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INVESTIGATING FACTORS ASSOCIATED WITH IMPULSE CONTROL BEHAVIOURS IN PARKINSON'S DISEASE

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SYNOPSIS

Destructive behaviours resulting from impaired impulse control can manifest in patients with Parkinson's disease (PD), more commonly in those who take dopamine agonist (DA) medication. 14-40% of those who take such medication develop these behaviours, known as impulse control behaviours (ICBs). There are risk factors associated with the presence or development of ICBs, including higher agonist dosage, longer duration of treatment, greater severity of motor symptoms, apathy and autonomic and cognitive functions. However, there is currently no clear, reliable procedure or test to predict who is most likely to develop these ICBs. This thesis investigated novel factors which may be associated with the incidence, frequency and change over time of ICBs, with the intention to provide the first steps towards future prediction and prevention of ICB development.

The most important results from this project highlight the potential predictive power of a dopamine genetic risk score (DGRS) for PD patients on DA medication who suffer from ICBs. The DGRS theoretically quantifies central dopamine neurotransmission within MCL regions which are implicated in impulse control. Some of the results in this thesis mirrored the inverted-U relationship between impulse control and dopamine previously reported, where PD patients with lower dopamine neurotransmission displayed worse impulse control and PD patients with higher dopamine neurotransmission displayed worsening impulse control over time. Moreover, lab-based behavioural impulsivity task performance was also associated with ICBs in PD patients on DA medication. We first confirmed that impulsive behaviour measured by the anticipatory response inhibition task was a valid measure of non-selective inhibition network activity. We then found that greater impulsive behaviour on the Balloon Analogue Risk Task (BART), was associated with higher ICB frequency. We also found preliminary

evidence that greater impulsive behaviour determined by the BART and Gambling task, measuring cognitive and limbic impulsivity, was associated with the DGRS in a young healthy sample. Finally, a possible relationship was observed between high concentrations of the metabolite of dopamine, homovanillic acid (HVA), and a high DGRS, in a young healthy cohort. It is possible that HVA could be important in confirming the DGRS theoretical quantification of central dopamine neurotransmission.

The results in this thesis replicate some important outcomes already reported in the literature and this work also presents several exciting novel findings. Collectively, this body of work highlights that a cumulative genetic score (DGRS) and behavioural impulsivity task measures are associated with ICBs in PD. The results presented provide insight for future investigations to perhaps predict which PD patients who take DA medication are most likely to develop ICBs.

DEDICATION

I would like to dedicate this thesis to my loving parents, Lesley and Malcolm Hall. Without their support, this would not have been possible.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
3MT	3-Methoxytyramine
AADC	Aromatic Amino Acid Decarboxylase
ACC	Anterior Cingulate Cortex
ADHD	Attention-Deficit/Hyperactivity-Disorder
AI	Anterior Insula
ALDH	Aldehyde Dehydrogenase
ANOVA	Analysis Of Variance
ARIT	Anticipatory Response Inhibition Task
AUC	Area Under the ROC Curve
BART	Balloon Analogue Risk Task
BF	Bayes Factor
BG	Basal Ganglia
BIS	Barratt Impulsiveness Scale
CGS	Cumulative Genetic Score
CI	Confidence Interval
CM	Centromedian Nucleus
CMA	Cingulate Motor Area
CNSVS	Central Nervous System Vital Signs
COMT	Catechol-O-Methyltransferase
CSF	Cerebral Spinal Fluid
DA	Dopamine Agonist
DAT	Dopamine Transporter
DGRS	Dopamine Genetic Risk Score
DLPFC	Dorsolateral Prefrontal Cortex
DMPFC	Dorsomedial Prefrontal Cortex
DN	De Novo
DOPA	Dihydroxyphenylalanine
DOPAC	3,4-Dihydroxyphenylacetic acid
DOPAL	3,4-Dihydroxyphenylacetaldehyde
DRT	Dopamine Replacement Therapy
ELISA	Enzyme-Linked Immunosorbent Assay
EPV	Events Per Variable
GPe	Globus Pallidus externa
GPi	Globus Pallidus interna
GWAS	Genome-Wide Association Studies
HC	Healthy Control
HVA	Homovanillic Acid
HW	Hardy-Weinberg
ICB	Impulse Control Behaviour

ICD	Impulse Control Disorder
IFG	Inferior Frontal Gyrus
KASP PCR	Kompetitive Allele Specific Polymerase Change Reaction
L-Dopa	Levodopa
LEDD	Levodopa Equivalent Daily Dose
M1	Motor Cortex
MAO	Monoamine Oxidase
MCL	Mesocorticolimbic
MFC	Medial Frontal Cortex
MRI	Magnetic Resonance Imaging
NA	Noradrenergic
NAc	Nucleus Accumbens
NCI	Neurocognitive Index
NDA	Non Dopamine Agonist
NE	Norepinephrine
NOH	Non-Overlapping Hypothesis
OH	Overlapping Hypothesis
OR	Odds Ratio
PD	Parkinson's Disease
PET	Positron Emission Tomography
PFC	Pre-Frontal Cortex
pHVA	plasma Homovanillic Acid
PMC	Pre-Motor Cortex
PRS	Polygenic Risk Score
QUIP	Questionnaire for Impulsive-Compulsive disorders in Parkinson's disease
RI	Response Inhibition
RM	Repeated Measures
ROC	Receiver Operating Characteristic
S1	Somatosensory Cortex
SB	Stop Both
SD	Standard Deviation
SE	Standard Error
SL	Stop Left
SMA	Supplementary Motor Area
SNc	Substantia Nigra pars compacta
SNP	Single Nucleotide Polymorphism
SNr	Substantia Nigra pars reticula
SPECT	Single-Photon Emission Computerized Tomography
SPV	Subjects Per Variable
SR	Stop Right
SSRT	Stop Signal Reaction Time
SST	Stop Signal Task
STN	Subthalamic Nucleus

UPDRS	Unified Parkinson's Disease Rating Scale
VAmc	lateral nucleus Ventralis Anterior pars magnocellularis
VApc	lateral nucleus Ventralis Anterior pars parvocellularis
VLm	Ventrolateral nucleus of thalamus pars medialis
VLo	nucleus Ventralis Lateralis pars oralis
VMPFC	Ventromedial Prefrontal Cortex
VNTR	Variable Number Tandem Repeat
VTA	Ventral Tegmental Area
WM	Working Memory

CHAPTER 1

General Introduction

1.1. Overview of the Thesis

Impulse control behaviours (ICBs), incorporating impulse control disorders and related behaviours, can develop in those with Parkinson's disease (PD), especially in individuals who take dopamine agonist (DA) medication, which is a form of dopamine replacement therapy. Although there are some risk factors associated with the development of these ICBs, which can influence a clinician's decision to withhold from prescribing this form of medication to patients, there is currently no clear, reliable procedure or test to determine those at the greatest risk of developing ICBs on DA medication. As a result, the work conducted in this thesis provides insight to some behavioural, genetic and biochemical tests and factors which could perhaps be utilised in the future to determine those most at risk from developing destructive ICBs. The introduction below presents a review of relevant topics, literature and highlights all factors which are included as predictive variables or factors associated with ICBs in the subsequent experimental chapters. Chapter 2 discusses the steps which took place to develop different regression models for statistical analyses within the experimental chapters. Chapter 3 is the first experimental chapter of the thesis where the role of dopaminergic genes in the prediction of ICBs is investigated in a PD cohort. This chapter utilises the Parkinson's Progression Markers Initiative database to investigate the use of a specific dopamine genetic risk score (DGRS) to predict ICBs for de novo PD patients and for those taking DA medication. Chapter 4 explores stop signal reaction time as a measure of motor impulse control over the course of two sessions in the Anticipatory Response Inhibition Task (ARIT) and how this compares to the more traditionally used Stop Signal Task. This chapter determines which task could be used in the following chapter to test for associations with ICBs in PD. Therefore, Chapter 5 builds on the results from the previous two chapters. It includes the use of predictive factors associated with ICBs in Chapter 3 along with the ARIT used in Chapter 4, to determine the association of behavioural, genetic, clinical and demographic factors with ICBs in PD

patients taking DA medication. Chapter 6 follows on from the previous chapters to explore the biochemical factor, homovanillic acid (HVA). This is a preliminary experiment in young healthy adults which investigates whether concentrations of the dopamine metabolite, HVA, are associated with the DGRS and behavioural measures of motor and cognitive impulse control. Chapter 7 concludes the results of all experimental chapters and presents limitations and potential future directions for this body of work.

1.2. Neurocircuitry of Impulse Control

Impulse control or impulsivity is a crucial aspect of self-restraint, where impairments can substantially affect day to day living for individuals. Historically, the first mention of impulsivity was by the Greek physician, Hippocrates (c460BC – 370BC) who included impulsiveness within one of four temperaments or humours, based upon relative proportions of bodily fluids (yellow bile (including impulsivity), black bile, blood and phlegm). This theory, termed humourism, was supported by Galen (AD 129-ca. AD 200) who developed these temperaments into categories which were largely involved in medical science at the time and for hundreds of years following: (choleric, melancholic, sanguine and phlegmatic). However, in the late 19th/ early 20th century, Wundt amongst others began to differentiate personality and bodily fluids and their work largely contributed to the catalyst of accepting psychology as an autonomous discipline (Feldman, 1932; Irwin, 1947; Moeller et al., 2001; Stelmack & Stalikas, 1991). Around this time, impulsivity began to be investigated as its own entity. Impulsivity was described as maladaptive behaviour where individuals either knowingly or unknowingly act upon an impulse, regardless of the consequences of their behaviour (Ainslie, 1975). In more modern literature, this perspective is still very relevant and there is a consistent view of impulsivity as a trait which can be defined as a "predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others" (DeYoung & Rueter, 2010; Moeller et al., 2001).

Impulsivity is a feature of several psychiatric disorders such as bipolar disorder, substance use disorders and personality disorders (Moeller et al., 2001). Impaired impulse control can also be a dominant feature of neurodevelopmental disorders including attention-deficit/hyperactivity-disorder (ADHD), autism spectrum disorder and intellectual disability

(McClain et al., 2017). Quite often, impairments in impulsivity can lead to diagnosis of impulse control disorders (ICDs). These ICDs are most commonly diagnosed in structured or semi-structured interviews conducted by a trained clinician, sometimes with the additional use of impulsivity questionnaires as a diagnostic tool alongside the interview (Hollander et al., 2006). These questionnaires can include the Barratt Impulsiveness Scale (BIS) and the Eysenck Impulsiveness Questionnaire (Leshem & Glicksohn, 2007).

ICDs and other related behaviours (referred to in this thesis as Impulse Control Behaviours (ICBs)) can also develop in those with Parkinson's disease (PD). These ICBs commonly manifest as compulsive shopping, compulsive gambling, hypersexuality, binge eating, hobbyism, punding and compulsive medication use/dopamine dysregulation syndrome (Weintraub, 2008). The questionnaire for impulsive-compulsive disorders in PD (QUIP) is a globally validated questionnaire, used as a screening tool specifically for ICBs in PD patients (Krieger et al., 2017; Marques et al., 2019; Papay et al., 2011; Probst et al., 2014; Weintraub et al., 2009). These ICBs highlight 'real world' impulsivity, which is subjective to the views of the individual completing the questionnaire or their physician. Later chapters in this thesis explore the relationship between these subjective impulsivity questionnaires and the more objective sensitive behavioural task measures of impulsivity. First, the following section discusses the neurocircuitry of impulse control.

1.2.1. Introduction to Neurocircuitry and Basal Ganglia Pathways

Impulse control can be divided into two main domains, motor and cognitive (Antonelli et al., 2011), which will be discussed in more detail later in this section. The cortico-basal-ganglia-thalamocortical networks link the cortex, basal ganglia (BG) and thalamus, and these regions are largely involved in the processes of impulse control (Dunovan et al., 2015; Jahfari et al.,

2011). Dopamine neurons (releasing the dopamine neurotransmitter) play a key role within the BG where structures of dopaminergic pathways project to the striatum which is the main input to the BG (Haber, 2014). Dopamine pathways play a pivotal role in goal directed behaviours (Haber, 2014), where disorders involving dopamine dysfunction or loss such as PD or ADHD, can lead to loss or reduced function of the behaviours controlled by these BG circuitry (Gasser et al., 2015; Vaidya & Stollstorff, 2008). A detailed explanation of the BG circuitry in PD will be discussed in a subsequent section of this introduction.

The dopaminergic pathways include the nigrostriatal, mesocortical and mesolimbic pathways, which are all linked with motor control, motivation, reward and cognition (Haber, 2014). The pathways begin in regions of the midbrain and project to regions of the BG (Luo & Huang, 2016). The nigrostriatal pathway originates in the substantia nigra pars compacta (SNc) and projects to the dorsal striatum in the BG. Whereas the mesocortical and mesolimbic pathways start in the ventral tegmental area (VTA) and retrorubral field, and project to areas of the pre-frontal cortex (PFC) and nucleus accumbens (NAc) (major component of the ventral striatum), respectively (Luo & Huang, 2016). The nigrostriatal pathway is largely involved in the preparation and execution of movement and perhaps premotor aspects of impulse control. Whereas the mesocorticolimbic (MCL) system (mesocortical and mesolimbic pathways) is more largely related to the monitoring of impulse control, involving the cognitive impulse control domain (Beste et al., 2010). The following section presents the route from the cortex to the thalamus and back to the cortex for the direct, indirect and hyperdirect pathways within the BG (Figure 1.1), which are strongly implicated in impulse control.

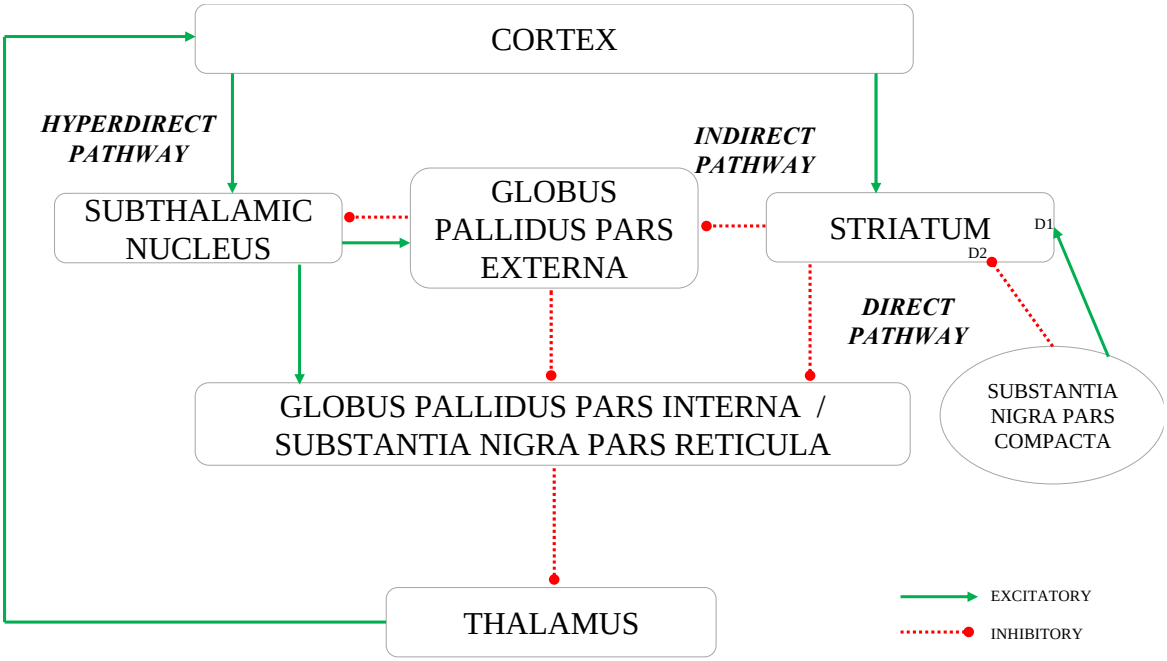

Figure 1.1 Direct, indirect and hyperdirect pathways of the Basal Ganglia.

Projections in the BG between each structure are either excitatory (glutamatergic) or inhibitory (GABAergic) which results in the increased/decreased excitation/inhibition of the connecting structure, therefore influencing its output (Haber et al., 2012; Lanciego et al., 2012; Milardi et al., 2019). In the direct pathway, the cortex sends excitatory signals to the striatum (comprising of the caudate nucleus, putamen and ventral striatum), whilst the SNc also projects excitatory signals to the dorsal striatum via D1 receptors. There are subsequent inhibitory projections to the globus pallidus interna (GPi) and substantia nigra pars reticula (SNr), therefore reducing activity of these structures and providing disinhibition to the thalamus which overall results in increased excitatory projections from the thalamus to the cortex (Haber et al., 2012; Lanciego et al., 2012; Milardi et al., 2019). In the indirect pathway, again the cortex projects excitatory signals to the striatum which sends (via neurons expressing D2 receptors which are also activated by the SNc) inhibitory signals to the globus pallidus externa (GPe), reducing inhibitory signals to the subthalamic nucleus (STN) which overall increases excitation here. As a result, the excitatory neurons of the STN excite the

GPi/SNr which subsequently suppresses the thalamic output to the cortex, increasing inhibition (Haber et al., 2012; Lanciego et al., 2012; Milardi et al., 2019). The hyperdirect pathway bypasses most of the indirect pathway. Excitatory projections travel directly from the cortex to the STN, which then excites the Gpi/SNr, reducing thalamic activity and aiding inhibition (Milardi et al., 2019; Nambu et al., 2002). The following sections will discuss how behavioural measures of motor and cognitive impulse control recruit these various cortico-BG-thalamocortical networks.

1.2.2. Motor Impulse Control

The motor domain of impulse control is termed response inhibition, which refers to the ability to supress or cancel unwanted actions, which in some cases can be a learned motor response. Objective response inhibition can be measured and quantified within a laboratory setting using behavioural tasks such as the Anticipatory Response Inhibition Task (ARIT), Stop Signal Task (SST) or the go/no-go task (Lappin & Eriksen, 1966; Slater-Hammel, 1960; Steele et al., 2013). The tasks utilised within this thesis are the SST and the ARIT. The stop signal paradigm was created in 1948 (Vince, 1948) and then developed into the SST in 1966 (Lappin & Eriksen, 1966), whilst the anticipated response version of the SST (the ARIT) was developed in 1960 (Slater-Hammel, 1960). Both tasks are now widely used in response inhibition literature (He et al., 2022; Verbruggen et al., 2019a; Verbruggen, Logan, & Stevens, 2008). The main differences between these two tasks are discussed in Chapter 4. In the SST and ARIT, participants are required to complete a number of Go trials involving a conditioned motor response and Stop trials which requires inhibition of the conditioned response (withheld movement). The primary dependent measure for each of these tasks is Stop Signal Reaction Time (SSRT), which measures the latency of this response inhibition process (Logan & Cowan,

1984; Verbruggen et al., 2019a). Logan and Cowan (1984) produced a horse race model of response inhibition which explains the behavioural outcome of each trial. Both the SST and the ARIT follow this horse race model framework. The model poses a trial-by-trial "horse" race between the going process which is initiated by the Go signal, and the stopping process which is initiated by the Stop signal. If the going process finishes first then the response is executed, but if the stopping process finishes first then the response is inhibited. There are specific neural networks involved in the stopping and going processes, which are described below.

Research has been conducted to determine the neural networks underlying inhibitory control, highlighting the vast importance of the BG pathways. In the response inhibition tasks mentioned above, Go trials require a conditioned motor response which often involves a single digit reaction to an audio or visual stimulus. The resultant reaction times contribute to the calculated SSRT value. The execution of a motor response, involving the nigrostriatal dopamine pathway, activates fronto-striato-pallidal regions as part of the direct BG pathway, which then leads to an increase in thalamocortical drive to the motor cortex to perform the motor response. Specifically, the origins of the motor network which drive this motor response are within the motor cortex (M1), pre-motor cortex (PMC), cingulate motor area (CMA), somatosensory cortex (S1), and supplementary motor area (SMA) (Alexander & Crutcher, 1990; Gasser et al., 2015). It is believed there are separate topographical channels in the motor network relating to somatotopy which act in parallel for movement production (Alexander & Crutcher, 1990). In the direct pathway, these channels project from motor regions of the cortex to the bilateral putamen, motor portions of the GPi and SNr and finally the thalamus (nucleus ventralis lateralis pars oralis (VLo), lateral nucleus ventralis anterior pars parvocellularis (VApc), lateral nucleus ventralis anterior pars magnocellularis (VAmc), ventrolateral nucleus

of thalamus pars medialis (VLm) and centromedian nucleus (CM) (Alexander & Crutcher, 1990; Aron & Poldrack, 2006; Gasser et al., 2015). The thalamus then facilitates the preparation and execution of movement by projection to the SMA (from VLo and lateral VAmc), PMC (from lateral VApc, VLo and VLm) and M1 (from VLo and CM) (Alexander & Crutcher, 1990; Aron & Poldrack, 2006; Nakano et al., 2000).

When the process of inhibition takes place on stop trials, regions are activated initially to conduct the Go response, then a very short period later (e.g., 220.2ms reported by Aron & Poldrack, 2006), specific regions are activated to produce the response inhibition. When isolating the neural networks involved in only the stopping process, a right lateralized network is engaged (Allen et al., 2018; Aron et al., 2003; Aron & Poldrack, 2006; Chen et al., 2020; Coxon et al., 2009; Dunovan et al., 2015; Maizey et al., 2020; Ray Li et al., 2008). The right inferior frontal gyrus (IFG) and pre-SMA, which are part of the pre-frontal cortex, activate the right STN and right caudate as part of the hyperdirect (cancellation of action) and indirect (suppression of action) pathways, respectively (Jahfari et al., 2011). Recent literature confirmed that the right IFG preceded pre-SMA activation in the process of response inhibition which is implemented via beta-band oscillations, highlighting its large importance in the initiation of response inhibition (Schaum et al., 2020, 2021). As previously mentioned, the indirect and hyperdirect pathways supress thalamocortical output by blocking the direct pathway and therefore inhibit a response (Aron & Poldrack, 2006; Chen et al., 2020; Dunovan et al., 2015; Jahfari et al., 2011; Ray Li et al., 2008; Schaum et al., 2020; Zandbelt & Vink, 2010). It has been suggested that the combination of both pathways may produce the most efficient and effective response inhibition (Jahfari et al., 2011), however there may be some segregation where the indirect pathway may be more involved in proactive inhibition

(preparation for stop cues) whilst the hyperdirect pathway may be more involved in reactive inhibition (responding to stop signals) (F. Zhang & Iwaki, 2019).

1.2.3. Cognitive Impulse Control

Cognitive impulse control refers to the ability to assess the consequences of a decision and subsequently modify the decision, which can often include decision making under risk depending upon the individual perception of 'risk vs reward' (Cazzell et al., 2012; Lauriola et al., 2014). In a lab-based setting, there are several tasks which measure cognitive impulse control (Buelow et al., 2014; Buelow & Barnhart, 2018), such as the Balloon Analogue Risk Task (BART) (Lejuez et al., 2002), Iowa Gambling Task (Lauriola et al., 2014; Zermatten et al., 2005), Columbia Card Task (Figner et al., 2009) and Game of Dice Task (Brand et al., 2005). The BART is used throughout this thesis measuring cognitive impulsivity, more specifically risk taking with regards to a reward or a loss (Antonelli et al., 2011; Lauriola et al., 2014; Lejuez et al., 2002).

The BART is a widely utilised tool measuring risk taking in healthy volunteers (Lejuez et al., 2002) and groups with disorders such as PD (Martini et al., 2018), ADHD (Humphreys & Lee, 2011) and substance use disorders (Ashenhurst et al., 2014; Galván et al., 2013). Most importantly, the BART was utilised in the study by MacDonald and colleagues (MacDonald et al., 2016), a study which provides a strong rationale for the work in this thesis, which will be discussed in a later section of the general introduction. During the BART, participants are given the choice to pump up a balloon which incrementally increases potential monetary winnings with each pump. Within a trial, potential winnings can be collected at any time however the balloon can also pop at any time. The greater number of pumps, the greater risk of the balloon popping and the loss of the accumulated amount. The main measures utilised from the BART

include the average number of pumps which quantifies risk taking behaviour (Claassen et al., 2011), and negative feedback which quantifies behaviour modification following loss (Martini et al., 2018) and is predominantly used in this thesis.

Research has been conducted to assess the neural networks activated during decision making under risk which often involves neural structures involved in the cognitive and limbic BG thalamocortical networks. As previously mentioned, the MCL system is largely responsible for reward and cognition (Haber, 2014). During decision making, the dopamine rich MCL and frontal regions are activated, specifically within structures including the midbrain (ventral tegmental area), striatum (NAc as part of the ventral striatum, caudate nucleus and putamen), globus pallidus, anterior insula (AI), the PFC and anterior cingulate cortex/medial frontal cortex (ACC/MFC) (Gentili et al., 2020; H. Rao et al., 2008; L. L. Rao et al., 2018). Regions of the prefrontal cortex (dorsolateral (DLPFC), dorsomedial (DMPFC) and ventromedial VMPFC) have been found to be most greatly associated with voluntary decision making, with regards to win options/reward seeking (collecting money) and risky decision making (Cazzell et al., 2012; Fukunaga et al., 2012; Gentili et al., 2020; Li et al., 2020; Manes et al., 2002; Qu et al., 2019; H. Rao et al., 2008; L. L. Rao et al., 2018). It has also been reported that the ACC, AI and IFG specifically drive loss aversion, which is making decisions against risk (Fukunaga et al., 2012; Li et al., 2020). Activation of the bilateral putamen and insula are associated with winning and losing outcomes of this decision making, respectively (Li et al., 2020; H. Rao et al., 2008).

1.2.4. Real World Impulsivity

The previous two sections described both motor and cognitive domains of impulse control and how specific dopamine pathways and neural networks work in parallel and produce motor and cognitive behavioural outcomes. However, there is some evidence to show this circuitry may be integrated for the motor, cognitive and limbic domains (Haber, 2014; Haber et al., 2000). During the planning of motor movement in impulse control, there are connections between the DLPFC (as part of the MCL system) and the rostral dorsal premotor cortex (Luppino et al., 2003). The rostral dorsal premotor cortex is responsible for executive motor behaviour such as motor planning and imagery (Picard & Strick, 2001). The connection between these cognitive and motor regions via rostral pre-motor regions supports the idea of integrated networks for cognitive/motor interaction tasks (Hanakawa, 2011). Additionally, it has been suggested that the mesolimbic dopamine system, which is often associated with reward, could contribute to response inhibition. Here, D2 receptor binding in regions of the mesolimbic system (specifically the amygdala and hippocampus) is associated with improved motor inhibitory control (Mann et al., 2021). Perhaps both the parallel and integrated networks are activated simultaneously within impulse control, and this simultaneity may help to capture the diverse nature of impulse control in the real world.

Real world impulsivity is a subjective measure of impulsivity, often measured using trait impulsivity questionnaires such as the BIS, Eysenck Impulsiveness Questionnaire and Dickman Impulsivity Inventory (Claes et al., 2000; Leshem & Glicksohn, 2007). The BIS, first created in 1959 (Barratt, 1959) is utilised in the final experimental Chapters 5 and 6 of this thesis to investigate any associations between self-reported trait impulsivity and objective lab-based measures of motor and cognitive impulsivity. The BIS is a self-report questionnaire which measures impulsivity as a trait or personality construct (Stanford et al., 2009), where a

higher score is related to higher levels of impulsivity. The BIS score is often calculated as the total score or split by the first and second order subscales: attentional (attention and cognitive instability), motor (motor and perseverance), non-planning (self-control and cognitive complexity) (Reise et al., 2013; Stanford et al., 2009). Whilst the self-reporting QUIP, as mentioned earlier, measures real world impulsivity specifically in PD patients as a screening tool for ICBs (Krieger et al., 2017; Marques et al., 2019; Papay et al., 2011; Probst et al., 2014; Weintraub et al., 2009). A positive relationship between the QUIP and BIS has previously been reported (Goerlich-Dobre et al., 2014).

There are studies which compare results from real world impulsivity questionnaires with motor/cognitive impulsivity tasks, which are included in this thesis. Some found that the BIS was not associated with SSRT in the SST (Aichert et al., 2012; S. Zhang et al., 2015), but others discovered a correlation trending towards significance (Farr et al., 2012). Moreover, the BIS has been found to be correlated with the average number of pumps on a monetary collection and a measure of risk seeking tendency (un-burst balloons/total number of pumps) in the BART (Gong et al., 2022; Lejuez et al., 2002). Another study found only that the motor subscale of the BIS was associated with the number of balloon bursts and the number of pumps on a trial when the balloon did not burst on the BART (Holmes et al., 2009). With regards to results of the QUIP, findings have been varied when comparing to BART performance (cognitive impulse control). Some patients with ICBs failed to reduce impulsive behaviour following a loss (Martini et al., 2018), whilst no association was found between ICBs and performance when determining the difference between the number of balloon pumps preceding and following a loss (Claassen et al., 2011). For motor impulse control, some found SSRT determined from the SST was no different between those with and without ICBs, identified by the QUIP (Hlavatá et al., 2020; Ricciardi et al., 2017; Vriend et al., 2018). On the other hand,

another study reported shorter SSRTs in ICB patients compared to non-ICB patients and controls (Claassen et al., 2015a). No such relationship has been investigated between results of the QUIP/BIS and SSRT derived from the ARIT.

Overall, there are mixed results from comparing real world impulsivity questionnaires with motor/cognitive impulsivity tasks. But it is possible that subjective real world impulsivity questionnaires, alongside objective behavioural measures of impulsivity could assist in the diagnosis, prediction, and ultimate prevention of impulsivity problems, specifically ICBs in PD.

1.3. Parkinson's Disease

1.3.1. Epidemiology and Aetiology

PD is the second most common neurodegenerative disorder in the world. Approximately 10 million people in the world have PD and the disease is most common in those over 60 years of age, however one in ten are under 50. PD does not necessarily reduce life expectancy, but it can reduce quality of life, which is where treatment is involved to maintain or improve quality of life (EPDA, 2022). Age is the most significant risk factor for developing PD, along with being male (ratio 3:2 male:female) and specific genetic mutations within the LRRK2 or PARK1 genes for example. Environmental factors such as smoking, head trauma, coffee, alcohol, pesticides and water pollutants have also been suggested as risk factors (E. Tolosa et al., 2006; S. Tolosa et al., 2021; Tysnes & Storstein, 2017).

1.3.2. Symptoms and Diagnosis

The clinical diagnosis of PD has been described as suboptimal (S. Tolosa et al., 2021). The prodromal symptoms of PD, displayed before formal diagnosis, can overlap with other conditions which makes it difficult to diagnose in this stage (E. Tolosa et al., 2006). Diagnosis of PD is generally confirmed based on the assessment of PD symptoms. The International Parkinson and Movement Disorder Society criteria of PD symptoms and features can be used alongside knowledge of medical history for the clinical diagnosis of PD (S. Tolosa et al., 2021). Symptoms of PD can be classified as motor or non-motor (Jankovic, 2008) and manifest in the prodromal (pre diagnosis) stage, early stage (post diagnosis) and late stage (S. Tolosa et al., 2021). During the prodromal stage, which lasts approximately 10-15 years, patients have most commonly reported sleep disorders, constipation, hyposmia, depression, urinary dysfunction, tremor, mild slowness and memory problems. During this stage, the non-motor symptoms often

precede the onset of classic motor symptoms (S. Tolosa et al., 2021; Tysnes & Storstein, 2017). Once diagnosis has taken place, motor symptoms in the early stage include tremor, bradykinesia, rigidity and gait alterations, whilst non-motor symptoms include problems with autonomic dysfunction (e.g., constipation, orthostatic hypotension, erectile dysfunction, urinary urgency, heat intolerance), hyposmia, sleep disorders, anxiety, depression, mild cognitive impairment and somatosensory disturbances (e.g., pain and other sensations). Again, these non-motor symptoms usually precede the motor symptoms in the early stage. Motor symptoms of the late-stage present as posture and balance difficulties, freezing of gait, dysarthria and dysphagia (for a review, see Tolosa et al., 2021). Dementia is a later-stage non-motor feature of PD and can develop in about 30% of patients (de Lau & Breteler, 2006). Imaging and genetic testing can also confirm the diagnosis of PD. With regards to imaging techniques, Positron emission tomography (PET) or single-photon emission computerized tomography (SPECT) imaging can assess synaptic striatal dopaminergic function and determine neurodegeneration. Structural magnetic resonance imaging (MRI) can distinguish PD from other types of Parkinsonism (Heim et al., 2017; E. Tolosa et al., 2006; S. Tolosa et al., 2021).

1.3.3. Neuropathology

PD is primarily characterised a result of dopaminergic neuron degeneration in the SNpc in the BG. PD is additionally characterised by the presence of intraneuronal proteinaceous cytoplasmic inclusions called Lewy bodies or Lewy neurites in the somata of neurons which contain aggregations of the misfolded protein alpha-synuclein (α-synuclein) (Dauer & Przedborski, 2003; Lotharius & Brundin, 2002). Neuronal damage from development of aggregated α-synuclein-containing inclusion bodies takes place in specific cell types. These

susceptible neurons have long and thin axons disproportionate to their somata and are also often poorly myelinated (Braak et al., 2003, 2004; Braak & Del Tredici, 2004). α-synuclein is predominantly expressed in neurons of the neocortex, hippocampus, substantia nigra, thalamus and the cerebellum (Kim et al., 2014). These neural regions are therefore largely important in the pathological stages of PD developed by Braak and colleagues (Braak et al., 2003, 2004). These 6 validated stages, split into pre- and post-symptomatic, outline how the Lewy inclusions develop and advance topographically through gray matter neural regions in PD (Dickson et al., 2010). It is important to note that others have suggested the neuropathology of these stages may differ depending on age at disease onset (Boeve, 2013; Halliday & McCann, 2010).

Pre-symptomatic (stages 1-3)

The development of aggregated α-synuclein-containing inclusion bodies occurs sequentially and begins in neurons of the dorsal motor nucleus of the vagal nerve, the adjoining intermediate reticular zone and the olfactory bulb and regions of the anterior olfactory nucleus (Braak et al., 2003, 2004). The dorsal motor nucleus of the vagal nerve has projections to the entire nervous system and is identified as the main starting point of inclusion body development and progression throughout the nervous system. In the first stage, only a small number of inclusion bodies develop within these regions. In stage 2 the pathology continues to spread within these structures and to regions of the reticular formation. The damaged neurons in stage 2 contribute to the "gain setting" system which contributes to preparation of action in the motor system via projections from medullary, spinal pre-motor and motor neurons. At the end of stage 2, the presence of inclusion bodies is mainly confined to the olfactory bulb, medulla oblongata and pons tegmentum (Braak et al., 2003, 2004). These regions are specifically involved in sleep disorders such as rapid eye movement (REM) sleep behaviour disorder, which are often reported as symptoms which precede PD diagnosis (Boeve, 2013; Bugalho et al., 2011).

Hyposmia and other autonomic symptoms involving cardiovascular, gastrointestinal, genitourinary and thermoregulatory systems also can precede the disease diagnosis (Palma & Kaufmann, 2014). It could be that if neuronal degeneration was determined in stages 1 and 2 then perhaps this pathological deterioration could be prevented (Palma & Kaufmann, 2014). In stage 3, the pathology moves upwards past the pontine tegmentum region of the pons and into the basal portions of the midbrain and forebrain. This is where the first inclusion bodies are observed in the SNpc, which is the hallmark of PD. At this stage, pathology also extends to the amygdala, cholinergic tegmental pedunculopontine nucleus, oral raphe nuclei, regions of the basal forebrain and the tuberomammillary nucleus of the hypothalamus (Braak et al., 2003, 2004).

Post-symptomatic (stages 4-6)

As the disease progresses into stage 4, the first characteristic motor symptoms of PD are displayed, in line with SNpc neuron degeneration (Greffard et al., 2006; Halliday & McCann, 2010). The loss of neuromelanin-containing nigrostriatal neurons in the SNpc results in the well-known images of SNpc depigmentation. The main site of projection for these neurons in the SNpc is the putamen, specifically the dorsolateral putamen, which is also the main site of projection of dopamine transporter (DAT) proteins, of which expression is also reduced in PD. This is compared to mesolimbic dopaminergic neurons located in the VTA adjacent to the SNpc, which are relatively spared of neurodegeneration in early PD. Therefore, the caudate (region of projection from the VTA) does not experience the same levels of dopamine reduction as the dorsolateral putamen (Dauer & Przedborski, 2003). This sparing of dopamine can lead to problems with impulsivity following administration of DA medication (Meder et al., 2019), which is to be discussed in the following section. The other main step in stage 4 is the inclusion of the temporal mesocortex in the progression of PD, which is within the cerebral cortex, along

with sections of Ammon's horn. The anteromedial temporal mesocortex is largely involved in limbic system projections from sensory areas to the prefrontal cortex (Braak et al., 2003, 2004). In stages 5 and 6, vulnerable regions of the SNpc are almost completely absent of pigmented neurons and PD takes over the entire neocortex, where the autonomic, limbic and motor systems are severely affected and patients can display the full range of associated PD symptoms (Braak et al., 2003, 2004).

1.3.4. Impulse Control Behaviours in Parkinson's Disease

In a consultant appointment for those with PD, a common question asked is "have you been more impulsive recently?" Impulsive behaviour is not uncommon in PD patients and ICBs can manifest often as side effects of dopamine replacement therapy (DRT) medication, specifically DA medication. DA medication appears to be the major risk factor for ICBs in PD. Other risk factors include being male, a higher score on the Unified Parkinson's disease rating scale (UPDRS), personal or family history of impulsive problems, earlier PD onset, being unmarried, higher DA dose, longer DA duration of treatment, amongst some others (Antonini et al., 2017; Cormier-Dequaire et al., 2018; Corvol et al., 2018; Gatto & Aldinio, 2019; Kraemmer et al., 2016; Marković et al., 2020; Nombela et al., 2014; Voon, Mehta, et al., 2011). DAs imitate dopamine neurotransmitters by directly acting on dopamine receptors and are often selected to treat those with PD who predominantly display motor symptoms (Brooks, 2000). Up to 40% of PD patients taking DAs suffer from ICBs (Bastiaens et al., 2013; Erga et al., 2018; Kraemmer et al., 2016; Weintraub et al., 2010).

A small number of studies have researched risk factors which can predict the development of ICBs over time. These longitudinal studies concluded DA use was a risk factor,

along with higher dosage, longer duration of treatment, greater severity of motor symptoms, apathy and autonomic and cognitive functions (Baig et al., 2019; Corvol et al., 2018; Ricciardi et al., 2018). These studies are key in relation to the overall aim of this thesis, to find factors which could perhaps be utilised in the future to determine those most at risk from developing destructive ICBs. In comparison to these studies, the risk factor of DA use along with duration of treatment is examined in Chapters 3 and 5, whilst dosage of DA medication is investigated in Chapter 5. Further to the variables examined in the studies mentioned above to determine risk factors of ICBs, this thesis adds another dimension by investigating results of motor and cognitive impulsivity behavioural tasks in Chapter 5.

As previously mentioned, these ICBs in PD can manifest as compulsive gambling, hypersexuality, binge eating, compulsive shopping, punding, hobbyism and compulsive medication use (Weintraub, 2008) which can be determined by the QUIP (Krieger et al., 2017; Marques et al., 2019; Papay et al., 2011; Probst et al., 2014; Weintraub et al., 2009). A key question arises from this literature: why is DA medication one of the greatest risk factors for ICBs?

To answer the question above, ICBs can be the result of an overdose of dopamine within MCL regions responsible for impulse control (Meder et al., 2019). As previously mentioned, in early, unmedicated (de novo) PD there is a reduction of dopamine in the nigrostriatal dopamine pathway (Dauer & Przedborski, 2003; Vaillancourt et al., 2013; Weintraub, 2008). Opposingly, structures constituting the MCL dopamine pathway, which are substantially involved in impulse control, remain relatively spared of dopamine reduction (Caminiti et al., 2017; Claassen et al., 2017; Cools et al., 2001, 2006; Gatto & Aldinio, 2019; Hollander & Evers, 2001; Kish et al., 1988; K. M. Smith et al., 2016; Weintraub, 2008). Moreover, there is

increased sensitivity of D2/D3 receptors following dopamine denervation from the midbrain to regions of the ventral striatum, which subsequently increases dopamine activity in connecting MCL regions (Prieto et al., 2009, 2011; Vriend, 2018; Vriend et al., 2014). This increase in dopamine is not enough to cause ICBs in early PD (Antonini et al., 2011; Ryu et al., 2019; Weintraub et al., 2013), it is in fact the addition of DAs which causes the overdose of dopamine within the MCL dopamine pathway (Cools et al., 2001; Goto & Grace, 2005). DAs primarily act upon D2 and D3 receptors, which are abundant in MCL regions, further increasing their dopaminergic activity (Gasser et al., 2015; Seeman, 2015). The overall result is a hyperdopaminergic state within the MCL dopamine pathway, which can lead to issues with dopamine modulation and ICB development (Gatto & Aldinio, 2019; Sinha et al., 2013; Vaillancourt et al., 2013; Weintraub, 2008). As a result, imaging studies report PD patients with ICBs display more dopaminergic dysfunctional connectivity within the regions highlighted above (e.g., ventral striatum and NAc as part of the MCL system) which constitute limbic and cognitive networks, compared to PD patients without ICBs (Roussakis et al., 2019).

As the disease progresses, both dosage and prolonged use of DAs can have a negative effect on impulse control. D2 autoreceptors are responsible for regulation of dopamine release from neurons (Ford, 2014); when dopamine is released from the axon terminal, these autoreceptors cause a transient inhibition in dopamine release (Ford, 2014; Ray, Miyasaki, et al., 2012). It is possible that long term activation of D2 autoreceptors via exogenous dopamine can lead to reduced inhibition of these autoreceptors (desensitisation), subsequent increased dopamine release and heightened risk of impulsive/risk-taking behaviours (Ford, 2014; Ray, Miyasaki, et al., 2012). Higher concentrations of dopamine have been found to activate D2 receptors to a greater extent than lower concentrations (Trantham-Davidson et al., 2004), which could also lead to reduced D2 receptor sensitivity. Furthermore, PD patients with ICBs have

been found to have lower D3 receptor levels (Barbosa et al., 2019) and reduced D2/D3 receptor binding (J. H. Ko et al., 2013), indicating a lower inhibitory effect and increased dopamine release in areas critical for executive function.

Other medications administered to treat the symptoms of Parkinson's disease are not often considered a risk factor for ICB development (Erga et al., 2017; Kraemmer et al., 2016; Weintraub et al., 2010). Levodopa (L-Dopa) is probably the most well-established form of DRT for PD, where administration results in the metabolism of L-Dopa into dopamine within dopaminergic neurons. However, there is some resistance to the prolonged use of L-dopa due to its potential role in inducing dyskinesia, motor complications, as well as its reduced effectiveness against PD symptoms in advanced PD (Nonnekes et al., 2016; Schapira et al., 2009). Over time, the capability of conversion of L-Dopa to dopamine in the nigrostriatal system is reduced and this dopamine is no longer released as efficiently in response to physiological stimuli due to storage in non-neuronal cells (Schapira et al., 2009). Recent findings suggest that reduced effects of L-Dopa may be because different symptoms of PD may not all respond to the same dosage, but also could be due to dose-limiting side effects or individual differences in pharmacodynamics/pharmacokinetics (i.e., delayed absorption) (Brooks, 2000; Nonnekes et al., 2016; Schapira et al., 2009). As a result, clinicians often prescribe DAs first to treat PD symptoms or alongside smaller dosages of L-Dopa to begin with in order to slow down this process of reduced effectiveness, consequently there is a greater risk of DA induced ICB development.

1.3.5. The Role of Genetics in Impulse Control Behaviours

As previously mentioned, not all PD patients on DA medication develop ICBs. The research in this thesis endeavours to investigate factors associated with the incidence, frequency or development of ICBs in PD. A key factor utilised in three experimental chapters of this thesis is the dopamine genetic risk score (DGRS). This section will outline the use of genetics to predict ICBs in PD and subsequently presents the DGRS in detail.

A number of studies have identified individual genetic polymorphisms associated with ICBs in PD. Of note, Kraemmer and colleagues (2016) reported the TC genotype of OPRK1 (rs702764) to be significantly associated with ICDs in PD and for those taking DA medication, along with HTR2A (rs6313 GA genotype), DDC (rs383709 -/AGAG genotype), DDC (rs3837091 -/- genotype) and DDC (rs1451375: AA genotype). Erga and others (2018) confirmed DRD1 (rs5326 minor allele) was associated with an increased risk of ICDs, whilst OPRK1 (rs702764 minor allele) was associated with a decreased risk of ICDs. Moreover, DRD1 (rs4532 T allele), DRD1 (rs4867798 C allele), GRIN2B (rs7301328 C allele) and DRD2/ANKK1 (rs1800497 T allele) have all been found to be associated with ICBs (Abidin et al., 2015). DRD3 (rs6280 AA genotype) and GRIN2B (rs7301328 CC genotype) can also be included in this list of significant associations (Lee et al., 2009). Some of these studies reported that the use of genetic and clinical factors improves the predictability of ICBs compared to clinical factors alone. Additionally, they have determined some individual genetic associations with the incidence of ICB, whilst this thesis provides evidence that a specific polygenic score from several genes is associated with the incidence but also change in ICBs in PD. Our DGRS may be more explicit in targeting genes within neural regions which are specifically implicated in impulse control.

A polygenic risk score (PRS) represents the risk estimate for a specific condition or disease for an individual, often using hundreds or thousands of genes (Torkamani et al., 2018). However, PRSs have been seen to lack clinical utility (Torkamani et al., 2018) and cannot be modified to target disease treatment or prevention unlike potential environmental factors. This is an emerging field where PRSs are somewhat robust and can potentially contribute to clinical action if correctly implemented (De Villiers et al., 2020; A. C. F. Lewis et al., 2021). To our knowledge, only three studies have investigated the association of polygenic risk scores and impulse control disorders in PD (Faouzi et al., 2021; Ihle et al., 2020; Weintraub et al., 2022). Ihle and colleagues (2020) used the most recent genome-wide association studies (GWAS) to form a PRS. This PRS included specific risk-increasing alleles within 90 weighted single nucleotide polymorphisms (SNPs) that were associated with PD. They found no associations with this PRS and impulse control disorders in PD, including within a DA PD cohort. Faouzi and others (2021) subsequently investigated a number of PRS from GWAS which were previously found to be associated with phenotypes such as psychiatric disorders and personality traits (e.g., impulsivity) to determine any potential associations with ICDs in PD. They utilised data from the PPMI database and the Drug Interaction With Genes in Parkinson's Disease study to find any associations between 40 PRS and ICDs. However, they found no associations between any PRS and ICDs in PD. Most recently, Weintraub and others (2022) formed a clinico-genetic predictor of ICDs from a cohort of 5770 participants. They investigated 17 SNPs and finalised a model involving just two SNPs (DRD2 rs1800497, OPRM1 rs179997) and seven clinical variables which confirmed very high risk of ICD development.

An alternative use of a genetic score is a cumulative genetic score (CGS) (Disner et al., 2014; Enge et al., 2020; Nikolova et al., 2011; Pearson et al., 2014). These scores are derived from specific alleles within genetic polymorphisms which are associated with a particular

behaviour or function and are often much smaller than a PRS. For example, Enge and colleagues (2020) produced a CGS where every allele of a specific dopamine polymorphism (DRD4 VNTR 7R, DAT1 VNTR 10R, COMT158val) which was previously found to be associated with impulsivity added a point to the total score. They found associations between a high (lower tonic dopamine activity) CGS and impulse control on the more demanding go/no-go task, whereas the low (higher tonic dopamine activity) CGS favoured the easier go/no-go task. These CGSs can increase effect size compared to investigating effects of individual genes (Enge et al., 2020), but they also involve the use of very specific genetic polymorphisms that are involved in certain behaviours or functions which may increase predictability of a behaviour/disease progression. The research presented in the current thesis utilises a small, specific cumulative genetic score.

The term dopamine genetic risk score (DGRS) is used throughout this thesis, which theoretically quantifies the influence of five polymorphisms within dopaminergic genes which modify dopamine neurotransmission in MCL regions (Caminiti et al., 2017; Pearson-Fuhrhop et al., 2013, 2014; K. M. Smith et al., 2016; Vriend et al., 2014): DRD1 rs4532, DRD2 rs1800497, DRD3 rs6280, catechol-O-methyltransferase (COMT) rs4680 and dopamine transporter (DAT) rs28363170. DRD1, DRD2 and DRD3 encode D1, D2, D3 receptors, respectively. Dopamine binds to G-coupled protein receptors, primarily categorised as D1-like (D1, D5) or D2-like (D2, D3, D4) subtypes, which can then modulate signalling cascades within the cell (Bhatia et al., 2022; Missale et al., 1998; Vallone et al., 2000). COMT is responsible for the degradation of dopamine after it enters the synaptic cleft (Witte & Flöel, 2012), whilst DAT is responsible for the reuptake of dopamine into pre-synaptic neurons (Hovde et al., 2019).

In theory, the DGRS quantifies widespread tonic dopamine neurotransmission. This depends on the specific mutations within each polymorphism with contributes to higher or lower levels of dopamine neurotransmission (for a summary see Pearson-Fuhrhop et al., 2013). Each polymorphism receives a score of 0 or 1, resulting in a total score of 0-5 where a higher score equates to higher dopamine neurotransmission. The theory of the DGRS was first developed by Pearson-Fuhrhop and colleagues (2013), where it was called a 'gene score'. In this study, they determined those with a lower gene score showed the greatest improvement in motor learning with L-Dopa compared to placebo, whilst a higher gene score had a worsening effect on motor learning. Subsequently, the more specific term DGRS, was first introduced by Pearson-Fuhrhop and others (2014), which is an extension of a genetic risk score (GRS), where a GRS is defined as "an estimate of the cumulative contribution of genetic factors to a specific outcome of interest in an individual", by Igo Jr. et al., (2019). Here, they discovered lower dopamine neurotransmission (low DGRS) was associated with higher depression levels (Pearson-Fuhrhop et al., 2014). MacDonald and others (2016) then used the DGRS within the theme of impulse control. The genes included in the DGRS modify dopamine neurotransmission within MCL regions (Caminiti et al., 2017; K. M. Smith et al., 2016; Vriend et al., 2014) and influence impulse control (Abidin et al., 2015; Congdon et al., 2009; Erga et al., 2018; Lee et al., 2009; K. M. Smith et al., 2016; Vriend et al., 2014). In MacDonald et al (2016), they concluded that the administration of DA medication, ropinirole, in healthy adults improved impulse control for those with lower DGRS and impulse control worsened for participants with a high DGRS. The measures of impulse control were SSRT from the ARIT and negative reinforcement from the BART. It is these results from the study by (MacDonald et al., 2016), which are discussed in more detail throughout the experimental chapters, which drive specific aims and hypotheses throughout this thesis. As mentioned above, the DGRS can explain patterns of impulsivity in healthy older adults. The DGRS is utilised throughout this

thesis to assess the potential predictability of these genetic polymorphisms to predict the incidence, frequency or change in impulsive behaviour for those with PD, specifically ICB development. Following the definition by Igo Jr. et al., (2019) and important results presented by MacDonald et al., (2016) and Pearson-Fuhrhop et al., (2013, 2014), the term DGRS is a suitable term to describe a way to measure the potential 'risk' of impulsive behaviour for individuals, depending on their genotype.

1.4. Central and Peripheral Dopamine

In the previous section of this introduction, the DGRS was introduced, which has the potential to quantify central levels of dopamine within MCL regions, particularly implicated in impulse control. Whilst this has some good preliminary evidence and rationale, it is currently a theory which needs to be further tested. A potential way to confirm differences in the quantity of dopamine levels between different DGRS is to compare these scores with a measure of directly metabolised dopamine, Homovanillic Acid (HVA), which can partially reflect central levels of dopamine.

1.4.1. Homovanillic Acid

The production of HVA can be derived both centrally (dopamine neurons) or peripherally (neuronal fibres, adrenal medulla, and neuroendocrine cells) (Amin et al., 1992; Rubí & Maechler, 2010). More specifically, the three main sources of HVA are endogenously from dopamine neurons and noradrenergic (NA) neurons (primary neurotransmitter is norepinephrine (NE)) and exogenously from diet contributions (Amin et al., 1992). The majority of endogenous centrally derived HVA comes from dopamine neurons in the brain, whilst there is a small contribution from central NA neurons (Amin et al., 1992). Likewise, there are also some peripheral dopaminergic nerves which contribute to HVA levels (Bell, 1988). Peripherally derived HVA is produced mostly via NA neurons from the peripheral nervous system which synthesise dopamine as a precursor (and therefore HVA) during the production of NE (Amin et al., 1992, 1995). The biosynthesis of HVA is outlined below and in Figure 1.2 (Meiser et al., 2013).

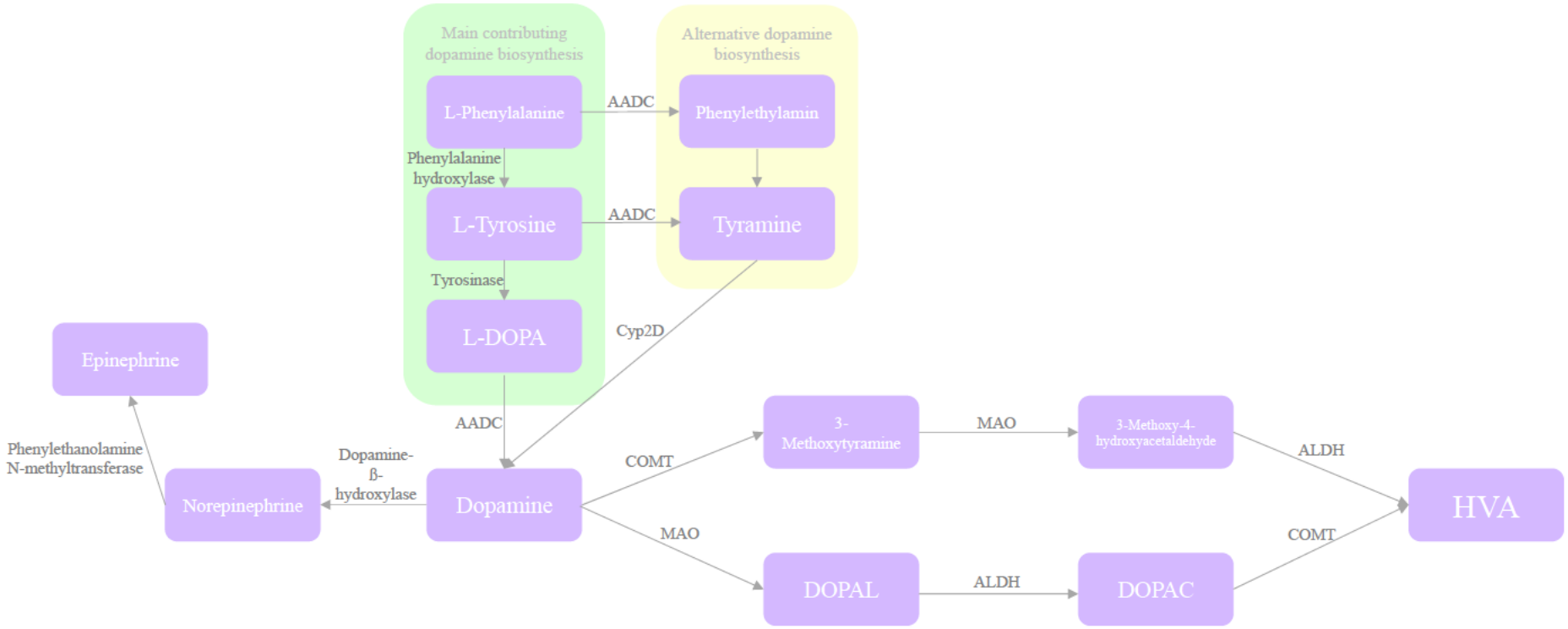

Figure 1.2 Pathways of Dopamine Biosynthesis.
AADC: aromatic amino acid decarboxylase; COMT: catechol-O-methyltransferase; MAO: monoamine oxidase; ALDH: aldehyde dehydrogenase. (Meiser et al., 2013).

The biosynthesis of HVA begins with tyrosine which is transported to the catecholaminergic neurons where HVA biosynthesis takes place (Elsworth & Roth, 1997) within two pathways (Meiser et al., 2013). The main contributing pathway begins at the amino acid, phenylalanine, which is hydroxylated by phenylalanine hydroxylase or tyrosine hydroxylase to form Tyrosine in the liver or within catecholaminergic neurons, respectively (Elsworth & Roth, 1997). Tyrosine is subsequently hydroxylated by Tyrosinase to form 3,4-dihydroxyphenylalanine (DOPA), which is decarboxylated by aromatic amino acid decarboxylase (AADC) to produce dopamine (Best et al., 2009; Meiser et al., 2013). The alternative pathway involves AADC converting Tyrosine to Tyramine before oxidisation by Cyp2D to dopamine (Meiser et al., 2013). In dopamine neurons, dopamine can be stored or released as a neurotransmitter, but in NA neurons co-release of both NE and dopamine can take place (Ranjbar-Slamloo & Fazlali, 2020). The production of NE from dopamine in NA neurons is synthesised by the enzyme Dopamine-ß-hydroxylase, which in turn can form Epinephrine by methylation via Phenylethanolamine N-methyltransferase (Meiser et al., 2013). Alternatively, in the production of HVA, when dopamine is released from neurons into the synaptic cleft following excitation, this dopamine can bind to receptors on post-synaptic neurons, but some dopamine is reabsorbed back into the nerve terminal. This re-absorbed dopamine is metabolised into 3,4-dihydroxyphenylacetaldehyde (DOPAL) by monoamine oxidase (MAO) and then 3,4-dihydroxyphenylacetic acid (DOPAC) by aldehyde dehydrogenase (ALDH). The small amount of dopamine left in the synaptic cleft is converted to 3-methoxytyramine (3-MT) by COMT and then 3-Methoxy-4-hydroxyacetaldehyde by MAO. Both DOPAC and 3-Methoxy-4-hydroxyacetaldehyde are converted to HVA, by COMT and ALDH, a metabolite of dopamine, which can then be measured within the blood plasma (pHVA) (Amin et al., 1992; Elsworth & Roth, 1997; Meiser et al., 2013). pHVA

concentrations can subsequently be quantified using an Enzyme-linked immunosorbent assay (ELISA) kit, which is utilised in the final experimental chapter of this thesis.

It is possible that HVA can be measured from blood plasma, urine and cerebral spinal fluid (CSF) and can partially reflect central dopaminergic neural activity (Amin, Davidson & Davis, 1992; Nemoda et al., 2011). Although measurements of HVA from the CSF may appear to reflect more central levels of dopamine due to the location within the central nervous system, it is also reported that neural HVA can often bypass the CSF (Amin et al., 1992). Additionally, the method of CSF extraction is by a lumbar puncture which is invasive and can cause complications such as prolonged headaches, lower limb pain and herniation (Boon et al., 2004; Evans, 1998). Alternatively, extracting blood plasma is less invasive but can still be painful, whilst taking a measure of urine is non-invasive and not painful but can be time consuming. These two measures may also be affected by peripheral and dietary HVA contributions (Amin et al., 1992). In order to estimate central levels of dopamine in HVA, COMT or MAO inhibitors which do not cross the blood brain barrier can be administered to supress peripherally sourced dopamine, theoretically resulting in only central derived levels of HVA (Amin et al., 1995; Siderowf & Kurlan, 1999). Estimated levels of central dopamine derived from HVA can be less than 10% in CSF, 25% for urine (Amin, Davidson & Davis, 1992) and 25-65% in blood plasma (Amin et al., 1992, 1995; Sternberg & Heninger, 1983). As previously mentioned, an exogenous source of HVA is from diet contributions (Amin et al., 1992). Diets consisting of foods high in monoamine and flavonoid content can increase levels and longevity of HVA, which is due to peripherally derived HVA or direct absorption (Combet et al., 2011; Kendler et al., 1983) Therefore a period of fasting and a low monoamine diet may remove the effect of diet on changes in pHVA levels (Davidson et al., 1987) and enable a more accurate measure

of HVA derived from central dopamine (Amin et al., 1995). All of the information above needs to be considered before confirming the approach to measure HVA.

The final experimental Chapter (6) of this thesis investigates whether blood plasma levels of HVA in young healthy adults, within a diet-controlled environment, are associated with levels of theoretically quantified central dopamine via the DGRS. This chapter may provide the first steps of confirming the theory of the DGRS but also confirming that pHVA can somewhat reflect levels of centrally derived dopamine.

CHAPTER 2

Regression Model Development for Statistical Analyses & Bayesian Statistics

2.1. Introduction to Regression Modelling

Regression models were conducted to a small or large extent throughout this thesis. These regression models were used at times to determine variables associated with ICBs in those with PD, impulsivity task performance or trait impulsivity. Additionally, these models were used to work towards predicting those with PD who are most likely to develop ICBs on DA medication, which incorporated the changes in impulsivity over time on medication to determine associations or predictors, often of impulse control measures. The following sections describe the processes involved in regression selection and implementation. All models were developed and implemented in MATLAB (MathWorks, versions 2016a – 2021b) with written custom code and utilisation of inbuilt functions.

2.2. Binary Logistic Regression Models

A multivariate binary logistic regression model established significant associations or predictors of incident ICB in Chapter 3. Chapter 3 utilised a DGRS to predict the incidence of ICBs in PD, via the QUIP. The QUIP, as discussed in Chapter 1, involves subjects answering 'yes' or 'no' in response to questions regarding a variety of impulsive behaviours and is often used as a tool alongside an interview from a specialised clinician to diagnose the presence of an ICB. The binary logistic regression model was selected to determine a binary response of 'yes' or 'no', in response to a positive score on the QUIP (positive ICB incidence) or a score of zero, respectively. These responses were transformed to indicator variables where 'yes' = 1 and 'no' = 0. This binary response was termed 'response variable' and the model utilised a binomial distribution with a logit (natural log odds) link. p represents the probability of Y response variable equalling 1 ($Y = 1$). β represents the regression coefficient of independent variable X, $\beta 0$ is the intercept and k is the total number of independent variables:

$$logit(Y = 1) = logit(p) = \ln\left[\frac{p}{1-p}\right]$$

$$\ln\left[\frac{p}{1-p}\right] = \beta 0 + \beta 1X1 + \beta 2X2 + \cdots + \beta kXk$$

$$\left[\frac{p}{1-p}\right] = e^{\beta 0+\beta 1X1+\beta 2X2+\cdots+\beta kXk}$$

$$p = \frac{e^{\beta 0+\beta 1X1+\beta 2X2+\cdots+\beta kXk}}{1-e^{\beta 0+\beta 1X1+\beta 2X2+\cdots+\beta kXk}}$$

A robust and objective set of recommended steps were followed to develop this model (Harrell, 2015; Harrell et al., 1985; Hendriksen et al., 2013; Steyerberg et al., 2013). Firstly, hypothesis-driven candidate independent or 'predictor' variables were identified from prior literature (Giladi et al., 2007; Kraemmer et al., 2016; Nombela et al., 2014; Voon, Mehta, et

al., 2011; Weintraub et al., 2006). These independent variables were either continuous or categorical variables. Secondly, subsequent linear regressions were run between all continuous variables to test for collinearity. If collinearity existed, variables were combined, or one removed to reduce the number of independent variables and increase the reliability of the model. Additionally, the relationship between each selected independent variable and the response variable was initially investigated using univariate binary logistic regression analyses, where the individual association between each independent variable and the response variable was determined. This process helped assess which variables could be excluded from the final model if the model was overparameterized. Sample size was acknowledged for the model where 10 events per variable (EPV) (10 participants per one independent variable) was advised (Harrell, 2015; Harrell et al., 1985; Hendriksen et al., 2013), which was why this model was only used in Chapter 3 as sample sizes were not large enough in Chapters 5 and 6. Although some recent literature has started to suggest an alternative method to assess sample size in binary logistic regression which incorporates the number of independent variables, total sample size and the events fraction: N = 10 x P / events fraction, P = predictor variables, N = required sample size, events fraction (probability $Y = 1$) = n participants ICB $\geq$ 1 / n total participants (van Smeden et al., 2019).

The list of independent variables was then finalised to be entered into the multivariate binary logistic regression model. This model included the selected independent variables and important interactions. Continuous variables (Duration (of DA medication) and UPDRS I&II) were entered directly into the model as independent variables. Categorical variables selected were gender and DGRS. Gender (male or female) was treated as a binary predictor variable and 'male' was selected as the reference variable, therefore results would display the likelihood of males displaying a positive QUIP score compared to females. The DGRS, introduced in

Chapter 1, was a categorical variable initially consisting of 5 polymorphisms where each participant had a score between 0-5. However, the score was reduced to 0-4 as the variable number tandem repeat in the DAT gene was unavailable. Rather than having 5 categories (one per score 0-4), to increase the sample size for each category, three DGRS groups were formed: low (DGRS 0-1), medium (DGRS 2) and high (DGRS 3-4). A reference variable was required for categorical variables in the binary logistic regression model: medium was selected for the DGRS. As a result, the output of the model determined if those with a low or high DGRS, compared to medium, were more likely to have a positive ICB incidence. Interactions were included (Harrell, 2015), treated as independent variables, which kept the model within the 10 EPV limit.

Once implemented, validation of the model (i.e., goodness-of-fit) was assessed against a constant model using a chi-squared test ($p < 0.05$). Two receiver operating characteristic (ROC) curves were produced: one with only participant demographic and clinical data, and a second with genetic data from the DGRS included. These ROC curves evaluated specific changes to the predictability of incident ICB with and without the addition of genetic measures, which has been investigated in similar studies (Erga et al., 2018; Kraemmer et al., 2016). The resultant area under the ROC curve (AUC) values were compared using DeLong's test (DeLong et al., 1988).

The output of the model produced coefficients which were the logit values (β), standard error (SE) and significance values (p). In order to interpret the coefficients of logistic regression models, these values were converted into odds or odds ratios (ORs) by exponentiation (e^{β}) (Hailpern & Visintainer, 2003; Sperandei, 2014). Interpretation of the odds or ORs are as follows. Continuous variables (Duration and UPDRS I&II) were treated within the model

where an increase or decrease of one unit of said variable increased the odds of an ICB ($Y = 1$) by a specific percentage or by X times (e.g., OR of 1.09 = 9% or 1.09 times more likely). For categorical variables (gender and UPDRS I&II), the OR determined the odds of a particular category having an ICB ($Y = 1$) compared to another category (reference variable) (e.g., OR of 18 = 18 times more likely to have an ICB if you are male compared to female). With regards to interpreting interactions including categorical and continuous variables, an example includes how one day increase in duration for males changes the odds of having an ICB (OR = $e^{(\beta\ duration + \beta\ interaction\ of\ duration * male\ gender)}$).

2.3. Linear Regression Models

Multiple Linear regression models were implemented in Chapter 5 to establish significant associations or predictors of ICBs. These particular models were chosen due to the continuous response variables, ICB frequency (determined by the QUIP rating scale, range 0 -112) and BIS percentage, compared to the binary response variable of ICB incidence. Independent variables were selected to find any linear relationship with ICB frequency and BIS percentage. Y is the response variable, β represents the regression coefficient of independent variable X, β_0 is the intercept, k is the total number of independent variables and ε is random error:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_k X_k + \varepsilon$$

These linear regression models were developed based on assumptions and recommendations (Ali & Younas, 2021; Casson & Farmer, 2014; Schneider et al., 2010; Uyanık & Güler, 2013) which are explained below. Previous literature highlighted potential independent variable candidates for inclusion in the model. These variables were either continuous or categorical. Continuous variables could be entered straight into the model, whilst a reference variable was selected for all categorical variables. Univariate linear regressions were run between these independent variables and the response variable to confirm any initial relationship. These univariate linear regressions were also graphed with a scatter plot to assess the visual pattern of results, if any. These patterns helped assess which variables could be included or excluded from the final model if the model was overparameterized. Correlation coefficients were determined between all candidate continuous independent variables which highlighted any collinearity. For all collinear variables, one was removed from the final model.

After the model was implemented, as advised (Casson & Farmer, 2014), a scatter plot of residual errors vs predicted values displaying a random scatter around the zero-line confirmed zero conditional mean error and constant variance of errors. This confirms the normality assumption, where we can complete statistical hypothesis testing with our values. Model validation was determined and interpreted using adjusted R^2 values (0.01 = small effect, 0.09 = medium effect, 0.25 = large effect, Foster et al., 2018). With regards to sample size, some literature suggests only 2 subjects per variable (SPV) (Austin & Steyerberg, 2015) are necessary for estimation of adequate linear regression outputs, whereas others suggest 10 (Casson & Farmer, 2014) or 20 (Schneider et al., 2010). Whilst considering the suggestions above and searching more of the literature, an appropriate way to find an adequate sample size seems to be also including R^2 and power calculations (Cohen, 1988; Cohen et al., 2003). Therefore, the effect size established from adjusted R^2 was used in the subsequent statistical power calculation (using G*Power 3.1.9.6, (Erdfelder et al., 1996) to conclude the appropriate sample size for an adequate power value for these linear regressions (Cohen, 1988). An acceptable value for statistical power (probability of rejecting null hypothesis) is above 0.80 (Jan & Shieh, 2019; Valentine et al., 2010). Each model was validated against a constant model (goodness-of-fit) using the F-statistic ($p < .05$).

Following the output of the model, the following were reported: coefficient values (β), standard error (SE), significance values (p) and 95% confidence interval range (95% CI β). The 95% CI β presents the possible range of the coefficients within the population (Cohen et al., 2003; Foster et al., 2018). Continuous variables were treated within the model output where an increase or decrease of one unit of said variable increased ICB frequency/BIS percentage by a specific value β. With regards to categorical variables, the variable in question (e.g., male) had an ICB frequency/BIS percentage of β more than/less than the reference variable (e.g.,

female). When interpreting interactions $\beta_3(\beta_1 * \beta_2)$ between continuous and categorical variables, for each unit increase in the continuous variable β_1, ICB frequency/BIS percentage changes by the amount $\beta_1 + \beta_3$ for the reference categorical variable ($\beta_2 = 1$) (Hayes & Montoya, 2017).

2.4. Bayesian Statistics

Bayesian statistics is a form of statistical data analysis based upon the theorem developed by Thomas Baye (Fornacon-Wood et al., 2022). Frequentist statistics is a more common method used for statistical analysis, and this method assesses the probability of data using significance testing of null hypotheses (Fornacon-Wood et al., 2022). Whereas Bayesian statistics assesses the probability of hypotheses, using previous knowledge (prior) and new (posterior) data (Ferreira et al., 2020; Fornacon-Wood et al., 2022; Hackenberger, 2019). The probabilities of two hypotheses are evaluated within a ratio, which is also called the Bayesian Factor (Hackenberger, 2019). The Bayesian Factor ranges from near zero to infinity and provides evidence to support the null or alternative hypothesis (Hackenberger, 2019). The formula for Bayes theorem is displayed below, where A is the prior probability of an outcome, given the new data, B. P is the probability (Ferreira et al., 2020; Fornacon-Wood et al., 2022).

$$P(A|B) = \frac{P(B|A) \cdot P(A)}{P(B)}$$

Bayesian statistics were used within Chapter 4 to confirm there were no differences in SSRT between sessions 1 and 2 for non-selective response inhibition in the ARIT and SST. Here, Equivalence Bayesian Paired Samples t-tests produced Bayes Factor values which identified the strength of evidence for the alternative hypothesis. It is possible that using Bayesian statistics provides another level of analysis, further to frequentist statistics, to add strength to results.

CHAPTER 3

Dopamine Genetic Risk Score Predicts Impulse Control Behaviors in Parkinson's Disease

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I confirm I participated in all aspects of the development of the research within this chapter, data/statistical analyses and the writing and revisions of the manuscript.

3.1. Abstract

Introduction: Up to 40% of Parkinson's disease patients taking dopamine agonist medication develop impulse control behaviors which can have severe negative consequences. The current study aimed to utilize dopamine genetics to identify patients most at risk of developing these behaviors. **Methods:** Demographic, clinical, and genetic data were obtained from the Parkinson's Progression Markers Initiative for de novo patients (n=327), patients taking dopamine agonists (n=146), and healthy controls (n=160). Impulsive behaviors were identified using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease. A dopamine genetic risk score was calculated for each patient according to polymorphisms in genes coding for dopamine D1, D2 and D3 receptors, and catechol-O-methyltransferase. A higher score reflected higher central dopamine neurotransmission. **Results:** Patients on agonists with a low dopamine genetic risk score were over 18 times more likely to have an impulsive behavior compared to higher scores ($p = 0.04$). The 38% of patients taking agonists who had at least one impulsive behavior were more likely to be male and report higher Unified Parkinson's Disease Rating Scale I&II scores. With increasing time on dopamine agonists (range 92-2283 days, mean 798±565 standard deviation), only patients with a high dopamine genetic risk score showed an increase in number of impulsive behaviors ($p = 0.033$). Predictive effects of the gene score were not present in de novo or healthy control. **Conclusions:** A dopamine genetic risk score can identify patients most at risk of developing impulsive behaviors on dopamine agonist medication and predict how these behaviors may worsen over time.

3.2. Introduction

Impulse control is an essential aspect of self-restraint. Dopamine systems are important regulators of impulse control, such that abnormal levels of dopamine can lead to problems with impulsivity (Sinha et al., 2013; Weintraub, 2008). A significant risk factor for problems with impulse control in Parkinson's disease (PD) patients is dopamine agonist (DA) medication. Up to 40% of patients administered DAs develop impulse control disorders (ICDs) e.g., pathological gambling, binge eating, compulsive shopping or hypersexuality (Bastiaens et al., 2013; Erga et al., 2018; Kraemmer et al., 2016). Here, we use the term impulse control behaviors (ICBs), a term commonly used to describe all ICDs and related behaviors (Abidin et al., 2015).

Sparing of specific dopaminergic networks in PD combined with dopamine medication may elevate the risk of ICBs. In early, unmedicated (de novo) PD there is a reduction of nigrostriatal dopamine (Vaillancourt et al., 2013; Weintraub, 2008). In contrast, dopamine is relatively spared in the amygdala, ventral striatum, prefrontal cortex and orbital frontostriatal circuits, constituting the mesocorticolimbic (MCL) system (Caminiti et al., 2017; Cools et al., 2001; K. M. Smith et al., 2016). The MCL system is heavily involved in impulse control (Weintraub, 2008). Furthermore, in PD there is heightened sensitivity of D2/D3 receptors following dopamine denervation from the midbrain to areas of the ventral striatum, which in turn further increases dopamine activity in the connecting MCL regions (Prieto et al., 2009; Vriend et al., 2014). However, dysregulation of MCL dopamine from PD mechanisms alone is insufficient to increase the incidence of ICBs in de novo PD compared to controls (Antonini et al., 2011; Ryu et al., 2019; Weintraub et al., 2013). The addition of DA medication is thought to cause a dopamine overdose within the relatively spared MCL system (Cools et al., 2001; Goto & Grace, 2005). DA medications primarily act on D2/D3 receptors (Gasser et al., 2015)

further increasing their activity. The resultant tonic hyperdopaminergic state can lead to problems with phasic dopamine modulation and over time the development of ICBs (Sinha et al., 2013; Vaillancourt et al., 2013; Weintraub, 2008).

Using genetics to guide precision medicine is fast gaining traction and may be applicable to reduce the incidence of ICB side-effects. Polymorphisms within single dopamine genes are individually associated with the incidence of ICBs in PD (Abidin et al., 2015; Cormier-Dequaire et al., 2018; Erga et al., 2018; Kraemmer et al., 2016; Lee et al., 2009), though no study to date has investigated the collective influence of multiple genetic polymorphisms as a genetic risk score on widespread central dopamine levels and ICBs. A polygenic dopamine genetic risk score (DGRS) (MacDonald et al., 2016; Pearson-Fuhrhop et al., 2013, 2014) is a strong candidate for quantifying widespread tonic dopamine neurotransmission. A DGRS quantifies the effect of polymorphisms within five key genes that modify dopamine neurotransmission within MCL regions (Caminiti et al., 2017; K. M. Smith et al., 2016; Vriend et al., 2014) and affect impulse control (Abidin et al., 2015; Congdon et al., 2009; Erga et al., 2018; Lee et al., 2009; K. M. Smith et al., 2016; Vriend et al., 2014): DRD1, DRD2, DRD3 (encoding D1, D2 and D3 receptors, respectively), catechol-O-methyltransferase (COMT), and dopamine transporter (DAT). A DGRS can predict impulse control in healthy older adults, including how impulse control will change with administration of DAs (MacDonald et al., 2016). In that study (MacDonald et al., 2016), both motor and cognitive aspects of impulse control were worse for participants with a low versus high DGRS at baseline. Ropinirole caused worsening impulse control for participants with a high DGRS, whereas participants with a low DGRS saw improvements.

The present study investigated whether a DGRS can predict ICBs in a large sample of PD patients. Demographic, clinical and genetic data were obtained from the Parkinson's Progression Markers Initiative (PPMI) database. The primary aim was to determine the association between DGRS and the development of ICBs, within de novo and PD patients on DAs. The secondary aim was to establish which demographic and clinical variables were associated with ICBs and whether they interacted with the DGRS. We hypothesized that patients on DAs with a low DGRS would be more likely to have an ICB, but that ICBs would reduce over time on medication. Conversely, we hypothesized that patients with a high DGRS would be less likely to have an ICB, but that ICBs would increase with greater time on medication. We further hypothesized that ICBs would be associated with male gender and a higher Unified Parkinson's Disease Rating Scale (UPDRS) I&II score (Cormier et al., 2013; Cormier-Dequaire et al., 2018; Kraemmer et al., 2016). Genetic and demographic data from healthy controls were included and no associations were expected with ICBs.

3.3. Materials and Methods

3.3.1. Participants

The PPMI is an ongoing, cohort database including demographic, clinical, imaging, genetic and biological data for PD patients and healthy controls. PPMI is a public-private partnership, funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners (http://www.ppmi-info.org). Clinical and demographic data from 2035 individuals were downloaded on 22 October 2018 and genetic data on 29 April 2019. Individuals were categorized into three groups: de novo (DN): with PD before medication, dopamine agonist (DA): with PD taking DA medication, or healthy control (HC).

3.3.2. Clinical Measures

Impulse control was measured via the short form of the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-short), a globally validated screening tool to identify ICBs with any positive score (Weintraub et al., 2009). The QUIP involved answering 'yes' or 'no' to 13 questions, resulting in a score of 1 or 0 for each question, respectively. Total scores therefore ranged from 0-13. QUIP score and current age were taken at maximum time since starting DAs/PD diagnosis/study enrolment, as appropriate. Duration refers to continuous time on DA medication/time since diagnosis at the time of the QUIP. Severity of PD symptoms in activities of daily living was assessed using the UPDRS parts I&II (Goetz et al., 2003). UPDRS parts III and IV were not available from a sufficient number of patients to include in the study.

3.3.3. Genetic Data

Five specific genetic polymorphisms were identified for analysis *a priori* (MacDonald et al., 2016). However, data was not available to analyze the variable number tandem repeat in the

DAT gene (rs28363170) as the untranslated regulatory region of this gene was not genotyped. Exome sequencing files for the remaining four single nucleotide polymorphisms (SNPs) were used. Exome sequencing was performed on whole-blood extracted DNA samples using an Illumina rapid capture expanded exome kit. Sequencing data was aligned against the University of California Santa Cruz reference human genome 19 to find the 4 genotype locations for each SNP using GATK (VariantsToTable, version 4.1.2.0). For complete methods, see Exome Sequencing Methods (project 116), (http://www.ppmi-info.org/data). The DGRS (Appendix 1) was adapted to a scale of 0-4 (higher score = higher dopamine levels) according to the SNP within the following genes: DRD1 (rs4532), DRD2 (rs1800497), DRD3 (rs6280) and COMT (rs4680) (Pearson-Fuhrhop et al., 2013, 2014). All genes apart from COMT ($p = .008$) were in Hardy-Weinberg equilibrium ($.07 > p < .86$).

3.3.4. Statistical Analysis

Data analysis and statistical modelling were performed in MATLAB (version R2020a, MathWorks) and R (R Core Team, version 3.6.3). Chi-square tests assessed Hardy–Weinberg equilibrium for each gene. Normality assumptions were checked using the Kolmogorov-Smirnov test. When normality was violated, data were analyzed using the Wilcoxon Rank-Sum test. Statistical significance was set at $p \leq 0.05$.

3.3.4.1. ICB incidence

ICB incidence was defined as any positive score on the QUIP. Candidate independent variables were age, DGRS, duration, gender and UPDRS I&II score (Bastiaens et al., 2013; Kraemmer et al., 2016; MacDonald et al., 2016; Voon, Sohr, et al., 2011; Weintraub et al., 2006). The DGRS was categorized into three ranges: low (DGRS 0-1), medium (DGRS 2, reference variable in regression analyses) and high (DGRS 3-4) to increase sample size for

each group. Linear regressions were run between continuous variables to test for collinearity. If collinearity existed, variables were removed from the model to avoid overparameterization. The relationship between each independent variable and the response variable was initially investigated using univariate binary logistic regression analyses (Appendix 2), which confirmed variables to include in the full model. A multivariate binary logistic model was developed which included the selected independent variables and important interactions. Model validation (i.e. goodness-of-fit) was assessed against a constant model using a chi-squared test ($p < 0.05$). Two receiver operating characteristic (ROC) curves were produced for each participant group's multivariate model to evaluate specific changes to the predictability of incident ICB following the inclusion of the DGRS (Appendix 3, 4). Resultant AUC values were compared using DeLong's test (DeLong et al., 1988).

3.3.4.2. QUIP score change on medication

Correlations between QUIP score (i.e. number of ICBs) and time on DA medication were run for each DGRS range (low, medium, high). Fisher z transformations identified differences between correlations.

3.4. Results

3.4.1. Participant Characteristics

Data from 506 individuals (36-89 years, mean 63.7 ± 9.92 standard deviation) were included in the analysis (DN = 327; DA = 146; HC = 160; 127 DA patients had data since de novo stage so contributed to both DN and DA groups). Patients had a DGRS of low, medium or high. The number of patients with each DGRS for every group was as follows: DN group Low: n = 44, Medium: n = 106, High: n = 177; DA group Low: n = 23, Medium: n = 50, High: n = 73; HC Low: n = 24, Medium: n = 45, High: n = 91.

Demographic and clinical data are presented in Table 3.1. Kolmogorov-Smirnov tests identified the QUIP score in all groups and the UPDRS I&II score in the DA group violated normality ($p < .001$), therefore a Wilcoxon rank sum test was used to compare scores between individuals with/without ICBs. All remaining variables were normally distributed ($p > 0.194$) so comparisons were made using unpaired t-tests. Patients in the DN group who identified an ICB had a higher UPDRS score ($p = 0.007$) than those without an ICB. In the DA group, a greater number of males ($p = 0.041$) and patients with a higher UPDRS ($p < 0.001$) presented with an ICB. In the HC group, there was no difference in variables between those with and without an ICB (all $p > 0.383$).

Table 3.1 Participant demographics and clinical assessments for de novo, dopamine agonist and healthy control groups, separated by incidence of impulse control behaviours.

De novo (DN)			
	ICB (n = 43)	**No ICB (n = 284)**	**p**
Age, years	61.3 (9.45)	62.7 (9.83)	.366
DGRS 0-4	2.39 (1.05)	2.54 (0.95)	.105
Duration, days	497 (316)	530 (357)	.569
Gender, %male (n, male:female)	58.1 (25:18)	67.6 (192:92)	.222
QUIP score	**1.58 (0.76)**	**0**	**<.001♦**
UPDRS I&II	**18.2 (9.73)**	**14.5 (8.13)**	**.007**
Dopamine agonist (DA)			
	ICB (n = 56)	**No ICB (n = 90)**	**p**
Age, years	62.8 (9.35)	63.3 (7.61)	.712
DGRS 0-4	2.39 (0.93)	2.44 (1.03)	.760
Duration, days	869 (554)	843 (567)	.785
Gender, %male (n, male:female)	**71.4 (40:16)**	**54.4 (49:41)**	**.041**
QUIP score	**1.96 (1.26)**	**0**	**<.001♦**
UPDRS I&II	**23.8 (12.2)**	**16.4 (11.0)**	**<.001♦**
Healthy control (HC)			
	ICB (n = 25)	**No ICB (n = 135)**	**p**
Age, years	65.5 (12.7)	66.9 (10.7)	.570
DGRS	2.48 (0.96)	2.54 (0.92)	.764
Gender, %male (n, male:female)	56.0 (14:11)	65.2 (88:47)	.383
QUIP score	**1.52 (0.71)**	**0**	**<.001♦**

Means for variables (±standard deviation). ICB: impulse control behaviour (n: number). DGRS: dopamine genetic risk score; QUIP: Questionnaire for impulsive-Compulsive Disorders in Parkinson's Disease; UPDRS: Unified Parkinson's Disease Rating Scale. Significant values in bold. ♦: Wilcoxon rank sum test.

3.4.2. ICB Incidence

3.4.2.1. Dopamine agonist group

DGRS, duration, gender and UPDRS I&II score were included in the model with DGRS x duration and DGRS x UPDRS I&II interactions (Table 3.2). Age was excluded to avoid over-parameterization following univariate analysis (Appendix 2).

Binary logistic regression function:

$$p = \frac{\exp(\beta_0(intercept) + \beta_1 DGRS + \beta_2 Duration + \beta_3 \text{Gender} + \beta_4 \text{UPDRS} + \beta_5 \text{DGRSxDuration} + \beta_6 \text{DGRSxUPDRS})}{1 + \exp(\beta_0(intercept) + \beta_1 \text{DGRS} + \beta_2 \text{Duration} + \beta_3 \text{Gender} + \beta_4 \text{UPDRS} + \beta_5 \text{DGRSxDuration} + \beta_6 \text{DGRSxUPDRS})}$$

Table 3.2 Variables associated with impulse control behaviours in the dopamine agonist group.

	β	SE	p value	Odds/OR	95 % CI (Odds/OR)
Intercept	**-3.819**	**1.141**	**<0.001**	**0.02**	**[0.002, 0.210]**
DGRS low	**2.896**	**1.417**	**0.04**	**18.1**	**[1.099, 298.4]**
DGRS high	1.851	1.274	0.146	6.40	[0.513, 79.18]
Duration (days)	0.0007	0.0006	0.206	1.00	[1.000, 1.002]
Gender (male)	**0.817**	**0.405**	**0.044**	**2.26**	**[1.015, 5.046]**
UPDRS I&II	**0.088**	**0.034**	**0.01**	**1.09**	**[1.021, 1.169]**
DGRS low * Duration	-0.001	0.001	0.161	1.00	[0.997, 1.001]
DGRS high * Duration	-0.0007	0.0008	0.257	1.00	[0.998, 1.001]
DGRS low * UPDRS I&II	-0.048	0.05	0.338	0.95	[0.863, 1.053]
DGRS high * UPDRS I&II	-0.032	0.042	0.455	0.97	[0.891, 1.053]

Response variable: positive score on Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (yes/no). DGRS: dopamine genetic risk score, UPDRS: Unified Parkinson's Disease Rating Scale. β: coefficient, SE: standard error, OR: odds ratio (OR = e^{β}), CI: Confidence Interval. Significant values in bold.

The multivariate binary logistic regression model was validated against a constant model ($p = 0.006$). The odds of a male having an ICB was more than twice that of a female (odds ratio = 2.26) and significantly contributed to the incidence of an ICB ($p = 0.044$). As a patient's UPDRS I&II score increased by 1, they had a 9% increase in the odds of an ICB ($\beta = 0.088$, $p = 0.01$). The incidence of an ICB was over 18 times more likely when a patient had a low compared to medium-range DGRS ($\beta = 2.896$, $p= 0.04$, odds ratio = 18.1). No gene individually showed this association with ICBs ($p > 0.357$). No other independent variables or interactions increased the likelihood of an ICB.

3.4.2.2. De novo group

Binary logistic regression model analyses determined the odds of having an ICB increased by 9% with every score increase of 1 on the UPDRS I&II ($\beta = 0.09$, $p = 0.003$, odds ratio = 1.09). Full analyses can be found in Appendix 5.

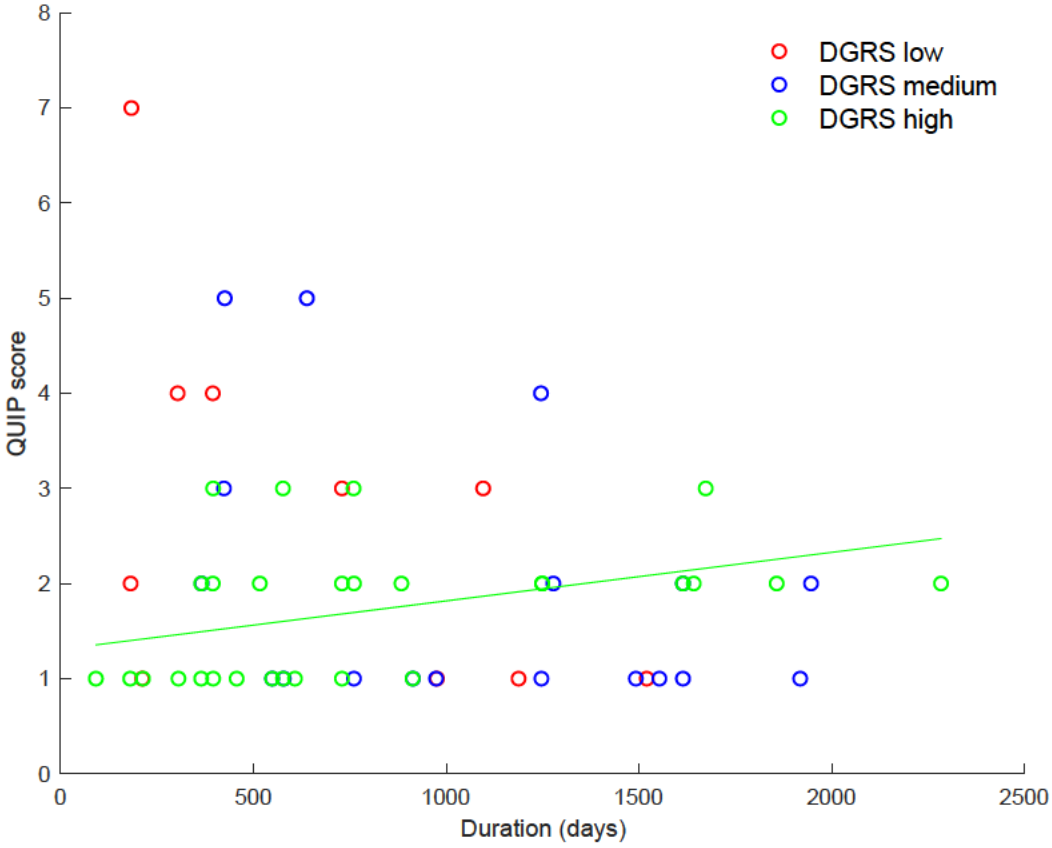
3.4.2.3. Healthy control group

No independent variables increased the probability of having an ICB in either the univariate or multivariate models ($p > 0.382$) and the multivariate model was not validated against a constant model ($p = 0.761$).

3.4.3. QUIP score change on medication

Figure 3.1 presents the relationship between QUIP score and time on DA medication for DGRS low, medium and high groups. The number of ICBs increased over time for the high DGRS group but the number of ICBs only tended to decrease over time for medium-range and low DGRS groups. There was a significant positive correlation between QUIP score and days on medication for patients with a high

DGRS (r = 0.405, p = 0.033). Correlations between time on medication and QUIP score were negative for patients with a low (r = -0.524, p = 0.120) and medium-range DGRS (r = -0.352, p = 0.152). Fisher Z transformations confirmed a significant difference between correlations in the high and both medium (p = 0.016) and low



DGRS groups (p = 0.018), but not between medium-range and low DGRS groups (p = 0.638).

Figure 3.1 Change in score on Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) over time on agonist medication, categorized by dopamine genetic risk score (DGRS).

3.5. Discussion

The present study was the first to investigate the relationship between an *a priori*, hypothesis-driven collection of genes and ICBs for people with PD. The novel finding is that dopamine gene profiling via a DGRS has predictive power for ICBs in PD patients on DA medication. As hypothesized, a low DGRS was associated with an increased likelihood of having an ICB on DA medication compared to higher scores. Furthermore, as hypothesized, DGRS influenced the change in ICBs over time on DA medication. Patients with higher DGRS scores increased the number of ICBs with time on DA medication, whereas patients with lower scores tended to reduce ICBs. This association between DGRS and ICBs in the context of an inverted-U relationship between dopamine and impulse control is shown in Figure 3.2. The apex of the inverted-U curve signifies the optimal range of dopamine corresponding to maximal impulse control. A reduction in ICBs may reflect a move along the curve towards the apex, and an increase in ICBs a move away from the apex. For all PD patients, regardless of medication status, a higher UPDRS I&II score was associated with increased odds of an ICB. Being male also increased the chance of having an ICB, but only for patients on DA medication. The predictive effects of the DGRS were not present in healthy controls, which supports the contention that the mechanisms of effect are specific to dopamine fluctuations during PD and dopamine therapy.

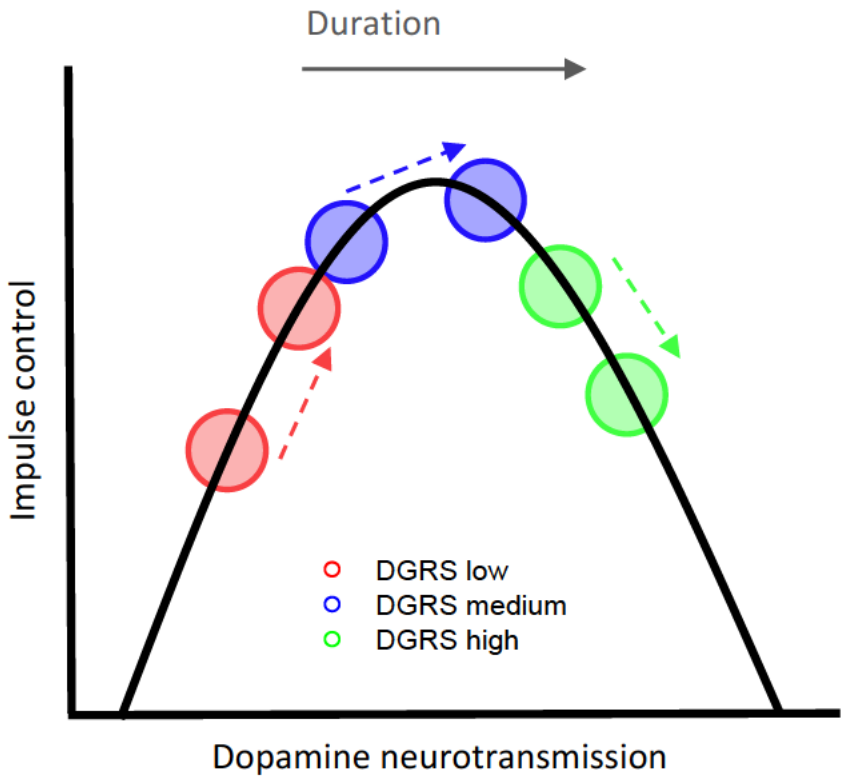


Figure 3.2 Inverted-U relationship between dopamine neurotransmission and impulse control.
Increased time on agonist medication (dashed arrows) moves individuals rightwards along the curve. Changes to impulse control depend on dopamine genetic risk score (DGRS) i.e. starting point on curve.

PD patients' DGRS were associated with the likelihood of presenting impaired impulse control on DA medication. In the current study, 38% of patients taking DA medication experienced at least one ICB. This percentage aligns with previous reports of 14-40% (Bastiaens et al., 2013; Erga et al., 2018; Kraemmer et al., 2016; Weintraub et al., 2010). Prior studies have found associations between individual dopaminergic gene polymorphisms and ICBs in PD (Abidin et al., 2015; Cormier-Dequaire et al., 2018; Erga et al., 2018; Kraemmer et al., 2016; Lee et al., 2009). Of particular note, using the PPMI database Kraemmer et al. (2016) reported that neither DRD2, DRD3 nor COMT polymorphisms were individually associated with ICBs. We also found no individual gene was associated with ICBs. It is only

by considering the influence of these genes collectively, along with DRD1 as a cumulative polygenic score, that the current study found a significant association (Table 3.2). This novel finding using a method to quantify the effect of multiple genes simultaneously highlights the importance of considering widespread effects on central dopamine. The resultant association between DGRS and impulse control mirrors that seen in healthy older adults (MacDonald et al., 2016). PD patients with low tonic dopamine levels (i.e. low DGRS) were around 18 times more likely to report an ICB (i.e. worse impulse control) compared to patients with a mid-range DGRS. Impaired impulse control can result from dopamine being either below or above an optimal range, illustrated via the left and right-hand side of the inverted-U curve, respectively (Figure 3.2). Low DGRS patients necessarily sit lower on the x axis of this curve, and therefore may present with ICBs as their levels of central dopamine neurotransmission fall below optimal levels.

The DGRS also accounted for changes in impulse control over time on DA medication. Patients with a high DGRS reported worse impulse control with increased time on DA medication, reflected by higher scores on the QUIP. However, patients with both a low and medium DGRS tended to report lower QUIP scores with more time on DA medication. These changes in impulse control over time for all three DGRS groups can also be explained by the inverted-U hypothesis. Greater time on DA medication is illustrated by a rightward shift along the curve (Figure 3.2) from increases in neurotransmission. The increase might result from increased medication dosage to combat neurodegenerative disease progression, and/or from decreased sensitivity of D2/D3 autoreceptors (Gasser et al., 2015). As DA medication dose was not available via the PPMI database we cannot speculate between these potential mechanisms of effect. Either way, an increase in dopamine shifts patients rightwards along the curve, moving patients with a lower DGRS (postulated to sit on the left-hand side) towards optimal

levels of dopamine (i.e. the curve apex), but moving high DGRS patients beyond optimal levels. Our results therefore indicate a higher DGRS might be beneficial for impulse control initially, but can be detrimental with exposure to DA medication.

Demographic and clinical factors associated with the presence of ICBs on DA medication replicate previous findings. As hypothesized, male gender and a higher UPDRS I&II score were significantly associated with the presence of an ICB, as previously reported (Cormier-Dequaire et al., 2018; Kraemmer et al., 2016; Voon, Sohr, et al., 2011). Sections IV and V of the UPDRS were unavailable, but UPDRS section IV has been found to have associations with ICBs in other studies (Cormier-Dequaire et al., 2018; Voon, Sohr, et al., 2011). Future inclusion of the full UPDRS might reveal interactions with DA medication and/or DGRS.

There are two main limitations of the present study. Firstly, genetic information on the polymorphism within the untranslated region of the DAT gene was unavailable in the PPMI database. The importance of DAT for impulse control behavior and its contribution to the DGRS has been acknowledged (MacDonald et al., 2016). In early PD DAT function is reduced in the MCL system, leading to increased dopamine concentration (Caminiti et al., 2017). With the addition of dopamine medication there can be a dopaminergic overdose within this region, resulting in ICB development (Vriend et al., 2014). Considering the reduced sensitivity, it is encouraging the DGRS was still able to predict ICB incidence on DA medication without the inclusion of DAT. Nevertheless, it will be beneficial to include DAT within the DGRS in future research. The second limitation is a smaller than desired sample size for the analyses of ICB score. Consequently, we were unable to run a multivariate binary logistic regression model to determine any significant associations between changes in ICB score and clinical, demographic

and genetic factors. To investigate these relationships using equivalent multivariate analyses, future studies should use larger cohorts.

In summary, **t**he key finding of the present study was the observed predictive power of a DGRS for ICBs in PD patients on DA medication. An inverted-U relationship between impulse control and dopamine neurotransmission aligns with how DA medication affected patients across the range of DGRS. DA patients with a low DGRS were more likely to have an ICB, but the number of ICBs decreased over time on DA medication. The opposite was observed for the group of patients with a high DGRS, who were less likely to have an ICB on DA medication but over time, the number of ICBs increased. In future research, more sensitive and objective laboratory-based measures could be used in conjunction with a DGRS to identify patients at risk of developing ICBs. This research will help to strengthen the relationship between the utilization of a DGRS and ICB prediction.

CHAPTER 4

Exploring Stop Signal Reaction Time Over Two Sessions of the Anticipatory Response Inhibition Task

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I confirm I participated in all aspects of the development of the research within this chapter, data/statistical analyses and the writing and revisions of the manuscript.

4.1. Abstract

Various behavioural tasks measure response inhibition encompassing the ability to cancel unwanted actions, evaluated via stop signal reaction time (SSRT). It is unclear whether SSRT is an unchangeable inherent measure of inhibitory network integrity or whether it can improve with repetition. The current study explored if and how SSRT changed over two sessions for the Anticipatory Response Inhibition Task (ARIT), and how this compared with the Stop Signal Task (SST). Forty-four participants repeated the ARIT and SST over two sessions. SSRT and its constituent measures (Go trial reaction time, stop signal delay) were calculated. SSRT reflecting non-selective response inhibition was consistent between sessions in the ARIT and SST (both $p > .293$). Reaction time and stop signal delay also remained stable across sessions in the ARIT (all $p > .063$), whereas in the SST, reaction time ($p = .013$) and stop signal delay ($p = .009$) increased. SSRT reflecting behaviourally selective stopping on the ARIT improved ($p < .001$) over two sessions, which was underpinned by changes to reaction time ($p < .001$) and stop signal delay ($p < .001$). Overall, the maximal efficiency of non-selective inhibition remained stable across two sessions in the ARIT. Results of the SST confirmed that non-selective inhibition can however be affected by more than inhibitory network integrity. Behaviourally selective stopping on the ARIT changed across sessions, suggesting the sequential neural process captured by the SSRT occurred more quickly in session two. These findings have implications for future studies that necessitate behavioural measures over multiple sessions.

4.2. Introduction

Response inhibition (RI) is the motor component of inhibitory control and encompasses the ability to supress or cancel unwanted actions. There are various behavioural tasks used to objectively measure RI. One of the most popular is the stop signal paradigm which was first created by Vince (1948), further developed into the stop signal task (SST) by Lappin & Eriksen (Lappin & Eriksen, 1966). Most recently the SST has been popularised by Logan and colleagues via the open-source STOP-IT software (Windows executable software for the stop-signal paradigm) which was first developed in 2008 (Verbruggen, Logan, & Stevens, 2008) and recently updated (Verbruggen et al., 2019a). The SST involves Go trials where participants form a default response to a Go signal, which is often a choice between responding with their left or right hand. Participants respond to this Go signal as fast as possible with the press of a specific button. The SST also contains Stop trials making up approximately 25% of total trials. During Stop trials, a visual or auditory signal is presented after the Go stimulus and participants must inhibit their conditioned response. The task uses a staircase design to adapt this stop signal to the performance of the participant, narrowing in on a stop signal delay (SSD) where the participant successfully withholds their response on 50% of the stop trials. Logan and Cowan (1984) posited a horse-race model of RI to explain the behavioural outcome on each trial of the SST. The horse-race model suggests a race between the going process (initiated by the Go signal) and stopping process (initiated by the Stop signal) on a trial-by-trial basis. If the going process finishes first, then the response is executed, but if the stopping process finishes first, the response is inhibited. Stop signal reaction time (SSRT) is the most widely utilised primary dependent measure for the SST as it is thought to indicate the latency of this stopping process/RI for an individual (Aron & Poldrack, 2006; G. P. H. Band et al., 2003; Ray Li et al., 2008; Verbruggen et al., 2013; Verbruggen & Logan, 2009).

Another method for investigating RI is via the anticipated response version of the SST. This version was developed by Slater-Hammel (1960) and follows the same horse race framework (Leunissen et al., 2017). This version of the SST constrains the Go response to an anticipated stationary target, to ensure response preparation takes place on both Go and Stop trials. When a Stop signal is presented before this anticipated target, participants must inhibit their Go response. Early versions of this anticipated response task, commonly named the anticipatory response inhibition task (ARIT), presented a clock face display and participants depressed a key to initiate a clockwise sweep dial revolution (Coxon et al., 2006; Stinear & Byblow, 2004). During Go trials, participants were required to release the key when the dial intercepted the target, 800ms after the start of the trial (Go response). Stop trials commenced in the same way, but the sweep dial stopped revolving before the target (Stop signal). Participants therefore had to inhibit their anticipated response when the Stop signal (the sweep hand stopping) was presented. More recent studies typically use a version of the ARIT involving one or two vertical bars which rise for 1000ms e.g. (Coxon et al., 2007, 2009, 2016; Gilbert et al., 2019; He et al., 2019; MacDonald et al., 2012, 2016; Zandbelt & Vink, 2010). This version of the ARIT has been increasing in popularity and is now available open-source (He et al., 2022). In the bimanual version, participants are required to release two depressed keys to intercept two bars with the target line at 800ms on Go trials. Participants then inhibit this bimanual lift response when the bars do not reach the target on Non-Selective Stop Both trials, with the latency of the non-selective stopping process reflected in the SSRT. During the more challenging Selective Stop trials, participants are required to keep only one key depressed when the corresponding bar does not reach the target and release the alternative key at the target line. The response of the continuing hand is invariably delayed, which is termed the stopping interference effect (Aron & Verbruggen, 2008; Y. T. Ko & Miller, 2011; Wadsley et al., 2019). These trials are termed Selective Stop trials which refers to selective cancellation at

a behavioural level, rather than a neural level. SSRTs are also calculated on these trials but are thought to reflect a more complex series of neural processes triggered by the stop signal; a sequential non-selective stop, uncouple and reprogram, then selective go process (Coxon et al., 2009; MacDonald et al., 2012, 2014, 2021; Wadsley et al., 2019).

Research conducted using both the ARIT and SST has revealed the neural mechanisms underlying inhibitory control, specifically the role of basal ganglia pathways. Execution of the motor response in Go trials activates fronto-striato-pallidal regions as part of the direct basal ganglia pathway, which then leads to an increase in thalamocortical drive to the motor cortex. Whereas inhibition on Stop trials engages a right lateralized network that includes the indirect (suppression of action) or hyperdirect (cancellation of action) pathway, that inhibits output from the motor cortex. This inhibitory network includes the subthalamic nucleus (STN), globus pallidus pars interna (GPi) and externa (Gpe) (indirect pathway), right inferior frontal gyrus (IFG) and pre- supplementary motor area (SMA) (Allen et al., 2018; Aron et al., 2003; Aron & Poldrack, 2006; Chen et al., 2020; Coxon et al., 2009; Dunovan et al., 2015; Maizey et al., 2020; Ray Li et al., 2008; Ray, Brittain, et al., 2012). The STN, once activated via the indirect or hyperdirect pathway, plays an important role in supressing thalamocortical output by blocking the direct pathway (Aron & Poldrack, 2006; Dunovan et al., 2015; Ray Li et al., 2008; Zandbelt & Vink, 2010). The integrity of these basal ganglia pathways is thought to be reflected in measures derived from RI tasks.

There is substantial literature investigating single session measures of RI using the ARIT and SST. The assumption is that RI, indexed via a SSRT, is an inherent ability which is specific to each individual and purely reflects the integrity of their inhibitory networks. Therefore, RI is not expected to change within a young healthy individual and SSRT should be

consistent across multiple sessions. A handful of previous studies have tested this assumption by investigating the effect of multiple sessions on RI in the SST. Two of these studies reported no improvement in SSRT for non-selective RI following 9 and 2 sessions, respectively (Chowdhury et al., 2020; Enge et al., 2014). While Chowdhury et al. found no behavioural improvement in stopping efficacy with multiple sessions, Enge et al. counterintuitively reported an increase in SSRT (i.e., a decrease in performance) over the course of multiple sessions. Enge and colleagues attributed this to participants progressively focusing more on fast responses in Go trials at the expense of accurate cancellation on Stop trials. This interpretation suggests strategizing during the task might be able to affect the SSRT measurement over multiple sessions. Conversely, another study using the SST for non-selective RI did find an improvement in SSRT throughout 10 sessions, where SSRT decreased with each session (Berkman et al., 2014). SSRT for selective stopping on the SST has shown a similar pattern of decreasing across sessions (Enz et al., 2022; Xu et al., 2015). To our knowledge, no study has specifically tested SSRT across multiple sessions of the ARIT. Coxon and colleagues (Coxon et al., 2016) reported behavioural results on the ARIT pre and post neuroimaging. Although SSRT was not reported as it was not a primary outcome measure, they did show that Go trial RT remained stable across the two behavioural sessions and only RT variability (1SD of response distribution) significantly decreased. To ensure we are correctly interpreting SSRT as an inherent measure of inhibitory network integrity, the consistency of SSRT across multiple sessions needs to be further explored.

The aim of the current study was therefore to assess if and how the SSRT measurement changed over two sessions for the ARIT, and how this compared with the SST. It was hypothesised that SSRT would not change between sessions on Non-Selective Stop Both trials of the ARIT as there would be no possible change in Go trial reaction times used to calculate

this measure due to constraining responses to a stationary target. It was suspected that a strategy focusing on accurate stopping at the expense of fast reaction times on Go trials of the SST (i.e. the opposite strategy to participants in the Enge et al. 2014 study) would be able to cause an improvement in inhibitory control, as seen previously (Berkman et al., 2014). Therefore, the second hypothesis was that SSRT in the SST would decrease from session one to session two. Due to the increased challenge at both a behavioural and neural level on Selective Stop trials in the ARIT, becoming better at fulfilling the trial requirements in session two might affect performance. Therefore, the third hypothesis was that SSRT would decrease from session one to session two for Selective Stop trials of the ARIT.

4.3. Materials and Methods

4.3.1. Participants

Forty-four healthy participants were recruited into the current study, all over the age of 18 years. The University of Birmingham Ethics Committee approved this research and written informed consent was obtained from each participant.

4.3.2. Procedure

Participants attended two identical sessions in the laboratory, 24 hours apart. Participants were seated ~1m away from a computer screen and keyboard, where they completed two behavioural tasks: the anticipatory response inhibition task (ARIT) and the stop signal task (SST). The order of behavioural tasks was counterbalanced.

4.3.3. Anticipatory Response Inhibition Task (ARIT)

The ARIT was displayed using custom code written in MATLAB (version R2016a, MathWorks). Participants completed two practise blocks, each containing 30 Go trials, followed by 6 experimental blocks of 30 trials. In total the experimental trials consisted of 120 Go trials and 60 Stop trials in a pseudo-randomised order.

Participants were initially presented with a grey screen containing two white vertical rectangles and a stationary horizontal black target line 4/5 of the way up the rectangles (Figure 4.1). All trials required participants to use their left and right index fingers to depress the 'z' and '? /' key, respectively. Once both keys were depressed, a black bar started rising within each of the white rectangles after a variable delay. The left black bar was controlled with the 'z' key, and the right black bar with the '? /' key. Both bars rose at equal rates, intercepting the

target (horizontal black line) at 800ms and filling the entire white rectangle at 1000ms, unless the keys were released which ceased the bars rising.

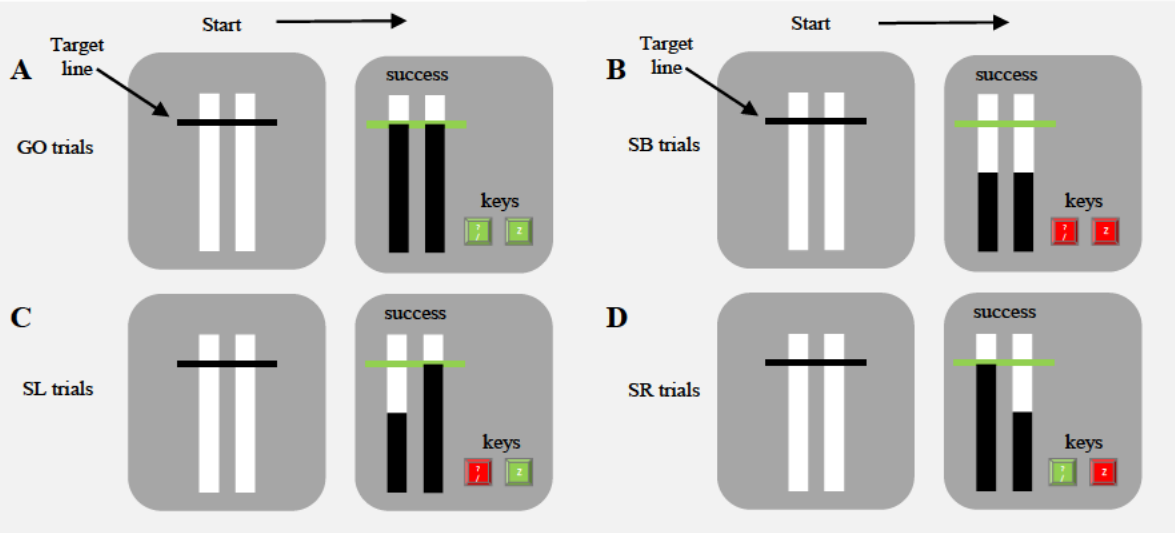


Figure 4.1 Visual display of (A) GO, (B) SB (Non-Selective Stop Both), (C) SL (Stop Left) and (D) SR (Stop Right) trials in the ARIT.
Green keys represent successful release at the target and red keys represent successfully keeping the key depressed. On successful Go trials, both keys are released at the target line. On successful SB trials, both keys are held down. On successful SL trials, the right key is lifted and the left key is held down. On successful SR trials, the left key is lifted and the right key is held down.

4.3.3.1. Go trials

Participants started each trial by pressing and holding down both response keys to initiate the rising of the bars. They were then required to release their fingers from both keys to intercept both bars with the target (successful releases were within 30ms of target, Figure 4.1A). Participants received visual feedback at the end of each trial which was shown above the white rectangles. 'Success' was displayed following a successful release of the keys and 'missed' followed an incorrect release (not within 30ms of target).

4.3.3.2. Stop trials

There were three types of Stop trials (20 each) that required participants to keep the key(s) depressed if the rising bar(s) never reached the target. Non-Selective Stop both (SB) trials required participants to keep both keys depressed when both bars automatically stopped rising before reaching the target (non-selective RI) (Figure 4.1B). Selective Stop trials comprised of stop left-go right (SL) and stop right-go left (SR) trials (Figure 4.1C & D), which required participants to keep pressing the key corresponding to the bar that stopped, whilst still releasing their finger from the alternative key when the bar arrived at the target. For every stop version, the bar initially stopped 550ms into the trial (stop signal delay, SSD). A staircase algorithm with increments of 50ms was then used to generate a 50% success rate for each Stop trial version. Following a successful Stop trial the SSD would increase by 50ms for the subsequent Stop trial, whereas the SSD would decrease by 50ms following an unsuccessful Stop trial. Participants received feedback following each trial which was displayed above the white rectangles. Following successful trials, 'success' was displayed, and 'unsuccessful stop' was presented following an unsuccessful trial where participants did not inhibit their response. Moreover, on Selective Stop trials, if the participants completed a successful stop on the required side and released the alternative key outside 30ms of the target, then 'successful stop, but missed target' appeared (these results were classed as a successful stop in the analyses as this delayed response - i.e. stopping interference effect - was expected).

4.3.4. Stop Signal Task (SST)

The SST was carried out using STOP-IT software (Verbruggen, Logan, & Stevens, 2008). Participants completed a practise block of 48 Go trials and 16 Stop trials. They then completed 128 experimental trials, divided into 2 blocks. In total these trials consisted of 96 Go trials and 32 Stop trials in a pseudo-randomised order.

4.3.4.1. Go trials

The start of a trial was indicated by a white '+' fixation cue (approximately 1cm across) displayed for 250ms in the centre of the computer screen with a black background. This cue was followed by the presentation of the Go stimulus. The Go stimulus was either a white square or circle (approximately 1cm in length) which required participants to respond with their left or right index finger as fast as possible using the 'z' or '? /' key, respectively (Figure 4.2A). Participants had up to 1250ms to respond to the Go stimulus once it was presented, before the trial ended and the stimulus disappeared. A blank screen would be displayed for 750ms before the start of the subsequent trial.

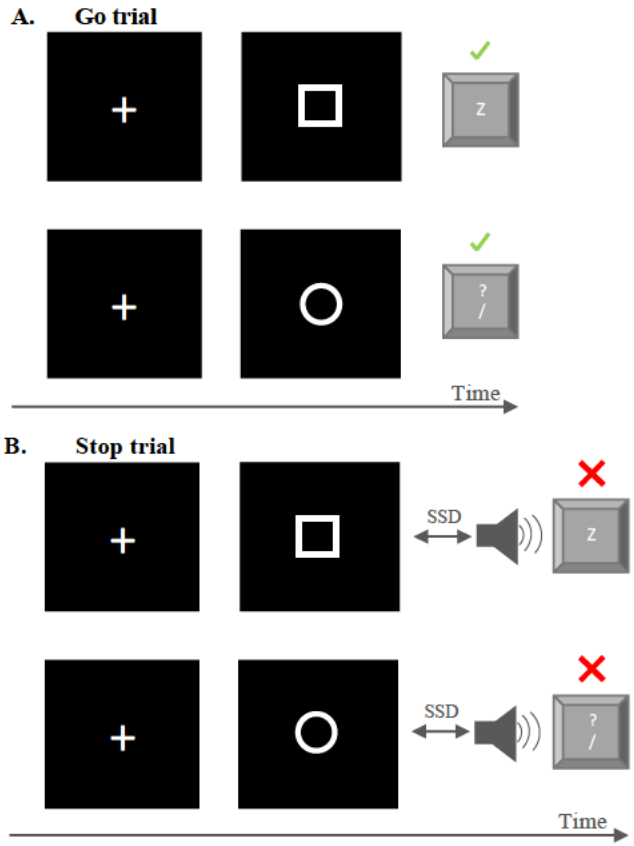


Figure 4.2 Visual representation of the Stop Signal Task.
Green tick marks represent a successful Go trial (**A**) where the participant presses the correct key corresponding to the symbol. Red crosses represent a successful Stop trial (**B**) where participants refrain from pressing the key following the stop signal.

4.3.4.2. Stop trials

Stop trials also commenced with the same '+' on the computer screen indicating the start of the trial, followed by a blank screen and subsequently the presentation of the Go stimulus. Shortly after the Go stimulus, a Stop stimulus was presented, which was a short audio tone lasting 75ms (750hz). Participants were instructed to inhibit their response and not depress the designated key (Figure 4.2B) if they heard the Stop tone (non-selective/complete RI). The time between the Go stimulus and the Stop stimulus represented the stop signal delay (SSD). The SSD was initially set at 300ms after the Go stimulus and a staircase algorithm was used to generate a 50% success rate, where the SSD would increase by 50ms on the subsequent Stop trial (regardless of whether the Go response was with the left or right hand) if the participant successfully inhibited their response, but the SSD would decrease by 50ms if the participant was unsuccessful (i.e. responded following the stop stimulus). The trial would end after 1250ms and the Go stimulus would disappear. There was an equal number of Go and Stop trials for each hand response. Mean reaction time and percentage of correct stops were provided as feedback at the end of each block and were displayed for 10 seconds.

4.3.5. Dependent measures

4.3.5.1. Anticipatory response inhibition task

Average reaction time (RT), reported in milliseconds relative to the start of the trial, was calculated for successful Go, SL (stop left-go right) and SR (stop right-go left) trials after removing outliers (±3SD, (MacDonald et al., 2012)). SSD (staircased to 50% success) and stop trial accuracy (% success) was calculated for SB SL, SR trials. SSRT was the primary dependent measure for the ARIT and calculated for each Stop trial version using the integration method (SSRT = nth Go trial RT (i.e. number of Go trials x probability of responding on Stop trials) – SSD) (Verbruggen et al., 2013).

4.3.5.2. Stop signal task

The RT, reported in milliseconds, was measured between the onset of the Go stimulus and the key response. Average RT across Go stimuli (outliers of ±3SD were removed for consistency between tasks), SSD (staircased to 50% success) and stop trial accuracy (% success) on Stop trials were calculated for each participant. SSRT was the primary dependent measure for the SST and was also calculated using the integration method.

4.3.6. Statistical Analysis

MATLAB (Version R2020a, MathWorks) and SPSS statistics (Version 27) were used to complete all statistical analyses. To investigate the effect of session on non-selective inhibitory control, a direct comparison was made between Stop Both trials in the ARIT and the Stop trials in the SST due to the similar requirement for complete RI in both conditions. A 2 Session (First, Second) x 2 Task (ARIT SB, SST) repeated measures analysis of variance (RM ANOVA) was run on SSRT and SSD. A similar Session x Task (ARIT, SST) RM ANOVA was run on average Go trial RT, which is a key measure used to calculate SSRT. To investigate the effect of session on Selective Stop trials of the ARIT, a 2 Session x 2 Selective Stop Type (SL, SR) RM ANOVA was run on SSRT, SSD and RT from these trials. Post hoc paired t-tests were used to investigate any significant main effects and interactions. One sample t-tests were used to compare the percentage of stop trial success (stop trial accuracy) in the ARIT (SB, SL, SR) and SST to the 50% staircasing target, and paired t-tests were used to assess the differences in stop trial accuracy from session 1 to session 2 for all trial types.

To investigate the generalizability of SSRT across tasks, linear regressions tested for a correlation between SSRTs calculated in the SB trials of the ARIT and the SST Stop trials, for

each session. Fisher z transformations identified any significant differences between the correlations. Values are reported as means ± standard error (SE) unless otherwise stated. Statistical significance was determined by $\alpha \leq 0.05$ and partial eta squared effect sizes are reported. Data which violated the assumption of sphericity are reported with Greenhouse-Geisser corrected p values.

4.4. Results

4.4.1. ARIT Stop both and SST

Eight participants were excluded from the main analysis due to SSRTs in the SST being below 100ms in either session which is not feasible for reactive recruitment of the inhibitory network (advised by (Congdon et al., 2012; Verbruggen et al., 2019a)). The SSRTs for these participants were so low due to unnaturally high RT (session 1 RT mean 778 ± 162ms, session 2 RT mean 733 ± 174ms) and SSD (Session 1 SSD mean 700 ± 162ms, session 2 SSD mean 650 ± 174ms) values, suggesting perhaps these individuals were waiting for the stop signal to improve stopping performance. Data from the remaining 36 participants were used to test the first two hypotheses (mean age: 20 ± 0.94 years, range 18-22 years, 12 males).

4.4.1.1. Stop signal reaction time (SSRT)

SSRT reflecting non-selective inhibitory control appeared to be consistent between the two sessions when measured using either the SST or ARIT. There was no main effect of Task ($F_{1,35}$ = 0.04, p = .840, hp^2 = .001), Session ($F_{1,35}$ = 1.14, p = .293, hp^2 = .032) or Task x Session interaction ($F_{1,35}$ = 1.82, p = .186, hp^2 = .049) (Figure 4.3A). As hypothesised for Stop Both trials of the ARIT, SSRT did not change between session one (226 ± 10ms) and session two (226 ± 77ms). Contrary to our second hypothesis, the decrease in SSRT from session one (236 ± 18ms) to session two (212 ± 11ms) in the SST was not significant. Equivalence Bayesian Paired Samples t-tests confirmed that SSRT for both the ARIT (overlapping hypothesis (OH) Bayesian Factor (BF) = 5.500, non-overlapping hypothesis (NOH) BF = 6.978) and SST (OH BF = 2.253, NOH BF = 2.394) were not meaningfully different from one another between sessions 1 and 2, with moderate and weak evidence, respectively. While an individual's SSRT for non-selective RI was correlated between tasks initially, this relationship was not sustained into the second session. There was a significant positive correlation between SSRT on the

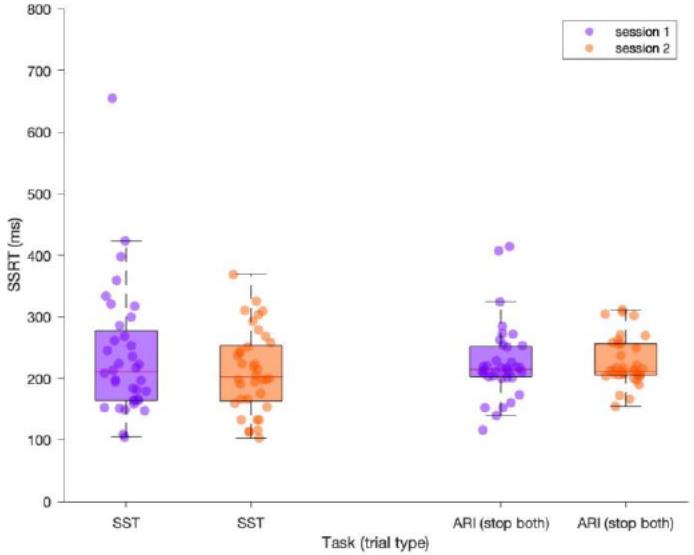
ARIT and SST in session one (r = 0.45, p = .006) but this disappeared in session two (r = -0.07, p = .702) (Figure 4.3B). Fisher z transformation confirmed a significant difference between the two correlations (z = 2.22, p =.013).

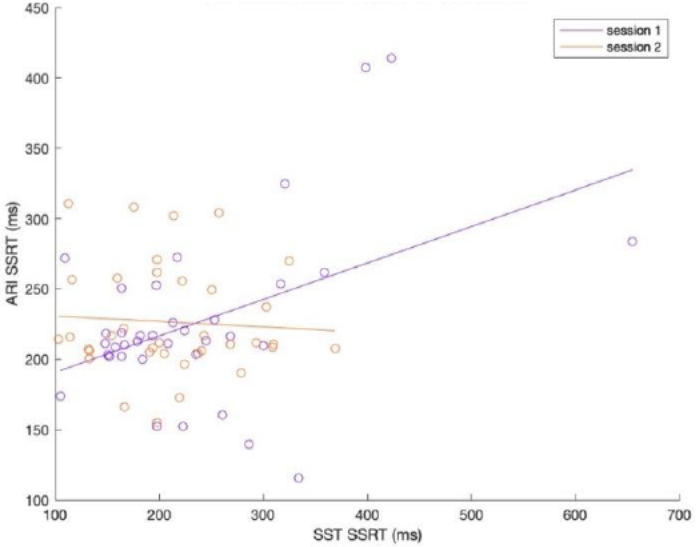
4.4.1.2. Reaction time (RT)

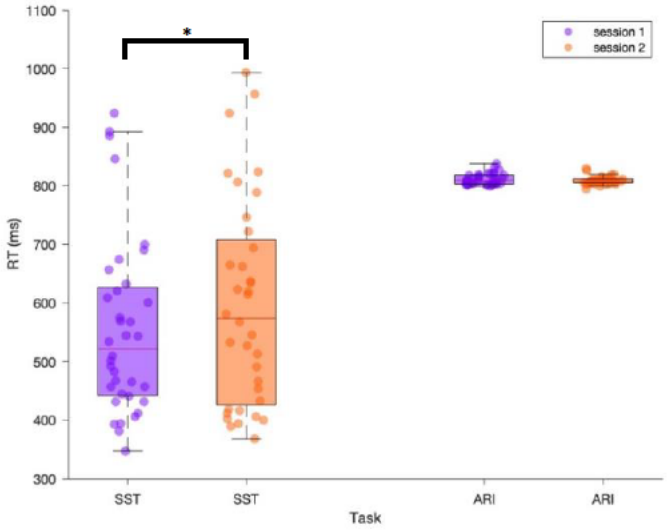
Reaction times on Go trials remained consistent over two sessions in the ARIT but were significantly delayed in session two of the SST. There was a main effect of Task ($F_{1,35}$ = 80.8, p < .001, hp^2 = .698), Session ($F_{1,35}$ = 6.00, p = .019, hp^2 = .146) and Task x Session interaction ($F_{1,35}$ = 7.77, p = .009, hp^2 = .182). Post hoc analysis revealed the mean decrease of 2ms from session one (811 ± 2ms) to session two (809 ± 1ms) in the ARIT was not significant (p = .063). However, the increase of 41ms from session one (555 ± 25ms) to session two (596 ± 29ms) in the SST was significant (p = .013; Figure 4.3C).

4.4.1.3. Stop signal delay (SSD)

Mirroring the RT results, the SSD was longer in session two of the SST but remained consistent for the ARIT. There was a main effect of Task ($F_{1,35}$ = 56.1, p < .001, hp^2 = .616), Session ($F_{1,35}$ = 5.02, p = .032, hp^2 = .125) and Task x Session interaction ($F_{1,35}$ = 6.94, p = .012, hp^2 = .165). Again, post hoc analysis revealed no significant changes in SSD for the ARIT (session one = 582 ± 9ms, session two = 583 ± 7ms; p = .884), but a significant increase in SSD for the SST (session one = 329 ± 30ms, session two = 375 ± 35ms; p = .009; Figure 4.3D).


session 1
session 2
SSRT (ms)
SST
SST
ARI (stop both)
ARI (stop both)
Task (trial type)


session 1
session 2
ARI SSRT (ms)
SST SSRT (ms)


*
session 1
session 2
RT (ms)
SST
SST
ARI
ARI
Task

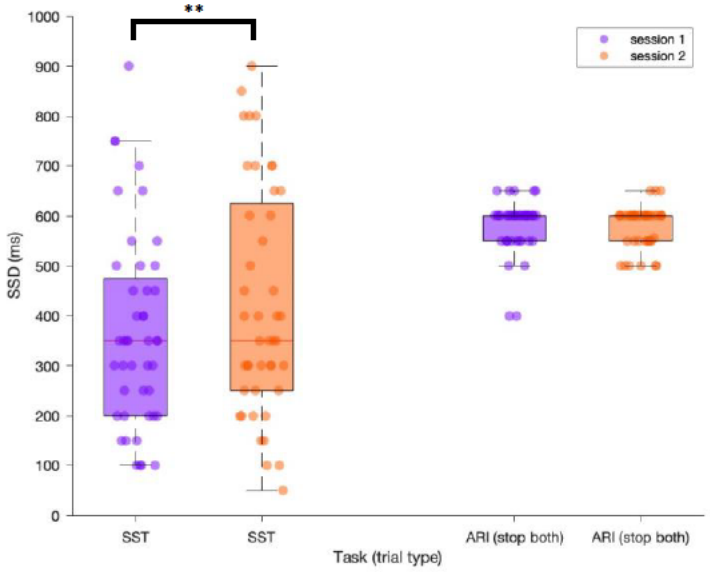

**
session 1
session 2
SSD (ms)
SST
SST
ARI (stop both)
ARI (stop both)
Task (trial type)

Figure 4.3 Mean SSRT (A), RT (C) and SSD (D) for the ARIT SB and SST in sessions 1 and 2, reported in milliseconds (ms). Shaded box plots represent the interquartile range (IQR) (75^{th} percentile (Q3) – 25^{th} percentile (Q1)). Red horizontal line represents the median. The vertical dashed lines represent the non-outlier minimum (Q1 - 1.5 x IQR) and maximum (Q3 + 1.5 x IQR). Data circles represent individual participant results. **(B)** Linear correlation between SSRT for the SST and ARIT SB in session 1 and session 2. Data circles represent individual participant SSRT. * $p < .05$, ** $p < .01$.

4.4.1.4. Stop trial accuracy

There were no differences in stop trial accuracy between session one and session two in either task. In the ARIT there was a non-significant increase of 0.14 ± 0.61% between session one (51.5 ± 0.56%) and session two (51.7 ± 0.40%) ($t_{1,35}$ = 0.23, p = .822). Additionally, in the SST there was a non-significant increase of 1.61 ± 1.58% between session one (49.9 ± 2.46%) and session two (51.6 ± 0.81%) ($t_{1,35}$ = 1.02, p = .314). When comparing mean stop trial accuracy in both sessions to the 50% staircasing target, only the ARIT task displayed percentages significantly greater than 50% (both p < .01).

4.4.2. ARIT Selective Stop Trials (Stop Left and Stop Right)

Data from the full 44 participants were included in the following analyses (mean age: 20 ± 1 years, range: 18-22 years, 15 males).

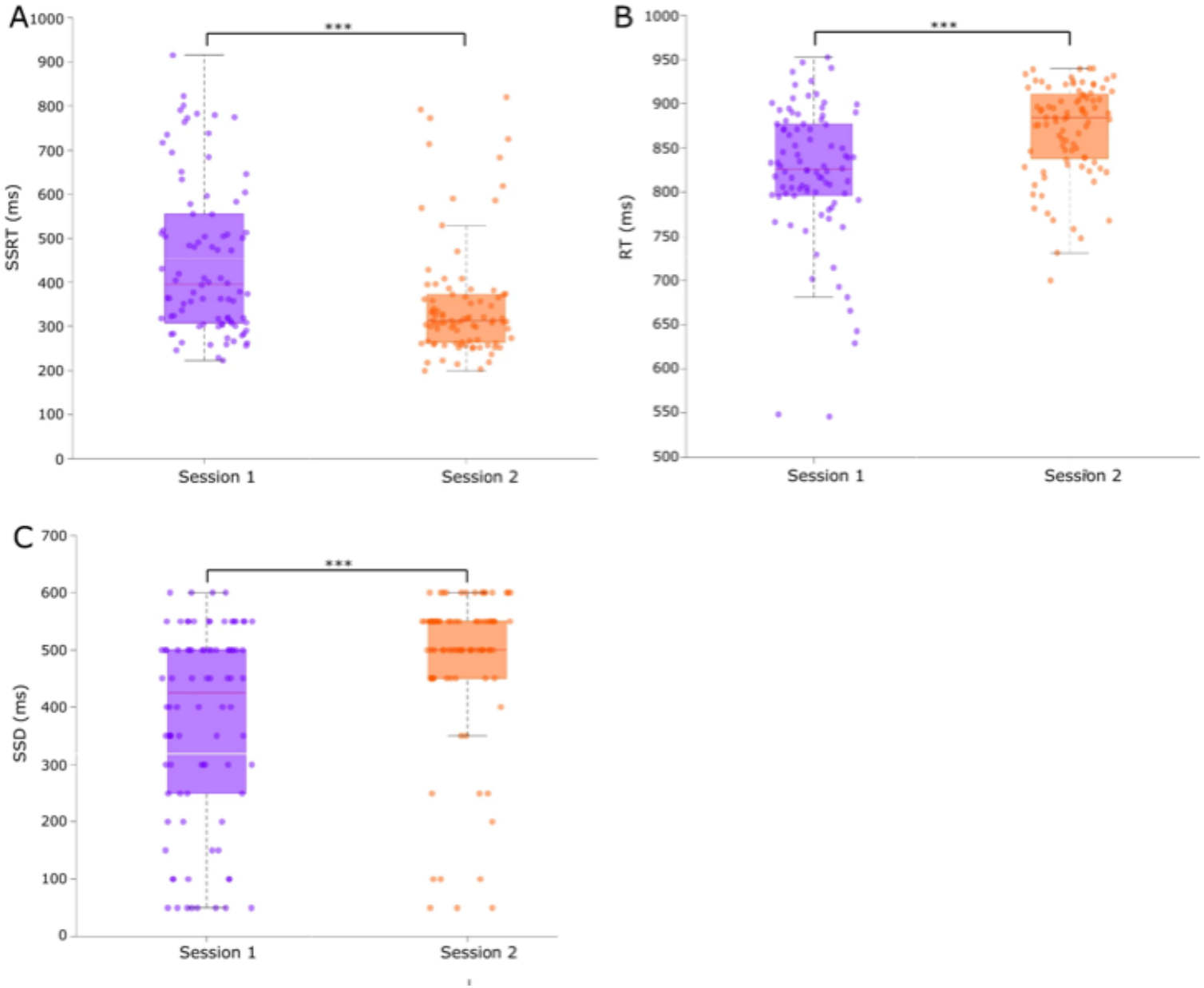
4.4.2.1. Stop signal reaction time

SSRT reflecting the more complex RI process during behaviourally selective stopping improved over the course of two sessions. There was a main effect of Session ($F_{1,43}$ = 31.4, p = <.001, hp^2 = .422) with a decrease of 98 ± 17ms in SSRT from session one (451 ± 21ms) to session two (353 ± 19ms; Figure 4.4A). There was no main effect of Stop type ($F_{1,43}$ = 1.76, p = .192, hp^2 = .039) or Stop type x Session interaction ($F_{1,43}$ = .128, p = .722, hp^2 = .003).

4.4.2.2. Reaction time

Regardless of which side was still responding on Selective Stop trials, there was a larger delay in RT relative to the target in session two compared to session one. There was a main effect of Session ($F_{1,43}$ = 36.1, p = <.001, hp^2 = .456) from a significant increase of 48 ± 8ms in RT from session one (822 ± 10ms) to session two (870 ± 7ms; Figure 4.4B). There was no main effect

of Stop type ($F_{1,43}$ = .825, p = .369, hp^2 = .019) or Stop type x Session interaction ($F_{1,43}$ = 1.59, p = .214, hp^2 = .036).


A
SSRT (ms)
1000
900
800
700
600
500
400
300
200
100
0
***
Session 1
Session 2
B
RT (ms)
1000
950
900
850
800
750
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650
600
550
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Session 1
Session 2
C
SSD (ms)
700
600
500
400
300
200
100
0
***
Session 1
Session 2

Figure 4.4 Mean SSRT (A), RT (B) and SSD (C) for behaviourally selective stopping on the ARIT (Selective Stop trials collapsed across side) in sessions 1 and 2, reported in milliseconds (ms).
Shaded box plots represent the interquartile range (IQR) (75^{th} percentile (Q3) – 25^{th} percentile (Q1)). Red horizontal line represents the median. The vertical dashed lines represent the non-outlier minimum (Q1 - 1.5 x IQR) and maximum (Q3 + 1.5 x IQR). Data circles represent individual participant results. *** $p < .001$.

4.4.2.3. Stop signal delay

In a similar pattern as RTs, SSD increased over the two sessions during both types of Selective Stop trials. There was no main effect of Stop type ($F_{1,43}$ = 1.70, p = .199, hp^2 = .038) or Stop type x Session interaction ($F_{1,43}$ = .462, p = .501, hp^2 = .011) but there was a main effect of Session ($F_{1,43}$ = 37.5, p = <.001, hp^2 = .466). There was a significant increase of 106 ± 17ms in SSD from session one (374 ± 21ms) to session two (480 ± 19ms; Figure 4.4C).

4.4.2.4. Stop trial accuracy

The stop trial accuracy improved over the two sessions during both types of Selective Stop trials. For SL, there was an increase of 4.39 ± 1.65% from session one (42.0 ± 1.90±) to session two (46.4 ± 1.56%) ($t_{1,43}$ = 2.66, p = .011). For SR, there was an increase of 5.18 ± 1.74% from session one (40.6 ± 1.56%) to session two (45.8 ± 1.20%) ($t_{1,43}$ = 2.98, p = .005). Both types of Selective Stop trials displayed a mean stop trial accuracy significantly lower than 50% in both sessions (all p < .027).

4.5. Discussion

The current study constitutes the first step towards exploring the consistency of SSRT across multiple sessions of the ARIT. Performing two experimental sessions of the ARIT had distinct effects on SSRT measured during non-selective RI versus the more complex RI process during behaviourally selective stopping. As hypothesised, there was no change over the two sessions for SSRT reflecting non-selective RI. This stability supports the idea that SSRT measuring non-selective inhibitory control on this task reflects the inherent ability of an individual to inhibit a response and is therefore not expected to change. The consistency of this measure was underpinned by no change in SSD for Non-Selective Stop trials as well as no change in RT on Go trials in this task. This finding was in contrast to inhibitory control on the SST which was associated with a longer SSD and delayed RT on Go trials in session two. However, contrary to our hypothesis, the comparable increases in both SSD and Go RT resulted in no significant change to overall SSRT (although with weak evidence) across sessions of the SST. Conversely, SSRT reflecting behaviourally selective cancellation on the ARIT decreased from session one to session two. This decrease was as predicted and observed because participants became better at fulfilling the demands on Selective Stop trials in session two, reflected by a longer SSD. Overall, these findings have implications for i) the extent of potential within-individual changes to SSRT during multiple-session study designs, and ii) how SSRT might be interpreted for non-selective versus selective stopping.

Stop signal reaction time to a non-selective stop signal during the ARIT did not change across sessions. Importantly, the two variables used to calculate SSRT also remained constant. As such, the staircase algorithm employed successfully converged on a stop signal presentation time in the first session which reflected maximal efficiency of the inhibitory process. The prepotent anticipated response was also unaffected by session, replicating previous findings

(Coxon et al., 2016), most likely from being constrained by the task design (Leunissen et al., 2017). The current findings suggest that SSRT calculated from Stop Both trials of the ARIT is indeed a valid measure of non-selective inhibition network activity. This measure would appear to fit Congdon and colleagues' (2012) definition of SSRT as a "heritable measure of interindividual variation in brain function". However, this cannot be confirmed by our study alone, and future studies should extend the number of sessions to ensure non-selective SSRT remains consistent. This is especially pertinent as the study by Berkman and colleagues (2014), despite constraining go responses on the SST, observed an improvement in RI throughout 10 sessions, as well as a proactive shift in the pattern of neural activation in RI networks. Therefore, despite the apparent robustness of movement execution and non-selective inhibition on the ARIT, future studies with a greater number of sessions and measures of neural activation are required to substantiate these findings.

Non-selective inhibitory control on the SST also appeared consistent between sessions. However, the consistency of the SSRT was supported by weak evidence and was belied by changes to SSD and Go RT across session. There was evidence of proactive slowing from session one to session two, reflected in the delayed going response. This slowing is purported to be an example of proactive motor RI (Brevers et al., 2020; Greenhouse & Wessel, 2013; Leotti & Wager, 2010; Schachar et al., 2004; Verbruggen et al., 2013; Verbruggen, Logan, Liefooghe, et al., 2008) and could be attributed to participants focusing on successful stopping at the expense of fast responses on Go trials (i.e. the opposite strategy to participants in Enge et al., 2014). A strategy to prioritise stopping performance would also explain the longer SSD in session two, which indicates participants had improved at responding to the stop signal. Importantly, employing such a strategy invalidates the independence assumption of the race model (Verbruggen et al., 2019a) and might explain why non-selective inhibitory performance

was no longer related between tasks in session two. Specific versions of the SST constrain responses to prevent such proactive slowing (Berkman et al., 2014; Chowdhury et al., 2020) and enable a more reliable interpretation of SSRT measures. Overall, when interpreting measures of inhibitory control on the SST, our results highlight the value in examining variables that constitute the SSRT despite no apparent change to SSRT itself, and that changes in these variables might suggest SSRT is able to be affected by more than purely inhibitory network integrity.

The SSRT measure needs to be interpreted differently for non-selective versus selective stopping. This difference is not necessarily surprising as SSRT in Selective Stop trials is more than a measure of pure (or global; i.e stop everything) inhibitory network activity. The stop cue on these trials triggers a sequential non-selective stop, response uncouple, reprogram, then selective go process (Cowie et al., 2016; Coxon et al., 2007; MacDonald et al., 2012, 2014, 2021; Wadsley et al., 2019) which leads to the delayed RT. SSRT therefore reflects a complex series of neural processes which are triggered by the stop cue and involve interactions between facilitatory and inhibitory prefrontal-basal ganglia networks (Coxon et al., 2009, 2012). Of note, the fact that participants still make a unimanual response on Selective Stop trials means both components used to calculate SSRT (SSD, RT) can be measured within the same trial type. This is in contrast to SSRTs for Stop Both trials or Stop trials in the SST, which use RTs from Go trials as there is necessarily no overt response on successful Stop trials. In this way, SSRTs for selective stopping are not comparable to SSRT from Non-Selective Stop trials of the ARIT. The direct link between RT and SSD within the same trial means the increase in RT on Selective Stop trials is likely to be directly caused by the later stop signal presentation (i.e. SSD) on these trials, rather than from a general proactive slowing strategy as discussed for the SST. Such a proactive strategy would have also delayed Go RTs in the ARIT, and as discussed

above, this was not observed. Overall, SSRT may not be the most appropriate term to describe what is being measured during the more complex RI process as it is capturing more than a simple 'stop signal reaction time.'

The behaviourally selective response to a stop cue can improve across sessions. The improvement (reflected in SSRT, SSD and accuracy) indicates participants became better at fulfilling the overall demands on Selective Stop trials. This may be because some, or all, of the sequential process captured by the SSRT (stop, uncouple, reprogram, then go) occurred over a shorter time scale in session two. The overall time required for this process can be reduced on Selective Stop trials of both the ARIT (Wadsley et al., 2019) and SST (Xu et al., 2015) through manipulations to overall task design. Wadsley and colleagues (2019) increased the asynchrony between left and right-side components of the default response, thereby reducing the amount of time needed for response uncoupling during behaviourally selective stopping and reducing the stopping interference effect. Xu and colleagues (2015) also decreased the interference effect by targeting the Go process in selective stopping, with specific training to shorten reaction times, although this came at a cost of incredibly short SSDs (averaging 98ms) which likely fundamentally changed RI behaviour. In the current study, we saw the improvement without alterations to task design, suggesting multiple sessions alone might be sufficient to increase the efficiency of this complex RI processes in young healthy adults. Interestingly, Enz and colleagues (2022) also reported improvements in SSRT over 3 sessions using a conditioned version of the SST which is more similar to Selective Stop trials of the ARIT than traditional SST versions. If our working hypothesis is correct, one would expect behavioural improvements to be mirrored by an improvement in neural activity within the various networks activated during the more complex RI process. During non-selective RI, a proactive shift in the pattern of RI network activation is possible. Regions like the right IFG which are initially

recruited during the implementation of RI, can be recruited earlier by inhibition cues following multiple sessions, therefore improving SSRT (Berkman et al. 2014). An increase in GABA mediated short-interval intracortical inhibition in the primary motor cortex (M1) could also contribute to these improvements (Chowdhury et al., 2020). On the other hand, it is possible participants may have simply become more comfortable with the increased cognitive challenge for selective stopping in the current study, thereby improving performance. The inclusion of neuroimaging in future multi-session experimental designs could help distinguish between these possible mechanisms of effect. Nevertheless, our findings indicate that selective stopping measures are susceptible to within-individual changes across multiple sessions. This has implications for future study designs that necessitate collecting behavioural measures over multiple sessions.

The extent of any within-individual changes to SSRT across sessions is also potentially relevant in a clinical context. SSRT is sensitive to cortical and basal ganglia impairments resulting from healthy aging (Bloemendaal et al., 2016; Coxon et al., 2012, 2016) and a wide range of pathologies such as PD (Gauggel et al., 2004; Obeso et al., 2011; Rahman et al., 2021), schizophrenia (Hughes et al., 2012), ADHD (Lipszyc & Schachar, 2010; Senderecka et al., 2012) and OCD (Lipszyc & Schachar, 2010; McLaughlin et al., 2016). It has been suggested that SSRT is a biomarker for specific pathologies and may hold promise for early diagnosis of cortical/basal ganglia dysfunction (McLaughlin et al., 2016; Rahman et al., 2021). However, to identify any impairments in inhibitory control over time because of pathology, natural trends in the SSRT measure over time need to be quantified first in healthy populations. Likewise, any improvements to SSRT as a result of practice need to be identified to quantify additional improvements in inhibitory control as a result of treatment interventions. To this end, the current study examined subtle changes in SSRT over two laboratory sessions, as might

commonly be done pre- and post-intervention or when using active non-invasive brain stimulation against sham over two sessions. To further understand if the SSRT as measured on these behavioural tasks has potential to detect pathology or effects of treatment in the future, more studies of this kind must initially take place in healthy subjects whilst ensuring the constraining of the Go response.

Although both the ARIT and SST measured response inhibition reflected by SSRT, there were some key differences in task designs. The ARIT involved bimanual responses on Go Trials, visual stop signals and individual trial feedback throughout the experiment which could encourage a form of motivation bias (Leotti & Wager, 2010). Whereas the SST involved a choice between unimanual responses, audio stop signals and no trial-by-trial feedback. It is unclear whether any or all of these task design features contributed to the differences in behavioural measures we saw between the two tasks, which could be an interesting avenue for future work. It is important to acknowledge the presence of some very low SSD values for Selective Stop trials in the ARIT for our cohort. Whilst these trials are known to be challenging, SSDs of 50 - 200ms point to particular difficulty meeting trial demands, which is somewhat surprising for young healthy adults. Perhaps these participants required a greater number of Selective Stop trials to arrive at their maximal RI efficiency. However, for some participants these low SSDs persisted until the end of session two. It is therefore possible that these values reflect motor or cognitive impairments on these trials. The impairment could be linked with overall trait impulsivity (Aichert et al., 2012) or even indicate underlying subtle but complex deficits in not only inhibitory control but also conflict monitoring and working memory, as can manifest in pathologies such as ADHD (Rapport et al., 2008; Senderecka et al., 2012).

The current study investigated the consistency of SSRT in the ARIT across two sessions. During non-selective RI, the maximal efficiency of the inhibitory process remained

unchanged for individuals. Results of the SST highlighted that SSRT for complete RI can be affected by more than purely inhibitory network integrity when Go trial reaction times are not constrained in task design. Behaviourally selective stopping measures were susceptible to within-individual changes across multiple sessions and subsequent studies are needed to explore whether the improvements are driven by changes to neural activity within the underlying networks. Future research should continue to investigate any within-individual changes to SSRT on the ARIT over a greater number of experimental sessions.

CHAPTER 5

Performance on the Balloon Analogue Risk Task and Anticipatory Response Inhibition Task is Associated with Severity of Impulse Control Behaviours in People with Parkinson's Disease

This chapter is a direct copy from the manuscript published in Experimental Brain Research Journal, with the addition of a pilot study (5.1) and two appendices (6 & 10): Hall, A., Weightman, M., Jenkinson, N., & MacDonald, H. J. (2023). Performance on the balloon analogue risk task and anticipatory response inhibition task is associated with severity of impulse control behaviours in people with Parkinson's disease. Experimental brain research.

I confirm I participated in all aspects of the development of the research within this chapter, data/statistical analyses and the writing and revisions of the manuscript.

5.1. Pilot Study: Determining the most effective version of the Anticipatory Response Inhibition Task for people with Parkinson's disease

Prior to the main study of Chapter 5, pilot testing took place in order to determine the most effective setup of the Anticipatory Response Inhibition Task (ARIT) for those with Parkinson's disease (PD). This particular task, which is an anticipated response version of the Stop Signal Task (SST), had yet to be conducted within a PD population. Prior research of the ARIT in healthy older adults presents worse stop signal reaction time (SSRT) compared to young healthy individuals in the ARIT (Coxon et al., 2012), and both older and young healthy adults show difficulties completing partial trials highlighted by zero partial trials completed or much lower bar stop times (Coxon et al., 2012; Hall et al., 2022; MacDonald et al., 2016). Additionally, PD patients show impaired performance on other versions of the SST compared to healthy controls (Gauggel et al., 2004; Obeso et al., 2011). Considering the information above, four different versions of the ARIT with varying difficulty were implemented in this pilot study to determine if full datasets could be collected in a PD cohort.

15 patients (58 - 80 years, mean 66.3 ± 5.73 standard deviation) took part in the pilot study and all reported diagnosed idiopathic PD. This pilot study was approved by the University of Birmingham Ethics Committee and all participants provided informed written consent. All patients were randomly assigned to complete one of four versions of the ARIT and were asked to provide open-ended feedback, discussing the difficulty of the task and any recommendations for future versions.

All versions of the ARIT followed the methodology described in Chapter 4 with some specific changes. The key differences of the four versions of the ARIT are presented in Table

5.1. The 'Default' version of the ARIT was utilised in previous work in healthy adults (MacDonald et al., 2016) and Chapter 4 of this thesis, containing the same staircase starting stop signal delay (SSD) value, time to fill bar and time to target line (Table 5.1). The remaining three versions were developed to reduce the difficulty of the task by changing one of the following parameters: staircase starting SSD value (Staircase version), time to reach the target/fill the bar (Speed version) and the exclusion of partial stop trials (Stop Both version).

Table 5.1 Four versions of the Anticipatory Response Inhibition Task.

	Staircase starting SSD value (ms)					
	Stop Both	**Stop Left**	**Stop Right**	**Time to fill bar (ms)**	**Time for bar to reach target line (ms)**	**Partial trials inclusion**
Default (n=5)	500	500	500	1000	800	✓
Staircase (n=4)	400	300	300	1000	800	✓
Speed (n=4)	500	500	500	1200	1000	✓
Stop both (n=2)	500	N/A	N/A	1000	800	✗

SSD: stop signal delay; ms: milliseconds; N/A: not applicable; ✓ = yes; ✗ = no.

SSRT was the primary outcome measure in this pilot study and was calculated using the integration method (SSRT = nth Go trial RT (i.e. number of Go trials x probability of responding on Stop trials) – SSD) (Verbruggen et al., 2013). Individualised Go trial reaction time (RT) was reported as this is a direct constituent of SSRT in the integration method calculation (nth Go trial RT), along with SSD (Figures 5.1-5.3). Unpaired t-tests with Welch's correction examined any differences between SSRT, RT and SSD for each ARIT Version.

Averages, standard deviations, t, p, 95% confidence intervals (CI) and effect sizes (Cohen's d: 0.20 = small, 0.50 = moderate, 0.80 = large, (Cohen, 1988)) are reported, where necessary.

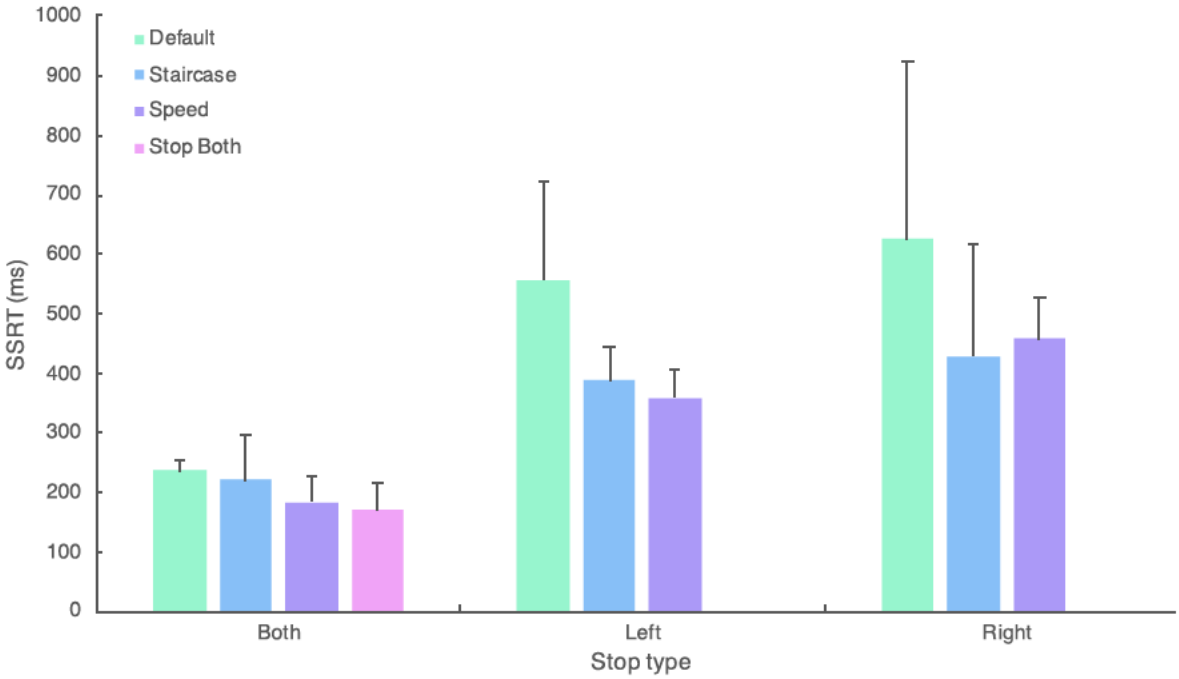


Figure 5.1 Mean and standard deviation SSRT for SB, SL and SR trials for Default, Staircase, Speed and Stop Both groups.
SSRT: stop signal reaction time; SB: stop both; SL: stop left, SR: stop right; ms: milliseconds.

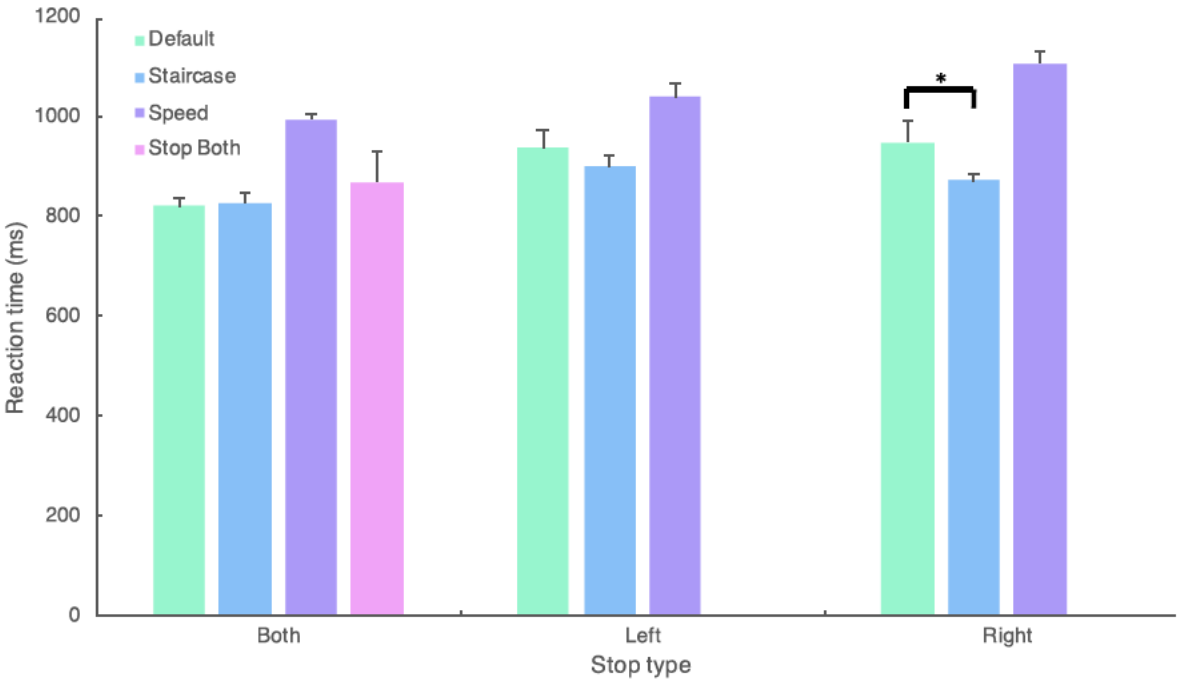


Figure 5.2 Mean and standard deviation reaction time for SB (go left and right average), SL (go right) and SR (go left) trials for Default, Staircase, Speed and Stop Both groups.
SB: stop both; SL: stop left, SR: stop right; ms: milliseconds. Significant values * $p < .05$.

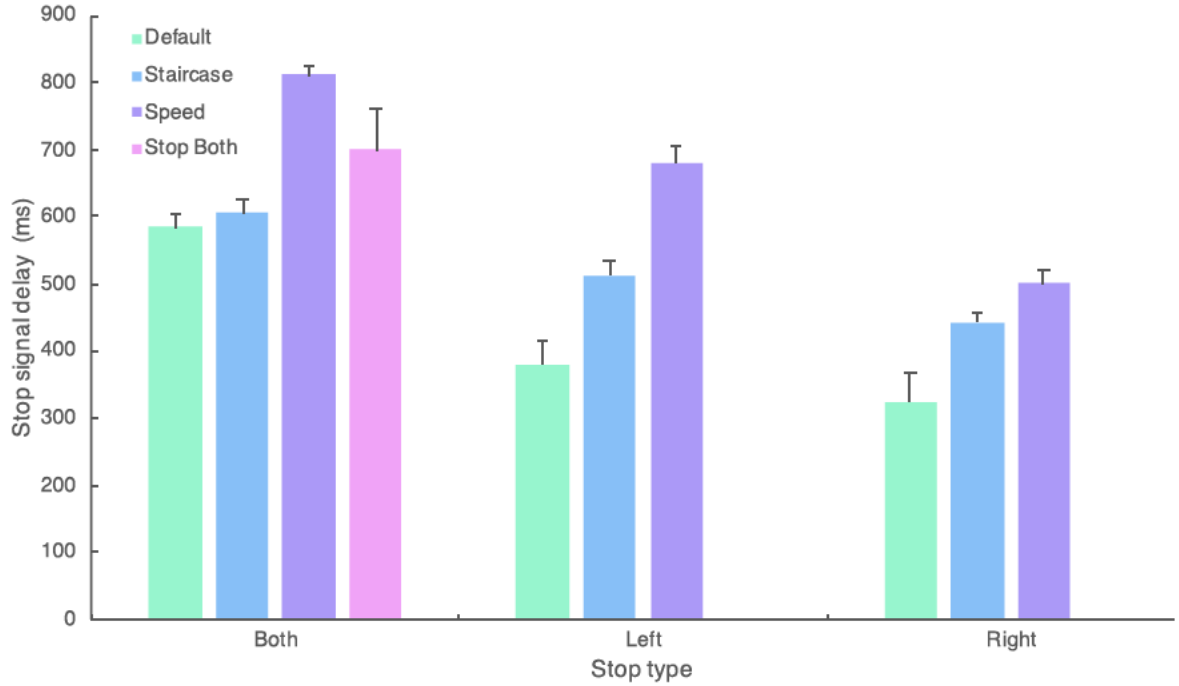


Figure 5.3 Mean and standard deviation SSD for SB, SL and SR trials for Default, Staircase, Speed and Stop Both groups.
SSD: stop signal delay; SB: stop both; SL: stop left, SR: stop right; ms: milliseconds.

Stop Both was removed from consideration for utilisation in Chapter 5 due to feedback of the task being "too easy" for the first two patients and because partial trials were successfully completed in other conditions. Considering the three remaining versions, unpaired t-test results of SSRT showed no significant differences between ARIT versions for each stop type (all $p > .052$) (Figure 5.1), indicating that no version was more difficult than any other. However, the average value for Default SSRT Stop Left (557ms ± 165) was almost significantly greater than Staircase (388ms ± 58.6) ($t_{(5.19)} = 2.14$, $p = .083$, 95% CI [-32.1, 371], Cohen's $d = 1.30$) and Speed (359 ± 48.2) ($t_{(4.83)} = 2.56$, $p = .052$, 95% CI [-3.15, 400], Cohen's $d = 1.54$). Values of RT and SSD were not directly comparable between Speed and the other versions, due to different times for the bar to reach the target line. RT results revealed a significantly longer (worse) time in Default (950ms ± 43.5) compared to Staircase (872ms ± 14.2) for Stop Right ($t_{(5.01)} = 3.73$, $p = .013$, 95% CI [24.1, 131], Cohen's $d = 2.27$). No significant differences were determined for SSD between Default and Staircase (all $p > .131$).

Despite no significant values, the Default version contained higher (worse) values of SSRT compared to the others, along with greater variation of SSRT results in partial trials. Default also displayed generally worse RT and SSD in partial trials compared with Staircase and had the largest amount of feedback from participants referring to high difficulty. This version was subsequently removed from consideration. Due to marginal differences between comparable results of Staircase and Speed, Staircase was chosen as the finalised version for the ARIT is it could then be more directly compared to task results in other chapters and previous publications if required.

5.2. Abstract

Introduction: Dopamine agonist medication is one of the largest risk factors for development of problematic impulse control behaviours (ICBs) in people with Parkinson's disease. The present study investigated the potential of dopamine gene profiling and individual performance on impulse control tasks to explain ICB severity. **Methods:** Clinical, genetic and task performance data were entered into a mixed-effects linear regression model for people with Parkinson's disease taking (n = 50) or not taking (n = 25) dopamine agonist medication. Severity of ICBs was captured via the Questionnaire for Impulsive-compulsive disorders in Parkinson's disease Rating Scale. A cumulative dopamine genetic risk score (DGRS) was calculated for each participant from variance in five dopamine-regulating genes. Objective measures of impulsive action and impulsive choice were measured on the Anticipatory Response Inhibition Task and Balloon Analogue Risk Task, respectively. **Results:** For participants on dopamine agonist medication, task performance reflecting greater impulsive choice ($p = .014$), and to a trend level greater impulsive action ($p = .056$), as well as a longer history of DA medication ($p < .001$) all predicted increased ICB severity. DGRS however, did not predict ICB severity ($p = .708$). No variables could explain ICB severity in the non-agonist group. **Conclusions:** Our task-derived measures of impulse control have the potential to predict ICB severity in people with Parkinson's and warrant further investigation to determine whether they can be used to monitor ICB changes over time. The DGRS appears better suited to predicting the incidence, rather than severity, of ICBs on agonist medication.

5.3. Introduction

Problematic impulse control behaviours (ICBs), incorporating impulse control disorders and other related behaviours, can develop in Parkinson's disease (PD) patients. These behaviours often manifest as compulsive gambling, binge eating, hypersexuality, compulsive shopping, punding, hobbyism and compulsive medication use (Weintraub, 2008). Previous research has identified factors associated with increased likelihood of developing ICBs in PD, including dopamine agonist (DA) medication (use, dose and duration), being male, unmarried, previous personal or family impulsive behaviour, higher Unified Parkinson's disease rating scale (UPDRS) score and younger age of PD onset (Antonini et al., 2017; Cormier-Dequaire et al., 2018; Corvol et al., 2018; Gatto & Aldinio, 2019; Kraemmer et al., 2016; Nombela et al., 2014; Voon, Mehta, et al., 2011). One of the most significant risk factors for ICBs in PD is DA medication, where 14-40% of patients taking this form of dopamine replacement therapy develop destructive ICBs (Bastiaens et al., 2013; Erga et al., 2018; Kraemmer et al., 2016). Clinically prescribed DAs predominantly act upon D2/D3 receptors (Gasser et al., 2015; Seeman, 2015), which are abundant in regions of the mesocorticolimbic (MCL) system (J. H. Ko et al., 2013; Seeman, 2015). The MCL system is largely responsible for impulse control and is relatively spared during the early, unmedicated stages of PD (Caminiti et al., 2017; Claassen et al., 2017; Cools, 2006; Gatto & Aldinio, 2019; K. M. Smith et al., 2016; Weintraub, 2008), compared to the decrease of dopamine in the nigrostriatal system (Dauer & Przedborski, 2003; Vaillancourt et al., 2013; Weintraub, 2008). It is therefore possible that the addition of DA medication causes a tonic hyperdopaminergic state in the MCL network, which hinders phasic dopamine modulation, and subsequent problems with impulsivity (Gatto & Aldinio, 2019; Meder et al., 2019; Sinha et al., 2013; Vaillancourt et al., 2013; Weintraub, 2008). This state has been termed the overdose-hypothesis (Cools et al., 2001; Ruitenberg et al., 2021; Vaillancourt et al., 2013). Moreover, increases in DA dose and the use of DA medication over

time are often associated with ICBs in PD, due to higher concentrations of dopamine activating D2 receptors to a greater extent compared to lower concentrations (Trantham-Davidson et al., 2004). (Trantham-Davidson et al. 2004). The working hypothesis being that increased and/or prolonged receptor activation may reduce D2 auto-receptor sensitivity (Gasser et al., 2015), leading to a blunted post-synaptic D2-mediated inhibitory effect, increased overall dopamine release and resultant impulsive behaviour (Ford, 2014; Ray, Miyasaki, et al., 2012). The two possible mechanisms of effect are not mutually exclusive, and may well act in concert, though both offer explanations as to why DA medication leads to dysfunctional levels of dopamine and ICB development in some patients.

Another factor which can influence ICB development is genetic. Previous literature has identified specific genetic polymorphisms associated with ICBs in PD patients, either individually (Erga et al., 2018; Kraemmer et al., 2016; Lee et al., 2009), or collectively as a very large polygenic risk score (Faouzi et al., 2021; Ihle et al., 2020). The first dopaminergic genetic score quantifying the influence of a small number of genes was developed by Nikolova and colleagues (2011). This method was subsequently expanded by Pearson-Fuhrhop and colleagues (2013, 2014) to produce a polygenic dopamine genetic risk score (DGRS) incorporating five specific genes selected a-priori for each being known to modify dopamine signalling within MCL regions (Caminiti et al., 2017; K. M. Smith et al., 2016; Vriend et al., 2014) and influence impulse control (Abidin et al., 2015; Congdon et al., 2009; Erga et al., 2018; Lee et al., 2009; K. M. Smith et al., 2016; Vriend et al., 2014). These genes include: DRD1 rs4532, DRD2 rs1800497, DRD3 rs6280 (encoding D1, D2, D3 receptors, respectively), catechol-O-methyltransferase (COMT) rs4680 and dopamine transporter (DAT) rs28363170. The quantitative aspect of the DGRS weights the influence of each polymorphism on widespread tonic dopamine neurotransmission, where a higher score is equal to higher

dopamine neurotransmission. It stands to reason that a PD patient's genetically determined levels of MCL dopamine neurotransmission will affect how they respond, and whether they develop ICBs, when dopamine tone is further increased with DA medication. Indeed, our previous work utilising the DGRS for the first time in PD (Hall et al., 2021) demonstrated that patients with a low DGRS had more ICBs identified via the QUIP-S, which decreased with time on DA medication. Conversely, patients with a higher DGRS had fewer ICBs, but this number increased with time on DA medication. We were unable to discern whether increasing dosage over time or time of exposure to DA medication per se were causing these changes in ICBs.

MacDonald and colleagues (2016) were first to use the DGRS to explain objective measures of behavioural impulsivity in a non-PD population. These objective measures were stop signal reaction time (SSRT) from the Anticipatory Response Inhibition Task (ARIT) for impulsive action, and decision making following negative reinforcement on the Balloon Analogue Risk Task (BART) for impulsive choice. They concluded that the administration of DA medication in healthy adults improved task measures of impulsive action and choice for those with a lower DGRS and worsened them for participants with a high DGRS. Previous literature has identified no change in impulsive behaviour for PD ICB patients after a loss on the BART, compared to non ICB patients who reduced their impulsive behaviour (Martini et al., 2018). Either shorter or no difference in SSRT has been found for ICB vs no ICB PD patients in the Stop Signal Task (Claassen et al., 2015b; Hlavatá et al., 2020; Ricciardi et al., 2017; Vriend et al., 2018). The ARIT and our specific measure of negative reinforcement in the BART have yet to be investigated in a PD cohort in the context of ICBs.

ICBs are routinely identified using the questionnaire for impulsive-compulsive disorders in Parkinson's disease (QUIP) and further clinically diagnosed during an interview (Krieger et al., 2017; Marques et al., 2019; Papay et al., 2011; Probst et al., 2014; Takahashi et al., 2022; Weintraub et al., 2009, 2012). The Questionnaire for Impulsive-compulsive disorders in Parkinson's disease short (QUIP-S) and QUIP rating scale (QUIP-RS) are two widely used self-report versions of this questionnaire. The QUIP-S involves only 13 questions with 'yes' or 'no' answers (Krieger et al., 2017; Weintraub et al., 2009), whereas the QUIP-RS includes 28 questions which are answered via a frequency rating scale with five different options and the final score is equated with ICB severity (Marques et al., 2019; Probst et al., 2014; Takahashi et al., 2022; Weintraub et al., 2012). The QUIP-RS offers a larger range of scores covering the same behaviours in more depth, which suggests the resultant ICB frequency (i.e., severity) score is capable of being a more sensitive measure of impulsivity, including changes over time (Marques et al., 2019), compared to ICB incidence from the QUIP-S (Probst et al., 2014; Weintraub et al., 2012). The Barratt Impulsiveness Scale (BIS) is also a self-report questionnaire that measures impulsivity but as a trait or personality construct (Stanford et al., 2009), rather than a diagnostic tool for pathological ICBs directly. Nevertheless, ICBs in PD (Filip et al., 2018), including those determined by the QUIP-S (Marín-Lahoz et al., 2018) and QUIP-RS (Takahashi et al., 2022) are associated with higher impulsivity on the BIS. One particular study of note determined a positive correlation between total QUIP-RS score and BIS score (Goerlich-Dobre et al., 2014), highlighting the potential adjunct use of the BIS in ICB diagnosis.

The primary focus of the present study was to investigate whether objective, sensitive lab-based measures of impulsive behaviour, genetic and disease specific measures were associated with the severity of every day impulsive behaviour measured by the QUIP in a

sample of PD patients taking DA medication. The first aim was to evaluate the validity of our objective lab-based task measures to be able to reflect the severity of subjective every day ICBs. This is a key issue to address as the ARIT and our specific measure of negative reinforcement in the BART have yet to be investigated in a PD cohort in the context of ICBs. We hypothesised that measures reflecting worse impulsivity on the tasks (higher SSRTs in the ARIT and more impulsive decision making in the BART) would be related to higher scores on the QUIP-RS. Our second aim was to identify prognostic risk factors for the severity of ICBs on dopamine agonists. We hypothesised that patients with a low DGRS would display worse task impulsivity and higher ICB frequency. Whereas those with a high DGRS would exhibit better impulsivity on the tasks and lower ICB frequency. We specifically wanted to investigate if DA medication dosage or time of exposure to DA medication could predict ICB frequency, following our previous results (Hall et al., 2021). We hypothesised that both DA medication dosage and time on DA medication would be higher for patients reporting a greater frequency of ICBs. When accounting for the influence of an individual's genetic profile, we hypothesised that for patients with a low DGRS, longer exposure to DA medication would result in a reduction in ICBs over time. In contrast, patients with a high DGRS were expected to show increasing ICB frequency with increasing time on DA medication. We did not expect to find any comparable results for patients taking dopamine medication which did not include DAs. Finally, we wanted to examine any relationship between clinically identified ICBs and subjective trait impulsivity via the BIS.

5.4. Materials and Methods

5.4.1. Participants

One hundred participants with PD were recruited for the current study via an advertisement on Parkinson's UK and all participants self-identified as having a PD diagnosis. 70 recruited participants were taking DA medication and the remaining 30 were taking dopamine medication not including agonists. This target of 70 DA participants was to allow for participant drop out whilst still achieving the target sample size of 61, calculated from a-priori power calculation to achieve 80% power. Participants were included in the study if they were between the ages of 40-80, had no history of neurological illness other than PD and had normal or corrected-to normal vision. All demographic, clinical, questionnaire, behavioural and genetic data were collected remotely or online by means of online software, post, emails, video calls or phone calls.

5.4.2. Clinical Impulsivity

5.4.2.1. ICB incidence

The QUIP-short comprised of 13 'yes' or 'no' questions regarding current impulse control behaviors lasting at least 4 weeks. Participants would receive a score of one for 'yes' and zero for 'no'. Any score greater than zero confirmed the incidence of an ICB.

5.4.2.2. ICB frequency

The QUIP-RS measured the frequency of ICBs. The questionnaire included four questions in each of the following categories: gambling, sex, buying, eating, hobbyism, punding and PD medication. Participants responded to each question with a choice from a 5-point scale (0: never, 1: rarely, 2: sometimes, 3: often, 4: very often) which represented impulsivity in the past

4 weeks or any 4-week period in a designated time frame. Total scores were calculated between 0-112.

5.4.3. Trait Impulsivity

5.4.3.1. Barratt Impulsiveness Scale

A 4-point scale (1: rarely/never, 2: occasionally, 3: often, 4: almost always/always) questionnaire comprising of 30 questions about everyday behaviours assessing attentional, motor and non-planning trait impulsivity (Patton et al., 1995). A higher score reflects greater impulsivity. Two patients did not provide answers for 2 questions relating to the work environment as they were retired, and one patient did not answer one of the questions. Therefore, each participant's result was normalised to a percentage where the score was divided by the total score possible from the number of questions answered and then multiplied by 100.

5.4.4. Impulsivity Task Performance

5.4.4.1. Anticipatory Response Inhibition Task (ARIT)

The ARIT was presented on a computer screen using custom code written in Inquisit 6 Lab (Version 6.5.1, Millisecond Software) and responses were made using a keyboard. Participants completed the task on their personal computers at home. Participants initially observed an instruction video and practised 20 Go and 9 Stop trials. Subsequently, they were required to complete 10 blocks of 40 experimental trials. The experimental trials consisted of 295 Go trials and 105 Stop trials in a randomised order.

For the experimental procedure, on each trial participants were presented with a screen containing two vertical white bars (Figure 5.4). The left bar was controlled with the 'z' key using the left index finger and the right bar was controlled with the '? /' key using the right

index finger. Every trial started with the participant holding down both keys which initiated a black bar rising within each of the white bars. Both black bars rose at equal rates and filled the white bars completely after 1000ms. The black bars intercepted a horizontal target line at 800ms. During Go trials, participants were required to intercept the horizontal target line with the rising bars by timing the removal of their fingers from both keys appropriately (successful releases were within 40ms above the target and 30ms below). Stop trials consisted of Non-Selective Stop Both (SB) trials and Partial Stop trials. During SB trials, participants were asked to keep both keys depressed when both bars stopped rising before reaching the target (Figure 5.4). Partial Stop trials comprised of Stop Left (SL) and Stop Right (SR) trials, where one bar stopped and the other continued rising. Here, participants were required to keep the key depressed corresponding to the bar that stopped rising and intercept the target line with the alternative bar by releasing the corresponding key (Figure 5.4). During Stop trials the bars initially stopped at 400ms for SB and 300ms for SL and SR. A staircase algorithm was utilised to generate a 50% success rate for each stop version. Following a successful Stop trial, the bar stop time increased by 25ms on the subsequent Stop trial but decreased by 25ms following an unsuccessful Stop trial. Stop signal reaction time from SB trials was calculated as the primary dependent measure using the integration method (Logan & Cowan, 1984; Verbruggen et al., 2019a).

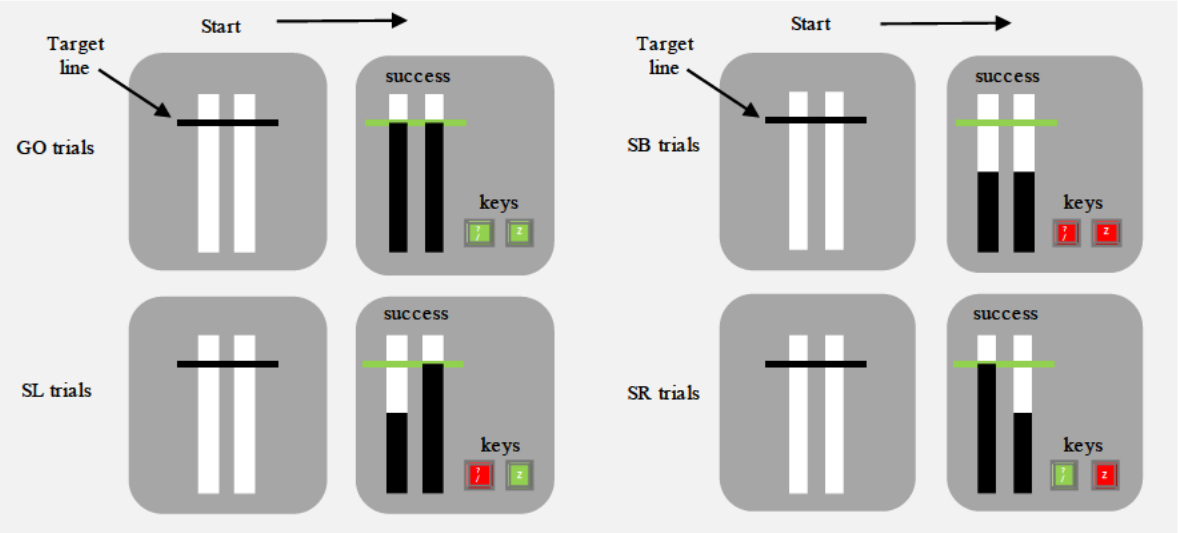


Figure 5.4 Visual display at the start of a trial (all left panels) and during a GO, SB (Non-Selective Stop Both), SL (Stop Left) and SR (Stop Right) trial in the Anticipatory Response Inhibition Task.
Green keys represent successful release of the key at the target and red keys represent successful cancellation and keeping the key depressed. On successful Go trials, both keys are released at the target line. On successful SB trials, both keys are held down. On successful SL trials, the right key is released, and the left key is held down. On successful SR trials, the left key is released, and the right key is held down.

5.4.4.2. Balloon Analogue Risk Task (BART)

The BART was displayed on the participant's personal computer screen using custom code written in Inquisit 6 Lab (Version 6.5.1, Millisecond Software) and responses were made using the mouse. Participants initially completed 5 practise trials and then 30 experimental trials.

The experimental procedure was as follows: at the beginning of each trial, participants were presented with a new balloon and two options: 'Pump up the balloon' or 'collect £££' (Figure 5.5). Participants could pump up the balloon, which incrementally increased potential earnings by £0.02 with each pump. If participants chose to collect their earnings, then the current trial would end, and the amount accumulated was added to the total winnings. However, the balloon could randomly explode on any pump and any potential earnings would be lost,

followed by the end of the trial. Each trial started with a 1 in 85 probability of the balloon exploding. With every pump of the balloon, one number was randomly selected and removed without replacement from an 85-length array. When number one was selected, the balloon would pop and the trial would end with no monetary collection. The risk of balloon explosion therefore increased with each pump (1/84, 1/83 etc), but so did the potential monetary reward. The average number of pumps on a collection trial (i.e., when the number of pumps was not artificially constrained by a balloon burst) following a successful monetary collection (average collection pumps) and following a loss (balloon explosion) were calculated for each participant. The difference between these means normalised to pumps after a loss (losses cancel) reflected positive reinforcement and normalised to pumps after a win (wins cancel) reflected negative reinforcement (MacDonald et al., 2016; Mata et al., 2012). Proportions further from zero indicated a greater change in behaviour following either a positive or negative outcome. In this context, behaviour modification reflects a change in impulsivity. Negative reinforcement was the main dependent measure in this task, given previous results (MacDonald et al., 2016).

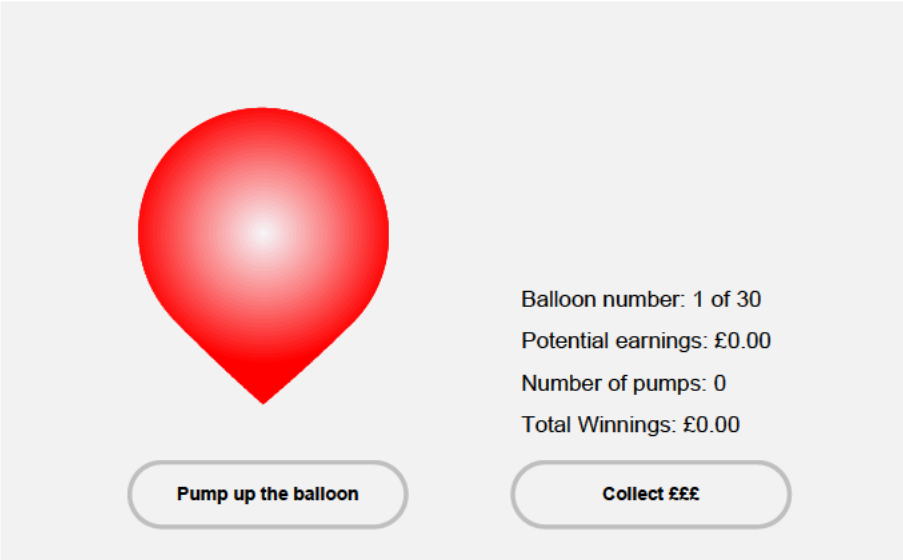


Figure 5.5 Visual display of the Balloon Analogue Risk Task.
'Pump up the balloon' and 'Collect £££' are the two available response options. Visual feedback of 'Balloon number', 'Potential earnings', 'Number of pumps' and 'Total winnings' are displayed throughout each trial.

5.4.5. Cognitive Function

5.4.5.1. Central Nervous System Vital Signs (CNSVS)

CNSVS is a computerised neurocognitive test battery comprising of neuropsychological tests to assess cognitive behaviour and acts as a tool, not for diagnosis, but for brief clinical evaluation of mild cognitive dysfunction (Gualtieri & Johnson, 2006). Participants completed all tests on their computer and made their responses using a keyboard. The scores produced from these tests contribute to neurocognitive clinical evaluation domains. Nine tests were included within the current research which were linked to 14 cognitive domains: composite memory, verbal memory, visual memory, psychomotor speed, reaction time, complex attention, cognitive flexibility, processing speed, executive function, reasoning, working memory, sustained attention, simple attention and motor speed (Appendix 6). Automated scoring reported raw patient test scores for each domain which were automatically normalised and age-matched to a large normative database to create standard scores. These scores were produced for the 14 domains along with the neurocognitive index (NCI) which represents a global score of neurocognition by taking an average of the domain scores for composite memory, psychomotor speed, reaction time, complex attention and cognitive flexibility. Standard scores for NCI and working memory were included in analyses.

5.4.6. Genetic Data

Five specific genetic polymorphisms which formed the DGRS were identified for each participant. Genetic analysis was conducted by LGC Genomics, and full methodology can be found at: http://www.lgcgenomics.com/. The single nucleotide polymorphisms within four genes were determined using kompetitive allele specific polymerase change reaction (KASP PCR) genotyping: DRD1 (rs4532), DRD2 (rs1800497), DRD3 (rs6280) and COMT (rs4680). This process produced a bi-allelic score for each single nucleotide polymorphism. The variable

number tandem repeat in the DAT gene (rs28363170) was analyzed using a separate PCR process. Here, the PCR was followed by PCR clean-up, sanger sequencing and genotype calling. The repeat length of DAT VNTR was determined by eye on the sequence trace files.

Dependent upon the specific mutation/number of repeats for each of the five polymorphisms, every participant received a score of 0 or 1 for each polymorphism according to whether it acts to decrease or increase dopamine transmission, respectively (MacDonald et al., 2016; Pearson-Fuhrhop et al., 2013, 2014). All gene scores were then summed for an overall DGRS between 0-5 (higher score = higher dopamine levels) (Appendix 7). All genes were in Hardy-Weinberg equilibrium (all $p > .291$), which was determined with chi-square tests. For the linear regression models discussed below relating to the DA group ($N = 50$), the sample size for each DGRS was as follows: DGRS 0 $n = 0$; DGRS 1 $n = 4$, DGRS 2 $n = 11$, DGRS 3 $n = 17$, DGRS 4 $n = 4$, DGRS 5 $n = 14$. The DGRS was split into two groups: DGRS low (DGRS 0-2) and DGRS high (DGRS 3-5) aiming to make as equal sample sizes as possible. The DGRS was utilised as a binary independent variable within the models.

5.4.7. Statistical Analysis

Statistical analysis and modelling were performed in MATLAB (version R2020a, MathWorks). As a preliminary analysis, comparisons were made for all available clinical, demographic, genetic and cognitive variables between those with and without an ICB. Seventeen participants with unavailable data for these variables due to errors in reporting and incomplete online datasets from the CNSVS were discarded from these analyses (DA $n = 12$, NDA $n = 5$). Kolmogorov-Smirnov tests identified any violations of normality. Wilcoxon rank sum tests were used to compare any variables which violated normality, while the remaining variables were compared using unpaired t-tests. A simple linear regression looked for a

correlation between ICB frequency on the QUIP-RS and BIS score in both DA and NDA groups. The following linear regression models identified the variables associated with clinical and trait impulsivity.

5.4.7.1. Clinical Impulsivity model

The response variable for this model was ICBs identified via the QUIP. A participant's score on the QUIP-S and QUIP-RS were strongly correlated ($R = 0.72$, $p < .001$). Therefore, we chose to predict results of the QUIP-RS because a larger scale range was likely to be more sensitive to changes in impulsivity. CNSVS NCI and WM were not included due to missing data, as their inclusion would have reduced the sample size of the model. DGRS, DA levodopa equivalent daily dose (DA LEDD), Negative Reinforcement from the BART, SSRT from Stop Both trials of the ARIT, and Years on DA were selected a-priori to be included in the model to test our hypotheses and build on previous literature (Hall et al., 2021; MacDonald et al., 2016). Univariate linear regression analyses identified any additional variables which could be included as independent predictors of ICB frequency in the full model (Appendix 8). However, any continuous variables identified were tested for collinearity against the pre-selected variables, and resultant correlated variables were not included in the final model (Appendix 9). Therefore, UPDRS I&II and Years Since Diagnosis were not included in the final model as they both correlated with Years on DA (both $p < 0.001$). Gender was also not included to not overparameterise the model. The final mixed-effects multiple linear regression model was formed with selected variables and hypothesised interactions:

$$y(ICB\ frequency)$$

$$= \beta_0(intercept) + \beta_1 DGRS + \beta_2 DA\ LEDD + \beta_3 \text{Years on DA}$$
$$+ \beta_4 \text{SSRT SB} + \beta_5 \text{Negative Reinforcement} + \beta_6 DGRS * Years\ on\ DA$$
$$+ \beta_7 DGRS * SSRT\ SB + \beta_8 DGRS * Negative\ Reinforcement + \varepsilon$$

Further linear regressions were run with this model to determine the contribution of each individual genetic polymorphism towards the response variable. This involved substituting the score (0 or 1) for each genetic polymorphism into the model in place of the full DGRS. The same model was run for the NDA group, without DA LEDD and Years on DA.

5.4.7.2. Trait Impulsivity model

The same independent variables and interactions from the clinical impulsivity model were selected for inclusion in the multiple linear regression model predicting BIS percentage as the response variable:

$$y\ (BIS\ percentage)$$

$$= (\beta_0(intercept) + \beta_1 DGRS + \beta_2 DA\ LEDD + \beta_3 \text{Years on DA}$$
$$+ \beta_4 \text{SSRT SB} + \beta_5 \text{Negative Reinforcement} + \beta_6 DGRS * Years\ on\ DA$$
$$+ \beta_7 DGRS * SSRT\ SB + \beta_8 DGRS * Negative\ Reinforcement + \varepsilon$$

The same model was run for the NDA group, without DA LEDD and Years on DA.

5.4.7.3. Model Validation

Effect sizes for all models were determined and interpreted using adjusted R^2 (0.01 = small, 0.09 = medium, 0.25 = large, Foster et al., 2018) and the achieved statistical power is reported

(G*Power 3.1.9.6). Validation against a constant model (i.e., goodness-of-fit) was assessed for all models and an alpha value of 0.05 was used for all analyses.

5.5. Results

5.5.1. Preliminary Analysis

Data from 83 participants (DA: n = 58, 45-77 years, mean 64.1 ± 8.80 standard deviation, NDA: n = 25, 46-79 years, mean 64.6 ± 8.60 standard deviation) were included in the preliminary clinical, demographic, genetic and cognitive comparisons between those with (QUIP-S > 1) and without (QUIP-S = 0) an ICB (Table 5.2). Of these participants, in the DA group, 16 participants had a low DGRS (0-2) and 42 had a high DGRS (3-5). Moreover, in the NDA group, 9 participants had a low DGRS and the remaining 16 presented a high DGRS. In the DA group, participants with an ICB were more likely to be male ($p = .008$) and presented with a higher BIS ($p = .002$) and QUIP-RS ($p = .010$) score. Scores on the UPDRS I&II trended towards being higher for those with an ICB than those without. These results were not likely to be due to changes in general cognitive function as there were no differences between CNSVS NCI and WM between ICB groups. In the NDA group, those with an ICB reported a greater number of years since diagnosis ($p = .039$), a higher QUIP-RS ($p = .008$) score, and the increased overall medication dosage (Total LEDD) trended towards significance ($p = .062$).

Table 5.2 Participant clinical, demographic, genetic and cognitive variables separated by incidence of impulse control behaviours via the QUIP-short.

Dopamine Agonist (DA)			
	ICB (n = 28)	**No ICB (n = 30)**	**p**
Age, years	63.3 (8.83)	64.7 (8.87)	.546
BIS percentage	**52.5 (10.5)**	**44.8 (7.85)**	**.002**
CNSVS NCI	87.9 (28.0)	97.7 (10.3)	.092
CNSVS WM	98.3 (20.8)	102 (17.8)	.436
DA LEDD	210 (110)	190 (119)	.495
DA type, % ropinirole	57.1 (16:8:4)	70.0 (21:5:4)	.477
(n, ropinirole:pramipexole:rotigotine)			
DGRS	3.21 (1.17)	3.07 (1.01)	.608
Gender, % male (n, male:female)	**67.9 (19:9)**	**33.3 (10:20)**	**.008**
ICB frequency (QUIP-RS)	**26.3 (12.6)**	**7.90 (9.94)**	**.010♦**
ICB frequency (QUIP-short)	**2.50 (1.32)**	**0**	**<.001♦**
Total LEDD	684 (431)	677 (596)	.961
UPDRS I&II	22.6 (11.6)	17 (10.3)	.057^
Years on DA	5.57 (4.01)	4.58 (3.31)	.309
Years since diagnosis	8.07 (5.79)	6.97 (4.67)	.426
Non-Dopamine Agonist (NDA)			
	ICB (n = 11)	**No ICB (n = 14)**	**p**
Age, years	62.6 (9.67)	66.1 (7.68)	.332
BIS percentage	52.2 (9.44)	46.6 (8.30)	.133
CNSVS NCI	84.9 (20.4)	93.5 (16.4)	.251
CNSVS WM	100.8 (12.4)	99.9 (14.3)	.861
DGRS	3.09 (1.14)	3.43 (1.16)	.473
Gender, % male (n, male:female)	81.8 (9:2)	64.3 (9:5)	.353
ICB Score (QUIP RS)	**24.8 (17.5)**	**9.43 (8.53)**	**.008**
ICB Score (QUIP-short)	**2.64 (1.75)**	**0**	**<.001♦**
Total LEDD	665 (520)	350 (271)	.062^
UPDRS I&II	20.9 (10.6)	14.9 (9.08)	.372
Years since diagnosis	**4.64 (2.73)**	**2.68 (1.73)**	**.039**

Means for variables (± standard deviation). ICB: impulse control behaviour (n: number); BIS percentage: Barratt impulsiveness scale; CNSVS: central nervous system vital signs; NCI: neurocognitive index: WM: working memory; DA: dopamine agonist; LEDD: levodopa equivalent daily dose; DGRS: Dopamine Genetic Risk Score; QUIP: Questionnaire for impulsive-Compulsive Disorders in Parkinson's Disease; RS: rating scale; UPDRS: Unified

Parkinson's Disease Rating Scale; Significant values in bold ($p < .05$). ♦: Wilcoxon rank sum test. ^: trending towards significance.

5.5.2. Linear Regression Models

The sample sizes for the following models were reduced (DA n = 50, NDA n = 22) due to incomplete datasets for included independent variables or the inability to genotype from the DNA sample. The following results are specific to DA medication, as NDA models were unable to explain any variability in the outcome variable (goodness-of-fit: clinical model p = .951, trait model p = .662). There was therefore nothing to report for these NDA models.

5.5.3. Clinical Impulsivity

Task performance and exposure time to DA medication were associated with the frequency of ICBs.

The Clinical Impulsivity model (Table 5.3) was validated against a constant model ($F_{7,41}$ = 3.15, p = .007) and explained 26% of the variance in ICB frequency scores according to the adjusted R^2 value (unadjusted R^2 = 0.381, i.e., large effect size). The statistical power achieved by the model was 97.2%, also indicating an appropriate sample size for the model. ICB frequency increased by 12.3 for every 1 unit increase in negative reinforcement (b = 12.4, p = .014). This statistic indicates that, as expected, people who made more impulsive decisions on the BART after a loss also reported a higher frequency of ICBs. The increase in ICB frequency of 0.07 for each millisecond increase in SSRT SB trended towards significance (b = 0.07, 0 = .056), indicating people with worse motor impulsivity tended to report a higher frequency of ICBs, as predicted. Of note, the two tasks were not correlated (Appendix 8, r = -0.13, p = .354) and the univariate analysis (Appendix 7) showed that neither task measure in isolation could explain variance in ICB frequency (ARIT SSRT Stop Both β = 0.03, p = .400; r = 0.09; BART Negative Reinforcement β = 6.92, p = .153; r = 0.22). Therefore, it appears that when

partitioning out variance amongst variables within the multiple linear regression model, each task significantly accounted for independent variance in the model, which highlights the potential contribution to two different aspects of ICB severity (e.g. via motor and cognitive impulse control).

Table 5.3 Multiple linear regression analysis of variables associated with the frequency of impulse control behaviours.

ICB (n = 23) no ICB (n = 27)

	β	**SE**	**p value**	**95 % CI (β)**
Intercept	-15.0	13.0	.254	[-41.3, 11.2]
DGRS low	9.09	24.1	.708	[-39.5, 57.7]
LEDD DA	-0.004	0.02	.862	[-0.04, 0.04]
Negative Reinforcement	**12.3**	**4.76**	**.014**	**[2.63, 21.9]**
SSRT stop both	0.07	0.03	.056^	[-0.002, 0.14]
Years on DA	**2.09**	**0.48**	**<.001**	**[1.11, 3.06]**
DGRS low * Negative Reinforcement	11.5	15.5	.463	[-19.8, 42.9]
DGRS low * SSRT stop both	0.009	0.08	.911	[-0.15, 0.17]
DGRS low * Years on DA	-1.19	1.15	.305	[-3.52, 1.13]

Response variable: score on Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease rating scale. ICB: impulse control behaviour (n: number); DGRS: dopamine genetic risk score; LEDD: levodopa equivalent daily dose; DA: Dopamine Agonist; SSRT: stop signal reaction time; β: coefficient, SE: standard error, CI: confidence interval. Significant values in bold ($p < .05$). ^: trending towards significance.

As hypothesised, ICB frequency increased by 2.09 for every year on DA medication ($b = 2.09$, $p < .001$). However, contrary to our hypotheses, these associations between clinical impulsivity and task performance/time on medication did not depend on a participant's DGRS (DGRS X Negative Reinforcement: $b = 11.5$, $p = 0.463$; DGRS X SSRT: $b = 0.009$, $p = 0.911$;

DGRS X Years on DA: b = -1.19, p = 0.305). DA dose (b = -0.004, p = 0.862) and DGRS alone (b = 9.09, p = 0.708) were also not predictive of ICB frequency score.

Interestingly, two of the DGRS constituent genes interacted with time on DAs to effect ICB frequency. When substituting COMT into the model ($F_{7,41}$ = 4.1, p = .001, R^2 = 0.444 i.e., large effect size, 95.7% power), the increase in ICB frequency from one year on DAs was 2.49 more for a COMT score of 1 (greater dopamine neurotransmission, b = 2.12) compared to 0 (b = -0.37, p = .048). Similarly for DAT ($F_{7,41}$ = 4.57, p <.001, R^2 = 0.471 i.e., large effect size, 95.6% power), the increase in ICB frequency from one year on DAs was 1.14 more for a DAT score of 1 (b = 2.56) compared to 0 (b =1.42, p = .014). DAT score also interacted with Negative Reinforcement. For participants with a DAT score of 1, a single unit increase in Negative Reinforcement reduced ICB frequency by 28 (b = -11.0) compared to participants with a score of 0 (b = 17.0, p = 026). No individual genetic polymorphism was independently associated with a change in ICB frequency (p > .288). Results from an alternative DGRS classification can be found in Appendix 10.

5.5.4. Trait Impulsivity

Trait impulsivity (BIS percentage) was significantly correlated with clinical impulsivity (ICB frequency) in both DA (R = 0.56, p <.001, Figure 5.6) and NDA (R = 0.74, p<.001, Figure 5.7) groups. This indicates that participants who reported higher levels of everyday trait impulsivity, also reported a higher frequency of ICBs.

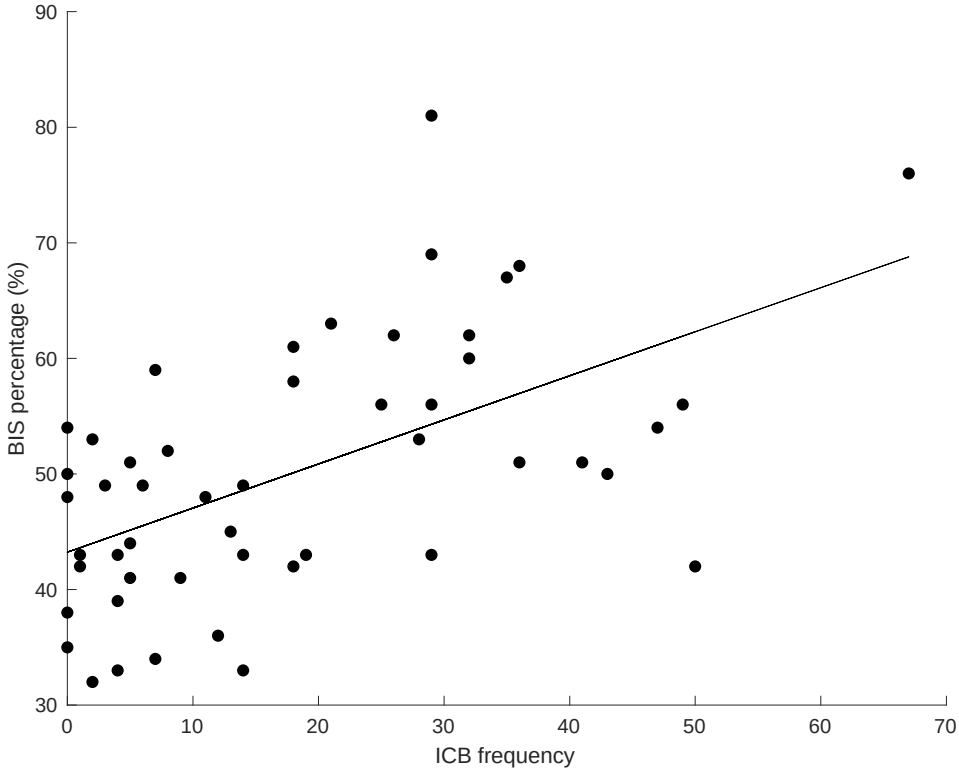


Figure 5.6 Linear correlation between impulse control behaviour (ICB) frequency measured via the QUIP-RS and Barratt Impulsiveness Scale (BIS) percentage score in the dopamine agonist group.

Data circles represent individual participants.

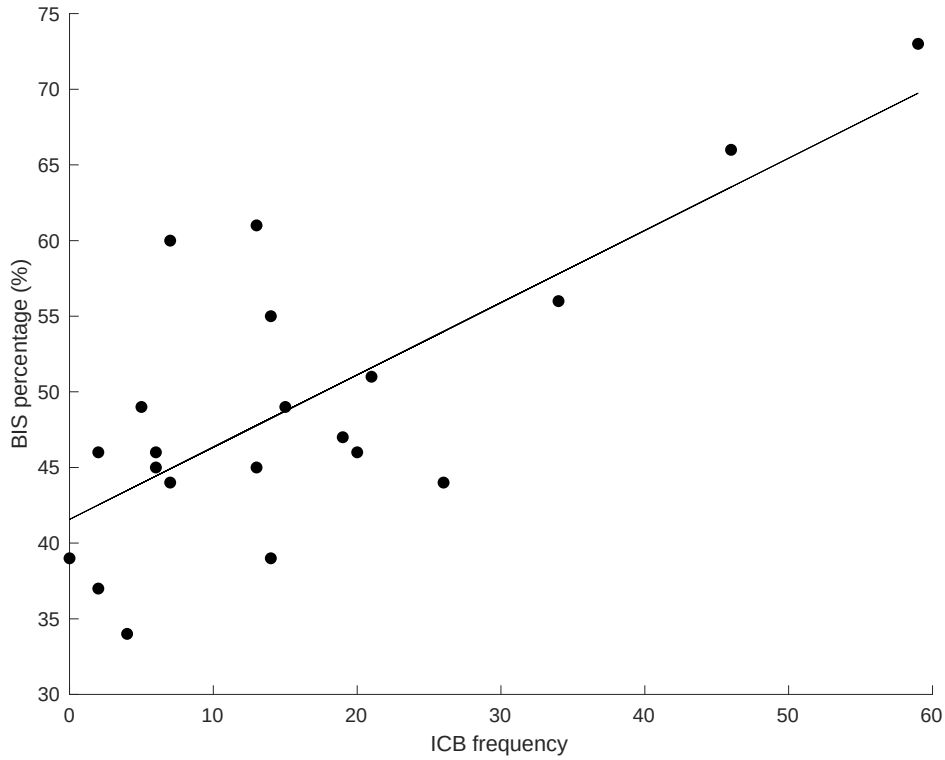


Figure 5.7 Linear correlation between impulse control behaviour (ICB) frequency measured via the QUIP-RS and Barratt Impulsiveness Scale (BIS) percentage score in the non-dopamine agonist group.
Data circles represent individual participants.

Long term exposure to DA medication predicted subjective, real-world trait impulsivity.

For trait impulsivity ($F_{7,41} = 1.98$, $p = .074$, $R^2 = 0.28$ i.e., large effect size, 83.5% power, Table 5.4), a participant's BIS increased by 1.14% with every year on DA medication ($b = 1.14$, $p = .003$). No other independent variables or interactions significantly predicted BIS percentage ($p > .358$).

Table 5.4 Multiple linear regression analysis of variables associated with Barratt Impulsiveness Scale percentage.

ICB (n = 23) no ICB (n = 27)

	β	SE	p value	95 % CI (β)
Intercept	**38.8**	**9.56**	**<.001**	**[19.5, 58.1]**
DGRS low	-4.37	17.7	.806	[-40.1, 31.4]
LEDD DA	-0.008	0.02	.582	[-0.04, 0.02]
Negative Reinforcement	1.79	3.50	.612	[-5.28, 8.87]
SSRT stop both	0.02	0.03	.358	[-0.03, 0.08]
Years on DA	**1.14**	**0.36**	**.003**	**[0.42, 1.86]**
DGRS low * Negative Reinforcement	-1.19	11.4	.917	[-24.2, 21.9]
DGRS low * SSRT stop both	0.004	0.06	.948	[-0.12, 0.12]
DGRS low * Years on DA	0.24	0.85	.780	[-1.47, 1.95]

Response variable: Barratt Impulsiveness Scale percentage. ICB: impulse control behaviour (n: number); DGRS: dopamine genetic risk score; LEDD: levodopa equivalent daily dose; DA: Dopamine Agonist; SSRT: stop signal reaction time; β: coefficient, SE: standard error, CI: confidence interval. Significant values in bold ($p < .05$).

5.6. Discussion

The focus of this study was to investigate the sensitivity of objective task measures, along with variation in dopamine genetics and disease specific measures, to determine the frequency of clinically identified ICBs. As such, the study produced several novel findings which were specific to DA medication. As hypothesised, task performance was associated with ICBs. Participants who made a greater number of impulsive decisions after a loss on the BART, or who tended to exhibit worse impulsivity on the ARIT, also reported a higher frequency of impulsive behaviours on the clinical screening tool. Interestingly, as performance on the two tasks were not related, the two performance measures seem to be associated with two distinct aspects of ICB severity. However, DGRS, an analogy of dopamine neurotransmission, did not interact with task performance to determine clinical impulsivity. Interestingly, the DAT polymorphism interacted with impulsive decision making on the BART to effect ICB frequency. The secondary aim of this study was to work towards identifying measures for prognostic use for ICBs on dopamine agonists, thus time on DA medication and DA dosage were incorporated into the models. Greater length of exposure to DA medication was associated with higher ICB frequency as predicted, whereas DA dosage was not. The DGRS did not interact with time on DAs, however when examining the influence of individual genes, more dopamine neurotransmission indexed via polymorphisms in COMT and DAT predicted higher ICB frequency with increasing exposure to DA medication. More time on DA medication was also associated with higher levels of trait impulsivity, which in turn was correlated with ICB frequency. The results of the current study present promising initial results highlighting the potential use of our task-derived measures of impulse control to predict ICB severity in people with Parkinson's disease on DA medication.

A linear relationship existed between task performance and clinically identified ICBs, but only for patients taking dopamine agonist medication. Patients who made more impulsive decisions on the BART after a loss also reported a higher frequency of ICBs. Our finding aligns with other studies that show ICB patients failing to reduce their impulsive behaviour following a loss on the BART, reflecting punishment (Martini et al., 2018), although this effect has not been previously confirmed to be agonist specific. However, when negative feedback is calculated slightly differently as the difference between number of balloon pumps directly preceding and following a loss, PD patients can show reduced impulsive behaviour irrespective of ICB and DA status (Claassen et al., 2011). For performance on the ARIT in our study, worse impulsive action (a longer SSRT) tended to be associated with increased ICB frequency. To our knowledge, we are the first to investigate the relationship between ICBs and ARIT performance, whilst other studies have produced valid data utilising the ARIT in other patient groups with dopamine or basal ganglia dysfunction, namely focal hand dystonia and ADHD (Gilbert et al., 2019; Stinear & Byblow, 2004). Findings using SSRT derived from the stop signal task have been mixed. Studies have reported no differences in SSRT between PD patients with and without ICBs (Hlavatá et al., 2020; Ricciardi et al., 2017; Vriend et al., 2018), as well as shorter SSRTs in ICB patients compared not only to PD patients without ICBs, but also to healthy control participants (Claassen et al., 2015b). The positive relationship between SSRT and ICB frequency in our study may be due to task design, as the ARIT explores control of internally generated, rather than the externally cued responses. PD patients find internally generated responses with an anticipatory component most difficult (Jahanshahi et al., 1995), which likely reflects a sensitivity of predictive timing processes to the ongoing deterioration of the prefrontal-basal ganglia network (Cunnington et al., 1995) and therefore potentially dopaminergic MCL function. Overall, our objective task measures show promise as sensitive markers of impulsivity problems on DAs leading to real-world impulsive behaviours. A

worthwhile next step will be to investigate whether impaired task performance is capable of preceding, and therefore forecasting, ICB development.

Contrary to our hypotheses, there was no association between DGRS and ICB frequency and no interaction between task measures and the full DGRS. This finding contrasts with our previous finding that the DGRS can explain the incidence of ICBs (Hall et al., 2021). However, there is a key distinction between the studies. Namely, our previous study was predicting the binary presence/absence of any ICB, whereas the current study tried to link the DGRS with a measure closer to ICB severity i.e., frequency of ICBs. The rationale for this was twofold: 1) to use the more finely grained and wider ranging responses on the QUIP-RS (compared to the QUIP-S) for maximal sensitivity to subtle changes in task measures e.g., a change in SSRT of a few milliseconds, and 2) because the smaller sample size in a binary outcome variable in the current study would have limited overall model sensitivity (23 QUIP-S $\geq$ 1, 27 = 0). Combined, perhaps our results speak to the DGRS being able to predict the development of an ICB, rather than determining the more subtle distinction between severity of behaviours. Interestingly, although the full DGRS did not interact with task measurers, the DAT polymorphism in isolation interacted with impulsive decision making on the BART to effect ICB frequency. A relationship between DAT and cognitive impulsivity task performance has previously been reported (MacDonald et al., 2016; Mata et al., 2012). DAT is responsible for the reuptake of dopamine into pre-synaptic neurons (Hovde et al., 2019) and predominantly removes dopamine from within the striatum, a key region for cognitive decision making (Mata et al., 2012; Vriend et al., 2014). A higher DAT score represents a less functional DAT protein, which leads to less clearance of dopamine from the synaptic cleft, and greater striatal dopamine neurotransmission (Cilia et al., 2010; Vriend et al., 2014). In our study, patients with higher striatal dopamine levels (i.e., DAT = 1) who made more impulsive decisions on the BART counterintuitively had

lower, rather than higher, clinical impulsivity. There is no immediately obvious reason for this paradoxical finding, but it should be interpreted with caution, as the study was not designed to primarily investigate single gene effects.

Increased exposure to DA medication, but not increasing dose, predicted higher trait impulsivity and increased ICB frequency. The effect of purely time on DAs separate from dose has not been widely reported. Of those who did isolate time on DAs, some studies reported a positive correlation with ICBs (Corvol et al., 2018; Giladi et al., 2007), whereas others did not (Bastiaens et al., 2013). The findings for DA dose are also somewhat mixed, although a greater proportion of studies have previously determined a positive association between DA dosage and ICBs (Bastiaens et al., 2013; Corvol et al., 2018; Joutsa et al., 2012; Lee et al., 2010; Marković et al., 2020; Perez-Lloret et al., 2012; Weintraub et al., 2006), than no relationship (Callesen et al., 2014; Erga et al., 2017; Housden et al., 2010; Isaias et al., 2008; Vela et al., 2016; Weintraub et al., 2010). The reduced D2 auto-receptor sensitivity hypothesis explained previously is one potential neural mechanisms of action underlying our effect of time on DAs. Epigenetics may also be playing a role. Dopamine medication may regulate DNA transcription over time to increase protein and therefore neurotransmitter production (Lepack et al., 2020), potentially leading to the increase in impulsive behaviour. In our study, COMT and DAT mutations resulting in greater dopamine neurotransmission were associated with higher ICB frequency with increasing time on DA medication. Again single-gene exploratory findings should be interpreted with caution but could point to future epigenetics work including these genes when investigating gene vs medication interactions in the context of ICB severity over time.

Participants who reported higher levels of everyday trait impulsivity, also reported a higher frequency of ICBs in both the DA and NDA groups. Impulsive trait behaviour is a risk factor for ICBs (Leeman & Potenza, 2011; Weintraub & Mamikonyan, 2019) and PD patients with ICBs have reported higher impulsivity on the BIS compared to those without ICBs (Hlavatá et al., 2020; Isaias et al., 2008; Marín-Lahoz et al., 2018; Takahashi et al., 2022). Our positive correlation between BIS and QUIP-RS in both DA and NDA groups has previously been reported in a group of PD patients, but it is uncertain how many of these patients were on DA medication (Goerlich-Dobre et al., 2014). The presence of a comparable relationship in both groups suggests that the behavioural manifestation of ICBs in an NDA group may be similar to those on DAs. However, our clinical model was unable to account for the variability in ICB severity for this group, indicating the underlying mechanisms for ICBs may be distinct for agonist vs non-agonist medication (Kelly et al., 2020).

It is important to acknowledge some limitations of the current study. Firstly, the NDA control group had a smaller sample size than the DA group due to recruitment time constraints. The smaller sample size and reduced variability may have contributed to our clinical model being unable to account for ICB frequency in the NDA group. Although it is worth noting the ICB variability was still sufficient to reveal a correlation with BIS scores, and the NDA group reported a similar average and range of QUIP scores compared to the DA group. Nevertheless, future work should aim to replicate this lack of effect with the clinical model in a larger group of PD patients who are taking only non-agonist medication. Additionally, it is important to acknowledge that we cannot confirm that those in the NDA group did not previously take DA medication. There is therefore a possibility that some of them may have been experiencing persistent ICB effects following termination of DAs. However, the relatively short average disease duration for this group (ICB = 4.64 years, no-ICB = 2.68 years) makes this unlikely.

Secondly, although we present novel findings by including time on DA medication in our models, this was a cross sectional study. A longitudinal study design is required to confirm interactions with time on an individual basis. A longitudinal design would also reveal whether task performance tracks with ICB changes over time. If this design was conducted with de novo patients, it could additionally reveal any changes to predictive variables that precede increases in ICBs, which is a crucial step towards identifying measures for prognostic use.

In summary, this study provides evidence that our objective measures from impulse control tasks and time of exposure to medication can explain ICB severity in people with PD and are specific to DA mechanisms of effect. On the other hand, the DGRS appears better suited to predicting the incidence, rather than severity, of ICBs on DAs. Future research should determine whether task performance can be used to monitor ICB changes over time within an individual on agonist medication, and crucially whether task measures can detect subtle impulsivity changes before larger changes in everyday behaviour progress to a clinically problematic level.

CHAPTER 6

Is there a relationship between the DGRS, metabolised dopamine and impulsivity task performance in young adults?

Preliminary Results

The data collection for this experimental chapter was halted in March 2020 due to the COVID-19 pandemic. Restricted laboratory testing was allowed to continue in the Summer of 2021. Due to these restrictions and the time constraints of this PhD, subsequent blood samples were collected from participants in person, but all other aspects of the study were completed online. Due to these constraints, only 19 participants completed the full study which was largely underpowered (power = 9% (G*Power 3.1.9.6)), so we acknowledge we cannot interpret these results as statistically meaningful. Therefore, descriptive results are reported and include discussion of visual patterns.

6.1. Abstract

Introduction: The working hypothesis is that the Dopamine Genetic Risk Score (DGRS) presented in previous chapters is able to quantify central dopamine neurotransmission in neural mesocorticolimbic regions. To begin investigating this, the DGRS was compared to the concentration of homovanillic acid in blood plasma (pHVA), a metabolite of central dopamine which reflects central dopaminergic neural activity. Some genetic polymorphisms which make up the DGRS are associated with sensitive, objective behavioural task-based measures of impulsivity (Hall et al., 2023), but these task-based measures have yet to be compared to levels of pHVA. **Methods:** 19 young healthy participants completed genotyping to produce a DGRS, provided three blood samples for average pHVA concentration whilst controlling their diet for foods high in monoamine and flavonoid content. Participants completed the Anticipatory Response Inhibition Task as a measure of response inhibition. The Balloon Analogue Risk Task and Gambling Task dependent measures examined cognitive decision making and risk-taking behaviours. Several impulsivity questionnaires were also completed: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Short and Rating Scale versions and the Barratt Impulsiveness Scale, whilst the Montreal Cognitive Assessment measured global cognitive function. **Results:** There was a positive relationship between pHVA and the DGRS, where participants in the higher DGRS group had higher pHVA concentrations. There was greater trial-by-trial impulsivity in both the BART and GT, for DGRS Low compared to High. There were no correlations between pHVA and impulsivity task measures. **Conclusions:** Although underpowered, these preliminary results suggest a potential relationship between DGRS and metabolised levels of dopamine, such that our DGRS does seem to be reflecting central levels of dopamine. We also provide the first preliminary evidence that the DGRS is associated with impulsivity task performance in young healthy adults.

6.2. Introduction

Previous chapters in this thesis describe the use of the Dopamine Genetic Risk Score (DGRS), which involves a working theory that this DGRS quantifies overall central dopamine neurotransmission in meso-cortico-limbic (MCL) regions resulting from the accumulation of specific mutations in five dopaminergic genes. To help confirm this hypothesis, we need to compare the DGRS with directly measured levels of dopamine. One way to do this is via measuring the main dopamine degradation product, homovanillic acid (HVA). HVA production can take place centrally, peripherally and from diet contributions (Amin et al., 1992; Bell, 1988; Rubí & Maechler, 2010). The endogenous central production of dopamine in the brain mostly takes place in dopamine neurons, whilst peripheral dopamine is often produced in noradrenergic (NA) neurons in the peripheral nervous system which synthesises dopamine as a precursor (and therefore HVA) during the production of norepinephrine (NE) (Amin et al., 1992, 1995).

The biosynthesis of HVA takes place within two pathways (Meiser et al., 2013) and begins with the transportation of tyrosine to catecholaminergic neurons (Elsworth & Roth, 1997) (Figure 1.2, Chapter 1). Within the pathway which contributes the most to HVA production, initially phenylalanine is hydroxylated to form tyrosine in the liver or catecholaminergic neurons (Elsworth & Roth, 1997). Subsequently, tyrosine is hydroxylated to form 3,4-dihydroxyphenylalanine (DOPA), which is decarboxylated to produce dopamine (Best et al., 2009; Meiser et al., 2013). In the alternative pathway of HVA biosynthesis, tyrosine is converted to tyramine before oxidisation to dopamine (Meiser et al., 2013). Dopamine is stored and released as a neurotransmitter in dopamine neurons, whilst in NA neurons the co-release of dopamine and NE is possible (Ranjbar-Slamloo & Fazlali, 2020). In NA neurons, dopamine is synthesised to produce NE and then, in turn, epinephrine by the process of

methylation (Meiser et al., 2013). In dopamine neurons, dopamine is released into the synaptic cleft which can bind to receptors on post-synaptic terminals, but dopamine can also be reabsorbed back into the nerve terminal. The re-absorbed dopamine is metabolised into 3,4-dihydroxyphenylacetaldehyde (DOPAL) by monoamine oxidase (MAO) and then 3,4-dihydroxyphenylacetic acid (DOPAC) by aldehyde dehydrogenase (ALDH). Whilst dopamine in the synaptic cleft is converted to 3-methoxytyramine (3-MT) by COMT and then 3-Methoxy-4-hydroxyacetaldehyde by MAO. Subsequently, both DOPAC and 3-Methoxy-4-hydroxyacetaldehyde form HVA through the action of catechol-methyltransferase (COMT) and ALDH (Amin et al., 1992; Elsworth & Roth, 1997; Meiser et al., 2013).

It is possible that HVA can partially reflect central dopaminergic activity (Amin et al., 1992; Nemoda et al., 2011). Levels of central dopamine in HVA have been estimated following the suppression of dopamine obtained peripherally by COMT and MAO inhibitors which do not cross the blood brain barrier (Amin et al., 1995; Siderowf & Kurlan, 1999). These estimated levels of central dopamine equate to 25-65% in blood plasma, 25% in urine and less than 3.5% in cerebral spinal fluid contributions (Amin et al., 1992, 1995; David E. Sternberg, George R. Heninger, 1983).

To our knowledge, there have been no studies investigating blood plasma HVA (pHVA) and a dopaminergic risk score. Previous research has explored the association between pHVA concentration and some dopaminergic genes included in the DGRS, most commonly in patient populations with neuropsychiatric conditions. Of note, COMT is one of the enzymes responsible for the central metabolism of dopamine into HVA (Nemoda et al., 2011). Greater enzyme activity resulting from the same polymorphism quantified within the DGRS, COMT Val158Met polymorphism, is associated with higher levels of HVA in peripheral blood plasma

(Zumárraga et al., 2010). The -141C Ins/Del polymorphism in the Dopamine Receptor D2 gene, which has been found to increase D2 receptor density (Thompson et al., 1997), was also was associated with an increase in pHVA which trended to significance in a sample of schizophrenia patients (Miura et al., 2015). Whilst the Dopamine Receptor D3 Ser9Ser polymorphism in patients with delusional disorder was associated with higher pre-treatment level of pHVA, indicating higher dopamine function (Morimoto et al., 2002). Finally, high levels of pHVA were correlated with increased Dopamine Transporter (DAT) density in the caudate and putamen for people in stages of cocaine abstinence (Bowers Jr et al., 1998). Therefore, it is possible that the combined DGRS will be associated with concentrations of pHVA.

The DGRS encompasses five genes which modify dopamine signalling within MCL regions (Caminiti et al., 2017; K. M. Smith et al., 2016; Vriend et al., 2014), and are implicated in impulse control (Abidin et al., 2015; Congdon et al., 2009; Erga et al., 2018; Lee et al., 2009; K. M. Smith et al., 2016; Vriend et al., 2014). Additionally, the DGRS is associated with the change in impulsive behaviour in individuals with Parkinson's disease (PD) (Hall et al., 2021). Our most recent study (Hall et al., 2023) investigated the relationship between the DGRS and behavioural tasks measuring impulsivity in a group of PD patients. The DGRS was not associated with measures of the Balloon Analogue Risk Task (BART) or the Anticipatory Response Inhibition Task (ARIT), however the DAT polymorphism interacted with decision making on the BART. The ARIT and BART have previously been described in this thesis to measure motor and cognitive/limbic impulsivity, respectively (Antonelli et al., 2011; Coxon et al., 2007). Another behavioural task of interest is the Gambling Task (GT), first implemented by Verbruggen and colleagues (2016) which was subsequently replicated (Eben et al., 2020). This task examined cognitive impulse control, specifically how trial outcome effects the

response speed of the next trial. Interestingly, levels of HVA were found to be much higher in a cohort of pathological gamblers, compared to controls (Bergh et al., 1997). Moreover, lower levels of pHVA were associated with repetitive behaviour disorders (M. H. Lewis et al., 1996), suggesting a potential relationship between pHVA and impulsivity. To our knowledge there is no previous research involving pHVA and behavioural impulsivity tasks.

Aims and Hypotheses:

The primary aim (1) of this experiment was to determine any relationship between pHVA concentration (quantifying metabolic dopamine) and the DGRS (quantifying dopamine neurotransmission). We hypothesised that those with a high DGRS would display higher concentrations of pHVA, whereas those with a low DGRS would display lower pHVA concentration. The secondary aim (2) was to investigate the relationship between the DGRS and impulsivity task performance/questionnaires in young healthy adults. Our hypotheses followed the inverted-U relationship between dopamine and impulse control at baseline (Figure 3.2, Chapter 3). We therefore hypothesised that those with a low DGRS would display worse impulsivity and greater behaviour modification on each task/questionnaire compared to those with a high DGRS. Finally, the third aim (3) was to investigate the relationship between pHVA concentration and impulsivity task performance. We again hypothesised an inverted-U relationship where a lower pHVA would display worse impulsivity and greater behaviour modification on each task/questionnaire compared to those with high pHVA.

6.3. Materials and Methods

6.3.1. Participants

88 young healthy adults provided written informed consent to partake in the research project. Inclusion criteria were 18-40 years old, no known history of neurological illness, normal or corrected-to-normal vision and not taking any medications which affect dopamine levels. The study was approved by the University of Birmingham ethics committee. All 88 participants provided a saliva sample to determine their DGRS (details of methods included in Experimental Protocol) and 3 participants were subsequently removed from analyses as one or more of their genetic mutations could not be determined to calculate their full DGRS. The DGRS for the remaining 85 participants were as follows: DGRS 0, n = 0; DGRS 1, n = 4; DGRS 2, n = 19; DGRS 3, n = 32, DGRS 4, n = 25, DGRS 5, n = 5. Due to time and testing constraints from the COVID-19 pandemic, only 19 healthy young adults (mean age 22 ± 3.6 years SD, range 18-29 years, 8 males) completed all aspects of the research project. The Montreal Cognitive Assessment (Appendix 11), a validated and reliable screening tool to measure global cognitive performance, was completed by all 19 participants and no cognitive impairments were detected (Gill et al., 2008; Lam et al., 2013).

6.3.2. Experimental Protocol

Genotyping was performed on all recruited participants to screen for the required DGRS so that clear differences could be investigated between high and low scores (final cohort of 19 participants: Low DGRS 0 - 2: N = 6, High DGRS 4 - 5: N = 13). Selected participants provided blood samples during three experimental sessions, each a minimum of one week apart. Impulsivity task performance and impulsivity questionnaire results were obtained from each participant: the Anticipatory Response Inhibition Task (ARIT), Balloon Analogue Risk Task (BART), Gambling Task (GT), Barratt Impulsiveness Scale (BIS), Questionnaire for

impulsive-compulsive disorders in Parkinson's disease short version (QUIP-S) and the QUIP rating scale (QUIP-RS). 13 participants completed all aspects of the study within the laboratory, the subsequent 6 participants attended the laboratory to provide blood samples but completed behavioural tasks and questionnaires online due to restrictions implemented following the COVID-19 pandemic.

6.3.3. Genotyping

Single saliva samples were collected from all participants using self-collection Oragene·DNA kits (OG-500 and OG-600) from DNA Genotek (Ottawa, Canada). These DNA samples were analysed by LGC Genomics (http://www.lgcgenomics.com/). Kompetitive allele specific polymerase change reaction (PCR KASP) genotyping was performed on four genes: DRD1 (rs4532), DRD2 (rs1800497), DRD3 (rs6280) and COMT (rs4680) to determine a bi-allelic score for each single nucleotide polymorphism (SNP) for each participant. This process involved the KASP Assay and Master mix being added to the DNA samples, followed by a thermal cycling reaction and finally an end-point fluorescent read (for full methods on KASP genotyping see: https://biosearch-cdn.azureedge.net/assetsv6/kasp-explanation-fact-sheet.pdf). The variable number of tandem repeat (VNTR) in the DAT rs28363170 gene was determined with a separate PCR process. A PCR, PCR clean up, sanger sequencing and genotype calling was followed by establishing the repeat length of DAT from the eye on the sequence trace files. Every participant received a dopamine genetic risk score (DGRS) of between 0-5 dependent upon the specific mutation/number of repeats for each of the five polymorphisms (higher score = higher dopamine levels) (Appendix 12). DRD1 ($p = .568$), DRD2 ($p = .054$), DRD3 ($p = .456$) and DAT ($p = .827$) genotype frequencies were in Hardy-Weinberg equilibrium (calculated with chi-square tests), however the observed genotype frequencies for COMT were not consistent with HW equilibrium ($p = .037$).

6.3.4. Venepuncture

Three blood samples were taken to quantify the levels of the dopamine metabolite, HVA in blood plasma as a measure of central dopaminergic activity (Amin et al., 1992; Sternberg & Heninger, 1983). Participants controlled their diet for 24 hours before each experimental session by eliminating food and drink high in monoamine and flavonoid content. This was monitored using a food diary (Appendix 13). These foods can largely increase peripheral contributions to HVA plasma concentration, therefore the blood samples would not reflect true levels of central dopaminergic activity if the diet was not controlled (Amin et al., 1992; Donnelly et al., 1996). Blood samples for each participant were drawn from the antecubital vein after an overnight fast while participants remained in a semi-supine position. Blood was drawn into 6ml EDTA vacutainers, which were centrifuged at 2000rpm, 8°C for 10 minutes and aliquoted into 1.5ml microcentrifuge tubes, before being frozen at -80°C for future analysis.

For analysis, plasma samples were thawed at room temperature and levels of HVA were analysed by quantitative sandwich ELISA (MyBioSource, Catalogue number: MBS064661), as per manufacturer's instructions. All three samples per participant were run in duplicate to account for variability within the samples. Samples from each participant were run within the same plate in all cases, to minimise the influence of inter-assay variability. AssayFit Pro software (https://www.assayfit.com/) was used to fit a cubic calibration curve to the absorbance levels of HVA. Concentration levels of HVA (ng/ml) were determined from the calibration curve for every sample (2 samples per participant per visit, 3 visits). Concentrations were averaged for each visit per participant and any outliers were removed following determination

by Dixon's test (Dixon, 1950, 1951). The concentrations were then averaged to provide one concentration for each participant.

6.3.5. Impulsivity Task Performance

6.3.5.1. Anticipatory Response Inhibition Task (ARIT)

The ARIT completed in the laboratory was displayed on a computer screen using custom code written in MATLAB (version R2016a, MathWorks) and controlled via two custom made switches, an A/D USB interface (National Instruments, Austin, TX) and micro- controller (Eleven Freetronics, Victoria, Australia) (Figure 6.1). The ARIT online version was presented using custom code written in Inquisit 6 Lab (Version 6.5.1, Millisecond Software) and responses were made on a keyboard (Figure 6.1). Participants performed the task in a seated position, approximately 1m away from a computer screen. Their forearms were rested on the table whilst they responded to stimuli on the computer screen using their index fingers.

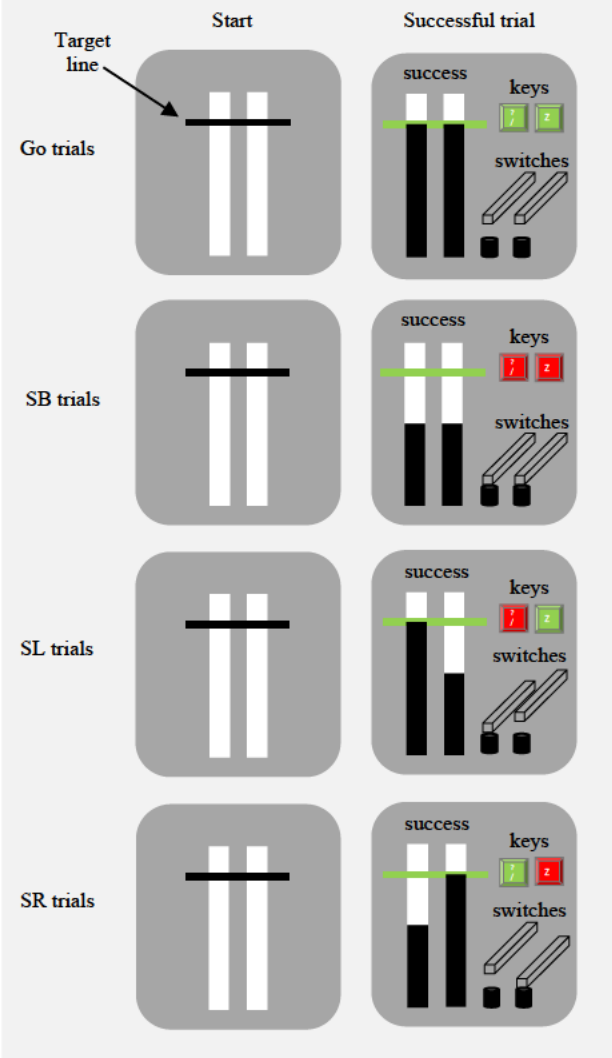


Figure 6.1 Anticipatory Response Inhibition Task: Visual display of Go, SB (stop both), SL (stop left go right) and SR (stop right go left) trials in ARIT.

Responses were completed on the switches in person and on keys online. On successful Go trials, both switches/keys were released at the target line. On successful SB trials, both switches/keys were held down. On successful SR trials, the left switch/key was lifted at the target and the right switch/key was held down. On successful SL trials, the right switch/key was lifted at the target and the left switch/key was held down.

Participants were initially presented with a screen containing two white vertical bars which were controlled by the two switches\keys. All trial types required both switches/keys to

be depressed to initiate a black bar rising within the two white bars after a variable delay. Both bars rose at equal rates, intercepting the target (horizontal black line) after 800ms and filling the entire white bar after 1000ms, unless the switches/keys were released which ceased the bars rising. Go trials were presented as 74% of total trials (296 of a total 400) and required participants to release their fingers from both switches/keys to intercept both bars with the target (successful releases were within 30ms of target). There were three versions of Stop trials: Stop both (SB) trials required participants to keep both switches/keys depressed when both bars automatically stopped rising before reaching the target, partial trials comprising of stop left-go right (SL) and stop right-go left (SR), which required participants to keep depressing the switch/key corresponding to the bar which stopped whilst releasing their finger from the alternative switch/key to intercept the remaining bar with the target. All versions of Stop trials were equally present for the remaining 26% of total trials (104 trials in total). For every stop version, the bar initially stopped 500ms into the trial. A staircase algorithm with increments of 25ms was then used to generate a 50% success rate for each stop trial version. Following a successful stop trial the bar would then stop 25ms later for the subsequent stop trial, whereas the bar would stop 25ms earlier following an unsuccessful stop trial. The minimum and maximum stop times for the bars were 25ms and 775ms, respectively.

Stop signal reaction time (SSRT) for SB was selected as the primary dependent measure for the ARIT as it indicates the latency of the stop process/response inhibition (Band et al., 2003; Verbruggen et al., 2019b; Verbruggen & Logan, 2008) and is a robust measure of inhibitory control latency (Hall et al., 2022). SSRT for SB was calculated using the integration method (SSRT = nth RT (number of go trials x probability of responding) – staircased bar stop time) (Logan & Cowan, 1984; Verbruggen et al., 2019b).

6.3.5.2. Balloon Analogue Risk Task (BART)

The BART was controlled using Inquisit 5 Lab (Millisecond Software, version 5.0.14.0, 2018) for both laboratory and online versions. Participants were seated approximately 1m away from the computer screen with their forearms rested on the table. Each trial began by presenting a small balloon and two options on the computer screen (Figure 6.2). The first option was to "Pump up the balloon" which incrementally increased the balloon size, triggered a balloon-inflation sound and increased the "Potential earnings" for that trial by £0.02 with each pump. The second option was the "Collect £££" button. Once pressed, the current trial ended and the potential earnings were added to "Total Winnings" for the task. However, each balloon could randomly explode on any pump and any potential earnings for that trial would be lost. Each balloon started with a 1 in 85 probability of exploding. With each balloon pump, a number was randomly selected and removed without replacement from an 85-length array. The selection of number one resulted in the balloon explosion. Therefore, the risk of the balloon exploding increased with each pump but the potential monetary reward also increased. The trial number, current potential earnings and current number of pumps (along with total accumulated winnings) were displayed on screen throughout each trial. Participants were informed that they would receive the total monetary reward they accumulated after 30 trials. A 7-point motivation scale relating to this pay-out (1 = hardly motivating at all, 7 = extremely motivating) was completed by each participant following the BART.

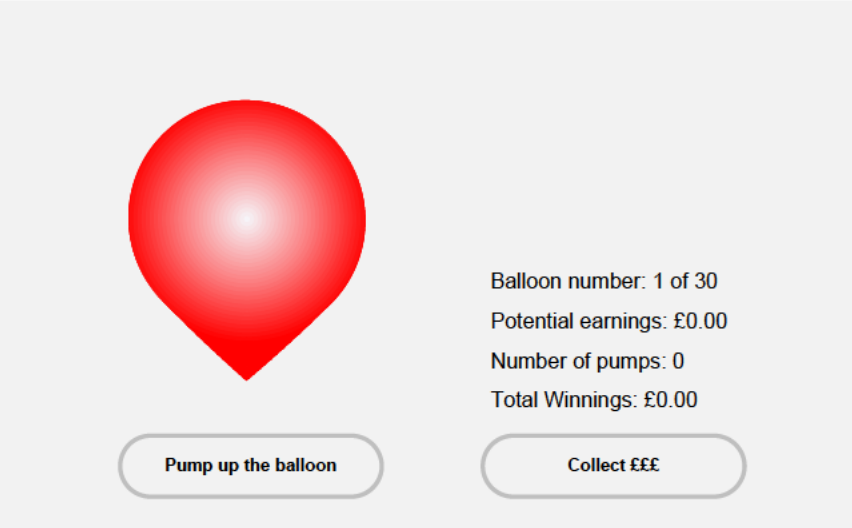


Figure 6.2

Visual display of the BART.
'Pump up the balloon' and 'Collect £££' are the two available response options. Visual feedback of 'Balloon number', 'Potential earnings', 'Number of pumps' and 'Total winnings' are displayed throughout each trial.

The number of balloon pumps for a win trial following a loss trial (when the balloon exploded, and no money was collected) versus following a win trial were calculated. Subsequently the means of these measures were normalised to pumps after a loss (losses cancel) (positive reinforcement) and pumps after a win (wins cancel) (negative reinforcement). The resultant proportions indicate the amount of behaviour modification as a consequence of the previous trial, a greater proportion equals greater behaviour modification and more impulsive decision making. Positive and negative reinforcement were the primary dependent measures for the BART.

6.3.5.3. Gambling Task (GT)

During the GT, participants performed the task seated, approximately 1m away from the computer screen with their forearms rested on the table. The gambling task was run via jsPsych software (www.jsPsych.org) in both the laboratory and online. Participants were instructed to

try to win as many points as possible over the course of the task by picking between two pie charts presented on the screen at the start of each trial. These two pie charts both displayed a different number of winnable points below (Figure 6.3). One pie chart always had a 100% guarantee of winning the number of points displayed below it indicated by a full green circle (20, 30, 40 or 50). The second pie chart represented a probability of winning (green) or not winning (red) the points displayed below it (probability of winning was one of the following: 0.25, 0.33, 0.50, 0.67). The points for the second pie chart were always greater than the first pie chart, however this option posed a greater risk of winning zero points as probability of winning was always below 1. Participants chose a pie chart by pressing the left/right arrow key on the keyboard with their respective left/right index finger. Participants were presented with 256 trials overall. At the end of the experiment the task generated the results of 10 trials at random and the sum of these 10 results was converted into a monetary reward (100 points = £1, maximum pay-out = £3). A 7-point motivation scale relating to this pay-out (1 = hardly motivating at all, 7 = extremely motivating) was completed by each participant following the task.

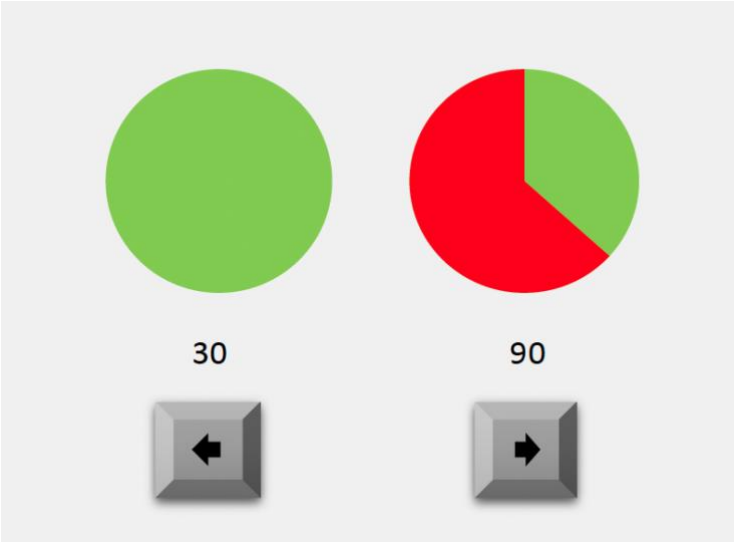


Figure 6.3

Visual display of the Gambling Task.
Participants select the left or right arrow key to choose the corresponding pie chart and number of points to be won.

The primary dependent measure for the GT was the Start Reaction Time (StartRT) after a gambled "loss" or a gambled or non-gambled "win", and after prior trial win probability. StartRT is defined as the time between the outcome of a trial and the start of a new trial as initiated by the participant (this decision itself does not lead to a reward or loss).

6.3.6. Impulsivity Questionnaires

6.3.6.1. Barratt Impulsiveness Scale (BIS)

All participants answered 30 questions on the BIS relating to real-world behaviours. Each behaviour was scored on a 4-point scale corresponding to an answer of Rarely/Never, Occasionally, Often, Almost always/Always (Stanford et al., 2009). The higher the overall score (range 0-120), the higher the level of trait impulsivity for each participant.

6.3.6.2. Questionnaire for Impulsive-Compulsive disorders in Parkinson's disease: short version (QUIP-S) and rating scale (QUIP-RS)

The QUIP-S and QUIP-RS are validated screening tools to identify incidence and frequency/severity of ICD behaviours, respectively. Both are self-administered but vary slightly in their scoring and interpretation. Questions on the QUIP-S are related to impulsive or compulsive gambling, sexual behaviour, buying and eating, and other associated behaviours (punding, hobbyism and walkabout) (Weintraub et al., 2009). A positive score on any of the 13 "yes or no" questions was recorded as an ICD behaviour. The QUIP-RS comprised of four questions in each of the following categories: "gambling", "sex", "buying", "eating", "performing tasks or hobbies" and "repeating simple activities" (Martinez-Martin et al., 2018; Probst et al., 2014; Weintraub et al., 2012). Participants rated each question by the frequency of the behaviour which resulted in a corresponding score (never (0), rarely (1), sometimes (2), often (3), very often (4)) in the past 4 weeks or any 4-week period in a designated time frame.

Total scores of between 0-96 were calculated for each participant. Questions regarding PD medication use were removed from both questionnaires.

6.3.7. Statistical analysis

Data analysis and statistical modelling were performed in MATLAB (version R2020a, MathWorks), SPSS Statistics (version 28) and Prism (Version 9.4.1). For method validation, any within individual outliers for pHVA concentration were reported following determination by Dixon's test (Dixon, 1950, 1951). Additionally, unpaired t-tests with Welch's correction investigated any differences between in person (completed in the laboratory) and online (completed at home) impulsivity behavioural task primary dependent measures (SSRT SB, Positive Reinforcement, Negative Reinforcement, StartRT). Averages, standard deviations, t and p values are reported.

For Aim 1, an unpaired t-test with Welch's correction examined any differences in concentrations of pHVA between the DGRS High and Low groups. Averages, standard deviations, t and p values, 95% confidence interval (CI) and effect size (Cohen's d: 0.20 = small, 0.50 = moderate, 0.80 = large, (Cohen, 1988) are reported.

For Aim 2, unpaired t-tests with Welch's correction examined any differences between the DGRS High and Low groups for SSRT SB, Positive and Negative Reinforcement and BART and GT Motivation Scales and impulsivity questionnaires. Averages, standard deviations, t and p values, 95% confidence interval for the difference between means (CI) and effect sizes (Cohen's d) were reported. For the BART, a mixed design ANOVA with 2 DGRS (High & Low) x 2 Reinforcement (Positive & Negative) was run to determine any relationship between the DGRS and Reinforcement. For the GT, two mixed design ANOVAs with 2 DGRS

x 3 Prior Trial Outcome (gambled loss, gambled win, non-gambled win) and 2 DGRS x 4 Prior Trial Win Probability (0.25, 0.33, 0.50, 0.67) were run to determine any relationship between the DGRS and StartRT. Averages, standard deviations, F and p values, and effect sizes (ηp^2: 0.01 = small, 0.06 = moderate, 0.14 = large, (Cohen, 1988) are reported.

For aim 3, quadratic regressions were run between pHVA and SSRT SB, Positive and Negative Reinforcement and StartRT prior trial type and prior trial win probability. Beta coefficients (ß), p values and effect sizes (R^2: 0.1 = small, 0.3 = medium, 0.5 = large, (Cohen, 1988) are reported.

6.4. Results

6.4.1. Method Validation

There was no within individual variability for pHVA concentrations, highlighted by no outliers within individuals from Dixon's test (Dixon, 1950, 1951) (all Q experimental < Q critical). We confirmed that there were no significant differences between all online and offline impulsivity task primary dependent measure results (Positive Reinforcement: in person = 0.31 ± 0.21, online = 0.37 ± 0.66, $t_{(4.31)} = -0.20$, p = .850, Negative Reinforcement: in person = -0.20 ± 0.14, online = -0.15 ± 0.34, $t_{(4.55)} = -0.36$, p = .734, StartRT: in person = 696 ± 247ms, online = 835 ± 602ms, $t_{(5.79)} = -0.55$, p = .606) other than SSRT SB: in person = 189 ± 26.3ms, online = 238 ± 14.9ms, $t_{(16.0)} = -5.25$, p < .001. Looking more closely at the results of SSRT SB, there are no differences in GoRT between in person (808 ± 8.33ms) and online (813 ± 7.79) ($t_{(10.5)} = -1.42$, p = .186), confirming no effect of the use of different software on overall reaction time. However, there were differences between Bar Stop Times (in person = 619 ± 27.3ms, online = 575 ± 15.8ms, $t_{(15.8)} = 4.45$, p < .001), which could simply mean that the small sample in the online group (n = 6) were worse at stopping, or that there were differences in motivation or understanding due to the environment.

6.4.2. pHVA and DGRS analyses (Aim 1)

Visually, the high DGRS group had greater mean pHVA concentration (6.18 ± 9.56 ng/ml) than the low DGRS group (3.81 ± 1.80 ng/ml) although the variance and lower sample sizes resulted in this being non-significant ($t_{(13.7)} = 0.86$, p = .403, 95% CI [-3.54, 8.29], Cohen's d = 0.28) (Figure 6.4). This visual pattern was in line with our first hypothesis.

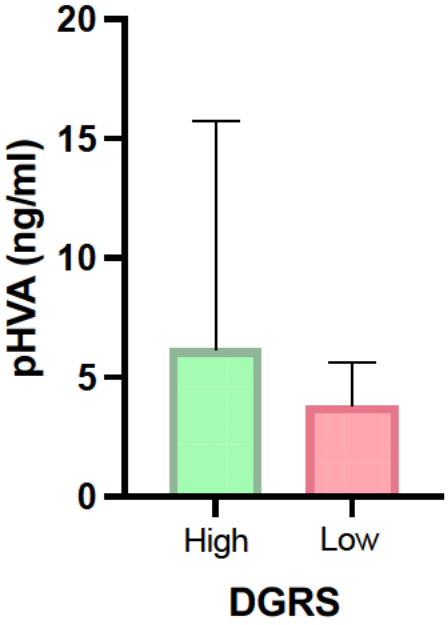


Figure 6.4 Comparison of average concentration of pHVA between DGRS high and low groups.
pHVA: plasma homovanillic acid; DGRS: dopamine genetic risk score; ng/ml: nanogram/millilitre.

6.4.3. DGRS and Impulsivity Task Performance/Questionnaire analyses (Aim 2)

6.4.3.1. Anticipatory Response Inhibition Task

There was no significant difference between SSRT in the DGRS high group (206 ± 31.8ms) compared to low (201 ± 38.3ms) ($t_{(8.34)} = 0.27$, $p = .797$, 95% CI [-36.6, 45.9], Cohen's $d = 0.14$) (Figure 6.5).

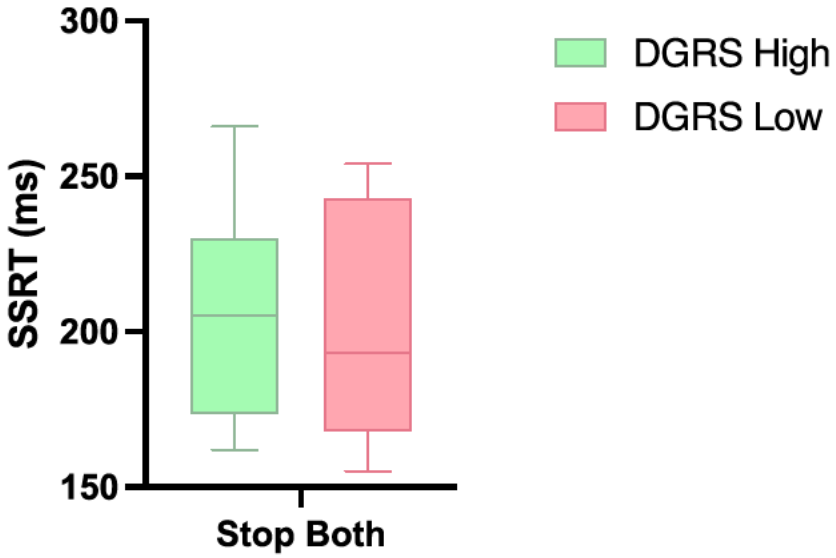


Figure 6.5 Comparison of average SSRT SB values between DGRS high and low groups.
SSRT SB: stop signal reaction time stop both; DGRS: dopamine genetic risk score; ng/ml: nanogram/millilitre.

6.4.3.2. Balloon Analogue Risk Task

Participants pumped the balloon more after a win and less after a loss, and participants with a low DGRS reported higher motivation:

For Positive and Negative Reinforcement measures in the BART, there was a main effect of Reinforcement Type ($F_{1,32} = 25.2$, $p < .001$, $\eta p^2 = .441$), where Positive Reinforcement (0.35 ± 0.08) was significantly greater than Negative Reinforcement (-0.19 ± 0.08, $p < .001$) (Figure 6.6A). There was no effect of DGRS ($F_{1,32} = 0.29$, $p = .593$, $\eta p^2 = 0.009$) or DGRS by Stop Type interaction ($F_{1,32} = 0.52$, $p = .476$, $\eta p^2 = 0.02$) (Figure 6.6A). Despite no significant result, it is interesting to note that visually DGRS low compared to high participants pumped the balloon more after a win. Positive Reinforcement values were 0.28 ±0.27 for DGRS High and 0.41 ± 0.52 for DGRS Low ($t_{(6.40)} = -0.59$, $p = .575$, 95% CI [-0.44, 0.17]). Whereas Negative Reinforcement values were -0.18 ± 0.20 for DGRS High and -0.20 ± 0.23 for DGRS Low ($t_{(8.82)} = 0.17$, $p = .866$, 95% CI [-0.29, 0.33]). For the BART, the Motivation Score for DGRS High (5.69 ± 0.75) was significantly lower than DGRS Low (6.33 ± 0.52) ($t_{(14)} = -2.16$, $p = .048$, 95% CI [-1.28, 0.005], Cohen's $d = 0.69$) (Figure 6.6B). It is therefore possible that there is a link between the self-reported motivation and the visual difference from positive reinforcement between DGRS groups.

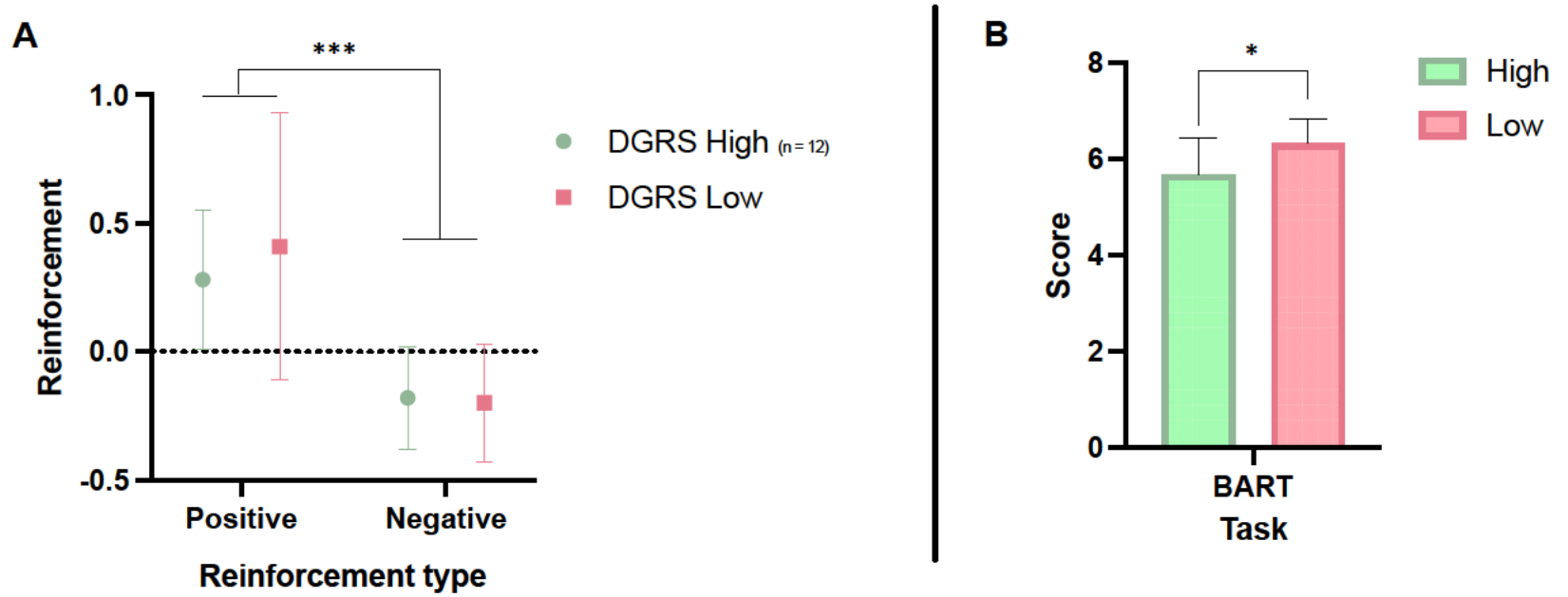


Figure 6.6 Balloon Analogue Risk Task Reinforcement and Motivation Scale Results.
A. Comparison of Positive and Negative Reinforcement values, split by DGRS High and Low. Significant main effect of Reinforcement type. **B.** Comparison of average BART Motivation Scale Scores between High and Low DGRS groups. BART: Balloon Analogue Risk Task; DGRS: dopamine genetic risk score. Significant values: * $p < .05$, *** $p < .001$.

6.4.3.3. Gambling Task

Participants with a low DGRS initiated the start of the following trial quicker after all prior trial types and win probabilities:

For StartRT as a function of Prior Trial Outcome (Figure 6.7A), there was a main effect of DGRS ($F_{1,67} = 10.1$, $p = .002$, $\eta p^2 = 0.13$), where StartRT for DGRS High (822 ± 54.4 ms) was significantly greater than DGRS Low (516 ± 79.2 ms, $p = .002$). There was no effect of Prior Trial Type ($F_{3,67} = 0.36$, $p = .783$, $\eta p^2 = 0.02$) or DGRS by Prior Trial Type interaction ($F_{3,67} = 0.03$, $p = .992$, $hp^2 = 0.001$). For StartRT as a function of Prior Trial Win Probability, there was a main effect of DGRS ($F_{1,68} = 9.61$, $p = .003$, $\eta p^2 = 0.12$), where StartRT for DGRS High (827 ± 52.4 ms) was significantly greater than DGRS Low (538 ± 77.1 ms, $p = .003$). There was no effect of Prior Trial Win Probability ($F_{3,68} = 0.13$, $p = .944$, $\eta p^2 = 0.01$) or DGRS by Prior Trial Win Probability interaction ($F_{3,68} = 0.02$, $p = .995$, $\eta p^2 = 0.001$) (Figure 6.7B). StartRT does not seem to link to self-reported motivation, where the Motivation Score for DGRS High was 5.00 ± 1.35 and 5.33 ± 1.63 for DGRS Low ($t_{(8.54)} = -0.43$, $p = .677$, 95% CI [-2.09, 1.43], Cohen's $d = -0.23$) (Figure 6.7C).

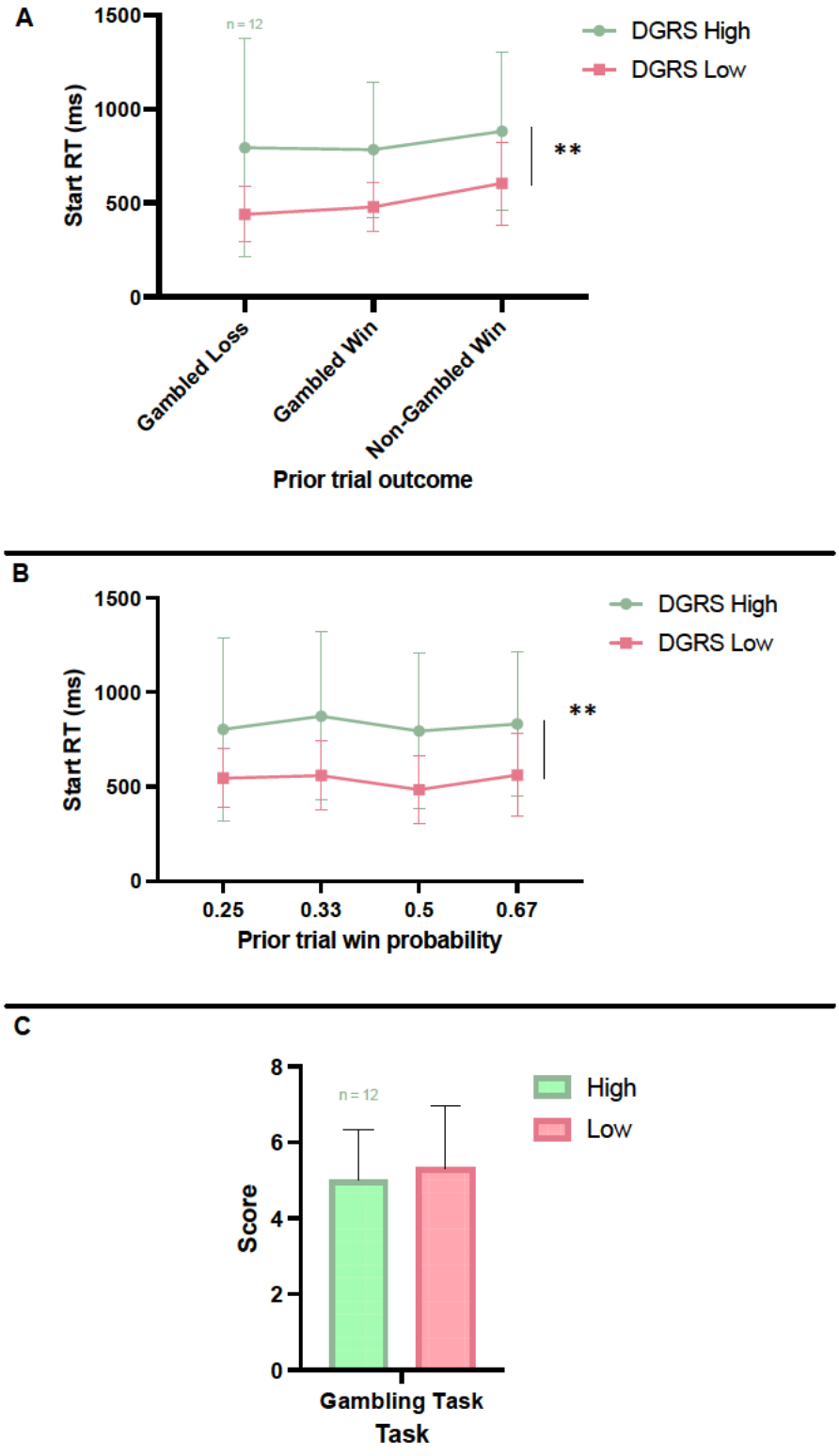


Figure 6.7 Gambling Task StartRT and Motivation Scale Results.

A. Comparison of StartRT as a function of prior trial outcome, split by DGRS High and Low. Significant main effect of DGRS. **B.** Comparison of StartRT as a function of prior trial win probability, split by DGRS High and Low. Significant main effect of DGRS. **C.** Comparison of average GT Motivation Scale Scores between High and Low DGRS groups. GT: Gambling Task; DGRS: dopamine genetic risk score. Significant values: ** $p < .01$.

6.4.3.4. Impulsivity Questionnaires

No differences between the DGRS groups were observed for the impulsivity questionnaires: For the QUIP-S, the High DGRS group had a score of 0.15 ± 0.55 and the Low DGRS group had a score of 1.00 ± 1.26 ($t_{(5.91)} = -1.57$, $p = .168$, 95% CI [-2.17, 0.48], Cohen's $d = -1.02$). For the QUIP-RS, the High DGRS group had a score of 12.7 ± 11.7 and the Low DGRS group had a score of 9.17 ± 11.7 ($t_{(9.76)} = 0.61$, $p = .555$, 95% CI [3.53, 5.77], Cohen's $d = 0.30$). For the BIS, the High DGRS group had a score of 53.2 ± 5.46 and the Low DGRS group had a score of 53.2 ± 9.04 ($t_{(6.75)} = 0.02$, $p = .988$, 95% CI [-9.44, 9.57], Cohen's $d = 0.01$) (Figure 6.8). We expected to see greater differences between DGRS groups for these questionnaires, however a low sample size and subjectivity may have prevented these expected results.

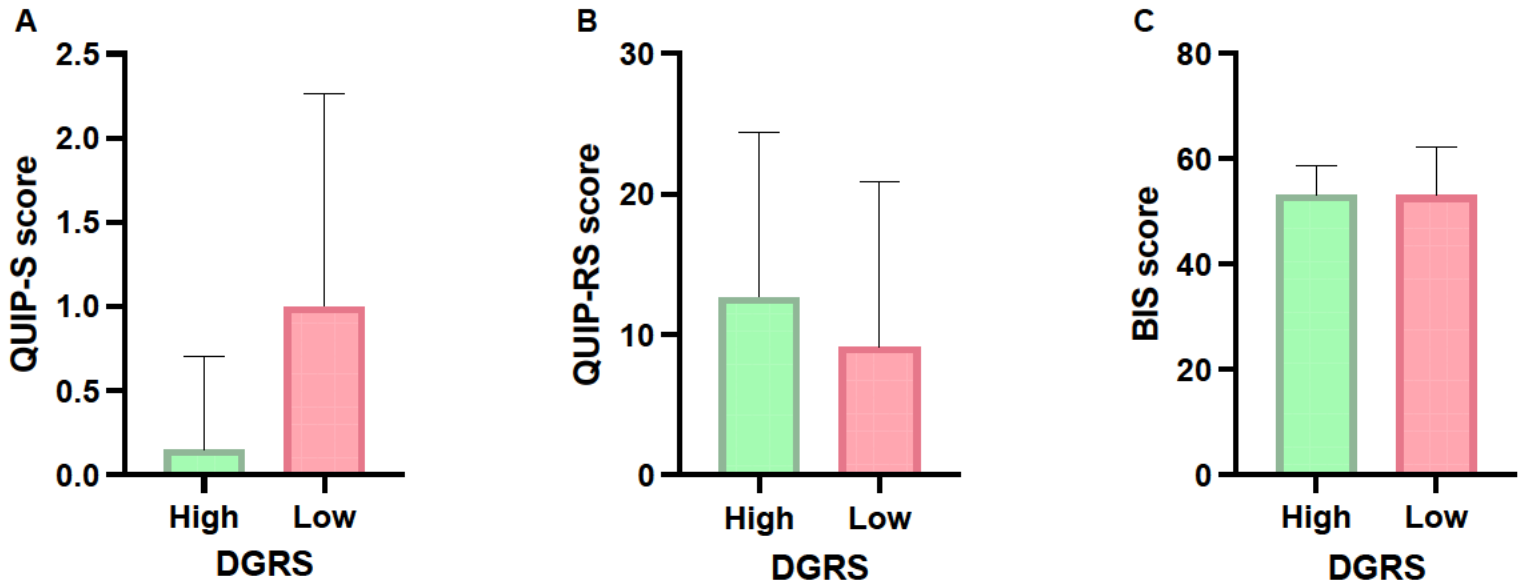


Figure 6.8 Impulsivity Questionnaire Results.
A. Comparison of average QUIP-S scores between High and Low DGRS groups. **B.** Comparison of average QUIP-RS scores between High and Low DGRS groups. **C.** Comparison of average BIS scores between High and Low DGRS groups. QUIP-S: questionnaire for impulsive-compulsive disorders in Parkinson's disease – short version. QUIP-RS: questionnaire for impulsive-compulsive disorders in Parkinson's disease – rating scale version; BIS: Barratt Impulsiveness Scale; DGRS: dopamine genetic risk score.

6.4.4. pHVA and Impulsivity Task Performance Analyses (Aim 3)

Any change in pHVA was not correlated with a change in impulsivity task measures:

Quadratic regressions revealed no significant relationship between pHVA concentration and SSRT SB (ß = -2.45, p = .475, R^2 = 0.04), Positive (ß = -0.37, p = .547, R^2 = 0.03) or Negative Reinforcement (ß = -0.28, p = .390, R^2 = 0.05). Additionally, there was no significant correlation between pHVA concentration and StartRT as a function of Prior Trial Outcome (After Gambled Loss: ß = <.001, p = .922, R^2 = 0.03; After Gambled Win: ß = <.001, p = .826, R^2 = 0.04; After Non-gambled Win: ß = <.001, p = .880, R^2 = 0.03) and Prior Trial Win Probability (0.67 Win Probability: ß = 0.17, p = .894 , R^2 = 0.05 ; 0.55 Win Probability: ß = -0.01, p = .990, R^2 = 0.03; 0.33 Win Probability: ß = -0.36 , p = .724, R^2 = 0.02; 0.25 Win Probability: ß = 0.25, p = .795, R^2 = 0.03). Perhaps a wider range of scores in a greater sample size is necessary to determine any relationship between these variables.

6.5. Discussion

We acknowledge this experiment was underpowered, as a smaller than desired sample size was utilised, so the results we present are preliminary patterns with limited interpretation. However our results indicate that we validated the general concept of our methods. All aspects of the study apart from venepuncture can take place successfully online, which allows for higher recruitment rates. Although perhaps clearer instructional videos are required for stop trials in the online version of the ARIT, to enable a clear relationship between in-person and online SSRT results. This experiment used reliable methods for HVA collection via blood plasma where no outliers were detected. This also confirms that participants successfully followed the controlled diet procedure. Below we speculate what our preliminary results may indicate.

The primary aim of this chapter was to investigate the relationship between a quantifiable measure of metabolised dopamine (pHVA) and a measure which theoretically quantifies central dopamine neurotransmission (DGRS). The most important initial descriptive results and visual patterns suggested a positive relationship between pHVA concentration and the DGRS. There were higher concentrations of pHVA in the high DGRS group and lower concentrations in the low DGRS group. Secondly, we investigated the relationship between the DGRS and impulsivity task performance. Participants modified their behaviour differently following a win compared to a loss in the BART. Here, individuals pumped the balloon up more following a win and less after a loss, regardless of DGRS group. Self-reported BART motivation was greater for DGRS Low than High, which may have been linked to the visual pattern of greater behaviour modification following a win for DGRS Low compared to High. StartRT in the GT was shorter for DGRS Low compared to High after all prior trial outcomes and prior trial win probabilities. The motivation scale for DGRS High and Low groups were

not different from one another, so do not seem to be accounting for the speed of starting the next trial. Finally, there were no correlations between pHVA and impulsivity task measures.

To our knowledge, this is the first study to investigate the relationship between pHVA and a dopamine genetic risk score specifically implicated in impulse control. It was therefore interesting that the high DGRS group seemed to have higher concentrations of pHVA, although this was combined with higher between individual variance. Previous research has found associations between pHVA concentration and specific dopaminergic genes included in the DGRS, as outlined in the introduction of this chapter (Bowers Jr et al., 1998; Laatikainen et al., 2013; Miura et al., 2015; Morimoto et al., 2002; Zumárraga et al., 2010). These associations were most commonly in patient populations with neuropsychiatric conditions such as schizophrenia, although no study to our knowledge, has used the same genetic polymorphisms as the DGRS, other than the COMT Val158Met polymorphism. Greater activity in the COMT Val158Met polymorphism is associated with higher levels of HVA in peripheral blood plasma of bipolar and schizophrenia patients (Zumárraga et al., 2010) and in the PFC, striatum, hippocampus and cerebellum of rats (Laatikainen et al., 2013). It is possible that using a weighted DGRS, COMT may play a particularly important role in the relationship between the DGRS and pHVA due to its role in the breakdown of dopamine (Amin et al., 1992).

A greater sample size could highlight a relationship between central and metabolised dopamine, via the DGRS and pHVA respectively. On the other hand, it could be that pHVA as an indicator of central dopamine is not sensitive enough to detect differences in neural dopamine levels. Only 25-65% of pHVA could be derivative of central contributions which is estimated by using COMT or MAO inhibitors which can supress peripherally obtained dopamine as they do not cross the blood brain barrier (Amin et al., 1995; Siderowf & Kurlan,

1999). Therefore, in order to confirm whether our DGRS does in fact quantify central levels of dopamine, the use of positron emission tomography (PET) or single-photon emission computerized tomography (SPECT) scans is suggested for future research to directly measure dopamine receptor function and release within specific neural regions (Brucke et al., 2000). Although some important preliminary results were discovered relating to a high and low DGRS, such as the visual relationship between the DGRS and pHVA, prospective screening of participant DGRS' in a greater sample size is a necessary step within future investigations of this kind. This is to ensure a larger and comparable sample size is present for each DGRS (0-5), therefore analyses can take place to find associations with the DGRS, split by equal High and Low groups or by each individual DGRS. This important step was planned for this experiment which we were unable to implement due to COVID-19.

When exploring preliminary results of impulsivity task performance between DGRS High and Low groups, patterns were observed for measures in the BART and GT, but not in the ARIT where effect sizes were generally smaller. This could be because in young healthy adults the DGRS is more sensitive to changes in impulsive choice rather than impulsive action with a gambling element. More particularly the DAT polymorphism of the DGRS may play a large role as it has been found to be associated with cognitive impulsive choice (Hall et al., 2023; MacDonald et al., 2016; Mata et al., 2012). Alternatively, there are key differences between the type of behaviour reflected by the primary dependent measures on these tasks; the SSRT of the ARIT considers impulsivity as a collective across all trials, whereas the measures of the BART and GT involve impulsivity and behaviour modification on a trial-by-trial basis where the result of the previous trial effects the behaviour or outcome on the following trial. It is possible that this trial-by-trial approach captures sensitive changes in cognitive impulsivity which are observed in DGRS differences. Future studies of this kind could assess SSRT on the

ARIT on a trial-by-trial basis by measuring partial EMG bursts on successful stop trials to detect these sensitive changes in impulsivity (Coxon, Stinear & Byblow, 2007; Jana et al., 2020). In addition, ARIT measures could include a StartRT component where the time to start each trial following a successful or unsuccessful stop is calculated.

The most interesting patterns observed were those in the BART and GT where the previous trial outcome had a large effect on the subsequent trial, more so for DGRS Low. In the BART, following a successful monetary collection, those with a low DGRS pumped the following balloon more than DGRS High. While only present visually within the data, it is worth highlighting as it aligns with the result reported by MacDonald and colleagues (2016) following both a monetary win and loss at baseline for the lower DGRS group, however this only reached significance for Negative Reinforcement. Whilst in the GT, after all prior trial types and win probabilities, those with DGRS Low started the subsequent trial quicker than DGRS High, and this reached significance even in the small sample size. There are only two previous studies which use this version of the GT and neither involve groups split by genotype (Eben et al., 2020; Verbruggen et al., 2016). Although both studies, along with three other similar studies involving gambling tasks, observed the shortest latency of the start response after a gambled loss (Corr & Thompson, 2014; Dixon et al., 2013; Eben et al., 2022a, 2022b). This behaviour interestingly contradicts post-error slowing (Dutilh et al., 2012), which also involves dopaminergic systems (Siegert et al., 2014), although a gambled loss is arguably distinct to a performance error. Of note, a review by Harris and Griffiths (2018) confirmed that those with a gambling problem preferred faster speed of play in gambling. This perhaps reflects that those in the DGRS Low group, do not specifically have a gambling problem per se, but are more likely to have worse impulsivity. It is commonly known that dopaminergic systems play a key role in gambling (Clark et al., 2009; Habib & Dixon, 2010), but the specific

directional influence of dopamine can be unclear (Clark, 2010; Sevy et al., 2006; Zack & Poulos, 2007). It is possible that gambling problems in those with high and low levels of dopamine neurotransmission can be explained by the inverted-U theory described in previous work (Hall et al., 2021; MacDonald et al., 2016). These results in the GT are not reflected by higher scores on the motivation scales for DGRS low compared to high, even though motivation is linked to impulsivity (Frijda, 2010) and these results were present on the BART. This may be because during the BART, participants are consciously aware of their potential winnings on a trial-by-trial basis, which may affect motivation. Here, those with a low DGRS, reflecting greater impulsivity, showed greater self-reported motivation. Participants were also more impulsive after a win on the BART which could be driven by motivation (Frijda, 2010). In contrast to this, in the GT participants received information about their reward at the end of the task, which was calculated from randomly selected trials, therefore they were less conscious of reward on a trial-by-trial basis. This design may result in lower motivation and reduce the possibility of determining any differences in motivation between DGRS groups. Despite no difference in self-reported motivation between DGRS groups, the faster StartRT in DGRS low compared to high, indicating greater impulsivity, suggests that motivation does not necessarily drive impulsivity on this task.

We did not observe any correlations between pHVA concentration and impulsivity task performance measures. It is possible that this is because a wide range of scores in a greater sample size is required for a robust correlation. This is compared to the DGRS which is categorised into two groups, so it may be easier to observe patterns of high vs low. Alternatively, if our theory is correct, the DGRS will quantify “purely” central dopamine levels, whereas pHVA can only reflect up to 65% of central dopamine levels. Therefore, this measure of pHVA may not be sensitive enough to reflect performance in impulsivity

tasks/questionnaires which are affected by variations in central dopamine. This relationship has not been researched within the literature so it remains to be seen if an association will be determined in larger sample sizes.

In summary, this experiment provides interesting and exciting preliminary results, outlining the potential relationship between metabolised dopamine and central levels of dopamine, via pHVA and the DGRS, respectively. These preliminary results contribute to the working theory that our DGRS can quantify central dopamine neurotransmission. Associations between the DGRS and impulsivity task performance were present, but not with pHVA and impulsivity task performance. It is possible that the measure of pHVA indicating 25-65% of central levels of dopamine may not be sensitive enough to reveal changes in impulsive behaviour. This is in comparison to the differences in impulsive behaviour observed by the two DGRS groups, where the DGRS is specifically constructed with the aim of quantifying high vs low levels of dopamine neurotransmission in MCL regions implicated in impulse control. These relationships can only be explored and confirmed with a greater sample size. If future studies confirm the alignment between pHVA and the DGRS, then pHVA concentration could be another predictive factor of those most likely to develop ICBs in PD. Although this will first need to be investigated in further healthy populations where there is no initial dopamine disturbance.

CHAPTER 7

General Discussion

7.1. Summary of Main Findings

The experiments within this thesis investigated genetic, behavioural and biochemical factors associated with the presence, frequency and change of impulsive behaviour, specifically impulse control behaviours (ICBs) measured by the Questionnaire for Impulsive-Compulsive disorders in Parkinson's disease (QUIP). There were several novel results which further the understanding of how these ICBs could be predicted for those with PD taking dopamine agonist (DA) medication. These novel results outline the potential role of specific genetic polymorphisms via the DGRS and behavioural impulsivity tasks in ICB prediction and monitoring.

The dopamine genetic risk score (DGRS) is a pivotal part of the research in this thesis within three out of four experimental chapters and is a suitable term to describe a way to measure the potential 'risk' of impulsive behaviour for individuals, depending on their genotype. The DGRS and the polymorphisms constructing it displayed important relationships with ICBs and impulsive behaviour. As already mentioned, the DGRS theoretically quantifies central dopamine neurotransmission within MCL regions which are implicated in impulse control. This theory has some strong background rationale (Pearson-Fuhrhop et al., 2013, 2014) and has been proven to explain the relationship between DA medication and impulsivity in a sample of healthy older adults (MacDonald et al., 2016). Chapter 3 followed on from this investigation in a cohort of PD patients taking DA medication. Here, the first novel finding was presented, where dopamine profiling from the DGRS displayed predictive power for PD patients on DA medication. These results somewhat mirrored the inverted-U relationship between impulse control and dopamine, previously reported by Macdonald and others (2016). The DGRS highlighted that PD patients with low dopamine neurotransmission in MCL regions displayed worse impulse control which improved with DA medication, whilst those with higher

dopamine neurotransmission had better levels of impulse control which worsened with DA medication. Although not all of these results reached statistical significance, this is discussed in the limitations section below. In Chapter 5, the DGRS on its own or part of an interaction with behavioural outcomes was not associated with ICB frequency, however the dopamine transporter (DAT) and catechol-O-methyltransferase (COMT) polymorphisms, indicating higher dopamine neurotransmission, were associated with greater impulsivity with increasing time on DA medication. Following these first results utilising the DGRS in PD, Chapter 6 highlighted a visual relationship in young healthy adults between the DGRS and plasma homovanillic acid (pHVA), the metabolite of dopamine. The results of this final experimental chapter, suggest the measure of HVA could be important in confirming the DGRS theory.

The other very key aspect of this thesis was the inclusion of behavioural impulsivity tasks, which are present within three experimental chapters, to determine any association with the DGRS, ICBs and HVA. Firstly, Chapter 4 investigated the behavioural aspect of motor impulse control to determine which lab-based impulsivity task would produce the most consistent stop signal reaction time (SSRT) measure. Results of this chapter suggested that SSRT, derived from Stop Both trials of the Anticipatory Response Inhibition Task (ARIT), is a valid measure of non-selective inhibition network activity, more so than the Stop Signal Task. Subsequently, Chapter 5 initially presented a pilot study which determined the most suitable version of the ARIT for those with PD to complete, where sufficient data could be extracted for analyses. The version which reduced the initial staircase stop signal delay value by 100ms for Stop Both trials was selected, reducing the difficulty of the task which was mirrored in the results and verbal feedback. The following main investigation of Chapter 5 examined the sensitivity of objective behavioural task measures, along with any interactions with the DGRS to determine the frequency of ICBs in PD patients taking DA medication. The use of the ARIT

in PD is novel, along with the relationship revealed between higher ICB frequency derived from the QUIP and impulsive behaviour on both the ARIT and BART. Although, this relationship between higher ICB frequency and impulsive behaviour on the ARIT did not quite reach significance. Finally, Chapter 6 investigated any association between behavioural impulsivity tasks and the DGRS and pHVA. Although only preliminary evidence with a limited sample size, the clearest initial patterns showed a relationship between greater impulsive behaviour modification in the GT and BART, and the DGRS.

7.2. Potential Limitations & Future Directions

There are several limitations to the research within this thesis, which should be kept in mind when interpreting results.

As outlined above, the DGRS is a pivotal part of the research in this thesis within three out of four experimental chapters. The working theory is that the DGRS quantifies central dopamine neurotransmission within MCL regions, which are implicated in impulse control. The results in our investigations display key relationships between the DGRS and impulsive behaviour, analysed with correlations and statistical modelling, which speculates this theory could be correct. Further adding to the evidence for this theory, Chapter 6 showed a visual relationship between pHVA and the DGRS. Although these results are promising, firstly it is important to note that only 25-65% of pHVA could be derivative of central contributions (Amin et al., 1992; Sternberg & Heninger, 1983). Secondly, we cannot 100% confirm that the DGRS quantifies central dopamine levels as they have not been directly measured. Positron emission tomography (PET) or single-photon emission computerized tomography (SPECT) scans would be needed to confirm this theory, as they can quantify the specific molecular target or measure receptor function and release within specific neural regions (Brucke et al., 2000; Zhu et al., 2014). Both PET and SPECT can produce high resolution images by using radioactive tracers at a cellular and molecular level (Wernick & Aarsvold, 2004). It is possible to use PET and SPECT imaging to assess D1 and D2 receptors (Brucke et al., 2000), D3 receptors (Stone et al., 2009), COMT (Graf et al., 2020) and DAT (Chalon et al., 2019), which make up the DGRS. The standardised uptake value of the image for the specific receptor or protein could be used as a quantification method (Zaidi & Karakatsanis, 2018). These values could be compared to the DGRS or each individual mutation. This method may have the potential to confirm the DGRS quantifies central dopamine neurotransmission within MCL regions.

It is possible that the presented inverted-U relationship between dopamine neurotransmission and impulse control may not be correct without further replication. Although some of the results presented in Chapter 3 describe this inverted-U pattern, other results do not quite support this relationship. The baseline odds of impulsivity for DGRS high compared to medium was not significant, it was only the significant increase in ICB score over time which showed the change for DGRS high on the inverted-U figure (figure 3.1), but not the baseline odds (table 3.2). This was the opposite for DGRS low, where the baseline odds were much higher than DGRS medium, but the change in ICB score over time was not significant, it was only significantly different from DGRS high. So, although the results presented contribute to the inverted-U theory, we cannot confirm that this is definitely the pattern of the data, without replication. In Chapter 5, a multiple linear regression model was used to determine any significant association between the DGRS low and ICB frequency, compared to DGRS high. Perhaps the best approach may be to run a linear and also quadratic regression model for this type of data in the future, as we do not know for certain whether the relationship between the DGRS and ICB frequency follows the inverted-U relationship.

Lower than desired sample sizes for the DGRS were present throughout the research. In Chapters 3, 5 and 6 we were forced to adjust the groups of the DGRS due to the lower than desired sample sizes and the absence of DAT availability in Chapter 3 (Chapter 3 = Low: 0-1, Medium: 2, High: 3-4; Chapter 5 = Low: 0-2, High: 3-5, Chapter 6 = Low: 0-2, High: 4-5). The sample sizes for each DGRS group were also never the same. Although we endeavoured to keep consistency between DGRS group classification and sample sizes, we cannot directly compare the results of the DGRS between each chapter. We can only discuss and speculate the effect of a high and low DGRS as a whole, without the further replication of results with the same DGRS groups. Be that as it may, these lower than desired sample sizes were out of our

control. We utilised the Parkinson's Progression Markers Initiative (PPMI) database in Chapter 3 which had a finite number of participants, and Chapters 5 and 6 were completed under time constraints and laboratory restrictions due to COVID-19. Although, it is important to note that necessary steps were taken in the planning of Chapter 6 to complete prospective screening of a large number of participants. This was to ensure a sufficient range and number of each DGRS, which was not available in previous chapters, but as mentioned this was halted by COVID-19. To summarise, lower than preferred sample sizes for DGRS analyses were present, but importantly results in the published chapters involving the DGRS were still adequately powered. Future research involving the DGRS should include prospective screening to ensure an increased sample size for each DGRS.

Lower than preferred sample size also prevented us from completing specific analyses throughout the thesis. The relationship between change in ICB score and DGRS groups in Chapter 3 was determined with correlations, but we were unable to run regression models to determine specific interactions between time on DA medication and DGRS group, when predicting ICB score. Again, this was due to the finite number of participants available for data analyses from the PPMI database. Furthermore, only the QUIP-short (QUIP-S) version was available from PPMI, which does not have the range that the QUIP-rating scale (QUIP-RS) offers. This prevented us from completing linear regression analyses with exposure to DA medication. In Chapter 5, we were unable to run binary logistic regression models to explore any association with ICB incidence rather than frequency, this would be to directly compare to results of Chapter 3. However, there was a significant correlation between the QUIP-S and the QUIP-RS in Chapter 5, which allows us to compare the results of both chapters to an extent, without direct replication of the methodology. Finally, a low sample size also prevented running linear regression models for the NDA group in Chapter 5 and did not allow for

meaningful statistical significance tests in Chapter 6. While we were unable to complete several analyses due to low sample sizes, we have produced very meaningful results throughout these chapters, which were publication worthy.

Chapters 3 and 5 investigate the effect of increasing time on DA medication, however these chapters incorporate a cross sectional study design, where each individual time point is a different participant. Although this element of exposure to DA medication produced novel findings, only a longitudinal design will confirm these changes within an individual and therefore further contribute to the prediction of ICBs. This is because, in our cross-sectional design, we were unable to confirm that the results we observed were not due to previous bouts of administered DA medication as well as current, which could be examined in a longitudinal design. To provide evidence for this, it has been concluded in the literature that after coming off DA medication, ICB symptoms can subside (Siri et al., 2015), but it is also possible that any use of DA can increase the risk of developing ICBs in the future (Marković et al., 2020). As a result, we cannot say for certain that previous bouts on DA medication did not affect our results for DA or NDA groups. Although, given the relatively short disease duration in Chapter 5, it is perhaps less likely that these patients went on agonists long enough to develop ICBs, which then persisted when they came off agonist medications. With this knowledge, to remain consistent in both chapters, we only used data from the most recent bout of DA medication for each participant. In Chapter 3, we captured information regarding the number of bouts of DA administration for each participant, however decided this was too simplistic a variable to include in analyses. It would be important for future investigations to include not only the number but perhaps also the duration of these previous bouts of DA medication, perhaps as confounding variables, to see how they impact the outcome variable. Alternatively, in a longitudinal design, ideally participants would be followed for a number of years from de novo,

over the course of their disease (Marković et al., 2020; Ricciardi et al., 2018). Here, participants can be genotyped for their DGRS and tested for ICBs and impulsive behaviour from impulsivity tasks at baseline, which can then be monitored over the course of several years, as it is reported ICBs can develop 14 months following first DA administration (Ricciardi et al., 2018). Analyses could split participants into groups depending on if they have ever taken DA medication (Corvol et al., 2018), how many bouts of DA medication, how long these lasted and accumulated bouts. This may be able to identify the predictive power of the DGRS and behavioural tasks in ICB development and change for those on DA medication, and how the number of bouts and duration of DA administration can affect this.

Finally, the ARIT is used within experimental Chapters 4, 5 and 6 in this thesis. The use of the ARIT in PD is in the very early stages, and while some novel results were presented in the current research, there are further investigations to be completed if it is to be used as a predictive or monitoring tool for ICBs in PD. Firstly, it needs to be confirmed that SSRT remains stable in a healthy population over a much longer period of time (compared to the two sessions investigated in Chapter 4), to establish there are no within-individual changes over time. This should first be completed in a young healthy population, before then investigating the effects of aging on response inhibition (RI) in an older healthy population (Coxon et al., 2012; Smittenaar et al., 2015). Subsequently, the ARIT can be implemented in an unmedicated PD population, to determine any disease effects on RI. The results of these mentioned investigations will confirm that any changes in RI within a PD DA cohort will likely be from the influence of DA medication. Therefore, the ARIT has the potential to be used as a monitoring tool for ICBs.

Another consideration for the ARIT is that the specific version we used may not only measure response inhibition and impulsive action. Although it seems appropriate to interpret the ARIT vs BART/GT results separately, given the ARIT and BART accounted for independent variability in Chapter 5, it is possible that aspects of motor, cognitive and limbic networks are present in all three tasks. In the BART and GT, motor components are used to make a physical response on each trial, but it is generally accepted that these tasks are related to decision making, risk-taking, reward and motivation (Antonelli et al., 2011; Lauriola et al., 2014; Lejuez et al., 2002) which aligns with activation in dopamine rich MCL regions (Gentili et al., 2020; Rao et al., 2008; Rao et al., 2018). Although we interpret measures of the ARIT (e.g., SSRT) purely as measures of motor impulse control, results may also be affected by reward and motivation, but to a lesser extent. The individual response on each stop trial of the ARIT outlines the ability of the participant to inhibit the motor response. But feedback indicating a successful or unsuccessful response is presented above the bars after every trial, which could influence trial-by-trial performance. This feedback could be seen as a form of reward and motivation for the following trial, which has been found in the SST (Leotti & Wager, 2010). It was mentioned in Chapter 1 that neural circuitry may be integrated for the motor, cognitive and limbic domains (Haber, 2014; Haber et al., 2000). Perhaps it could be the case that neural networks and structures activated in response inhibition tasks, such as the ARIT, could also be linked to more cognitive aspects of impulse control. For example, in response inhibition tasks the inferior frontal gyrus (IFG) (part of the pre-frontal cortex) is responsible for the initiation of inhibiting a response (Jahfari et al., 2011; Schaum et al., 2020, 2021), but it has also been reported that the IFG drives decision making against risk (Fukunaga et al., 2012). Moreover, D2 receptor binding in regions of the mesolimbic system, often linked with reward, is associated with improved motor inhibitory control (Mann et al., 2021). Therefore, when analysing results, it should be considered that the ARIT may target more than

just motor impulse control. To investigate this, a number of different versions of the ARIT could be produced with varying levels of feedback and reward. Specific data could then be analysed, starting with examining variables on a trial-by-trial basis such as SSRT and the time to start the following trial after a prior trial success vs target miss. Reward processing measures obtained via EEG (Greenhouse & Wessel, 2013) could also be used to assess which neural regions are activated and to what extent, during each of these ARIT versions.

To summarise, this body of work provides a narrative of some of the first steps of implementing a cumulative genetic score and behavioural impulsivity tasks to investigate factors which could be associated with impulsive behaviour, specifically ICBs in PD. Whilst replicating some important results already reported to add to the literature, this work also presents several novel findings, providing insight for future investigations to perhaps predict which PD patients taking DA medication are most likely to develop ICBs.

LIST OF REFERENCES

Abidin, S. Z., Tan, E. L., Chan, S. C., Jaafar, A., Lee, A. X., Abd Hamid, M. H. N., Abdul Murad, N. A., Pakarul Razy, N. F., Azmin, S., Ahmad Annuar, A., Lim, S. Y., Cheah, P. S., Ling, K. H., & Mohamed Ibrahim, N. (2015). DRD and GRIN2B Polymorphisms and their Association with the Development of Impulse Control Behaviour Among Malaysian Parkinson's Disease Patients. *BMC Neurology*, *15*(59), 1–10. https://doi.org/10.1186/s12883-015-0316-2

Aichert, D. S., Wstmann, N. M., Costa, A., MacAre, C., Wenig, J. R., Mller, H. J., Rubia, K., & Ettinger, U. (2012). Associations between trait impulsivity and prepotent response inhibition. *Journal of Clinical and Experimental Neuropsychology*, *34*(10), 1016–1032. https://doi.org/10.1080/13803395.2012.706261

Ainslie, G. (1975). Specious reward: A behavioral theory of impulsiveness and impulse control. *Psychological Bulletin*, *82*(4), 463–496. https://doi.org/10.1037/h0076860

Alexander, G. E., & Crutcher, M. D. (1990). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends in Neurosciences*, *13*(7). https://doi.org/10.1016/0166-2236(90)90107-L

Ali, P., & Younas, A. (2021). Understanding and interpreting regression analysis. *Evidence-Based Nursing*, *24*(4), 116–118. https://doi.org/10.1136/ebnurs-2021-103425

Allen, C., Singh, K. D., Verbruggen, F., & Chambers, C. D. (2018). Evidence for parallel activation of the pre-supplementary motor area and inferior frontal cortex during response inhibition: A combined MEG and TMS study. *Royal Society Open Science*, *5*(2). https://doi.org/10.1098/rsos.171369

Amin, F., Davidson, M., & Davis, K. L. (1992). Homovanillic Acid Measurement in Clinical Research: A Review of Methodology. *Schizophrenia Bulletin*, *18*(1), 123–148. https://doi.org/10.1093/schbul/18.1.123

Amin, F., Davidson, M., Kahn, R. S., Schmeidler, J., Stern, R., Knott, P. J., & Apter, S. (1995). Assessment of the central dopaminergic index of plasma HVA in schizophrenia. *Schizophrenia Bulletin*, *21*(1), 53–66. https://doi.org/10.1093/schbul/21.1.53

Antonelli, F., Ray, N., & Strafella, A. P. (2011). Impulsivity and Parkinson's disease: More than just disinhibition. *Journal of the Neurological Sciences*, *310*(1–2), 202–207. https://doi.org/10.1016/j.jns.2011.06.006

Antonini, A., Barone, P., Bonuccelli, U., Annoni, K., Asgharnejad, M., & Stanzione, P. (2017). ICARUS study: Prevalence and clinical features of impulse control disorders in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *88*(4), 317–324. https://doi.org/10.1136/jnnp-2016-315277

Antonini, A., Siri, C., Santangelo, G., Cilia, R., Poletti, M., Canesi, M., Caporali, A., Mancini, F., Pezzoli, G., Ceravolo, R., Bonuccelli, U., & Barone, P. (2011). Impulsivity and Compulsivity in Drug-Naïve Patients with Parkinson's Disease. *Movement Disorders*, *26*(3), 464–468. https://doi.org/10.1002/mds.23501

Aron, A. R., Fletcher, P. C., Bullmore, E. T., Sahakia, B. J., & Trevor W. Robbins. (2003). Stop-signal inhibitiondisrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience*, *6*(2), 115–116.

Aron, A. R., & Poldrack, R. A. (2006). Cortical and Subcortical Contributions to Stop Signal Response Inhibition: Role of the Subthalamic Nucleus. *Journal of Neuroscience*, *26*(9), 2424–2433. https://doi.org/10.1523/JNEUROSCI.4682-05.2006

Aron, A. R., & Verbruggen, F. (2008). Stop the Presses: Dissociating a Selective From a Global Mechanism for Stopping. *Psychological Science*, *19*(11), 1146–1153. https://doi.org/10.1111/j.1467-9280.2008.02216.x

Ashenhurst, J. R., Bujarski, S., Jentsch, J. D., & Ray, L. A. (2014). Modeling Behavioral Reactivity to Losses and Rewards on the Balloon Analogue Risk Task (BART): Moderation by Alcohol Problem Severity. *Experimental and Clinical Psychopharmacology*, *22*(4), 298–306. https://doi.org/10.1037/a0036837

Austin, P. C., & Steyerberg, E. W. (2015). The number of subjects per variable required in linear regression analyses. *Journal of Clinical Epidemiology*, *68*, 627–636. https://doi.org/10.1016/j.jclinepi.2014.12.014

Baig, F., Kelly, M. J., Lawton, M. A., Ruffmann, C., Rolinski, M., Klein, J. C., Barber, T., Lo, C., Ben-Shlomo, Y., Okai, D., & Hu, M. T. (2019). Impulse control disorders in Parkinson disease and RBD: A longitudinal study of severity. *Neurology*, *93*(7), E675–E687. https://doi.org/10.1212/WNL.0000000000007942

Band, G. P. H., van der Molen, M. W., & Logan, G. D. (2003). Horse-race Model Simulations of the Stop-signal Procedure. *Acta Psychologica*, *112*, 105–142. https://doi.org/10.1016/S0001-6918(02)00079-3

Band, G. P., van der Molen, M. W., & Logan, G. D. (2003). Horse-race model simulations of the stop-signal procedure. *Acta Psychologica*, *112*, 105–142.

Barbosa, P., Hapuarachchi, B., Djamshidian, A., Strand, K., Lees, A. J., De Silva, R., Holton, J. L., & Warner, T. T. (2019). Lower nucleus accumbens a-synuclein load and D3 receptor levels in Parkinson's disease with impulsive compulsive behaviours. *Brain*, *142*(11), 3580–3591. https://doi.org/10.1093/brain/awz298

Barratt, E. S. (1959). ANXIETY AND IMPULSIVENESS RELATED TO PSYCHOMOTOR EFFICIENCY. *Perceptual Alzd Motor Skills*, *9*, 191–198.

Bastiaens, J., Dorfman, B. J., Christos, P. J., & Nirenberg, M. J. (2013). Prospective Cohort Study of Impulse Control Disorders in Parkinson's Disease. *Movement Disorders*, *28*(3), 327–333. https://doi.org/10.1002/mds.25291

Bell, C. (1988). Dopamine release from sympathetic nerve terminals. *Progress in Neurobiology*, *30*(2–3), 193–208. https://doi.org/10.1016/0301-0082(88)90006-8

Bergh, C., Eklund, T., Södersten, P., & Nordin, C. (1997). Altered Dopamine Function in Pathological Gambling. *Psychological Medicine*, *27*, 473–475. https://doi.org/10.1017/S0033291796003789

Berkman, E. T., Kahn, L. E., & Merchant, J. S. (2014). Training-induced changes in inhibitory control network activity. *Journal of Neuroscience*, *34*(1), 149–157. https://doi.org/10.1523/JNEUROSCI.3564-13.2014

Best, J. A., Nijhout, H. F., & Reed, M. C. (2009). Homeostatic mechanisms in dopamine synthesis and release: A mathematical model. *Theoretical Biology and Medical Modelling*, *6*(1), 1–20. https://doi.org/10.1186/1742-4682-6-21

Beste, C., Willemssen, R., Saft, C., & Falkenstein, M. (2010). Response inhibition subprocesses and dopaminergic pathways: Basal ganglia disease effects. *Neuropsychologia*, *48*, 366–373. https://doi.org/10.1016/j.neuropsychologia.2009.09.023

Bhatia, A., Lenchner, J. R., & Saadabadi, A. (2022). Biochemistry, Dopamine Receptors. In *StatPearls*. StatPearls Publishing, Treasure Island (FL). http://europepmc.org/abstract/MED/30855830

Bloemendaal, M., Zandbelt, B., Wegman, J., van de Rest, O., Cools, R., & Aarts, E. (2016). Contrasting neural effects of aging on proactive and reactive response inhibition. *Neurobiology of Aging*, *46*, 96–106. https://doi.org/10.1016/j.neurobiolaging.2016.06.007

Boeve, B. F. (2013). Idiopathic REM sleep behaviour disorder in the development of Parkinson's disease. In *The Lancet Neurology* (Vol. 12, pp. 469–482). https://doi.org/10.1016/S1474-4422(13)70054-1

Boon, J. M., Abrahams, P. H., Meiring, J. H., & Welch, T. (2004). Lumbar puncture: Anatomical review of a clinical skill. *Clinical Anatomy*, *17*(7), 544–553. https://doi.org/10.1002/ca.10250

Bowers Jr, M. B., Malison, R. T., Seibyl, J. P., & Kosten, T. R. (1998). Plasma Homovanillic Acid and the Dopamine Transporter During Cocaine Withdrawal. *Biological Psychiatry*, *43*(4), 278–281.

Braak, H., & Del Tredici, K. (2004). Poor and protracted myelination as a contributory factor to neurodegenerative disorders. *Neurobiology of Aging*, *25*, 19–23. https://doi.org/10.1016/j.neurobiolaging.2003.04.001

Braak, H., Ghebremedhin, E., Rüb, U., Bratzke, H., & Del Tredici, K. (2004). Stages in the development of Parkinson's disease-related pathology. In *Cell and Tissue Research* (Vol. 318, pp. 121–134). https://doi.org/10.1007/s00441-004-0956-9

Braak, H., Tredici, K. Del, Rüb, U., De Vos, R. A. I., Jansen Steur, E. N. H., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. In *Neurobiology of Aging* (Vol. 24).

Brand, M., Kalbe, E., Labudda, K., Fujiwara, E., Kessler, J., & Markowitsch, H. J. (2005). Decision-making impairments in patients with pathological gambling. *Psychiatry Research*, *133*, 91–99. https://doi.org/10.1016/j.psychres.2004.10.003

Brevers, D., Cheron, G., Dahman, T., Petieau, M., Palmero-Soler, E., Foucart, J., Verbanck, P., & Cebolla, A. M. (2020). Spatiotemporal brain signal associated with high and low levels of proactive motor response inhibition. *Brain Research*, *1747*, 147064. https://doi.org/10.1016/j.brainres.2020.147064

Brooks, D. J. (2000). Dopamine agonists: Their role in the treatment of Parkinson's disease. *Journal of Neurology Neurosurgery and Psychiatry*, *68*, 685–689. https://doi.org/10.1136/jnnp.68.6.685

Brucke, T., Djamshidian, S., Bencsits, G., Pirker, W., Asenbaum, S., & Podreka, I. (2000). SPECT and PET imaging of the dopaminergic system in Parkinson's disease. *Journal of Neurology, Supplement*, *247*(4), 2–7. https://doi.org/10.1007/pl00007769

Buelow, M. T., & Barnhart, W. R. (2018). Test-Retest Reliability of Common Behavioral Decision Making Tasks. *Archives of Clinical Neuropsychology*, *33*, 125–129. https://doi.org/10.1093/arclin/acx038

Buelow, M. T., Frakey, L. L., Grace, J., & Friedman, J. H. (2014). The Contribution of Apathy and Increased Learning Trials to Risky Decision-Making in Parkinson's Disease. *Archives of Clinical Neuropsychology*, *29*, 100–109.

Bugalho, P., Da Silva, J. A., & Neto, B. (2011). Clinical features associated with REM sleep behavior disorder symptoms in the early stages of Parkinson's disease. *Journal of Neurology*, *258*, 50–55. https://doi.org/10.1007/s00415-010-5679-0

Callesen, M. B., Weintraub, D., Damholdt, M. F., & Møller, A. (2014). Impulsive and compulsive behaviors among Danish patients with Parkinson's disease: Prevalence, depression, and personality. *Parkinsonism and Related Disorders*, *20*, 22–26. https://doi.org/10.1016/j.parkreldis.2013.09.006

Caminiti, S. P., Presotto, L., Baroncini, D., Garibotto, V., Moresco, R. M., Gianolli, L., Volonté, M. A., Antonini, A., & Perani, D. (2017). Axonal damage and loss of connectivity in nigrostriatal and mesolimbic dopamine pathways in early Parkinson's disease. *NeuroImage: Clinical*, *14*, 734–740. https://doi.org/10.1016/j.nicl.2017.03.011

Casson, R. J., & Farmer, L. D. M. (2014). Understanding and checking the assumptions of linear regression: a primer for medical researchers. *Clinical and Experimental Ophthalmology*, *42*, 590–596. https://doi.org/10.1111/ceo.12358

Cazzell, M., Li, L., Lin, Z. J., Patel, S. J., & Liu, H. (2012). Comparison of neural correlates of risk decision making between genders: An exploratory fNIRS study of the Balloon Analogue Risk Task (BART). *NeuroImage*, *62*, 1896–1911. https://doi.org/10.1016/j.neuroimage.2012.05.030

Chalon, S., Vercouillie, J., Payoux, P., Deloye, J. B., Malherbe, C., Le Jeune, F., Arlicot, N., Salabert, A. S., Guilloteau, D., Emond, P., & Ribeiro, M. J. (2019). The Story of the Dopamine Transporter PET Tracer LBT-999: From Conception to Clinical Use. *Frontiers in Medicine*, *6*(90), 1–5. https://doi.org/10.3389/fmed.2019.00090

Chen, W., de Hemptinne, C., Miller, A. M., Leibbrand, M., Little, S. J., Lim, D. A., Larson, P. S., & Starr, P. A. (2020). Prefrontal-Subthalamic Hyperdirect Pathway Modulates Movement Inhibition in Humans. *Neuron*, *106*, 579–588. https://doi.org/10.1016/j.neuron.2020.02.012

Chowdhury, N. S., Livesey, E. J., & Harris, J. A. (2020). Stop Signal Task Training Strengthens GABA-mediated Neurotransmission within the Primary Motor Cortex. *Journal of Cognitive Neuroscience*, *32*(10), 1984–2000. https://doi.org/10.1162/jocn_a_01597

Cilia, R., Ko, J. H., Cho, S. S., van Eimeren, T., Marotta, G., Pellecchia, G., Pezzoli, G., Antonini, A., & Strafella, A. P. (2010). Reduced dopamine transporter density in the ventral striatum of patients with Parkinson's disease and pathological gambling. *Neurobiology of Disease*, *39*, 98–104. https://doi.org/10.1016/j.nbd.2010.03.013

Claassen, D. O., Stark, A. J., Spears, C. A., Petersen, K. J., van Wouwe, N. C., Kessler, R. M., Zald, D. H., & Donahue, M. J. (2017). Mesocorticolimbic hemodynamic

response in Parkinson's disease patients with compulsive behaviors. *Movement Disorders*, *32*(11), 1574–1583. https://doi.org/10.1002/mds.27047

Claassen, D. O., Van Den Wildenberg, W. P. M., Harrison, M. B., Van Wouwe, N. C., Kanoff, K., Neimat, J. S., & Wylie, S. A. (2015a). Proficient motor impulse control in Parkinson disease patients with impulsive and compulsive behaviors. *Pharmacology Biochemistry and Behavior*, *129*, 19–25. https://doi.org/10.1016/j.pbb.2014.11.017

Claassen, D. O., Van Den Wildenberg, W. P. M., Harrison, M. B., Van Wouwe, N. C., Kanoff, K., Neimat, J. S., & Wylie, S. A. (2015b). Proficient motor impulse control in Parkinson disease patients with impulsive and compulsive behaviors. *Pharmacology Biochemistry and Behavior*, *129*, 19–25. https://doi.org/10.1016/j.pbb.2014.11.017

Claassen, D. O., Wildenberg, W. P. M. van den, Ridderinkhof, K. R., Jessup, C. K., Harrison, M. B., Wooten, G. F., & Scott A. Wylie. (2011). The Risky Business of Dopamine Agonists in Parkinson Disease and Impulse Control Disorders. *Behavioural Neuroscience*, *125*(4), 492–500. https://doi.org/10.1037/a0023795.The

Claes, L., Vertommen, H., & Braspenning, N. (2000). Psychometric properties of the Dickman Impulsivity Inventory. *Personality and Individual Differences*, *29*, 27–35. https://doi.org/10.1016/S0191-8869(99)00172-5

Clark, L. (2010). Decision-making During Gambling: An Integration of Cognitive and Psychobiological Approaches. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *365*, 319–330. https://doi.org/10.1098/rstb.2009.0147

Clark, L., Lawrence, A. J., Astley-Jones, F., & Gray, N. (2009). Gambling Near-Misses Enhance Motivation to Gamble and Recruit Win-Related Brain Circuitry. *Neuron*, *61*, 481–490. https://doi.org/10.1016/j.neuron.2008.12.031

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*. Lawrence Erlbaum Associates Publishers.

Cohen, J., Cohen, P., West, S., & Aiken, L. (2003). *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences*.

Combet, E., Lean, M. E. J., Boyle, J. G., Crozier, A., & Davidson, D. F. (2011). Dietary flavonols contribute to false-positive elevation of homovanillic acid, a marker of catecholamine-secreting tumors. *Clinica Chimica Acta*, *412*(1–2), 165–169. https://doi.org/10.1016/j.cca.2010.09.037

Congdon, E., Constable, R. T., Lesch, K. P., & Canli, T. (2009). Influence of SLC6A3 and COMT variation on neural activation during response inhibition. *Biological Psychology*, *81*(3), 144–152. https://doi.org/10.1016/j.biopsycho.2009.03.005

Congdon, E., Mumford, J. A., Cohen, J. R., Galvan, A., Canli, T., & Poldrack, R. A. (2012). Measurement and reliability of response inhibition. *Frontiers in Psychology*, *3*(37), 1–10. https://doi.org/10.3389/fpsyg.2012.00037

Cooley, S. A., Heaps, J. M., Bolzenius, J. D., Salminen, L. E., Baker, L. M., Scott, S. E., & Paul, R. H. (2015). Longitudinal change in performance on the Montreal Cognitive Assessment in older adults. *Clinical Neuropsychology*, *29*(6), 824–835. https://doi.org/10.1080/13854046.2015.1087596.Longitudinal

Cools, R. (2006). Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. In *Neuroscience and Biobehavioral Reviews* (Vol. 30, pp. 1–23). https://doi.org/10.1016/j.neubiorev.2005.03.024

Cools, R., Altamirano, L., & Esposito, M. D. '. (2006). Reversal learning in Parkinson's disease depends on medication status and outcome valence. *Neuropsychologia*, *44*, 1663–1673. https://doi.org/10.1016/j.neuropsychologia.2006.03.030

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cerebral Cortex*, *11*, 1136–1143. https://doi.org/10.1093/cercor/11.12.1136

Cormier, F., Muellner, J., & Corvol, J. C. (2013). Genetics of impulse control disorders in Parkinson's disease. *Journal of Neural Transmission*, *120*(4), 665–671. https://doi.org/10.1007/s00702-012-0934-4

Cormier-Dequaire, F., Bekadar, S., Anheim, M., Lebbah, S., Pelissolo, A., Krack, P., Lacomblez, L., Lhommée, E., Castrioto, A., Azulay, J. P., Defebvre, L., Kreisler, A., Durif, F., Marques-Raquel, A., Brefel-Courbon, C., Grabli, D., Roze, E., Llorca, P. M., Ory-Magne, F., … Corvol, J. C. (2018). Suggestive Association Between OPRM1 and Impulse Control Disorders in Parkinson's Disease. *Movement Disorders*, *33*(12), 1878–1886. https://doi.org/10.1002/mds.27519

Corr, P. J., & Thompson, S. J. (2014). Pause for Thought: Response Perseveration and Personality in Gambling. *Journal of Gambling Studies*, *30*, 889–900. https://doi.org/10.1007/s10899-013-9395-4

Corvol, J. C., Artaud, F., Cormier-Dequaire, F., Rascol, O., Durif, F., Derkinderen, P., Marques, A. R., Bourdain, F., Brandel, J. P., Pico, F., Lacomblez, L., Bonnet, C., Brefel-Courbon, C., Ory-Magne, F., Grabli, D., Klebe, S., Mangone, G., You, H., Mesnage, V., … Elbaz, A. (2018). Longitudinal analysis of impulse control disorders in Parkinson disease. *Neurology*, *91*(3), e189–e201. https://doi.org/10.1212/WNL.0000000000005816

Cowie, M. J., MacDonald, H. J., Cirillo, J., & Byblow, W. D. (2016). Proactive modulation of long-interval intracortical inhibition during response inhibition. *Journal of Neurophysiology*, *116*, 859–867. https://doi.org/10.1152/jn.00144.2016

Coxon, J. P., Goble, D. J., Leunissen, I., Van Impe, A., Wenderoth, N., & Swinnen, S. P. (2016). Functional Brain Activation Associated with Inhibitory Control Deficits in Older Adults. *Cerebral Cortex*, *26*, 12–22. https://doi.org/10.1093/cercor/bhu165

Coxon, J. P., Stinear, C. M., & Byblow, W. D. (2006). Intracortical inhibition during volitional inhibition of prepared action. *Journal of Neurophysiology*, *95*, 3371–3383. https://doi.org/10.1152/jn.01334.2005

Coxon, J. P., Stinear, C. M., & Byblow, W. D. (2007). Selective Inhibition of Movement. *Journal of Neurophysiology*, *97*, 2480–2489. https://doi.org/10.1152/jn.01284.2006

Coxon, J. P., Stinear, C. M., & Byblow, W. D. (2009). Stop and go: The neural basis of selective movement prevention. *Journal of Cognitive Neuroscience*, *21*(6), 1193–1203. https://doi.org/10.1162/jocn.2009.21081

Coxon, J. P., van Impe, A., Wenderoth, N., & Swinnen, S. P. (2012). Aging and inhibitory control of action: Cortico-subthalamic connection strength predicts stopping performance. *Journal of Neuroscience*, *32*(24), 8401–8412. https://doi.org/10.1523/JNEUROSCI.6360-11.2012

Cunnington, R., Iansek, R., Bradshaw, J. L., & Phillips, J. G. (1995). Movement-related potentials in Parkinson's disease. Presence and predictability of temporal and spatial cues. *Brain*, *118*(4), 935–950. https://doi.org/10.1093/brain/118.4.935

Dauer, W., & Przedborski, S. (2003). Parkinson's Disease: Models and mechanisms. *Neuron*, *39*, 889–909. https://doi.org/10.1016/s0896-6273(03)00568-3

David E. Sternberg, George R. Heninger, R. H. R. (1983). Plasma Homovanillic Acid as an Index of Brain Dopamine Metabolism: Enhancement with Debrisoquin. *Life Sciences*, *32*(21), 2447–2452.

Davidson, M., Giordano, A. B., Mohs, R. C., Mykytyn, V. v., Platt, S., Aryan, Z. S., & Davis, K. L. (1987). Control of exogenous factors affecting plasma homovanillic

acid concentration. *Psychiatry Research*, *20*(4), 307–312. https://doi.org/10.1016/0165-1781(87)90091-6

de Lau, L. M. L., & Breteler, M. M. B. (2006). Epidemiology of Parkinson's disease. In *Lancet Neurol* (Vol. 5, pp. 525–535). https://doi.org/10.1016/S1016-3190(10)60044-4

De Villiers, C. B., Kroese, M., & Moorthie, S. (2020). Understanding polygenic models, their development and the potential application of polygenic scores in healthcare. *Journal of Medical Genetics*, *57*, 725–732. https://doi.org/10.1136/jmedgenet-2019-106763

DeLong, E. R., DeLong, D. M., & Clarke-Pearson, D. L. (1988). Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves : A Nonparametric Approach. *Biometrics*, *44*(3), 837–845.

DeYoung, C. G., & Rueter, A. R. (2010). Impulsivity as a Personality Trait. In *Handbook of Self-Regulation, Third Edition: Research, Theory, and Applications* (pp. 345–363).

Dickson, D. W., Uchikado, H., Fujishiro, H., & Tsuboi, Y. (2010). Evidence in Favor of Braak Staging of Parkinson's Disease. *Movement Disorders*, *25*(1), 78–82. https://doi.org/10.1002/mds.22637

Disner, S. G., McGeary, J. E., Wells, T. T., Ellis, A. J., & Beevers, C. G. (2014). 5-HTTLPR, HTR1A, and HTR2A cumulative genetic score interacts with mood reactivity to predict mood-congruent gaze bias. *Cognitive, Affective and Behavioral Neuroscience*, *14*, 1259–1270. https://doi.org/10.3758/s13415-014-0267-x

Dixon, M. J., MacLaren, V., Jarick, M., Fugelsang, J. A., & Harrigan, K. A. (2013). The Frustrating Effects of Just Missing the Jackpot: Slot Machine Near-Misses Trigger

Large Skin Conductance Responses, But No Post-reinforcement Pauses. *Journal of Gambling Studies*, *29*, 661–674. https://doi.org/10.1007/s10899-012-9333-x

Dixon, W. J. (1950). Analysis of Extreme Values. *The Annals of Mathematical Statistics*, *21*(4), 488–506. http://www.jstor.org/stable/2236602

Dixon, W. J. (1951). Ratios Involving Extreme Values. *The Annals of Mathematical Statistics*, *22*(1), 68–78. https://doi.org/10.1214/aoms/1177729693

Donnelly, C. L., McEvoy, J. P., Wilson, W. H., & Narasimhachari, N. (1996). A Study of the Potential Confounding Effects of Diet, Caffeine, Nicotine and Lorazepam on the Stability of Plasma and Urinary Homovanillic Acid Levels in Patients with Schizophrenia. *Biological Psychiatry*, *40*, 1218–1221. https://doi.org/10.1016/0006-3223(95)00650-8

Dunovan, K., Lynch, B., Molesworth, T., & Verstynen, T. (2015). Competing basal ganglia pathways determine the difference between stopping and deciding not to go. *ELife*, *4*, 1–24. https://doi.org/10.7554/eLife.08723

Dutilh, G., Vandekerckhove, J., Forstmann, B. U., Keuleers, E., Brysbaert, M., & Wagenmakers, E. J. (2012). Testing Theories of Post-error Slowing. *Attention, Perception, and Psychophysics*, *74*, 454–465. https://doi.org/10.3758/s13414-011-0243-2

Eben, C., Chen, Z., Billieux, J., & Verbruggen, F. (2022a). Outcome Sequences and Illusion of Control - Part I: An Online Replication of Langer & Roth (1975). *International Gambling Studies*, *00*(00), 1–12. https://doi.org/10.1080/14459795.2022.2133906

Eben, C., Chen, Z., Billieux, J., & Verbruggen, F. (2022b). Outcome Sequences and Illusion of Control – Part II: the Effect on Post-loss Speeding. *International Gambling Studies*, 1–20. https://doi.org/10.1080/14459795.2022.2135227

Eben, C., Chen, Z., Vermeylen, L., Billieux, J., & Verbruggen, F. (2020). A Direct and Conceptual Replication of Post-loss Speeding When Gambling. *Royal Society Open Science*, *7*(200090). https://doi.org/10.1098/rsos.200090

Elsworth, J. D., & Roth, R. H. (1997). Dopamine synthesis, uptake, metabolism, and receptors: Relevance to gene therapy of Parkinson's disease. *Experimental Neurology*, *144*(1), 4–9. https://doi.org/10.1006/exnr.1996.6379

Enge, S., Behnke, A., Fleischhauer, M., Küttler, L., Kliegel, M., & Strobel, A. (2014). No evidence for true training and transfer effects after inhibitory control training in young healthy adults. *Journal of Experimental Psychology: Learning Memory and Cognition*, *40*(4), 987–1001. https://doi.org/10.1037/a0036165

Enge, S., Sach, M., Reif, A., Lesch, K. P., Miller, R., & Fleischhauer, M. (2020). Cumulative Dopamine Genetic Score predicts behavioral and electrophysiological correlates of response inhibition via interactions with task demand. *Cognitive, Affective and Behavioral Neuroscience*, *20*, 59–75. https://doi.org/10.3758/s13415-019-00752-w

Enz, N., Schmidt, J., Nolan, K., Mitchell, M., Alvarez Gomez, S., Alkayyali, M., Cambay, P., Gippert, M., Whelan, R., & Ruddy, K. (2022). Self-regulation of the brain's right frontal Beta rhythm using a brain-computer interface. *Psychophysiology*. https://doi.org/10.1111/psyp.14115

Erdfelder, E., Faul, F., & Buchner, A. (1996). GPOWER: A general power analysis program. *Behavior Research Methods, Instruments, and Computers*, *28*, 1–11. https://doi.org/10.3758/BF03203630

Erga, A. H., Alves, G., Larsen, J. P., Tysnes, O. B., & Pedersen, K. F. (2017). Impulsive and Compulsive Behaviors in Parkinson's Disease: The Norwegian ParkWest Study. *Journal of Parkinson's Disease*, *7*, 183–191. https://doi.org/10.3233/JPD-160977

Erga, A. H., Dalen, I., Ushakova, A., Chung, J., Tzoulis, C., Tysnes, O. B., Alves, G., Pedersen, K. F., & Maple-Grødem, J. (2018). Dopaminergic and Opioid Pathways associated with impulse control Disorders in Parkinson's Disease. *Frontiers in Neurology*, *9*(109). https://doi.org/10.3389/fneur.2018.00109

Evans, R. W. (1998). Complications of lumbar puncture. *Neurologic Clinics*, *16*(1), 83–105. https://doi.org/10.1016/S0733-8619(05)70368-6

Faouzi, J., Couvy-Duchesne, B., Bekadar, S., Colliot, O., & Corvol, J. C. (2021). Exploratory analysis of the genetics of impulse control disorders in Parkinson's disease using genetic risk scores. *Parkinsonism and Related Disorders*, *86*, 74–77. https://doi.org/10.1016/j.parkreldis.2021.04.003

Farr, O. M., Hu, S., Zhang, S., & Li, C. shan R. (2012). Decreased saliency processing as a neural measure of Barratt impulsivity in healthy adults. *NeuroImage*, *63*, 1070–1077. https://doi.org/10.1016/j.neuroimage.2012.07.049

Feldman, S. (1932). Wundt's Psychology. *The American Journal of Psychology*, *44*(4), 615–629. https://doi.org/10.2307/1414528

Ferreira, D., Barthoulot, M., Pottecher, J., Torp, K. D., Diemunsch, P., & Meyer, N. (2020). Theory and practical use of Bayesian methods in interpreting clinical trial data: a narrative review. *British Journal of Anaesthesia*, *125*(2), 201–207. https://doi.org/10.1016/j.bja.2020.04.092

Figner, B., Mackinlay, R. J., Wilkening, F., & Weber, E. U. (2009). Affective and Deliberative Processes in Risky Choice: Age Differences in Risk Taking in the Columbia Card Task. *Journal of Experimental Psychology: Learning Memory and Cognition*, *35*(3), 709–730. https://doi.org/10.1037/a0014983

Filip, P., Linhartová, P., Hlavatá, P., Šumec, R., Baláž, M., Bareš, M., & Kašpárek, T. (2018). Disruption of multiple distinctive neural networks associated with impulse

control disorder in Parkinson's disease. *Frontiers in Human Neuroscience*, *12*(462), 1–13. https://doi.org/10.3389/fnhum.2018.00462

Ford, C. P. (2014). The Role of D2-Autoreceptors in Regulating Dopamine Neuron Activity and Transmission. *Neuroscience*, *282*, 13–22. https://doi.org/10.1016/j.neuroscience.2014.01.025.The

Fornacon-Wood, I., Mistry, H., Johnson-Hart, C., Faivre-Finn, C., O'Connor, J. P. B., & Price, G. J. (2022). Understanding the Differences Between Bayesian and Frequentist Statistics. *International Journal of Radiation Oncology Biology Physics*, *112*(5), 1076–1082. https://doi.org/10.1016/j.ijrobp.2021.12.011

Foster, G. C., Lane, D., Scott, D., Hebl, M., Guerra, R., Osherson, D., & Zimmer, H. (2018). *An Introduction to Psychological Statistics*. https://irl.umsl.edu/oer/4

Frijda, N. H. (2010). Impulsive Action and Motivation. *Biological Psychology*, *84*, 570–579. https://doi.org/10.1016/j.biopsycho.2010.01.005

Fukunaga, R., Brown, J. W., & Bogg, T. (2012). Decision making in the Balloon Analogue Risk Task (BART): Anterior cingulate cortex signals loss aversion but not the infrequency of risky choices. *Cognitive, Affective and Behavioral Neuroscience*, *12*, 479–490. https://doi.org/10.3758/s13415-012-0102-1

Galván, A., Schonberg, T., Mumford, J., Kohno, M., Poldrack, R. A., & London, E. D. (2013). Greater risk sensitivity of dorsolateral prefrontal cortex in young smokers than in nonsmokers. *Psychopharmacology*, *229*, 345–355. https://doi.org/10.1007/s00213-013-3113-x

Gasser, T., Wichmann, T., & DeLong, M. R. (2015). Parkinson Disease and Other Synucleinopathies. In *Neurobiology of Brain Disorders: Biological Basis of Neurological and Psychiatric Disorders* (pp. 281–302). https://doi.org/10.1016/B978-0-12-398270-4.00019-7

Gatto, E. M., & Aldinio, V. (2019). Impulse Control Disorders in Parkinson's Disease. A Brief and Comprehensive Review. *Frontiers in Neurology*, *10*(351). https://doi.org/10.3389/fneur.2019.00351

Gauggel, S., Rieger, M., & Feghoff, T. A. (2004). Inhibition of ongoing responses in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *75*, 539–544. https://doi.org/10.1136/jnnp.2003.016469

Gentili, C., Vanello, N., Podina, I., Popita, R., Voinescu, B., Pietrini, P., & David, D. (2020). You do not have to act to be impulsive: Brain resting-state activity predicts performance and impulsivity on the Balloon Analogue Risk Task. *Behavioural Brain Research*, *379*. https://doi.org/10.1016/j.bbr.2019.112395

Giladi, N., Weitzman, N., Schreiber, S., Shabtai, H., & Peretz, C. (2007). New onset heightened interest or drive for gambling, shopping, eating or sexual activity in patients with Parkinson's disease: The role of dopamine agonist treatment and age at motor symptoms onset. *Journal of Psychopharmacology*, *21*(5), 501–506. https://doi.org/10.1177/0269881106073109

Gilbert, D. L., Huddleston, D. A., Wu, S. W., Pedapati, E. V., Horn, P. S., Hirabayashi, K., Crocetti, D., Wassermann, E. M., & Mostofsky, S. H. (2019). Motor cortex inhibition and modulation in children with ADHD. *Neurology*, *93*, E599–E610. https://doi.org/10.1212/WNL.0000000000007899

Gill, D. J., Freshman, A., Blender, J. A., & Ravina, B. (2008). The Montreal Cognitive Assessment as a Screening tool for Cognitive Impairment in Parkinson's Disease. *Movement Disorders*, *23*(7), 1043–1046. https://doi.org/10.1002/mds.22017

Goerlich-Dobre, K. S., Probst, C., Winter, L., Witt, K., Deuschl, G., Möller, B., & Van Eimeren, T. (2014). Alexithymia-an independent risk factor for impulsive-

compulsive disorders in Parkinson's disease. *Movement Disorders*, *29*(2), 214–220. https://doi.org/10.1002/mds.25679

Goetz, C. G., Poewe, W., Rascol, O., Sampaio, C., & Stebbins, G. T. (2003). The Unified Parkinson's Disease Rating Scale (UPDRS): Status and recommendations. *Movement Disorders*, *18*(7), 738–750. https://doi.org/10.1002/mds.10473

Gong, Y., Yan, J., Deng, Y., Bao, C., Yi, Q., Liu, J., & Zhang, Z. (2022). Examining impulsivity and risky decision making among school youth in balloon analogue risk task. *Translational Pediatrics*, *11*(1), 127–137. https://doi.org/10.21037/tp-21-594

Goto, Y., & Grace, A. A. (2005). Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. *Nature Neuroscience*, *8*(6), 805–812. https://doi.org/10.1038/nn1471

Graf, I., Willeit, M., Kasper, S., & Praschak-Rieder, N. (2020). The Impact of Genetic Polymorphisms on Neuroreceptor Binding: Results from PET and SPECT Neuroreceptor Imaging Studies BT - PET and SPECT of Neurobiological Systems. In R. A. J. O. Dierckx, A. Otte, E. F. J. de Vries, A. van Waarde, & A. A. Lammertsma (Eds.), *PET and SPECT of Neurobiological Systems* (pp. 153–190). Springer International Publishing. https://doi.org/10.1007/978-3-030-53176-8_6

Greenhouse, I., & Wessel, J. R. (2013). EEG signatures associated with stopping are sensitive to preparation. *Psychophysiology*, *50*, 900–908. https://doi.org/10.1111/psyp.12070

Greffard, S., Verny, M., Bonnet, A.-M., Beinis, J.-Y., Gallinari, C., Meaume, S., Piette, F., Hauw, J.-J., & Duyckaerts, C. (2006). Motor Score of the Unified Parkinson Disease Rating Scale as a Good Predictor of Lewy Body-Associated Neuronal Loss in the Substantia Nigra. *Arch Neurol*, *63*(584–588). http://www.u106.eu.org/~charles/tel.htm

Gualtieri, C. T., & Johnson, L. G. (2006). Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. *Archives of Clinical Neuropsychology*, *21*, 623–643. https://doi.org/10.1016/j.acn.2006.05.007

Haber, S. N. (2014). The place of dopamine in the cortico-basal ganglia circuit. In *Neuroscience* (Vol. 282, pp. 248–257). Elsevier Ltd. https://doi.org/10.1016/j.neuroscience.2014.10.008

Haber, S. N., Adler, A., & Bergman, H. (2012). The Basal Ganglia. In *The Human Nervous System* (pp. 678–738). Academic Press. https://doi.org/10.1016/B978-0-12-374236-0.10020-3

Haber, S. N., Fudge, J. L., & McFarland, N. R. (2000). Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *Journal of Neuroscience*, *20*(6), 2369–2382. https://doi.org/10.1523/jneurosci.20-06-02369.2000

Habib, R., & Dixon, M. R. (2010). Neurobehavioral Evidence for the "Near-Miss" Effect in Pathological Gamblers. *Journal of the Experimental Analysis of Behavior*, *93*(3), 313–328. https://doi.org/10.1901/jeab.2010.93-313

Hackenberger, B. K. (2019). Bayes or not bayes, is this the question? *Croatian Medical Journal*, *60*(1), 50–52. https://doi.org/10.3325/cmj.2019.60.50

Hailpern, S. M., & Visintainer, P. F. (2003). Odds Ratios and Logistic Regression: Further Examples of their use and Interpretation. *The Stata Journal: Promoting Communications on Statistics and Stata*, *3*(3), 213–225. https://doi.org/10.1177/1536867x0300300301

Hall, A., Jenkinson, N., & MacDonald, H. J. (2022). Exploring stop signal reaction time over two sessions of the anticipatory response inhibition task. *Experimental Brain Research*, *240*(11), 3061–3072. https://doi.org/10.1007/s00221-022-06480-x

Hall, A., Weaver, S. R., Compton, L. J., Byblow, W. D., Jenkinson, N., & MacDonald, H. J. (2021). Dopamine genetic risk score predicts impulse control behaviors in Parkinson's disease. *Clinical Parkinsonism & Related Disorders*, *5*, 100113. https://doi.org/10.1016/j.prdoa.2021.100113

Hall, A., Weightman, M., Jenkinson, N., & MacDonald, H. J. (2023). Performance on the Balloon Analogue Risk Task and Anticipatory Response Inhibition Task is Associated with Severity of Impulse Control Behaviours in People with Parkinson's Disease. *Experimental Brain Research*. https://doi.org/10.1007/s00221-023-06584-y

Halliday, G. M., & McCann, H. (2010). The progression of pathology in Parkinson's disease. In *Annals of the New York Academy of Sciences* (Vol. 1184, pp. 188–195). https://doi.org/10.1111/j.1749-6632.2009.05118.x

Hanakawa, T. (2011). Rostral premotor cortex as a gateway between motor and cognitive networks. In *Neuroscience Research* (Vol. 70, Issue 2, pp. 144–154). https://doi.org/10.1016/j.neures.2011.02.010

Harrell, F. E. (2015). Regression Modeling Strategies. In *Springer*. https://doi.org/10.1198/tech.2003.s158

Harrell, F. E., Lee, Kerry, L., Malchar, D., & Roichorl, T. A. (1985). Regression Models for Prognostic Prediction: Advantages, Problems, and Suggested Solutions. *Cancer Treatment Reports*, *69*(10), 1071–1077.

Harris, A., & Griffiths, M. D. (2018). The Impact of Speed of Play in Gambling on Psychological and Behavioural Factors: A Critical Review. *Journal of Gambling Studies*, *34*, 393–412. https://doi.org/10.1007/s10899-017-9701-7

Hayes, A. F., & Montoya, A. K. (2017). A Tutorial on Testing, Visualizing, and Probing an Interaction Involving a Multicategorical Variable in Linear Regression Analysis.

Communication Methods and Measures, *11*, 1–30. https://doi.org/10.1080/19312458.2016.1271116

He, J. L., Fuelscher, I., Coxon, J., Chowdhury, N., Teo, W. P., Barhoun, P., Enticott, P., & Hyde, C. (2019). Individual differences in intracortical inhibition predict motor-inhibitory performance. *Experimental Brain Research*, *237*, 2715–2727. https://doi.org/10.1007/s00221-019-05622-y

He, J. L., Hirst, R. J., Puri, R., Coxon, J., Byblow, W., Hinder, M., Skippen, P., Matzke, D., Heathcote, A., Wadsley, C. G., Silk, T., Hyde, C., Parmar, D., Pedapati, E., Gilbert, D. L., Huddleston, D. A., Mostofsky, S., Leunissen, I., MacDonald, H. J., … Puts, N. A. J. (2022). OSARI, an Open-Source Anticipated Response Inhibition Task. *Behavior Research Methods*, *54*, 1530–1540. https://doi.org/10.3758/s13428-021-01680-9

Heim, B., Krismer, F., De Marzi, R., & Seppi, K. (2017). Magnetic resonance imaging for the diagnosis of Parkinson's disease. In *Journal of Neural Transmission* (Vol. 124, pp. 915–964). Springer-Verlag Wien. https://doi.org/10.1007/s00702-017-1717-8

Hendriksen, J. M. T., Geersing, G. J., Moons, K. G. M., & de Groot, J. A. H. (2013). Diagnostic and prognostic prediction models. *Journal of Thrombosis and Haemostasis*, *11*(SUPPL.1), 129–141. https://doi.org/10.1111/jth.12262

Hlavatá, P., Linhartová, P., Šumec, R., Filip, P., Světlák, M., Baláž, M., Kašpárek, T., & Bareš, M. (2020). Behavioral and Neuroanatomical Account of Impulsivity in Parkinson's Disease. *Frontiers in Neurology*, *10*. https://doi.org/10.3389/fneur.2019.01338

Hollander, E., Baker, B. R., Kahn, J., & Stein, D. J. (2006). Conceptualizing and Assessing Impulse-Control Disorders. In *Clinical manual of impulse-control disorders.* (pp. 1–18). American Psychiatric Publishing, Inc.

Hollander, E., & Evers, M. (2001). New developments in impulsivity. *The Lancet*, *358*, 949–950.

Holmes, K. M., Bearden, C. E., Barguil, M., Fonseca, M., Monkul, S. E., Nery, F. G., Soares, J. C., Mintz, J., & Glahn, D. C. (2009). Conceptualizing impulsivity and risk taking in bipolar disorder: Importance of history of alcohol abuse. *Bipolar Disorders*, *11*, 33–40. https://doi.org/10.1111/j.1399-5618.2009.00720.x

Housden, C. R., O'Sullivan, S. S., Joyce, E. M., Lees, A. J., & Roiser, J. P. (2010). Intact reward learning but elevated delay discounting in Parkinson's disease patients with impulsive-compulsive spectrum behaviors. *Neuropsychopharmacology*, *35*, 2155–2164. https://doi.org/10.1038/npp.2010.84

Hovde, M. J., Larson, G. H., Vaughan, R. A., & Foster, J. D. (2019). Model systems for analysis of dopamine transporter function and regulation. *Neurochemistry International*, *123*, 13–21. https://doi.org/10.1016/j.neuint.2018.08.015

Hughes, M. E., Fulham, W. R., Johnston, P. J., & Michie, P. T. (2012). Stop-signal response inhibition in schizophrenia: Behavioural, event-related potential and functional neuroimaging data. *Biological Psychology*, *89*, 220–231. https://doi.org/https://doi.org/10.1016/j.biopsycho.2011.10.013

Humphreys, K. L., & Lee, S. S. (2011). Risk Taking and Sensitivity to Punishment in Children with ADHD, ODD, ADHD+ODD, and Controls. *Journal of Psychopathology and Behavioral Assessment*, *33*, 299–307. https://doi.org/10.1007/s10862-011-9237-6

Igo Jr., R. P., Kinzy, T. G., & Cooke Bailey, J. N. (2019). Genetic Risk Scores. *Current Protocols in Human Genetics*, *104*(1), 1–20. https://doi.org/10.1002/cphg.95.Genetic

Ihle, J., Artaud, F., Bekadar, S., Mangone, G., Sambin, S., Mariani, L. L., Bertrand, H., Rascol, O., Durif, F., Derkinderen, P., Scherzer, C., Elbaz, A., Corvol, J. C., Corvol, J. C., Elbaz, A., Vidailhet, M., Brice, A., Artaud, F., Bourdain, F., … Faurie-Grepon, A. (2020). Parkinson's disease polygenic risk score is not associated with impulse control disorders: A longitudinal study. *Parkinsonism and Related Disorders*, *75*, 30–33. https://doi.org/10.1016/j.parkreldis.2020.03.017

Irwin, J. R. (1947). Galen on the temperaments. *Journal of General Psychology*, *36*(1), 45–64. https://doi.org/10.1080/00221309.1947.9918106

Isaias, I. U., Siri, C., Cilia, R., de Gaspari, D., Pezzoli, G., & Antonini, A. (2008). The relationship between impulsivity and impulse control disorders in Parkinson's disease. *Movement Disorders*, *23*(3), 411–415. https://doi.org/10.1002/mds.21872

Jahanshahi, M., Jenkins, H., Brown, R. G., Marsden, C. D., Passingham, R. E., & Brooks, D. J. (1995). Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. *Brain*, *118*, 913–933. https://doi.org/10.1093/brain/119.3.1045

Jahfari, S., Waldorp, L., van den Wildenberg, W. P. M., Scholte, H. S., Ridderinkhof, K. R., & Forstmann, B. U. (2011). Effective connectivity reveals important roles for both the hyperdirect (fronto-subthalamic) and the indirect (fronto-striatal-pallidal) fronto-basal ganglia pathways during response inhibition. *Journal of Neuroscience*, *31*(18), 6891–6899. https://doi.org/10.1523/JNEUROSCI.5253-10.2011

Jan, S. L., & Shieh, G. (2019). Sample size calculations for model validation in linear regression analysis. *BMC Medical Research Methodology*, *19*(54), 1–9. https://doi.org/10.1186/s12874-019-0697-9

Jana, S., Hannah, R., Muralidharan, V., & Aron, A. R. (2020). Temporal Cascade of Frontal, Motor and Muscle Processes Underlying Human Action-Stopping. *ELife*, *9*, 1–28. https://doi.org/10.7554/eLife.50371

Jankovic, J. (2008). Parkinson's disease: Clinical features and diagnosis. In *Journal of Neurology, Neurosurgery and Psychiatry* (Vol. 79, Issue 4, pp. 368–376). BMJ Publishing Group. https://doi.org/10.1136/jnnp.2007.131045

Joutsa, J., Martikainen, K., Vahlberg, T., & Kaasinen, V. (2012). Effects of dopamine agonist dose and gender on the prognosis of impulse control disorders in Parkinson's disease. *Parkinsonism and Related Disorders*, *18*(10), 1079–1083. https://doi.org/10.1016/j.parkreldis.2012.06.005

Julayanont, P., Brousseau, M., Chertkow, H., Phillips, N., & Nasreddine, Z. S. (2014). Montreal Cognitive Assessment Memory Index Score (MoCA-MIS) as a Predictor of Conversion from Mild Cognitive Impairment to Alzheimer's Disease. *Journal of the American Geriatrics Society*, *62*, 679–684. https://doi.org/10.1111/jgs.12742

Kelly, M. J., Baig, F., Hu, M. T. M., & Okai, D. (2020). Spectrum of impulse control behaviours in Parkinson's disease: Pathophysiology and management. In *Journal of Neurology, Neurosurgery and Psychiatry* (Vol. 91, pp. 703–711). BMJ Publishing Group. https://doi.org/10.1136/jnnp-2019-322453

Kendler, K. S., Mohs, R. C., & Davis, K. L. (1983). The effects of diet and physical activity on plasma homovanillic acid in normal human subjects. *Psychiatry Research*, *8*(3), 215–223. https://doi.org/10.1016/0165-1781(83)90065-3

Kim, W. S., Kagedal, K., & Halliday, G. M. (2014). Alpha-synuclein biology in Lewy body diseases. In *Alzheimer's Research and Therapy* (Vol. 6, Issue 73, pp. 1–9). BioMed Central Ltd. https://doi.org/10.1186/s13195-014-0073-2

Kish, S. J., Shannak, K., & Hornykiewicz, O. (1988). *Uneven Pattern of Dopamine Loss in the Striatum of Patients with Idiopathic Parkinson's Disease* (pp. 876–880).

Ko, J. H., Antonelli, F., Monchi, O., Ray, N., Rusjan, P., Houle, S., Lang, A. E., Christopher, L., & Strafella, A. P. (2013). Prefrontal Dopaminergic Receptor Abnormalities and Executive Functions in Parkinson's Disease. *Human Brain Mapping*, *34*, 1591–1604. https://doi.org/10.1002/hbm.22006

Ko, Y. T., & Miller, J. (2011). Nonselective motor-level changes associated with selective response inhibition: Evidence from response force measurements. *Psychonomic Bulletin and Review*, *18*, 813–819. https://doi.org/10.3758/s13423-011-0090-0

Kraemmer, J., Smith, K., Weintraub, D., Guillemot, V., Nalls, M. A., Cormier-Dequaire, F., Moszer, I., Brice, A., Singleton, A. B., & Corvol, J. C. (2016). Clinical-genetic model predicts incident impulse control disorders in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *87*(10), 1106–1111. https://doi.org/10.1136/jnnp-2015-312848

Krieger, D. M., Cardoso, S. V., Caumo, W., Valença, G., Weintraub, D., & Rieder, C. R. de M. (2017). Parkinson's Disease Impulsive-Compulsive Disorders Questionnaire - Current Short (QUIP-CS) - Translation and validation of content of Portuguese Version. *Jornal Brasileiro de Psiquiatria*, *66*, 111–115. https://doi.org/10.1590/0047-2085000000158

Laatikainen, L. M., Sharp, T., Harrison, P. J., & Tunbridge, E. M. (2013). Sexually Dimorphic Effects of Catechol-O-Methyltransferase (COMT) Inhibition on

Dopamine Metabolism in Multiple Brain Regions. *PLoS ONE*, *8*(4). https://doi.org/10.1371/journal.pone.0061839

Lam, B., Middleton, L. E., Masellis, M., Stuss, D. T., Harry, R. D., Kiss, A., & Black, S. E. (2013). Criterion and Convergent Validity of the Montreal Cognitive Assessment with Screening and Standardized Neuropsychological Testing. *Journal of the American Geriatrics Society*, *61*, 2181–2185. https://doi.org/10.1111/jgs.12541

Lanciego, J. L., Luquin, N., & Obeso, J. A. (2012). Functional Neuroanatomy of the Basal Ganglia. *Cold Spring Harbor Perspectives in Medicine*, *2*. https://doi.org/10.1101/cshperspect.a009621

Lappin, J. S., & Eriksen, C. W. (1966). Use of a delayed signal to stop a visual reaction-time response. *Journal of Experimental Psychology*, *72*, 805–811. https://doi.org/10.1037/h0021266

Lauriola, M., Panno, A., Levin, I. P., & Lejuez, C. W. (2014). Individual Differences in Risky Decision Making: A Meta-analysis of Sensation Seeking and Impulsivity with the Balloon Analogue Risk Task. *Journal of Behavioral Decision Making*, *27*(1), 20–36. https://doi.org/10.1002/bdm.1784

Lee, J. Y., Kim, J. M., Kim, J. W., Cho, J., Lee, W. Y., Kim, H. J., & Jeon, B. S. (2010). Association between the dose of dopaminergic medication and the behavioral disturbances in Parkinson disease. *Parkinsonism and Related Disorders*, *16*(3), 202–207. https://doi.org/10.1016/j.parkreldis.2009.12.002

Lee, J. Y., Lee, E. K., Park, S. S., Lim, J. Y., Kim, H. J., Kim, J. S., & Jeon, B. S. (2009). Association of DRD3 and GRIN2B with Impulse Control and Related Behaviors in Parkinson's Disease. *Movement Disorders*, *24*(12), 1803–1810. https://doi.org/10.1002/mds.22678

Leeman, R. F., & Potenza, M. N. (2011). Impulse control disorders in Parkinson's disease: Clinical characteristics and implications. In *Neuropsychiatry* (Vol. 1, Issue 2, pp. 133–147). https://doi.org/10.2217/npy.11.11

Lejuez, C. W., Richards, J. B., Read, J. P., Kahler, C. W., Ramsey, S. E., Stuart, G. L., Strong, D. R., & Brown, R. A. (2002). Evaluation of a Behavioral Measure of Risk Taking: The Balloon Analogue Risk Task (BART). *Journal of Experimental Psychology: Applied*, *8*(2), 75–84. https://doi.org/10.1037/1076-898X.8.2.75

Leotti, L. A., & Wager, T. D. (2010). Motivational Influences on Response Inhibition Measures. *Journal of Experimental Psychology: Human Perception and Performance*, *36*(2), 430–447. https://doi.org/10.1037/a0016802

Lepack, A. E., Werner, C. T., Stewart, A. F., Fulton, S. L., Zhong, P., Farrelly, L. A., Smith, A. C. W., Ramakrishnan, A., Lyu, Y., Bastle, R. M., Martin, J. A., Mitra, S., O'Connor, R. M., Wang, Z. J., Molina, H., Turecki, G., Shen, L., Yan, Z., Calipari, E. S., … Maze, I. (2020). Dopaminylation of histone H3 in ventral tegmental area regulates cocaine seeking. *Science*, *368*(6487), 197–201. https://doi.org/10.1126/science.aaw8806

Leshem, R., & Glicksohn, J. (2007). The construct of impulsivity revisited. *Personality and Individual Differences*, *43*, 681–691. https://doi.org/10.1016/j.paid.2007.01.015

Leunissen, I., Zandbelt, B. B., Potocanac, Z., Swinnen, S. P., & Coxon, J. P. (2017). Reliable estimation of inhibitory efficiency: to anticipate, choose or simply react? *European Journal of Neuroscience*, *45*, 1512–1523. https://doi.org/10.1111/ejn.13590

Lewis, A. C. F., Green, R. C., & Vassy, J. L. (2021). Polygenic risk scores in the clinic: Translating risk into action. *Human Genetics and Genomics Advances*, 104743. https://doi.org/10.1016/j.xhgg.2021.100047

Lewis, M. H., Bodfish, J. W., Powell, S. B., Wiest, K., Darling, M., & Golden, R. N. (1996). Plasma HVA in adults with mental retardation and stereotyped behavior: biochemical evidence for a dopamine deficiency model. *American Journal of Mental Retardation : AJMR*, *100*(4), 413–418.

Li, X., Pan, Y., Fang, Z., Lei, H., Zhang, X., Shi, H., Ma, N., Raine, P., Wetherill, R., Kim, J. J., Wan, Y., & Rao, H. (2020). Test-retest reliability of brain responses to risk-taking during the balloon analogue risk task. *NeuroImage*, *209*. https://doi.org/10.1016/j.neuroimage.2019.116495

Lipszyc, J., & Schachar, R. (2010). Inhibitory control and psychopathology: A meta-analysis of studies using the stop signal task. *Journal of the International Neuropsychological Society*, *16*, 1064–1076. https://doi.org/10.1017/S1355617710000895

Logan, G. D., & Cowan, W. B. (1984). On the Ability to Inhibit Thought and Action: A Theory of an Act of Control. *Psychological Review*, *91*(3), 295–327. https://doi.org/10.1037/a0035230

Lotharius, J., & Brundin, P. (2002). Pathogenesis of Parkinson's Disease: Dopamine, Vesicles and α-Synuclein. *Nature Reviews Neuroscience*, *3*, 932–942. https://doi.org/10.1038/nrn983

Luo, S. X., & Huang, E. J. (2016). Dopaminergic neurons and brain reward pathways: From neurogenesis to circuit assembly. In *American Journal of Pathology* (Vol. 186, Issue 3, pp. 478–488). Elsevier Inc. https://doi.org/10.1016/j.ajpath.2015.09.023

Luppino, G., Rozzi, S., Calzavara, R., & Matelli, M. (2003). Prefrontal and agranular cingulate projections to the dorsal premotor areas F2 and F7 in the macaque monkey. *European Journal of Neuroscience*, *17*(3), 559–578. https://doi.org/10.1046/j.1460-9568.2003.02476.x

MacDonald, H. J., Coxon, J. P., Stinear, C. M., & Byblow, W. D. (2014). The fall and rise of corticomotor excitability with cancellation and reinitiation of prepared action. *Journal of Neurophysiology*, *112*, 2707–2717. https://doi.org/10.1152/jn.00366.2014

MacDonald, H. J., Laksanaphuk, C., Day, A., Byblow, W. D., & Jenkinson, N. (2021). The role of interhemispheric communication during complete and partial cancellation of bimanual responses. *Journal of Neurophysiology*, *125*, 875–886. https://doi.org/10.1152/jn.00688.2020

MacDonald, H. J., Stinear, C. M., & Byblow, W. D. (2012). Uncoupling response inhibition. *Journal of Neurophysiology*, *108*, 1492–1500. https://doi.org/10.1152/jn.01184.2011

MacDonald, H. J., Stinear, C. M., Ren, A., Coxon, J. P., Kao, J., Macdonald, L., Snow, B., Cramer, S. C., & Byblow, W. D. (2016). Dopamine Gene Profiling to Predict Impulse Control and Effects of Dopamine Agonist Ropinirole. *Journal of Cognitive Neuroscience*, *28*(7), 909–919. https://doi.org/10.1162/jocn

Maizey, L., Evans, C. J., Muhlert, N., Verbruggen, F., Chambers, C. D., & Allen, C. P. G. (2020). Cortical and subcortical functional specificity associated with response inhibition. *NeuroImage*, *220*, 117110. https://doi.org/10.1016/j.neuroimage.2020.117110

Manes, F., Sahakian, B., Clark, L., Rogers, R., Antoun, N., Aitken, M., & Robbins, T. (2002). Decision-making processes following damage to the prefrontal cortex. *Brain*, *125*(3), 624–639. https://doi.org/10.1093/brain/awf049

Mann, L. G., Hay, K. R., Song, A. K., Errington, S. P., Trujillo, P., Zald, D. H., Yan, Y., Kang, H., Logan, G. D., & Claassen, D. O. (2021). D2-Like Receptor Expression in the Hippocampus and Amygdala Informs Performance on the Stop-Signal Task in

Parkinson's Disease. *Journal of Neuroscience*, *41*(48), 10023–10030. https://doi.org/10.1523/JNEUROSCI.0968-21.2021

Marín-Lahoz, J., Pagonabarraga, J., Martinez-Horta, S., Fernandez de Bobadilla, R., Pascual-Sedano, B., Pérez-Pérez, J., Gironell, A., & Kulisevsky, J. (2018). Parkinson's Disease: Impulsivity Does Not Cause Impulse Control Disorders but Boosts Their Severity. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00465

Marković, V., Stanković, I., Petrović, I., Stojković, T., Dragašević-Mišković, N., Radovanović, S., Svetel, M., Stefanova, E., & Kostić, V. (2020). Dynamics of impulsive–compulsive behaviors in early Parkinson's disease: a prospective study. *Journal of Neurology*, *267*, 1127–1136. https://doi.org/10.1007/s00415-019-09692-4

Marques, A., Vidal, T., Pereira, B., Benchetrit, E., Socha, J., Pineau, F., Elbaz, A., Artaud, F., Mangone, G., You, H., Cormier, F., Galitstky, M., Pomies, E., Rascol, O., Derkinderen, P., Weintraub, D., Corvol, J. C., & Durif, F. (2019). French validation of the questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS). *Parkinsonism and Related Disorders*, *63*, 117–123. https://doi.org/10.1016/j.parkreldis.2019.02.026

Martinez-Martin, P., Rodriguez-Blazquez, C., & Catalan, M. J. (2018). Independent and Complementary Validation of the QUIP-RS in Advanced Parkinson's Disease. *Movement Disorders Clinical Practice*, *5*(3), 341–342. https://doi.org/10.1002/mdc3.12603

Martini, A., Ellis, S. J., Grange, J. A., Tamburin, S., Dal Lago, D., Vianello, G., & Edelstyn, N. M. J. (2018). Risky decision-making and affective features of impulse

control disorders in Parkinson's disease. *Journal of Neural Transmission*, *125*(2), 131–143. https://doi.org/10.1007/s00702-017-1807-7

Mata, R., Hau, R., Papassotiropoulos, A., & Hertwig, R. (2012). DAT1 Polymorphism is Associated with Risk Taking in the Balloon Analogue Risk Task (BART). *PLoS ONE*, *7*(6), e39135. https://doi.org/10.1371/journal.pone.0039135

McClain, M. B., Hasty Mills, A. M., & Murphy, L. E. (2017). Inattention and hyperactivity/impulsivity among children with attention-deficit/hyperactivity-disorder, autism spectrum disorder, and intellectual disability. *Research in Developmental Disabilities*, *70*, 175–184. https://doi.org/10.1016/j.ridd.2017.09.009

McLaughlin, N. C. R., Kirschner, J., Foster, H., O'Connell, C., Rasmussen, S. A., & Greenberg, B. D. (2016). Stop Signal Reaction Time Deficits in a Lifetime Obsessive-Compulsive Disorder Sample. *Journal of the International Neuropsychological Society*, *22*(7), 785–789. https://doi.org/10.1017/S1355617716000540

Meder, D., Herz, D. M., Rowe, J. B., Lehéricy, S., & Siebner, H. R. (2019). The role of dopamine in the brain - lessons learned from Parkinson's disease. In *NeuroImage* (Vol. 190, pp. 79–93). Academic Press Inc. https://doi.org/10.1016/j.neuroimage.2018.11.021

Meiser, J., Weindl, D., & Hiller, K. (2013). Complexity of dopamine metabolism. *Cell Communication and Signaling*, *11*(1), 1–18. https://doi.org/10.1186/1478-811X-11-34

Milardi, D., Quartarone, A., Bramanti, A., Anastasi, G., Bertino, S., Basile, G. A., Buonasera, P., Pilone, G., Celeste, G., Rizzo, G., Bruschetta, D., & Cacciola, A. (2019). The Cortico-Basal Ganglia-Cerebellar Network: Past, Present and Future

Perspectives. *Frontiers in Systems Neuroscience*, *13*(61). https://doi.org/10.3389/fnsys.2019.00061

Missale, C., Nash, S. R., Robinson, S. W., Jaber, M., & Caron, M. G. (1998). Dopamine Receptors: From Structure to Function. In *PHYSIOLOGICAL REVIEWS* (Vol. 78, Issue 1). www.physiology.org/journal/physrev

Miura, I., Kanno-Nozaki, K., Hino, M., Horikoshi, S., Ota, T., Mashiko, H., Niwa, S.-I., & Yabe, H. (2015). Influence of −141C Ins/Del Polymorphism in DRD2 Gene on Clinical Symptoms and Plasma Homovanillic Acid Levels in the Treatment of Schizophrenia With Aripiprazole. *Journal of Clinical Psychopharmacology*, *35*(3), 333–334.

Moeller, F. G., Barratt, E. S., Dougherty, D. M., Schmitz, J. M., & Swann, A. C. (2001). Psychiatric aspects of impulsivity. In *American Journal of Psychiatry* (Vol. 158, Issue 11, pp. 1783–1793). https://doi.org/10.1176/appi.ajp.158.11.1783

Morimoto, K., Miyatake, R., Nakamura, M., Watanabe, T., Hirao, T., & Suwaki, H. (2002). Delusional Disorder: Molecular Genetic Evidence for Dopamine Psychosis. *Neuropsychopharmacology*, *26*(6), 794–801. https://doi.org/10.1016/S0893-133X(01)00421-3

Nakano, K., Kayahara, T., Tsutsumi, T., & Ushiro, H. (2000). Neural circuits and functional organization of the striatum. *Journal of Neurology*, *247*(5), 1–15.

Nambu, A., Tokuno, H., & Takada, M. (2002). Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. *Neuroscience Research*, *43*, 111–117. https://doi.org/10.1016/S0168-0102(02)00027-5

Nazem, S., Siderowf, A. D., Duda, J. E., ten Have, T., Colcher, A., Horn, S. S., Moberg, P. J., Wilkinson, J. R., Hurtig, H. I., Stern, M. B., & Weintraub, D. (2009). Montreal Cognitive Assessment Performance in Patients with Parkinson's Disease with

"Normal" Global Cognition According to Mini-Mental State Examination Score. *American Geriatric Society*, *57*(2), 304–308. https://doi.org/10.1111/j.1532-5415.2008.02096.x.Montreal

Nemoda, Z., Szekely, A., & Sasvari-Szekely, M. (2011). Psychopathological Aspects of Dopaminergic Gene Polymorphisms in Adolescence and Young Adulthood. *Neuroscience and Biobehavioral Reviews*, *35*(8), 1665–1686. https://doi.org/10.1016/j.neubiorev.2011.04.002

Nikolova, Y. S., Ferrell, R. E., Manuck, S. B., & Hariri, A. R. (2011). Multilocus Genetic Profile for Dopamine Signaling Predicts Ventral Striatum Reactivity. *Neuropsychopharmacology*, *36*, 1940–1947. https://doi.org/10.1038/npp.2011.82

Nombela, C., Rittman, T., Robbins, T. W., & Rowe, J. B. (2014). Multiple Modes of Impulsivity in Parkinson's Disease. *PLoS ONE*, *9*(1), 18–21. https://doi.org/10.1371/journal.pone.0085747

Nonnekes, J., Timmer, M. H. M., de Vries, N. M., Rascol, O., Helmich, R. C., & Bloem, B. R. (2016). Unmasking Levodopa Resistance in Parkinson's Disease. In *Movement Disorders* (Vol. 31, Issue 11, pp. 1602–1609). John Wiley and Sons Inc. https://doi.org/10.1002/mds.26712

Obeso, I., Wilkinson, L., Casabona, E., Bringas, M. L., Álvarez, M., Álvarez, L., Pavón, N., Rodríguez-Oroz, M. C., Macías, R., Obeso, J. A., & Jahanshahi, M. (2011). Deficits in inhibitory control and conflict resolution on cognitive and motor tasks in Parkinson's disease. *Experimental Brain Research*, *212*, 371–384. https://doi.org/10.1007/s00221-011-2736-6

Palma, J.-A., & Kaufmann, H. (2014). Autonomic disorders predicting Parkinson's disease. *Parkinsonism & Related Disorders*, *20S1*, 94–98.

Papay, K., Mamikonyan, E., Siderowf, A. D., Duda, J. E., Lyons, K. E., Pahwa, R., Driver-Dunckley, E. D., Adler, C. H., & Weintraub, D. (2011). Patient versus informant reporting of ICD symptoms in Parkinson's disease using the QUIP: Validity and variability. *Parkinsonism and Related Disorders*, *17*, 153–155. https://doi.org/10.1016/j.parkreldis.2010.11.015

Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology*, *51*(6), 768–774. https://doi.org/10.1002/1097-4679(199511)51:6<768::aid-jclp2270510607>3.0.co;2-1

Pearson, R., McGeary, J. E., & Beevers, C. G. (2014). Association between serotonin cumulative genetic score and the Behavioral Approach System (BAS): Moderation by early life environment. *Pers Individ Dif*, *70*, 140–144. https://doi.org/10.1016/j.paid.2014.06.041.Association

Pearson-Fuhrhop, K. M., Dunn, E. C., Mortero, S., Devan, W. J., Falcone, G. J., Lee, P., Holmes, A. J., Hollinshead, M. O., Roffman, J. L., Smoller, J. W., Rosand, J., & Cramer, S. C. (2014). Dopamine Genetic Risk Score Predicts Depressive Symptoms in Healthy Adults and Adults with Depression. *PLoS ONE*, *9*(5), e93772. https://doi.org/10.1371/journal.pone.0093772

Pearson-Fuhrhop, K. M., Minton, B., Acevedo, D., Shahbaba, B., & Cramer, S. C. (2013). Genetic Variation in the Human Brain Dopamine System Influences Motor Learning and Its Modulation by L-Dopa. *PLoS ONE*, *8*(4), e61197. https://doi.org/10.1371/journal.pone.0061197

Perez-Lloret, S., Rey, M. V., Fabre, N., Ory, F., Spampinato, U., Brefel-Courbon, C., Montastruc, J. L., & Rascol, O. (2012). Prevalence and pharmacological factors associated with impulse-control disorder symptoms in patients with parkinson

disease. *Clinical Neuropharmacology*, *35*(6), 261–265. https://doi.org/10.1097/WNF.0b013e31826e6e6d

Picard, N., & Strick, P. L. (2001). Imaging the premotor areas. *Current Opinion in Neurobiology*, *11*(6), 663–672. https://doi.org/10.1016/S0959-4388(01)00266-5

Prieto, G. A., Perez-Burgos, A., Fiordelisio, T., Salgado, H., Galarraga, E., Drucker-Colin, R., & Bargas, J. (2009). Dopamine D2-class receptor supersensitivity as reflected in Ca2+ current modulation in neostriatal neurons. *Neuroscience*, *164*, 345–350. https://doi.org/10.1016/j.neuroscience.2009.08.030

Prieto, G. A., Perez-Burgos, A., Rivero, M. P., Galarraga, E., Drucker-Colin, R., & Bargas, J. (2011). Upregulation of D2-class signaling in dopamine-denervated striatum is in part mediated by D3 receptors acting on CaV2.1 channels via PIP2 depletion. *Journal of Neurophysiology*, *105*, 2260–2274. https://doi.org/10.1152/jn.00516.2010

Probst, C. C., Winter, L. M., Möller, B., Weber, H., Weintraub, D., Witt, K., Deuschl, G., Katzenschlager, R., & Van Eimeren, T. (2014). Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease (QUIP) and the QUIP-rating scale in a German speaking sample. *Journal of Neurology, Neurosurgery and Psychiatry*, *261*, 936–942. https://doi.org/10.1007/s00415-014-7299-6

Qu, Y., Lin, L. C., & Telzer, E. H. (2019). Culture modulates the neural correlates underlying risky exploration. *Frontiers in Human Neuroscience*, *13*. https://doi.org/10.3389/fnhum.2019.00171

Rahman, S., Ummatul, S., Choudhury, S., Islam, N., Roy, A., Basu, P., Anand, S. S., Islam, M. A., Shahi, M. S., Nayeem, A., Chowdhury, M. T. I., Chowdhury, M. S. J. H., Taylor, J. P., Baker, M. R., Baker, S. N., & Kumar, H. (2021). Comparing Stop

Signal Reaction Times in Alzheimer's and Parkinson's Disease. *Canadian Journal of Neurological Sciences*, 1–10. https://doi.org/10.1017/cjn.2021.184

Ranjbar-Slamloo, Y., & Fazlali, Z. (2020). Dopamine and Noradrenaline in the Brain; Overlapping or Dissociate Functions? *Frontiers in Molecular Neuroscience*, *12*(January), 1–8. https://doi.org/10.3389/fnmol.2019.00334

Rao, H., Korczykowski, M., Pluta, J., Hoang, A., & Detre, J. A. (2008). Neural correlates of voluntary and involuntary risk taking in the human brain: An fMRI Study of the Balloon Analog Risk Task (BART). *NeuroImage*, *42*(2), 902–910. https://doi.org/10.1016/j.neuroimage.2008.05.046

Rao, L. L., Zhou, Y., Zheng, D., Yang, L. Q., & Li, S. (2018). Genetic Contribution to Variation in Risk Taking: A Functional MRI Twin Study of the Balloon Analogue Risk Task. *Psychological Science*, *29*(10), 1679–1691. https://doi.org/10.1177/0956797618779961

Rapport, M. D., Alderson, R. M., Kofler, M. J., Sarver, D. E., Bolden, J., & Sims, V. (2008). Working memory deficits in boys with attention-deficit/hyperactivity disorder (ADHD): The contribution of central executive and subsystem processes. *Journal of Abnormal Child Psychology*, *36*(6), 825–837. https://doi.org/10.1007/s10802-008-9215-y

Ray Li, C. S., Yan, P., Sinha, R., & Lee, T. W. (2008). Subcortical processes of motor response inhibition during a stop signal task. *NeuroImage*, *41*, 1352–1363. https://doi.org/10.1016/j.neuroimage.2008.04.023

Ray, N. J., Brittain, J. S., Holland, P., Joundi, R. A., Stein, J. F., Aziz, T. Z., & Jenkinson, N. (2012). The role of the subthalamic nucleus in response inhibition: Evidence from local field potential recordings in the human subthalamic nucleus. *NeuroImage*, *60*(1), 271–278. https://doi.org/10.1016/j.neuroimage.2011.12.035

Ray, N. J., Miyasaki, J. M., Zurowski, M., Ko, J. H., Cho, S. S., Pellecchia, G., Antonelli, F., Houle, S., Lang, A. E., & Strafella, A. P. (2012). Extrastriatal dopaminergic abnormalities of DA homeostasis in Parkinson's patients with medication-induced pathological gambling: A [11C] FLB-457 and PET study. *Neurobiology of Disease*, *48*(3), 519–525. https://doi.org/10.1016/j.nbd.2012.06.021

Reise, S. P., Moore, T. M., Sabb, F. W., Brown, A. K., & London, E. D. (2013). The Barratt Impulsiveness Scale-11: Reassessment of its Structure in a Community Sample. *Psychological Assessment*, *25*(2), 631–642. https://doi.org/10.1037/a0032161

Ricciardi, L., Haggard, P., de Boer, L., Sorbera, C., Stenner, M. P., Morgante, F., & Edwards, M. J. (2017). Acting without being in control: Exploring volition in Parkinson's disease with impulsive compulsive behaviours. *Parkinsonism and Related Disorders*, *40*, 51–57. https://doi.org/10.1016/j.parkreldis.2017.04.011

Ricciardi, L., Lambert, C., De Micco, R., Morgante, F., & Edwards, M. (2018). Can we predict development of impulsive-compulsive behaviours in Parkinson's disease? *Journal of Neurology Neurosurgery and Psychiatry*, *89*, 476–481. https://doi.org/10.1136/jnnp-2017-317007

Roussakis, A. –A, Lao–Kaim, N. P., & Piccini, P. (2019). Brain Imaging and Impulse Control Disorders in Parkinson's Disease. *Current Neurology and Neuroscience Reports*, *19*, 5–11. https://doi.org/10.1007/s11910-019-0980-5

Rubí, B., & Maechler, P. (2010). Minireview: New roles for peripheral dopamine on metabolic control and tumor growth: Let's seek the balance. *Endocrinology*, *151*(12), 5570–5581. https://doi.org/10.1210/en.2010-0745

Ruitenberg, M. F. L., van Wouwe, N. C., Wylie, S. A., & Abrahamse, E. L. (2021). The role of dopamine in action control: Insights from medication effects in Parkinson's

disease. In *Neuroscience and Biobehavioral Reviews* (Vol. 127, pp. 158–170). Elsevier Ltd. https://doi.org/10.1016/j.neubiorev.2021.04.023

Ryu, D.-W., Kim, J.-S., Yoo, S.-W., Oh, Y.-S., & Lee, K.-S. (2019). The Impact of Impulsivity on Quality of Life in Early Drug-Naïve Parkinson's Disease Patients. *Journal of Movement Disorders*, *12*(3), 172–176. https://doi.org/10.14802/jmd.19004

Schachar, R., Levin, H. S., Max, J. E., Purvis, K., & Chen, S. (2004). Attention Deficit Hyperactivity Disorder Symptoms and Response Inhibition After Closed Head Injury in Children: Do Preinjury Behavior and Injury Severity Predict Outcome? *Developmental Neuropsychology*, *25*(1–2), 179–198. https://doi.org/10.1080/87565641.2004.9651927

Schapira, A. H. V., Emre, M., Jenner, P., & Poewe, W. (2009). Levodopa in the treatment of Parkinson's disease. In *European Journal of Neurology* (Vol. 16, pp. 982–989). https://doi.org/10.1111/j.1468-1331.2009.02697.x

Schaum, M., Pinzuti, E., Sebastian, A., Lieb, K., Fries, P., Mobascher, A., Jung, P., Wibral, M., & Tüscher, O. (2020). Cortical network mechanisms of response inhibition. *BioRxiv*. https://doi.org/10.1101/2020.02.09.940841

Schaum, M., Pinzuti, E., Sebastian, A., Lieb, K., Fries, P., Mobascher, A., Jung, P., Wibral, M., & Tüscher, O. (2021). Right inferior frontal gyrus implements motor inhibitory control via beta-band oscillations in humans. *ELife*, *10*, 1–26. https://doi.org/10.7554/eLife.61679

Schneider, A., Hommel, G., & Blettner, M. (2010). Linear Regression Analysis. *Dtsch Arztebl Int*, *107*(44), 776–782. https://doi.org/10.3238/arztebl.2010.0776

Seeman, P. (2015). Parkinson's Disease Treatment May Cause Impulse-Control Disorder Via Dopamine D3 Receptors. *Synapse*, *69*, 183–189. https://doi.org/10.1002/syn.21805

Senderecka, M., Grabowska, A., Szewczyk, J., Gerc, K., & Chmylak, R. (2012). Response inhibition of children with ADHD in the stop-signal task: An event-related potential study. *International Journal of Psychophysiology*, *85*(1), 93–105. https://doi.org/10.1016/j.ijpsycho.2011.05.007

Sevy, S., Hassoun, Y., Bechara, A., Yechiam, E., Napolitano, B., Burdick, K., Delman, H., & Malhotra, A. (2006). Emotion-based Decision-making in Healthy Subjects: Short-term Effects of Reducing Dopamine Levels. *Psychopharmacology*, *188*(2), 228–235.

Siderowf, A., & Kurlan, R. (1999). *MONOAMINE OXIDASE AND CATECHOL-O-METHYLTRANSFERASE INHIBITORS*. *83*(2), 445–467.

Siegert, S., Herrojo Ruiz, M., Brücke, C., Huebl, J., Schneider, G. H., Ullsperger, M., & Kühn, A. A. (2014). Error signals in the subthalamic nucleus are related to post-error slowing in patients with Parkinson's disease. *Cortex*, *60*, 103–120. https://doi.org/10.1016/j.cortex.2013.12.008

Sinha, N., Manohar, S., & Husain, M. (2013). Impulsivity and apathy in Parkinson's disease. *Journal of Neuropsychology*, *7*(2), 255–283. https://doi.org/10.1111/jnp.12013

Siri, C., Cilia, R., Reali, E., Pozzi, B., Cereda, E., Colombo, A., Meucci, N., Canesi, M., Zecchinelli, A. L., Tesei, S., Mariani, C. B., Sacilotto, G., Zini, M., & Pezzoli, G. (2015). Long-Term Cognitive Follow-Up of Parkinson's Disease Patients With Impulse Control Disorders. *Movement Disorders*, *30*(5), 696–704. https://doi.org/10.1002/mds.26160

Slater-Hammel, A. T. (1960). Reliability, accuracy, and refractoriness of a transit reaction. *Research Quarterly of the American Association for Health, Physical Education, & Recreation*, *31*, 217–228.

Smith, K. M., Xie, S. X., & Weintraub, D. (2016). Incident impulse control disorder symptoms and dopamine transporter imaging in Parkinson disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *87*(8), 864–870. https://doi.org/10.1136/jnnp-2015-311827.Incident

Smith, T., Gildeh, N., & Holmes, C. (2007). The Montreal cognitive assessment: Validity and utility in a memory clinic setting. *Canadian Journal of Psychiatry*, *52*, 329–332. https://doi.org/10.1177/070674370705200508

Smittenaar, P., Rutledge, R. B., Zeidman, P., Adams, R. A., Brown, H., Lewis, G., & Dolan, R. J. (2015). Proactive and Reactive Response Inhibition across the Lifespan. *PLoS ONE*, *10*(10), 1–16. https://doi.org/10.1371/journal.pone.0140383

Sperandei, S. (2014). Understanding logistic regression analysis. *Biochemia Medica*, *24*(1), 12–18. https://doi.org/10.11613/BM.2014.003

Stanford, M. S., Mathias, C. W., Dougherty, D. M., Lake, S. L., Anderson, N. E., & Patton, J. H. (2009). Fifty Years of the Barratt Impulsiveness Scale: An Update and Review. *Personality and Individual Differences*, *47*, 385–395. https://doi.org/10.1016/j.paid.2009.04.008

Steele, V. R., Aharoni, E., Munro, G. E., Calhoun, V. D., Nyalakanti, P., Stevens, M. C., Pearlson, G., & Kiehl, K. A. (2013). A large scale (N=102) functional neuroimaging study of response inhibition in a Go/NoGo task. *Behavioural Brain Research*, *256*, 529–536. https://doi.org/10.1016/j.bbr.2013.06.001

Stelmack, R. M., & Stalikas, A. (1991). Galen and the humour theory of temperament. *Personality and Individual Differences*, *12*(3), 255–263. https://doi.org/https://doi.org/10.1016/0191-8869(91)90111-N

Steyerberg, E. W., Moons, K. G. M., Windt, D. A. van der, Hayden, J. A., Perel, P., Schroter, S., Riley, R. D., Hemingway, H., & Altman, D. G. (2013). Prognosis Research Strategy (PROGRESS) 3: Prognostic Model Research. *Plos Medicine*, *10*(2). https://doi.org/10.1371/jour

Stinear, C. M., & Byblow, W. D. (2004). Impaired inhibition of a pre-planned response in focal hand dystonia. *Experimental Brain Research*, *158*(2), 207–212. https://doi.org/10.1007/s00221-004-1891-4

Stone, J. M., Davis, J. M., Leucht, S., & Pilowsky, L. S. (2009). Cortical Dopamine D2/D3 receptors are a common site of action for antipsychotic drugs-an original patient data meta-analysis of the SPECT and PET in vivo receptor imaging literature. *Schizophrenia Bulletin*, *35*(4), 789–797. https://doi.org/10.1093/schbul/sbn009

Takahashi, M., Koh, J., Yorozu, S., Kajimoto, Y., Nakayama, Y., Sakata, M., Yasui, M., Hiwatani, Y., Weintraub, D., & Ito, H. (2022). Validation of the Japanese Version of the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS). *Parkinson's Disease*, *2022*, 1–6. https://doi.org/10.1155/2022/1503167

Thompson, J., Thomas, N., Singleton, A., Piggott, M., Lloyd, S., Perry, E. K., Morris, C. M., Perry, R. H., Ferrier, I. N., & Court, J. A. (1997). D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. *Pharmacogenetics*, *7*(6), 479–484. https://doi.org/10.1097/00008571-199712000-00006

Tolosa, E., Wenning, G., & Poewe, W. (2006). The diagnosis of Parkinson's disease. In *Lancet Neurology* (Vol. 5, pp. 75–86). https://doi.org/10.1016/S1474-4422(05)70285-4

Tolosa, S., Scholz, W., Tolosa, E., Garrido, A., Scholz, S. W., & Poewe, W. (2021). Challenges in the diagnosis of Parkinson's disease. In *Lancet Neurol* (Vol. 20). www.thelancet.com/neurology

Torkamani, A., Wineinger, N. E., & Topol, E. J. (2018). The personal and clinical utility of polygenic risk scores. *Nature Reviews Genetics*, *19*, 581–590. https://doi.org/10.1038/s41576-018-0018-x

Trantham-Davidson, H., Neely, L. C., Lavin, A., & Seamans, J. K. (2004). Mechanisms underlying differential D1 versus D2 dopamine receptor regulation of inhibition in prefrontal cortex. *Journal of Neuroscience*, *24*(47), 10652–10659. https://doi.org/10.1523/JNEUROSCI.3179-04.2004

Tysnes, O. B., & Storstein, A. (2017). Epidemiology of Parkinson's disease. In *Journal of Neural Transmission* (Vol. 124, pp. 901–905). Springer-Verlag Wien. https://doi.org/10.1007/s00702-017-1686-y

Uyanık, G. K., & Güler, N. (2013). A Study on Multiple Linear Regression Analysis. *Procedia - Social and Behavioral Sciences*, *106*, 234–240. https://doi.org/10.1016/j.sbspro.2013.12.027

Vaidya, C. J., & Stollstorff, M. (2008). Cognitive Neuroscience of Attention Deficit Hyperactivity Disorder: Current Status and Working Hypotheses. *Dev Disanil Res Rev*, *14*(4), 261–267. https://doi.org/10.1002/ddrr.40.Cognitive

Vaillancourt, D. E., Schonfeld, D., Kwak, Y., Bohnen, N. I., & Seidler, R. (2013). Dopamine overdose hypothesis: Evidence and clinical implications. In *Movement Disorders* (Vol. 28, Issue 14, pp. 1920–1929). https://doi.org/10.1002/mds.25687

Valentine, J. C., Pigott, T. D., & Rothstein, H. R. (2010). How many studies do you need? A primer on statistical power for meta-analysis. *Journal of Educational and Behavioral Statistics*, *35*(2), 215–247. https://doi.org/10.3102/1076998609346961

Vallone, D., Picetti, R., & Borrelli, E. (2000). Structure and function of dopamine receptors. *Neuroscience and Biobehavioral Reviews*, *24*, 125–132. https://doi.org/10.1016/S0149-7634(99)00063-9

van Smeden, M., Moons, K. G. M., de Groot, J. A. H., Collins, G. S., Altman, D. G., Eijkemans, M. J. C., & Reitsma, J. B. (2019). Sample size for binary logistic prediction models: Beyond events per variable criteria. *Statistical Methods in Medical Research*, *28*(8), 2455–2474. https://doi.org/10.1177/0962280218784726

Vela, L., Martínez Castrillo, J. C., García Ruiz, P., Gasca-Salas, C., Macías Macías, Y., Pérez Fernández, E., Ybot, I., Lopez Valdés, E., Kurtis, M. M., Posada Rodriguez, I. J., Mata, M., Ruiz Huete, C., Eimil, M., Borrue, C., del Val, J., López-Manzanares, L., Rojo Sebastian, A., & Marasescu, R. (2016). The high prevalence of impulse control behaviors in patients with early-onset Parkinson's disease: A cross-sectional multicenter study. *Journal of the Neurological Sciences*, *368*, 150–154. https://doi.org/10.1016/j.jns.2016.07.003

Verbruggen, F., Aron, A. R., Band, G. P., Beste, C., Bissett, P. G., Brockett, A. T., Brown, J. W., Chamberlain, S. R., Chambers, C. D., Colonius, H., Colzato, L. S., Corneil, B. D., Coxon, J. P., Dupuis, A., Eagle, D. M., Garavan, H., Greenhouse, I., Heathcote, A., Huster, R. J., … Boehler, C. N. (2019a). A Consensus Guide to Capturing the Ability to Inhibit Actions and Impulsive Behaviors in the Stop-signal Task. *ELife*, *8*, 1–26. https://doi.org/10.7554/elife.46323

Verbruggen, F., Aron, A. R., Band, G. P., Beste, C., Bissett, P. G., Brockett, A. T., Brown, J. W., Chamberlain, S. R., Chambers, C. D., Colonius, H., Colzato, L. S., Corneil, B.

D., Coxon, J. P., Dupuis, A., Eagle, D. M., Garavan, H., Greenhouse, I., Heathcote, A., Huster, R. J., … Boehler, C. N. (2019b). A consensus guide to capturing the ability to inhibit actions and impulsive behaviors in the stop-signal task. *ELife*, *8*, 1–25. https://doi.org/10.7554/elife.46323

Verbruggen, F., Chambers, C. D., Lawrence, N. S., & Mclaren, I. P. L. (2016). Winning and Losing : Effects on Impulsive Action. *Journal of Experimental Psychology:*

Verbruggen, F., Chambers, C. D., & Logan, G. D. (2013). Fictitious Inhibitory Differences: How Skewness and Slowing Distort the Estimation of Stopping Latencies. *Psychological Science*, *24*(3), 352–362. https://doi.org/10.1177/0956797612457390

Verbruggen, F., & Logan, G. D. (2008). Response Inhibition in the Stop-signal Paradigm. In *Trends in Cognitive Sciences* (Vol. 12, Issue 11, pp. 418–424). https://doi.org/10.1016/j.tics.2008.07.005

Verbruggen, F., & Logan, G. D. (2009). Models of Response Inhibition in the Stop-Signal and Stop-Change Paradigms. *Neurosci Biobehav Rev*, *33*(5), 647–661. https://doi.org/10.1016/j.neubiorev.2008.08.014.Models

Verbruggen, F., Logan, G. D., Liefooghe, B., & Vandierendonck, A. (2008). Short-Term Aftereffects of Response Inhibition: Repetition Priming or Between-Trial Control Adjustments? *Journal of Experimental Psychology: Human Perception and Performance*, *34*(2), 413–426. https://doi.org/10.1037/0096-1523.34.2.413

Verbruggen, F., Logan, G. D., & Stevens, M. A. (2008). STOP-IT: Windows executable software for the stop-signal paradigm. *Behavior Research Methods*, *40*(2), 479–483. https://doi.org/10.3758/BRM.40.2.479

Vince, M. A. (1948). The intermittency of control movements and the psychological refractory period. *The British Journal of Psychology. General Section*, *38*(Pt 3), 149–157. https://doi.org/10.1111/j.2044-8295.1948.tb01150.x

Voon, V., Mehta, A. R., & Hallett, M. (2011). Impulse control disorders in Parkinson's disease. *Current Opinion in Neurology*, *24*(4), 324–330. https://doi.org/10.1097/wco.0b013e3283489687

Voon, V., Sohr, M., Lang, A. E., Potenza, M. N., Siderowf, A. D., Whetteckey, J., Weintraub, D., Wunderlich, G. R., & Stacy, M. (2011). Impulse Control Disorders in Parkinson Disease: A multicenter Case-Control Study. *Annals of Neurology*, *69*(6), 986–996. https://doi.org/10.1002/ana.22356

Vriend, C. (2018). The neurobiology of impulse control disorders in Parkinson's disease: from neurotransmitters to neural networks. In *Cell and Tissue Research* (Vol. 373, Issue 1, pp. 327–336). https://doi.org/10.1007/s00441-017-2771-0

Vriend, C., Leffa, D. T., Trujillo, J. P., Gerrits, N. J. H. M., de Boer, F. E., Berendse, H. W., van der Werf, Y. D., & van den Heuvel, O. A. (2018). Functional connectivity alterations in Parkinson's disease during the stop-signal task. *BioRxiv*. https://doi.org/10.1101/304584

Vriend, C., Nordbeck, A. H., Booij, J., van der Werf, Y. D., Pattij, T., Voorn, P., Raijmakers, P., Foncke, E. M. J., van de Giessen, E., Berendse, H. W., & van den Heuvel, O. A. (2014). Reduced Dopamine Transporter Binding Predates Impulse Control Disorders in Parkinson's Disease. *Movement Disorders*, *29*(7), 904–911. https://doi.org/10.1002/mds.25886

Wadsley, C. G., Cirillo, J., & Byblow, W. D. (2019). Between-hand coupling during response inhibition. *Journal of Neurophysiology*, *122*(4), 1357–1366. https://doi.org/10.1152/jn.00310.2019

Waldron-Perrine, B., & Axelrod, B. N. (2012). Determining an Appropriate Cutting Score for Indication of Impairment on the Montreal Cognitive Assessment. *International Journal of Geriatric Psychiatry*, *27*, 1189–1194. https://doi.org/10.1002/gps.3768

Weintraub, D. (2008). Dopamine and Impulse Control Disorders in Parkinson's Disease. *Annals of Neurology*, *64*, 93–100. https://doi.org/10.1002/ana.21454

Weintraub, D., Koester, J., Potenza, M. N., Siderowf, A. D., Stacy, M., Voon, V., Whetteckey, J., Wunderlich, G. R., & Lang, A. E. (2010). Impulse Control Disorders in Parkinson Disease: a cross-sectional study of 3090 patients. *Archives of Neurology*, *67*(5), 589–595. https://doi.org/10.1001/archneurol.2010.65

Weintraub, D., & Mamikonyan, E. (2019). Impulse control disorders in Parkinson's disease. *American Journal of Psychiatry*, *176*(1), 5–11. https://doi.org/10.1176/appi.ajp.2018.18040465

Weintraub, D., Mamikonyan, E., Papay, K., Shea, J. A., Xie, S. X., & Siderowf, A. (2012). Questionnaire for impulsive-compulsive disorders in Parkinson's Disease-Rating Scale. *Movement Disorders*, *27*(2), 242–247. https://doi.org/10.1002/mds.24023

Weintraub, D., Papay, K., & Siderowf, A. (2013). *Screening for impulse control symptoms in patients with de novo Parkinson disease*. www.neurology.org

Weintraub, D., Posavi, M., Fontanillas, P., Tropea, T. F., Mamikonyan, E., Suh, E., Trojanowski, J. Q., Cannon, P., Van Deerlin, V. M., & Chen-Plotkin, A. S. (2022). Genetic prediction of impulse control disorders in Parkinson's disease. *Annals of Clinical and Translational Neurology*, *9*(7), 936–949. https://doi.org/10.1002/acn3.51569

Weintraub, D., Siderowf, A. D., Potenza, M. N., Goveas, J., Morales, K. H. D., Duda, J. E., Moberg, P. J., & Stern, M. B. (2006). Dopamine Agonist Use is Associated with

Impulse Control Disorders in Parkinson's Disease. *Arch Neurol*, *63*(7), 969–973. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1761054/pdf/nihms12138.pdf

Weintraub, D., Stewart, S., Shea, J. A., Lyons, K. E., Pahwa, R., Driver-dunckley, E. D., Adler, C. H., Potenza, M. N., Miyasaki, J., Siderowf, A. D., Duda, J. E., Hurtig, H. I., Colcher, A., Horn, S. S., Stern, M. B., & Voon, V. (2009). Validation of the Questionnaire for Impulsive-CompulsiveDisorders in Parkinson's Disease (QUIP). *Movement Disorders*, *24*(10), 1461–1467. https://doi.org/10.1002/mds.22571.Validation

Wernick, M. N., & Aarsvold, J. N. (2004). *Emission tomography: the fundamentals of PET and SPECT*. Elsevier.

Witte, A. V., & Flöel, A. (2012). Effects of COMT polymorphisms on brain function and behavior in health and disease. *Brain Research Bulletin*, *88*, 418–428. https://doi.org/10.1016/j.brainresbull.2011.11.012

Xu, J., Westrick, Z., & Ivry, R. B. (2015). Selective inhibition of a multicomponent response can be achieved without cost. *Journal of Neurophysiology*, *113*(2), 455–465. https://doi.org/10.1152/jn.00101.2014

Zack, M., & Poulos, C. X. (2007). A D2 Antagonist Enhances the Rewarding and Priming Effects of a Gambling Episode in Pathological Gamblers. *Neuropsychopharmacology*, *32*, 1678–1686. https://doi.org/10.1038/sj.npp.1301295

Zaidi, H., & Karakatsanis, N. (2018). Towards enhanced pet quantification in clinical oncology. *British Journal of Radiology*, *91*. https://doi.org/10.1259/bjr.20170508

Zandbelt, B. B., & Vink, M. (2010). On the Role of the Striatum in Response Inhibition. *PLoS ONE*, *5*(11), e13848. https://doi.org/10.1371/journal.pone.0013848

Zermatten, A., Van Der Linden, M., D'Acremont, M., Jermann, F., & Bechara, A. (2005). Impulsivity and decision making. *Journal of Nervous and Mental Disease*, *193*(10), 647–650. https://doi.org/10.1097/01.nmd.0000180777.41295.65

Zhang, F., & Iwaki, S. (2019). Common Neural Network for Different Functions: An Investigation of Proactive and Reactive Inhibition. *Frontiers in Behavioral Neuroscience*, *13*(124), 1–13. https://doi.org/10.3389/fnbeh.2019.00124

Zhang, S., Hu, S., Hu, J., Wu, P. L., Chao, H. H., & Li, C. S. R. (2015). Barratt impulsivity and neural regulation of physiological arousal. *PLoS ONE*, *10*(6), 1–17. https://doi.org/10.1371/journal.pone.0129139

Zhu, L., Ploessl, K., & Kung, H. F. (2014). PET/SPECT imaging agents for neurodegenerative diseases. *Chemical Society Reviews*, *43*, 6683–6691. https://doi.org/10.1039/c3cs60430f

Zumárraga, M., Dávila, R., Basterreche, N., Arrue, A., Goienetxea, B., Zamalloa, M. I., Erkoreka, L., Bustamante, S., Inchausti, L., González-Torres, M. A., & Guimón, J. (2010). Catechol O-methyltransferase and Monoamine Oxidase A Genotypes, and Plasma Catecholamine Metabolites in Bipolar and Schizophrenic Patients. *Neurochemistry International*, *56*(6–7), 774–779. https://doi.org/10.1016/j.neuint.2010.02.015

Appendix

Appendix 1. Occurrence of polymorphisms for dopamine genetic risk score

	DRD1 rs4532			DRD2 rs1800497			DRD3 rs6280			COMT rs4680		
	A/A	A/G	G/G	C/C	C/T	T/T	T/T	C/T	C/C	G/G	G/A	A/A
Score	0	1	1	1	0	0	0	1	1	0	1	1
Predict freq	0.29	0.50	0.14	0.68	0.29	0.03	0.33	0.49	0.18	0.28	0.50	0.23
Actual freq	0.42	0.45	0.13	0.67	0.27	0.06	0.52	0.38	0.10	0.32	0.39	0.29

DRD1: dopamine receptor D1; DRD2: dopamine receptor D2; DRD3: dopamine receptor D3; COMT: catechol-O-methyltransferase. A: adenine; G: guanine; C: cytosine; T: thymine. Predict freq: expected mutation frequency in population. Actual freq: observed frequency in current population.

Appendix 2. Univariate binary logistic regression analyses in the DA group.

Dopamine Agonist (DA) Group

When considering each independent variable in isolation (Table A2), neither DGRS low (β = 0.313, p = 0.542) or high (β = 0.101, p = 0.791) increased the probability of an ICB in comparison to DGRS medium. This was also the case for duration, where there was no increase in the probability of an ICB with each day (β = -0.01, p = 0.783). However, being male (β = 0.738, p = 0.042) and a higher score on the UPDRS I & II (β = 0.058, p < 0.001) each increased ICB probability. The odds of an ICB in men was 109% higher compared to women, and the probability of an ICB amongst men was 0.68 ($p = e^{0.738}/1+e^{0.738}$). When a person's UPDRS score increased by 1, they had a 6% increase in the odds of an ICB.

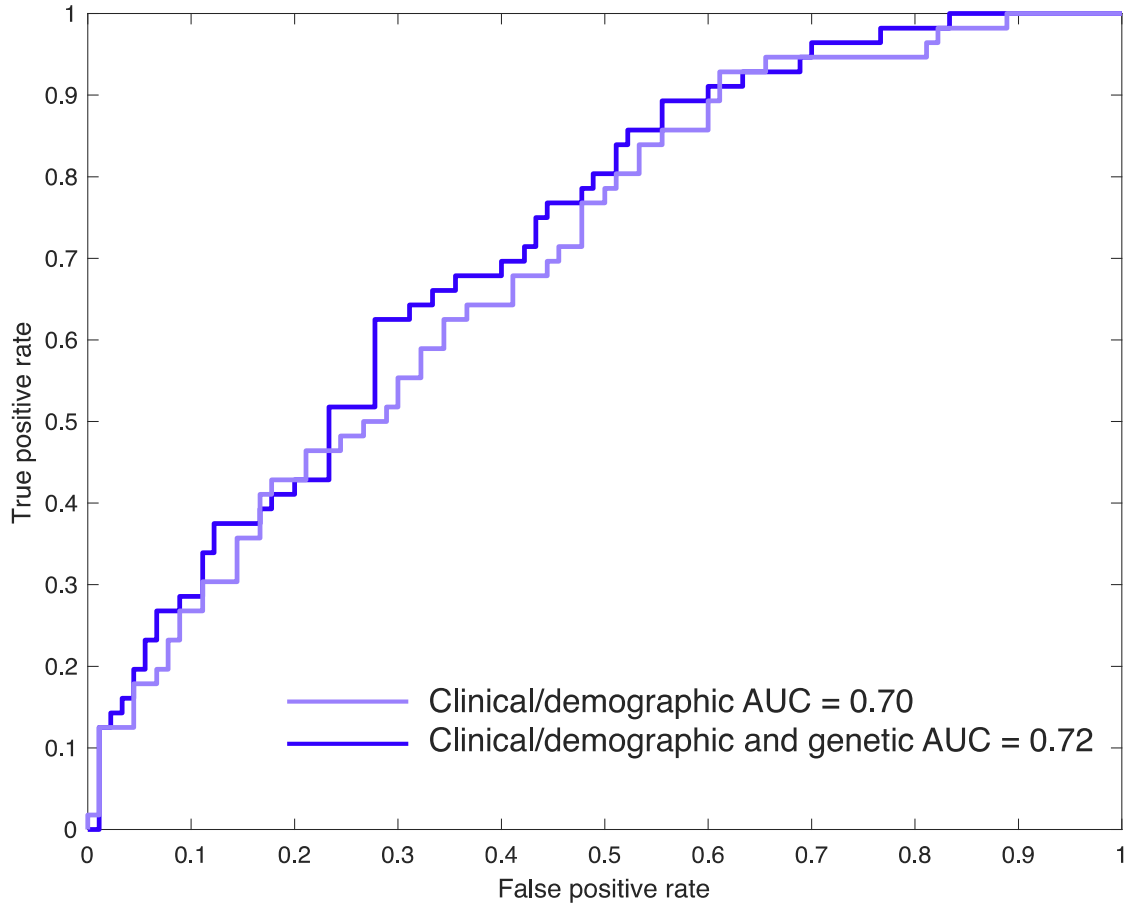
Table A2. Variables associated with impulse control behaviours in the dopamine agonist group.

Univariate analysis

	β	**SE**	**p value**	**Odds/OR**
DGRS low	0.313	0.514	0.542	1.37
DGRS high	0.101	0.380	0.791	1.11
Duration (days)	-0.01	0.0003	0.783	0.99
Gender (male)	**0.738**	**0.364**	**0.042**	**2.09**
UPDRS I&II	**0.058**	**0.017**	**<0.001**	**1.06**

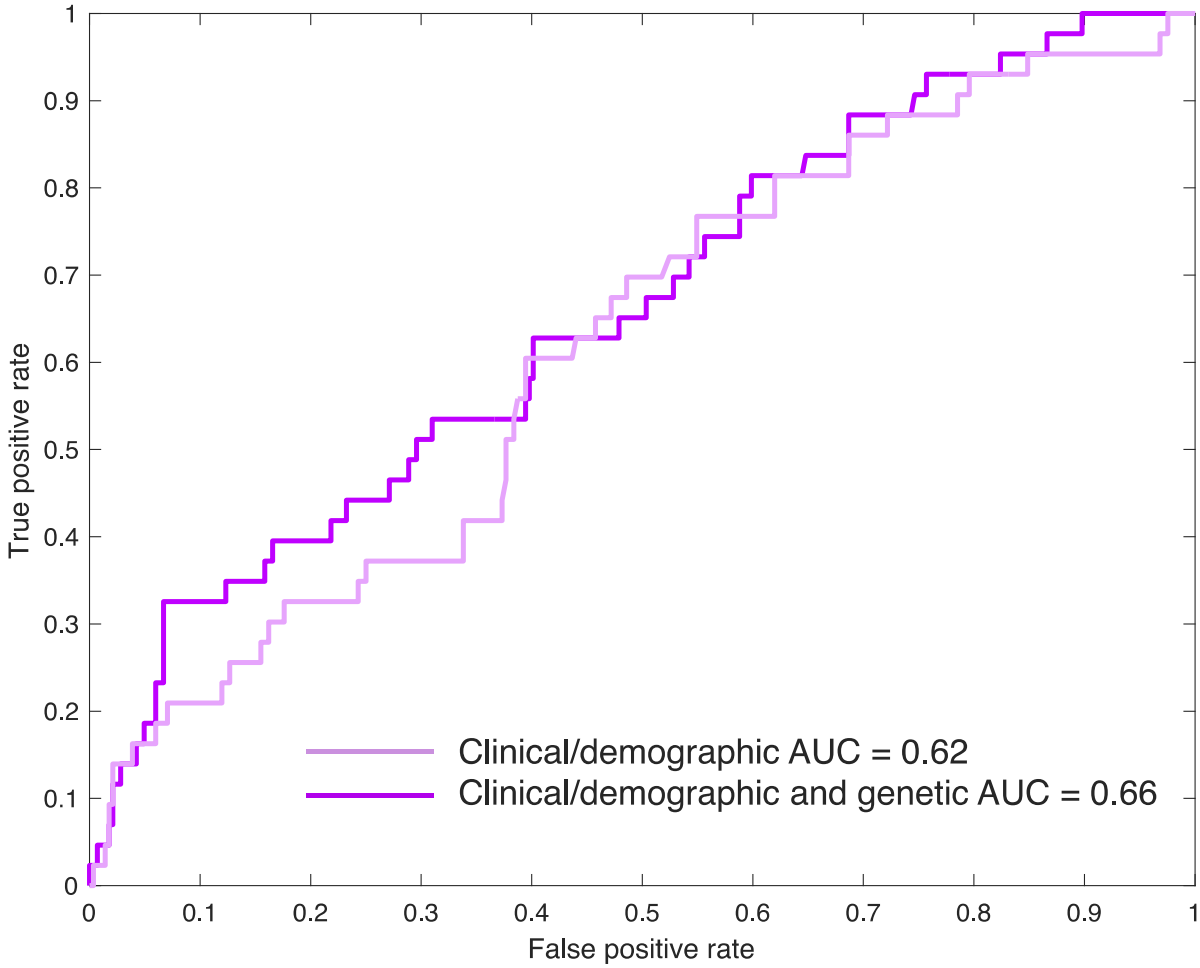
Response variable: positive score on Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (yes/no). DGRS: dopamine genetic risk score, UPDRS: Unified Parkinson's Disease Rating Scale. β: coefficient, SE: standard error, OR: odds ratio (OR = eβ). Significant values in bold.

Appendix 3. Receiver operating characteristic (ROC) curve for clinical/demographic vs clinical/demographic and genetic associations with incident ICD behaviour (DA group). AUC: area under the curve.



The AUC for the DA group was 0.70 (95% confidence interval (CI), upper and lower bounds = 0.61 to 0.78) for clinical and demographic variables, which increased to 0.72 (95% CI 0.64 to 0.81) with the addition of the DGRS. However, these values were not significantly different (p = 0.326, DeLong's test).

Appendix 4. Receiver operating characteristic (ROC) curve for clinical/demographic vs clinical/demographic and genetic associations with incident ICD behaviour (DN group). AUC: area under the curve.



The ROC curves illustrate that the AUC for the DN group multivariate model was 0.62 (95% CI 0.57 to 0.75) for clinical and demographic variables, which increased to 0.66 (95% CI 0.53 to 0.71) with the addition of the DGRS (p = 0.414, DeLong's test).

Appendix 5. Model development and results in the de novo group

De Novo (DN) Group

During model development, of the selected variables (DGRS, gender, UPDRS I&II, age and duration), collinearity was identified between duration and age ($p = 0.002$), and UPDRS and age ($p = 0.023$), so age was removed from the model. The relationship between each selected independent variable and the response variable was initially investigated using univariate binary logistic regression analyses.

When considering each independent variable in isolation (Table A5), only a higher score on the UPDRS I&II ($\beta = 0.047$, $p = 0.008$) increased ICB probability. When a participant's UPDRS I&II score increased by 1, they had a 5% increase in the odds of an ICB. Having neither a low ($\beta = 0.525$, $p = 0.266$) nor high DGRS ($\beta = -0.178$, $p = 0.633$) had an increased probability of an ICB in comparison to a medium DGRS. Additionally, for each day increase in duration, there was not an increase in the probability of an ICB ($\beta = -0.0003$, $p = 0.568$).

Table A5. Variables associated with impulse control behaviours in the de novo group.

Univariate analysis

	Coefficient	SE	p value	Odds/OR
DGRS low	0.525	0.471	0.266	1.69
DGRS high	-0.178	0.372	0.633	0.84
Duration (days)	-0.0003	0.0005	0.568	1.00
Gender (male)	-0.407	0.334	0.223	0.67
UPDRS I&II	**0.047**	**0.018**	**0.008**	**1.05**

Response variable: positive score on Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (yes/no). DGRS: dopamine genetic risk score, UPDRS: Unified Parkinson's Disease Rating Scale. β: coefficient, SE: standard error, OR: odds ratio (OR = e^{β}). Significant values in bold.

Following univariate analysis (Table A5), gender was removed from the multivariate model to avoid overparameterization (p = 0.223).

Binary logistic regression function:

$$p = \frac{\exp\left(\beta_0(intercept) + \beta_1 DGRS + \beta_2 Duration + \beta_4 \text{UPDRS} + \beta_5 \text{DGRSxDuration} + \beta_6 \text{DGRSxUPDRS}\right)}{1 + \exp\left(\beta_0(intercept) + \beta_1 \text{DGRS} + \beta_2 \text{Duration} + \beta_4 \text{UPDRS} + \beta_5 \text{DGRSxDuration} + \beta_6 \text{DGRSxUPDRS}\right)}$$

The multivariate binary logistic regression model (Table A5.1) approached significance when validated against a constant model (p = 0.054). The odds of having an ICB increased by 9% with every score increase of 1 on the UPDRS I&II (β = 0.09, p = 0.003, odds ratio = 1.09). An increase in UPDRS I&II score increased the odds of an ICB in the medium-range DGRS group (odds ratio = $e^{0.09}$ = 1.09) to a greater extent than for those with a high DGRS (odds ratio = $e^{0.09\text{-}0.084}$ = 1.01)), although this did not reach significance (p = 0.053). All remaining independent variables and interactions did not change the odds of having an ICB.

Table A5.1 Variables associated with impulse control behaviours in the de novo group.

	Coefficient	SE	p value	Odds/OR
Intercept	**-3.247**	**0.854**	**<0.001**	**0.04**
DGRS low	1.955	1.244	0.116	7.07
DGRS high	0.947	1.045	0.365	2.58
Duration (days)	-0.0005	0.001	0.616	1.00
UPDRS I&II	**0.09**	**0.03**	**0.003**	**1.09**
DGRS low * Duration	-0.002	0.002	0.418	1.00
DGRS high * Duration	0.0008	0.001	0.511	1.00
DGRS low * UPDRS I&II	-0.036	0.048	0.455	0.97
DGRS high * UPDRS I&II	-0.084	0.043	0.053	0.92

Response variable: positive score on Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (yes/no). DGRS: dopamine genetic risk score, UPDRS: Unified Parkinson's Disease Rating Scale. β: coefficient, SE: standard error, OR: odds ratio (OR = e^{β}). Significant values in bold.

To our knowledge this is the first study to investigate genetic associations with ICBs in de novo PD. Current findings show 13% of the de novo group reported an ICB compared to similar studies reporting 17.5% - 18.7% (Antonini et al., 2011; Ryu et al., 2019; Weintraub et al., 2013). As expected, this was similar to the 15% reported in the HC group. There was a non-significant trend for increase in ICBs for de novo patients with a low DGRS compared to those with mid-range scores. This trend may be less robust than the relationship found for DA patients due to reduced dopamine disruption in the de novo stage. In the context of the inverted-U hypothesis, less disruption can be conceptualised as a smaller rightward shift for de novo patients compared to DA, resulting in less distinct levels of impulse control between DGRS levels.

UPDRS I&II score was the only factor associated with the incidence of ICBs for de novo patients. Each single point increase in UPDRS I&II score resulted in an increase in the odds of having an ICB. This relationship has not been previously reported in a de novo cohort, only with medicated PD patients (Cormier-Dequaire et al., 2018; Voon, Sohr, et al., 2011). No variable in the current study overlaps with previously reported demographic and clinical factors associated with ICBs in de novo PD, such as being male, a lower Montreal Cognitive Assessment score and a higher Geriatric Depression Scale score (Antonini et al., 2011; Ryu et al., 2019; Weintraub et al., 2013). It is clear that a smaller number of factors contribute to ICBs during de novo PD compared to when patients are medicated. This is likely due to reduced dopamine disruption within the MCL system in the de novo stage of PD before DA administration.

Appendix 6. Central Nervous System Vital Signs Neurocognitive tests and domains.

Test	Description	Domain
Verbal Memory	15 words presented to then remember and recognise when positioned within 15 new words. Followed by delayed recall of the original 15 words.	Verbal Memory Composite Memory
Visual Memory	15 geometric figures presented to then remember and recognise when positioned within 15 new geometric figures. Followed by delayed recall of the original 15 geometric figures.	Visual Memory Composite Memory
Finger Tapping	Press the space bar with right index finger as many times as possible in 10s. One practise, 3 test trials. Repeated with left index finger.	Motor Speed Psychomotor Speed
Symbol Digit Coding	8 symbols presented corresponding to digits 2-9. Below, the symbols are presented in a random order with blank boxes which require the correct corresponding digit to be inserted.	Processing Speed Psychomotor Speed
Stroop Test	1) Participants press the space bar as soon as possible when the words (RED, YELLOW, BLUE and GREEN) are displayed in black. 2) Participants press the space bar as soon as possible when the colour of the word matches what the word says. 3) Participants press the space bar as soon as possible when the colour of the word does not match what it says.	Reaction time Cognitive Flexibility Complex Attention
Shifting Attention	For each trial, a circle and a square, either painted red or blue, are displayed at the bottom of the screen. A single red or blue circle or square appears at the top of the screen and participants have to match one of the bottom shapes to the top shape depending on the rule displayed (match by shape or match by colour).	Executive Function Cognitive Flexibility Complex Attention
Continuous Performance Test	Participants are presented with stimuli (letters) at random. They only respond with the space bar when the letter 'B' is presented.	Simple Attention Complex Attention

Non-Verbal Reasoning	Participants have to determine the next or missing step of a sequence. There are 15 matrices to complete that increase in difficulty.	Reasoning
4-Part Continuous Performance	Successive shapes are presented. 1) Participants respond to any shape. 2) Participants respond to a specified shape. 3) Participants respond when two consecutive shapes match. 4) Participants respond if a shape matches this shape – 2.	Working Memory Sustained Attention

Appendix 7. Occurrence of polymorphisms for dopamine genetic risk score

	DRD1 rs4532			DRD2 rs1800497			DRD3 rs6280			COMT rs4680			DAT rs28363170		
	A/A	A/G	G/G	C/C	C/T	T/T	T/T	C/T	C/C	G/G	G/A	A/A	9/9	9/10	10/10
Score	0	1	1	1	0	0	0	1	1	0	1	1	1	1	0
Predict freq	0.39	0.47	0.14	0.58	0.36	0.06	0.36	0.48	0.15	0.17	0.49	0.35	0.09	0.42	0.49
Actual freq	0.36	0.52	0.18	0.56	0.39	0.04	0.36	0.50	0.14	0.18	0.47	0.35	0.10	0.39	0.49

DRD1: dopamine receptor D1; DRD2: dopamine receptor D2; DRD3: dopamine receptor D3; COMT: catechol-O-methyltransferase; DAT: dopamine transporter. A: adenine; G: guanine; C: cytosine; T: thymine. Predict freq: expected mutation frequency in population. Actual freq: observed frequency in current population.

Appendix 8. Univariate linear regression analysis of variables associated with the frequency of impulse control behaviours.

ICB (n = 23) no ICB (n = 27)				
	β	**SE**	**p value**	**95 % CI (β)**
Average collection pumps	-0.005	0.21	.980	[-0.43, 0.42]
Age	0.18	0.26	.490	[-0.35, 0.71]
DGRS low	-0.04	5.11	.994	[-10.3, 10.2]
Gender (male)	**9.76**	**4.47**	**.034**	**[0.77, 18.8]**
LEDD DA	-0.006	0.02	.765	[-0.05, 0.04]
LEDD Total	0.004	0.006	.513	[-0.008, 0.02]
Negative Reinforcement	6.92	4.77	.153	[-2.67, 16.5]
Positive Reinforcement	-5.24	5.71	.363	[-16.7, 6.25]
SSRT stop both	0.03	0.03	.400	[-0.04, 0.10]
UPDRS I&II	**0.88**	**0.19**	**<.001**	**[0.50, 1.27]**
Years on DA	**1.40**	**0.43**	**.002**	**[0.52, 2.27]**
Years since diagnosis	**1.10**	**0.32**	**.001**	**[0.44, 1.75]**

Response variable: score on Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease rating scale. ICB: impulse control behaviour (n: number); DGRS: dopamine genetic risk score; LEDD: levodopa equivalent daily dose; DA: Dopamine Agonist; SSRT: stop signal reaction time; UPDRS: Unified Parkinson's Disease Rating Scale; β: coefficient, SE: standard error, CI: confidence interval. Significant values in bold ($p < .05$).

Appendix 9. Continuous Independent variable collinearity for the Dopamine Agonist group.

Coefficient	**Years since diagnosis**	**Years on DA**	**DA LEDD**	**UPDRS**	**SSRT both**	**Negative Reinforcement**
Years since diagnosis		**0.85 (<.001)**	0.12 (.420)	**0.65 (<.001)**	-0.18 (.224)	-0.07 (.647)
Years on DA	**0.85 (<.001)**		0.26 (.065)	**0.55 (<.001)**	-0.14 (.330)	-0.24 (.099)
DA LEDD	0.12 (.420)	0.26 (.065)		-0.03 (.837)	-0.24 (.090)	-0.28 (.051)
UPDRS	**0.65 (<.001)**	**0.55 (<.001)**	-0.03 (.837)		0.08 (.559)	0.12 (.408)
SSRT both	-0.18 (.224)	-0.14 (.330)	-0.24 (.090)	0.08 (.559)		-0.13 (.354)
Negative Reinforcement	-0.07 (.647)	-0.24 (.099)	-0.28 (.051)	0.12 (.408)	-0.13 (.354)	

Correlation coefficient (p value). LEDD: levodopa equivalent daily dose; DA: dopamine agonist; UPDRS: Unified Parkinson's Disease Rating Scale; Significant values in bold ($p < .05$).

Appendix 10. Alternative DGRS Classification

Following all main analyses in Chapter 5, post-hoc analyses investigated the effect on the clinical and trait impulsivity models by categorising the DGRS into three groups: DRGS low (DGRS 0-2, n = 15), DGRS medium (DGRS 3, n = 17, reference variable) and DGRS high (DGRS 4-5, n = 18). This was to provide a more direct comparison with our previous analyses in Chapter 3 (Hall et al., 2021) and to investigate the effects of smaller, more precise changes in basal dopamine neurotransmission.

Splitting the DGRS into low, medium and high revealed an interaction with time on DA medication.

In the Clinical Impulsivity model ($F_{11,38}$ = 3.54, p = .002, R^2 = 0.535 i.e., large effect size, 95.3% power, Table A10), participants with a high DGRS exhibited a smaller increase in ICB frequency (by 2.12) for each year on DA medication (β = 0.47, p = .034) compared to participants with a medium range DGRS (β = 2.60). However overall, when not accounting for genetics, this model also found that for every year on DA medication, ICB frequency increased by 2.60 (β = 2.60, p < .001). The Trait Impulsivity model was not validated, so results are not reported.

Table A10 Multiple linear regression analysis of variables associated with the frequency of impulse control behaviours.

ICB (n = 23) no ICB (n = 27)				
	β	**SE**	**p value**	**95 % CI (β)**
Intercept	-9.28	18.7	.623	[-41.2, 28.6]
DGRS low	-6.58	26.3	.804	[-59.9, 46.8]
DGRS high	-15.9	23.0	.495	[-62.5, 30.8]
LEDD DA	0.02	0.02	.350	[-0.02, 0.06]
Negative Reinforcement	-1.01	9.07	.912	[-19.4, 17.4]
SSRT stop both	0.03	0.05	.594	[-0.08, 0.14]
Years on DA	**2.60**	**0.58**	**<.001**	**[1.41, 3.78]**
DGRS low * Negative Reinforcement	26.5	16.3	.112	[-6.44, 59.5]
DGRS low * SSRT stop both	0.07	0.09	.417	[-0.10, 0.24]
DGRS low * Years on DA	-1.95	1.14	.095	[-4.25, 0.35]
DGRS high * Negative Reinforcement	16.4	10.2	.118	[-4.38, 37.1]
DGRS high * SSRT stop both	0.08	0.07	.249	[-0.06, 0.22]
DGRS high * Years on DA	**-2.12**	**0.96**	**.034**	**[-4.08, -0.17]**

Response variable: score on Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease rating scale. ICB: impulse control behaviour (n: number); DGRS: dopamine genetic risk score; LEDD: levodopa equivalent daily dose; DA: Dopamine Agonist; SSRT: stop signal reaction time; β: coefficient, SE: standard error, CI: confidence interval. Significant values in bold ($p < .05$).

This model confirmed previously reported results that time on DA medication is a risk factor for ICB development and increasing frequency (Corvol et al., 2018; Giladi et al., 2007). Although the DGRS used in Chapter 5, which was split into high vs low, did not interact with DA exposure, when utilising the alternative DGRS, split into three ranges, the interaction between exposure to DA medication and DGRS high (compared to DGRS medium) was

associated with ICB frequency. This interaction showed that those with a high DGRS displayed a smaller increase in impulsivity compared to a medium DGRS with increasing time on DA medication, whilst no interaction was present for DGRS low. We expected an interaction between these variables, but the direction was different to what was expected and previously reported (Chapter 3, (Hall et al., 2021)). However, there were some key differences in design between the experiments in the two chapters which could explain the disparity between results. Firstly, the sample size for the current experiment was much smaller than the cohort in our previous work (Hall et al., 2021), which reduces the number and spread of DGRS results and ICB frequency scores. Moreover, the current chapter includes DAT compared to the four-gene score that was necessary from the PPMI data in Chapter 3. Another key difference is that the measure of the incidence of ICBs in Chapter 3 was derived from the QUIP-S with a much shorter range of scores, compared to the current QUIP-RS which reflects ICB severity (Marques et al., 2019) rather than just incidence.

It is also possible to speculate about theoretical reasons for the different result in this chapter. The relationship between impulse control, dopamine neurotransmission and the DGRS is presented in an inverted-U (Figure 3.2, Chapter 3). This inverted-U theory is presented in Chapter 3, and informs hypotheses in Chapters 5 and 6, where a lower DGRS is associated with worse impulsivity (left side of inverted-U), which can improve (move towards apex of curve) with DA medication. The opposite is indicated for a high DGRS where a better baseline impulsivity (right side of inverted-U) worsens (moves away from apex of curve) with DA medication. As there was no individual effect of the DGRS within Chapter 5, we are not informed of the baseline position of each DGRS group on the inverted-U, therefore we cannot determine the movement of each DGRS group along the curve with time on DA medication results. Whilst this may be true, it could be possible that our interpretation of the DGRS for our

participants and where they are situated on the inverted-U curve is incorrect. Only further investigation of the DGRS and behavioural impulsivity tasks, where there is a greater sample size and prospective screening of DGRS groups, will help to confirm or disprove this inverted-U theory.

Appendix 11. Montreal Cognitive Assessment (MoCa)

The MoCa is a validated and reliable screening tool to measure global cognitive performance and detect cognitive impairment in the general population and in several patient populations including PD (Gill et al., 2008; Lam et al., 2013). The MoCa assesses several cognitive domains: Attention, Executive, Language, Memory and Visuospatial. Participants receive an overall score of between 0-30. A normal score printed on the assessment states a score ≥ 26, however others decide to select an optimal cut off score to detect impairment with scores below this value which can range from between 20-26 (Cooley et al., 2015; Julayanont et al., 2014; Nazem et al., 2009; T. Smith et al., 2007; Waldron-Perrine & Axelrod, 2012). Participants were scored out of 30, with a normal score being equal to or greater than 26. A description of each task in the MoCa and the associated domain is presented in Table A11 and a copy of the question-and-answer sheet can be found in Figure A11.

Table A11. Montreal Cognitive Assessment tasks.

Task/Domain	Description
Visuospatial Executive	1) Participants are required to connect numbers to letters using a pen in ascending order (e.g. 1 – A – 2 – B – etc). 2) Participants are required to copy a drawing of a cube. 3) Participants are required to draw a clock in a blank space and set the time to 10 past 11.
Naming/ Language	Participants are required to verbally name three animals from images (camel, lion, rhino).
Memory	The examiner reads 5 words out loud at one word per second, which the participant is required to repeat. Participants are then told they will be asked to recall these words at the end of the test.
Attention	1) Examiner reads 5 numbers, participants are required to verbally repeat the sequence back to them.

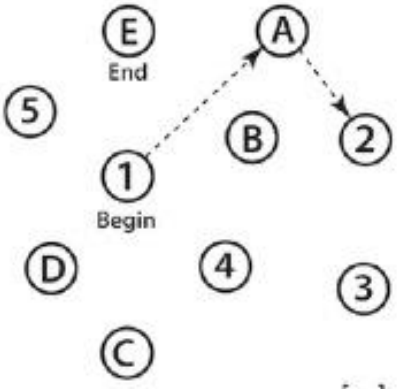
	2) Examiner reads 3 numbers, participants are required to say the numbers in the backwards order. 3) Examiner reads a list of letters, participants are required to tap their hand once every time they hear the letter A. 4) Participants are required to verbally count by subtracting 7 from 100 and continue to subtract 7 from each answer.
Language	1) The examiner reads 2 sentences which the participant is required to repeat. 2) The participant is required to say as many words beginning with the letter 'F' in 60s.
Abstraction/ Executive	Participants are required to explain what a pair of words have in common. This is repeated with a new pair of words.
Delayed Recall/ Memory	Participants are asked to recall the words from the earlier memory task.
Orientation/ Memory	Participants are required to tell the examiner, the date, month, year, place and city they are in.

Figure A11. Montreal Cognitive Assessment question-and-answer sheet.

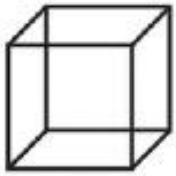
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE



Copy cube



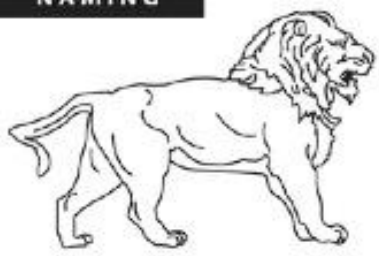
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

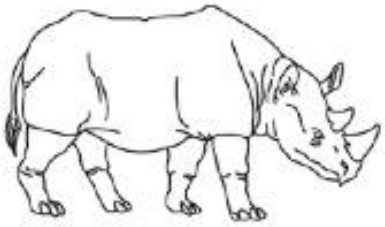
[ ] Contour [ ] Numbers [ ] Hands

POINTS __/5

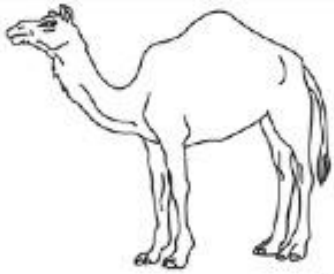
NAMING



[ ]



[ ]



[ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

Appendix 12. Occurrence of polymorphisms for dopamine genetic risk score

	DRD1 rs4532			DRD2 rs1800497			DRD3 rs6280			COMT rs4680			DAT rs28363170		
	A/A	A/G	G/G	C/C	C/T	T/T	T/T	C/T	C/C	G/G	G/A	A/A	9/9	9/10	10/10
Score	0	1	1	1	0	0	0	1	1	0	1	1	1	1	0
Predict freq	0.40	0.46	0.14	0.80	0.19	0.01	0.31	0.49	0.20	0.28	0.5	0.25	0.04	0.33	0.62
Actual freq	0.37	0.53	0.11	0.84	0.11	0.05	0.26	0.58	0.26	0.16	0.74	0.11	0.05	0.32	0.63

DRD1: dopamine receptor D1; DRD2: dopamine receptor D2; DRD3: dopamine receptor D3; COMT: catechol-O-methyltransferase; DAT: dopamine transporter. A: adenine; G: guanine; C: cytosine; T: thymine. Predict freq: expected mutation frequency in population. Actual freq: observed frequency in current population.

Appendix 13. Food Diary prior to blood samples

Name: _____

Participant ID (experimenter use only): _____

Date of visit 1: ____ /____ /_____ Time of visit 1: ____ : ____

Date of visit 2: ____ /____ /_____ Time of visit 2: ____ : ____

Date of visit 3: ____ /____ /_____ Time of visit 3: ____ : ____

Thank you again for agreeing to participate in this part of our study. Please complete the applicable information above about the three visits you will make to the University of Birmingham in order to give three blood samples. Please refer to the participant information sheet for information on the blood sampling and contact [redacted] for any further information or queries.

Please complete the food diary below for the 24 hours before each blood sample. Please remember to: i) avoid foods high in monoamine content for 24 hours prior to blood collection (please see information on page 2 ii) keep your diet consistent in the 24 hours prior to each session, assessed by the food diary, and iii) arrive for the session after an over-night fast (only consume water in the morning before blood sample i.e. don't have breakfast). You can resume your normal diet after the session.

	Breakfast	Lunch	Dinner	Snacks
24 hours before visit 1				
24 hours before visit 2				
24 hours before visit 3				

Foods high in monoamine content to avoid:

- strong or aged cheeses like cheddar, blue cheese, or gorgonzola
- cured or smoked meats or fish, such as sausage or salami
- beers on tap or home-brewed
- some overripe fruits
- certain beans, such as fava or broad beans
- some sauces or gravies like soy sauce, teriyaki sauce, or bouillon-based sauces
- pickled products like sauerkraut
- sourdough breads
- fermented soy products like miso soup, bean curd, or tempeh; some forms of tofu are also fermented and should be avoided such as “stinky tofu”
- avocados
- anchovies
- raspberries
- wines