferior right frontal cortex and fronto-basal-ganglia circuits which act as a mechanism to "apply the brakes" to an ongoing action (Aron et al., 2014). These networks are affected in Parkinson's (Jahanshahi, Obeso, Rothwell, et al., 2015), but, again, previous research is unclear. Studies that have used the Go/No-Go task, a measure of action restraint, with PwP have shown mixed results as to whether they are impaired compared to HCs (e.g. Al-Khaled et al., 2015; Bokura et al., 2005; Crescentini et al., 2012; Geffe et al., 2016; Martini et al., 2018) and studies that have used the Stop Signal task, a measure of action cancellation or withholding, have shown similarly mixed results (e.g. Bissett et al., 2015; Gauggel et al., 2004; Nombela et al., 2014). However, for both

tasks, the presence of additional ICBs does not seem to affect response inhibition (e.g. Bentivoglio et al., 2013; Martini et al., 2018; Rossi et al., 2010).

Overall, despite theoretical evidence to suggest changes in impulsivity and response inhibition in PwP and ICBs, the experimental evidence has been mixed. Parkinson's is heterogenous and varies in presentation from patient to patient, and thus from participant group to participant group between each study. This makes it difficult to infer which tasks may be more relatively affected, and as a consequence of which factors of Parkinson's pathology or the effects of medication. As research into ICBs is still relatively new, many studies have not accounted for the presence of additional ICBs in their sample, making it even more difficult to disentangle the effects of Parkinson's from the effects of medication and, thus, presentation of ICBs. Due to these differences, it can be difficult to make conclusions about tasks and participant groups. One way of reducing the heterogeneity between studies is to use the same tasks in the same participants spanning all three groups of interest: PwP, PwP+ICBs, and HCs.

The present study comprised a variety of tasks and questionnaires of impulsivity, encapsulating impulsive action (restraint and cancellation), interference effects, task switching, decision making under ambiguous and objective risk, delay discounting, trait impulsivity, and sensitivity to reward and punishment. Tasks were primarily chosen that have previously been used with PwP, and for which there is an existing evidence base for the domains of impulsivity and inhibitory control that they purport to measure (see Table 16 and Table 18). For example, action restraint and cancellation were measured with the Go/No-Go and Stop Signal tasks respectively, response conflict was measured with the Stroop and Eriksen Flanker tasks, decision making under objective risk was measured with the Cambridge Gambling Task, decision making under ambiguous risk was measured with the Iowa Gambling Task and Balloon Analogue Risk Task, delay discounting was measured with the Kirby Monetary Choice questionnaire, sensitivity to punishment and reward were both measured with the Behavioural Inhibition Systems/Behavioural Approach Systems Questionnaire, set-switching was measured with the Trail Making Test, and both the UPPS-P and Barratt Impulsiveness Scale were used to measure trait impulsivity.

As an additional consideration to minimise any effects of fatigue or repeating similar movements for an extended period – which might be particularly important for PwP – task choice was also influenced by whether they could be completed through an interleaved mix of computer-based format and pencil-and-paper based format. We aimed to find out whether PwP with additional impulse control behaviours (PwP+ICBs) show higher levels of impulsivity and less inhibitory control than PwP without ICBs, and whether PwP without ICBs show higher levels of impulsivity than age-matched healthy control (HC) participants on the most meaningful dependent variables of interest in such tasks. The most meaningful dependent variables for each task/questionnaire were chosen to reflect the core aspect of impulsivity e.g. commission

errors on the Go/No-Go task are the most indicative of failed action restraint. No directional hypotheses are specified and thus all analyses are two-tailed due to the inconclusiveness of the literature thus far (see Table 16).

In PwP+ICBs, the dopamine overdose hypothesis would predict impairments in aspects of impulsivity associated with the mesocorticolimbic pathway (decision making under ambiguous risk, sensitivity to reward, and delay discounting) but not the nigrostriatal pathway (set switching, decision making under objective risk, and sensitivity to punishment) due to the respective overdosing and restoration of each pathway due to dopamine agonist medication, compared to HCs. PwP+ICBs may show impaired performance in tasks associated with the mesocorticolimbic pathways compared to PwP without ICBs. If the study yields these patterns of results, then we will have shown support for the dopamine overdose hypothesis. PwP without ICBs are likely to exhibit normal functioning in tasks associated with the mesocorticolimbic pathway compared to HCs but may experience normal or impaired in the nigrostriatal pathway and fronto-basal-ganglia circuits (action restraint and action cancellation) depending on the adequacy of their medication at controlling Parkinson's. Significant group differences here would demonstrate that Parkinson's itself impairs performance (and performance may well be correlated with the MDS-UPDRS scores). Mixed findings are more prevalent in the literature to date, but non-significant findings here may indicate that the two Parkinson's groups experience symptoms that are too mild to impact the experimental results or may indicate that Parkinson's and/or medication does not affect performance on these tasks to any significant level. Any clinically significant impairment in PwP+ICBs may be specific to those behaviours, potentially due to social and individual factors, but may not exhibit a capturable behavioural change on artificial experimental tasks in a lab setting.

This is the first time that such a comprehensive selection of tasks has been used with these three groups of participants; this may help to account for some of the discrepancies in the literature that may be due to variance in samples and participant characteristics, where it is unclear whether performance is intact or impaired.

4.3. Method

The pre-registered protocol including methods and analysis plans can be found on the Open Science framework (https://osf.io/frzpv/) and in Appendix C[13].

For each task, we identified the key dependent variable(s) on which to compare the three groups, with planned comparisons (two-tailed) between PwP and PwP+ICBs, as well as PwP

[13] The COVID-19 pandemic stopped data collection prematurely and which cannot be resumed until it is safe to do so. Therefore, the data presented here are with a reduced sample size compared to that which was pre-registered, however all analyses performed were done in accordance with the pre-registered plans. The Eriksen flanker task and Iowa Gambling Task were also included but data are not presented for the purposes of this thesis.

and HCs. This provides the basis for our confirmatory pre-registered analyses. We also pre-registered additional comparisons on a purely exploratory basis, which were clearly identified as such. Any results arising from these exploratory analyses must be replicated in an independent sample in future research.

4.3.1. Participants

Planned sample size (25 participants per group[14]) was limited by available resources including funding and available opportunities to recruit people with Parkinson's and ICBs in the local area. Participants must have been between the ages of 50-80 and free from any other neurological or mental health problems except depression and anxiety (as these commonly co-occur with Parkinson's). Participants must not have been undergoing deep brain stimulation treatment or participating in a treatment manipulation clinical trial. The study included 15 participants with idiopathic Parkinson's (PwP; 10 males, mean age 68.53 ± 5.77 years), 20 participants with idiopathic Parkinson's and an active ICB (PwP+ICB; 12 males, mean age 64.25 ± 5.58 years), and 24 healthy control (HC; 11 males, mean age 65.92 ± 6.41 years) participants (see Table 17 for detailed participant characteristics). We excluded 8 additional participants with Parkinson's (not described here) from further testing as they met the criteria for dementia according to the Montreal Cognitive Assessment (MoCA; a score of 25/30 or below) which has been validated for use in Parkinson's (Gill, Freshman, Blender, & Ravina, 2008; Nasreddine et al., 2005; Zadikoff et al., 2008).

Parkinson's participants were allocated to the ICB or non-ICB group based on whether they scored positively for any ICBs according to the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP), which screens for current experiences of ICBs (gambling, sex, eating, hobbyism, punding, walkabout, and medication abuse) lasting a period of 4 weeks or more (Weintraub et al., 2009). The QUIP Rating Scale (QUIP-RS) was used to report the severity of all potential ICBs (Weintraub et al., 2012).

All participants completed the Geriatric Depression Scale (30 item version; Yesavage et al., 1982) which has been validated for use in Parkinson's (Ertan, Ertan, Kızıltan, & Uygucgil, 2005). All Parkinson's participants completed the motor section of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS; Goetz et al., 2008) to assess their motor symptoms and identify the Hoehn & Yahr (1967) staging of disease severity. Additionally, three extra questions from section 2 (motor experiences of daily living) of the MDS-UPPDRS were used to classify patients as having tremor dominant or postural instability and gait dominant Parkinson's (Stebbins et al., 2013) as this may differentially affect impulsivity (Tolleson et al., 2017; Wylie et al., 2012). We also asked PwP whether they (subjectively) experience significant ON/OFF fluctuations with their medication.

[14] This was further constrained by the COVID-19 pandemic and the need to halt data collection prematurely.

Table 17. Participant characteristics including means ± SDs and ranges where appropriate. All ps > 0.05 where no significant group differences are reported.

	PwP+ICB (N = 20)	PwP (N = 15)	HC (N = 24)
Age (years)	64.25 ± 5.58 (51-72) (Compared to PwP; $p = 0.04$, $d = 0.75$)	68.53 ± 5.77 (60-80)	65.92 ± 6.41 (53-80)
Male:Female	12:8	10:5	11:13
MoCA	28.45 ± 1.36 (26-31)	28.40 ± 1.35 (26-30)	27.71 ± 1.57 (25-30)
GDS	9.96 ± 5.91 (1-24) (Compared to PwP; $p = 0.04$, $d = 0.71$) (Compared to HC; $p < 0.001$, $d = 1.27$)	6.36 ± 4.13 (1-14)	3.83 ± 3.41 (0-12)
MDS-UPDRS (Section III)	29.75 ± 13.25 (11-54)	23.27 ± 6.72 (12-36)	
H&Y Stage	2.10 ± 0.91 (1-3)	2 ± 0.76 (1-3)	
Parkinson's duration (years)	8.10 ± 5.46 (1.50-21)	7.78 ± 4.12 (1.92-14)	
TD:PIGD	2:17	5:10	
Dopamine agonist LEDD (mg/day)	133.60 ± 221.55 (0-650) (Compared to PwP; $p = 0.25$, $d = 0.24$, one-tailed)	85.71 ± 158.40 (0-480)	
Dopamine agonist + levodopa LEDD (mg/day)	577.35 ± 338.07 (0-1380) (Compared to PwP; $p = 0.17$, $d = 024$, one-tailed)	467.86 ± 286.84 (100-1120)	
Number of patients with each ICB type *(note that some patients experienced multiple ICBs)*	Hobbyism = 10; Hypersexuality = 6; Binge Eating = 6; Shopping = 5; Punding = 5; Gambling = 1; Dopamine dysregulation = 1; Walkabout = 0		
QUIP Rating Scale Combined score	17.30 ± 12.02 (3-36) (Compared to PwP; $p = 0.002$, $d = 1.12$) (Compared to HC; $p < 0.001$, $d = 1.38$)	6.33 ±6.95 (0-18)	4.63 ± 4.83 (0-17)

MoCA = Montreal Cognitive Assessment, GDS = Geriatric Depression Scale, MDS-UPDRS = Unified Parkinson's Disease Rating Scale, H&Y = Hoehn & Yahr, TD:PIGD = tremor dominant/postural instability and gait dominant, QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale.

There were significant differences between groups for age (where the PwP+ICB group were younger than the PwP group) but as ICBs are known to be more common amongst younger people with Parkinson's, the group difference is unsurprising (Weintraub et al., 2010). There were also significant group differences as expected for the QUIP rating scale scores, which was significantly higher for the PwP+ICB group compared to both the PwP and HCs but did not differ between PwP and HCs. There were also significant group differences on the Geriatric Depression Scale, which was higher for PwP+ICBs compared to HCs.

Participants were recruited from an existing database of participants within our lab and additional recruitment was supported by the National Institute for Health Research Clinical Research Network Portfolio, Salford Royal NHS Foundation Trust, Parkinson's UK, and local Parkinson's support groups. Participants were reimbursed for any relevant expenses incurred as a result of their participation at the University of Manchester.

4.3.2. Ethical considerations

Participants were given three different health-related screening tools: the QUIP for detecting the presence of ICBs, the Montreal Cognitive Assessment for detecting cognitive impairment, and the Geriatric Depression Scale. Participants were asked to disclose in advance if they considered themselves to have difficulties with impulse control, cognitive impairment, or depression. If they scored positively on any of these measures without self-disclosing to us, we contacted them after their participation and sent a letter to their GP.

Two researchers were present throughout sessions with Parkinson's participants, to protect against the event where an ICB may have posed a risk to a lone researcher. The study received ethical approval from the NHS Research Ethics Committee and Health Research Authority (Ref: 19/NW/0094; see Appendix D).

4.3.3. Tasks and procedure

Over a maximum of two sessions lasting no more than 3 hours each, and taking place no more than 2 weeks apart, participants completed a variety of tasks and assessments which measure different aspects of impulsivity. The order that tasks and assessments were administered were pseudo-counterbalanced across all participants (see pre-registration in Appendix C for details).

All computer tasks were run on either computer 1 with a refresh rate of 60Hz and a screen resolution of 1920x1080px or computer 2 with a refresh rate of 75Hz and a screen resolution of 1024x768px.

4.3.3.1. Go/No-Go task (action restraint)

The task was programmed with the PsychoPy coder (Peirce, 2007, 2009) and run on computer 1 with all stimulus timings locked to the refresh rate. On a plain grey background, a central white fixation cross (100px) was presented for a fixed duration of 500ms followed by a variable

blank delay of between 250-500ms drawn from a rectangular distribution. Go and No-Go stimuli were black uppercase letters (Go signals: A, E, I, O, or U; No-Go signal: K; all 250px) which were presented centrally for 150ms followed by a blank duration of 1500ms, during which the participant was expected to respond by pressing the spacebar on Go trials or to withhold their response on No-Go trials (Figure 7).

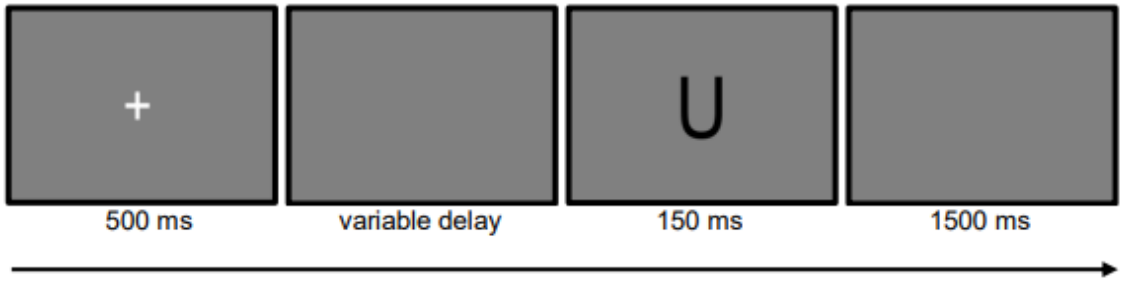

Figure 7. Go/No-Go task procedure. After a central fixation cross and a blank variable delay, the Go stimuli (A, E, I, O, or U) or No-Go stimulus (K) is presented for 150ms, followed by a blank delay of 1500ms in which the participant must either respond to the Go signal or withhold from responding to the No-Go signal.

It is recommended that the Go/No-Go task has a proportion of 20% No-Go trials or less, a variety of Go signals to maximise the number of false alarms, and a maximum of 1500ms in which the participant can respond in order to encourage fast responses (Elson, 2017; Wessel, 2018; Young, Sutherland, & McCoy, 2018). The current study had 17% No-Go trials and a maximum of 1650ms to respond to account for the possibility for people with Parkinson's to make slower motor responses generally, whilst still encouraging speeded responses. There were a total of 360 randomly ordered trials presented in blocks of 90 trials, with trials within each block randomly and independently shuffled for each participant. The total task lasted approximately 10-15 minutes, and the participant was encouraged to take a break at the end of each block. Participants completed 12 practice trials initially which included written feedback on each trial ("Correct", "Missed", "Incorrect") that was not present in the main task. They were able to repeat the practice block until they were comfortable with the task instructions.

4.3.3.2. Stop Signal task (response inhibition)

The task was programmed with the PsychoPy coder and was run on computer 1. All stimulus timings were locked to the refresh rate. A central light grey fixation cross (size: 175px) was presented on a black background for 500ms followed by a variable blank delay of between 250-500ms drawn from a rectangular distribution. The Go signal (a green left or right chevron arrow, size: 600px) was then displayed centrally for 70ms. On Stop trials, the Go signal was followed by a centrally displayed Stop signal (a hollow red square, size: 650px) for 70ms, following a variable stop signal delay (Figure 8). The stop signal delay started at 205ms (after the onset of the Go signal) on the first Stop trial and then subsequently increased or decreased by 50ms following a successful or unsuccessful stop trial respectively, in a one-up/one-down

fixed-step staircase procedure. The minimum stop signal delay was 5ms after Go signal onset and the maximum was 1505ms.

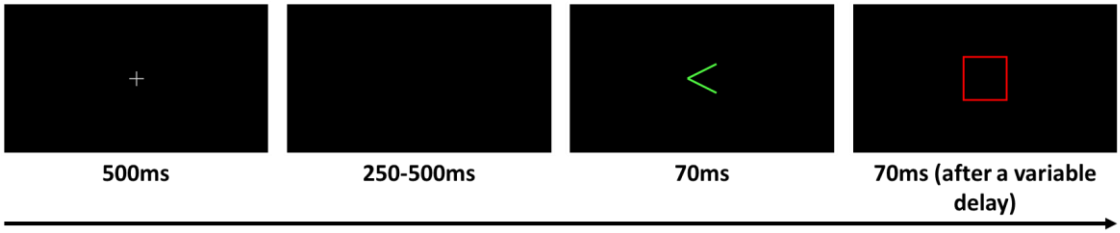

Figure 8. Stop Signal task procedure for Stop trials. After a central fixation cross, and a variable blank delay, the Go signal is presented for 70ms followed by a variable stop signal delay which changes trial by trial depending on task performance. On Go trials, the procedure is the same except that the Go signal is followed by a blank duration.

On all trials there was a maximum duration of 1500ms plus the current stop signal delay, during which the participant was expected to either respond or to withhold their response depending on the trial type. If a participant responded, the trial ended 500ms after the response time instead. In accordance with the consensus recommendations from Verbruggen et al. (2019), a Stop signal was present on 25% of trials. There were a total of 384 randomly ordered trials split into 4 blocks of 96 trials (the trials in each block were randomly and independently shuffled for each participant) and the participant was encouraged to take a break at the end of each block. At the end of each block the participant saw feedback based on their performance in the last block. Specifically, they saw their median response time for all trials on which they provided a response, and a feedback message based on their Stop accuracy. If their Stop accuracy in the last block was less than or equal to 40% they received the message "Try and stop yourself from pressing the button when you see the red square", for between 40% and 60% accuracy the message read "Remember to keep responding as QUICKLY yet as ACCURATELY as you can", and if accuracy was greater than or equal to 60% the message read "Try to respond to the arrows quickly without waiting to see if the red square appears". This helped participants to adhere to task instructions.

Verbruggen et al. (2019) have suggested a minimum of 50 Stop trials when participants are behaving optimally and others have suggested that 72 Stop trials is optimal (Campbell, Chambers, Allen, Hedge, & Sumner, 2017). We expected our sample to be more variable but, given the limitation of our sample size, using more than 96 Stop trials was unlikely to contribute to an increase in overall power (Baker et al., 2019). Participants completed 12 practice trials with written feedback ("Correct go", "Incorrect arrow", "Missed arrow", "Failed stop", or "Successful stop") that was not present in the main task. They were able to repeat the practice block until they were comfortable with the task instructions.

As recommended by Congdon et al. (2012) the initial criteria for detecting participants as outliers were: (1) less than 25% or greater than 75% Stop accuracy, (2) responding on less

than 60% of Go trials, (3) greater than 10% errors (responding to the wrong arrow) on Go trials, and (4) a stop signal reaction time estimate that is negative or less than 50ms as this indicates that the race model has been violated and a stop signal reaction time should not be estimated (Verbruggen et al., 2019). These criteria are designed to produce a balance between reliable stop signal reaction times whilst retaining a suitable number of participants and keeping within-subjects variance low (Congdon et al., 2012).

4.3.3.3. Stroop task (response conflict, set switching)

We used The Delis–Kaplan Executive Function System Color-Word Interference Test based on the original Stroop task (Delis, Kaplan, & Kramer, 2001; Stroop, 1935). We verbally checked whether participants experienced colour-blindness; 1 participant was exempt from completing the Stroop due to colour blindness. Each participant completed four conditions, each of which was presented upon an A4 card; two are without interference where Card A required colour naming (the participant must state the ink colour of square patches) and Card B required word naming (the participant must simply read the words which are all in black ink on white paper). Card C introduced inhibitory control as the participant must state the ink colour of colour-words and inhibit the automatic tendency to read the word itself, and Card D contained a mixture of inhibitory control and task switching as the participant was required to state the word if it was outlined by a black square but state the ink colour if the word was not outlined (Figure 9).

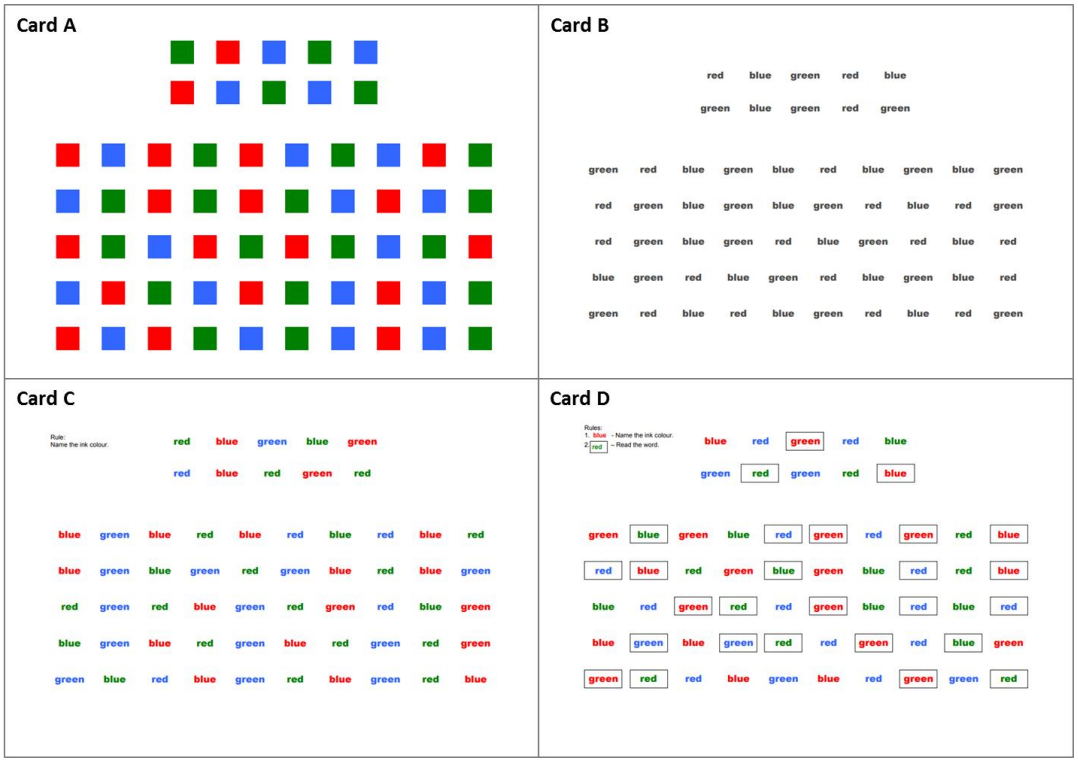

Figure 9. The Stroop task contains four conditions, and the participant is presented with each card in turn. Card A requires the participant to name the colour of the ink, Card B requires the participant to read the word, Card C requires the participant to name the colour of the ink (and ignore the word), and Card D requires the participant to switch between instructions and to name the colour of the ink unless it is inside a black square in which case they should read the word.

Each condition had 10 practice trials and 50 experimental trials, and the instructions were standardised and read aloud by the researcher before each condition. Participants repeated the practice once more if they got more than 50% uncorrected errors to make sure they understood task instructions. Participants were timed with a stopwatch for the experimental trials within each condition from the moment the researcher said the word "Go" until the time at which the participant said their answer for the final trial. Completion times, uncorrected errors, and self-corrected errors were recorded for each condition.

4.3.3.4. Trail Making Test (set switching)

Participants completed Trail A and Trail B. Trail A required the participant to draw a line chronologically between the numbers 1-25 without lifting their pencil from the paper. Trail B is similar except the participant must alternate between numbers and letters (1-A-2-B etc; Figure 10). For both trails, the researcher provided verbal standardised instructions and demonstrated the task on a sample sheet. The participant was timed with a stopwatch whilst they completed the trail. In the event of an error the researcher instructed the participant to return to the last correct circle and if the participant missed a circle, they were reminded to touch all circles. The clock was stopped when the end is reached.

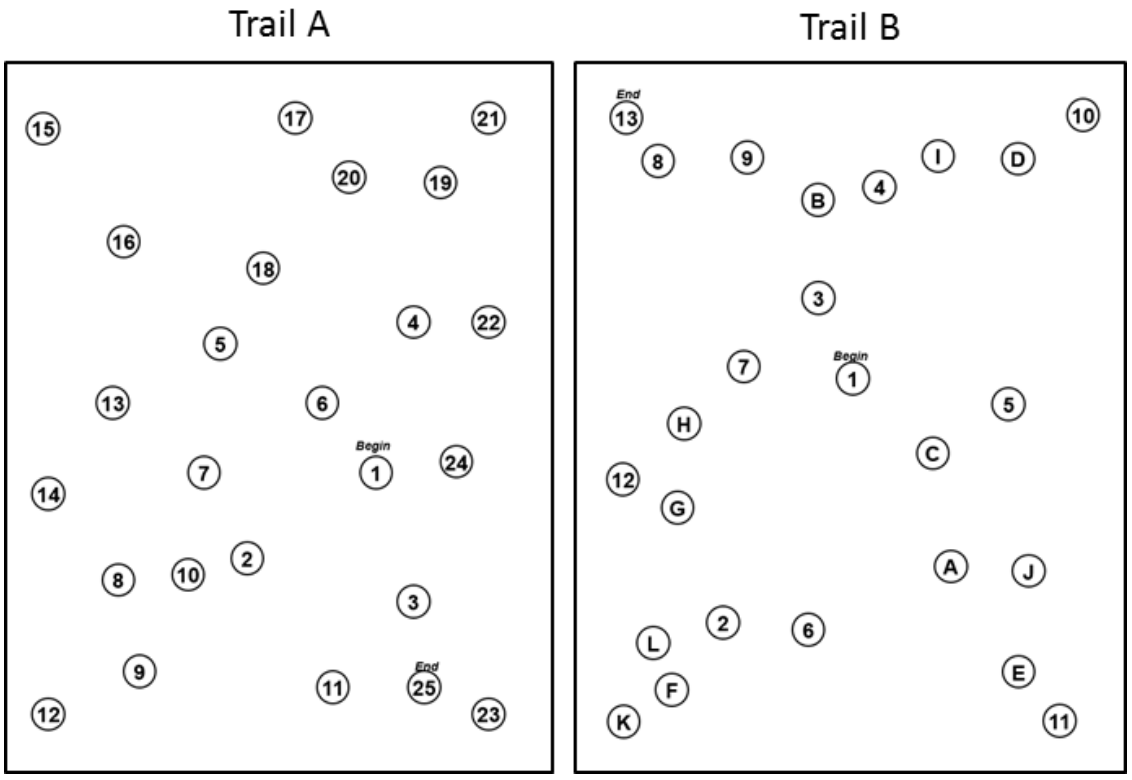

Figure 10. Trail Making Test. In Trail A the participant must draw a line incrementally through the numbers until they reach the end, and in Trail B they must switch between letters and numbers incrementally until they reach the end.

4.3.3.5. Balloon Analogue Risk Task (decision making under ambiguous risk)

The task was programmed with PsychoPy builder (Peirce et al., 2019) and run on computer 2. Participants were instructed to try to win as many points as possible by blowing up a computerised balloon (Lejuez, Aklin, Zvolensky, & Pedulla, 2003; Lejuez et al., 2002). The participant started with 0 points and earned 5 points with each pump of the balloon by pressing the spacebar, but each pump increased the chance of the balloon popping. The participant could choose to bank their points and move on to the next trial at any point, but if the balloon popped before they managed to do so they lost the accumulated points for that trial (Figure 11). There were 30 trials with a maximum number of pumps between 1 and 88 before the balloon popped, spaced at 3 pump intervals. Each participant received the same trials but in an order shuffled randomly and independently for each participant. Participants first completed two practice trials, where the maximum pump was set to 88 and 43 respectively, so that all participants started with a similar anchor.

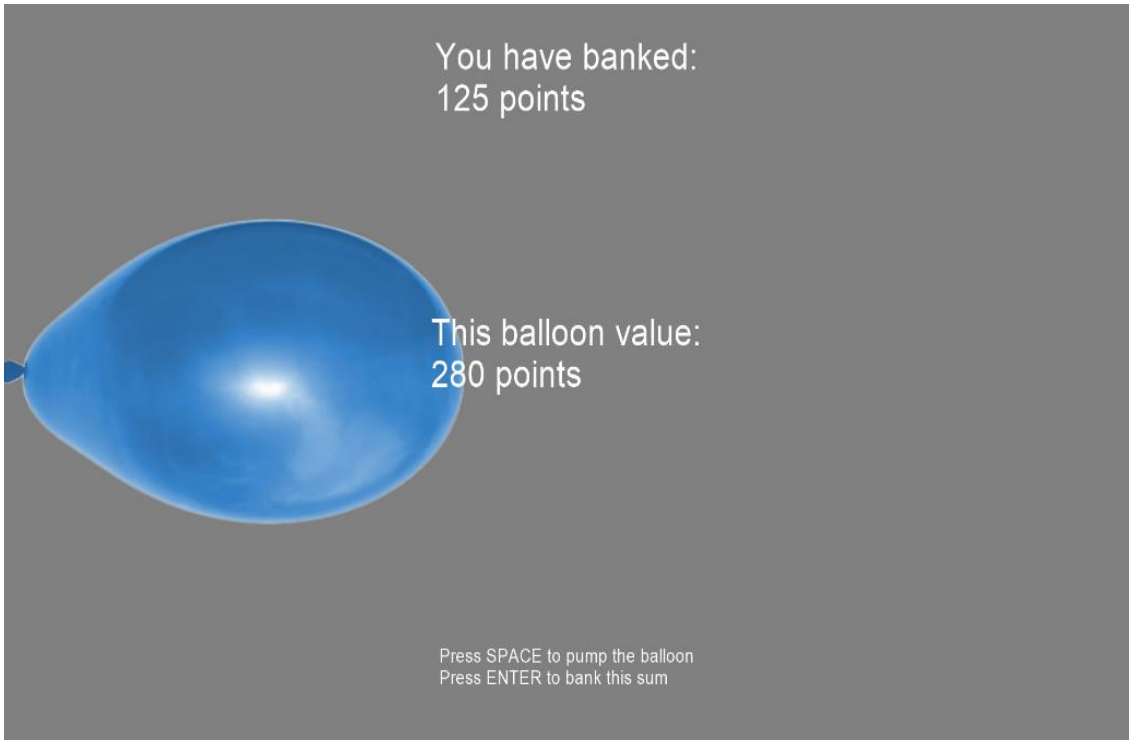

Figure 11. Balloon Analogue Risk Task. In this example trial, the participant has already banked a total of 125 points from previous balloons and has so far pumped the current balloon up to a value of 280 points. The participant can now choose to continue to pump the balloon which may increase the value of the balloon or cause the balloon to pop (and thus the participant would lose the accumulated 280 points), or they can choose to bank the 280 points that they have accumulated to give a total of 405 banked points and move onto a new balloon.

4.3.3.6. Cambridge Gambling Task (decision making under objective risk)

The task was programmed in PsychoPy coder and was based on the original task as described by Rogers et al. (1999). It was run on computer 2 and full experimental details are depicted in Figure 12. Participants had to choose whether a (randomly) hidden yellow token was under a red box or a blue box, depending on the ratio of 10 red and blue boxes displayed at the top of

the screen (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, or 9:1). After selecting their choice with the left (z) or right (m) keys, they then had to place a stake on their decision. The stake options were a percentage of the current points total (which started at 100 points on the first trial) which was displayed numerically to the participant but was equivalent to 5%, 25%, 50%, 75%, and 95% of the current points total. The possible bet choices either ascended or descended in order at intervals of 1500ms and the participant had to press the spacebar to stop the next option being displayed and to select the current option as their choice; if they did not respond, the final stake option that was presented was chosen automatically. On half of blocks the stake choices ascended and on the other half they descended; half of participants completed the ascending condition first and half completed the descending condition first in a counterbalanced design. At the end of the trial, the location of the token was revealed, and their stake added or subtracted from their points total depending on whether their decision was correct or incorrect respectively. If the participant's score reached 1 point or less the block ended, and the bank reset to 100 points for the next block. Each block contained 9 trials with each possible ratio of box colours (the trial order within each block is randomly and independently shuffled per participant), and there were 4 ascending blocks and 4 descending blocks. The task took approximately 20mins and participants were encouraged to take a break at the end of each block.

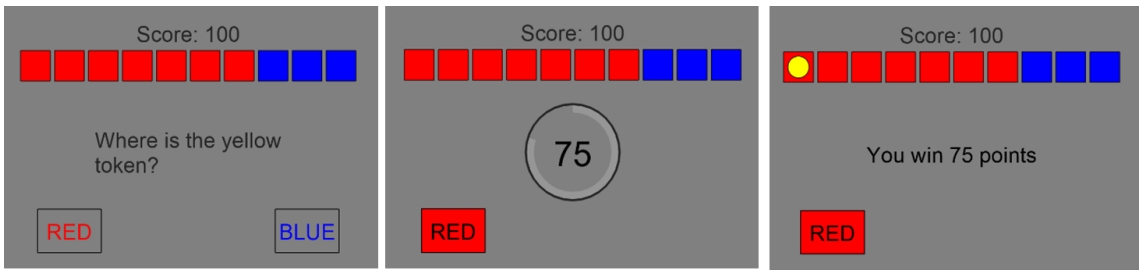

Figure 12. In the Cambridge Gambling Task the participant must select the box colour they believe contains the hidden yellow token (left panel) and then place a stake on their choice (middle panel) where the options are shown in increasing or decreasing order and are always equal to 5%, 25%, 50%, 75% and 95% of their current points total. The yellow token is revealed (right panel) and their total winnings for that trial displayed, which gets added to their points total on the next trial.

4.3.3.7. Kirby Monetary Choice Questionnaire (delay discounting)

The participant was presented with two hypothetical options per trial. Option A was a smaller reward that could be received now, and option B was a larger reward that could be received at a delay of *x* days; the options were taken directly from the 27 item Kirby delay discounting questionnaire (Kirby et al., 1999). The options were displayed using a PowerPoint presentation on computer 2 in a fixed order, and the researcher manually recorded the participant's verbal responses. The data was processed according to the method described in Kaplan et al. (2016).

4.3.3.8. Barratt Impulsiveness Scale (trait impulsivity)

The Barratt Impulsiveness Scale (Barratt, 1959; Patton, Stanford, & Barratt, 1995) comprises 30 questions assessing impulsivity, with the following factors: attention and cognitive instability (attentional impulsivity), motor and perseverance (motor impulsivity), and self-control and cognitive complexity (non-planning impulsivity). Missing values were replaced with the median value for that second order factor (attentional, motor, or non-planning impulsivity). Where there were more than 2 missing values on any 2nd order factor, we excluded that participant from analysis.

4.3.3.9. Behavioural Inhibition Systems/Behavioural Approach Systems (sensitivity to punishment/reward)

The Behavioural Inhibition System/Behavioural Approach System questionnaire (BIS/BAS; Carver & White, 1994) consists of 24 questions that probe BAS Drive, BAS Fun Seeking, BAS Reward Responsiveness, and BIS. The BAS measures relate to sensitivity to reward and the BIS measure to sensitivity to punishment. We replaced any missing values with the median value for that factor (BAS Drive, BAS Fun Seeking, BAS Reward Responsiveness, or BIS). Where there were more than 2 missing values on any factor, we excluded that participant from analysis.

4.3.3.10. UPPS-P (trait impulsivity)

The questionnaire comprises 59 questions that measure the following factors of impulsivity: negative urgency and positive urgency (emotion based rash action), lack of premeditation and lack of perseverance (deficits in conscientiousness), and sensation seeking (Lynam, Smith, Whiteside, & Cyders, 2006). Any missing values were replaced with the median value for that factor (negative urgency, positive urgency, lack of premeditation, lack of perseverance, or sensation seeking). Where there were more than 2 missing values on any factor, we excluded that participant from analysis.

4.3.4. Data processing

We used R (Version 3.5.2; R Core Team, 2019)[15] for all data processing and analyses.

4.3.4.1. At the individual participant level

For response time (RT) measures we trimmed RT data firstly by removing anticipatory RTs (< 150ms) as these are likely to have been initiated prior to stimulus/target onset. Remaining RT outliers were removed per participant, per condition using a non-recursive moving SD criterion

[15] We also used the R packages *bookdown* (version 0.17; Xie, 2016, 2020), *broom* (version 0.7.1; Robinson, Hayes, & Couch, 2020), *cowplot* (version 0.9.4; Wilke, 2019), *janitor* (version 2.0.1; Firke, 2020), *kableExtra* (version 1.3.1; Zhu, 2020), *knitr* (version 1.28; Xie, 2015, 2019), *papaja* (version 0.1.0.9842; Aust & Barth, 2018), *rstatix* (version 0.6.0; Kassambara, 2020), *tidyverse* (version 1.3.0; Wickham, et al., 2019), *trimr* (version 1.0.1; Grange, 2015), and *viridis* (version 0.5.1; Garnier, 2018) for all our analyses and to generate a draft of this chapter.

as detailed by Van Selst & Jolicoeur (1994), and as implemented by Grange (2015) in the *trimr* package for R.

4.3.4.2. At the group level

After calculating the mean RTs for remaining trials for each condition and for each participant, we removed outliers per condition that fell beyond the upper and lower boundaries using Tukey's (1977) boxplot method. These boundaries are calculated as 3 multiplied by the interquartile range, i.e. the difference between the 25th and 75th percentiles as per the following formulae: $Upper\ boundary = Q3 + (3 * (Q3 - Q1))$ $Lower\ boundary = Q1 - (3 * (Q3 - Q1))$. RT data was then checked to see whether it violated the assumptions of normality according to the Shapiro-Wilk test and, if necessary, that variable (and any other variables to be included within the same statistical test) were log10 transformed. For normally distributed data, we proceeded with parametric inferential statistical tests but if the data were not normally distributed after transformation we proceeded with the equivalent non-parametric test on the original, untransformed, data.

4.3.5. Statistical analyses

For almost all dependent variables (unless stated otherwise), data that were expected to be normally distributed (and either did not violate the assumptions of normality with the Shapiro-Wilk test or were successfully transformed) were analysed with a one-way between-subjects ANOVA with a factor of group (levels: PwP, PwP+ICBs, HCs) with planned independent t-tests for the following group pairs: PwP and PwP+ICBs, PwP and HCs (a = .025 to correct for multiple comparisons). If data were expected to be non-normal (and verified as such with the Shapiro-Wilk test) or remained non-normal after attempting transformation, they were analysed with a Kruskal-Wallis test with planned Mann-Whitney U group comparisons (PwP and PwP+ICBs, PwP and HCs; a = .025).

4.4. Results

As stated in the pre-registration, we defined a key dependent variable for each task or questionnaire which constitutes the main analyses; these are presented in Table 18.

Table 18. Summary results table for the key dependent variables of interest for each task

DOMAIN: Task (measure)	PwP	PwP+ICBs	HCs	Summary
ACTION RESTRAINT				
Go/No-Go task (commission errors)	21% ± 14%	9% ± 5%	9% ± 9%	**PwP showed significantly less action restraint than PwP+ICBs and HCs**
RESPONSE INHIBITION				
Stop Signal task (stop signal reaction time)	316ms ± 33ms	306ms ± 49ms	299ms ± 29ms	No significant group differences
RESPONSE CONFLICT				
Stroop task (interference effect)	28ms ± 11ms	24ms ± 8ms	25ms ± 10ms	No significant group differences
SET SWITCHING				
Trail Making test (switch cost)	29ms ± 30ms	43ms ± 27ms	31ms ± 18ms	No significant group differences
DECISION MAKING UNDER AMBIGIOUS RISK				
Balloon Analogue Risk task (adjusted pumps)	33.85 ± 11.26	36.65 ± 13.21	38.72 ± 10.68	No significant group differences
DECISION MAKING UNDER OBJECTIVE RISK				
Cambridge Gambling Task (risk adjustment index)	.32 ± .85	-.19 ± .47	-.06 ± .32	No significant group differences
DELAY DISCOUNTING				
Kirby Monetary Choice (overall *k*)	.02 ± .02	.02 ± .02	.02 ± .03	No significant group differences
TRAIT IMPULSIVITY				
Barratt Impulsiveness Scale (total score)	61.17 ± 10.59	59.80 ± 7.00	53.94 ± 9.05	**Main effect of group, but no significant pairwise comparisons**
TRAIT IMPULSIVITY				
UPPS-P (sensation seeking score)	27.27 ± 9.62	28.10 ± 8.83	25.71 ± 8.17	No significant group differences
SENSITIVITY TO REWARD				
Behavioural Approach Systems questionnaire (total score)	54.20 ± 5.66	56.48 ± 7.13	57.00 ± 8.31	No significant group differences
SENSITIVITY TO PUNISHMENT				
Behavioural Inhibition Systems questionnaire (total score)	20.60 ± 3.87	20.68 ± 4.17	21.87 ± 3.62	No significant group differences

4.4.1. Go/No-Go

A total of 12 PwP, 18 PwP+ICB, and 23 HC participants completed the Go/No-Go task.

4.4.1.1. Commission errors

Commission errors (Figure 13) were calculated as the percentage of erroneous responses recorded on No-Go trials. A Kruskal-Wallis test showed a significant main effect of group ($H(2) = 9.20$, $p = .01$) and planned Mann-Whitney U comparisons showed that PwP made significantly more commission errors (21% ± 14%) compared to both PwP+ICBs (9% ± 5%; $U(N_{PwP} = 12, N_{PwP+ICB} = 17) = 60$, $p = .006$) and HCs (9% ± 9%; $U(N_{PwP} = 12, N_{HCs} = 23) = 41.5$, $p = .008$).

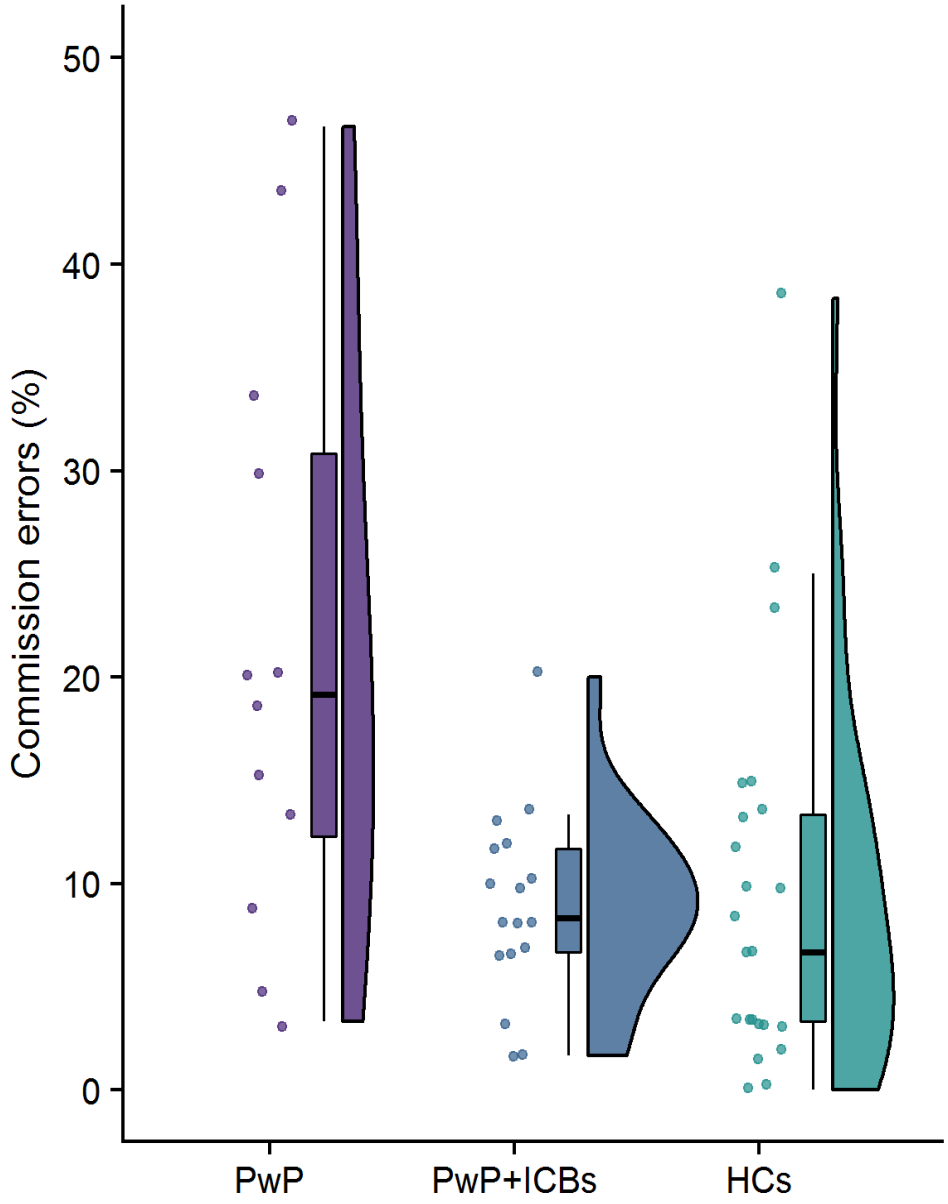

Figure 13. The percentage of No-Go trials on which the participant erroneously responded and produced a commission error, plotted for all three participant groups. The raincloud plots should be interpreted in the same way as described in Chapter 2.

4.4.1.2. Exploratory analysis: Go RT

For RTs on correct Go trials, a one-way ANOVA showed a significant main effect of group ($F(2,49) = 4.76$, $p = .01$) and planned t-tests showed that there were no significant differences in Go RTs between PwP (402.59 ± 48.22) and PwP+ICBs (423.50 ± 48.94; $t(27) = 1.14$, $p = .26$) but that PwP had significantly faster Go RTs compared to HCs (462.501 ± 68.10; $t(33) = 2.71$, $p = 0.01$).

4.4.1.3. Exploratory analysis: No-Go RT

For RTs on incorrect No-Go trials, a one-way ANOVA showed a significant main effect of group ($F(2,44) = 3.33$, $p = .04$) and planned t-tests showed that there were no significant differences in No-Go RTs between PwP (346.09 ± 34.73) and PwP+ICBs (369.80 ± 34.64; $t(26) = 1.80$, $p = .08$) but that PwP had significantly faster No-Go RTs compared to HCs (376.25 ± 28.65; $t(29) = 2.63$, $p = .01$).

4.4.1.4. Exploratory analysis: Omission errors

Omission errors comprised a very small number of trials overall and so no meaningful comparisons can be made; PwP made omission errors on only .41% (± .44%) of trials on average, PwP+ICBs on .19% (± .26%), and HCs on .14% (± .24%) of trials.

4.4.2. Stop Signal task

Of those that completed the Stop Signal task, 1 PwP was excluded from analysis for a low Stop Accuracy which prevents a reliable estimation of stop signal reaction time (SSRT) (Congdon et al., 2012; Verbruggen et al., 2019), and 3 PwP+ICBs were excluded for having a high proportion of Go trials where they responded with the incorrect button according to the direction of the arrow. A total of 14 PwP, 17 PwP+ICBs, and 23 HC participants remained for analysis.

4.4.2.1. Stop signal reaction time

The stop signal reaction time (SSRT; Figure 14) is an estimation of the time it takes for the Stop process to overtake the Go process, and was calculated according to the integration method (Verbruggen et al., 2019). All Go trials where used (including choice errors and anticipatory errors) and omission errors were assigned the maximum RT recorded for that participant. For each participant the mean SSD was subtracted from the *n*th percentile of the Go-RT distribution, where *n* is the percentage of failed stops, in order to estimate the SSRT (Verbruggen et al., 2019; Verbruggen & Logan, 2009). A slower SSRT is indicative of reduced inhibitory control. A one-way ANOVA showed a non-significant main effect of group ($F(2,51) = .90$, $p = .41$) and planned t-tests showed that there were no significant differences in SSRT between PwP (315.81 ± 32.84) and PwP+ICBs (305.71 ± 48.83; $t(29) = .81$, $p = .42$) nor compared to HCs (298.96 ± 28.89; $t(35) = 1.58$, $p = .12$).

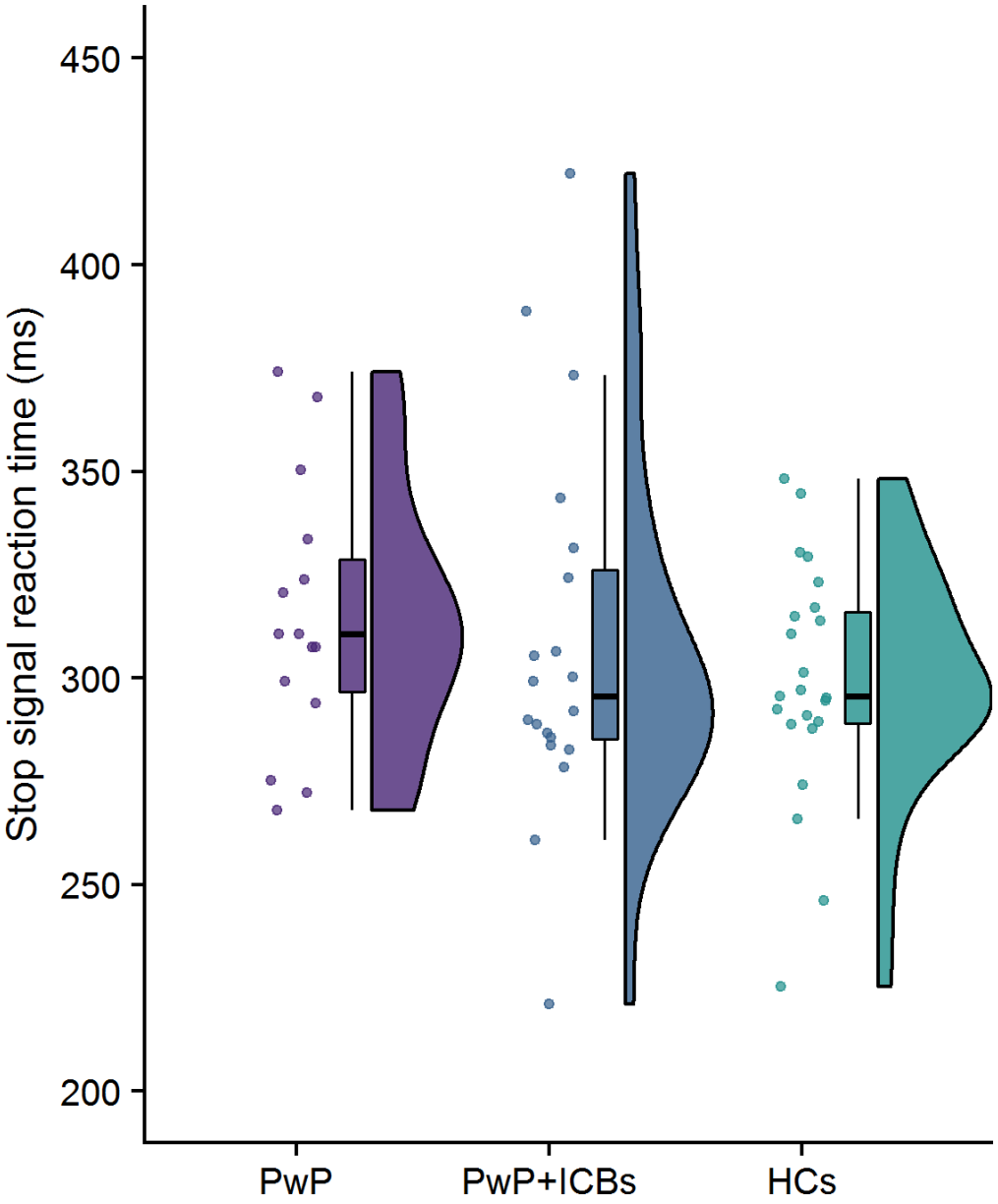

Figure 14. The stop signal reaction time, an estimation of the time it takes for the Stop process to overtake the Go process, for all three participant groups.

4.4.3. Stroop task

One participant did not complete the Stroop task due to self-declared colour-blindness. A total of 14 PwP, 18 PwP+ICB, and 24 HC participants remained for analysis. The interference effect was the key dependent variable of interest.

4.4.3.1. Interference effect

The interference effect was calculated by subtracting the time taken to complete Card A from the time taken to complete Card C (Jensen, 1965; MacLeod, 1991). A Kruskal-Wallis test showed no significant main effect of group ($H(2) = .33$, $p = .85$) and planned Mann-Whitney U comparisons showed that PwP did not have a significantly different interference score (28.07 ±

11.22) compared to PwP+ICBs (24.44 ± 7.88; $U(N_{PwP} = 14, N_{PwP+ICB} = 18) = 115$, $p = .69$) nor compared to HCs (25.19 ± 10.14; $U(N_{PwP} = 14, N_{HCs} = 24) = 187$, $p = .58$).

4.4.3.2. Exploratory analysis: Switch cost

Switch cost was calculated by subtracting the time taken to complete Card C from the time taken to complete Card D. A one-way ANOVA showed no significant main effect of group ($F(2,53) = .30$, $p = .74$) and planned t-tests showed that PwP did not have significantly different switch costs (4.76 ± 9.49) compared to PwP+ICBs (4.84 ± 9.22; $t(31) = .02$, $p = .98$) nor compared to HCs (7.03 ± 12.04; $t(35) = .60$, $p = .55$).

4.4.4. Trail Making Test

A total of 15 PwP, 20 PwP+ICB, and 24 HC participants completed the Trail Making Test.

4.4.4.1. Task switching

Switch costs was calculated as the time taken to complete Trail B minus the time taken to complete Trail A, which accounts for individual differences in motor slowing which was likely to disproportionately affect the Parkinson's participants. A Kruskal-Wallis test showed no significant main effect of group ($H(2) = 2.03$, $p = .36$) and planned Mann-Whitney U comparisons showed that PwP did not have significantly different switch costs (29.38 ± 29.69) compared to PwP+ICBs (43.01 ± 26.91; $U(N_{PwP} = 15, N_{PwP+ICB} = 20) = 175$, $p = .42$) nor compared to HCs (31.10 ± 17.90; $U(N_{PwP} = 15, N_{HCs} = 24) = 187$, $p = .85$).

4.4.4.2. Exploratory analysis: Trail B

For completeness, we also analysed the raw scores for part B. A one-way ANOVA showed no significant main effect of group ($F(2,56) = 1.37$, $p = .29$) and planned t-tests showed that PwP did not have significantly different completion times for Trail B (75.16 ± 22.31) compared to PwP+ICBs (80.78 ± 30.35; $t(33) = .60$, $p = .55$) nor compared to HCs (68.70 ± 21.58; $t(37) = .90$, $p = .37$).

4.4.5. Balloon Analogue Risk Task

A total of 15 PwP, 20 PwP+ICB, and 24 HC participants complete the Ballooon Analogue Risk Task. The adjusted average number of pumps on unexploded balloons (Figure 15) was calculated as the main variable of interest, as the number of pumps on exploded balloons is constrained by the task and not the participants' own risk-taking behaviour (Lejuez et al., 2002, 2003).

4.4.5.1. Adjusted number of pumps

A one-way ANOVA showed no significant main effect of group ($F(2,56) = .80$, $p = .46$) and planned t-tests showed that PwP did not have a significantly different average number of pumps on unexploded balloons (33.85 ± 11.26) compared to PwP+ICBs (36.65 ± 13.21; $t(33) = .66$, $p = .51$) nor compared to HCs (38.72 ± 10.68; $t(37) = 1.36$, $p = .18$).

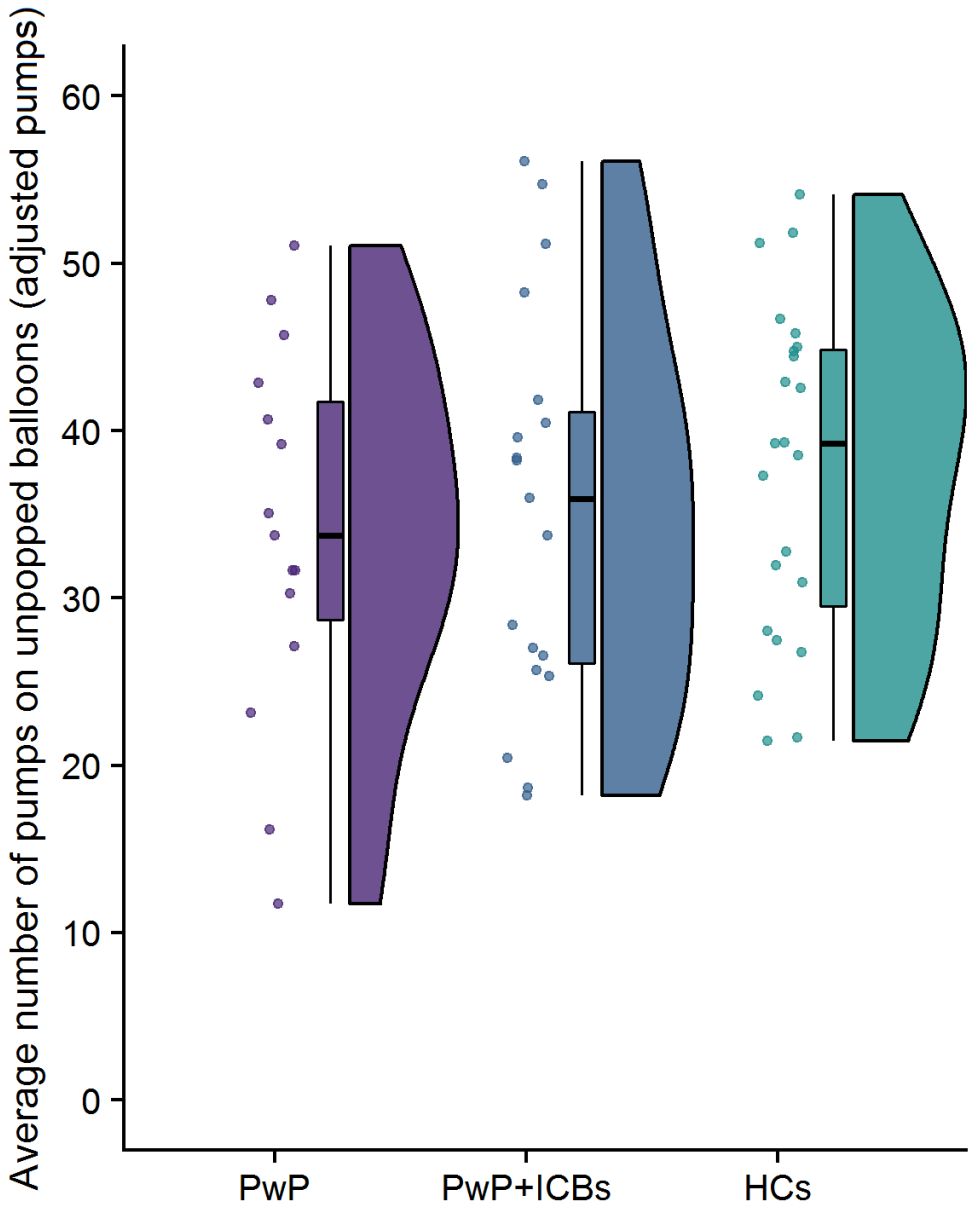

Figure 15. Adjusted number of pumps on unexploded balloons on the Balloon Analogue Risk Task

4.4.6. Cambridge Gambling Task

A total of 15 PwP, 21 PwP+ICB, and 24 HC participants completed the Cambridge Gambling Task. The risk adjustment index (Figure 16) was calculated as the % of the total points score participants were prepared to risk in order to earn more points as a function of the box ratio, according to the following formula: $\frac{(2\times(\%bet^{9:1}))+(\%bet^{8:2})-(\%bet^{7:3})-(2\times(\%bet^{6:4})}{\%bet^{overall}}$ where %bet refers to the average bet (out of the possible options of 5%, 25%, 50%, 75%, and 95%) chosen for that ratio (9:1, 8:2, 7:3, or 6:4). A lower risk adjustment index score is indicative of more risky decision making (DeVito et al., 2008). A Kruskal-Wallis test showed no significant main effect of group ($H(2) = 2.39$, $p = .30$) and planned Mann-Whitney U comparisons showed that PwP did

not have significantly different risk adjustment indexes (.32 ± .85) compared to PwP+ICBs (-.19 ± .47; $U(N_{PwP} = 15, N_{PwP+ICB} = 20) = 191$, $p = .18$) nor compared to HCs (-.06 ± .32; $U(N_{PwP} = 15, N_{HCs} = 22) = 138.5$, $p = .42$).

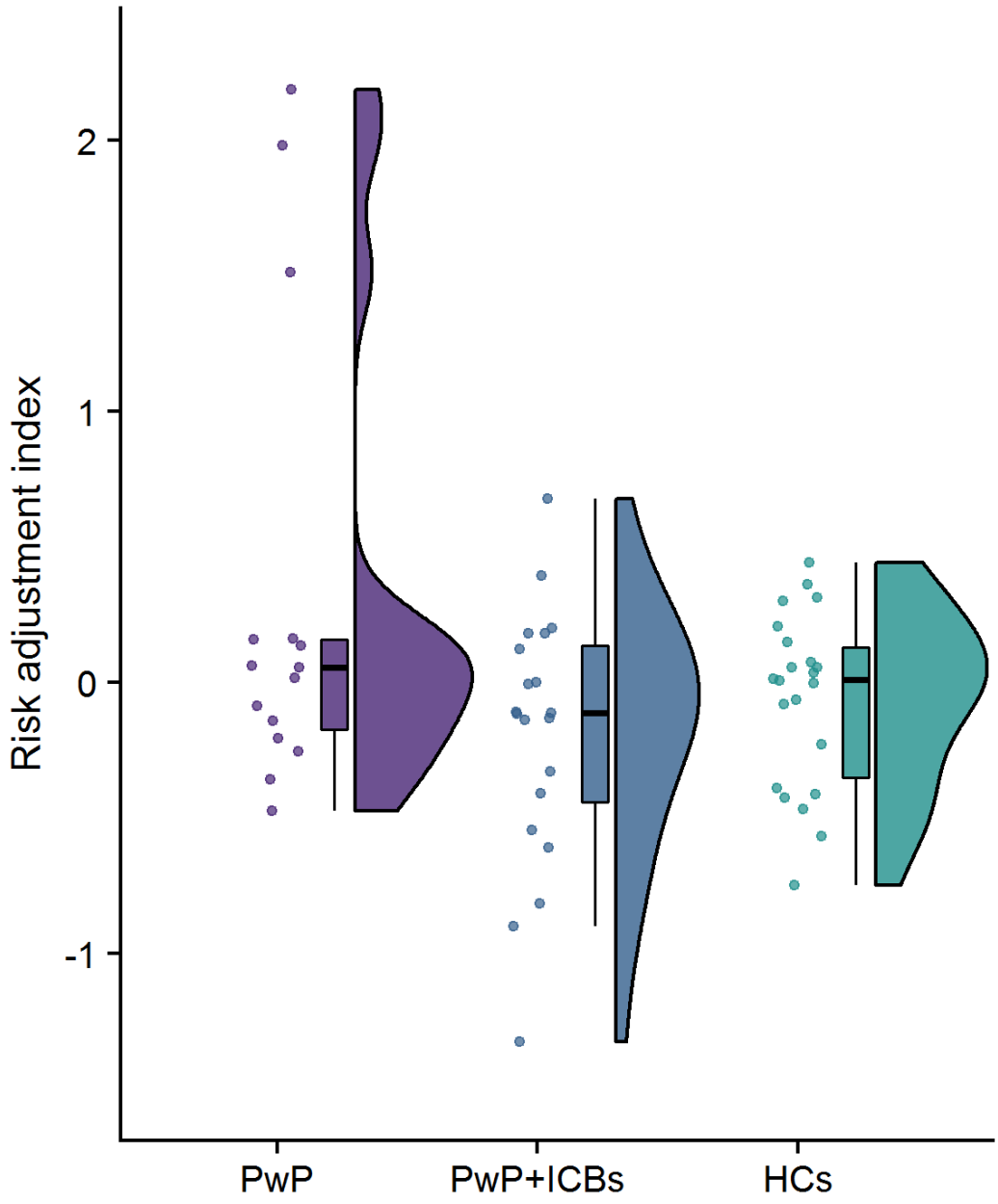

Figure 16. The risk adjustment index was calculated for all three participant groups. A more negative score is indicative of more risky decision making, whereas a more positive score is indicative of less risky decision making

4.4.7. Kirby Monetary Choice Questionnaire

A total of 15 PwP, 20 PwP+ICB, and 24 HC participants completed the Kirby Monetary Choice Questionnaire. The *k* value was calculated for each item using the formula $k = \frac{\frac{A}{V}-1}{D}$ where *V* is the smaller immediate reward, *A* is the larger delayed reward, and *D* is the delay in days. At the participant level, the *k* values were sorted from smallest to largest and consistency was

calculated for each item by summing how many times they selected the smaller delay for all items with a smaller *k* and how many times they selected the larger delay for all items with a larger *k*, and then dividing this total number by the total number of items (27). However, when calculating individual *k* values for each magnitude of large reward (small: £25, £30, £35; medium: £50, £55, £60; large: £75, £80, £85) the total number was instead divided by 9. The *k* with the highest consistency score was identified for that participant. Higher levels of *k* are indicative of higher levels of delay discounting.

4.4.7.1. Overall k values

The overall *k* values are shown in Table 18. A Kruskal-Wallis test showed no significant main effect of group ($H(2) = .44$, $p = .80$) and planned Mann-Whitney U comparisons showed that PwP dd not have significantly different *k* values (.02 ± .02) compared to PwP+ICBs (.02 ± .02; $U(N_{PwP} = 15, N_{PwP+ICB} = 20) = 163$, $p = .68$) nor compared to HCs (.02 ± .03; $U(N_{PwP} = 15, N_{HCs} = 24) = 156$, $p = .50$).

4.4.7.2. Exploratory analysis: k values for small, medium, and large rewards

Kruskal-Wallis tests showed no significant main effects of group for the *k* value for small, medium, or large rewards (Table 19), nor any significant group comparisons.

Table 19. Summary data for k values on the Kirby Monetary Choice Questionnaire for small, medium, and large rewards for each group

	PwP	PwP+ICB	HC	Statistical test
***k* (small rewards)**	.03 ± .04	.03 ± .04	.03 ± .04	$H(2) = .57$, $p = .75$
***k* (medium rewards)**	.03 ± .04	.02 ± .02	.02 ± .04	$H(2) = .55$, $p = .76$
***k* (large rewards)**	.02 ± .03	.02 ± .02	.02 ± .02	$H(2) = .13$, $p = .94$

4.4.8. Barratt Impulsiveness Scale

A total of 15 PwP, 19 PwP+ICB, and 24 HC participants completed the Barratt Impulsiveness Scale. The total score was the key dependent variable of interest. Previous research has suggested that the factors of the Barratt Impulsiveness Scale (attention, motor, and non-planning) are not valid in PwP as there is low internal consistency on the motor subscale, and that another factor structure may exist in this population (Ahearn, McDonald, Barraclough, & Leroi, 2012; Smulders, Esselink, Cools, & Bloem, 2014). Analysis on these second order factors are shown for completeness but should be interpreted with caution.

4.4.8.1. Total score

Total scores are shown in Table 18. A one-way ANOVA showed that there was a significant main effect of group on the total score ($F(2,55) = 3.83$, $p = .03$). Planned t-tests showed that PwP did not have significantly higher scores (61.17 ± 10.59) compared to PwP+ICBs (59.80 ± 7.00; $t(32) = .45$, $p = .65$) nor compared to HCs (53.94 ± 9.05; $t(37) = 2.27$, $p = .028$, where $a = .025$ for multiple comparisons).

4.4.8.2. Exploratory analysis: Attention, motor, and non-planning scores

One-way ANOVAs showed no significant main effects of group for attention, motor, or non-planning scores (Table 20), nor any significant group comparisons, where $a = .025$ for multiple comparisons.

Table 20. Summary data for the Barratt Impulsiveness Scale sub-scores for attention, motor, and non-planning impulsivity

	PwP	PwP+ICB	HC	Statistical test
Attention	15.78 ± 2.93	16.45 ± 3.01	13.71 ± 2.88	$F(2,55) = 5.11$, $p = .009$
Motor	22.01 ± 4.95	20.15 ± 3.68	20.45 ± 2.86	$F(2,55) = 1.16$, $p = .32$
Non-planning	23.39 ± 4.61	23.21 ± 3.23	19.78 ± 5.12	$F(2,55) = 4.37$, $p = .02$

4.4.9. Behavioural Approach/Inhibition Systems

A total of 15 PwP, 20 PwP+ICB, and 24 HC participants completed the Behavioural Approach/Inhibition Systems.

4.4.9.1. Total Behavioural Approach Systems score

A one-way ANOVA showed that there was no significant main effect of group on the total Behavioural Approach Systems score ($F(2,55) = .71$, $p = .50$). Planned t-tests showed that PwP did not have significantly higher scores (54.20 ± 5.66) compared to PwP+ICBs (56.48 ± 7.13; $t(33) = 1.02$, $p = .32$) nor compared to HCs (57.00 ± 8.31; $t(36) = 1.14$, $p = .26$).

4.4.9.2. Total Behavioural Inhibition Systems score

A one-way ANOVA showed that there was no significant main effect of group on the total Behavioural Inhibition Systems score ($F(2,55) = .69$, $p = .50$). Planned t-tests showed that PwP did not have significantly higher scores (20.60 ± 3.87) compared to PwP+ICBs (20.68 ± 4.17; $t(33) = .05$, $p = .96$) nor compared to HCs (21.87 ± 3.62; $t(36) = 1.03$, $p = .31$).

4.4.10. UPPS-P

A total of 15 PwP, 20 PwP+ICB, and 24 HC participants completed the UPPS-P. The sensation seeking sub-score was the main dependent variable of interest. A one-way ANOVA showed that there was no significant main effect of group on the total sensation seeking score ($F(2,56) = .42$, $p = .66$). Planned t-tests showed that PwP did not have significantly higher scores (27.27 ± 9.62) compared to PwP+ICBs (28.10 ± 8.83; $t(33) = .26$, $p = .79$) nor compared to HCs (25.71 ± 8.17; $t(37) = .54$, $p = .59$).

4.5. Discussion

This study aimed to investigate various dimensions of impulsivity comprising action restraint, response inhibition, response conflict, set switching, decision making under ambiguous and objective risk, delay discounting, trait impulsivity, and sensitivity to reward and punishment. By administering tasks and questionnaires across the same participants in three groups (PwP,

PwP+ICBs, and HCs) we aimed to minimise the effects of participant heterogeneity which may be one of the reasons that it is difficult to draw clear conclusions from the published literature so far. As completion of data collection was postponed due to the COVID-19 pandemic, the sample size presented here is smaller than planned, which does limit the conclusions that can be drawn from this study at present.

4.5.1. PwP with and without additional ICBs

Although the systematic review (Chapter 3) suggested that PwP+ICBs showed higher trait impulsivity on the Barratt Impulsiveness Scale, higher delay discounting rates on the Kirby Monetary Choice questionnaire, and high levels of impulsivity on tasks of decision making under ambiguous risk (for gambling ICBs) compared to PwP without ICBs, we did not find any significant group differences on most of these measures, and numerically (given the restrictions at drawing statistical inferences on an incomplete sample size) little-to-no differences. There was, however, a significant main effect of group for trait impulsivity on the Barratt Impulsiveness Scale, although with no significant differences on the pairwise comparisons (but PwP and PwP+ICBs both scored numerically higher than HCs). We additionally found no group differences for response inhibition on the Stop Signal task, response conflict on the Stroop task, set switching on the Trail Making Test, decision making under objective risk on the Cambridge Gambling Task, sensation seeking scores on the UPPS-P questionnaire, nor sensitivity to reward and punishment on the Behavioural Inhibition/Approach Systems questionnaire.

The results on the Balloon Analogue Risk Task (decision making under ambiguous risk), Monetary Choice Questionnaire (delay discounting), and Behavioural Approach Systems questionnaire (sensitivity to reward) are in contrast to those that might be expected as a result of the overdose hypothesis which would predict higher impulsivity in the PwP+ICB group (see Table 16). There may be more complicated relationships in the data that need to be explored with a higher sample size. For example, a higher severity score on the QUIP-RS may be associated with higher impulsivity on these measures, thus a more nuanced relationship between ICB status and impulsivity, or it may additionally depend on the type of ICB experienced. Much of the previous literature with ICBs has focused on the main four; gambling, hypersexuality, binge eating, and compulsive shopping, whereas fewer studies have specifically looked at participants with hobbyism, punding, walkabout, hoarding, and dopamine dysregulation. In this study, there was a greater variety of ICBs experienced by the PwP+ICB participants; half of participants experienced hobbyism, and fewer experienced the main four impulse control disorders that have been examined in the literature to date. As this sample only contained one participant with a gambling ICB, this may have been a qualitatively different sample to other studies, hence the lack of comparable results.

We did, however, find that PwP made significantly more commission errors on the Go/No-Go task than PwP+ICBs, which is indicative of reduced action restraint. The data for the

Parkinson's group in this shows a high level of variance with a relatively small sample size (Figure 13), and so it is unclear if this pattern of results will remain with the final sample size, although the PwP+ICB participants do show much more consistent behaviour within that participant group. According to the dopamine overdose hypothesis, PwP should experience reduced action restraint compared to HC, although this would not be expected to be greater than in PwP+ICBs. The non-significant differences between the PwP+ICB and HC groups may have been driven by outlying participants in the HC group which otherwise break the more consistent pattern of the remaining HC participants. The full sample size will be better able to establish the true patterns in the expected data.

Of interest to note, although not the primary focus of the study, is the high proportion of participants who reported experiencing ICBs. The study used an opportunistic sampling method and assigned participants to the PwP or PwP+ICB groups based on participants' responses on the QUIP-Current scale. The current sample contains 20 PwP+ICBs and 15 PwP, contrary to our expectations that the PwP+ICB sample would be the most difficult to recruit due to the previously reported rarity of such symptoms (Voon, 2015; Weintraub et al., 2010). ICBs have recently been discovered to be more prevalent than originally thought, with a 5-year cumulative incidence rate of up to 50% (Corvol et al., 2018). The QUIP and QUIP Rating Scale were published in 2012, and have only recently been recommended by the Movement Disorders Society's Rating Scale Reviews Committee (Evans et al., 2019), and so it seems likely that estimates will increase as more widespread usage of these clinical tools increases. Indeed, higher incidence rates would reflect the informal reports given to us by the participants and Patient and Public Involvement volunteers[16] that have formed part of the research throughout this thesis, who believe that ICBs are underreported, underdiagnosed, and consequently underestimated in the scientific literature.

The high rate of participants presenting with ICBs in this study does raise additional questions for the previous literature on impulsivity and inhibition in Parkinson's. In most cases, ICBs are not explicitly screened in patient samples or only certain types of ICB (e.g. gambling) are specifically screened for inclusion. It is therefore difficult to disentangle the effects of *Parkinson's* from the effects of *ICBs* on impulsivity and inhibition throughout the previous literature. In recent years, reporting of ICBs has increased as the screening instruments have become available. As the field moves forwards, a larger uptake in standardised screening methods and a focus on all ICBs will help to reduce or eliminate these issues.

4.5.2. PwP and HC participants

Again, a recent systematic review (Chapter 3) suggested that PwP show few reliably clear differences in performance compared to HCs on the domains of impulsivity examined here. In

[16] For more details about the contribution of Patient and Public Volunteers, see *Chapter 5*.

the present study, we found null results for all comparisons except for action restraint on the Go/No-Go task, where PwP made significantly more commission errors than HCs. Although PwP and PwP+ICBs showed no significant differences for RT on Go trials or on No-Go trials, PwP were significantly faster for both trial types compared to HCs. This suggests they may have failed to make an adequate trade-off between accuracy and RT, and favoured speed over providing accurate responses (Bokura et al., 2005).

Both the Go/No-Go and Stop Signal tasks are associated with the right inferior frontal gyrus (Aron et al., 2014; Simmonds, Pekar, & Mostofsky, 2008), which can be affected in Parkinson's due to knock on effects from the basal ganglia (Gauggel et al., 2004; Jahanshahi, Obeso, Baunez et al., 2015); if the significant group difference is due to neurological differences, it is surprising that there are no additional significant differences for stop signal reaction time. Performance on the Go/No-Go and Stop Signal Tasks correlate positively in the general population (Reynolds et al., 2006), however recent evidence suggests that the key neural processes involved in inhibition in the Go/No-Go task and Stop Signal task are more distinct than generally thought. The action restraint mechanism in the Go/No-Go task may relate to temporally earlier response selection mechanisms, whereas the action cancellation mechanism in the Stop Signal Task occurs later (Raud et al., 2020). The results here may then reflect changes in distinct neural areas between PwP and HCs but does not explain why action restraint does not differ between the PwP+ICB and HC groups.

The study used a sample of PwP with mild to moderate Parkinson's (Hoehn and Yahr stages 1-3) who showed no evidence of general slowing in any of the experimental tasks and, indeed, evidence of speeded responses in the Go/No-Go task. If there are disease-related impairments, they may be disguised behaviourally by the relatively milder symptom severities shown by participants in this sample. Again, a small sample size makes it difficult to draw stronger conclusions about the strength of the evidence of any null effects.

4.5.3. General implications

The only clear differences in impulsivity between groups emerged in the Go/No-Go task. PwP shows a significantly higher percentage of commission errors (erroneous responses to the No-Go signal) which indicates reduced action restraint compared to both PwP+ICBs and HCs. As seen in Figure 13, the PwP group had more variable rates of commission errors more generally, whereas there was much less variance in the PwP+ICB group. This variance may be accounted for more fully with the final sample size, and so any conclusions based on this significant result should be treated with caution. Although previous research has suggested that PwP with postural instability and gait dominant symptoms may struggle with motor impulsivity more than those with a tremor dominant subtype (Wylie et al., 2012), the sample of participants of each subtype in this study is too small to make any meaningful comparisons, but this could perhaps be explored further in future.

As many results may be predicted in context of the dopamine overdose hypothesis, exploratory analyses on the final data set could be performed to correlate key dependent variables from each task/questionnaire with the QUIP rating scale scores for PwP and PwP+ICBs. This may provide some additional insight where there are currently no clear group differences[17]. If there are no clear correlations between severity scores for impulsivity, as measured by the QUIP, and the various key variables from the tasks used in the current study, this may provide clearer evidence that the development of impulse control disorders may not contribute to a broad change in impulsivity outside of the clinically significant behaviour itself. If there are correlations for certain variables, ascertaining whether these map onto changes that might be predicted by the dopamine overdose hypothesis is a crucial next step. For example, the hypothesis would predict that PwP+ICB participants with higher QUIP rating scale scores would show more impulsive behaviour for decision making under ambiguous risk (i.e. a high number of pumps on unexploded balloons in the Balloon Analogue Risk Task), sensitivity to reward (i.e. higher scores on the Behavioural Approach Systems questionnaire), and delay discounting (i.e. higher *k* values on the Kirby Monetary Choice Questionnaire).

4.5.4. Strengths and limitations

The study was rigorously planned and pre-registered in an attempt to create the most robust and transparent study of impulsivity in Parkinson's to date with minimal researcher degrees of freedom. All tasks were designed to conform to the best practice recommendations; for example, the Stop Signal task is often used with a variety of parameters that make the results difficult to interpret. Ensuring an adequate ratio of stop trials to go trials, and carefully testing the assumptions of the race model, is crucial for ensuring high quality data (Congdon et al., 2012; Verbruggen et al., 2019). The present study did use the best practice recommendations, and so we can be confident that the data meets this high-quality standard. Code is available for all tasks created for this study using open-source software to allow other researchers to implement the same tasks in different populations to allow for a more comparable evaluation between studies.

For some tasks, completion time was measured with a stopwatch which may have reduced the precision of the data. In the Trail Making Test the non-significant group differences in switch cost were numerically small, at its largest the PwP+ICB group were 14ms slower than the PwP group, and in the Stroop task numerical differences in the interference effect were even smaller still; the largest group difference was 4ms between the PwP and PwP+ICB groups. Measurement error may have masked any group differences here, given that greater precision is likely needed. This could be resolved by videoing participants and having strict cut-off times for the beginning to the end of the trails in the Trail Making Task and the cards in the Stroop

[17] Due to the incomplete dataset, correlations at this stage would be uninformative and introduce more bias into the remainder of the data collection and so were not performed.

task. The Stroop task could also additionally be implemented using a computer-based experimental paradigm, however in this study we tried to strike a balance between computer-based and paper-based for the comfort of the participants and based on feedback from a Patient and Public Involvement volunteer who completed a test run-through of the initial study protocol before we started data collection.

The small sample size is a limitation, particularly for the PwP group who have a substantially lower sample size than the PwP+ICB and HC groups. We specifically recruited participants with mild to moderate symptoms of Parkinson's as the ability to complete the tasks may be reduced in participants with more severe symptoms. Additionally, participating in the study required both a time commitment (6 hours total for each participant, often spread over 2 days) and the need to travel to the laboratory to complete the research, which may have biased our sample further towards mild symptoms rather than moderate. Therefore, any results may not be generalisable from mild Parkinson's to more moderate symptoms and beyond.

One of the biggest strengths of the study is that we used a range of tasks and measures in the same participants. Therefore, the range of symptom severities, medications and dosages, types of ICBs, and all other complexities associated with Parkinson's and ICBs that contribute to its heterogenous nature are controlled for across measures. Any aspect of Parkinson's (e.g. disease severity or duration) or ICB status (type of ICB, severity, dopamine agonist LEDD) is *consistent* across all tasks in this cross-sectional design.

4.5.5. Conclusions

Overall, the study showed evidence for no significant group differences between PwP and HCs and PwP+ICBs for almost all measures, although this must be taken in context of the incomplete sample size. Interestingly, PwP show significantly reduced action restraint compared to both HCs and PwP+ICBs on the Go/No-Go task, although this may be due to higher variance and smaller sample size in that participant group.

The final sample size is necessary to make any reliable conclusions, but at present the data support the trend found in Chapter 2 and Chapter 3 that there are no consistent group differences on these behavioural and experimental measures of impulsivity and inhibitory control, and that many group differences that do exist in the literature seem to occur only in very specific circumstances and are therefore unlikely to be significantly meaningful.

4.6. References

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Preface to Chapter 5

This chapter discusses the development of a proof-of-concept intervention to reduce impulse control behaviours in Parkinson's and was conducted in parallel to the empirical work and systematic review described in the previous chapters. The intervention itself was due to be trialled in people with Parkinson's in early 2020 as part of the PhD project in collaboration with MRes student, Elizabeth Yule, in order to prepare for a future grant application for the development of a bigger pilot randomised controlled trial. However, due to the onset of the COVID-19 pandemic, this plan was revised for the purposes of the PhD project and has instead been postponed for the future. Therefore, this chapter now focuses on the development of the intervention and in future will form the foundations of a publishable paper which will include the completed proof-of-concept intervention pilot study once it is feasible to run the study.

Author Contributions: The initial study plan and methods were conceptualised by Ellen Poliakoff, Jennifer McBride, and Iracema Leroi. The Patient and Public Involvement volunteer sessions were organised by Jade Pickering and Parkinson's UK, and facilitated by Parkinson's UK. The Go/No-Go training task was programmed by Jade Pickering with input from Elizabeth Yule. The chapter draft was written by Jade Pickering.

Chapter 5 - Development of a proof-of-concept behavioural response inhibition training tool for impulse control behaviours in Parkinson's disease

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5.1. Abstract

Whilst Parkinson's is primarily a neurodegenerative disorder of movement, non-motor symptoms such as impulse control behaviours (ICBs) have a profound impact on everyday life. ICBs such as gambling, hypersexuality, binge eating, and compulsive shopping are associated with the use of dopamine agonist medications, and the current best course of treatment for ICBs is to withdraw from these dopaminergic medications even though this can have detrimental effects on the motor symptoms. Here, I develop a proof-of-concept pilot study for a prototype behavioural intervention designed to reduce the impact of ICBs and explore the possibility that this could allow patients to continue with otherwise problematic dopaminergic medication.

The behavioural intervention has been designed to be completed by patients independently, at home, on a personal electronic device, and was developed with substantial input from Patient and Public Involvement volunteers with personal experience of Parkinson's and ICBs. The pilot study will aim to examine the feasibility and acceptability of the intervention to assess whether further development is needed in order to pave the way for a larger randomised controlled trial. I discuss the development process, the protocol for the proposed pilot study, and the process for moving towards a randomised controlled trial in the future.

5.2. Background

Parkinson's is a neurodegenerative disorder associated with the loss of dopamine producing cells in the substantia nigra pars compacta and affects approximately 1 in 350 adults in the UK, with prevalence expected to increase approximately 18% by 2025 (Parkinson's UK, 2018). By the time the symptoms of Parkinson's become apparent, it is estimated that between 30 to 50% of substantia nigra neurons have already been lost (Cheng, Ulane, & Burke, 2010). This loss means that less dopamine is available to the basal ganglia which has a primary role in motor control and thus Parkinson's generally presents with motor symptoms such as rigidity,

bradykinesia (slowness of movement), tremor, freezing of gait, and problems with balance and walking (Jankovic, 2008).

People with Parkinson's (PwP) also experience many non-motor symptoms such as cognitive impairment, psychiatric problems (depression, anxiety, psychosis), sleep disturbance, pain, and problems with digestion, speech, swallowing, and writing. The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS; Goetz et al., 2008) aims to provide a comprehensive assessment of Parkinson's symptoms and includes both the motor and non-motor symptoms. However, the primary targets for Parkinson's medication are the motor symptoms.

Levodopa has been the main medicinal treatment option since 1967, but dopamine agonists have been used increasingly particularly since the late 1990s when pramipexole and ropinirole were approved in the EU and USA (European Medicines Agency, 2019; Tolosa, Martí, Valldeoriola, & Molinuevo, 1998; U.S. Food & Drug Administration, 2005, 2007). Dopamine agonists are effective at controlling the motor symptoms of Parkinson's, especially in the early stages, but there are increasing concerns about the effects they may have on impulsive behaviour (Antonini et al., 2010; Grall-Bronnec et al., 2018).

Some PwPs go on to develop problematic impulse control behaviours (ICBs) such as gambling, hypersexuality, compulsive shopping, overeating, hobbyism, punding, and medication abuse (Voon, 2015; Voon & Fox, 2007; Weintraub et al, 2010). This is thought to occur largely as a direct result of dopamine agonist medication interacting with other risk factors such as early onset Parkinson's, personality traits, or a history of substance abuse. Indeed, a recent study reported the cumulative incidence of ICBs (in PwP who were taking dopamine agonists) to be 51.5% over a 5-year period (Corvol et al, 2018). In patients who do not take dopamine agonists the recorded prevalence (12.4%) is still higher than in the general population (1.1-1.6%; Callesen et al, 2013; Corvol et al, 2018).

The dopamine overdose hypothesis has provided an explanation as to how dopaminergic medications cause ICBs (Cools et al., 2001; Cools, 2006; Vaillancourt et al, 2013). The dorsal striatum is strongly affected in Parkinson's compared to the ventral striatum, especially in the early course of the disease, and due to the inability of dopaminergic medication to specifically target the most affected areas, the ventral striatum, associated with reward-related behaviour and decision making, is effectively "overdosed" by the medication. Similarly, the ventral tegmental area remains relatively unaffected in Parkinson's and projects to the frontal cortex via the mesocortical pathway, and thus also experiences this overstimulation effect due to the non-specificity of the medication (Cools et al., 2001; Cools, 2006; Vaillancourt et al, 2013).

The most common method of treating ICBs is to simply withdraw the dopamine agonist medications which usually results in a partial, if not full, remission of the ICB (Macphee et al.,

2013) but this may have significant consequences for the motor symptoms of Parkinson's that were otherwise under control even when substituting dopamine agonists with levodopa (Lee et al., 2019; Mamikonyan et al., 2008). Other avenues for treatment include support groups and psychological therapies (Macphee et al., 2013), but access to such services can be difficult and costly depending on the local health services available.

Previous research has suggested that training on a task of inhibitory motor control, such as the Go/No-Go or Stop Signal task, generalises and reduces risky behaviour in non-Parkinson's populations (Lawrence, Van Beurden, Javaid, & Mostazir, 2019; Verbruggen, Adams, & Chambers, 2012). In the Go/No-Go task participants must respond quickly to a repeated Go signal but withhold their response when presented with a less frequent No-Go Signal. The Stop Signal task is similar but instead of a Go or No-Go signal, there is a Go signal on 100% of trials and on a small proportion of these trials it is quickly followed by a Stop signal where the participant must withhold their response. Both tasks require the inhibition of a motor action, but in the Stop Signal task this is a prepotent motor response i.e. it is already being cognitively prepared on presentation of the Stop signal.

Inhibitory control training has been shown to lead to a reduction in impulsive decision-making, albeit with some constraints. For example, engaging in a Stop Signal task can reduce gambling behaviours in a healthy population up to at least 2 hours later (Verbruggen et al., 2012), but the effect seems to disappear after 24 hours (Verbruggen et al., 2013). Whilst there appears to be some transfer of motor cautiousness to risky monetary decision-making, the exact mechanisms, long-term effects, and potential applications are less clear. There is some overlap between impulsive behaviours (such as restrained eating, emotional eating, obesity, and risky gambling) and inhibitory control performance on Go/No-Go and Stop Signal tasks; the two measures appear to be correlated (Jasinska et al, 2012; Nederkoorn et al., 2004, 2007, 2012; Verbruggen et al., 2013).

Short term effects of inhibitory control training have been found to additionally reduce other gambling behaviours, food consumption, and substance consumption behaviours (Bowley et al., 2013; Houben & Jansen, 2011; Jones, Christiansen, Nederkoorn, Houben, Field, 2013; Lawrence et al., 2015). Indeed, there is additional evidence to suggest that inhibitory control training is more beneficial in those who have poorer inhibitory control or increased impulsive behaviour to begin with (Houben & Jansen, 2011; Lawrence et al., 2015), particularly when a salient stimulus is incorporated into the training (Houben & Jansen, 2011; Jones & Field, 2013; Lawrence et al., 2015; Johannes, Buijzen, & Veling, 2020).

The long-term effects of inhibitory control training on eating behaviours have been successfully examined in a large trial using the FoodT mobile application (https://www.exeter.ac.uk/foodt/). The app utilises stimulus-relevant inhibitory control training to translate this generalised

mechanism into a home-based intervention, and has shown success at reducing problematic eating behaviours by training inhibitory control in response to negative (chocolate, takeaways, and other unhealthy foods) and positive (fruits, vegetables, and other healthy foods) food stimuli (Lawrence et al., 2019) in the form of a Go/No-Go task, which particularly helps those who experience problematic eating behaviours at baseline (Lawrence et al., 2019).

Although the exact mechanisms remain unclear, taken together the evidence suggests that an inhibitory control training tool may provide an effective and easy to deliver home-based intervention for ICBs experienced by people with Parkinson's. There is a clear need for a complementary, evidence-based avenue for self-help, and the use of technology and individually targeted behavioural tools is of rising importance to people with Parkinson's (Bek et al, 2016), and indeed one of the top ten priorities for research identified by Parkinson's UK (Deane et al, 2014). Thus, the present study was designed with input from people with Parkinson's and aimed to develop and pilot a prototype proof-of-concept behavioural training tool to reduce ICBs in PwP. Unfortunately, due to the COVID-19 pandemic, we had to suspend progress with launching our pilot[18] but here we present the results of the intervention development as well as the general methods.

5.3. Intervention Development

5.3.1. Patient and Public Involvement

The initial tool was conceptualised by the research team and the first study envisioned as a randomised controlled trial (RCT) with a waitlist control group. In July 2017, we hosted a Patient and Public Involvement (PPI) event about our plans for the research project at the University of Manchester which was supported by facilitators and a Research Involvement Award from Parkinson's UK. In attendance were three researchers (JP, JM, and EP), 10 PPI volunteers with Parkinson's/ICBs, 3 PPI volunteers who were family members of people with Parkinson's/ICBs, and 1 facilitator from Parkinson's UK. We followed this initial meeting up with teleconferences and email conversations with these and additional volunteers.

We presented our plans for the training tool and the RCT to the volunteers. We proposed a training tool to reduce the impact of an ICB as a potential alternative to withdrawing from the problematic medications in the first instance, as these might otherwise be helpful to treat the symptoms of Parkinson's itself. We envisioned this tool to be a "joint" Stop Signal task (see Schuch & Tipper, 2007), where patients would enrol onto the study with a partner (a spouse, family member, or friend for example) and they would both practice inhibitory control with this task together on the same screen, with the patient responding to either left or right stimuli and the partner responding to the opposite (Figure 17). The tool would be used in their own home

[18] The planned study will still go ahead at a future date, but not as part of this PhD project and thesis.

for a set amount of time each day, and the study would last approximately 10-12 weeks. We explained that previous research had shown that a) practising response inhibition had been shown to reduce monetary risk-taking and eating behaviours (Verbruggen, Adams, & Chambers, 2012) and b) watching another person successfully inhibit can help you to inhibit more successfully (Schuch & Tipper, 2007).

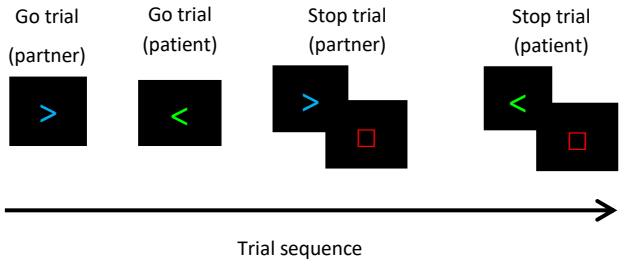

Figure 17. Trial types from the planned "joint" Stop Signal Task, where the partner (for example) responds to rightward arrows on Go trials and inhibits from responding to rightward arrows on Stop trials, where the patient completes the same task but with the leftward arrows. The trials are interleaved so that the patient and partner are completing the task together on the same device.

Next, we provided the attendees with more detailed information about the study design. We proposed a waiting-list control study where Group 1 and Group 2 would both provide baseline information at Week 0. Then, from Week 0 (T1) to Week 5/6 (T2) Group 1 would use the training tool and Group 2 would not. At Week 5/6 (T2) both groups would return to the lab for some assessments, and then continue practising until Week 10 or 12 where they would return for the final assessment.

Finally, we asked an open-ended question as to what, if any, baseline and outcome measures that they thought we should include in order to assess the impact that is most important to them. The PPI volunteers then gave us feedback on the overall concept of the study, the research design, the outcome measures, discussed potential barriers for people with Parkinson's, and provided their own ideas and input based on their lived experience.

The PPI volunteers were generally enthusiastic at the idea of a behavioural intervention to target ICBs, and thought that alternative strategies to manage ICBs were particularly important especially to those who rely on the problematic medication to treat the motor symptoms of Parkinson's. However, they had several concerns. They raised the issue that ICBs are complex, personal, and differ widely from patient to patient, and that a one-size-fits-all approach did not align with their lived experience. They suggested that some form of personalisation would make a significant improvement, both in terms of motivating engagement with the home training as well as overall impact on the outcomes of interest. They were also concerned about enrolling with a partner who would be required to practise with them; this was not always feasible depending on the support network they had available. They appreciated that accountability to another person may be useful for them, but perhaps not with such strong involvement, so we

removed the joint aspect of the task. They struggled with understanding the application of the Stop Signal Task to impulsivity in general due to the complex nature of the task, which also reflected our experiences running lab studies with this task, and so we reverted to a Go/No-Go task such as in the FoodT app. Finally, they were concerned about the length of time they would need to be enrolled in the study, and how much time per day they would be required to practise, although other recent investigations into home-based interventions suggest that 120 minutes per week is acceptable to PwP (Bek et al., 2021).

Following the input from the volunteers, we revised the study design to better balance the scientific rationale with the valuable information from the volunteers about their lived experiences and needs of the service users. Important outcome measures of note that were either suggested or emphasised by the PPI volunteers included the severity of the ICBs, overall quality of life, feelings of being in control, stress levels, anxiety, and self-reflection and awareness. Whilst there were concerns about enrolling onto the study with a partner to the degree that we had initially planned, the volunteers did feel that there was value in enrolling with an informant with a lesser degree of responsibility; they felt that a third-party (i.e. not the patient themselves and not the researcher) would have a degree of additional insight into ICB severity above and beyond that of the patient themselves, and so we included relevant measures for the partner too, such as carer burden and ways of coping.

We also revised our use of language based on their feedback; specifically, we originally defined our end-user as "a person with an impulse control disorder". The volunteers argued that defining a person has having an impulse control *disorder* ignores the experiences of those who have difficulties with *behaviours* but who do not meet criteria for diagnosis and who the intervention may even be most beneficial for. Therefore, we refer exclusively to ICBs which includes those with a diagnosis of an impulse control disorder, and those that may fall below that cut-off.

Based on the feedback from our PPI volunteers, the text which follows is the revised methodology for a proof-of-concept behavioural intervention.

5.3.2. The training tool

Our prototype tool consists of a game-like task modelled closely on the original FoodT app's implementation of a Go/No-Go task, but instead of food pictures participants will see a selection of pictures related to their ICB which will be chosen by the participant themselves. The pictures are shown onscreen one at a time and each is either outlined in green or red; if it is green participants have to press the designated key (e.g. spacebar) as quickly as they can, and if it is red they are asked not to press anything. Each picture will be shown relatively quickly (500-1000ms after another) which encourages the participant to respond quickly and therefore makes it more difficult to refrain from pressing the spacebar when the picture is outlined in red.

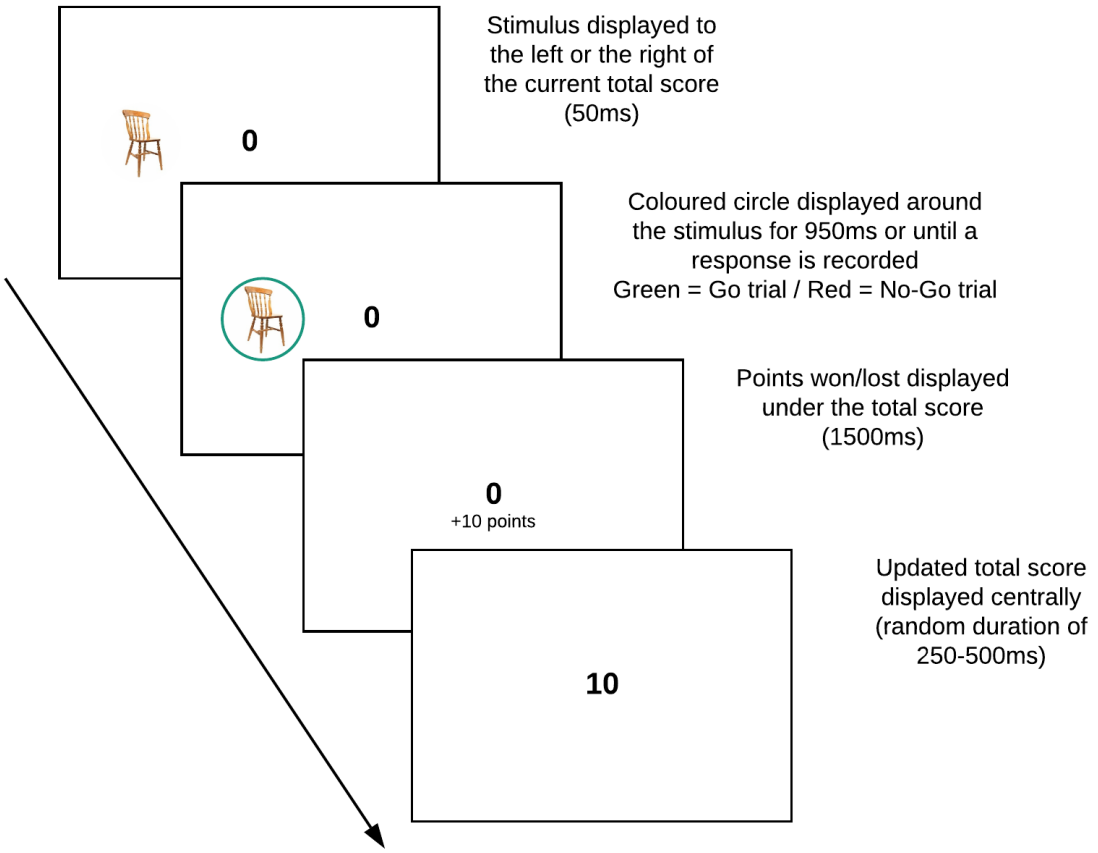

Figure 18. Example Go trial with a neutral stimulus

Crucially, the pictures associated with the negative ICB behaviour always appear with a red outline, positive pictures (e.g. people smiling, natural landscapes etc) always appear with a green outline, and neutral pictures (e.g. an item of clothing, or a piece of furniture) appear with either a green or red outline. This repeated practice builds up an association between stopping/inhibiting the action (e.g. refraining from pressing the spacebar) with stopping the problematic ICB behaviour. This has been shown to be an effective way to reduce impulsive behaviours both with the FoodT training app and with gambling behaviours in an experimental setting (Lawrence et al., 2019; Verbruggen et al., 2012).

The tool was programmed in PsychoPy v1.85.6 (Peirce, 2007, 2009) to be run on a laptop in the participants' own homes. There are a maximum of 6 blocks containing 40 trials each. 3 blocks last approximately 5 minutes and 6 blocks last approximately 10 minutes and participants will be encouraged to use the tool for at least 5 minutes every day; therefore, they can stop at block 3. At the end of block 1 and 2 participants will be shown their total score with a message encouraging them to take a break before continuing. After participants have completed block 3, they will be shown their total score and a message informing them that they have completed enough of the task for the day, with the option to continue on to the next block or to quit and view their final results. If a participant reaches the end of block 6 (i.e. after 240 trials have been completed and approximately 10 minutes have passed) they will be

automatically shown their final results and the task will end. This process will allow us to obtain a clearer idea of engagement with the training based on how often participants choose to go beyond block 3. The 40 trials within each block consist of 40% Go trials with positive pictures (16 trials), 10% Go trials with neutral pictures (4 trials), 10% No-Go trials with neutral pictures (4 trials), and 40% No-Go trials with negative pictures (16 trials). Trial order will be randomly shuffled at the beginning of each block.

For a visual illustration of a single trial see Figure 18. The block begins with a countdown of "3", "2", "1", "Go!" with each number/word displayed for 600ms (total 2400ms). The total score (starting at 0 points) is permanently displayed in the centre of the screen during each block. After an inter-trial interval of a random duration between 250-500ms, the stimulus appears on the screen for a maximum duration of 1000ms at one of two possible locations: vertically centred on the left of the horizontal axis or vertically centred to right of the horizontal axis. After the picture stimulus has been displayed for an initial 50ms, a green or red hollow circle appears around the picture for the remaining 950ms of the stimulus duration. The colour of the circle indicates whether the participant should press the spacebar or withhold from pressing it. If a response is recorded the stimulus disappears from the screen for a 1500ms inter-trial interval before the next trial begins, but if a response is not recorded the stimulus stays on-screen for the full 1000ms before the 1500ms inter-trial interval. The points won or lost for that trial (e.g. "+20" or "-10") will be displayed below the total score as soon as a response is recorded or the stimulus disappears (whichever comes first) and remain on screen until the next trial starts. At the beginning of the next trial the points won/lost will disappear and the total score will update.

Participants win or lose points during the task depending on their performance. The points system was designed to encourage fast yet accurate responses, and with more weight placed on No-Go trials (see Figure 19). Participants can score the most points per trial for responding correctly; this will give them 20 points for No-Go trials and if the RT is fast enough (< 750ms) they will receive 20 points on Go trials or 10 points if the RT was slower (>= 750ms). Incorrect responses on Go trials will result in a loss of 10 points, and incorrect responses on No-Go trials will result in a loss of 20 points. The points system was designed to promote effective inhibitory control, but the system may be adjusted during or after piloting based on participant feedback.

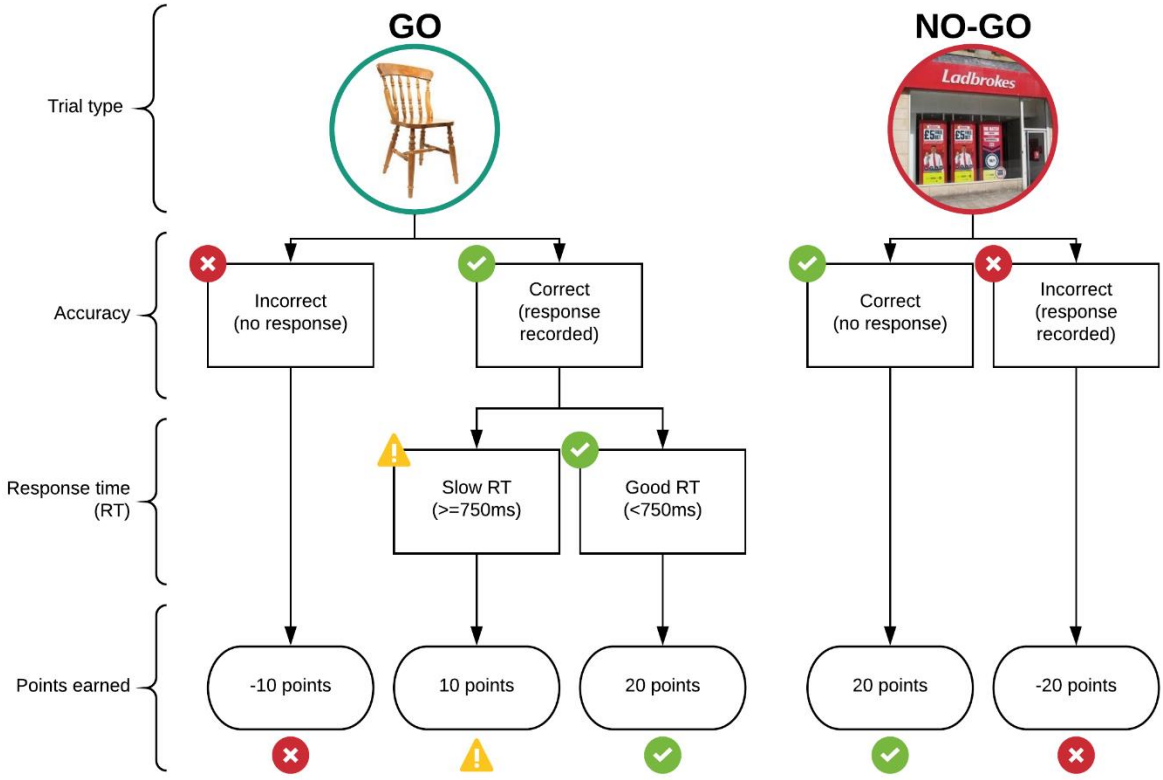

Figure 19. Points earned on Go trials and No-Go trials, which is dependent on the accuracy of the response and (for Go trials) the response time.

5.3.3. Study design

5.3.3.1. Research questions

We aim to test the feasibility and acceptability of the training in a small number of participants to demonstrate proof of concept before planning and designing an RCT. Our findings may indicate that further refinement and development is needed.

Important questions include the acceptability of (i) the instructions and explanations of concepts behind the training; (ii) the tasks themselves; (iii) the frequency and duration of the training. We also need to test out possible outcome measures, including reported ICBs (self and other), anxiety, coping, and care-giver burden.

5.3.3.2. Participants

In this case series design we will recruit and monitor 2-5 people with Parkinson's and ICBs over several weeks whilst they use the training tool in their own homes.

Table 21. Demographic details and baseline and outcomes measures including whether the patient, partner, or both provide the data for each measure

Demographic details	
Age	
Gender	
Relationship of partner	
Disease duration	
MoCA	
Baseline and outcome measures	**Measure completed by…**
Unified Parkinson's Disease Rating Scale Sections III-IV	Patient (although some questions can be answered more fully with the partner's input)
Hoehn and Yahr staging of Parkinson's symptoms	Patient
QUIP-Current	Patient and partner, independently
QUIP-RS	Patient and partner, independently
Geriatric Depression Scale	Patient
Parkinson Anxiety Scale[a]	Patient
Parkinson's Disease Questionnaire[b,c]	Patient
Beck Cognitive Insight Scale[d]	Patient
Brief Illness Perception Questionnaire[e]	Patient
General Self Efficacy Scale[f]	Patient
Multidimensional Health Locus of Control Scale[g]	Patient
Ways Of Coping Questionnaire[h,i]	Partner only
Caregiver Burden Scale[j]	Partner only

[a] Leentjens, Dujardin, Pontone, Starkstein, Weintraub, & Martinez-Martin (2014), [b] Jenkinson, Fitzpatrick, Peto, & Greenhall (1997), [c] Martinez-Martin et al. (2011), [d] Beck, Baruch, Balter, Steer, & Warman (2004), [e] Broadbent, Petri, Main, & Weinman (2006), [f] Schwarzer & Jerusalem (1995), [g] Wallston, Wallston, & Devellis (1978), [h] Lundqvist & Ahlström (2006), [i] Folkman, Lazarus, Dunkel-Schetter, DeLongis, & Gruen (1986), [j] Zarit, Reever, & Bach-Peterson (1980).

Participants will be recruited through local networks such as the Salford Royal NHS Foundation Trust, our lab's existing database of people with Parkinson's who have participated in research with us before, and the Parkinson's UK website. Participants will be within comfortable travelling distance of the University of Manchester[19] and will enrol with a partner who is in close contact with them (such as a spouse, family member, or carer). We will exclude participants that score below the standard cut-off on the Montreal Cognitive Assessment (26/30), which has been validated for use in Parkinson's (Gill, Freshman, Blender, & Ravina, 2008; Nasreddine et al., 2005; Zadikoff et al., 2008), if they have a history of neurological (except Parkinson's) or psychiatric problems (except ICBs, anxiety, and depression), if they have had deep brain stimulation surgery, or if they are actively participating in a treatment manipulation clinical trial. The study has received full ethical approval by an NHS Research Ethics Committee (NRES Committee North West – Liverpool Central).

[19] If the COVID-19 pandemic and consequent social distancing measures remain in place, we plan to redesign the study to be run online or to provide laptops to participants.

5.3.3.3. T1 (baseline)

Participants and their partners will be given the option of visiting the University of Manchester or receiving a home visit. Informed consent will be taken from both the participant and their partner as well as basic demographic details and baseline measurements (as seen in Table 21). Participants will choose the pictures they most associate with their ICB (as an example perhaps a lottery ticket, scratch card, betting shop, or casino for those with gambling ICBs) at their first initial study visit (and asked to think about this and prepare some ideas in advance of the session), which will then be incorporated into the training tool by the researcher on that same day.

We will conduct a short, 15 minute, semi-structured interview with the participant (and partner, if the participant wishes) to explore any aspects of their ICB which we were unable to capture in the questionnaires and to discuss any methods that they have already tried in order to manage their ICB (see Figure 20 for the interview schedules).

Participants and their study partners will then be shown the training tool, provided with instructions, and given the opportunity to ask questions. They will be provided with an email address and phone contact for the researcher and told they will be given weekly phone calls from the researcher to check on their progress and address any unexpected problems. These phone calls will also be used to check that the tool is not having any unexpected negative effects such as increasing ICB severity, as one PPI volunteer raised concerns that the training tool could replace, rather than reduce, the patient's initial ICB symptoms. Optional home visits will be offered if any problems occur that cannot be addressed over the phone.

Semi-structured interview schedules

Before using the training tool

- Is there any aspect of your ICB that you that we haven't captured in any of the questionnaires you've filled in, but you feel is important?
- Have you tried any other methods to manage the ICB?
  - What worked?
  - What didn't?
- What might be helpful to manage an ICB?

After using the training tool

- How did you find using the tool at home?
- Was the tool easy to use?
  - What did you like about it?
  - What did you dislike about it?
  - Was the level of support from us appropriate?
- What did you think about the paper diaries?
  - Did it enable you to report everything you thought was relevant?
- How well did it fit into your daily routine?
  - Were you able to motivate yourself to keep using it?
  - What factors affected your ability to keep up with the training?
  - What would have made it more motivating?
- Did you notice any improvements in how your ICB affected you?
  - Strength of the urge to engage in behaviours
  - Frequency of engaging in behaviours
- Is there any aspect of your wellbeing that we didn't capture in the questionnaires?
- Do you have any suggestions for how to improve the tool?
- Any other comments, questions, or suggestions?
- If it were available for everyone, would you use it?

Figure 20. Semi-structured interview schedules

Participants will be asked to attempt to incorporate the training tool into their everyday routine to increase the chances of engagement with the tool. They will be asked to practice every day for the duration of the study (4 weeks) for at least 5 minutes up to a maximum of 10 minutes.

Participants will also be given a booklet containing a paper diary that has been optimised for, and designed with, people with Parkinson's (Vega et al, 2018; see Figure 21). The diary requires very little writing, which many people with Parkinson's find difficult, and is designed to be intuitive and easy to use. Participants will select the experiences of daily living that affect them the most (e.g. urge to participate in an ICB related activity, time spent engaged in ICB related activity) and will asked to fill the diary in to report on these personalised experiences at least once a day.

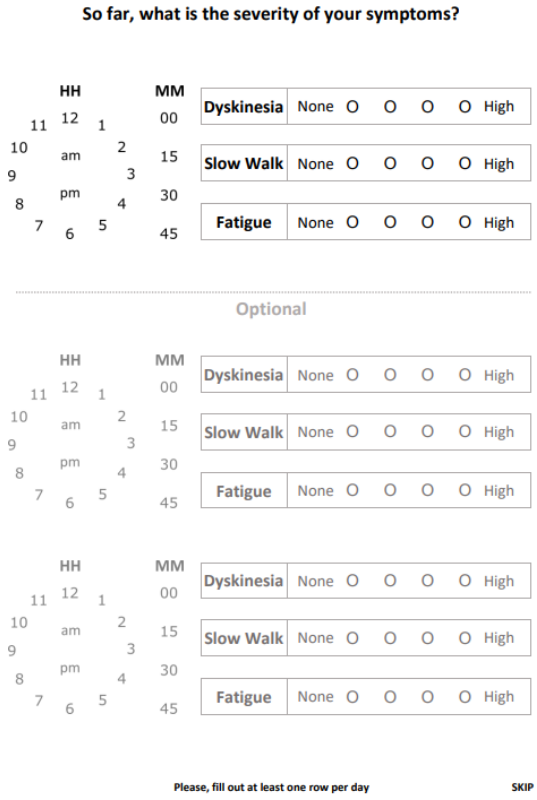

Figure 21. Example of the paper-based diary including the time that the diary is filled out, and a scale for the severity of three different symptoms affected by Parkinson's or ICBs, as chosen by the participant. From Vega et al. (2018) and available at https://paperstream.netlify.com/

5.3.3.4. T2 (4 weeks after baseline)

Participants and (optionally) their partners will meet with the researchers a second time after 4 weeks of using the training tool and complete the same measures that were taken at baseline (see Table 21). We will also conduct a second semi-structured interview with the participants (and their partners, if preferred) for approximately 30 minutes about their experiences taking part in the study and using the training tool such as how well it fit into their daily routine, what they liked and disliked, and any suggestions they have for improvements (see Figure 20). This

will also provide an opportunity for participants to expand on any of their answers to the quantitative outcome measures.

5.3.4. Analysis

Due to the small number of participants, all quantitative data will be reported in a case series design. The full pre-training and post-training interviews will be transcribed and then analysed using thematic analysis (Braun & Clarke, 2006).

5.3.4.1. Feasibility and acceptability

Acceptability and feasibility will be assessed through adherence and semi-structured interviews. We will look to see how many days participants engaged with the tool, and for how long (including how frequently they elected to complete more than the mandatory 3 blocks). We will also look to see how frequently participants engaged with the paper diaries, and whether these were filled in alongside the tool or at a different time of day. We additionally expect the qualitative analysis of the post-training interview to provide us with more detailed information on the feasibility and acceptability of the proposed intervention.

If participants are routinely electing to complete more than the mandatory 3 blocks, and this is supported as a positive choice by the interviews, this may mean that we have underestimated acceptability of the study and we may be able to increase our minimum expectation of participants. It's possible that only certain participants are happy to complete more blocks, in which case we could potentially increase the maximum number of blocks allowed per day (assuming no adverse effects on ICBs) or increase the number of allowable training sessions per day. On the other hand, we may discover that participants are rarely, if ever, electing to complete more blocks than the mandatory number. Again, the interviews will provide more information as to why this may be, and whether the acceptability of the training tool is adequate.

Participants are asked to adhere to both the training tool and the paper diaries daily, but for the purposes of the study adhering to the tool is more important to achieve the end goal of reduced ICB behaviour. If the paper diaries are problematic for adherence, we will endeavour to incorporate this measure of personalised symptom severity some other way. For example, it could be incorporated into the tool itself if participants decide that, in this instance, the use of pen and paper is not as preferable as has been reported elsewhere (Vega et al., 2018).

5.3.4.2. Outcomes

We will report the absolute scores for all questionnaires and measures listed in Table 21 at T1 and T2, as well as the change in score and whether this was in the desired direction. Whilst the PPI feedback helped us to decide what outcome measures to include in the study, the interview (specifically the question "Is there any aspect of your wellbeing that we didn't capture in the questionnaires?") will provide an opportunity for study participants to share whether they think

we have captured the right outcomes, and whether there are any measures missing (or, perhaps, irrelevant).

Complete adherence to the paper diaries will mean that each patient will be producing a daily score (or scores, depending on the number of personalised questions they choose to incorporate) related to the symptom or experience that they have chosen to monitor. We will be able to plot these scores over time and perform exploratory analysis of whether these correlate with performance on the training task itself. Performance on the training task will be evaluated in terms of their accuracy and response times for Go and No-Go trials (with a focus on No-Go trials that incorporated the ICB-salient stimuli) as well as their total scores achieved on the task each day.

5.4. Discussion and future plans

We proposed a prototype behavioural intervention which uses inhibitory control training to try and reduce ICBs in people with Parkinson's, based on previous literature which shows strong evidence for the transfer of effective response inhibition to a variety of impulsive and risky behaviours such as eating, gambling, and alcohol intake in the general population (Houben & Jansen, 2011; Jasinka et al., 2012; Jones et al., 2011, 2013; Lawrence et al., 2019; Verbruggen et al., 2012) and that this may be due to a reduction in explicit liking of the stimuli (Johannes et al., 2020).

Having developed the rationale for the training and consulted people with Parkinson's about the planned training, we need to test the feasibility and acceptability of the training in a small number of participants before planning and designing an RCT. Three potential outcomes may be predicted as a result of the pilot; 1) concluding that the intervention is not feasible or acceptable, 2) discovering the need to further develop the intervention before commencing with an RCT, or 3) commencing with a full RCT.

For the proposed intervention to prove unfeasible or unacceptable to participants, we may see such feedback in the post-training interviews or witness adverse outcomes during the study. For example, PPI volunteers expressed concerns that the prototype intervention could become an ICB in and of itself. We have built-in safety checks for this (regular phone calls) and, if this happens, we will withdraw that participant from the study immediately and re-evaluate the use of the prototype intervention.

Significant changes may be needed for the tool if, for example, feasibility and acceptability is revealed to be low either through sub-optimal engagement with the tool and/or paper diaries, or by self-report during the post-training interviews. In this event, we will endeavour to explore ways to improve feasibility and acceptability with participants during the post-training interview (see Box 1) and with further input from PPI volunteers if significant work is needed.

Finally, for the commencement of a full proof-of-concept RCT, the pilot would need to show good evidence of feasibility and acceptability. Given the sample size of the pilot study and the case series design, it would be difficult to make conclusions about any evidence of improvement in the behaviours of interest, as we cannot produce evidence of a statistically significant reduction of ICBs; however, we would require an absence of adverse outcomes (such as the tool becoming a new ICB) in order to move forward with a full RCT. The pilot study is likely to identify some minor changes that need to be made to the intervention, such as the usability of the tool, motivating elements of the tool, and plain English communication of core concepts, but these will be addressed before commencing with an RCT (Figure 22). The RCT will be delivered via an app which can be installed or downloaded to participants' personal electronic device such as a mobile phone or tablet. Further work would be needed to develop an app where the task is the same but the overall interface maximises general user experience and accessibility, and to also translate the scientific goals into a product suitable for the end-user.

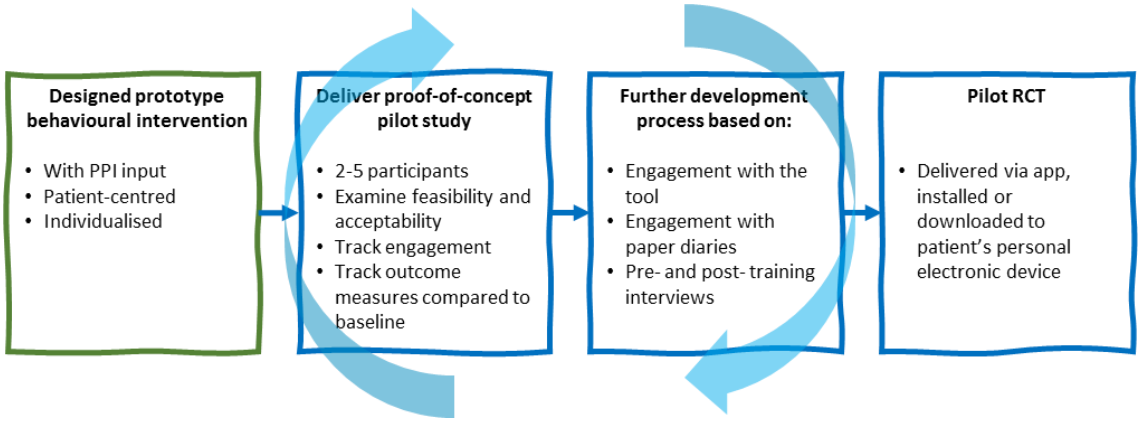

Figure 22. Development process for the intervention. Left panel (green) describes the development process contained within this chapter. Panels 2 and 3 show the iterative process of piloting and refining based on participant feedback which is planned for the proof-of-concept pilot study. Panel 4 describes the eventual pilot RCT which will be deliverable via an app to the participant's personal electronic device.

The proposed intervention prototype is in alignment with some of the top 10 research priorities for people with Parkinson's identified by Parkinson's UK and as informed by stakeholders (Deane et al., 2014), specifically priority 2) stress and anxiety, 4) personalised treatments, and 7) monitoring symptoms. Although any effects of the proposed intervention are unlikely to be as strong as more formal intervention by medical practitioners and is not designed to be used in cases where the ICB is severely affecting a patient's quality of life or the patient lacks insight, the intervention is designed to hopefully provide an interim solution to reducing mildly problematic ICBs.

In the context of its designed use-case, the proposed solution has several key advantages. Firstly, it aligns with the needs of people with Parkinson's, as demonstrated by the extensive patient and public involvement work. Patient and public involvement is an incredibly valuable tool as patients have experiential knowledge that researchers usually do not (Staley, 2015).

Taking this unique yet important approach so early in the development process means that the intervention starts from a place of maximal acceptability and feasibility before it is even formally assessed. As highlighted by the considerable changes that were made to the initial proposal, patient and public involvement is essential to ensuring that interventions are designed with the actual needs (as opposed to the assumed needs) of PwP in mind. Secondly, the intervention is accessible and flexible as the training is carried out at home (see also Bek et al., 2021), which increases the potential reach of end-users who will be able to use the tool. Thirdly, and relatedly, the intervention is low cost since it can be delivered via personal electronic devices which, again, expands the potential user-base. Finally, the intervention is personalised to the behaviour the person wishes to address (as in similar interventions; Adams et al., 2021), in response to the feedback from the patient and public involvement, which promotes empowerment and self-control for the user.

In conclusion, we have developed a proof-of-concept behavioural intervention based on the scientific rationale that training inhibitory motor control transfers to a reduction in impulsive behaviours, and effectively balanced this with extensive input from the end-users who informed the development through patient and public involvement. We have outlined the methodological plans to deliver the intervention over several weeks in participants' own homes, and the analysis plans to track the level of engagement in the tool and paper diaries, the outcome measures chosen in collaboration with PPI volunteers, and finally the feasibility and acceptability of the intervention through pre- and post-training interviews. The intervention targets a pressing need for PwP who experience ICBs, and delivery of the proof-of-concept prototype will further help to refine the intervention before commencing with a pilot randomised controlled trial in future.

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Chapter 6 - General discussion

Parkinson's is a heterogenous disease with diverse presentations of symptoms that stem from the loss of dopamine producing cells in the substantia nigra. The loss of dopamine primarily affects motor function due to reduced levels of dopamine in the basal ganglia, but also causes knock-on effects for cortical loops that are implicated in cognition, emotion, and motivation (Vanderah & Gould, 2015). The use of dopamine agonist medications to treat the (primarily) motor symptoms of Parkinson's can result in additional ICBs for many PwP due to an effective overdosing of the mesocorticolimbic pathways.

The first aim of this PhD project was to examine whether (and how) Parkinson's, and/or Parkinson's related ICBs, affect various aspects of impulsivity and inhibitory control due to the loss of dopamine in the fronto-basal-ganglia circuits, or the surplus of dopamine in the mesocorticolimbic pathways (discussed in section *6.1. An exploration of impulsivity and inhibitory control*). A second aim was to develop a behavioural intervention that may reduce the severity or impact of ICBs as an alternative to the current best practice of withdrawing from dopamine agonists. This was achieved by taking a patient-centred approach and balancing the scientific rationale with the needs of the end-users (discussed in section *6.2. Developing a patient-centred intervention for ICBs*).

6.1. An exploration of impulsivity and inhibitory control

In Chapter 2, we examined response inhibition (Stop Signal task) and response conflict (Simon task) using both traditional button-press measures of responding as well as a more sensitive measure of response force to reflect the ongoing cognitive control required to provide responses according to the task instructions. The button-press data showed no significant differences between PwP and HCs for the stop signal reaction time on the Stop Signal task, or interference effects on the Simon task. In both the Stop Signal task and the Simon task, PwP and HCs showed a greater percentage of partial errors in response force for the trial types requiring inhibitory control (Stop trials and incongruent trials respectively) compared to those not requiring inhibitory control (Go trials and congruent trials) which suggests that this more sensitive measure is, as predicted, reflecting the increased cognitive control required for such trials and capturing information that is lost through binary button-press measures. Crucially, however, the two groups showed similar rates of partial errors in response force, which suggests that PwP may not be impaired for these types of response inhibition and response conflict mechanisms.

In an unpublished study from our group, that does not form part of this thesis (see *Postscript to Chapter 2*), we additionally validated the measure by recruiting an additional group of younger participants (N = 16, mean age = 20.37 years) on the same tasks and measures to compare with the older healthy participants. Here we found that, for the Stop Signal task, the older

participants had a significantly longer stop signal reaction time, and yet the younger participants showed a significantly higher proportion of errors on Stop trials. This could mean that a higher proportion of partial errors reflect significantly better inhibitory control, as the incorrect response is withheld at the last crucial moment, whereas with worse inhibitory control this partial error more likely than not results in an incorrectly executed "full" button-press response. Therefore, taken together, our non-significant results between PwP and HCs on both the button-press and response force measures do seem to indicate that PwP do not show reduced response inhibition, particularly in the mild to moderate stages of the disease.

It is possible that training inhibitory control processes could result in changes to the rate of partial errors, which would further help to aid the interpretation of high and low rates of partial errors. For example, more successful stops (according to the button press) may well be correlated with higher partial errors if the movement was triggered by the Go signal, but successfully stopped by good inhibitory control.

To further investigate the meaning of a high proportion of partial errors on Stop trials (i.e. whether they reflect better or worse inhibitory control), future research could aim to use the same measure as in this study in other populations where a significantly slower stop signal reaction time is more evident. For example, children with attention deficit hyperactivity disorder consistently show slower stop signal reaction times compared to typically developing children (Alderson et al., 2007), and so if more, or less, partial errors were also evident in this clinical population, it would help to better elucidate whether partial errors are indicative of better or worse inhibitory control. Not only would this better help to place these findings in context by aiding interpretability, but it would allow for future studies to use the same methods in other populations. Furthermore, force response measures could be used conjointly with other methods such as EEG to more fully understand the underlying mechanisms of successful inhibition, partial errors, and full errors of inhibitory control.

We demonstrated the importance of the additional sensitive measure of ongoing inhibitory cognitive control instead of a binary all-or-nothing button press, which has previously been used as a valuable tool to measure activation of competing motor plans, inhibition, and control in both healthy participants and neurological patients (McBride et al., 2012, 2013, 2018). Previous research had suggested that where there is no observable behavioural deficit on the Stop Signal task in PwP, a functional deficit can be observed in the blood oxygen level dependent signal in the inferior frontal gyrus (Vriend et al., 2015). Therefore, it would have been possible that this additional measure of response force may have identified a behavioural deficit that the button-press measures were not sensitive enough to find. However, no behavioural deficit could be found with either measure, which suggests that any potential functional deficit may not be sufficient as to translate to real-world implications, at least in the mild-to-moderate stages of Parkinson's. To complement these findings, the systematic review in

Chapter 3 showed a high number of null results when comparing PwP (and PwP+ICBs, which we did not screen for in Chapter 2) to HCs for the Stop Signal Task and the Simon task. An exception to this is in the Simon task where statistically significant group differences emerge in the literature when looking at distributional analyses (although, not in the analyses in Chapter 2); however, the link between the last segment of the delta plot and inhibition strength has recently been challenged (Gajdos et al., 2019).

Chapter 3 was designed to take a more critical look at the literature to date and to separate a potential consensus narrative in the literature from a more rigorous review. Following a systematic search of the literature, 246 studies were synthesised. These studies all used some measure(s) of impulsivity and inhibitory control and compared at least one of the following: a group of PwP with a group of HCs, a group of PwP+ICBs with a group of PwP, two or more groups of PwP who differed on some other trait (e.g. tremor dominant compared to postural stability and gait dominant symptoms, freezing of gait compared to no freezing of gait), or PwP ON/OFF medication or deep brain stimulation. Generally, results were mixed and very few clear group differences emerged from the synthesis.

Results were unclear when comparing PwP and HCs for response inhibition, oculomotor inhibition, and decision-making under objective risk. For most measures of personality traits, such as the Barratt Impulsiveness Scale, Temperament and Character Inventory, and Behavioural Inhibition and Approach Systems Questionnaires, and measures of set shifting and delayed gratification, PwP largely showed no significant differences compared to HCs. For a measure of decision making under ambiguous risk that requires learning (i.e. Iowa Gambling task) PwP made overall more disadvantageous decisions and showed a reduced ability to learn to avoid disadvantageous decisions through the course of the task, which suggests that there may be an impairment of learning rather than in decision making itself. Additionally, PwP show a greater difficulty with response suppression in tasks of response conflict compared to HCs.

Fewer studies exist (38 of the 246 total studies) that make direct comparisons between PwP+ICBs and PwP, and so this should be an avenue for further research more generally, for example across tasks as in Chapter 4 but also across ICBs (e.g. gambling, hypersexuality, hobbyism, punding) to elucidate any associations between ICB type and more general impulsive traits and/or behaviours. The available studies largely showed no significant group differences across measures of response inhibition, response conflict, and set shifting. Inconclusive results were found for decision making under ambiguous and objective risk, however clearer differences emerged in terms of delayed gratification where PwP+ICBs showed higher delay discounting scores overall. There is more evidence to suggest that PwP+ICBs show higher trait impulsivity than PwP, especially on the Barratt Impulsiveness Scale total scores (see Smulders et al., 2014 and Ahearn et al., 2012 for discussions on the issues of validity when using the sub scores in PwP) but few studies have used other measures of trait impulsivity to date.

The systematic review presented in Chapter 3 did not demonstrate an absence of evidence, or even evidence of absence in the form of null results, but merely an absence of clarity. The process of completing a systematic review did not provide the answers that I was seeking and did not achieve the aims I had planned. Chapter 3 was an ambitious undertaking and although there was a lack of clear results this is still very much a result in itself and it had the additional benefit of providing inspiration for the study in Chapter 4. In hindsight, a more narrowly focused question may have been more appropriate, but the exercise of taking a broad viewpoint from the beginning is what ultimately provided me with the necessary knowledge to know that a more narrowly focused question and search strategy was indeed necessary. A logical follow-up to this paper would consist of a more narrowly focused systematic review and additional meta-analysis, with tighter constraints on the inclusion and exclusion criteria such as focusing on specific tasks and measures. This should incorporate the nuances of study design, and measurement, as many tasks are different between studies. For example, the Go/No-Go task has been presented via a computer with carefully controlled timed stimuli, as a simpler cognitive screening exercise designed to be used at a patient's bedside in clinical settings, and will sometimes be analysed by a total score (number of commission errors), percentage (e.g. of commission errors), or by response times. These methodological differences may be a contributing factor to the results reported by each paper.

The lack of research that has been conducted examining differences between PwP+ICBs and PwP to date, as well as the generally mixed findings for comparisons of PwP and HCs which may be due to the heterogeneity of symptoms in Parkinson's (see section *6.3. Heterogenous nature of Parkinson's*), led to the study described in Chapter 4. This study aimed to take some key measures from the systematic review across several domains of impulsivity and apply them to three participant groups: PwP+ICBs, PwP without ICBs and healthy control participants. By using the same measures across the same participants, we hoped to reduce some of the between-study heterogeneity of Parkinson's participants. Additionally, the measures used were designed with high methodological rigour, using recommendations for best practice, and all methods and analyses were pre-registered to reduce any researcher degrees of freedom. However, the study lacked clear hypothesis testing and was more theoretically exploratory, despite the extensive literature that exists to date.

Although data collection was necessarily ended prematurely due to the onset of the COVID-19 pandemic, preliminary results show largely null results between groups across all measures, and specifically for response inhibition (stop signal reaction time in the Stop Signal task), response conflict (interference effect on the Stroop task), set shifting (switch cost on the Trail Making test), decision making under ambiguous risk (adjusted number of pumps on the Balloon Analogue Risk Task), decision making under objective risk (risk adjustment index on the Cambridge Gambling task), delay discounting (overall *k* on the Kirby Monetary Choice

Questionnaire), trait impulsivity (total score on the Barratt Impulsiveness Scale and sensation seeking score on the UPPS-P), and sensitivity to reward and punishment (total scores on the Behavioural Approach Systems questionnaire and Behavioural Inhibition Systems questionnaire respectively). Only the measure of action restraint (commission errors on the Go/No-Go task) showed any group differences, where PwP performed significantly worse than both PwP+ICBs and HCs. The results are currently highly variable in PwP, as shown in Figure 13, but if the result were to remain statistically significant upon completion of data collection it may provide evidence for a clinical dissociation between action restraint (Go/No-Go) and action cancellation (Stop Signal Task) in Parkinson's. In the general population, these two measures are positively correlated (Reynolds et al., 2006).

Although it is difficult to draw conclusions from these results alone, as the sample size is not yet as high as was pre-registered (particularly for the PwP group), some results are surprising and in stark contrast to those in the systematic review; PwP+ICBs do not show higher delay discounting scores in this study nor do they show higher levels of trait impulsivity than PwP or HCs as in the review results, despite trait impulsivity being a risk factor for the development of ICBs.

Recent evidence that sought to systematically review investigations of structural and functional differences between PwP and PwP+ICBs, found inconclusive evidence for any structural differences in relevant areas of the brain for motivation and cognitive control but did find abnormal functional activity in PwP+ICBs even before the ICBs developed, particularly for regions associated with cognitive control and motivation compared to PwP (Martini et al., 2020). It's important to note, therefore, that the PwP in our studies may consist of a subset that will develop ICBs, or who have an increased risk factor. Additionally, in tasks that involved reward-related cues, risk-taking, and delay discounting, there was an increased blood oxygen level dependent signal in PwP+ICBs compared to PwP (Martini et al., 2020). Therefore, similarly to the finding that functional deficits in PwP during the Stop Signal task are not reflected by observable behavioural deficits (Vriend et al., 2015; and see Chapter 2), perhaps a similar pattern exists in PwP+ICBs. Although there may be functional deficits in brain regions associated with the different types of tasks included in the systematic review in Chapter 3 and the cross-section study in Chapter 4, it is possible that this is reflected in the ICB behaviour itself, but there is no observable behavioural deficit in the experimental tasks and measures.

Bayes factors on the final sample size will be able reveal more about the strength of the evidence for these experimental measures, and whether any strong conclusions can be made from the available results. Additionally, many previous studies focus on PwP+ICBs who are experiencing the four main impulse control disorders (pathological gambling, hypersexuality, binge eating, and compulsive buying) and less so on hobbyism, punding, walkabout, hoarding, and dopamine dysregulation syndrome. As this study used the QUIP to differentiate PwP with

and without ICBs, we have captured a range of ICBs over and above the main four. There may be distinct differences in the way that behavioural impulsivity presents (or does not present, as the case may be) in those with clinical problems with impulsivity. An interesting avenue for further exploration would be to examine the different types of ICBs and whether they are associated with different changes in behaviour as measured on the experimental measures used here.

Additionally, there is some evidence for shared mechanisms underpinning different types of impulsivities, and so we might expect to see correlations between some measures. For example, lack of planning and lack of perseverance is correlated with prepotent response inhibition (Cyders & Coskunpinar, 2011), and so performance on the Go/No-Go or Stop Signal Task may be correlated with the attentional subscale of the Barratt Impulsiveness Scale or the premeditation/perseverance subscales of the UPPS-P. Additionally, sensation seeking and delay discounting on the Kirby Monetary Choice Questionnaire could be correlated (Cyders & Coskunpinar, 2011). In future analysis of this study with a full sample size, these remaining questions can be investigated.

Whilst the focus of this thesis has been on dopamine and dopaminergic medications, it is important to note other neurotransmitters that contribute to changes in impulsive behaviour. For example, increasing or decreasing serotonergic function can lead to changes in sensitivity to punishment and noradrenaline on reward dependence (Evenden, 1999). Whilst Parkinson's is primarily a disorder of dopamine neuron degeneration, other neurotransmitters see a depletion too such as serotonin and gamma-aminobutyric acid (Barone, 2010; Delaville et al., 2011; Politis & Niccolini, 2015). It is difficult to disentangle the effects of different Parkinson's pathology, which is more complicated still not only by the dopaminergic medications but also the high incidence of PwP taking serotonin medications e.g. for common co-morbidities such as depression (Richard et al., 1997). Future research could seek to disentangle these collinearities of serotonin and dopaminergic medications in Parkinson's.

6.2. Developing a patient-centred intervention for ICBs

Chapter 5 describes the development of an intervention for Parkinson's related ICBs. The onset of ICBs is strongly associated with the commencement of dopamine agonist medication which is used to treat the motor symptoms of Parkinson's. Currently, the best available treatment is to reduce the dosage or withdraw from the dopamine agonists completely to resolve the symptoms of the ICB(s), however this presents a dilemma for the patient where they must choose between controlling the symptoms of the ICB by withdrawing from medication, or between controlling the symptoms of Parkinson's by staying on the medication. Our focus group and work with Patient and Public Involvement volunteers confirmed the need for an alternative way of managing, or at least reducing the impact of, behaviours, and they were generally enthusiastic about our proposal. We proposed a complementary method to potentially reduce

the impact of ICBs, based upon a wealth of recent literature that suggests that training inhibitory action control (for example through Go/No-Go and Stop Signal tasks) generalises to a reduction of risk-taking behaviours, particularly monetary decisions and binge eating behaviours (e.g. Lawrence et al., 2015; Verbruggen et al., 2012).

Initially, we proposed a waiting-list control trial consisting of a joint Stop Signal task to be completed by the patient with a partner over several weeks, based upon additional literature that suggests watching another person successfully inhibit an action helps the observer successfully inhibit their own actions (e.g. Schuch & Tipper, 2007). Following extensive feedback from patient and public involvement (PPI) volunteers, we revised our methodology, planned a proof-of-concept pilot study to focus more on individual patients and their lived experiences, and incorporated additional potential outcome measures proposed by the PPI volunteers that could be used to track the impact of participants' ICB(s) over the course of the study. The study development highlighted the importance of taking a patient-centred approach to balance the scientific rationale with the lived experience of those most affected by the output (Staley, Abbey-Vital, & Nolan, 2017), and is currently used as a case study by Parkinson's UK.

The immediate next step for this venture is the pilot study, which will assess the acceptability and feasibility of the eventual RCT. The study will also provide the opportunity to further refine the protocol with input from PwP, both through quantitative data of engagement (i.e. time spent on the training tool) but also qualitative data from the interviews. We have now obtained funding for the pilot study and plan to apply for further funding for a larger trial.

6.3. Heterogenous nature of Parkinson's

Parkinson's is a heterogenous disease, and whilst there are general symptoms common to many patients, there is no "one size fits all" profile of symptoms that defines Parkinson's. As discussed in the introduction in Chapter 1, Parkinson's primarily effects motor control, but also affects cognition, emotion, and motivation, and involves a host of both motor and non-motor symptoms. Additionally, it has a high misdiagnosis rate as the lack of homogeneity makes the disease difficult to diagnose with certainty ante-mortem. Data-driven approaches using statistical cluster analyses have attempted to find and label subtypes of Parkinson's with varying results (e.g. Erro et al., 2013; Krishnagopal, 2020; Lewis, Foltynie, Blackwell, Robbins, Owen, & Barker, 2005; Ma, Chan, Gu, Li, & Feng, 2015). Thus, at present, there is still no single best approach to subtyping Parkinson's (Armstrong & Okun, 2020).

This presents great difficultly when conducting research aimed at separating features of behaviour associated with Parkinson's from those present in a non-Parkinson's population. Small sample sizes, as is typical with experimental cognitive and behavioural research in Parkinson's, means that a result from one study is not easily generalisable beyond the scope of that study. Samples between studies are rarely fully comparable due to the heterogenous nature of

Parkinson's, and therefore this may explain the unclear results from the systematic review in Chapter 3. For example, a certain underlying factor (or factors) of Parkinson's may contribute to a reduction in effective response inhibition on the Stop Signal task, but if this factor is not captured in the sample of any given study, or not clearly described, it is difficult to make conclusions regarding performance on this task based on a small sample of PwP. Ideally, a data-driven approach similar to that which has been employed in an attempt to identify Parkinson's subtypes might be able to uncover the aspects, symptoms, or pathologies of Parkinson's that contribute to, for example, a lack of response inhibition on the Stop Signal task, given a large enough sample of well-described participants. Generally, such approaches on secondary data would be possible following a greater uptake of openness and data sharing amongst researchers of cognitive and behavioural deficits in Parkinson's which, at present, is lacking.

Additionally, many previous studies with PwP+ICBs tend to select for samples containing very specific ICBs such as pathological gambling, rather than considering the full breadth of ICBs that may also include behaviours that may have less of a severe personal impact such as hobbyism and punding (see Chapter 3). In Chapter 4, 50% of the PwP+ICB sample (10 out of 20 participants) scored positively for hobbyism on the QUIP, whereas only one patient scored positively for gambling behaviours. Therefore, in the study presented in Chapter 4, results may have been impacted by the ICBs within the sample differing from those in the general literature. Future work should seek to examine the contribution to impulsivity and inhibitory control the different individual ICBs make. Additionally, the high incidence of hobbyism ICBs here may represent an underdiagnosis that the PPI volunteers in Chapter 5 felt existed, and these behaviours may also generally go unrecognised in the literature.

6.4. Quality of behavioural research in Parkinson's

The last decade has seen a paradigm shift begin to occur, particularly in the psychological and biological sciences. Reproducibility of research is generally low, and research waste is created when datasets are not shared, researcher degrees of freedom are unaccounted for, and key methodological details are missing from publications (Chan et al., 2014; Ioannidis, 2005; Munafò et al., 2017). Adoption of open, transparent, and reproducible research practices in cognitive and behavioural research in Parkinson's would greatly improve our capacity to overcome the limitations associated with difficulty with participant recruitment and thus small sample sizes, as for example datasets can be shared and pooled for a larger scale analysis, multiverse analysis (Steegen, Tuerlinckx, Gelman, & Vanpaemel, 2016), and easier meta-analyses. In addition, confidence in findings can increase if degrees of freedom are accounted for through pre-registration and/or fully transparent methodological reporting.

Chapter 4 of this thesis may represent one of the most transparent and reproducible such studies to date. The study intended to represent a high standard of methodological quality by

conforming to best practice for the tasks and measures used, not only in designing the individual tasks, but also in implementing the study with participants as well as decisions on data processing, outlier removal, and statistical analysis throughout. Once data collection is complete, all data and analysis scripts will also be shared. Very few of the studies included in the systematic review pre-registered their study or analyses, or shared raw data and analysis scripts, so it is our hope that we can attempt to pave the way for changes in the way research is conducted in this field in future.

6.5. Conclusions

Overall, this thesis uncovered many challenges for behavioural research in Parkinson's and ICBs. Although there are theoretical reasons to expect impaired performance (i.e. higher impulsivity or reduced response inhibition) on certain measures such as decision-making under ambiguous risk, sensitivity to reward, and delay discounting in PwP+ICBs due to the association with the mesocorticolimbic pathways, and in set shifting, decision-making under objective risk, and sensitivity to punishment in PwP due to associations with the nigrostriatal pathway, the pattern of results both across the literature and in our cross-sectional study of impulsivity do not reflect this quite so clearly. This may largely be due to the heterogenous nature of Parkinson's, and the difficulties of conducting research on small sample sizes with between-groups comparisons rather than larger scale and data-driven approaches. It may also be that the mild to moderate symptoms of PwP generally included in such research does not bring out these expected findings which may be only more applicable to more severe cases at later stages. Finally, we have suggested a general shift towards data sharing that can be used to apply more precise meta-analytic methods and quantify the contribution of the various aspects of Parkinson's that differ between patients, such as disease severity and medication status.

I also presented a protocol for a patient-centred behavioural intervention for PwP that was generally well-received by PPI volunteers, but which required substantial changes to reflect the needs of the end-users. Through a partnership with the PPI volunteers, a complete prototype of the planned intervention is complete and the next step is to complete a proof-of-concept study with 2-5 people with Parkinson's who experience ICBs to get more in-depth feedback and to test the feasibility and acceptability of the proposed intervention.

Further work into the more complex behaviour changes that may or may not occur in PwP with additional ICBs is important, particularly due to the mixed findings in the literature so far. Most importantly, however, continued work into both understanding ICBs and helping to alleviate them is considered crucial by the patients most affected by these issues, and who played a key role in shaping the content of this thesis.

6.6. References

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Appendices

Appendix A. Ethical documentation for Chapter 2; Participant information sheet and consent form for PwP, participant information sheet and consent form for HCs, and letter of ethical approval.

Appendix B. Pre-registration of Chapter 3's systematic review on PROSPERO (also available at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017051751)

Appendix C. Pre-registration of the study contained within Chapter 4 (also available on the Open Science Framework at: https://osf.io/frzpv/)

Appendix D. Ethical documentation for Chapter 4; Participant information sheet for PwP, participant information sheet for HCs, consent form for both PwP and HCs, and letter of ethical approval.

Appendix A. Ethical documentation for Chapter 2; Participant information sheet and consent form for PwP, participant information sheet and consent form for HCs, and letter of ethical approval.

MANCHESTER 1824

The University of Manchester

School of Psychological Sciences
The University of Manchester
Oxford Road
Manchester M13 9PL

Information Sheet for participants with Parkinson's disease

Title of Study: Representing Action in Parkinson's disease

Introduction

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study and why have I been chosen?

We are interested in how people with Parkinson's disease respond to the sight of different objects and actions in their environment and how they communicate about them. We will compare how people with Parkinson's disease and volunteers who do not have the disease are able to respond to pictures of actions and objects by making an action (such as a reaching movement) or how quickly you can name and describe pictures and video clips. We will aim to test up to 60 people with Parkinson's disease and up to 60 without. We invite you to take part as a participant with Parkinson's disease.

Do I have to take part?

No. Taking part is entirely voluntary. If you do not want to take part, you do not have to give a reason. If you decide to take part but change your mind, you can withdraw at any time from the study, by simply informing the investigator named below before, during or after the session. If you decide to withdraw, your expenses (and those of anyone who accompanies you) will still be reimbursed.

What will I have to do if I take part?

If you agree to take part, we will invite you to participate in up to 9 different testing sessions. You may choose to take part in as few or as many as you wish. Your participation will still be very useful, even if you are only able to attend one session. The sessions will take place either at the University of Manchester or the Wellcome Trust Clinical Research Facility (Grafton Street, Manchester) or, if you wish, we can visit you in your own home for some sessions. During the sessions, we will ask you to complete some questionnaires (for example, about different aspects of your mood and behaviour) and some short memory, thinking and language tests. We will also ask you to watch some video clips and look at

some pictures and make judgments about them, while we measure your reaction times, hand or eye movements and/or video record you. At each session, we will measure your Parkinson's disease symptoms by asking you to make some movements (for example opening and closing your hand as quickly as you can). We will also ask you how long you have had Parkinson's and what medication you are currently taking. If we need further information, we will contact your clinical team, with your permission, to check your current medication dose and details about your illness history.

We will also ask your partner, or a companion who is in close contact with you (friend, relative or carer) to complete a questionnaire about how you communicate about things in everyday life. If your partner/companion does not attend the session with you, we may ask you to pass on the questionnaire to them to complete at home.

We will let you know exactly what is involved in each session before you arrive so you can decide if you are happy to take part (for example, you may not wish to be videoed). See the flow diagram at the end to see which sessions you would be able to take part in.

For one session, we will ask you if you would be willing to delay your first dose of medication, so that we can see how you perform with and without your normal medication. If you agree to take part in this session, with your permission, we will write to your GP to let them know that you are participating.

Each session will last under 3 hours and you will have frequent rest-breaks throughout the session. Any expenses which, you or a companion (for example, a friend or carer), incur in attending the testing session will be repaid to you in full on the day.

What if there is a problem?

So far as we know, there is negligible risk associated with taking part in the study. Aside from asking you to withhold your first dose of medication for some testing sessions, you will not be required to change your routine medication in any way.

Complaints

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 2757583 or 0161 2758093 or by email to research.complaints@manchester.ac.uk

What are the possible benefits of taking part?

Although taking part will not benefit you personally in terms of an actual or potential improvement of your condition, our results will help us to understand how Parkinson's

disease affects how people communicate and interact with the world around them. In the long term, we hope this will suggest strategies for improving movement and communication in Parkinson's disease. If you wish, we will tell you the results of the study when it ends.

Will the details of my results be confidential?

All of the information which we collect about you during the study will be kept confidential, and will be accessible only by the people running the study. If your results are included in a paper published in a medical or scientific journal, or in a presentation given at a conference, you will not be identifiable by name or other information.

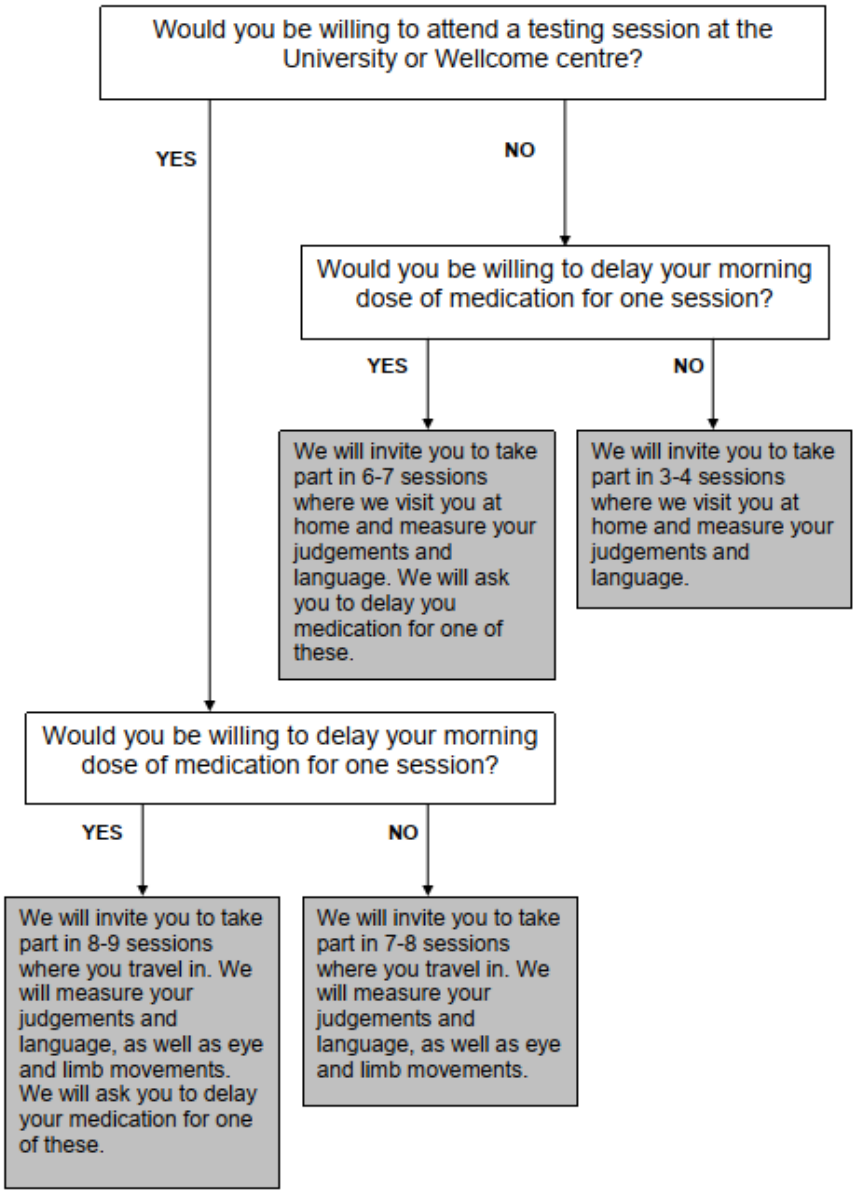
If you agree to being videoed as part of the study, the video footage will be stored securely. It will be viewed by members of our research team for analysis, but will not be viewed by anyone else unless you give us written permission to do so on the consent form. In this case, short video clips extracted from your recording will be viewed by other research participants (but your identity will be protected by hiding or scrambling your face). Please think carefully about this and we understand that you may not wish your video footage to be used in this way. It will be destroyed 5 years after the data are published in a scientific journal.

What do I do now?

The researcher organising the study will contact you within a day or two. She can answer any of your questions, and you can let her know if you agree to take part. Thank you very much for considering taking part in our study. Please discuss this information with your friends, family and G.P. if you wish.

If you wish to obtain further information about this study, you may contact:
Dr Ellen Poliakoff (0161 275 7333)
School of Psychological Sciences,
University of Manchester,
Manchester, M13 9PL
Email: Ellen.Poliakoff@manchester.ac.uk

Flow diagram of the study



MANCHESTER 1824

The University of Manchester

Consent form for participants with Parkinson's disease

Title of study: Representing Action in Parkinson's Disease

Name of Researcher: Dr Ellen Poliakoff

Please initial box

1. I confirm that I have read and understand the information sheet dated 14 May 2014 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I consent to being video-recorded as part of the above study. ☐
4. I consent to a video of me (with my face obscured) being viewed by other research participants ☐
5. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records ☐
6. I consent to withholding my medication on one occasion, as detailed in the information sheet. ☐
7. I consent to my GP being informed of my participation, as detailed in the information sheet. ☐
8. I understand that my partner/companion will be asked to complete some questionnaires about me. ☐
9. I agree that the researchers may contact me between research visits if any further information is needed. ☐
10. I agree to take part in the above study. ☐
11. I agree to being contacted about future research opportunities ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Researcher	Date	Signature

School of Psychological Sciences
The University of Manchester
Oxford Road
Manchester M13 9PL

Information Sheet for Control Participants

Title of Study: Representing Action in Parkinson's disease

Introduction

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study and why have I been chosen?

We are interested in how people with Parkinson's disease respond to the sight of different objects and actions in their environment and how they communicate about them. We will compare how people with Parkinson's disease and volunteers who do not have the disease are able to respond to pictures of actions and objects by making an action (such as a reaching movement) or how quickly you can name and describe pictures and video clips. We will aim to test up to 60 people with Parkinson's disease and up to 60 without. We invite you to take part as a control participant who does not have Parkinson's disease.

Do I have to take part?

No. Taking part is entirely voluntary. If you do not want to take part, you do not have to give a reason. If you decide to take part but change your mind, you can withdraw at any time from the study, by simply informing the investigator named below before, during or after the session. If you decide to withdraw, your expenses (and those of anyone who accompanies you) will still be reimbursed.

What will I have to do if you take part?

If you agree to take part, we will invite you to participate in up to 9 different testing sessions. You may choose to take part in as few or as many as you wish. Your participation will still be very useful, even if you are only able to attend one session. The sessions will take place either at the University of Manchester or the Wellcome Trust Clinical Research Facility (Grafton Street, Manchester) or, if you wish, we can visit you in your own home for some sessions. During the session, we will ask you to complete some questionnaires (for example, about different aspects of your mood and behaviour) and some short memory, thinking and language tests. We will also ask you to watch some video clips and look at some pictures and make judgments about them, while we measure your reaction times, hand or eye movements and/or video record you.

We will also ask your partner, or a companion who is in close contact with you (friend, relative or carer) to complete a questionnaire about how you communicate about things in everyday life. If your partner/companion does not attend the session with you, we may ask you to pass on the questionnaire to them to complete at home.

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Each session will last under 3 hours and you will have frequent rest-breaks throughout the session. Any expenses which, you or a companion (for example, a friend), incur in attending the testing session will be repaid to you in full on the day.

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Although taking part will not benefit you personally in terms of an actual or potential improvement of your condition, our results will help us to understand how Parkinson's disease affects how people communicate and interact with the world around them. In the long term, we hope this will suggest strategies for improving movement and communication in Parkinson's disease. If you wish, we will tell you the results of the study when it ends.

Will the details of my results be confidential?

All of the information which we collect about you during the study will be kept confidential, and will be accessible only by the people running the study. If your results are included in a paper published in a medical or scientific journal, or in a presentation given at a conference, you will not be identifiable by name or other information.

If you agree to being videoed as part of the study, the video footage will be stored securely. It will be viewed by members of our research team for analysis, but will not be viewed by anyone else unless you give us written permission to do so on the consent form. In this case, short video clips extracted from your recording will be viewed by other research participants (but your identity will be protected by hiding or scrambling your face). Please think carefully

about this and we understand that you may not wish your video footage to be used in this way. It will be destroyed 5 years after the data are published in a scientific journal.

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Thank you very much for considering taking part in our study. Please discuss this information with your friends and family if you wish.

If you wish to obtain further information about this study, you may contact:

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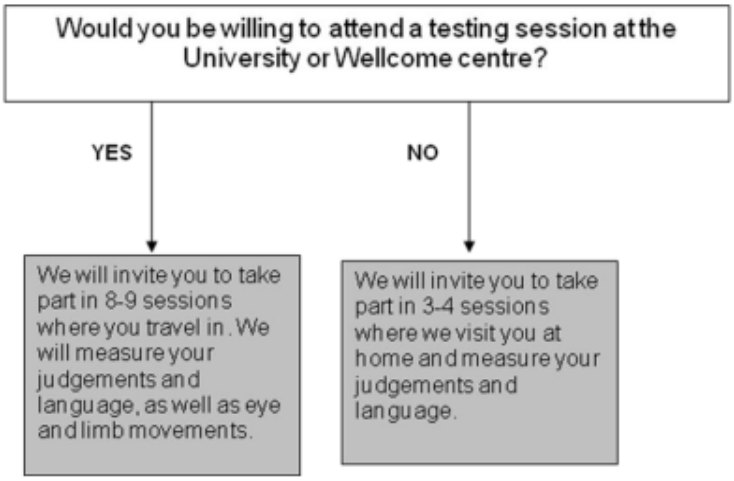
School of Psychological Sciences,
University of Manchester,
Manchester, M13 9PL *Email:* Ellen.Poliakoff@manchester.ac.uk

Flow Diagram of the Study



MANCHESTER 1824

The University of Manchester

Consent form for control participants

Title of Project: Representing Action in Parkinson's Disease

Name of Researcher: Dr Ellen Poliakoff

Please initial box

1. I confirm that I have read and understand the information sheet dated 14 May 2014 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I consent to being video-recorded as part of the above study. ☐
4. I consent to my video (with my face obscured) being viewed by other research participants ☐
5. I understand that relevant sections of my data collected during the study may be looked at by individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records ☐
6. I agree that the researchers may contact me between research visits if any further information is needed. ☐
7. I agree to take part in the above study. ☐
8. I agree to being contacted about future research opportunities ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Combining the strengths of UMIST and The Victoria University of Manchester

NHS
National Research Ethics Service
NRES Committee North West - Liverpool Central
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Barlow House
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27 April 2011

Dr Ellen Poliakoff
Senior Lecturer in Psychology
University of Manchester
School of Psychological Sciences
Zochonis Building
University of Manchester
M13 9PL

Dear Dr Poliakoff

Study title: **Representing Action in Parkinson's disease: Perception, Language and Gesture**
REC reference: **11/NW/0143**

Thank you for your letter of 21 April 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
REC application	3.1	07 March 2011
Investigator CV		01 March 2011
Response to Request for Further Information	2	21 April 2011
Participant Information Sheet: For control participants	1	01 February 2011
Participant Information Sheet: Controls	2	21 April 2011
CV for Elena Gomez		
CV for Kathryn McDonald		
CV for Emma Gowen		
CV for Mark kellett		
CV for Jeremy Dick		
Protocol	1	01 February 2011
Participant Information Sheet: PD	2	21 April 2011
Participant Consent Form: Controls	2	21 April 2011
CV for Fernando Cuetos		
CV for Judith Holler		
Participant Consent Form: Consent form including video patient	1	01 February 2011
Evidence of insurance or indemnity		04 March 2011
Referees or other scientific critique report		25 February 2011
Questionnaire: Geriatric depression scale		
Questionnaire: The Edinburgh laterality inventory		
Participant Consent Form: PD	2	21 April 2011
Advertisement	2 PD	21 April 2011
Advertisement	2 Controls	21 April 2011
Covering Letter		03 March 2011
Letter from Sponsor		04 March 2011
Letter of invitation to participant	2	21 April 2011
GP/Consultant Information Sheets	2	21 April 2011

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/NW/0143	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Professor Sobhan Vinjamuri
Chair

Email: carol.ebenezer@northwest.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mrs Catherine Barrow*
Rachel Georgiou
Elena Herrera

Appendix B. Pre-registration of Chapter 3's systematic review on PROSPERO

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Impulsivity and inhibitory control in Parkinson's disease: a systematic review

Jade Pickering, Ellen Poliakoff, Jennifer McBride, Iracema Leroi

Citation

Jade Pickering, Ellen Poliakoff, Jennifer McBride, Iracema Leroi. Impulsivity and inhibitory control in Parkinson's disease: a systematic review. PROSPERO 2017 CRD42017051751 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017051751

Review question

Does the evidence suggest that people with Parkinson's disease (PD), without Impulse Control Disorders (ICDs), display more impulsive behaviour and less inhibitory control over actions, compared to healthy controls?
Do people with PD that also develop ICDs display more impulsive behaviour and less inhibitory control over actions, compared to those with PD that do not have ICDs?
What additional factors influence impulsive behaviour and inhibitory control in PD? E.g. the contribution of levodopa/dopamine agonist medications or deep brain stimulation.

Searches

The following electronic databases will be searched: Scopus, Web of Science, Cochrane Library, PubMed, PsycINFO, Open Grey, and ProQuest Dissertations & Theses Global. Automatic alerts, if available, will be set up so that new publications are not missed after the initial search dates and before finalisation of the manuscript. References lists of relevant papers will be hand searched. There will be no restriction on the date of publication or language at this stage.
The search strategy will include key words related to impulsivity and inhibitory control in Parkinson's, whilst attempting to exclude irrelevant studies such as those with animal subjects or neural inhibition.

Types of study to be included

Inclusion: Experimental tasks or questionnaire reports of impulsivity/inhibition control will be included. The authors of any studies included must have reported that the particular method they have used acts as a measure of either impulsivity or inhibitory control, or used an established measure of impulsivity or inhibitory control and reported the appropriate behavioural results. The study must include patients with Parkinson's.Exclusion: Review papers, drug trials, intervention studies, RCTs, qualitative research, prevalence studies, case studies or case series studies. Any study that does not have human PD patients in the sample, but instead relies on tissue samples or animal models. Studies where there is no appropriate control group. Studies where the measure used is a diagnostic tool.

Condition or domain being studied

Parkinson's disease is a neurodegenerative motor disorder characterised by a slowness of movement (bradykinesia), rigidity, tremor, and freezing of gait. Some people with Parkinson's develop Impulse Control Disorders due to dopamine agonist medication which usually includes one or more of the following symptoms: excessive gambling, shopping, hobbyism, punding, hypersexuality, or abuse of dopaminergic medication.

Participants/population

Inclusion: Participant groups with Parkinson's disease who may, or may not, have an additional ICD.
Exclusion: Participants where there is no adequate control group. Between-subjects studies must include a healthy control group unless the comparison is between two groups of people with Parkinson's. Within-subjects studies are expected to comprise largely of ON/OFF studies.

Intervention(s), exposure(s)

Reported performance on experimental, behavioural tasks of impulsivity or inhibitory control will be reviewed, where there is an appropriate measure of inhibitory control or impulsivity. Such tasks may include the Stop Signal task, Simon task, gambling tasks, or delay discounting tasks, amongst others. Additionally, questionnaires of impulsivity such as the Barratt Impulsiveness Scale will be included, unless they are

intended as a diagnostic tool.

Comparator(s)/control
All studies must either directly compare impulsivity or inhibitory control in PD without ICDs with PD-ICDs, or one or both groups with a healthy control group. Some studies may compare two groups of PD patients on another sub-variable of PD. Additionally, within-subjects control groups will be included where patients are tested with deep brain stimulation turned on/off, or on/off medication, even where there is no healthy control group.

Main outcome(s)
The primary interest is the level of impulsive behaviour, or lack of inhibitory control, displayed in each group.

Additional outcome(s)
It is expected that a range of different behavioural measures will have been used to assess different subtypes of impulsivity/inhibitory control in the literature; we will review what these measures tell us, and how impulsivity/inhibitory control is defined in this clinical population.
Some studies may have used additional methodology such as fMRI, or EEG recordings. We will additionally review any relevant findings from these measures if the study has met inclusion criteria.

Data extraction (selection and coding)
After de-duplication of the search results, at least two reviewers will independently screen the titles and abstracts against the inclusion/exclusion criteria. Once the full text has been retrieved for the remaining studies, at least two reviewers will independently screen the full text against the inclusion criteria and decide on the final studies for inclusion in the review. At all stages, discrepancies will be discussed between the reviewers and an additional reviewer will assist where discrepancies cannot be resolved.
Extracted data will include, where available: The sample sizes and groups used, plus relevant demographic information such as age, gender, and for the PD groups UPDRS/H&Y scores. We will include the tasks/measures used, what was being measured, and summarise the main findings.

Risk of bias (quality) assessment
To the best of our knowledge, there is no existing scale that serves to assess the quality of the types of experimental studies to be included in this review. Therefore, we will endeavour to modify an existing scale in order to assess the appropriateness of the patient and control samples, and the task or questionnaire used. This assessment process will be conducted by at least two independent reviewers, and discrepancies discussed and resolved by a third party if necessary.

Strategy for data synthesis
Results will be synthesised descriptively, as the studies are expected to be too heterogeneous to allow for a meta-analysis.

Analysis of subgroups or subsets
As the review is a qualitative synthesis, most sub-group comparisons cannot be defined clearly in advance. The only planned qualitative comparison is between PD patients that have ICDs and those that do not have ICDs.

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Organisational affiliation of the review
University of Manchester

Review team members and their organisational affiliations
Miss Jade Pickering. University of Manchester
Dr Ellen Poliakoff. University of Manchester
Dr Jennifer McBride. University of Manchester
Dr Iracema Leroi. University of Manchester

Type and method of review

Systematic review

Anticipated or actual start date
19 September 2016

Anticipated completion date
31 December 2019

Funding sources/sponsors
Part of a project funded by the Economic and Social Research Council

Conflicts of interest
None known

Language
English

Country
England

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Humans; Impulsive Behavior; Parkinson Disease; Synaptic Transmission

Date of registration in PROSPERO
13 March 2017

Date of first submission
24 August 2018

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	No	No
Data analysis	Yes	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

13 March 2017
04 September 2018

Appendix C. Pre-registration of the study contained within Chapter 4 (also available on the Open Science Framework at: https://osf.io/frzpv/)

Pre-registration: Impulsivity and inhibition in Parkinson's with and without additional impulse control disorders

Jade S Pickering[1], Marta Majewska[1], Jennifer McBride[1], Iracema Leroi[1,2], Ellen Poliakoff[1]

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1 Acknowledgements

We thank Parkinson's UK for helping to facilitate Patient and Public Involvement (PPI) for the study, the PPI volunteers for providing input on the initial design of the study, Professor Chris Chambers for his comments on an early draft of the pre-registration, Jonathan Reardon for his input on the programming, and Dr Matthew Sullivan for his input on the final design. The study was funded by the Economic and Social Research Council, a Parkinson's UK Research Involvement Award, and was completed in part fulfilment of JSP's PhD and MM's MRes degrees.

2 Aims

The study comprises different tasks that probe various dimensions of impulsivity, such as motor inhibition, risky decision making, task switching, and questionnaires examining impulsive personality traits. We aim to find out whether people with Parkinson's with additional impulse control disorders (PwP+ICDs) show higher levels of impulsivity and less inhibitory control than PwP without ICDs, and whether PwP without ICDs show higher levels of impulsivity than age-matched healthy control (HC) participants on any of these tasks.

The dopamine overdose hypothesis suggests that performance on such tasks of impulsivity and inhibitory control may be due a combination of disease-related degeneration and the compensatory effect of dopaminergic medication (Cools, Barker, Sahakian, & Robbins, 2001; Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013). As neurodegeneration contributes to the reduction of dopamine producing cells in the substantia nigra (which projects to the nigrostriatal pathway), dopaminergic medication aims to restore function along that same pathway. However, this leads to a relative "overdosing" in another main dopaminergic pathway. The mesocorticolimbic pathway projects from the (relatively) unaffected ventral tegmental area, which is also responsible for dopamine producing cells, and is thought to be associated with the development of ICDs in Parkinson's (Weintraub et al., 2006; Weintraub, 2008; Weintraub, 2009; Voon, 2015).

Therefore, a combination of neurodegeneration in both groups of PwP in the current study may lead to a change in impulsivity, but according to the overdose hypothesis PwP+ICDs may show an increase in impulsivity more generally across different dimensions. This is the first time that a pre-registered study has used multiple tasks with these three groups of participants. For each task, we will identify a key dependent variable on which to compare the three groups, with planned

comparisons (two-tailed) between PwP and PwP+ICDs, as well as PwP and HCs. This provides the basis for our confirmatory pre-registered analyses. We will pre-register additional comparisons on a purely exploratory basis, which will be clearly identified as such. Any results arising from these data must be replicated in an independent sample in future research.

The authors confirm that the pre-registration plans were completely finalised after testing two pilot participants and one Patient and Public Involvement volunteer but before data collection for this analysis had commenced. The document was, however, uploaded after data collection had commenced.

3 Participants and recruitment

Sample size is limited by available resources including funding and available opportunities to recruit people with Parkinson's and ICDs. Therefore, we will include the following numbers of participants:

- 25 people with diagnosed idiopathic Parkinson's (with no history of ICDs)
- 25 people with diagnosed idiopathic Parkinson's (with an active ICD)
- 25 control participants without Parkinson's

If any participants need to be excluded from the study after arriving for testing (they chose to withdraw from the study, were not eligible for any reason according to the inclusion/exclusion criteria), they will be replaced with a new participant. However, we will not replace participants if they only need to be excluded from specific tasks (due to difficulties with instructions, technical problems, or if a participant chooses to participate in some tasks but not others), but we will fully report all reasons for exclusion.

All participants will be between the ages of 50-80 and we will aim to age-match participants as closely as possible between each group. We will check for age differences between groups with a one-way between-subjects ANOVA and post-hoc independent t-tests. However, ICDs are known to be associated with age (Weintraub et al, 2010), and therefore significant age differences may still occur as a feature of the samples.

Participants will be free from any other neurological or mental health problems except depression and anxiety (as these commonly co-occur with Parkinson's). Participants must not be undergoing deep brain stimulation treatment or participating in a treatment manipulation clinical trial.

Participants will be recruited from a variety of sources. Our lab (Body Eyes and Movement, or BEAM) at the University of Manchester has an existing database of PwP and HCs who have consented to be contacted for future research opportunities (GDPR compliant). These volunteers will be approached in the first instance. The study is also listed on the National Institute for Health Research Clinical Research Network Portfolio which aims to promote recruitment for health research in the UK. PwP will additionally be recruited through established networks with the Movement Disorders clinic at Salford Royal NHS Foundation Trust, an advertisement on the Parkinson's UK website, and links with local Parkinson's support groups. Many HCs will be recruited as friends and family of participants with Parkinson's, but we will also aim to recruit HCs from other sources such as the University of the Third Age (U3A), poster advertisements at the University of Manchester and in local community, and an online advertisement on the Salford Citizen Science website. Due to funding constraints, our recruitment strategy will focus primarily on the immediate Greater Manchester area, and branch out geographically if we exhaust our more local options.

Participants (and their companion's) will be reimbursed for any relevant travel expenses to and from the university and for those participants that elect to complete two session on the same day we will provide them with lunch on the university campus. Participants will also be provided with refreshments throughout the sessions.

All participants will be tested at the University of Manchester. The study has received ethical approval from the NHS Research Ethics Committee and Health Research Authority (Ref: 19/NW/0094).

4 Neuropsychological assessment

Participants will be excluded if they meet criteria for dementia according to the Montreal Cognitive Assessment (MoCA; a score of 25/30 or below) which has been validated for use in Parkinson's (Gill, Freshman, Blender, & Ravina, 2008; Nasreddine et al., 2005; Zadikoff et al., 2008). All participants will complete the Geriatric Depression Scale to quantify depression (Yesavage et al., 1982). Parkinson's participants will be allocated to the ICD or non-ICD group based on whether they score positively for any ICDs according to the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) which screens for current experiences of ICDs (gambling, sex, eating, hobbyism, punding, walkabout, and medication abuse) lasting a period of 4 weeks or more (Weintraub et al., 2009). The QUIP Rating Scale (QUIP-RS) will then be used to probe the severity of all potential ICDs according to the recommended cut-offs (Weintraub et al., 2012). We will use the same questionnaire to exclude healthy (both younger and older) participants if they are experiencing non-Parkinson's ICDs (except the questions about dopamine medication abuse).

We also intend to exclude participants that have a past (remitted) ICD by using the version of the QUIP that specifically assesses history of ICD. However, we are currently unsure of the proportion of people with Parkinson's with a remitted ICD as understanding, diagnosis, and prevalence of ICDs are still under-researched. Therefore, as a purely exploratory endeavour, we will still ask these volunteers to participate in the session and complete an exploratory analysis between this group and the Parkinson's with and without ICD groups on the main dependent variables if enough potential participants fit this group.

All Parkinson's participants will undergo the motor section of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS; Goetz et al., 2008) to assess their motor symptoms and identify the Hoehn & Yahr staging of disease severity (1967). Additionally, three extra questions from section 2 (motor experiences of daily living) of the MDS-UPDRS will be used to classify the patients as having tremor dominant or postural instability and gait dominant Parkinson's (Stebbins et al., 2013) as this may differentially affect impulsivity (Tolleson et al, 2017; Wylie et al., 2012). We will calculate the levodopa-equivalent daily dose (LEDD) according to the recommendation by Tomlinson et al. (2010), once for dopamine agonists and once for dopamine agonists and levodopa. We will ask PwP whether they experience significant (subjectively) ON/OFF fluctuations with their medication. Data will be reported in *Table 1*.

Table 1. Demographic and neuropsychological details of participants

	PwP+ICD	PwP-ICD	HC
Age (years)	Mean ± SD (Range)	Mean ± SD (Range)	Mean ± SD (Range)
Gender (M/F)	N/N	N/N	N/N
MoCA	Mean ± SD (Range)	Mean ± SD (Range)	Mean ± SD (Range)
GDS	Mean ± SD (Range)	Mean ± SD (Range)	Mean ± SD (Range)

MDS-UPDRS (Section III)	Mean ± SD (Range)	Mean ± SD (Range)	
H&Y stage	Mean ± SD (Range)	Mean ± SD (Range)	
Parkinson's duration (years)	Mean ± SD (Range)	Mean ± SD (Range)	
TD/PIGD	N/N	N/N	
Dopamine agonist LEDD	Mean ± SD (Range)	Mean ± SD (Range)	
Dopamine agonist + levodopa LEDD	Mean ± SD (Range)	Mean ± SD (Range)	
ICD and QUIP-RS	• N gambling (Mean ± SD (Range)) • N sex (Mean ± SD (Range)) • N eating (Mean ± SD (Range)) • N hobbyism (Mean ± SD (Range)) • N punding (Mean ± SD (Range)) • N walkabout (Mean ± SD (Range)) • N medication abuse (Mean ± SD (Range))		

MoCA = Montreal Cognitive Assessment, GDS = Geriatric Depression Scale, MDS-UPDRS = Unified Parkinson's Disease Rating Scale, H&Y = Hoehn & Yahr, TD/PIGD = tremor dominant/postural instability and gait dominant, LEDD = Levodopa Equivalent Daily Dose, QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale. [1] denotes significant differences between PwP and PwP+ICD groups, and [2] denotes significant differences between the PwP and HC groups. [3] The hobbyism and punding scores are given a combined severity rating in the QUIP-RS, [4] The QUIP-RS does not score the severity rating of walkabout behaviour.

5 Design

In this cross-sectional, between-groups design, and over a maximum of two sessions lasting no more than 3 hours each and taking place no more than 2 weeks apart, participants will complete a variety of tasks and assessments which measure different aspects of impulsivity. Tasks and questionnaires will be pseudo-counterbalanced across all participants to prevent order effects, provide adequate breaks from the screen in order to reduce fatigue, and to minimise the time spent writing in succession as these may adversely affect PwP. We will counterbalance order using 5 different possible orders and each consecutive participant within each group will use testing order n where $n \in (1{:}5)$, looping so that within each group of 25 participants, 5 participants complete each testing order. If a participant is excluded and replaced, the next participant within that group will receive the excluded participant's counterbalanced order. Some aspects of the testing session will be in a fixed order (see Table 2).

Table 2. Order of testing. Five possible orders were chosen by shuffling the list of computer-based tasks and paper/verbal tasks within each session. These lists were then placed in a fixed order of computer/paper tasks to ensure reduced fatigue from screen time. Some aspects were in a fixed order, such as participant background details, the QUIP questionnaires, and the GDS questionnaire. We also ensured that the Go/No-Go and Stop Signal tasks did not occur together. Within each group, 5 participants will complete each testing order.

	Order #1	Order #2	Order #3	Order #4	Order #5
• Briefing, Participant Information Sheet, consent form • Demographic details (date of birth, sex)					

	Order #1	Order #2	Order #3	Order #4	Order #5
• Double check exclusion criteria (history of, or current experience of, neurological or mental health problems, undergoing deep brain stimulation, currently participating in an interventional clinical trial) • Cognitive assessment (Montreal Cognitive Assessment) • Co-morbidities, medications and dosages • GP details (name and address) • (PwP only) Parkinson's duration according to participants' best estimation					
	Session 1				
Computer	Iowa Gambling Task	Iowa Gambling Task	Eriksen Flanker Task	Go/No-Go	Stop Signal Task
Computer	Stop Signal Task	Go/No-Go	Go/No-Go	Eriksen Flanker Task	Eriksen Flanker Task
Other	Stroop	Behavioural Inhibition & Approach Systems	UPPS-P	Behavioural Inhibition & Approach Systems	UPPS-P
Other	Trail Making Test	Barratt Impulsiveness Scale	Trail Making Test	Barratt Impulsiveness Scale	Behavioural Inhibition & Approach Systems
Computer	Eriksen Flanker Task	Stop Signal Task	Iowa Gambling Task	Stop Signal Task	Iowa Gambling Task
Computer	Go/No-Go	Eriksen Flanker	Stop Signal Task	Iowa Gambling Task	Go/No-Go
• PwP only: UPDRS, H&Y • QUIP-current • QUIP-current-severity • QUIP-past					
	Session 2				
Computer	Cambridge Gambling Task	Kirby Delay Discounting	Balloon Analogue Risk Task	Kirby Delay Discounting	Cambridge Gambling Task
Other	UPPS-P	Trail Making Test	Barratt Impulsiveness Scale	UPPS-P	Trail Making Test
Other	Behavioural Inhibition & Approach Systems	UPPS-P	Behavioural Inhibition & Approach Systems	Stroop	Barratt Impulsiveness Scale
Other	Barratt Impulsiveness Scale	Stroop	Stroop	Trail Making Test	Stroop
Computer	Kirby Delay Discounting	Cambridge Gambling Task	Cambridge Gambling Task	Balloon Analogue Risk Task	Balloon Analogue Risk Task
Computer	Balloon Analogue Risk Task	Balloon Analogue Risk Task	Kirby Delay Discounting Task	Cambridge Gambling Task	Kirby Delay Discounting
• Geriatric Depression Scale • Debrief					

Due to the practical set-up of the laboratory, the study will be completed on two separate computers in two separate rooms. All the tasks within Session 1 will be completed in Room 1 and all the tasks within Session 2 will be completed in Room 2 to enable two participants to take part simultaneously. Due to this constraint, some participants will complete Session 1 first and some will complete Session 2 first. Where possible we will try to ensure that a mixture of participants complete Session 1 and 2 first within each testing order, but this may not always be possible.

The researchers responsible for data collection (JSP and MM) are not blind to the purposes of the study. We will not attempt to blind the researchers as to which group participants belong to, as this is very difficult when PwP present with visible motor complications such as bradykinesia and tremor, and JSP is the only researcher responsible for data collection who is trained in performing the UPDRS in people with Parkinson's.

All computer tasks will either be run on Computer 1 (in Session 1) with a refresh rate of 60Hz and a screen resolution of 1920x1080px, or Computer 2 (in Session 2) with a refresh rate of 75Hz and a screen resolution of 1024x768px. This is to facilitate parallel testing rather than due to task requirements. All tasks on Computer 1 will be completed in a darkened room to reduce visual noise as these tasks require concentration and measures of response time. The lights will be turned on during breaks and between tasks. The tasks on Computer 2 will not be completed in darkness as these tasks do not require the same precision in vision, attention, and responding, which allows us to reduce potential fatigue in our participants.

6 Data processing

As we use similar data pre-processing methods for more than one task, we will detail the common methods here and refer back to them for each separate task description and add any deviations where appropriate. All analyses will be completed in R (with RStudio).

6.1 At the individual participant level

For response time (RT) measures we will trim RT data firstly by removing anticipatory RTs (< 150ms) as these are likely to have been initiated prior to stimulus/target onset. Remaining RT outliers will be removed per participant, per condition using a non-recursive moving SD criterion as detailed by Van Selst and Jolicoeur (1994), and as implemented by Grange (2015) in the trimR package for R.

6.2 At the group level

After calculating the mean RTs for remaining trials for each condition and for each participant, we will remove outliers per condition that fall beyond the upper and lower boundaries using Tukey's (1997) boxplot method. These boundaries are calculated as 3 multiplied by the interquartile range, i.e. the difference between the 25th and 75th percentiles as per the following formulae:

$$Upper\ boundary = Q3 + (3 * (Q3 - Q1))$$

$$Lower\ boundary = Q1 - (3 * (Q3 - Q1))$$

RT data will then be checked that they do not violate the assumptions of normality according to the Shapiro-Wilk test and, if necessary, we will use a log10 transformation on that variable (and any other variables to be included within the same statistical test) for all groups. If the data are then normally distributed, we will proceed with parametric inferential statistical tests, but if the data continue to be non-normally distributed, we will proceed with the equivalent non-parametric test on the original, untransformed, data.

7 Statistical analyses

For almost all dependent variables (unless stated otherwise), data that are expected to be normally distributed (and either do not violate the assumptions of normality with the Shapiro-Wilk test *or* are successfully transformed) will be analysed with a one-way between-subjects ANOVA with a factor of group (levels: PwP, PwP+ICDs, HCs) with planned independent t-tests for the following group pairs: PwP and PwP+ICDs, PwP and HCs. If data are expected to be non-normal (and verified as such with the Shapiro-Wilk test) *or* remain non-normal after attempting transformation, they will be analysed with a Kruskal-Wallis test with planned Mann-Whitney U group comparisons (PwP and PwP+ICDs, PwP and HCs).

8 Tasks and measures

In the following sections of the document we will, for each task, highlight the dependent variable(s) of interest that form part of our confirmatory analysis plans. We will additionally plan, and clearly distinguish, exploratory analysis for any other variables.

8.1 Go/No-Go task (action restraint)

The task was programmed with the PsychoPy coder (Peirce, 2007, 2009) and will be run on computer 1. All stimulus timings are locked to the refresh rate. On a plain grey background, a central white fixation cross (100px) is presented for a fixed duration of 500ms followed by a variable blank delay of between 250-500ms drawn from a rectangular distribution. Go and No-Go stimuli are black uppercase letters (Go signals: A, E, I, O, or U; No-Go signal: K; all 250px) which are presented centrally for 150ms followed by a blank duration of 1500ms, during which participants are expected to respond by pressing the spacebar on Go trials or withhold their response on No-Go trials. It is recommended that the Go/No-Go task has a proportion of 20% No-Go trials or less, a variety of Go signals to maximise the number of false alarms, and a maximum of 1500ms in which participants can respond in order to encourage fast responses (Elson, 2017; Wessel, 2018; Young, Sutherland, & McCoy, 2018). The current study has 17% No-Go trials and a maximum of 1650ms to respond to account for the possibility for people with Parkinson's to make slower motor responses generally, whilst still encouraging speeded responses. There are a total of 360 randomly ordered trials presented in blocks of 90 trials, with trials within each block randomly and independently shuffled for each participant. The total task lasts approximately 10-15 minutes, and participants will be encouraged to take a break at the end of each block. Participants will complete 12 practice trials initially which includes written feedback ("Correct", "Missed", "Incorrect") on each trial that is not present in the main task. They will be able to repeat the practice block until they are comfortable with the task instructions.

Participants will only be included in the analysis if they complete 80% or more of available trials. We will remove RT outliers according to the method detailed above, where per condition outlier removal refers to correct Go and incorrect No-Go trials only (see Data processing).

8.1.1 Key dependent variable

Commission errors will be calculated as the percentage of No-Go trials on which participants failed to withhold their response and, instead, erroneously pressed the spacebar.

8.1.2 Confirmatory analysis

Commission errors (expected to be non-normal) will be analysed using the appropriate statistical tests as outlined in the Statistical analyses section.

8.1.3 Exploratory analysis

RTs for correct Go and failed No-Go trials (expected to be normally distributed) will be analysed using the appropriate statistical tests as outlined in the Statistical analyses section.

Omission errors (which will not be affected by the outlier removal process and are expected to be non-normal) will also be reported, although we expect there to be a very small number of them.

8.2 Stop Signal task (response inhibition)

The task was programmed with the PsychoPy coder and will be run on computer 1. All stimulus timings are locked to the refresh rate. A central light grey fixation cross (size: 175px) is presented on a grey background for 500ms followed by a variable blank delay of between 250-500ms drawn from a rectangular distribution. The Go signal (a green left or right chevron arrow, size: 600px) is then displayed centrally for 70ms. On Stop trials, the Go signal is followed by a centrally displayed Stop signal (a hollow red square, size: 650px) for 70ms, following a variable stop signal delay. The stop signal delay starts at 205ms (after the onset of the Go signal) on the first Stop trial and then subsequently increases or decreases by 50ms following a successful or unsuccessful stop trial respectively, in a one-up/one-down fixed-step staircase procedure. The minimum stop signal delay is 5ms after Go signal onset and the maximum is 1505ms.

On all trials there is a maximum duration of 1500ms plus the current stop signal delay during which participants are expected to respond or withhold their response depending on the trial type. If a participant responds, the trial ends 500ms after the response time instead. In accordance with the consensus recommendations from Verbruggen et al. (2019), a Stop signal is present on 25% of trials. There are a total of 384 randomly ordered trials split into 4 blocks of 96 trials (the trials in each block were randomly and independently shuffled for each participant) and participants will be encouraged to take a break at the end of each block. At the end of each block we will present the participant with feedback based on their performance in the last block. Specifically, they will be able to see their median response time for all trials on which they provided a response, and they will receive a feedback message based on their Stop accuracy. If their Stop accuracy in the last block was less than or equal to 40% they will receive the message "Try and stop yourself from pressing the button when you see the red square", for between 40% and 60% accuracy the message will read "Remember to keep responding as QUICKLY yet as ACCURATELY as you can", and if accuracy is greater than or equal to 60% the message will read "Try to respond to the arrows quickly without waiting to see if the red square appears". We hope this will further encourage participants to adhere to task instructions.

Verbruggen et al. (2019) have suggested a minimum of 50 Stop trials when participants are behaving optimally and others have suggested that 72 Stop trials is optimal (Campbell, Chambers, Allen, Hedge, & Sumner, 2017). We expect our sample to be more variable but, given the limitation of our sample size, using more than 96 Stop trials is unlikely to contribute to an increase in overall power (Baker et al., 2019). Participants will complete 12 practice trials with written feedback ("Correct go", "Incorrect arrow", "Missed arrow", "Failed stop", or "Successful stop") that is not present in the main task. They are able to repeat the practice block until they are comfortable with the task instructions.

Participants will only be included in the analysis if they complete 80% or more of available trials. As recommended by Congdon et al. (2012) we used the following outlier criteria to further exclude participants: (1) less than 25% or greater than 75% Stop accuracy, (2) responding on less than 60% of Go trials, (3) greater than 10% errors (responding to the wrong arrow) on Go trials, and (4) stop signal reaction time estimate that is negative or less than 50ms as this indicates that the race model has been violated and a stop signal reaction time should not be estimated (Verbruggen et al,, 2019). These criteria are more likely to produce a balance between reliable stop signal reaction times, retaining a suitable number of participants, and keeping within-subject variance low (Congdon et al., 2012). RTs on Go trials (except missed trials) and unsuccessful Stop trials will be subjected to the per participant outlier removal process as detailed in the *Data processing* section. After calculating the mean RTs for each participant, we will remove outliers at the group level and test for normality using the same methods detailed in the *Data processing* section.

8.2.1 Key dependent variable

Stop signal reaction time will be calculated according to the integration method (Verbruggen et al., 2019).

We will use all Go trials (this includes choice errors or anticipatory errors, whereas for omission errors we will assign the maximum RT recorded for that participant), and subtract the mean SSD from the *n*th percentile of the Go-RT distribution, where *n* is the percentage of failed stops (Verbruggen & Logan, 2009; Verbruggen et al., 2019).

8.2.2 Confirmatory analysis

Stop signal reaction time (expected to be normally distributed) will be analysed using the appropriate statistical tests as outlined in the *Statistical analyses* section.

8.2.3 Exploratory analysis

Additionally, and following the same outlier removal procedure as detailed above, the average RT on Go trials (expected to be normally distributed) will be analysed using the appropriate statistical tests as outlined in the Statistical analyses section.

Furthermore, the percentage of correct Go trials and correct Stop trials (the latter of which should be approximately 50% due to the staircase procedure) are expected to be non-normal and will be analysed using the appropriate statistical tests as outlined in the *Statistical analyses* section.

8.3 Eriksen Flanker task (response conflict)

The task was programmed with the PsychoPy coder based on a version by Jangraw (2015) and will be run on computer 1. All stimulus timings are locked to the refresh rate. On a plain grey background, a black fixation cross (30px) is presented centrally for a fixed duration of 500ms followed by a variable blank delay of between 50-250ms drawn from a rectangular distribution.

Stimuli are black Unicode arrows (size: 4° visual angle) pointing either to the left (U+2190) or right (U+2192). First, following the variable delay, four parallel arrows (flankers) are presented on the screen all pointing in the same direction, so that two arrows are above the centre of the screen and two arrows are below the centre of the screen with a gap between each pair. 50ms after the flanker arrows' onset, a single target arrow is presented in the centre of the screen that can either be pointing in the same direction as the flankers (congruent) or the opposite direction (incongruent). After a further 50ms both the target arrow and flanking arrows disappear. Presentation times are based on findings by Mattler (2003). Participants are instructed to ignore the direction of the

surrounding (flanking) arrows and respond according to the direction of the central target arrow. The maximum time in which participants can respond is within 1550ms of target onset. There are a total of 440 trials (220 congruent, 220 incongruent) presented in five blocks of 88 trials each, with equal numbers of congruent and incongruent trials within each block. Trial order is shuffled randomly and independently for each participant. The task lasts approximately 20 minutes, and participants will be encouraged to take a break at the end of each block. Participants will complete 2 blocks of 8 practice trials initially which includes written feedback ("Correct", "Missed", "Incorrect") after each trial that is not present in the main task. They will be able to repeat the practice block until they are comfortable with the task instructions. At the end of each block, in both the practice and main task, participants will be able to see their median RT for that block as well as their overall accuracy. This is to encourage participants to try and make speeded yet accurate responses.

Participants will only be included in the analysis if they complete ≥80% of available trials. We will use the same outlier removal process at the participant level and the group level for each condition as detailed in the *Data processing* section.

8.3.1 Key dependent variable

The interference effect will be calculated by subtracting the mean correct RT for congruent trials from the mean correct RT for incongruent trials.

8.3.2 Confirmatory analysis

The interference effect (expected to be normally distributed) will be analysed using the appropriate statistical tests as outlined in the Statistical analyses section.

8.3.3 Exploratory analysis

The proportion of correct incongruent trials (expected to be non-normal) will be analysed using the appropriate statistical test as outlined in the *Statistical analyses* section. To analyse the interaction between the factors of condition (congruent, incongruent) and group (PwP, PwP+ICDs, HCs), a two-way mixed ANOVA will be used to analyse the mean RT on correct trials. We expect RT on incongruent trials to be slower than congruent trials for all groups.

8.4 Stroop Task (response conflict, set-switching)

We will firstly check (verbally) whether participants experience colour-blindness and if they do then they will not participate in this task. Participants complete four conditions, each of which is presented upon an A4 card; two are without interference where Card A requires colour naming (participants must state the ink colour of square patches) and Card B requires word naming (participants must simply read the words which are all in black ink on white paper). Card C introduces inhibitory control as participants must state the ink colour of colour-words and inhibit the automatic tendency to read the word itself, and Card D contains a mixture of inhibitory control and task switching as participants must state the word if it is outlined by a black square but state the ink colour if the word is not outlined.

Each condition has 10 practice trials and 50 experimental trials, and the instructions are standardised and read aloud by the researcher before each condition. Participants will repeat the practice once more if they get more than 50% uncorrected errors to make sure they understand task instructions. Participants are timed for the experimental trials within each condition from the moment the researcher says the word "Go" until the time at which the participant says their final answer. Completion times, uncorrected errors, and self-corrected errors will be recorded for each condition. If participants are unable to complete card A or B (10 or more uncorrected errors), it will be interpreted as an inability to follow task instructions, and so they will not complete Card C and D and will be excluded from analysis.

8.4.1 Key dependent variable

The interference effect is calculated by subtracting the time taken to complete Card A from the time taken to complete Card C (Jensen, 1965; Macleod, 1991).

8.4.2 Confirmatory analysis

The interference effect (expected to be normally distributed) will be analysed using the appropriate statistical tests as outlined in the *Statistical analyses* section.

8.4.3 Exploratory analysis

Switch cost will be calculated by subtracting the time taken to complete Card C from the time taken to complete Card D. The switch cost (expected to be normally distributed) will be analysed using the appropriate statistical tests as outlined in the *Statistical analyses* section.

8.5 Trail Making Test (set-switching)

Participants will complete Trail A and Trail B. Trail A requires participants to draw a line chronologically between the numbers 1-25 without lifting their pencil from the paper. Trail B is similar except participants must alternate between numbers and letters (1-A-2-B etc). For both trails, the researcher provides verbal standardised instructions and demonstrates the task on a sample sheet. The participant is timed whilst they complete the trail and in the event of an error the researcher instructs the participant to return to the last correct circle, and if the participant misses a circle they will be reminded to touch all circles. The clock is stopped when the end is reached. We will report the time taken to complete part A and the time taken to complete part B.

8.5.1 Key dependent variable

The time taken to complete part B minus the time taken to complete part A will provide an estimation of task switching that accounts for individual differences in motor slowing, which is likely to disproportionately affect the Parkinson's participants.

8.5.2 Confirmatory analysis

The key dependent variable (expected to be normally distributed) will be analysed using the appropriate statistical tests as outlined in the Statistical analyses section.

8.5.3 Exploratory analysis

We will compare the raw scores for the time taken to complete part B (expected to be normally distributed) between groups using the appropriate statistical tests as outlined in the *Statistical analyses* section.

8.6 Balloon Analogue Risk Task (decision making under ambiguous risk)

The task was programmed with PsychoPy builder (Peirce et al., 2019) and will be run on computer 2. Participants are instructed to try to win as many points as possible by blowing up a computerised balloon (Rogers et al., 1999). Participants start with 0 points and earn 5 points with each pump of the balloon by pressing the spacebar, but each pump increases the chance of the balloon popping. Participants can choose to bank their points and move on to the next trial at any point, but if the balloon pops before they manage to do so they will lose their points for that trial. There are 30 trials with a maximum number of pumps between 1 and 88 before the balloon pops, spaced at 3 pump intervals. Each participant receives the same trials but in an order shuffled randomly and independently for each participant. Participants first complete two practice trials, where the maximum pump was set to 88 and 43 respectively, so that all participants start with a similar anchor.

As the continuous pressing of the spacebar may be difficult for people with Parkinson's, we will end the task early if any participant takes longer than 15 minutes to complete the task, or if the participant is uncomfortable performing repeated manual movements. Participants will only be included in the analysis if they complete 100% of available trials. Participants will be excluded if they have no unexploded balloons at the end of the task. No trials will be removed at the participant level, but outliers at the group level will be removed as detailed in the *Data processing* section.

8.6.1 Key dependent variable

The adjusted average number of pumps on unexploded balloons serves as the main variable of interest, as the number of pumps on exploded balloons is constrained by the task and not the participants' own risk-taking behaviour (Lejuez, 2002, 2003).

8.6.2 Confirmatory analysis

The key dependent variable (expected to be normally distributed) will be analysed using the appropriate statistical tests as outlined in the Statistical analyses section.

8.6.3 Exploratory analysis

We will compare the difference in exploded and unexploded balloons ($Balloons_{unexploded} - Balloons_{exploded}$), where a positive score indicates more risk averse behaviour (less unexploded balloons) and a negative score indicates more risk taking behaviour (more unexploded balloons). The data are expected to be normally distributed and will be analysed using the appropriate statistical tests as outlined in the *Statistical analyses* section. We will also compare the final points total (expected to be normally distributed) in the same way.

8.7 Iowa Gambling Task (decision making under ambiguous risk)

The task was an edited version of one originally programmed by Freegard (2015) in OpenSesame (Mathôt, Schreijj, & Theeuwes, 2012). Participants sequentially draw 100 cards from 4 possible decks in any order of their choosing by clicking the mouse on their selection. Decks A and B give hypothetical rewards of £100 each time, but also have the possibility of infrequent high loss (deck A) or frequent high loss (deck B), which results in an overall net loss. Decks C and D give smaller rewards of £50 each time, but with smaller overall losses; deck C contains frequent low losses and deck D contains infrequent low losses. Therefore, decks A and B are the bad decks (overall net loss) and decks C and D are the good decks (overall net gain). Over the course of 100 trials, participants should learn to preferentially select from the good decks. Within each 10 consecutive choices within each card a fixed set of outcome possibilities are randomly and independently shuffled for those 10 trials for that participant. Participants have unlimited time to choose their cards per trial and will therefore be encouraged to take a break whenever they wish. Participants will be told that the goal was to accumulate as much hypothetical money as possible, and a points total was displayed at the top of the screen which started at £2000 and changed depending on the participants' previous card selection. A previous total was displayed too so that participants were able to reflect on gains and losses per trial.

Participants will only be included in the analysis if they complete 100% of available trials.

8.7.1 Key dependent variable

Total score (number of choices from advantageous card decks minus number of choices from disadvantageous card decks).

8.7.2 Confirmatory analysis

The total score (expected to be normally distributed) will be analysed using the appropriate statistical tests as outlined in the *Statistical analyses* section.

8.7.3 Exploratory analysis

For each consecutive 20 choices (1-20, 21-40, etc) we will calculate the total score for that bin (number of choices from advantageous decks minus number of choices from disadvantageous decks). We will do a two-way mixed ANOVA with a factor of group (PwP, PwP+ICD, HC) and a factor of bin (1-20, 21-40, 41-60, 61-80, 81-100) with the total score as the dependent variable. We will explore any main or interaction effects with post-hoc tests.

8.8 Cambridge Gambling Task (decision making under objective risk)

The task was programmed in PsychoPy coder and is based on the original task as described by Rogers et al. (1999). It will be run on computer 2 and full details can be found in Figure 1. Participants must choose whether a (randomly) hidden yellow token is under a red box or a blue box, depending on the ratio of 10 red and blue boxes displayed at the top of the screen (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1). After selecting their choice with the left (z) or right (m) keys, they must place a stake on their decision. The stake is a percentage of the current points total (which starts at 100 points on the first trial) which is displayed numerically to the participant but is equivalent to 5%, 25%, 50%, 75%, and 95% of the points total. The possible bet choices either ascend or descend in order at intervals of 1500ms and the participant must press the spacebar to select their choice; if they don't respond, the final stake option that was presented is chosen automatically. On half of blocks the stake choices ascend and on the other half they descend; half of participants completed the ascending condition first and half completed the descending condition first in a counterbalanced design. The location of the token is then revealed and their stake added or subtracted from their points total depending on whether their decision was correct or incorrect respectively. If the participants' score reaches 1 point or less, the block ends and the bank resets to 100 points for the next block. Each block contains 9 trials with each possible ratio of box colours (the trial order within each block is randomly and independently shuffled per participant), and there are 4 ascending blocks and 4 descending blocks. The task takes approximately 20mins and participants will be encouraged to take a break at the end of each block.

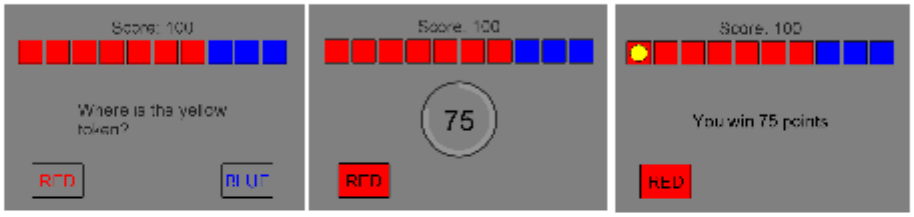

Figure 1. In the Cambridge Gambling Task participants must select the box colour they believe contains the hidden yellow token (left panel) and then place a stake on their choice (middle panel) where the options are shown in increasing or decreasing order and are always equal to 5%, 25%, 50%, 75% and 95% of their current points total. The yellow token is revealed (right panel) and their total winnings for that trial displayed, which gets added to their points total on the next trial.

Participants will only be included in the analysis if they complete at least 3 out of 4 blocks in each condition (ascending/descending). The data for trials where the box ratios were 5:5 will not be used for analysis.

Deliberation times will be characterised as the mean time taken to choose between the red or blue options for each of the box ratios (9:1, 8:2, 7:3, 4:6). However, if participants stop actively deliberating during the task, for example by distractions or talking, this will be noted by the researcher and that trial will be excluded from deliberation time analysis. We will also measure the quality of decision making, which is the % of choices that align with the most likely outcome.

8.8.1 Key dependent variable

Risk adjustment will be calculated as the % of total points score participants were prepared to risk in order to earn more points as a function of the box ratio, according to the following formula:

$$Risk\ adjustment\ index\ = \frac{(2 * (\%bet\ 9{:}1)) + (\%bet\ 8{:}2) - (\%bet\ 7{:}3) - (2 * (\%bet\ 6{:}4))}{Average\ \%\ bet}$$

Where $\%bet$ refers to the average bet (out of the possible options of 5%, 25%, 50%, 75%, and 95%) chosen for that ratio, and where higher risk adjustment index scores are indicative of less risky decision making (DeVito et al., 2008).

8.8.2 Confirmatory analysis

The risk adjustment index (expected to be normally distributed) will be analysed using the appropriate statistical tests as outlined in the *Statistical analyses* section.

8.8.3 Exploratory analysis

Deliberation times (expected to be normally distributed) will be analysed with a two-way mixed ANOVA with a factor of group (PwP, PwP+ICD, and HC) and box ratio (9:1, 8:2, 7:3, 6:4). We expect deliberation times to be shorter for bigger ratios and longer for smaller ratios. We will perform post-hoc t-tests on any significant main or interaction effects.

Quality of decision making (expected to be non-normal) will be analysed using the appropriate statistical tests as outlined in the *Statistical analyses* section.

8.9 Kirby Delay Discounting (delay discounting)

Participants will be presented with two hypothetical options per trial. Option A will be a smaller reward that can be received now, and option B will be a larger reward that can be received at a delay of *x* days; the options are taken directly from the 27 item Kirby delay discounting questionnaire (Kirby, Petry, & Bickel, 1999). The options will be displayed within a PowerPoint presentation on computer 2 in a fixed order, and the researcher will manually record the participants' verbal responses. The data will be processed according to the method described in Kaplan et al. (2016). Briefly, the *k* value will be calculated for each item using the formula $k = \frac{\frac{A}{V}-1}{D}$ where V is the smaller immediate reward, A is the larger delayed reward, and D is the delay in days. At the participant level, the *k* values will be sorted from smallest to largest and consistency will be calculated for each item by summing how many times they selected the smaller delay for all items with a smaller k and how many times they selected the larger delay for all items with a larger *k*, and then dividing this total number by the total number of items (27). However, when calculating individual *k* values for each magnitude of large reward (small: £25, £30, £35; medium: £50, £55, £60; large: £75, £80, £85) the total number is instead divided by 9. The *k* with the highest consistency score is identified for that participant.

As participants will be responding verbally at a pace controlled by the researcher, no missing data is expected to occur.

8.9.1 Key dependent variable

k **(delay discounting index) value with the highest consistency score.**

8.9.2 Confirmatory analysis

The delay discounting index, *k* (expected to be normally distributed), will be analysed using the appropriate statistical tests as outlined in the *Statistical analyses* section.

8.9.3 Exploratory analysis

The delay discounting index, *k* (expected to be normally distributed), will be analysed separately for each magnitude of larger delayed reward (small, medium, large).

8.10 Barratt Impulsiveness Scale (trait impulsivity)

The Barratt Impulsiveness Scale (Patton, Stanford, & Barratt, 1995) comprises 30 questions assessing impulsivity, with the following factors: attention and cognitive instability (attentional impulsivity), motor and perseverance (motor impulsivity), and self-control and cognitive complexity (non-planning impulsivity. To reduce the number of potential missing values, we will ask participants to check they have filled in every question once they have finished. If there are still any missing values after this (or items where the participant accidentally circled more than one answer), we will replace them with the median value for that 2nd order factor (attentional, motor, or non-planning impulsivity). We chose to replace missing values with the median because with such a small number of items, this is less likely to be skewed by an extreme value on some other item in that factor. If there are more than 2 missing values on any 2nd order factor we will exclude that participant from analysis.

8.10.1 Key dependent variable

Mean total score.

8.10.2 Confirmatory analysis

The mean score (expected to be normally distributed) will be analysed using the appropriate statistical tests as outlined in the *Statistical analyses s*ection.

8.10.3 Exploratory analysis

The mean scores for the 2nd order factors (attentional, motor, and non-planning impulsivity) will each be analysed separately using the appropriate statistical tests as outlined in the *Statistical analyses* section.

8.11 Behavioural Inhibition Systems/Behavioural Approach Systems (sensitivity to punishment/reward)

The Behavioural Inhibition System/Behavioural Approach System questionnaire (BIS/BAS; Carver & White, 1994) consists of 24 questions that probe BAS Drive, BAS Fun Seeking, BAS Reward Responsiveness, and BIS, where the BAS measures relate to sensitivity to reward and the BIS measure to sensitivity to punishment. To reduce the number of potential missing values, we will ask participants to check they have filled in every question once they have finished. If there are any missing values after this, we will replace them with the median value for that factor (BAS Drive, BAS Fun Seeking, BAS Reward Responsiveness, or BIS). If there are more than 2 missing values on any factor we will exclude that participant from analysis.

8.11.1 Key dependent variable

Mean overall BIS score and mean overall BAS score.

8.11.2 Confirmatory analysis

The mean BIS score and mean BAS score (both expected to be normally distributed) will be analysed separately using the appropriate statistical tests as outlined in the *Statistical analyses* section.

8.11.3 Exploratory analysis

The mean BAS Drive, BAS Fun Seeking, and BAS Reward Responsiveness sub-scales (all expected to be normally distributed) will be analysed separately using the appropriate statistical tests as outlined in the *Statistical analyses* section.

8.12 UPPS-P (trait impulsivity)

The questionnaire comprises 59 questions that measure the following factors of impulsivity: negative urgency and positive urgency (emotion based rash action), lack of premeditation and lack of perseverance (deficits in conscientiousness), and sensation seeking. The mean scores for each 1st order factor will be calculated as long as 70% of the items have been answered (Lynam, Whiteside, Smith, and Cyders, 2006). To reduce the number of potential missing values, we will ask participants to check they have filled in every question once they have finished. If there are any missing values after this, we will replace them with the median value for that factor (negative urgency, positive urgency, lack of premeditation, lack of perseverance, or sensation seeking). If there are more than 2 missing values on any factor we will exclude that participant from analysis.

8.12.1 Key dependent variable

Mean sensation seeking score.

8.12.2 Confirmatory analysis

The mean sensation seeking score (expected to be normally distributed) will be analysed using the appropriate statistical tests as outlined in the *Statistical analyses* section.

8.12.3 Exploratory analysis

The mean negative urgency, positive urgency, lack of premeditation and lack of perseverance scores (all expected to be normally distributed) will be analysed separately using the appropriate statistical tests as outlined in the *Statistical analyses* section.

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Appendix D. Ethical documentation for Chapter 4; Participant information sheet for PwP, participant information sheet for HCs, consent form for both PwP and HCs, and letter of ethical approval.

MANCHESTER 1824
The University of Manchester

IRAS ID: 219356

Examining control of behaviours in Parkinson's

Participant Information Sheet (PIS) for participants with Parkinson's

This PIS should be read in conjunction with The University privacy notice (http://documents.manchester.ac.uk/display.aspx?DocID=37095)

Introduction

You are being invited to take part in a PhD research study. Before you decide whether to take part, it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for taking the time to read this.

Who will conduct the research?

- Jade Pickering, School of Biological Sciences, University of Manchester
- Dr Ellen Poliakoff, School of Biological Sciences, University of Manchester
- Dr Jennifer McBride, School of Biological Sciences, University of Manchester
- Professor Iracema Leroi, School of Biological Sciences, University of Manchester

What is the purpose of the research?

We are interested in how people with Parkinson's behave when faced with different decisions, and how quickly they can respond to different pictures and objects. A small number of people with Parkinson's report that they have problems stopping themselves from engaging in problematic behaviours (e.g. overeating, gambling) or have a tendency to make poor, or risky, choices. We will examine the ways in which people with Parkinson's may be affected by these behaviours.

Why have I been chosen?

We invite you to take part as a participant with Parkinson's. We will compare people with Parkinson's that report these kind of problems with people with Parkinson's that don't have these problems, as well as healthy people of a similar age.

What would I be asked to do if I took part?

If you agree to take part, we will invite you to participate in up to 2 different testing sessions. Your participation will still be very useful, even if you are only able to attend one session. The sessions will take place at the University of Manchester. During the session, we will ask you to complete some questionnaires (for example, about different aspects of your mood and behaviour) and some short memory and thinking tests. We will also ask you to make judgements about different pictures, shapes, and objects on a computer screen, while we measure your response times, hand movements, or eye movements. At each session, we will measure your Parkinson's symptoms by asking you some questions and assessing your movements (for example opening and closing your

hand as quickly as you can). We will also ask you how long you have had Parkinson's, what medication you are currently taking, and for some basic demographic details.

Each session will last under 3 hours and you will have frequent rest-breaks throughout the session. Any expenses which you or a companion (for example, a friend or carer) incur in attending the testing session will be repaid to you in full on the day.

What happens if I do not want to take part or if I change my mind?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason and without detriment to yourself. Simply inform the researcher before, during, or after the session. If you decide to withdraw, your expenses (and those of anyone who accompanies you) will still be reimbursed.

However, it will not be possible to remove your data from the project once it has been anonymised and forms part of the dataset as we will not be able to identify your specific data. This does not affect your data protection rights. Should you lose the capacity to consent at the second visit your data from the first visit will still be retained.

Will my data be used for future research?

When you agree to take part in a research study, information about you may be provided to researchers running other research studies in the BEAM lab at the University of Manchester. The future research should not be incompatible with this research project and will concern Parkinson's. Where your information relates to your health and care it will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/).

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you regarding any other matter or to affect your care. It will not be used to make decisions about future services available to you.

Will I be paid for participating in the research?

You will not be paid for your participation, but any expenses which you or a companion (for example, a friend or carer) incur in attending the testing session will be repaid to you in full on the day.

What is the duration of the research?

The study will involve a total of 2 sessions lasting a maximum of 3 hours each. You may choose to attend both sessions on the same day (one in the morning, one in the afternoon), or on different days at a maximum of 2 weeks apart. If you can only attend one session, this will still be very useful to us.

Where will the research be conducted?

The research will be conducted in the Zochonis Building, Brunswick Street, University of Manchester, M13 9GB.

Will the outcomes of the research be published?

The results of the study will be presented at academic conferences and published in peer-reviewed academic journals. If you wish, we will tell you the results of the study when it ends.

What if there is a problem?

So far as we know, there is negligible risk associated with taking part in the study. You will not be required to change your routine medication in any way, nor will we require you to continue your current course of medication if you wish to discuss changes with your GP, although this may make you ineligible to take part in the second session. However, some of the tests that we use can sometimes indicate the possible presence of undiagnosed dementia, depression, or impulse control disorder(s). Whilst we are not health professionals, and cannot provide you with a diagnosis, we will send a letter to both you and your GP if we believe you may benefit from discussing this further with your GP.

What will happen to my personal information?

In order to undertake the research project we will need to collect the following personal information/data about you:

- Name
- Contact details (to be used to arrange visits with you and speak to you about your participation in the study, such as if we would like further information from you). You can also opt in to be contacted about future studies; if you do not consent to this, we will not use your contact details after study completion.
- A brief medical history including details of medication and treatments for your Parkinson's, the duration of your Parkinson's, and any co-occurring health problems you may have
- Demographic details such as gender, date of birth, education level
- GP details

Only the research team will have access to this information. An anonymised dataset may be uploaded to a data repository in the interests of open science and transparency.

We are collecting and storing this personal information in accordance with the General Data Protection Regulation (GDPR) and Data Protection Act 2018 which legislate to protect your personal information. The legal basis upon which we are using your personal information is "public interest task" and "for research purposes" if sensitive information is collected. For more information about the way we process your personal information and comply with data protection law please see our Privacy Notice for Research Participants
http://documents.manchester.ac.uk/display.aspx?DocID=37095.

The University of Manchester, as Data Controller for this project, takes responsibility for the protection of the personal information that this study is collecting about you. In order to comply

with the legal obligations to protect your personal data the University has safeguards in place such as policies and procedures. All researchers are appropriately trained and your data will be looked after in the following way:

The researchers listed at the end of this information sheet at the University of Manchester will have access to your personal identifiable information, that is data which could identify you, but they will anonymise it within 4 weeks of your visit. However your consent form will be retained for 5 years separately to the study data. All electronic data will be held on secure servers at the University of Manchester, and all paper based data (questionnaires etc) will be held in a locked filing cabinet at the university, accessible only to the researchers.

You have a number of rights under data protection law regarding your personal information. For example you can request a copy of the information we hold about you. This is known as a Subject Access Request. If you would like to know more about your different rights, please consult our privacy notice for research (http://documents.manchester.ac.uk/display.aspx?DocID=37095) and if you wish to contact us about your data protection rights, please email dataprotection@manchester.ac.uk or write to The Information Governance Office, Christie Building, University of Manchester, Oxford Road, M13 9PL. at the University and we will guide you through the process of exercising your rights.

You also have a right to complain to the Information Commissioner's Office (https://ico.org.uk/concerns), Tel 0303 123 1113

Will my participation in the study be confidential?

Your participation in the study will be kept confidential to the study team and those with access to your personal information as listed above. After your visit, your data will be de-identified and only linked back to you via a participant ID known only to the research team and stored separately to your data on a secure server.

There may be circumstances where we need to disclose information to individuals outside the research team:

- In the event that there are concerns about your safety or the safety of others we may need to contact your GP
- In the event of incidental or unexpected findings that could have implications for your health or may need further investigation we may need to inform your GP. We will send a copy of this information to you.
- Individuals from the University, the site where the research is taking place, and regulatory authorities may need to review the study information for auditing and monitoring purposes or in the event of an incident.

If your results are included in a paper published in a medical or scientific journal, or in a presentation given at a conference, you will not be identifiable to anyone else by name or other information.

Confidential data will be destroyed 5 years after the data are published in a scientific journal.

Who has reviewed the research project?

The project has been reviewed by the NHS Research Ethics Committee and received approval from the Health Research Authority.

What if I want to make a complaint?

Minor complaints

If you have a minor complaint then you need to contact the researcher(s) in the first instance.

JADE PICKERING, JADE.PICKERING@POSTGRAD.MANCHESTER.AC.UK

ELLEN POLIAKOFF, ELLEN.POLIAKOFF@MANCHESTER.AC.UK, 0161 275 9333

Formal Complaints

If you wish to make a formal complaint or if you are not satisfied with the response you have gained from the researchers in the first instance then please contact

The Research Governance and Integrity Manager, Research Office, Christie Building, University of Manchester, Oxford Road, Manchester, M13 9PL, by emailing: research.complaints@manchester.ac.uk or by telephoning 0161 275 2674.

What Do I Do Now?

Please discuss this information with your friends, family, and GP if you wish. If you have any queries about the study or if you are interested in taking part then please contact the researcher(s):

JADE PICKERING, JADE.PICKERING@POSTGRAD.MANCHESTER.AC.UK

ELLEN POLIAKOFF, ELLEN.POLIAKOFF@MANCHESTER.AC.UK, 0161 275 9333

The project has been reviewed by the NHS Research Ethics Committee and received approval from the Health Research Authority.

[19/NW/0094]

MANCHESTER 1824
The University of Manchester

IRAS ID: 219356

Examining control of behaviours in Parkinson's and aging

Participant Information Sheet (PIS) for control participants

This PIS should be read in conjunction with The University privacy notice (http://documents.manchester.ac.uk/display.aspx?DocID=37095)

Introduction

You are being invited to take part in a PhD research study. Before you decide whether to take part, it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for taking the time to read this.

Who will conduct the research?

- Jade Pickering, School of Biological Sciences, University of Manchester
- Dr Ellen Poliakoff, School of Biological Sciences, University of Manchester
- Dr Jennifer McBride, School of Biological Sciences, University of Manchester
- Professor Iracema Leroi, School of Biological Sciences, University of Manchester

What is the purpose of the research?

We are interested in how people with Parkinson's behave when faced with different decisions, and how quickly they can respond to different pictures and objects. A small number of people with Parkinson's report that they have problems stopping themselves from engaging in problematic behaviours (e.g. overeating, gambling) or have a tendency to make poor, or risky, choices. We will examine the ways in which people with Parkinson's may be affected by these behaviours. We will also examine how decision making differs in healthy aging.

Why have I been chosen?

We invite you to take part as a control participant who does not have Parkinson's. We will compare people with Parkinson's that report these kind of problems with people with Parkinson's that don't have these problems, as well as healthy people of a similar age. We will also compare healthy older people to healthy younger people.

What would I be asked to do if I took part?

If you agree to take part, we will invite you to participate in up to 2 different testing sessions. Your participation will still be very useful, even if you are only able to attend one session. The sessions will take place at the University of Manchester. During the session, we will ask you to complete some questionnaires about yourself (for example, about different aspects of your mood and behaviour and some basic demographic details) as well as some short memory and thinking tests. We will also ask you to make judgements about different pictures, shapes, and objects on a computer screen, while we measure your response times, hand movements, or eye movements.

Each session will last under 3 hours and you will have frequent rest-breaks throughout the session. Any expenses which you or a companion (for example, a friend or carer) incur in attending the testing session will be repaid to you in full on the day.

What happens if I do not want to take part or if I change my mind?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason and without detriment to yourself. Simply inform the researcher before, during, or after the session. If you decide to withdraw, your expenses (and those of anyone who accompanies you) will still be reimbursed.

However, it will not be possible to remove your data from the project once it has been anonymised and forms part of the dataset as we will not be able to identify your specific data. This does not affect your data protection rights.

Will my data be used for future research?

When you agree to take part in a research study, information about you may be provided to researchers running other research studies in the BEAM lab at the University of Manchester. The future research should not be incompatible with this research project and will concern Parkinson's. Where your information relates to your health and care it will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/).

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you regarding any other matter or to affect your care. It will not be used to make decisions about future services available to you. Should you lose the capacity to consent at the second visit your data from the first visit will still be retained.

Will I be paid for participating in the research?

You will not be paid for your participation, but any expenses which you or a companion (for example, a friend or carer) incur in attending the testing session will be repaid to you in full on the day. If you are a Psychology undergraduate student, you can choose to receive course credits for your participation instead of a travel reimbursement.

What is the duration of the research?

The study will involve a total of 2 sessions lasting a maximum of 3 hours each. You may choose to attend both sessions on the same day (one in the morning, one in the afternoon), or on different days at a maximum of 2 weeks apart. If you can only attend one session, this will still be very useful to us.

Where will the research be conducted?

The research will be conducted in the Zochonis Building, Brunswick Street, University of Manchester, M13 9GB.

Version 6 control participants; Date 16/09/2019

Will the outcomes of the research be published?

The results of the study will be presented at academic conferences and published in peer-reviewed academic journals. If you wish, we will tell you the results of the study when it ends.

What if there is a problem?

So far as we know, there is negligible risk associated with taking part in the study. You will not be required to change your routine medication in any way, nor will we require you to continue your current course of medication if you wish to discuss changes with your GP, although this may make you ineligible to take part in the second session. However, some of the tests that we use can sometimes indicate the possible presence of undiagnosed dementia, depression, or impulse control disorder(s). Whilst we are not health professionals, and cannot provide you with a diagnosis, we will send a letter to both you and your GP if we believe you may benefit from discussing this further with your GP.

What will happen to my personal information?

In order to undertake the research project we will need to collect the following personal information/data about you:

- Name
- Contact details (to be used to arrange visits with you and speak to you about your participation in the study, such as if we would like further information from you). You can also opt in to be contacted about future studies; if you do not consent to this, we will not use your contact details after study completion.
- A brief history of relevant neurological or mental health problems, and any medications of treatments you may be undergoing.
- Demographic details such as gender, date of birth, education level
- GP details

Only the research team will have access to this information. An anonymised dataset may be uploaded to a data repository in the interests of open science and transparency.

We are collecting and storing this personal information in accordance with the General Data Protection Regulation (GDPR) and Data Protection Act 2018 which legislate to protect your personal information. The legal basis upon which we are using your personal information is "public interest task" and "for research purposes" if sensitive information is collected. For more information about the way we process your personal information and comply with data protection law please see our Privacy Notice for Research Participants
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There may be circumstances where we need to disclose information to individuals outside the research team:

- In the event that there are concerns about your safety or the safety of others we may need to contact your GP
- In the event of incidental or unexpected findings that could have implications for your health or may need further investigation we may need to inform your GP. We will send a copy of this information to you.
- Individuals from the University, the site where the research is taking place, and regulatory authorities may need to review the study information for auditing and monitoring purposes or in the event of an incident.

If your results are included in a paper published in a medical or scientific journal, or in a presentation given at a conference, you will not be identifiable to anyone else by name or other information.

Confidential data will be destroyed 5 years after the data are published in a scientific journal.

Who has reviewed the research project?

The project has been reviewed by the NHS Research Ethics Committee and received approval from the Health Research Authority.

What if I want to make a complaint?

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What Do I Do Now?

Please discuss this information with your friends, family, and GP if you wish. If you have any queries about the study or if you are interested in taking part then please contact the researcher(s):

JADE PICKERING, JADE.PICKERING@POSTGRAD.MANCHESTER.AC.UK

ELLEN POLIAKOFF, ELLEN.POLIAKOFF@MANCHESTER.AC.UK, 0161 275 9333

The project has been reviewed by the NHS Research Ethics Committee and received approval from the Health Research Authority.

[19/NW/0094]

Version 6 control participants; Date 16/09/2019

IRAS ID: 219356

Examining control of behaviours in Parkinson's

Consent Form for participants

Researcher: Jade Pickering

If you are happy to participate please complete and sign the consent form below

	Activities	Initials
1	I confirm that I have read the attached information sheet (Version 6, Date 16/09/2019) for the above study and have had the opportunity to consider the information and ask questions and had these answered satisfactorily.	
2	I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving a reason and without detriment to myself. I understand that it will not be possible to remove my data from the project once it has been anonymised and forms part of the data set. I agree to take part on this basis	
3	I agree to my GP being informed of any necessary and relevant adverse information related to my participation in this study as detailed in the information sheet.	
4	I understand that relevant sections of my data collected during the study may be looked at by individuals from the University of Manchester, from regulatory authorities, or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
5	I agree that any data collected may be published in anonymous form in academic books, reports, or journals, or at academic conferences	
6	I agree that the researchers may contact me between research visits if any further information is needed	
7	(Optional) I agree that the researchers may contact me in future about other research projects.	
8	(Optional) I agree that the researchers may retain my contact details in order to provide me with a summary of the findings for this study.	
9	I agree to take part in this study	

Data Protection

The personal information we collect and use to conduct this research will be processed in accordance with data protection law as explained in the Participant Information Sheet and the Privacy Notice for Research Participants (http://documents.manchester.ac.uk/display.aspx?DocID=37095).

Version 2 participants; Date 16/09/2019

_____	_____	_____
Name of Participant	Signature	Date

_____	_____	_____
Name of the person taking consent	Signature	Date

[1 copy of the consent form to be retained by the participant, and 1 copy to be retained by the researchers]

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Ellen Poliakoff
Zochonis Building, 1st floor
University of Manchester
Manchester
M13 9PL

Email: hra.approval@nhs.net

16 April 2019

Dear Dr Poliakoff

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Developing a training tool to reduce impulsivity in people with Parkinson's who have additional Impulse Control Disorders**
IRAS project ID:	**219356**
REC reference:	**19/NW/0094**
Sponsor	**University of Manchester**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **219356**. Please quote this on all correspondence.

Yours sincerely,
Juliana Araujo

Approvals Specialist

Email: hra.approval@nhs.net

Copy to: *Sponsor Representative: Ms Lynne Macrae, University of Manchester*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Advertisement (Parkinson's UK, Salford Citizen Science)]	3	23 October 2018
Copies of advertisement materials for research participants [Advertisement - university]	1	30 November 2018
Copies of advertisement materials for research participants [Advertisement (Parkinson's UK, Salford Citizen Science)]	4	01 April 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance letter]	1	16 January 2019
GP/consultant information sheets or letters [Study 2 - GP referral for participants]	1	18 July 2018
GP/consultant information sheets or letters [Study 2 - GP referral]	1	18 July 2018
GP/consultant information sheets or letters [Study 1 - GP referral for participants]	1	02 August 2018
GP/consultant information sheets or letters [Study 1 - GP referral]	1	02 August 2018
HRA Schedule of Events [HRA Schedule of Events Validated]		21 January 2019
HRA Statement of Activities [HRA Statement of Activities Validated]		21 January 2019
Interview schedules or topic guides for participants [Study 2 - interview schedule]	1	26 November 2018
IRAS Application Form [IRAS_Form_17012019]		17 January 2019
Letter from funder [Funding letter]	1	26 March 2015
Letter from sponsor [Sponsor letter]	1	16 January 2019
Letters of invitation to participant [Study 2 - consent to contact]	1	26 November 2018
Letters of invitation to participant [Letter of invitation to participant]	1	02 July 2018
Letters of invitation to participant [Study 1 - consent to contact]	1	26 November 2018
Non-validated questionnaire [Home diaries - template page (example)]		28 January 2019
Non-validated questionnaire [Study 1 - Task instructions]	1	03 December 2018
Non-validated questionnaire [Home diaries - cover]	1	14 January 2019
Other [Sponsor conditions]	1	30 November 2018
Other [Insurance form]	1	07 November 2018
Other [Combined liability letter]	1	07 May 2018
Other [Employer's liability certificate]	1	01 June 2018
Other [Client salutation]	1	31 May 2018
Participant consent form [Study 2 consent (partners)]	2	30 November 2018
Participant consent form [Study 1 - consent PD and HC]	1	30 November 2018
Participant consent form [Study 2 consent (PD participants)]	3	14 January 2019
Participant information sheet (PIS) [Study 1 PIS (control participants)]	4	14 January 2019
Participant information sheet (PIS) [Study 1 PIS (PD participants)]	4	14 January 2019
Participant information sheet (PIS) [Study 2 PIS (partners)]	3	14 January 2019
Participant information sheet (PIS) [Study 2 PIS (PD participants)]	3	14 January 2019
Participant information sheet (PIS) [University of Manchester - privacy notice]	1	14 May 2018
Participant information sheet (PIS) [Study 1 PIS (control participants)]	5	01 April 2019

Participant information sheet (PIS) [Study 1 PIS (PD participants)]	5	01 April 2019
Participant information sheet (PIS) [Study 2 PIS (partners)]	4	01 April 2019
Participant information sheet (PIS) [Study 2 PIS (PD participants)]	4	01 April 2019
Research protocol or project proposal [Protocol]	3	01 April 2019
Response to Request for Further Information [Cover Letter]		04 April 2019
Sample diary card/patient card [Study 1 - case report form]	1	14 January 2019
Sample diary card/patient card [Study 2 - case report form]	1	14 January 2019
Summary CV for Chief Investigator (CI) [CV - Ellen Poliakoff]		25 October 2018
Summary CV for student [CV - Jade Pickering]		26 November 2018
Summary CV for supervisor (student research) [CV - Jennifer McBride]	1	24 August 2018
Summary CV for supervisor (student research) [CV - Iracema Leroi]	1	23 July 2018
Validated questionnaire [Beck Anxiety Inventory]	1	23 October 2018
Validated questionnaire [Beck Cognitive Insight Scale]	1	23 October 2018
Validated questionnaire [Brief Illness Perception Questionnaire]	1	23 October 2018
Validated questionnaire [Caregiver Burden Scale]	1	23 October 2018
Validated questionnaire [General Self-Efficacy Scale]	1	23 October 2018
Validated questionnaire [Geriatric Depression Scale]	1	23 October 2018
Validated questionnaire [Montreal Cognitive Examination v1]	1	23 October 2018
Validated questionnaire [Montreal Cognitive Examination v2]	1	23 October 2018
Validated questionnaire [Montreal Cognitive Examination v3]	1	23 October 2018
Validated questionnaire [Multidimensional Health Locus of Control Scale]	1	23 October 2018
Validated questionnaire [Parkinson Anxiety Scale]	1	23 October 2018
Validated questionnaire [Parkinson's Disease Questionnaire]	1	23 October 2018
Validated questionnaire [Questionnaire for Impulsive-Compulsive Disorders in Parkinson's - past ICD]	1	23 October 2018
Validated questionnaire [Questionnaire for Impulsive-Compulsive Disorders in Parkinson's - current ICD]	1	23 October 2018
Validated questionnaire [Questionnaire for Impulsive-Compulsive Disorders in Parkinson's - severity rating scale]	1	23 October 2018
Validated questionnaire [Unified Parkinson's Disease Rating Scale]	1	23 October 2018
Validated questionnaire [Ways of Coping questionnaire]	1	23 October 2018
19 NW 0094 IRAS 219356 Provisional Opinion.pdf		11 March 2019
19 NW 0094 IRAS 219356 Valid Invite Letter 04 02 19.pdf		05 February 2019
219356 Further Information Favourable Opinion 16042019.pdf		16 April 2019