MOVEMENT AND COGNITION IN AUTISM AND PARKINSON'S DISEASE: SIMILARITIES, POINTS OF DISTINCTION, AND UNDERLYING BIOLOGICAL MECHANISMS

by

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Abstract

An increased prevalence of Parkinson's Disease (PD) diagnosis is apparent in the autistic (ASD) population. However, genetic studies have failed to provide evidence for a strong link between the two conditions, meaning it may not be the case that autistic individuals are genetically more likely to develop PD. Anecdotally, movement differences in ASD have been likened to those exhibited by individuals with PD. Given that PD diagnosis is primarily movement-based, similarities in ASD and PD movement may explain the increased PD diagnosis prevalence in the autistic population: if it is indeed the case that autistic movement appears parkinsonian, this may facilitate autistic individuals meeting diagnostic criteria for PD. This could have serious implications for the specificity of the PD diagnostic process. With a lack of direct comparison studies assessing behavioural and cognitive profiles in ASD and PD, it is unclear whether quantifiable similarities exist between the two conditions. Extant evidence for a potential overlap between the two conditions relies on the comparison of findings from separate research studies, and thus is limited due to variation in participant demographics and tasks used.

In this thesis I conducted the first direct comparison of behavioural and cognitive profiles in ASD and PD, in addition to members of the general population. Chapter 2 demonstrated many similarities in the kinematic features of animations (free movement) produced by the ASD and PD groups, but only the similarity in jerk between ASD and PD was distinct from performance in the general population. All three groups were additionally comparable with respect to movement-based theory of mind ability. Chapter 3 conducted a more sensitive investigation of autistic and parkinsonian movement using a restricted movement task devoid of theory of mind demands. Here, kinematic features were uncovered that differed between the three groups (e.g., speed modulation, sub-movements and reaction time). This Chapter also determined the utility of movement assessments for classifying

group membership, demonstrating higher levels of classification accuracy when trait questionnaires were combined with kinematic features in a range of classification models. This highlights that clinical diagnostic processes may be improved through the incorporation of kinematic assessments.

Alongside providing insight into the behavioural and cognitive similarities between ASD and PD, the thesis presented novel findings with respect to ASD and PD separately. For example, Chapters 2 and 3 conducted the first kinematic assessments of older autistic adults, revealing that some, but not all, components of younger autistic movement remain distinct from non-autistic movement in older age. In addition, the first assessment of individuals with PD on the tasks presented in Chapters 2 and 3 revealed novel kinematic features that differed in this population (e.g., speed modulation), and patterns of movement speed differences between the two Chapters were aligned with the motor motivation hypothesis of PD.

Finally, Chapter 4 investigated biological mechanisms underlying movement differences between the three groups, setting out evidence from two pharmacological intervention studies. Specifically, movement differences resulting from PD dopaminergic medication and the dopamine antagonist haloperidol were explored. These studies implicated dopamine in a range of ASD- and PD-relevant kinematic features, strengthening the proposal that movement differences in ASD and PD are the product of dopaminergic mechanisms. Results across the three Chapters are consistent with hyper-dopaminergic functioning in ASD and hypo-dopaminergic functioning in PD. Overall, this thesis provides a greater understanding of the overlap between behavioural and cognitive presentations of ASD and PD, as well as underlying biological mechanisms which may account for this overlap.

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Table of Contents

List of Abbreviations

Analysis of Variance (ANOVA)
Autism Diagnostic Interview (ADI)
Autism Diagnostic Observation Schedule (ADOS)
Autism Quotient (AQ)
Autism Spectrum Disorder (ASD)
Bayes Factor (BF)
Body Mass Index (BMI)
Broad Autism Phenotype (BAP)
Broad Autism Phenotype Questionnaire (BAPQ)
Bruininks Motor Ability Test (BMAT)
Confidence Intervals (CI)
Control (CTRL)
Degrees of Freedom (DoF)
Deoxyribonucleic acid (DNA)
Dependent Variable (DV)
Diagnostic and Statistical Manual of Mental Disorders (DSM)
Dopamine (DA)
Generalised Anxiety Disorder Assessment (GAD)
Genome Wide Association Studies (GWAS)
Hi-C-coupled Multi-marker Analysis of GenoMic Annotation (H-MAGMA)
Intelligence Quotient (IQ)
International Classification of Diseases 10th Revision (ICD-10)
K-Nearest Neighbours (KNN)
Linear Mixed Model (LMM)
Linkage disequilibrium (LD)
Matrix Reasoning Item Bank (MaRs-IB)
Movement Assessment Battery for Children (MABC-2)
Movement Disorders Society (MDS)
Multiple-Choice Question (MCQ)
Multi-marker Analysis of GenoMic Annotation (MAGMA)
Parkinson's Disease (PD)
Patient Health Questionnaire (PHQ)
Polygenic Risk Scores (PRS)
Positron Emission Tomography (PET)
Random Forest (RF)
Ritvo Autism Asperger Diagnostic Scale (RAADS)
Single Nucleotide Polymorphisms (SNP)
Single-Photon Emission Computed Tomography (SPECT)
Spectral Arc Length (SPARC)
Standard Deviation (SD)
Standard Error (SE)
Support Vector Machine (SVM)
Toronto Alexithymia Scale (TAS)
Unified Parkinson's Disease Rating Scale (UPDRS)
United Kingdom (UK)
United States of America (USA)
Working Memory Capacity (WMC)

List of Figures

List of Tables

Chapter 1 – Introduction

1.1 General Introduction

Autism Spectrum Disorder (ASD, or autism[1]) is a developmental condition with known differences in social cognition, language and communication (American Psychiatric Association, 2013). However, recent studies have shed light upon movement differences in autism (Fournier et al., 2010; Gowen & Hamilton, 2013; Leary & Hill, 1996; Mari et al., 2003). Conversely, Parkinson's Disease (PD) is a neurodegenerative disorder characterised by differences in motor function including bradykinesia (slowed movement), gait differences and postural instability (Jankovic, 2008; Moustafa et al., 2016; Zanardi et al., 2021), but a growing body of research has highlighted differences in social and emotional processing (Czernecki et al., 2021). Thus, both conditions are characterised by co-occurring differences in motor function and social cognition (Eddy & Cook, 2018).

Overlapping traits in ASD and PD have garnered recent attention, with a number of review articles commenting on similarities at genetic, behavioural and cognitive levels (Hollander et al., 2009; Mai et al., 2023; Morato Torres et al., 2020). Such attention follows reports of alarmingly high rates of parkinsonism (i.e., PD symptoms) and PD diagnosis in ASD compared to the general population (Croen et al., 2015; Geurts et al., 2022; Hand et al., 2020; Starkstein et al., 2015). As such, a key question of interest is whether autistic individuals are indeed more likely to develop PD, or whether older autistic adults simply exhibit behaviour that looks like PD "from the outside". Genetic investigations of ASD and PD do link a number of PD-specific genes to ASD (Labonne et al., 2020; Yin et al., 2016),

[1] I will use identity-first terminology (e.g., "autistic person") following the preferences of the global autistic community (Keating et al., 2022).

however a strong genetic correlation between the two conditions is not apparent (Sey et al., 2020; Smeland et al., 2021). This lends weight to the theory that behavioural similarities between ASD and PD may at least be partly responsible for the increased PD diagnosis prevalence in the autistic population (hereafter "misdiagnosis hypothesis"). Given that PD assessments are primarily behavioural, and ancillary investigations are not common (Bloem et al., 2021), it is possible that PD diagnosis rates in ASD may be higher than in the general population due to movement similarities between the two groups. Further investigation of this theory becomes increasingly relevant as recent studies have proposed that movement differences could be used to algorithmically detect PD (e.g., Lamba et al., 2021). If this were the case, similarities between autistic and parkinsonian movement could lead to autistic individuals being classified into a PD group.

Early studies anecdotally highlight similarities between autistic and parkinsonian movement (Mari et al., 2003; Minshew et al., 2004; Vilensky et al., 1981). At present, no direct comparison studies exist between ASD and PD. Despite this, both conditions appear to show gait differences (Jankovic, 2008; Lum et al., 2021), postural instability (Jankovic, 2008; Minshew et al., 2004) and bradykinesia (Jankovic, 2008; Mari et al., 2003), all core features of PD. In addition, fine motor control similarities have been noted such as handwriting (Godde et al., 2018; Van Gemmert et al., 2003), as well as emotion production (Ricciardi et al., 2015; Trevisan et al., 2018). Aside from movement, various cognitive similarities are apparent between ASD and PD, most notably in terms of theory of mind (Peron et al., 2009; White et al., 2011) and emotion perception (Gray & Tickle-Degnen, 2010; Uljarevic & Hamilton, 2013), two domains which often rely on the interpretation of movement cues (Edey et al., 2017; Sowden et al., 2021). However, such similarities are drawn from separate research studies, meaning that results may be confounded by different sample demographics

or tasks used. As such, a primary aim of the current thesis was to conduct the first direct comparison study of autistic and parkinsonian movement, as well as movement-based theory of mind, whilst either matching or controlling for a range of confounding demographic variables. These studies also had the secondary benefit of adding to the sparce older autistic adult literature (Mason et al., 2022) and investigating movement-based theory of mind for the first time in PD.

Understanding the nature of the relationship between ASD and PD is of great importance for the autistic population. If it is the case that autistic individuals are more likely to develop PD, as demonstrated by a genetic overlap, this would highlight a need to adapt current clinical procedures. For example, greater awareness of the co-occurrence between the two conditions would be needed, as well as the establishment of interdisciplinary clinical care teams to ensure communication between movement disorder specialists and psychiatrists (as noted by Morato Torres et al., 2020). Conversely, if the overlap between ASD and PD is limited to behavioural and cognitive levels, it may be considered that such similarities between the two conditions plays a role in the increased prevalence of PD diagnosis in the autistic population. This would have serious implications from a clinical diagnostic point-of-view. If it is the case that older autistic individuals are sometimes falsely diagnosed with PD on the basis of outward appearances, and are potentially receiving unnecessary medications as a result, the PD diagnosis procedure must be overhauled to guard against this.

Any similarities between ASD and PD may arise from a common biological mechanism. Therefore, an additional aim of the thesis was to uncover the biological mechanisms underlying autistic and parkinsonian movement. Given that dopamine function has been linked to both ASD (Pavăl, 2017) and PD (Rizek et al., 2016), as well as movement

(Eichhorn et al., 1996; Lange et al., 2006; Quattrocchi et al., 2018; Tomassini et al., 2016), the second half of the thesis investigates the role of dopamine in a range of movement processes.

1.2 Literature Review

1.2.1 Overview on Autism

What is autism?

Autism is a condition characterised by socio-communicative differences and restricted or repetitive behaviours (American Psychiatric Association, 2013). It is considered a developmental condition, with characteristics emerging in early childhood. Approximately 1 in 100 individuals are diagnosed with autism globally (Zeidan et al., 2022). However, given a lack of diagnosis availability in developing countries and cultural differences affecting diagnosis rates (Onaolapo & Onaolapo, 2017), this prevalence may in fact be higher. A diagnosis is obtained through autism specialists, who use both interview-style and observational-based assessments to assess core autistic traits. Typically these diagnoses occur in childhood, but there is growing appreciation of the need to improve autism diagnosis processes in adulthood (Huang et al., 2020).

Whilst core features such as differences in social cognition have been extensively reviewed (e.g., Uljarevic & Hamilton, 2013; Wilson, 2021), there is a growing body of research suggesting movement differences in autism (Fournier et al., 2010; Wang et al., 2022). These differences emerge in childhood, both in the form of delayed motor development and motor atypicalities (Posar & Visconti, 2022). Varcin and Nelson (2016) noted that differences in motor processing are an important early indicator of autism, and therefore may hold utility as a biomarker of the condition. In addition, recent calls have been made to include movement differences as "specifiers" to autism diagnoses (i.e., condition-

relevant but non-selective symptoms used to further clarify a diagnosis; Licari et al., 2022). However, knowledge of movement differences in autism is not widespread. In a study of 2,084 autistic children, 35.4% of the sample met criteria for motor difficulties according to the Vineland Adaptive Behavior Scales (Sparrow & Cicchetti, 1985), but motor difficulties had only been reported by the participants' diagnosing clinicians in 1.34% of the sample (Licari et al., 2020). Thus, it is clear that more needs to be done to understand the movement profiles of autistic individuals.

Older autistic adult literature

Due to the developmental nature of autism, much research focuses on the stages of early childhood and adolescence. However, autism is a life-long condition, and it is important to understand how autism progresses across the lifespan. Unfortunately, there is a clear reduction in knowledge of the presentation and health implications of autism in later stages of life due to a lack of research studies conducted in older age groups, something which has been highlighted by numerous review papers (Happé & Charlton, 2011; Mukaetova-Ladinska et al., 2012; Sonido et al., 2020; Wright et al., 2019). A recent literature review conducted by Mason et al. (2022) suggests that autism research in older adults is becoming more abundant, with a 392% increase in older autistic adult research since 2012, compared to 196% in childhood, 254% in adolescents and 264% in adults. However, the authors note that there is still a long way to go, given that research into older autistic adults only made up 0.4% of all autism research published between 2012 and 2022.

Though studies are limited, we do now have some understanding of aging in autism. Whereas some abilities are lower than the general population throughout the lifespan in autism, this is not the case for all abilities. For example, executive dysfunction is apparent in autistic children and adults (Hill, 2004), but not all executive functions differ from the general

population in later life; attention, working memory and fluency appear to be lower in older autistic versus non-autistic adults, whereas other cognitive functions including planning and cognitive flexibility are comparable between groups (Geurts & Vissers, 2012). In addition, whilst poor quality of life, low health status and psychiatric symptoms are more common in autistic individuals – compared to their non-autistic counterparts – in both young and older adults (Lever & Geurts, 2016b; Rydzewska et al., 2019; van Heijst & Geurts, 2015; Yarar et al., 2022), clinical levels of psychiatric conditions such as anxiety, social phobia and eating disorders have been found to be more prevalent in younger compared to older autistic adults (Lever & Geurts, 2016b; Yarar et al., 2022). Finally, Yarar et al. (2020) reported no differences in theory of mind ability between young and older autistic adults. However, whilst young autistic adults performed less well than young non-autistic adults, a decline in performance with age in the non-autistic population meant that older autistic and non-autistic performance was comparable. These results, along with work by Lever and Geurts (2016a), highlight a discrepancy between autistic and non-autistic performance at a younger age that does not extend to older age (though see Torenvliet et al., 2022). Overall, this body of literature demonstrates that not all autistic traits follow the same trajectory across the lifespan.

A core problem with studying older autistic adults is that there are not many older adults diagnosed with autism. This is because diagnosis usually occurs in childhood and, given that autism was only added to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III in 1980, there is a "lost-generation" of adults with autism (Lai & Baron-Cohen, 2015). As such, some studies have opted to investigate the relationship between autistic *traits* in the older population and various dependent variables. For example, evidence that executive function is impaired in older autistic adults is supported by studies of autistic traits; Stewart et al. (2018) evidenced that individuals over the age of 60 classified as being on

the Broad Autism Phenotype (BAP) according to the BAP Questionnaire (BAPQ; Hurley et al., 2007) had poorer performance in working memory and episodic memory compared to non-BAP individuals (also see Stewart et al., 2023). In addition, elevated rates of psychiatric diagnoses have been observed in individuals with high compared to low levels of autistic traits in the older population (Stewart et al., 2021). By contrast, the theory of mind pattern of performance described previously for young and older autistic and non-autistic adults was not supported in a study of autistic traits (Stewart, Wallace, et al., 2020); here, BAP individuals exhibited poorer theory of mind performance than non-BAP individuals at both younger and older ages (in line with Torenvliet et al., 2022).

This thesis primarily focuses on movement; thus, it is relevant to note that studies of motor function in older autistic adults are not prominent in the literature. Indeed, Mason et al. (2022) categorised extant studies of older autistic adults into a number of themes, of which any mention to movement or motor function did not occur. Instead, the most popular themes were general health (8%), genetics (7.5%), reviews (7.5%) and cognition (7.1%). When inspecting the full list of studies acquired in their search, only one study made reference to older adult motor function (Linke et al., 2020). This study revealed poorer motor function in autistic adults as indexed by the Bruininks Motor Ability Test (BMAT; Bruininks & Bruininks, 1978). Autistic adults performed less well on BMAT subscales for manual dexterity, coordination, and strength and flexibility, but were comparable to non-autistic adults in fine motor, balance and mobility subscales. In addition, two papers in Mason's literature search made reference to parkinsonian-like traits in older autistic adults (one of which involved a behavioural assessment); these are discussed in-depth in the next section (Geurts et al., 2022; Starkstein et al., 2015). This limited literature clearly indicates a need for future work to fully identify and understand movement differences in older autistic adults.

Summary: Autism is a developmental condition associated with differences in both social cognition and motor function. Research into older autistic adults is sparse, with a particular lack of studies investigating movement differences in this age group.

1.2.2 Parkinson's Disease in the Autistic Population

A growing appreciation of links between developmental and neurodegenerative disorders, including both co-occurrence and overlapping symptoms, has emerged in recent years (Croen et al., 2015; Gupta et al., 2023; Hand et al., 2020; Morato Torres et al., 2020). The current thesis focuses on links between autism and Parkinson's Disease specifically.

What is Parkinson's Disease?

Parkinson's Disease is a neurodegenerative condition characterised by bradykinesia (slowed movement), tremors and muscular rigidity (Jankovic, 2008; Moustafa et al., 2016; Rizek et al., 2016; Uwishema et al., 2022; Zanardi et al., 2021). A wide range of non-motor symptoms are also apparent including mood disorders, cognitive decline, and sleep problems (Czernecki et al., 2021; Rizek et al., 2016; Uwishema et al., 2022). PD is caused by degeneration of dopamine neurons in the substantia nigra of the basal ganglia and the accumulation of Lewy bodies composed of misfolded α-synuclein (Kalia & Kalia, 2015; Rizek et al., 2016), with symptoms worsening following progression of these pathologies. Whilst dopaminergic medication (e.g., levodopa and dopamine agonists) can treat symptoms to an extent, degeneration continues over time and medications become less effective.

Diagnosing PD generally follows a procedure in which behavioural indicators (including bradykinesia and at least one of three core features: rigidity, resting tremor, postural instability) are integrated with observations of patients' responses to dopamine agonists (Jankovic, 2008; Rizek et al., 2016). Whilst ancillary investigations are not common

(Bloem et al., 2021), more complex cases may be subject to various forms of imaging (e.g., positron emission tomography (PET) or single-photon emission computed tomography (SPECT)) to differentiate PD from other parkinsonian disorders.

Is Parkinson's Disease prevalent in autism?

Current studies within the autism literature point to an increased prevalence of parkinsonism in the autistic population. Starkstein et al. (2015) conducted an examination of parkinsonian motor signs in autistic adults using the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS; Martínez-Martín et al., 1994). They reported that 32% of their test sample met the diagnostic criteria for parkinsonism, with 25% of individuals not taking antipsychotic medications meeting the criteria. Similarly, a study of autistic adolescents revealed significantly more bradykinetic and rigid motor behaviour in the autistic group compared to the non-autistic group as measured by the UPDRS (Mostert-Kerckhoffs et al., 2020). A further study of 296 autistic participants from the Netherlands and 209 autistic participants from the USA demonstrated positive screening for parkinsonism via the Parkinsonism Screening Questionnaire in 17% and 33% of autistic participants respectively (Geurts et al., 2022). Together these studies demonstrate that high levels of parkinsonism are observed when conducting PD assessments in an autistic sample.

Importantly, these studies consider the relevance of antipsychotics. Antipsychotic medication is commonly prescribed in the autistic population (Houghton et al., 2017), and has been found to cause parkinsonism (Brigo et al., 2014). As such, increased parkinsonism in ASD may be due to the high use of antipsychotics in this group compared to the general population. Reassuringly, both Starkstein and Mostert-Kerckhoff's studies demonstrated elevated parkinsonism in samples of autistic individuals *not* taking antipsychotics. In addition, Geurts' study failed to find a difference in antipsychotic use between samples with and

without parkinsonism. Thus, the idea that high rates of parkinsonism only arise from high prevalence of antipsychotic use is rejected.

Turning to studies of PD diagnosis prevalence, Croen et al. (2015), who conducted a study of the health status of autistic individuals, reported a PD prevalence of 0.93% compared to 0.03% in the non-autistic sample. Whilst this value is lower than the percentages of parkinsonism reported by Starkstein et al. (2015) and Geurts et al. (2022), the discrepancy in findings may be accounted for by the age groups sampled. All participants in Starkstein's study were over the age of 39, whereas only 20.7% of the autistic individuals sampled by Croen and colleagues were over the age of 39. Participants in Geurts' study were over the age of 50, compared to 9.5% of the sample studied by Croen et al. (2015). It is likely that PD prevalence rates would be higher in older populations. Indeed, when Hand et al. (2020) assessed PD prevalence rates in an older sample of over 65 year olds, a prevalence of 6.6% was reported in a sample of 4785 autistic individuals compared to a 1.2% PD diagnosis prevalence in the non-autistic population. These prevalence rates are substantially higher that those reported by Croen and colleagues. Overall, whilst PD prevalence rates in the autistic population may not be as high as the number of individuals passing parkinsonism screening assessments, it is clear that PD diagnoses are much more prevalent in the autistic population than in the non-autistic population.

Summary: Parkinson's Disease is a neurodegenerative condition characterised by movement differences. Increased parkinsonism and Parkinson's Disease diagnosis prevalence is apparent in the autistic population compared to the non-autistic population.

1.2.3 Autism and Parkinson's Disease Genetic Overlap

Following reports of an increased prevalence of Parkinson's Disease diagnosis and parkinsonism in the autistic population (Croen et al., 2015; Geurts et al., 2022; Hand et al., 2020; Starkstein et al., 2015), it is important to determine whether it is the case that autistic individuals are indeed more likely to develop PD. A crucial step towards answering this question is to determine the genetic relationship between ASD and PD – that is, whether there is overlap between the genes associated with ASD and the genes associated with PD.

Specific genes

Genetic investigations of PD have resulted in the discovery of a number of important risk genes for PD (Bloem et al., 2021; Nuytemans et al., 2010). Interestingly, many of these genes have also been associated with ASD, including PARK2 (Conceição et al., 2017; Glessner et al., 2009; Yin et al., 2016), PINK1 (Zhou et al., 2019) and LRRK2 (Labonne et al., 2020). Therefore, it is likely that the DNA of autistic individuals will contain some important PD risk genes, meaning that they may have a genetic predisposition to PD. Beyond these PD risk genes, a range of other genes have been implicated in the genetic aetiologies of both ASD and PD, such as RIT2 (Emamalizadeh et al., 2017), Sema5a (Ding et al., 2008; Melin et al., 2006), CNTNAP4 (Wang et al., 2010; Zhang et al., 2020), RAB39B (Mata et al., 2015; Woodbury-Smith et al., 2017), GPR38/PaelR (Fujita-Jimbo et al., 2012) and CD38 and CD157/BST1 (Higashida et al., 2019; Yokoyama et al., 2015). However, this evidence overlooks the fact that genetic aetiologies for conditions are not comprised of a single gene, rather a combination of many risk variants. A broader picture of polygenic overlap is necessary to more fully understand the genetic relationship between ASD and PD.

Genome wide association studies

There are locations throughout a person's DNA in which differences in nucleotides can be found. These specific locations are referred to as single nucleotide polymorphisms (SNPs), which are the most common form of genetic variation. SNPs are often located within genes, meaning they can affect the functioning of the gene and are causally implicated in different conditions. Genome wide association studies (GWAS) have been conducted for both ASD and PD in which summary statistics provide a measure of effect size for each SNP with regards to their association with the condition. A recent GWAS for ASD was conducted by Grove et al. (2019), in which summary statistics were generated from 18,381 cases and 27,969 controls. All cases were diagnosed with ASD before 2013 by a psychiatrist according to International Classification of Diseases 10th Revision (ICD-10; DiSantostefano, 2009). Turning to PD, Nalls et al. (2019) generated summary statistics from 37,688 individuals with PD, 18,618 UK Biobank proxy-cases who have a first degree relative with PD, and 1,417,791 controls. Information regarding which SNPs are associated with each condition can be used to further understand the genetic overlap between ASD and PD.

Genetic overlap

GWAS summary statistics for ASD and PD can be compared to identify the extent to which SNPs are associated with both conditions, for example by employing the cross-trait Linkage Disequilibrium Score Regression technique (Bulik-Sullivan et al., 2015). This technique incorporates knowledge of linkage disequilibrium (LD), the non-random association of variants at different positions of the genome. More specifically, LD scores can be calculated for each SNP as the sum of its correlations with all other SNPs. If an SNP has a large LD score, it is more likely to be associated with a causal variant and therefore the specified trait. It is necessary to account for LD scores when investigating the links between

genotypes and phenotypes to ensure that causal SNPs are identified rather than SNPs associated with causal variants due to large LD scores.

Null results have been presented when assessing the polygenic relationship between ASD and PD via cross-trait Linkage Disequilibrium Score Regression. The Brainstorm Consortium et al. (2018) reported a non-significant (but numerically negative) genetic correlation between ASD and PD (correlation = -0.20) using ASD GWAS data from The Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium (2017) and PD GWAS data from Nalls et al. (2014). Sey et al. (2020) also found a non-significant (but numerically positive) genetic correlation between ASD and PD (correlation = 0.02) using more recent GWAS data from Grove et al. (2019) and Nalls et al. (2019) respectively. In addition, Smeland et al. (2021) reported no evidence for cross-trait enrichment between ASD and PD when using GWAS data from Grove et al. (2019) and Nalls et al. (2019). It is possible that relationships may emerge with the development of larger GWAS. However, overall, these studies clearly suggest that the genetics underlying ASD and PD are not significantly correlated.

To address the limited power that arises from focusing on individual genes, methods which group genes prior to analysis may increase the likelihood of uncovering a genetic relationship between conditions. A technique called Multi-marker Analysis of GenoMic Annotation (MAGMA) has been developed which collapses GWAS data into gene-level groupings prior to assessing genotype-phenotype relationships or genetic relationships between conditions (de Leeuw et al., 2015). This approach has provided novel insight into ASD-related genes (Grove et al., 2019). Sey et al. (2020) used a modified version of this technique known as Hi-C-coupled MAGMA (H-MAGMA) to provide insight into gene-level overlap between ASD and PD. Again, no genetic relationship was found between ASD and

PD using GWAS data from Grove et al. (2019) and Nalls et al. (2019). Thus, no studies at present provide convincing evidence that ASD and PD are genetically correlated.

Genetic risk

An additional approach for investigating the genetic overlap of conditions is facilitated by the calculation of polygenic risk scores (PRS). PRS are a single value estimate of an individual's propensity to a phenotype and can be calculated using individual-level genetic data and GWAS data for the phenotype of interest (Choi et al., 2018). Specifically, PRS are calculated as the sum of risk variants corresponding to the phenotype of interest, weighted by the effect size estimate from a GWAS on the phenotype. PRS have utility in predicting symptoms of both ASD and PD. For example, PD PRS have been associated with cognitive and motor decline in PD (Paul et al., 2018) and ASD PRS have been associated with infant neuromotor development (Serdarevic et al., 2020). Calculating participants' PRS for both ASD and PD can provide insight into genetic overlap. In a large sample of participants, a significant correlation between PRS for ASD and PD would indicate that there is shared genetic risk for PD and ASD. Ellis et al. (2020) calculated a range of polygenic risk scores for 5160 individuals with Huntington's Disease, including those relating to ASD and PD using the Grove et al. (2019) and Nalls et al. (2019) GWAS datasets. No significant correlation was found between ASD and PD PRS.

Family studies

A small amount of genetic overlap is expected between first-degree relatives. Therefore, if autistic individuals have increased levels of PD risk genes, first-degree relatives of autistic individuals are more likely to have these genes than members of the general population. This means that if autistic individuals are genetically more likely to develop PD, this should extend to first-degree relatives of autistic individuals, albeit to a lesser extent.

Interestingly, a study of older individuals with (N = 739) and without (N = 11,666) a first-degree autistic relative revealed that the two groups did not significantly differ in their rates of PD diagnosis (Stewart, Corbett, et al., 2020). This brings into question whether the increased prevalence of parkinsonism and PD diagnosis in the autistic population arises from increased genetic risk, and raises the possibility that this result stems from the presence of PD-like movement characteristics in the autistic population (i.e., the misdiagnosis hypothesis).

Summary: Whilst specific PD genes have been linked to ASD, a significant genetic correlation between the two conditions is not apparent.

1.2.4 Movement in Autism and Parkinson's Disease

It is possible that an increased prevalence of parkinsonism in the autistic population is due to movement similarities between the two conditions. Whilst anecdotal evidence supports such similarities (Figure 1.1), autistic and parkinsonian movement have never been directly compared. As such, we rely on interpretation of each separate research silo to build a picture of whether movement similarities exist.

Figure 1.1

Anecdotal Evidence for Overlap Between Autism and Parkinson's Disease

"The connection you are investigating between PD and autism is of interest to me as 18 months prior to my diagnosis my husband used to observe that I didn't swing my arms when walking. He used to liken me to a character called Jake in a drama called Touch. Jake was, I believe, on the autism spectrum."

"What caught my eyes when I read about the trial on similarities between PD movements and Autism movements is that I have been showing signals of PD since my childhood. On top of that, my sister, who is a doctor, insists that she can see Autism in my behaviour, although I am 56 and I was never diagnosed by a specialist as being autistic."

"My wife worked with teenagers with Asperger's for many years. Only a couple days ago she said I have started walking in a similar way to some of her students."

Note. Figure contains quotes from participants with Parkinson's Disease referencing observed links to autistic behaviour.

Gross motor function

Much of the behavioural overlap between ASD and PD falls under the category of motor differences, with both conditions exhibiting differences in gross motor function. The defining characteristics of PD (e.g., slowed movement, problems with gait and posture; Jankovic, 2008) cause disruption to everyday activities. Indeed, the UPDRS diagnostic tool includes questions relating to eating, dressing and getting out of a chair. Similarly, studies of autistic individuals have revealed difficulties with gross motor tasks (Ament et al., 2015; Green et al., 2009; Liu, 2013; Staples & Reid, 2010). The use of the Movement Assessment Battery for Children (MABC-2) has highlighted particular impairments in everyday tasks involving catching and balance (Ament et al., 2015). Green et al. (2009) revealed that, in a sample of 101 autistic participants, 79% had "definite" movement problems on the M-ABC and an additional 10% were borderline. Such difficulties with gross motor function can be better understood through the examination of specific motor function and movement differences.

Despite a lack of direct comparison studies between ASD and PD, there are many examples of early studies of autistic behaviour noting similarities between autistic and parkinsonian motor function. Bradykinesia – or slowness of movement – is a core feature of parkinsonian movement (Jankovic, 2008) that has also been reported in the autistic population (e.g., Mari et al., 2003; Maurer & Damasio, 1982). Mari et al. (2003) stated explicitly that the slowed movement they observed in ASD had "a strong resemblance to Parkinsonian-type bradykinesia". Similarly, individuals with PD often exhibit a complete freezing during their movements, a form of akinesia (Perez-Lloret et al., 2014). This can be likened to catatonia, characterised by a lack of movement, which has been observed in ASD (Kakooza-Mwesige et al., 2008; Mazzone et al., 2014; Realmuto & August, 1991; Wing & Shah, 2000). Severe

catatonic features have been reported by 17% of caregivers of autistic individuals over the age of 15 (Wing & Shah, 2018). Thus, a slowness (or absence) of movement is characteristic of both ASD and PD.

Gait differences are also apparent in both conditions. Indeed, Vilensky et al. (1981) conducted a study of autistic movement and stated that "the gait differences between the autistic and normal subjects resembled differences between the gaits of parkinsonian patients and of normal adults". Difference in gait is a core feature of PD (Jankovic, 2008; Mazzoni et al., 2012); a meta-analysis of 72 studies reported reduced baseline walking speed, stride length, swing time and hip excursion in PD (Zanardi et al., 2021). Multiple studies have highlighted gait differences in autistic compared to non-autistic individuals including increased stance time and reduced stride length (Vilensky et al., 1981), increased stride length variability (Rinehart, Tonge, Iansek, et al., 2006), a lack of smoothness in gait (Nobile et al., 2011; Rinehart, Tonge, Iansek, et al., 2006), and a difficulty following a straight line (Nobile et al., 2011; Rinehart, Tonge, Bradshaw, et al., 2006). A recent meta-analysis of 18 studies highlighted extensive gait abnormalities in autism (Lum et al., 2021). Thus, as highlighted by Vilensky et al. (1981), gait differences are apparent in both ASD and PD.

Gait differences are related to postural instability, another key characteristic of PD. Individuals with PD often exhibit rigidity in the neck, trunk, elbows and knees resulting in flexed posture, and struggle to readjust and maintain posture due to the loss of postural reflexes (Jankovic, 2008). Comparably, differences observed in ASD include postural abnormalities in the trunk (Nobile et al., 2011; Rinehart, Tonge, Bradshaw, et al., 2006), head (Rinehart, Tonge, Bradshaw, et al., 2006) and arms (Rinehart, Tonge, Iansek, et al., 2006), and autistic individuals have been found to struggle to make adjustments to posture as seen in PD (Maurer & Damasio, 1982). Reduced postural stability in autism has been explicitly

likened to that of PD by Minshew et al. (2004): "this type of generalized postural dysfunction [observed in autistic participants] can be seen with Parkinson disease".

It is clear that autistic movement can be likened to the core features of PD including bradykinesia, gait differences, and postural instability. Given that PD diagnosis relies on behavioural measures indexing these movement features, it is clear how an autistic individual may present with elevated parkinsonian traits during such an assessment.

Fine motor function

When examining performance on fine motor tasks, such as handwriting, differences have been found in both ASD and PD (Beversdorf et al., 2001; Godde et al., 2018; Grace et al., 2017; Johnson et al., 2013; McLennan et al., 1972; Thomas et al., 2017; Van Gemmert et al., 2003). Specifically, autistic individuals have been found to produce handwriting with larger stroke height and width or "macrographia" (Beversdorf et al., 2001; Johnson et al., 2013), greater size variability (Godde et al., 2018; Grace et al., 2017; Johnson et al., 2013) and with less fluency (Godde et al., 2018; Grace et al., 2017) compared to non-autistic individuals. Within the PD population, handwriting is also observed to have less fluency (Thomas et al., 2017). However, contrary to what is seen in ASD, smaller handwriting or "micrographia" is often observed in PD (McLennan et al., 1972; Thomas et al., 2017; Van Gemmert et al., 2003).

In addition to differences in the handwriting produced, the *way* in which handwriting movements are made varies in ASD and PD (as characterised by "kinematic features" extracted from movement trajectories). One key example is jerk – or the rate of change in the acceleration profile. Individuals in the general population move with a profile that is consistent with the minimum mean squared jerk model (Flash & Hogan, 1985; Todorov & Jordan, 1998). Here, point-to-point movements are made by accelerating and decelerating

gradually, which minimises jerk. By contrast, kinematic analyses have revealed increased jerk in the movement profiles of autistic individuals (Cook et al., 2013; Edey et al., 2016) and individuals with PD (Alberts et al., 2000). A lack of movement smoothness is also reflected in an increased number of sub-movements (or alternations between acceleration and deceleration) in both ASD (Cook et al., 2023) and PD (Castiello et al., 2000; Flash et al., 1992; Lange et al., 2006). However, ASD and PD may differ with respect to velocity and acceleration in fine motor control: whilst the slowness of movement observed in gross motor function tests in PD appears to extend to fine motor function (Alberts et al., 2000; Broderick et al., 2009; Flash et al., 1992; Jankovic, 2008; Lange et al., 2006; Van Gemmert et al., 2003; Viviani et al., 2009), faster movement profiles have been observed in ASD handwriting (Cook et al., 2013; Grace et al., 2017; Johnson et al., 2013). Thus, it is likely that ASD and PD have both similarities and differences in the kinematic features of their movement profiles.

It is particularly important to quantify similarities between ASD and PD handwriting given the suggestion from an increasing number of studies to use handwriting analysis as a method of PD diagnosis (Al-Yousef et al., 2020; Carvajal-Castano et al., 2022; Dehghanpur Deharab & Ghaderyan, 2022; Drotár et al., 2016; Gerger & Gümüşçü, 2022; Kamble et al., 2021; Lamba et al., 2021; Netšunajev et al., 2021; Rios-Urrego et al., 2019). If similarities between ASD and PD handwriting features are found in direct comparison studies, the use of such methods to diagnose PD may lead to an increased misdiagnosis of PD in the autistic population.

Emotion expression

Movement cues are often used to express emotions, both in terms of facial expressions and full body movements (e.g., Dael et al., 2012; Edey et al., 2017; Sowden et al., 2021). For example, fast movements are often associated with high arousal emotions such as anger and

happiness, whereas slower movements are often interpreted as communicating sadness. Given differences in motor function in both PD and ASD, it is unsurprising that studies have highlighted differences in emotion expression in the two populations.

Reduced expressivity has been reported in PD facial expressions (e.g., Jacobs et al., 1995; Peron et al., 2012; Ricciardi et al., 2015). This is the case for both static and dynamic facial expressions, with particular impairments in producing "happy" and "surprise" emotions (Ricciardi et al., 2015). In addition to reduced expressivity ratings from observers, analysis of movement distance between neutral and emotional facial expressions has confirmed a reduction in expressivity in PD compared to the general population (Bandini et al., 2017). Further to this, analysis of facial expression kinematics in PD has revealed lower peak velocity in posed smiling and voluntary grinning (Marsili et al., 2014). These findings are expected given that slowed movement is a core feature of PD. Importantly, the ability of the general population to correctly identify emotions expressed by individuals with PD is lower compared to inferences made regarding non-PD emotional expressions (Ricciardi et al., 2017). Thus, these movement differences translate to real-world emotional communication difficulties.

In parallel, differences in facial expression production have been noted in autism (Keating & Cook, 2020). A recent meta-analysis by Trevisan et al. (2018) determined that autistic individuals produce facial expressions less frequently and for shorter periods of time (e.g., Czapinski & Bryson, 2003; Loveland et al., 1994). Contrary to what has been found in the PD literature, autistic emotional expressions do not appear to be less intense than the general population (e.g., Mathersul et al., 2013). However, as in PD, autistic facial expressions are less accurately perceived by the general population (e.g., Brewer et al., 2016). It is clear that there is a reduced ability of the general population to correctly identify

emotional facial expressions produced by both ASD and PD. This is particularly important as a reduced ability to convey emotions in ways others can understand can cause stigma, dehumanisation and loneliness (Prenger et al., 2020).

The reduction of emotional facial expression in PD has been found to extend to the production of emotional speech (Peron et al., 2012; Schroder et al., 2010). Similarly, differences in vocal production have been noted in studies of autism (Fusaroli et al., 2017), in addition to lower subjective ratings of the emotion produced in spontaneous speech (Hubbard & Trauner, 2007). It is also highly relevant to note that autistic diagnostic criteria in both the Autism Diagnostic Interview (ADI) and Autism Diagnostic Observation Schedule (ADOS) include specific mentions of prosody (Lord et al., 2000; Lord et al., 1994). This highlights a clear link between a diagnostic feature of autism and traits observed in PD.

Summary: A range of similar movement differences have been observed in ASD and PD including, gross motor function, fine motor control and emotion expression. Due to a lack of direct comparison studies, this insight comes from comparing separate research studies in ASD and PD populations.

1.2.5 Cognition in Autism and Parkinson's Disease

Social cognition

As discussed, both ASD and PD populations exhibit differences in emotion expression, leading to less accurate perception by the general population (e.g., Brewer et al., 2016; Ricciardi et al., 2017). However, from the perspective of the *clinical groups*, it is the general population who express emotions using different movement cues. As such, it follows that ASD and PD populations would have difficulty perceiving emotional expressions made by the general population. Indeed, a meta-analysis of 34 studies revealed deficits of

individuals with PD in recognising both facial and vocal emotion (Gray & Tickle-Degnen, 2010), two areas in which differences in production have been observed (Peron et al., 2012). Though worse performance has been observed when individuals with PD are not taking dopaminergic medication, both medicated and unmedicated groups have been found to have a difference in emotion recognition ability relative to the general population (Sprengelmeyer et al., 2003). A relationship between emotion production and perception has been explicitly evidenced by Ricciardi et al. (2015) and Ricciardi et al. (2017), who demonstrate a positive correlation between scores on a task of facial emotion recognition (the Ekman Test) and ratings of expressiveness in facial expression production. Alongside this PD literature, a number of meta-analyses have provided evidence for emotion recognition differences in ASD (Lozier et al., 2014; Uljarevic & Hamilton, 2013). Certain studies have reported selective impairments in the recognition of anger in ASD (Keating et al., 2022; Lozier et al., 2014). Similarly, studies in PD have provided evidence for worse performance in recognising negative emotions including anger (Lawrence et al., 2007; Sprengelmeyer et al., 2003), disgust (Sprengelmeyer et al., 2003; Suzuki et al., 2006), fear and sadness (Ariatti et al., 2008).

In addition to emotion recognition, differences in theory of mind attribution have been reported in both groups. Appropriate mental state attribution has been tested in many paradigms including those using static images, stories and dynamic movement-based stimuli. For example, the Reading the Mind in the Eyes Test requires participants to interpret images of the eye region by selecting a word that best describes what the individual is thinking or feeling (Baron-Cohen et al., 2001). Whilst this task has been commonly used to evidence differences in theory of mind ability in both ASD and PD (Bodden et al., 2010; Orso et al., 2020; Penuelas-Calvo et al., 2019; Seubert-Ravelo et al., 2021), the task itself has come under

heavy criticism with suggestions that its task demands are more akin to emotion recognition (Oakley et al., 2016; Quesque & Rossetti, 2020). The Yoni Task (Shamay-Tsoory & Aharon-Peretz, 2007), by contrast, takes a story-based approach in which participants are asked to select the appropriate picture to answer first-order questions (e.g., what Yoni identifies with) and second-order questions (e.g., whose success Yoni envies). This task has been used to show differences in performance by both ASD (Tin et al., 2018) and PD (Bodden et al., 2010) groups. The Faux Pas Test (Stone et al., 1998) employs situational judgement questions; participants are asked to identify whether stories contain a faux pas or a minor conflict but no faux pas. Both PD (Del Prete et al., 2020; Kawamura & Koyama, 2007; Peron et al., 2009; Roca et al., 2010) and ASD (Tin et al., 2018) have demonstrated impaired performance on this task. Finally, the Animation Perception Task uses dynamic movement-based stimuli to express mental states (i.e., two triangles move around the screen to depict various mental states). Whilst this task has not been conducted in PD, autistic individuals exhibit a reduction in the use of mental state words, and the use of inappropriate mental state words, to describe animations (Abell et al., 2000; Castelli et al., 2002; Livingston et al., 2021; White et al., 2011; Wilson, 2021). In sum, ASD and PD appear to exhibit differences in theory of mind ability across a range of tasks.

Motivation

Differences in socio-cognitive performance in ASD and PD may relate to differences in motivation and reward processing. A paper by Contreras-Huerta et al. (2020) argued that, whilst the majority of socio-cognitive studies focus on whether or not an individual has the capacity to complete a given task, one's motivation to complete the task is often overlooked. A lack of motivation is common in individuals with PD (Pedersen et al., 2009). This may be due to a combination of a reduction in reward sensitivity and an increase in perceived effort

costs causing individuals to choose not to act (Le Heron et al., 2018; Muhammed et al., 2016). A lack of motivation in PD has been explicitly linked to task performance in the motor domain. Mazzoni et al. (2007) highlighted that individuals with PD were able to perform a set number of movements within a required speed range, but that the number of attempts to reach this criterion were higher than in members of the general population. These findings informed the motor motivation hypothesis, which states that slowness of movement in PD is not due to an *inability* to move quickly, rather a lack of motivation to do so arising from an altered cost-benefit ratio. Further evidence for the motor motivation hypothesis comes from Gepshtein et al. (2014); participants with PD completed a rapid sequential movement task in which hitting targets and penalties led to monetary gain and loss respectively. PD participants behaved similarly to that of an "ideal planner" in low energy cost conditions: when movements were assisted by gravity the PD participants were able to account for their individual motor variability in order to maximise expected monetary gain. However, when energy costs were increased by countering movements against gravity, performance in the PD group decreased. Thus, it appears that modifying the cost-reward trade-off can motivate individuals with PD to successfully complete motor tasks.

A role for motivation has also been proposed to account for autistic traits. The social motivation hypothesis of autism posited that socio-communicative autistic traits arise from a lack of motivation to engage in social situations as autistic individuals find social stimuli less rewarding (Chevallier et al., 2012). It has since been concluded, however, that differences in reward sensitivity extend to both social and non-social stimuli (Clements et al., 2018). For example, as in PD, decreased reward sensitivity in ASD has been seen to affect individuals' effort-based decision making (Damiano et al., 2012). It is possible that apparent "differences"

in various behavioural and cognitive domains in ASD and PD may instead arise from differences in motivation and reward processing in the two groups.

Cognitive rigidity

Both ASD and PD have been associated with cognitive rigidity and a difficulty switching between tasks. A recent review reported that a lack of flexibility is common in executive function assessments in ASD (Craig et al., 2016). Meta-analytical evidence highlights difficulties in set-shifting in the Wisconsin Card Sorting Test (Westwood et al., 2016). Further to this, a study by Watanabe et al. (2019) observed that autistic individuals were less likely than non-autistic individuals to deviate from a chosen task in a spontaneous task-switching test, instead opting to repeat the same task. Interestingly, the rigidity of this behaviour was associated with the severity of their restricted repetitive behaviours, a core characteristic of autism (American Psychiatric Association, 2013). Turning to PD, executive dysfunction is considered a core cognitive feature of the condition and an impairment in task switching specifically has been observed using measures such as the Wisconsin Card Sorting Test (Dirnberger & Jahanshahi, 2013). It has also been noted by Hollander et al. (2009) that repetitive behaviours are prevalent in both ASD and PD. Overall, it is clear that cognitive rigidity and task switching difficulties are core characteristics of both ASD and PD.

Summary: Similar cognitive profiles exist in ASD and PD, including differences compared to the general population in emotion perception and theory of mind ability, motivation and reward sensitivity, and executive functions including task switching (i.e., cognitive rigidity).

1.2.6 Limitations of Existing Research

Although behavioural and cognitive similarities have been observed between ASD and PD, evidence comes from distinct research silos. Consequently, there are many forms of variation in participant samples and experimental design which may inhibit the ability to directly compare results.

Differences in group demographics

Given that there are no direct comparison studies comparing ASD and PD, demographic differences in extant studies are apparent. For example, PD studies often recruit individuals from an older age group compared to ASD studies, and other demographic factors such as gender and Intelligence Quotient (IQ) may not be comparable. These differences between groups may either obscure behavioural or cognitive similarities that exist, or facilitate the observation of apparent similarities which would not exist for matched groups.

As previously noted, only 0.4% of autism studies between 2012 and 2022 recruited older adults (Mason et al., 2022). By contrast, due to the late onset of PD, studies of PD tend to recruit individuals over the age of 50. This is problematic because both movement and theory of mind ability have been found to vary with age (Ketcham et al., 2002; Maylor et al., 2002; Pardini & Nichelli, 2009). A meaningful comparison between ASD and PD must therefore be made between similarly aged groups. Whilst studies of older autistic adults exist, the movement literature is extremely limited (note that only two studies were identified in a meta-analysis by Mason et al., 2022). This means that, at present, it is not possible to compare movement studies across autistic individuals and individuals with PD from similar age groups. Turning to theory of mind, whilst some studies of older autistic adults exist, the findings are mixed. Some studies have shown that differences in theory of mind ability extend into older autistic adulthood (Torenvliet et al., 2022), whereas others report a possible age

protective effect whereby differences between autistic and non-autistic individuals are not apparent in older age (Lever & Geurts, 2016a; Yarar et al., 2020). As such, it is unclear whether older autistic adult performance on theory of mind tasks is comparable or not to that of individuals with PD.

Beyond age, other demographic factors have been associated with movement and theory of mind ability which are likely to differ between samples, including gender (Baron-Cohen et al., 2015; Kirkland et al., 2013; Miller & Cronin-Golomb, 2010) and IQ (Buitelaar et al., 1999; Forti et al., 2011). This means that differences between groups may arise from variability in demographic factors. Importantly, elevated traits of depression, anxiety and alexithymia have been observed in both ASD (Hollocks et al., 2019; Kinnaird et al., 2019) and PD (Alvarado-Bolanos et al., 2020; Broen et al., 2016; Reijnders et al., 2008). Given that these clinical traits have been associated with movement and theory of mind ability (Hezel & McNally, 2014; Nestor et al., 2022; Pijpers et al., 2005; Pisani et al., 2021; Sachdev & Aniss, 1994), it is possible that similarities inferred between ASD and PD in these domains may be the result of co-occurring clinical traits rather than the conditions themselves.

Overlooked experimental paradigms

Comparing separate ASD and PD literature is further limited by the wide variety of tasks used. For example, theory of mind tasks require inferences to be made from a range of stimuli including static images (e.g., Reading the Mind in the Eyes Test), dynamic movement-based stimuli (e.g., the Animation Perception Task), and descriptions/depictions of situations (e.g., the Yoni Task; the Faux Pas Test). Each of these tasks tap into different aspects of theory of mind; the Faux Pas Test is purely situational whereas the Animation Perception Task relies purely on movement cues to represent mental states. It is unclear whether these measures are generalisable, meaning that existing studies in the ASD and PD literature may

not be comparable. Given differences in movement in both groups, it is likely that both autistic individuals and individuals with PD exhibit differences in movement-based theory of mind. However, no studies using the Animation Perception Task exist in the PD population. Further, whilst some measures of theory of mind have been used independently in older autistic adults (e.g., the Faux Pas Test; Lever & Geurts, 2016a; Torenvliet et al., 2022), the Animation Perception Task has only been used as part of a composite theory of mind score (Yarar et al., 2020). As such, it is unclear whether individuals with PD and older autistic adults have specific differences in movement-based theory of mind.

With respect to movement, various measures have been used to quantify differences between clinical groups and the general population including gait measures and emotion expression. Handwriting and other simple drawing tasks, in particular, have been widely analysed in both groups to quantify kinematic features (Beversdorf et al., 2001; Godde et al., 2018; Grace et al., 2017; Johnson et al., 2013; McLennan et al., 1972; Thomas et al., 2017; Van Gemmert et al., 2003). However, whilst a small number of movement studies exist in older autistic adults, the measures have been restricted to standardised tests such as the BMAT and UPDRS which assess the ability to successfully complete motor function tasks including finger tapping and force exertion (Linke et al., 2020; Starkstein et al., 2015). Kinematic features extracted from movement profiles have not been assessed. Therefore, there is a need to quantify kinematic differences in the older autistic population.

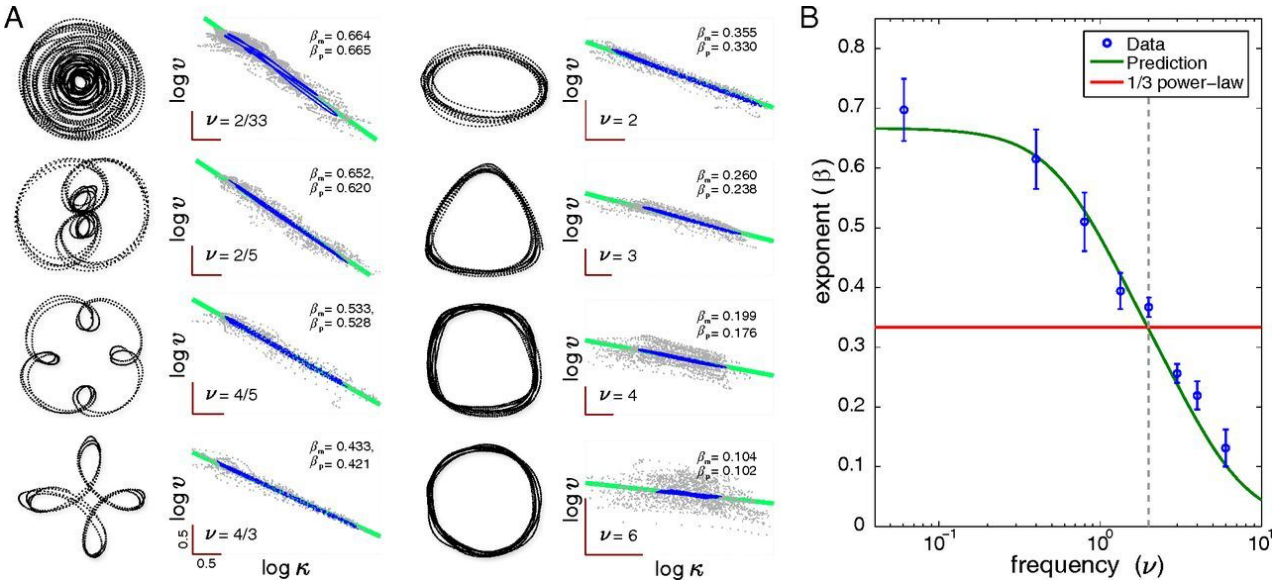
Some kinematic features that are important in the ASD literature have been overlooked in the PD literature. For example, in the general population, movement speed is modulated according to the curvature of shapes (Huh & Sejnowski, 2015), whereby individuals speed up along straight parts of a shape and slow down for corners. By contrast, in the autistic population individuals move with steeper speed modulation – moving fast along

straight sections and “slamming on the breaks” as they approach corners (Cook et al., 2023; Fourie, 2022). This speed profile may be responsible for the apparent lack of smoothness in autistic movements. Despite the observation of a lack of movement smoothness in PD, speed modulation in PD-produced movements has not been assessed. However, a visual perception study revealed that compared to the general population, PD participants opted for a movement profile closer to a constant velocity when determining which of a range of elliptical movements appeared most “natural” (Dayan et al., 2012). If we assume that individuals’ own movement profiles influence perception of movements observed (Aglioti et al., 2008; De Marco et al., 2020; Edey et al., 2017; Kilner et al., 2007), Dayan and colleagues’ study suggests that lower speed modulation values may be used in PD compared to the general population. Thus, it is likely that both ASD and PD groups differ from the general population in terms of speed modulation, but in opposite directions.

Speed modulation values can be extracted from movement trajectories of symmetrical shapes characterised by different angular frequencies; that is, the number of curvature oscillations per two π of angular displacement (i.e., an ellipse has an angular frequency of 2 as you meet two “corners” during one full cycle of the shape; for other examples see Figure 1.2A). Different speed modulation values have been observed for these shapes in the general population, with more gradual speed modulation for higher angular frequency shapes (Figure 1.2; Cook et al., 2023; Huh & Sejnowski, 2015; Matic & Gomez-Marin, 2019; Matic & Gomez-Marin, 2020; Matic & Gomez-Marin, 2022). To fully understand differences in speed modulation in ASD and PD, values should be assessed across the angular frequency spectrum.

Figure 1.2

Speed Modulation for Shapes Across the Angular Frequency Spectrum



Note. Participants were members of the general population. (A) Different angular frequency shapes and their speed-curvature relationships (i.e., speed modulation). Black dots = movement trajectories, ν = angular frequency, log k = log curvature, log v = log velocity, β_m = measured beta estimate between log k and log v, β_p = predicted beta estimate. (B) Power law exponents (β) plotted against angular frequency (ν). Green line = prediction, blue dots = mean exponent values, error bars = standard deviation, red line = 1/3 power law (i.e., the assumption that all movements adhere to a 1/3 beta exponent). Figure taken from Huh and Sejnowski (2015).

Summary: Due to a lack of direct comparison studies between ASD and PD, comparisons between the two conditions must be made by reflecting on separate research studies. As such, comparisons may be confounded by differences in sample demographics and different experimental tasks used to index behaviour.

1.2.7 Potential Mechanistic Overlap

Whilst reviewing extant literature highlights behavioural and cognitive similarities between ASD and PD, it is important to consider *why* these similarities may occur. Similar presentations in ASD and PD are likely to arise if the two conditions have similar underlying biological mechanisms. This may explain the increased prevalence of PD diagnosis in the

autistic population – it may not be the case that ASD individuals are indeed more likely to have co-occurring PD, rather a shared underlying biological mechanism between the two conditions may lead to similar presentations and thus increase the likelihood of meeting diagnostic criteria for both conditions. To validate this theory, ASD and PD must share a biological mechanism which relates to motor function, as this is a core component of PD diagnosis. Dopamine is a logical candidate given its strong links to movement (Bartholomew et al., 2016; Lange et al., 2006; Rueda-Orozco & Robbe, 2015; Tucha et al., 2006). This section therefore presents evidence for differences in dopamine function in ASD and PD, as well as dopaminergic modulation of movement, to propose dopamine dysfunction as a shared biological mechanism underpinning movement differences in ASD and PD.

Dopamine function in autism and Parkinson's Disease

Dopamine is strongly implicated in the pathology of PD. Dopamine system dysfunction, specifically degeneration of dopamine neurons in the substantia nigra, is the hallmark of PD (Rizek et al., 2016). The death of dopamine neurons in this region of the basal ganglia disrupts dopaminergic function in the nigrostriatal pathway which facilitates movement, leading to movement difficulties in PD. Increased α-synuclein levels in PD also has links to dopamine function (Kalia & Kalia, 2015; Rizek et al., 2016); α-synuclein plays an important role in synaptic transmission, with elevated levels reducing dopamine release (Venda et al., 2010). Given that dopamine dysfunction is the cause of PD symptoms, dopaminergic medications are the primary form of treatment for PD. This includes both levodopa (the precursor to dopamine) to boost dopamine levels and dopamine agonists to stimulate surviving dopamine neurons. Overall, dopamine is a strong component of both PD pathology and mechanisms of treatment.

Less is known about the pathology of ASD, primarily due to the heterogeneous presentation of the condition. However, as in PD, differences in both basal ganglia function (e.g., volume and cell density) and increased α-synuclein levels have been reported (Morato Torres et al., 2020; Sriwimol & Limprasert, 2018; Subramanian et al., 2017). Increased understanding of the pathology of ASD has prompted the dopamine hypothesis (Pavăl, 2017). The hypothesis states that many of the behavioural and cognitive differences observed in ASD, including movement, reward processing and repetitive behaviours, may be the result of changes to the dopamine system. Evidence for the dopamine hypothesis comes from a range of methodologies, with results conflicted with respect to whether a hyper- or hypo-dopaminergic state is apparent (Kosillo & Bateup, 2021). For example, PET neuroimaging studies have revealed lower presynaptic dopamine levels in autistic children (Ernst et al., 1997) and increased radioligand binding to the dopamine active transporter in the orbitofrontal cortex (Nakamura et al., 2010), thus indicating hypo-dopaminergia. Turning to pharmacology, dopaminergic medications have been found to alter behavioural differences in ASD, with dopamine *antagonists* reducing irritability and aggression (Hirsch & Pringsheim, 2016; Sharma & Shaw, 2012), suggesting that these behaviours arise from a hyper-dopaminergic state. Finally, evidence for both hyper- or hypo-dopaminergic functioning comes from animal studies. Gunaydin et al. (2014) reported that optogenetic stimulation of the mesolimbic pathway increased sociability in mice, whereas dopamine antagonism in a mouse model of ASD led to the reduction of stereotypic motor behaviour (Presti et al., 2003). This pattern of results would lead to the conclusion that reduced sociability in ASD arises from hypo-dopaminergia, whereas motor differences may be the product of hyper-dopaminergia. In sum, dopamine dysfunction is apparent in ASD but evidence is conflicting with regards to the direction of this difference.

The role of dopamine in movement and motivation

Dopamine is robustly associated with the speed, or "vigour", of movements. Observational studies have linked mice dorsolateral striatal firing rates to walking speed (Rueda-Orozco & Robbe, 2015) and bradykinesia to the degeneration of the dopamine system in PD (Alberts et al., 2000; Broderick et al., 2009; Lange et al., 2006; Tucha et al., 2006). Further to this, intervention studies have provided causal evidence for the role of dopamine in movement speed. Optogenetic stimulation to D1 neurons in mice has been found to prompt faster movements (Bartholomew et al., 2016). Additionally, human studies have highlighted reduced movement speed following the administration of dopamine receptor antagonists (Quattrocchi et al., 2018; Tomassini et al., 2016) and faster movement in Parkinson's following dopamine agonism (Eichhorn et al., 1996; Lange et al., 2006). Beyond vigour, dopamine has been implicated in other components of movement including the invigoration of movements (Bova et al., 2020; da Silva et al., 2018), generating a range of different movement speeds (Baraduc et al., 2013), and signalling the start and end points of sub-movements (Collins et al., 2016).

A role of dopamine in reward processing and motivation is also widely evidenced (Costello et al., 2024). The opportunity costs model states that dopamine signals the average reward availability of an environment, with high dopamine signalling indicating a higher level of reward availability (Niv et al., 2007). More recent findings have implicated a role for dopamine in both encoding expected reward and anticipating effort costs (Varazzani et al., 2015). This information can then be used to inform decision-making behaviour, influencing whether actions will be taken, and the vigour with which they are taken. Indeed, the basal ganglia are thought to modulate vigour according to context-specific cost/reward functions (Turner & Desmurget, 2010). The opportunity costs model can explain mechanisms

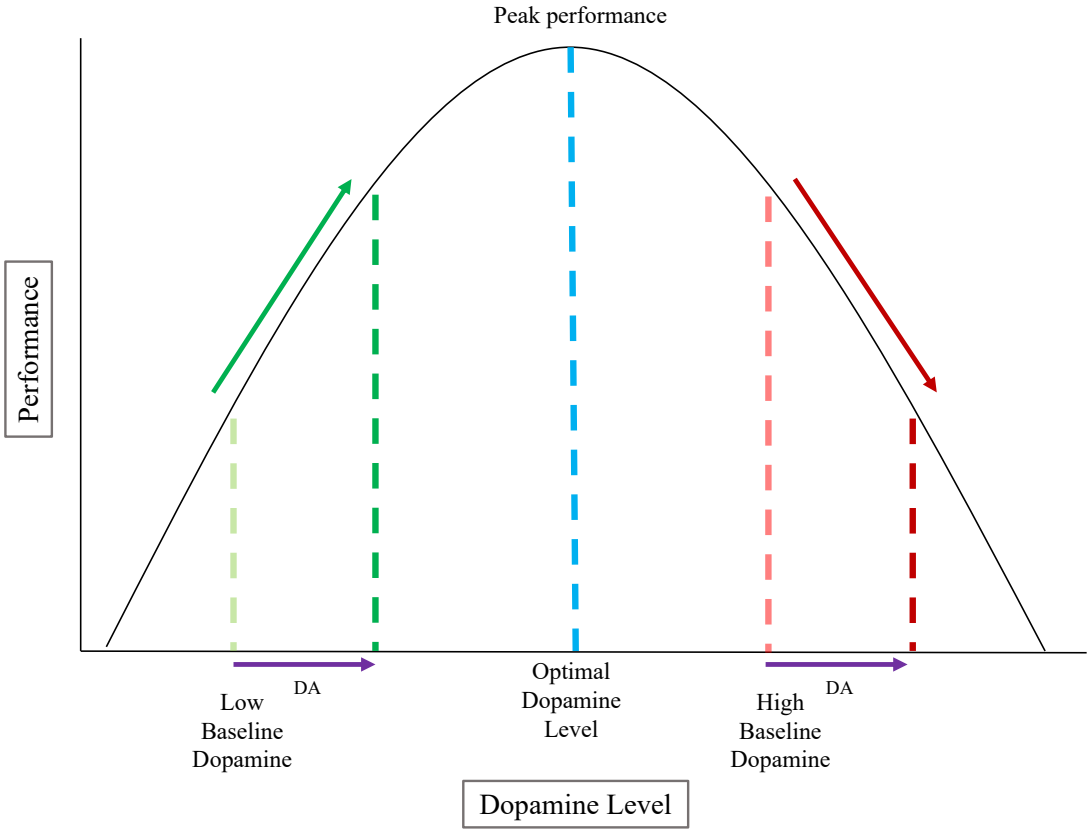
underlying motor motivation. As previously discussed, the motor motivation hypothesis posits that slow movement in PD arises from a lack of motivation to move quickly (Mazzoni et al., 2007). According to the opportunity costs model, low levels of dopamine in PD should signal low average reward availability, and this would reduce motivation to move quickly. This raises the question as to whether dopamine governs movement processes *per se*, or rather the motivation to engage in movement processes.

Inverted-U-shaped dopamine function

To implicate dopamine in various abilities, manipulating individuals' dopamine levels via pharmacological interventions is common practice. Interestingly, many studies have reported that effects of dopaminergic drugs on behaviour – primarily cognitive control – are modulated by baseline striatal dopamine synthesis capacity, with opposing drug effects in low versus high baseline dopamine groups (Frank & O'Reilly, 2006; Hofmans et al., 2020; Schuster et al., 2022). An inverted-U-shaped function has been proposed for the relationship between dopamine levels and performance, whereby optimal performance arises from middle levels of dopamine and both low and high dopamine are associated with impairments (Cools & D'Esposito, 2011). This pattern can lead to opposing drug effects. As seen in Figure 1.3, low and high baseline dopamine groups would sit either side of an optimal dopamine level. An increase in dopamine levels, for example by a dopamine agonist, would cause dopamine levels to become either closer to or further away from the optimal value respectfully, thus resulting in either improved or worsened performance. Figure 1.4 translates this function into the subsequent relationship between baseline dopamine and drug effects. A negative linear relationship is observed, whereby positive drug effects are seen in individuals with low baseline dopamine, and negative drug effects are seen in those with high baseline dopamine.

Figure 1.3

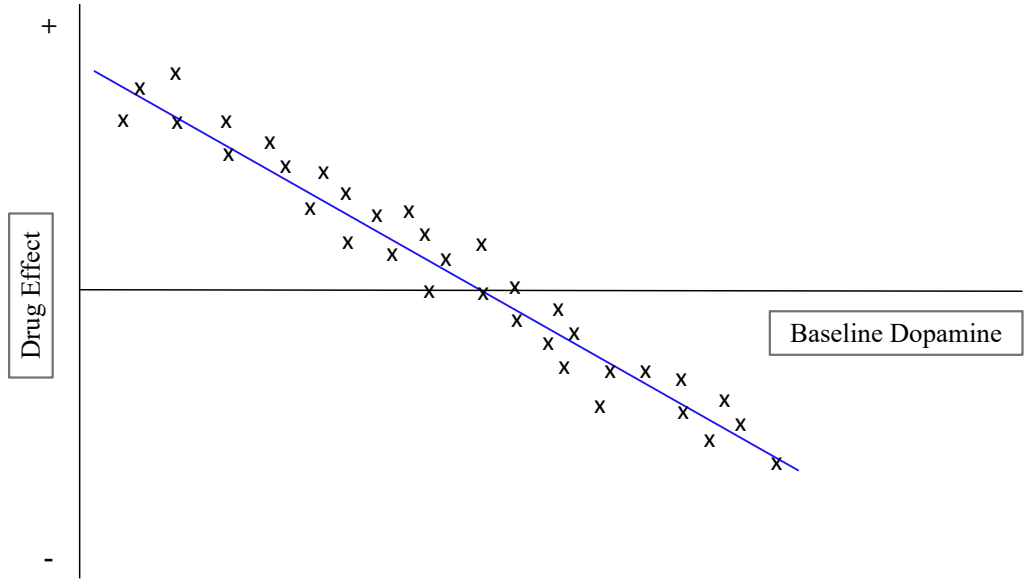
The Inverted-U-Shaped Dopamine Function



Note. This theory proposes that there is an optimal dopamine level for performance (blue dotted line). Low baseline dopamine (light green dotted line) would fall below this optimal level, and high baseline dopamine (light red dotted line) would fall above it. Increasing dopamine (DA) levels (purple arrow) would cause the dopamine levels of those with low baseline dopamine to shift closer to the optimal level (dark green dotted line). By contrast, the dopamine levels of those with high baseline dopamine would shift further from the optimal level (dark red dotted line). As such, performance would be respectively improved and worsened.

Figure 1.4

The Relationship Between Baseline Dopamine and Observed Drug Effect for an Inverted-U-Shaped Dopamine Function



Note. Those with low baseline dopamine exhibit positive drug effects, whereas those with high baseline dopamine exhibit negative drug effects.

An inverted-U-shaped function implies that disrupted function can arise from both a hyper- and hypo-dopaminergic state. In other words, opposing underlying biological states may lead to similarities in performance. This is relevant for the case of ASD and PD. Similarities and differences between ASD and PD may be due to opposite biomarkers which create the same behaviour in some cases (i.e., those abilities governed by an inverted-U-shaped function), but opposite behaviour in others (i.e., those with a linear relationship between dopamine and performance). Therefore, when investigating the biological basis of abilities in which we see similarities and differences between ASD and PD performance, measures of baseline dopamine should be incorporated. This will enable the inspection of whether an inverted-U-shaped function exists between dopamine levels and performance.

Whilst some studies have utilised PET imaging to index baseline striatal dopamine synthesis capacity, working memory capacity can serve as a proxy for this, with low working memory capacity indicating low dopamine synthesis capacity (Cools et al., 2008; Landau et al., 2009). Consequently, working memory performance should be taken into account to fully understand the nature of the relationship between dopamine and functions such as movement.

Summary: Both ASD and PD are associated with dysfunction of the dopamine system. Dopamine has been implicated in both movement and motivation; however, it is unclear whether an inverted-U-shaped function exists for the relationship between dopamine and these abilities.

1.3 The Current Thesis

1.3.1 Aims of the Current Thesis

The three main aims of the current thesis are to (1) directly compare ASD and PD on a range of movement and theory of mind tasks; (2) provide insight into older autistic movement and theory of mind; and (3) advance understanding of the biological mechanisms underlying movement differences.

Directly comparing autism and Parkinson's Disease

As previously noted, there is an increased prevalence of PD in the autistic population compared to the non-autistic population. However, a review of the literature does not provide strong evidence for shared genetic risk for ASD and PD. Instead, many behavioural and cognitive similarities can be identified between ASD and PD, particularly in domains such as movement that are utilised in PD diagnosis. This may mean that autistic individuals already pass threshold on a number of PD assessments due to similarities in autistic and parkinsonian

movement profiles, meaning a diagnosis of PD is more readily concluded (or potentially misdiagnosed) in autistic individuals.

Given that no direct comparison studies exist, the current literature does not enable a controlled comparison between ASD and PD groups; existing studies vary with respect to tasks used and the demographics of the samples tested, which means conclusions of similarities may be confounded by extraneous variables. Thus, here I conduct the first direct comparison study of both free movement and restricted movement, as well as movement-based theory of mind ability, in ASD and PD. First, Chapter 2 quantifies differences in theory of mind ability in the two groups compared to a general population sample using movement-based stimuli – a task which has not yet been used in PD. Kinematic features extracted from participants' own theory of mind animations (in which two triangles are moved around the screen to depict mental and non-mental states) are compared as a measure of free movement. Next, Chapter 3 conducts a more controlled movement-based investigation of ASD and PD, identifying kinematic similarities and differences between the two groups when drawing restricted shapes. This information is then used to inform the development of classification algorithms to determine whether trait questionnaires and/or kinematic features are most useful in predicting group membership. These Chapters reveal similarities and differences between autistic and parkinsonian traits, which sheds light upon whether autistic individuals may be more likely to receive a PD diagnosis (or misdiagnosis) due to similarities in behavioural presentations.

In daily life, any similarities observed between autistic and parkinsonian traits are likely to relate to PD performance on dopaminergic medication. This is because the majority of individuals with PD are regularly taking dopaminergic medication to alleviate their symptoms. Chapter 2 assesses functional day-to-day differences in movement and theory of

mind ability by allowing PD participants to be on their dopaminergic medication when completing the tasks. Given that PD difficulties remain following medication administration (i.e., medication does not fully restore movement differences (Tucha et al., 2006) and in some cases has been found to not impact theory of mind ability (Peron et al., 2009)), the comparison between ASD and PD "ON-medication" is unlikely to substantially differ from that of ASD and PD "OFF-medication". However, it is important to note that individuals with PD will *not* be taking medication when they initially obtain a diagnosis, meaning that any confusion between autistic and parkinsonian movement in the diagnostic process would be with respect to unmedicated PD movement profiles. As such, another aim of the thesis was to identify similarities between the movement profiles of autistic individuals and individuals with PD when not taking their dopaminergic medication. This question was addressed in Chapter 3, in which PD participants completed tasks before taking their dopaminergic medication in the morning. Overall, these studies provide insight into both the daily functioning of individuals with PD, as well as their performance in an unmedicated state.

Contributing to the older adult autism literature

The older autistic adult literature is sparse, making up only 0.4% of autism studies conducted between 2012 and 2022. Beyond comparing ASD and PD performance, both Chapter 2 and Chapter 3 contribute to this limited older autistic adult literature. Here, I detail the first direct comparison study of autistic and non-autistic kinematic features in older adults, using both the Animation Production Task which includes free movement (Chapter 2), and a further controlled assessment of kinematics during restrictive movement (the Shapes Tracing Task; Chapter 3). In addition, I provide insight into theory of mind differences in older autistic adults (Chapter 2), a field which has garnered conflicting findings in previous studies. Specifically, I employed a movement-based theory of mind measure that has only been used

previously in a composite theory of mind score. Thus, this thesis leads to a greater awareness of behaviours exhibited by autistic adults in older age.

Understanding the biological mechanisms underlying movement differences

Whilst Chapters 2 and 3 provide insight into movement similarities and differences between ASD and PD, it is unclear how these movement features arise. Chapter 4 details the results of two pharmacological intervention studies which reveal the role of dopamine in complex movement processes. Specifically, this Chapter focuses on movement features deemed to be relevant in classifying group membership to further understand the biological basis underlying movement features of ASD and PD. A measure of baseline striatal dopamine synthesis capacity is incorporated into the second pharmacological intervention to identify whether the relationship between dopamine and movement follows an inverted-U-shaped function.

Summary: The current thesis conducts the first direct comparison study of autistic and parkinsonian movement, as well as theory of mind ability in the two groups. It further adds to the older autistic adult literature, in addition to shedding light on the biological mechanisms underlying movement differences.

1.3.2 Participatory Research

Overview of participatory research

For research into clinical conditions to reach its full potential for impact, studies must incorporate the expertise of people with lived experience. Participatory research refers to the involvement and consultation of lived-experience experts throughout the research process, and aims to incorporate vital insights from individuals who are members of the populations being studied (Cornwall & Jewkes, 1995). Participatory research can be incorporated at all stages of the research process, from setting priorities and designing studies to disseminating

results. There are many benefits to participatory research including, first and foremost, the empowerment of lived-experience experts to inform researchers of their priorities and shape research with their expertise. Participatory research can also lead to a number of practical efficiencies such as increased participant recruitment and retention (Crocker et al., 2018). This practice has been adopted by a growing number of researchers and recent calls have been made to consult people with lived experience in both the ASD (Fletcher-Watson et al., 2019; Gowen et al., 2019; Keating, 2021) and PD (Meinders et al., 2022) literature.

Participatory research in this thesis

To set the broad aims of the current work, I utilised existing data on the research priorities of ASD and PD groups. Participatory research activities with autistic individuals indicate that this group want to see research into aging in autism, co-occurring medical conditions and clearer diagnoses. For example, Pellicano et al. (2014) reported the research priorities of 122 autistic adults, highlighting that each of these themes were rated between "important" and "very important" on average (*aging in autism*: "what does the future hold for autistic adults?"; *co-occurring medical conditions*: "Why do autistic people appear to be more at risk from some medical conditions than non-autistic people?"; *clearer diagnoses*: "How can we better recognise the signs and symptoms of autism?"). In fact, aging in autism was the third highest priority of autistic adults, and both "lifespan issues" and "co-occurring conditions" were identified as themes in open-ended questions. In addition, Autistica's Top 10 Questions for Autism Research, a James Lind Alliance Priority Setting Partnership, included references to autistic adults and diagnosis improvement ("How can autism diagnostic criteria be made more relevant for the adult population? And how do we ensure that autistic adults are appropriately diagnosed?"). Overall, the current thesis addresses these research

priorities by aiming to further understand the relationship between aging autism and PD, with a view to make diagnostic processes more selective.

The thesis also addresses a number of PD research priorities (Schipper et al., 2014). For example, themes such as medical research (including medication and diagnosis) and psychological research (psychological and cognitive functioning) have been highlighted. These themes were ranked as the second and third most important by the PD lived experience experts (with fundamental research coming in first). Each of these themes is addressed in the thesis, including understanding theory of mind ability in PD ("psychological functioning"; Chapter 2), improving selectivity of PD movement criteria by comparing performance to another clinical population ("diagnosis"; Chapters 2 and 3), and understanding the action of medication on movement processes ("medication"; Chapter 4).

I further conducted my own participatory research activities to inform the specific goals of the work and improve the study design. These activities followed guiding principles of recognition and remuneration (lived experience experts were paid and acknowledged for their time), setting a purpose (each activity had clear outcome goals), and respect and role clarity (clear roles with flexible contribution formats and commitment levels were established which were attuned to the participants' strengths and expertise). First, the thesis plan was presented to the Birmingham Psychology Autism Research Team Consultancy Committee, a group of autistic individuals and autism researchers, to receive feedback on the broad thesis aims and specific project plans. Next, PD lived-experience experts (recruited via Parkinson's UK Patient and Public Involvement Network) commented on the research goals and study design. Whilst piloting the task, these individuals provided important insights into the feasibility for PD participants to complete the tasks both on and off dopaminergic medication, and the understandability of instructions provided. Finally, autistic lived-experience experts

piloted the task to ensure that the instructions were clear, and the tasks were possible to complete. Thus, participatory research in this thesis ensured that I was asking the right questions and that my studies were feasible and accessible.

Summary: Participatory research is an important practice for ensuring that the lived-experience expertise of groups being studied is heard and incorporated. The current thesis used participatory research activities to inform study goals and improve study design.

1.3.3 Experimental Measures

The current thesis employed two movement tasks: the Animation Production Task (Chapter 2) and the Shapes Tracing Task (Chapters 3 and 4). Movement trajectories were obtained from each task and various kinematic features were calculated. Table 1 details the kinematic features assessed in each Chapter, including definitions and calculations.

Table 1.1

Kinematic Features Assessed in the Thesis

Variable	Definition	Calculation	Restricted use?	Chapter 2?	Chapter 3?	Chapter 4?
Speed	The change in position (x and y coordinates) over time	First-order derivative of the positional non-null data (averaged across the trial)	N/A	x	x	x
Acceleration	The change in speed over time	Second-order derivative of the positional non-null data (averaged across the trial)	N/A	x	x	
Jerk	The change in acceleration over time	Third-order derivative of the positional non-null data (averaged across the trial)	N/A	x	x	
Minimum speed	Minimum speed values used during a trial	The average of the bottom 10% of speed values (per trial)	N/A	x	x	x
Maximum speed	Maximum speed values reached during a trial	The average of the top 10% of speed values (per trial)	N/A	x	x	x
Sub-movements	Frequency of alternations between acceleration and deceleration	The percentage of frames in which a change in acceleration sign was observed (per trial)	N/A	x	x	
Mean rotation	The average rotation of a moving object around its own axis	The differential of each triangles' orientation in degrees over time (a weighted average for the two triangles per trial)	Yes- specific to the triangles production task	x		
Synchronous movement	The amount of time during which two objects are moving	The proportion of frames during which the speed of both the red and the blue triangle was greater than zero	Yes- specific to the triangles production task	x		
Spectral Arc Length (SPARC)	An alternative, speed-independent, measure of movement smoothness	The arc length of the magnitude spectrum arising from a Fourier transform of the speed profile (values calculated for each repeated identical sub-element of a shape and averaged to obtain a single value per trial)	Yes- values are higher for longer trajectories, meaning that SPARC must be calculated on pre-defined identical shapes		x	
Speed modulation	The extent of the modulation of movement speed to the curvature of a trajectory	The gradient between instantaneous movement speed and curvature, converted to an absolute value.	Yes- specific to the shapes tracing task		x	x
Speed meta-modulation	The extent of the modulation of speed modulation values to the angular frequency of the shape being drawn	The gradient between speed modulation values and the shape's angular frequency	Yes- specific to the shapes tracing task; requires data from a range of angular frequency shapes			x

Chapter 2 – Examining Movement and Movement-Based Theory of Mind in Autism and Parkinson's Disease

There are anecdotal similarities between ASD and PD in both behavioural and cognitive domains, but no direct comparison studies have been conducted. Chapter 2 presents the first direct comparison study between autistic individuals, individuals with PD, and control participants with respect to movement and movement-based theory of mind. The Animation Production Task assessed how individuals used movement cues to represent mental states. This task had not yet been employed in older autistic populations or those with PD. Subsequently, the Animation Perception Task assessed individuals' accuracy in attributing mental states to animations created by others. This task had not been used in PD and had only been used as part of a composite theory of mind score in older autistic adults. This Chapter aimed to provide a greater understanding of behavioural and cognitive traits exhibited by autistic adults in older age, and whether these were comparable to those exhibited by individuals with PD. Participants with PD were ON their dopaminergic medication when completing the tasks, meaning comparisons between groups related to everyday functioning.

A pre-registration for the study can be found online at https://osf.io/ek6h7. Content from the pre-registration has been reproduced in the current Chapter. Supplementary materials for this Chapter can be found in Appendix 1. Data and analysis scripts can be found online at https://osf.io/dge6t/?view_only=588a08aa1eb04942a2f1f8bbccc9dede.

2.1 Introduction

Within clinical populations, a co-occurrence of differences in motor function and social cognition is common (Cook, 2016; Eddy & Cook, 2018). This is unsurprising given that, in social interactions, movement cues play an important role in representing mental states and emotions (Dael et al., 2012; Sowden et al., 2021). Experimental findings have demonstrated that in a variety of social cognition paradigms, such as those indexing action prediction, imitation and emotion recognition, performance is improved when there is similarity between the kinematics of the movement of the participant and the observed individual (Aglioti et al., 2008; De Marco et al., 2020; Edey et al., 2017; Kilner et al., 2007). In other words, more accurate socio-cognitive inferences occur in interactions between people who move in a similar way to express emotions and mental states. It is thought that this is because these movements will be more likely to trigger appropriate mental state labels within the observer. Appropriate mental state labels are, therefore, more likely to be attributed to the situation and this will likely result in emotional responses from the observer that are contextually relevant. By contrast, when observing someone whose movements for a given mental state are very different from your own, appropriate mental state labels will not be triggered and mental state inferences will be less well matched.

The relevance of movement in social cognition has important implications for understanding difficulties faced by those with movement disorders. Parkinson's Disease is a condition characterised by bradykinesia (slowed movement), gait differences and postural instability (Jankovic, 2008; Moustafa et al., 2016; Zanardi et al., 2021). Whilst motor symptoms are primarily emphasised, socio-cognitive differences such as in emotion recognition and theory of mind are also apparent – abilities in which movement cues are vital (Czernecki et al., 2021; Gray & Tickle-Degnen, 2010; Ricciardi et al., 2017). By contrast,

ASD is a condition in which socio-cognitive differences are considered core features (American Psychiatric Association, 2013). A wide body of literature suggests differences between autistic and non-autistic individuals in emotion recognition (Keating et al., 2022; Uljarevic & Hamilton, 2013) and theory of mind (Abell et al., 2000; White et al., 2011). However, recent literature has shed light upon co-occurring movement differences as indexed by performance on a variety of motor tasks including coordination, fine motor control and whole-body movement (Fournier et al., 2010; Wang et al., 2022). Interestingly, differences in gross motor control in autism have been found to correlate with social skills (Wang et al., 2022). Thus, it may be theorised that, due to a lack of movement similarity, social interactions between ASD/PD populations and the general population are more likely to suffer from a mismatch in the perceived internal state of the observer and the actual internal state of the individual being observed.

Theory of mind, the ability to appropriately attribute mental states to others, has been found to differ in both ASD and PD populations. There are many ways in which mental states can be expressed, and the most popular tasks rely on static images or stories rather than dynamic movement-based stimuli. The Reading the Mind in the Eyes Test is a classic measure that has been used frequently in both ASD and PD to propose differences in theory of mind (Bodden et al., 2010; Orso et al., 2020; Penuelas-Calvo et al., 2019; Seubert-Ravelo et al., 2021). This task, in which participants are asked to attribute emotions and thoughts to images of the eye region of the face, has been heavily criticised as a measure of theory of mind on the basis that its task demands are more akin to emotion recognition (Oakley et al., 2016; Quesque & Rossetti, 2020). In a different visual-based task, the Yoni task (Shamay-Tsoory & Aharon-Peretz, 2007), participants are asked to select the appropriate picture to answer first-order questions (e.g., what Yoni identifies with) and second-order questions (e.g.,

whose success Yoni envies). Impairments in this task have been reported in both ASD (Tin et al., 2018) and PD (Bodden et al., 2010). Alternative measures of theory of mind employ situational judgement questions. For example, in the Faux Pas Test (Stone et al., 1998), participants are asked to identify whether stories contain a social faux pas or a minor conflict but no faux pas. Cognitive understanding (e.g., why do you think the character said it?) and affective understanding (e.g., how do you think the character felt?) are also assessed. Evidence in PD suggests an impairment on the cognitive component of the faux pas test (Del Prete et al., 2020; Kawamura & Koyama, 2007; Peron et al., 2009; Roca et al., 2010), and similar evidence has been presented in ASD (Tin et al., 2018). Thus, theory of mind differences in ASD and PD are apparent across a variety of non-movement-based tasks.

Movement is an important component in representing mental states, but the aforementioned tasks do not allow for investigation of movement-based theory of mind inferences. This literature cannot address the question of whether movement differences in ASD and PD may co-occur with differences in movement-based theory of mind ability. By contrast, the Animations Task asks participants to ascribe mental states to videos of two moving triangles (Abell et al., 2000; Schuster et al., 2021). In conjunction, participants can be asked to produce their own animations to represent mental states (Edey et al., 2016; Schuster et al., 2021). This task has been widely used in the autism literature to demonstrate theory of mind differences, including a reduction in the use of mental state words, and the use of inappropriate mental state words, to describe animations (Abell et al., 2000; Castelli et al., 2002; Livingston et al., 2021; White et al., 2011; Wilson, 2021). Further investigations have revealed bi-directional difficulties between autistic and non-autistic adults arising from kinematic differences in the animations produced by the two groups (Edey et al., 2016). Whilst many studies have used the Animations Task in the younger autistic population, it has

only been used in the older autistic population as part of a composite theory of mind score (Yarar et al., 2020), meaning that it is unclear whether older autistic adults have differences in movement-based theory of mind specifically. In addition, the Animations Task has not yet been employed in the PD population, but administration of the dopamine antagonist haloperidol results in reduced accuracy in labelling animations (Schuster et al., 2023). Haloperidol acts by blocking D2 receptors (Bymaster et al., 1999), which are highly prevalent in the basal ganglia (Camps et al., 1989). Given that the pathology of PD relates to the degeneration of dopamine neurons in the substantia nigra of the basal ganglia, it is likely that a similar pattern of task performance will be observed in PD as under haloperidol. Therefore, the current study assesses whether differences in movement-based theory of mind are apparent in older autistic adults and individuals with PD.

The Animations Task also includes a component which enables the assessment of how individuals represent mental states themselves. Participants have free reign in how they depict both mental and non-mental states using the movement of two triangles. Evidence from separate research studies indicates that there are both similarities and differences in the movements of autistic individuals and those with PD. For example, parkinsonian movement appears to be slower than that of the general population (Alberts et al., 2000; Broderick et al., 2009; Flash et al., 1992; Jankovic, 2008; Lange et al., 2006; Van Gemmert et al., 2003; Viviani et al., 2009), whereas autistic movements are characterised by faster movement profiles (Cook et al., 2013; Grace et al., 2017; Johnson et al., 2013). However, whilst members of the general population move with minimum jerk (i.e., accelerating and decelerating gradually in movements from one point in space to the next (Flash & Hogan, 1985; Todorov & Jordan, 1998)), jerky movements have been observed in both autistic individuals (Cook et al., 2013; Edey et al., 2016) and individuals with PD (Alberts et al.,

2000). Such jerky movements are comprised of periods of rapidly changing acceleration and/or deceleration, and these alternations may be used to interpret movement trajectories as a series of sub-movements. There is evidence to suggest a greater number of sub-movements in the trajectories of both ASD (Cook et al., 2023) and PD (Castiello et al., 2000; Flash et al., 1992; Lange et al., 2006) samples. However, it is important to note that these observations are generally made from fixed or constrained movements which do not allow individuals free reign. To be comparable to movements made in everyday life to depict mental states, assessments of free movement should be made (i.e., those in which individuals are able to make choices about their movement trajectories). This Chapter sets out to investigate whether similar movement profiles would be used by ASD and PD groups when depicting mental states, in addition to whether groups would also be comparable with respect to movement-based theory of mind ability.

Both ASD and PD groups appear to exhibit differences in movement and theory of mind compared to the general population, but a lack of direct comparisons studies between the clinical groups means that it is unclear what the relative abilities are. As previously discussed, a range of paradigms have been used to index movement and theory of mind ability, and the generalisability of performance on these tasks is not known. In addition, demographic differences in the participants used are apparent. For example, ASD participants are typically either children (Abell et al., 2000) or young adults (e.g., Castelli et al., 2002; mean age = 33 years) whereas, due to the late onset of PD, studies of PD tend to recruit individuals over the age of 50 (Orso et al., 2020). This is problematic as both movement and theory of mind ability have been found to vary with age (Ketcham et al., 2002; Maylor et al., 2002; Pardini & Nichelli, 2009). A meaningful comparison between ASD and PD performance must therefore be made between similarly aged groups (i.e., comparing older

autistic adults to individuals with PD). The current literature is not sufficient for this given that movement studies in older autistic adults are extremely limited (note that only two studies were identified in a meta-analysis by Mason et al., 2022), and theory of mind assessments in older autistic adults present conflicting findings; that is, some studies have evidenced that theory of mind differences in autism extend to older age (Torenvliet et al., 2022), whereas others have reported no difference between autistic and non-autistic older adult performance due to an ageing-related decline in the non-autistic group (Lever & Geurts, 2016a; Yarar et al., 2020). Beyond age, other potential confounds of theory of mind and movement include characteristics such as gender (Baron-Cohen et al., 2015; Kirkland et al., 2013; Miller & Cronin-Golomb, 2010) and IQ (Buitelaar et al., 1999; Forti et al., 2011), and clinical traits such as depression (Nestor et al., 2022; Sachdev & Aniss, 1994), anxiety (Hezel & McNally, 2014; Pijpers et al., 2005) and alexithymia (Pisani et al., 2021). Indeed, elevated levels of such traits are observed in both ASD (Hollocks et al., 2019; Kinnaird et al., 2019) and PD (Alvarado-Bolanos et al., 2020; Broen et al., 2016; Reijnders et al., 2008), meaning any similarities between groups may be due to these co-occurring traits. Thus, matching and/or controlling for such variables will allow us to identify, separate from confounding factors, the extent to which movement and theory of mind in ASD and PD are similar.

Due to a lack of direct comparison studies, and the use of a wide variety of tasks, the existing literature does not provide clear insights into the movement and socio-communicative differences exhibited by older autistic adults and those with PD. Quantifying these differences in a controlled experiment is vital for pinpointing the specific domains in which these differences occur, and the similarities between the presentation of ASD and PD. The current study set out to analyse movement differences in animations produced by autistic individuals, individuals with PD, and control participants and, in conjunction, investigate

where differences in movement-based theory of mind ability co-occur. To index kinematics, participants produced 30-second animations for mental state, non-mental state and physical words by moving two triangles on a touchscreen device (Animation Production Task). To index theory of mind ability, participants watched mental and non-mental state animations and rated the extent to which they believed the animation depicted each of four target words (Animation Perception Task). This Chapter conducts the first direct comparison study of motor function and social cognition in ASD and PD compared to the general population.

2.2 Methods

2.2.1 Participants

The current study recruited autistic individuals (ASD; N = 31), individuals with PD (PD; N = 33), and control participants (CTRL; N = 31). Table 2.1 displays descriptive statistics for each group including age, gender, non-verbal reasoning score and years since diagnosis (see Appendix 1 for ethnicity information). Co-occurring movement or developmental disorders were set as exclusion criteria. Participants were recruited via Parkinson's UK, Autistica, the University of Birmingham Psychology Autism Research Database, the University of Birmingham Older Adults Database, and social media. Informed consent was given by all participants and remuneration of £10 per hour was provided. The experimental procedure was approved by the local Research Ethics Committee (ERN_18-1800B and ERN_16-0281AP5).

2.2.2 Procedure

First, participants completed an online screening form, a set of questionnaires and the Matrix Reasoning Item Bank (MaRs-IB; Chierchia et al., 2019). Following this, participants

completed the Animation Production Task and Animation Perception Task at home using a touch-screen device that was sent out to them (Samsung Galaxy Tab A7; 10.40-inch touchscreen; 2000x1200 pixels). The tasks were programmed in PsychoPy and run on Pavlovia (PsychoJS platform version 2021.1.3). PD participants completed these tasks approximately 1 hour after taking their first dose of medication in the morning. Participants also completed two additional testing days, data from which are analysed in subsequent chapters.

Online questionnaires

Participants first reported demographic information to enable an eligibility check (i.e., official clinical diagnosis of ASD or PD) and to facilitate group matching (e.g., age, gender). Following this, participants completed the Autism Quotient (AQ; Baron-Cohen et al., 2006; Baron-Cohen et al., 2001) and the Ritvo Autism Asperger Diagnostic Scale (RAADS; Ritvo et al., 2011) as measures of autistic traits, section 2 of the Unified Parkinson's Disease Rating Scale (UPDRS; Part II: Motor Aspects of Experiences of Daily Living; Martínez-Martín et al., 1994) as a measure of parkinsonian traits, the Toronto Alexithymia Scale (TAS; Bagby et al., 1994) as a measure of alexithymic traits, the Patient Health Questionnaire (PHQ; Spitzer et al., 1999; Spitzer et al., 2000) as a measure of depression, and the Generalised Anxiety Disorder Assessment (GAD; Spitzer et al., 2006) as a measure of anxiety. Questionnaires were completed on Qualtrics and were presented in a random order.

Matrix Reasoning Item Bank

Participants completed the Matrix Reasoning Item Bank (MaRs-IB; Chierchia et al., 2019) on Gorilla. The task lasted 8 minutes and in each trial participants had to select the appropriate shape to fill the empty cell of a 3 x 3 matrix. Scores were calculated as the proportion of correct responses within 8 minutes. The task is a validated measure of non-

verbal reasoning ability, and such a task-specific measure has been argued to be most appropriate for group matching autistic and non-autistic samples (Dawson et al., 2007; Mottron, 2004).

The Animation Tasks

Participants used the touch-screen device to complete the Animation Tasks (Schuster et al., 2021). A new online version of this task was developed specifically for this study, which enabled the recording and replaying of animations. Animations were inspired by those developed by Heider and Simmel (1944); they involved two triangles moving around a screen to depict various words. The task was comprised of two components: production and perception (Figure 2.1). The Animation Production Task was always completed prior to the Animation Perception Task.

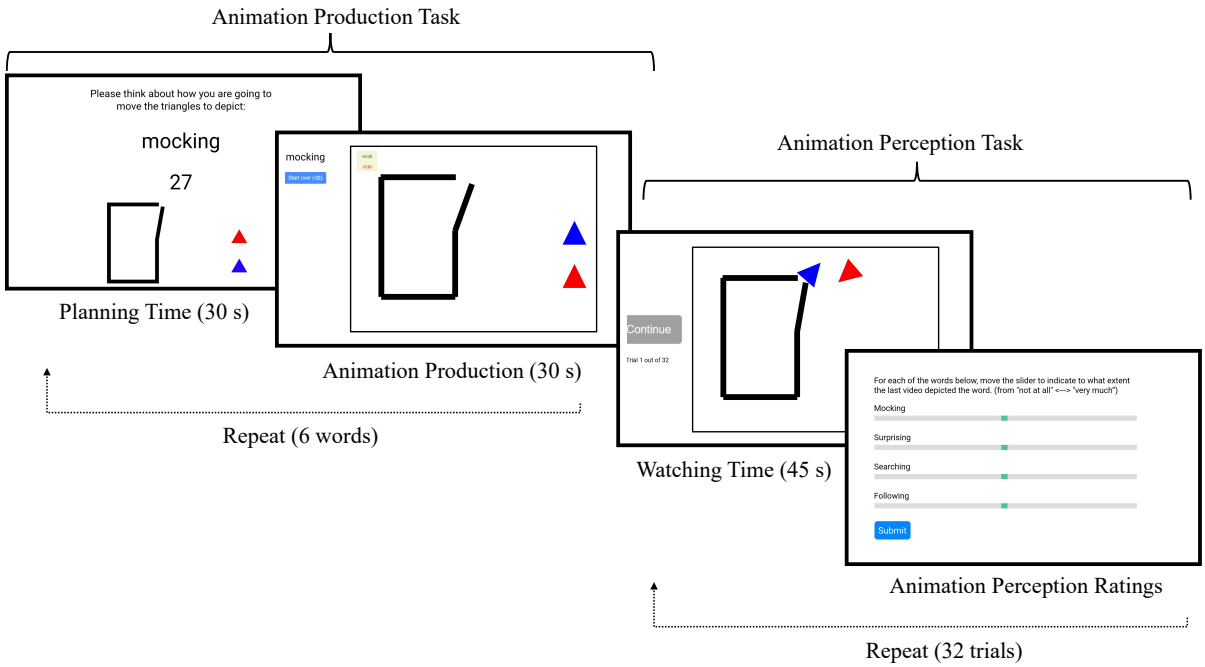
In the Animation Production Task, participants created 30-second animations depicting 6 words (mental state: surprising and mocking; non-mental state: searching and following; physical: bouncing and drifting). These categories reflected those of Abell et al. (2000). To produce these animations, participants moved a red and a blue triangle around the screen using their index fingers. Prior to each animation production phase, participants had 30 seconds to plan their actions. Animations could be remade if participants were not happy with what they had produced. Movement trajectories were recorded during each trial as the x and y coordinates of the triangles' positions across time, at a 60 Hz refresh rate.

In the Animation Perception Task, participants watched 32 animations and rated the extent to which they depicted each of 4 target words (mental state: surprising, mocking; non-mental state: searching, following) on separate sliding scales. Participants were able to replay the video before providing their ratings. The 32 animations presented to each participant were randomly selected from pools of pre-existing animations created by control participants in

Schuster et al. (2021). The set of animations shown to each participant contained 8 animations corresponding to each target word. These 8 animations for each word were randomly selected from 8 speed bins to ensure the animations comprised a wide range of kinematics.

Figure 2.1

Animation Production Task and Animation Perception Task Trial Structure



Note. Participants first depicted six words in the Animation Production Task (following 30 seconds of planning time), followed by the completion of 32 trials in the Animation Perception Task (during which animations were first watched and then rated on sliding scales).

2.2.3 Data Pre-Processing

Animation production

Various parameters were calculated using the x and y coordinates of the triangles' positions (derived from the triangles' centre points) across time. Kinematics included speed, acceleration and jerk, minimum speed, maximum speed and sub-movements, whilst animation features included mean rotation and synchronous movement. When calculating

parameters (except synchronous movement), separate values were calculated from the movement trajectories of each triangle and then a weighted average was calculated based on the proportions of movement time of each triangle. These weighted averages were used as dependent variables (DVs).

Speed, acceleration and jerk were calculated as the first-, second-, and third-order derivates of the positional non-null data. That is, speed refers to the distance moved (in pixels) over time (in seconds); acceleration refers to the change in speed over time; jerk refers to the change in acceleration over time. These values were obtained using a smooth differential filter at each stage of differentiation (see Huh & Sejnowski, 2015). Minimum and maximum speed values were taken as the average of the bottom and top 10% of speed values within a given trial. Sub-movements were calculated as the percentage of frames across the animation in which a change in acceleration sign was observed.

Mean rotation was calculated as the average rotation of the triangles around their own axis, or the differential of each triangles' orientation in degrees over time. Synchronous movement was calculated as the proportion of time in each trial during which the speed of both the red and the blue triangle was greater than zero.

Outliers were removed from each DV, which were defined as values further than 2 standard deviations away from the mean. Various transformations were applied to the data to ensure normality, such as a square root transformation (speed, acceleration, jerk, mean rotation, maximum speed), a reciprocal transformation (minimum speed) and a square transformation (sub-movements). Finally, variables were z-scored to centre the data.

Animation perception

Accuracy scores for each trial were calculated by subtracting the mean rating for all non-target words from the rating for the target word. This score range (-100,100) was shifted

to positive integers (0, 200) and outliers were removed. A square transformation and z-score transformation were applied to normalise and centre the data. It should be noted that one PD participant did not complete the Animation Perception Task, thus reducing the PD sample size to 32.

2.2.4 Analyses

Group matching analyses were run in R Studio (2022.07.2). Linear mixed models (LMMs) were run in MATLAB 2022A using MATLAB's *fitlme* function. Bayesian analyses were conducted in JASP (0.17.2.1). Data and analysis scripts are available online at https://osf.io/dge6t/?view_only=588a08aa1eb04942a2f1f8bbccc9dede.

Group matching

To verify group matching on age, non-verbal reasoning, depression, anxiety and alexithymia, ANOVAs were conducted with group as a between-participant factors; any significant differences were explored using post-hoc t-tests between groups. To assess group differences in gender, a chi squared analysis was run. Variables that were not matched between groups were included as control variables in subsequent LMM analyses.

Group differences

Differences in parkinsonian traits (UPDRS) and autistic traits (RAADS and AQ) between groups were assessed using ANOVAs, in which group was entered as a between-participant factor. Again, post-hoc t-tests were used to unpack any group differences.

Animation production

To assess differences in animations produced between groups, LMMs were employed for each parameter with participant group, word-type (mental state, non-mental state, physical), and their interaction as fixed effects. Age, depression, anxiety and alexithymia were

also included as fixed effects given that they significantly differed between groups, and their predictions of the DVs were assessed. Participant ID was included as a random effect. As such, the model formula was as follows:

DV ~ Group * Word-Type + Age + Depression + Anxiety + Alexithymia + (1|Participant ID)

For cases in which a main effect of group or word-type was significant, post-hoc analyses were conducted to identify between which groups/word-types there were significant differences; this was achieved by running the model above on subsets of the data containing only two groups or two word-types.

To obtain p-values for the fixed effects, ANOVAs were conducted on the model coefficients.

For cases in which a main effect of group was not found, Bayesian ANOVAs were conducted to assess evidence for the null hypothesis. Residuals of the DV after controlling for age, depression, anxiety and alexithymia were used as input values, and fixed factors of group and word-type were used, as well as a random factor of participant ID. Bayes Factors (BF_{01}) are reported for the main effect of group, which provide a ratio of the likelihood for the observed data under the null hypothesis compared to the alternative hypothesis (Dienes, 2016). Values of greater than 10, 3-10 and 1-3 were taken as strong, moderate and anecdotal evidence for the null hypothesis respectively (Lee & Wagenmakers, 2014).

Animation perception

To investigate whether groups differed in Animation Perception accuracy, an LMM was employed for accuracy scores with participant group, word-type, movement bin, and their interactions as fixed effects. Again, age, depression, anxiety and alexithymia were included as

fixed effects. Random effects were included for trial number to account for fatigue or practice effects, and animation ID and participant number to account for variance between animation videos and participants. Again, an ANOVA was conducted on the model coefficients to obtain p-values. The model formula was as follows:

DV ~ Group * Word-Type * Movement Bin + Age + Depression + Anxiety + Alexithymia + (1|Trial number) + (1|AnimationID) + (1|Participant ID)

A non-significant main effect of group was followed up with a Bayesian ANOVA conducted on accuracy residuals (after controlling for age, depression, anxiety and alexithymia), with group, word-type and bin as fixed factors, and trial number, animation ID and participant ID as random factors. Bayes Factors (BF_{01}) are reported for the main effect of group.

2.2.5 Pre-Registration and Power Analysis

A pre-registration for the study can be found online at https://osf.io/ek6h7. Certain questionnaires were added to the protocol as control variables following discussions with collaborators post-pre-registration (e.g., the RAADS indexing autistic traits, the PHQ indexing depression, and the GAD indexing anxiety). In addition, all participants completed the UPDRS as an index of parkinsonian traits. Two additional words were included in the Animation Production Task (physical: bouncing, drifting). Additional variables were also calculated from the Animation Production data (e.g., mean rotation and synchronous movement as in Schuster et al. (2021), and minimum and maximum speed). Contrary to the

pre-registered analyses, the current Chapter does not investigate predictors of Animation Perception accuracy due to the lack of group differences in accuracy.

A number of *a priori* power analyses were calculated with G*power (Erdfelder et al., 1996) to determine the sample size for the current study. For Animation Production, data from Edey et al. (2016) was used which demonstrated increased jerk in animations produced by autistic individuals compared to non-autistic individuals; with a Cohen's d effect size of 0.79 and 0.05 alpha level, it was determined that a minimum of 27 participants were required per group to achieve a power level of 0.80 on a two-tailed test.

For Animation Perception, data from White et al. (2011) was used due to their comparable study design, similar methods of scoring (objective rather than subjective ratings of responses) and recruitment of adult participants. The study demonstrated group differences between autistic and non-autistic adults on two objective measures of task performance: "Multiple-Choice Question (MCQ)-categorisation total" (i.e., total score for categorising animations into "no interaction", "physical interaction" and "mental interaction") and "MCQ-feelings" (i.e., total score for selecting the correct feeling within the mentalizing animations). Cohen's d effect sizes were calculated for the difference between means on each measure using data provided in the paper (sample size, mean and standard deviation for each group). With Cohen's d effect sizes of 1.35 and 1.83 respectively, and 0.05 alpha level, it was determined that a minimum of 10 and 6 participants were required per group respectively to achieve a power level of 0.80 on a two-tailed test.

Thus, at least 30 participants were recruited in each group to exceed the highest sample size recommended by these power analyses. Note that it was not possible to conduct an a priori power analysis for the exact proposed statistical analyses (i.e., linear mixed

models) due to a lack of suitable power analysis methods and existing data (e.g., the Animation Tasks have not been run in the PD population).

2.3 Results

2.3.1 Group Matching

Descriptive statistics for each group are listed in Table 2.1, in addition to tests of equivalence. Groups did not significantly differ in terms of gender or non-verbal reasoning ability. A significant difference in age was found between the three groups which, when unpacked, reflected a difference between the PD and ASD groups ($t(60.79) = 3.69$, $p < .001$). Nevertheless, both clinical groups were age-matched to the CTRL group (ASD: $t(58.12) = 1.32$, $p = .191$; PD: $t(55.96) = 1.80$, $p = .077$). Group differences were found in depression scores, whereby both the clinical groups had higher scores than CTRLs (ASD: $t(41.57) = 4.61$, $p < .001$; PD: $t(45.33) = 5.17$, $p < .001$), but did not differ from each other ($t(56.98) = 0.20$, $p = .840$). Anxiety scores also differed between groups: the ASD group had higher scores than both the PD group ($t(56.01) = 3.31$, $p = .002$) and the CTRL group ($t(57.55) = 4.51$, $p < .001$), but the PD and CTRL groups did not differ ($t(59.99) = 1.41$, $p = .163$). Finally, there was a significant group difference in alexithymia scores, which reflected higher levels of alexithymic traits in the ASD group compared to the other two groups (PD: $t(61.99) = 5.43$, $p < .001$; CTRL: $t(52.99) = 6.17$, $p < .001$); the PD and CTRL group did not differ with respect to alexithymic traits ($t(55.30) = 0.25$, $p = .801$).

Table 2.1

Descriptive Statistics and Tests of Equivalence for the Autism, Parkinson's Disease and Control Groups

	ASD	PD	CTRL	Test of equivalence
Gender	14 M, 16 M, 1 O	19 M, 14 F, 0 O	16 M, 16 F, 0 O	$X^2(4)= 2.91$, $p = .572$
Age	55.42[7.91]	62.45[7.31]	58.47[10.25]	$F(2, 93) = 5.42$, $p = .006$**
Non-verbal reasoning	0.58[0.15]	0.55[0.13]	0.58[0.16]	$F(2, 91) = 0.36$, $p = .697$
Depression	8.1[5.65]	7.8[4.51]	2.9[2.56]	$F(2, 90) = 13.48$, $p < .001$***
Anxiety	9.8[6.04]	5.2[4.61]	3.5[4.87]	$F(2, 90) = 11.99$, $p < .001$***
Alexithymia	61.19[12.65]	43.58[13.31]	44.28[8.69]	$F(2, 93) = 22.75$, $p < .001$***
Years since diagnosis	4.16[2.72]	3.81[2.49]	-	-
Parkinsonian traits	3.58[3.81]	10.64[5.59]	0.97[1.67]	$F(2, 93) = 49.70$, $p < .001$***
Autistic traits (RAADS)	32.52[8.04]	10.43[9.43]	6.31[6.35]	$F(2, 90) = 96.59$, $p < .001$***
Autistic traits (AQ)	37.65[7.09]	18.39[6.91]	16.09[5.87]	$F(2, 93) = 99.84$, $p < .001$***

Note. Table contains means (M) and standard deviations (SD): M[SD]. Significant p-values in tests of equivalence indicate differences between groups. ASD = Autism Spectrum Disorder, PD = Parkinson's Disease, CTRL = Control, M = male, F = female, O = other. *** $p < .001$, ** $p < .01$ and * $p < .05$.

2.3.2 Group Differences

Assessments of parkinsonian traits via UPDRS scores confirmed that the PD group scored significantly higher than the CTRL group ($t(37.86) = 9.50$, $p < .001$). Interestingly, the ASD group *also* scored significantly higher than the CTRL group ($t(40.90) = 3.50$, $p = .001$), though their levels remained significantly lower than the PD group ($t(56.67) = 5.93$, $p < .001$). This indicates that, whilst the autistic participants were not comparable to the PD group itself, they did have elevated parkinsonian traits compared to members of the general population.

In terms of autistic traits, the ASD group scored higher than both the CTRL and PD groups on the AQ (ASD-CTRL: $t(58.20) = 13.12$, $p < .001$; ASD-PD: $t(61.50) = 10.99$; $p < .001$) and the RAADS (ASD-CTRL: $t(57.07) = 14.33$, $p < .001$; ASD-PD: $t(56.92) = 9.83$, $p < .001$). There were no significant differences between the PD and CTRL group on either

measure (AQ: $t(61.94) = 1.45$, $p = .152$; RAADS: $t(50.40) = 2.01$, $p = .050$), though mean scores were numerically higher in the PD group.

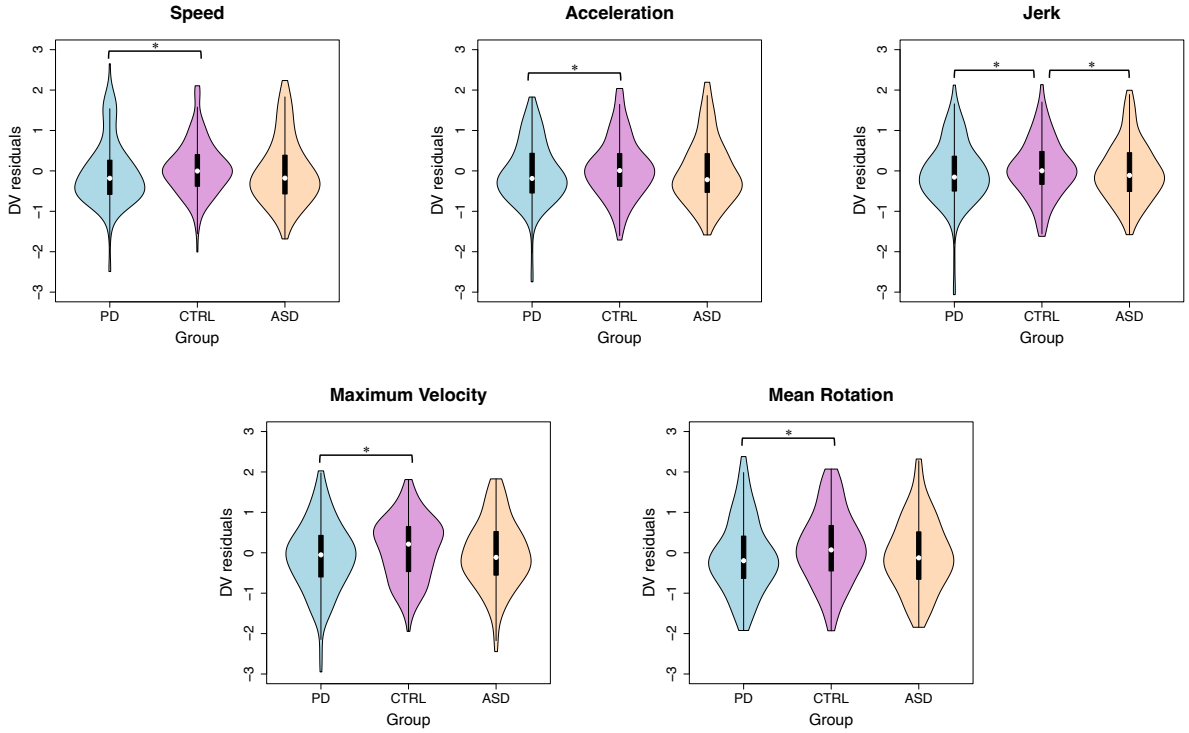
2.3.3 Animation Production

Groups can be distinguished by kinematic features.

Group differences were observed for speed ($F(2, 514) = 5.10$, $p = .006$), whereby the PD group moved more slowly than CTRLs ($F(1, 345) = 7.37$, $p = .007$; beta estimate = 0.291, 95% Confidence Intervals (95% CI) [-0.503, -0.285]). Similarly, group differences in acceleration ($F(2, 523) = 5.09$, $p = .006$) reflected a significant main effect of group between PD and CTRL ($F(1, 348) = 6.50$, $p = .011$), whereby the PD group moved with lower acceleration than CTRLs (beta estimate = -0.286, 95% CI [-0.506, -0.065]. Jerk also significantly differed between groups ($F(2, 523) = 4.95$, $p = .007$); animations produced by both PD and ASD groups had lower jerk than CTRLs (PD-CTRL: $F(1, 350) = 6.24$, $p = .013$, beta estimate = -0.295, 95% CI [-0.526, -0.063]; ASD-CTRL: $F(1, 351) = 4.19$, $p = .041$, beta estimate = -0.196, 95% CI [-0.384, -0.001]). ASD and PD groups did not differ with respect to jerk ($p > .05$). Maximum speed differed between groups ($F(2, 521) = 8.66$, $p < .001$); as was the case for average speed, the PD group had a significantly lower maximum speed than CTRLs ($F(1, 346) = 12.95$, $p < .001$, beta estimate = -0.338, 95% CI [-0.523, -0.153]). Finally, group differences in mean rotation were observed ($F(2, 515) = 9.50$, $p < .001$), whereby the PD group had a lower mean rotation than CTRLs ($F(1, 344) = 14.37$, $p < .001$). See Figure 2.2 for violin plots of group differences.

Figure 2.2

Violin Plots Depicting Group Differences in Animation Production Task Dependent Variables



Note. Residuals for each dependent variable (after controlling for age, depression, anxiety and alexithymia) are plotted for PD (blue), CTRL (purple) and ASD (orange) groups respectively. * indicates a significant main effect of group. White dot = median, box = interquartile range. PD = Parkinson's Disease, CTRL = Control, ASD = Autism Spectrum Disorder.

Some kinematic features are the same between groups.

There were no group differences regarding synchronous movement, minimum speed and sub-movements (all $p > .05$). As such, Bayesian ANOVAs were conducted on these variables to identify BF_{01} factors for the main effect of group. Strong evidence for the null hypothesis was found for all three variables (synchronous movement $BF_{01} = 28.55$; minimum speed $BF_{01} = 31.93$; sub-movements $BF_{01} = 32.24$). BF_{01} values for the main effect of group for each group comparison are reported in Table 2.2.

Table 2.2

Bayes Factors for Variables with No Group Differences

	All groups	ASD-CTRL	ASD-PD	PD-CTRL
Synchronous Movement	28.55	7.39	6.92	6.73
Minimum Speed	31.93	6.90	7.07	6.61
Sub-movements	32.24	7.23	6.96	6.58

Note. Table contains BF_{01} values for the main effect of group obtained in Bayesian ANOVAs. ASD = Autism Spectrum Disorder, PD = Parkinson's Disease, CTRL = Control.

As noted above, no differences (all $p > .05$) in speed, acceleration, jerk, mean rotation and maximum speed were found between the ASD and PD groups, nor between the ASD and CTRL groups (except jerk). BF_{01} values for the main effect of group for these group comparisons are reported in Table 2.3.

Table 2.3

Bayes Factors for Specific Group Comparisons with No Main Effect of Group

	ASD-CTRL	ASD-PD
Speed	4.46	6.84
Acceleration	4.76	6.90
Jerk	-	7.22
Mean Rotation	2.57	6.65
Maximum Speed	3.13	6.03

Note. Table contains BF_{01} values for the main effect of group obtained in Bayesian ANOVAs. ASD = Autism Spectrum Disorder, PD = Parkinson's Disease, CTRL = Control.

Animations varied in kinematic values based on word-type.

Main effects of word-type were observed for all DVs, but the direction of these effects differed between variables (see Figure 2.3). In the majority of cases, physical animations were associated with higher levels of the DV and non-mental state animations were associated with the lowest. This pattern was clearly observed for jerk and mean rotation. The word-type difference observed for jerk ($F(2, 523) = 14.60$, $p < .001$), reflected higher jerk in physical animations than both mental state animations ($F(1, 342) = 6.85$, $p = .009$, beta estimate =

0.118, 95% CI [0.029, 0.207]) and non-mental state animations ($F(1, 346) = 25.15$, $p < .001$, beta estimate = 0.211, 95% CI [0.128, 0.294]). Mental state animations also had significantly higher jerk than non-mental state animations ($F(1, 354) = 8.11$, $p = .005$, beta estimate = 0.100, 95% CI [0.031, 0.169]). Similarly, mean rotation differed based on word-type ($F(2, 515) = 38.66$, $p < .001$): physical animation had higher mean rotation than both mental state animations ($F(1, 333) = 32.19$, $p < .001$, beta estimate = 0.285, 95% CI [0.186, 0.383]) and non-mental state animations ($F(1, 336) = 98.48$, $p < .001$, beta estimate = 0.420, 95% CI [0.337, 0.504]). Mental state animations also had significantly higher mean rotation than non-mental state animations ($F(1, 357) = 10.05$, $p = .002$, beta estimate = 0.136, 95% CI [0.052, 0.221]).

In the case of acceleration (main effect of word-type: $F(2, 523) = 21.39$, $p < .001$), lower levels of the DV were observed in non-mental state animations compared to both physical animations ($F(1, 346) = 35.73$, $p < .001$, beta estimate = 0.255, 95% CI [0.171, 0.339]) and mental state animations ($F(1, 353) = 28.86$, $p < .001$, beta estimate = 0.185, 95% CI [0.117, 0.252]), but physical animations were not significantly higher in acceleration than mental state animations ($p > .05$).

Conversely, for speed (main effect of word-type: $F(2, 514) = 46.80$, $p < .001$), higher levels of the DV were observed in physical animations compared to mental state animations ($F(1, 333) = 58.02$, $p < .001$; beta estimate = 0.349, 95% CI [0.259, 0.439]) and non-mental state animations ($F(1, 332) = 52.46$, $p < .001$; beta estimate = 0.317, 95% CI [0.231, 0.404]), but mental state and non-mental state animations did not differ ($p > .05$).

For both synchronous movement and sub-movements, physical animations had the highest levels of the DV, but mental state animations had the lowest. When unpacking the main effect of word-type on synchronous movement ($F(2, 516) = 92.41$, $p < .001$), it was

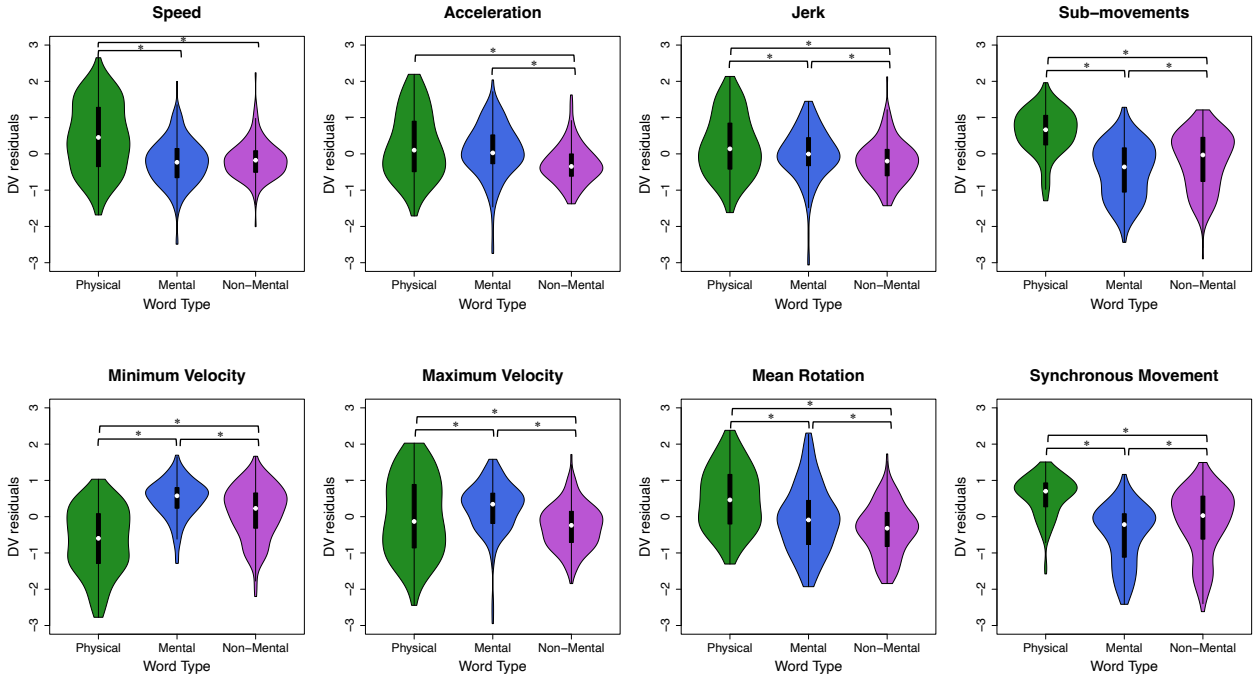
apparent that physical animations had the longest time in which both triangles are moving, significantly longer than non-mental state animations ($F(1, 350) = 83.15$, $p < .001$, beta estimate = 0.362, 95% CI [0.284, 0.440]) and mental state animations ($F(1, 342) = 214.86$, $p < .001$, beta estimate = 0.546, 95% CI [0.473, 0.619]). Synchronous movement was also significantly longer in non-mental state animations compared to mental state animations ($F(1, 336) = 16.10$, $p < .001$, beta estimate = 0.186, 95% CI [0.095, 0.278]). The same pattern was observed for sub-movements (main effect of word-type: $F(2, 542) = 105.10$, $p < .001$). Physical animations had the highest proportion of sub-movements compared to both non-mental state animations ($F(1, 362) = 108.95$, $p < .001$, beta estimate = 0.393, 95% CI [0.319, 0.467]) and mental state animations ($F(1, 359) = 209.48$, $p < .001$, beta estimate = 0.538, 95% CI [0.465, 0.611]). Non-mental state animations had a higher proportion of sub-movements than mental state animations ($F(1, 359) = 12.66$, $p < .001$, beta estimate = 0.146, 95% CI [0.065, 0.227]).

Finally, in some cases, mental state animations were associated with the highest levels of the DV. Minimum speed varied between animation types ($F(2, 529) = 115.69$, $p < .001$), whereby mental state animations had a lower minimum speed than both non-mental state animations ($F(1, 360) = 27.46$, $p < .001$, beta estimate = 0.178, 95% CI [0.111, 0.244]) and physical animations ($F(1, 348) = 216.83$, $p < .001$, beta estimate = 0.576, 95% CI [0.499, 0.653]). Non-mental state animations also had a higher minimum speed than physical animations ($F(1, 346) = 89.88$, $p < .001$, beta estimate = 0.404, 95% CI [0.320, 0.488]). By contrast, for maximum speed (main effect of word-type: $F(2, 521) = 17.97$, $p < .001$), mental state animations again had the highest maximum speed compared to both physical animations ($F(1, 342) = 6.06$, $p = .014$, beta estimate = 0.125, 95% CI [0.025, 0.225]) and non-mental state animations ($F(1, 353) = 58.17$, $p < .001$, beta estimate = 0.263, 95% CI [0.201, 0.562]),

but physical animations had a higher maximum speed than non-mental state animations ($F(1, 343) = 7.28$, $p = .007$, beta estimate = 0.134, 95% CI [0.036, 0.232]).

Figure 2.3

Violin Plots Depicting Word-Type Differences in Production Task Dependent Variables



Note. Residuals for each dependent variable (after controlling for age, depression, anxiety and alexithymia) are plotted for mental state words (blue), non-mental state words (purple) and physical words (green). * indicates a significant main effect of word-type. White dot = median, box = interquartile range.

Non-group-matched variables did not predict kinematic features.

Neither age, depression, anxiety or alexithymia predicted speed, acceleration, jerk, mean rotation, synchronous movement, minimum speed, maximum speed or sub-movements (all $p > .05$).

2.3.4 Animation Perception

No significant group differences were found with respect to accuracy score ($p > .05$; three-group $BF_{01} = 104.44$; PD-CTRL $BF_{01} = 12.11$; ASD-CTRL $BF_{01} = 12.88$; ASD-PD $BF_{01} = 10.81$). Given that a selective difference in theory of mind ability would be reflected by an interaction between group and word-type (whereby accuracy would differ between groups for mental state but not non-mental state words), it is important to note that no such interaction was found ($p > .05$; three-group $BF_{01} = 4866.08$; PD-CTRL $BF_{01} = 473.08$; ASD-CTRL $BF_{01} = 74.74$; ASD-PD $BF_{01} = 211.43$). A significant main effect of word-type was observed ($F(1, 2837) = 26.16$, $p < .001$) whereby mental state animations were interpreted with significantly lower accuracy than non-mental state words (beta estimate = -0.414, 95% CI [-0.573, -0.255]). Age was a significant positive predictor of Animation Perception accuracy ($F(1, 2837) = 7.64$, $p = .006$, beta estimate = 0.010, 95% CI [0.003, 0.016]).

2.4 Discussion

The current Chapter analysed movement differences in animations produced by autistic individuals, individuals with PD, and control participants. Results demonstrate clear dissociations between kinematics produced by the PD group and the general population during free movement. Specifically, when on their medication, PD movement profiles were slower, had a lower maximum speed, lower acceleration and lower mean rotation than CTRLs. Differences in these particular movement features align well with a literature that has reported a reduction in "vigour" in PD (Alberts et al., 2000; Broderick et al., 2009; Flash et al., 1992; Jankovic, 2008; Lange et al., 2006; Van Gemmert et al., 2003; Viviani et al., 2009). Kinematics produced by autistic individuals fell between those of PD and CTRLs, with no significant differences with respect to either group. This diverges from literature suggesting

faster movements in autism compared to the general population (Cook et al., 2013; Grace et al., 2017; Johnson et al., 2013). However, it should be noted that extant studies tend to assess movement in younger samples of autistic individuals (e.g., Cook et al., 2013; mean age = 41.07) or children (e.g., Grace et al., 2017; mean age = 10.58) which may account for the discrepancy in findings.

Whilst ASD and PD performance did not significantly differ on a range of kinematic features, similar performance between the two groups could be distinguished from CTRLs only in terms of jerk: ASD and PD groups had lower jerk in their movement profiles than CTRLs. This is an unusual finding as both PD and ASD are typically associated with jerky movements (Alberts et al., 2000; Cook et al., 2013; Edey et al., 2016). A possible explanation may be the nature of the jerk measure used. Here, jerk was calculated as the second derivative of speed and, as such, the measure was inherently related to speed values. It may be that the CTRL group had the highest jerk values as they were moving the fastest, meaning that the pattern of jerk values was epiphenomenal of the pattern of speed values. Slower movements are indeed expected in PD, whereas fast movements are typically observed in ASD. The slower movements observed in the ASD group here may be a result of the inherent link to theory of mind. The movement task required participants to depict various scenarios and did not provide them with clear instructions or a trajectory to follow. It may be that the autistic participants moved more slowly due to a lack of confidence in their mental state depictions. More broadly, other task demands such as sustained attention and working memory may have disrupted natural kinematics, given differences in executive functioning in both young and older autistic adults (Geurts & Vissers, 2012; Hill, 2004). A follow-up study of raw kinematic features independent of theory of mind and other cognitive task demands is required to verify this hypothesis.

The current study allowed for an assessment of how kinematics are generally used to depict different situations. Physical animations were drawn the fastest, with greater acceleration, jerk and number of sub-movements, higher mean rotation and longer time with both triangles moving. By contrast, non-mental state animations were the lowest with respect to the kinematic DVs (acceleration, jerk, rotation, sub-movements), with the exception of synchronous movement (of which mental state animations had the lowest values) and speed (of which both mental and non-mental state animations were comparable). Finally, mental state animations had the highest minimum and maximum speed. Thus, this provides clear evidence that kinematic features are an important component for depicting and distinguishing between various social and non-social situations, in line with extant literature (Dael et al., 2012; Schuster et al., 2021; Sowden et al., 2021). These differences in kinematics can be understood when considering the requirements and features of the animations produced. For example, it is rational for mental state animations to contain the lowest proportion of synchronous movement as these mental state interactions are often depicted with movement in one triangle followed by a response by the other triangle. In addition, it is likely that fast animations would not lend themselves to representing a complex narrative, as is required in both mental and non-mental state animations. Therefore, it may be that increased kinematic values (such as speed) are more likely to be used for physical animations in which a narrative does not need to be depicted.

In addition to analysing movement differences, the current study investigated whether there were differences in theory of mind between ASD, PD and CTRL groups. Interestingly, no differences in perception accuracy were found between groups (neither across all trials nor specific to mental state animation trials). This is in contrast to extant literature demonstrating theory of mind differences in both ASD (e.g., Abell et al., 2000) and PD (e.g., Orso et al.,

2020). However, current evidence in the PD and older autistic adult literature does not relate to movement-based theory of mind; therefore, it is possible that theory of mind differences in the two groups may relate to different components of theory of mind (e.g., cognitive/situational, as indexed in the Faux Pas Task). One possible explanation for these results is that – in line with results by Lever and Geurts (2016a) and Yarar et al. (2020) – a selective ageing-related decline in the non-autistic group may result in equal performance between all three groups. However, in the current Chapter, accuracy in fact positively correlates with age, which opposes current literature (Pardini & Nichelli, 2009). Furthermore, accuracy was high for all groups (ASD mean[standard deviation] = 46.11[44.78]; PD = 40.42[41.92]; CTRL = 43.98[45.29]; on a scale from -100 to 100). This demonstrates that participants generally selected the correct answer: positive scores indicate a higher target word rating than the average of the non-target word ratings; a score of 0 indicates equal ratings on target and non-target words – i.e., words cannot be distinguished; a negative score indicates a lower target word rating than the average of the non-target word ratings. Given that the mean accuracy score was not 100 (i.e., 100% accuracy), ceiling effects were not responsible for the lack of group differences. Thus, it appears that all groups exhibited the same relatively high level of accuracy.

The presence of group differences in movement but absence of group differences in movement-based theory of mind brings into question whether production and perception are as intertwined as current literature suggests. If one's own movements for representing mental states are used as a "blueprint" for interpreting others' movement-based mental state representations, it follows that movement differences between groups should result in differences in theory of mind inferences. It is possible that ASD and PD groups *do* differ from the general population in some features of movement, but these may not be the variables that

are important for making mental states inferences. For example, synchronous movement significantly differed between the different animation word-types, meaning it could be used to infer whether an animation contained a mental state depiction, a non-mental state depiction or simply a physical depiction. However, synchronous movement in the animations produced did not significantly differ between groups. This implies that participants across the three groups should have similar synchronous movement "blueprints" which are utilised when interpreting animations in the Animation Perception Task. Similar "blueprints" should lead to similar performance across all three groups if their inferences are influenced by the proportion of synchronous movement in the animations. To further evidence a link between production and perception, future work should conduct a systematic assessment of which kinematic features are important for conducting mental state inferences in the Animation Perception Task, and subsequently investigate whether ASD and PD groups differ from the control participants with respect to these variables in the Animation Production Task. This would reveal whether movement differences between groups exist for the variables that are used to make mental state inferences.

There are a number of possible explanations for the lack of differences between the groups in theory of mind beyond that of a true similarity between groups. Study design, for example, may be a factor contributing to increased accuracy. Firstly, participants completed the task at home rather than in a laboratory setting which may have boosted their ability, thus accounting for the relatively high accuracy scores. It is also possible that at-home testing boosted performance to a greater extent in the clinical groups, as anxiety with in-person testing may be exacerbated in ASD and PD groups, causing performance in all three groups to equalise. Secondly, studies showing theory of mind differences in ASD in the Animation Perception Task do not generally require participants to complete the production section of

the task (Abell et al., 2000; Castelli et al., 2002; Livingston et al., 2021; White et al., 2011). In the current study, participants must first consider how to depict the given scenarios in their own animations before perceiving and rating others' animations. These personal depictions could be used to set expectations for what they will see in the perception task, thus increasing perception accuracy. However, this boost in performance may again differentially affect the ASD and PD groups. It has been proposed that both autistic individuals and those under low dopamine conditions (such as in PD), exhibit differences in the weighting of prior beliefs compared to incoming sensory information (Friston et al., 2012; Pellicano & Burr, 2012; Van de Cruys et al., 2014; Vilares & Kording, 2017). Performance in the Animation Perception Task for these individuals may be particularly improved by first-hand experience creating their own animations prior to the perception component. The utility of experience in the production task for performance in the perception task could be tested by recruiting separate participant samples who either perform the production task before or after the perception task, or not at all. Comparing this effect across groups may reveal that the production component of the task is particularly beneficial for both the ASD and PD groups, leading to the normalisation of their performance.

In line with previous studies (Livingston et al., 2021; Schuster et al., 2021; Schuster et al., 2023; White et al., 2011), non-mental state inferences were more accurate than mental state inferences for all participant groups. This may be because non-mental state animations such as "following" or "searching" have logical physical representations which can be readily identified through the triangles' movement. By contrast, mental state animations are more subjective, as there are many ways to physically depict a higher-order mental state interaction such as "mocking" or "surprising". As such, mental state animations may have greater inter-participant variability compared to non-mental state animations, leading to increased

difficulty when labelling mental state animations. Whilst some studies have demonstrated equal performance on mental state and non-mental state animation identification in the general population (Abell et al., 2000; Castelli et al., 2002; Livingston et al., 2021), this may be accounted for by the lack of variation in animations used. For example, many of these studies only used animations made by a limited number of creators (sometimes just one creator), which would reduce the variability between the animations. This is likely to differentially improve mental state perception accuracy, as this word category often holds more inter-animation variability, thus leading to equal performance between the two conditions.

To conclude, the current study highlights a range of kinematic similarities and differences between the three groups on a task of free movement. Autistic and parkinsonian movement did not significantly differ on any kinematic feature which raises the possibility that autistic individuals and individuals with PD share movement similarities. However, there was only one kinematic feature in which the similar performance between ASD and PD groups was distinct from CTRLs (i.e., jerk). Clear kinematic differences were apparent between PD and CTRL groups on this free movement task. Unanticipated findings were uncovered with regards to ASD and CTRL group differences (e.g., lower jerk values in the ASD group), but this may be due to the theory of mind requirement in movement production. As such, future studies should utilise pure kinematic assessments to compare movement between the three groups. A lack of group difference in theory of mind was also revealed, possibly due to task design elements (e.g., at-home testing and production prior to perception). Finally, in line with extant literature, word-type was a clear predictor of both kinematic features and task accuracy, demonstrating that mental state, non-mental state and

physical scenarios differ both in the ways they are depicted and the accuracy with which they are perceived.

Chapter 3 – An Assessment of Autistic and Parkinsonian Movement Profiles to Inform Selective Classification Algorithms

The previous Chapter revealed no significant movement differences between ASD and PD, supporting the theory that movement similarities between the two conditions may contribute to a misdiagnosis of PD in ASD. However, there was only one kinematic feature in which both groups differed from members of the general population. In the previous Chapter, movement was indexed in a task with theory of mind and executive function demands, and the free movement profiles obtained could not be used to calculate certain kinematic features (e.g., speed modulation and SPARC). As such, a task of restricted movement with no theory of mind demands and minimal executive function demands may be more sensitive to detect group differences. Chapter 3 employed the Shapes Tracing Task to compare restricted movement in ASD and PD. Following group comparisons of kinematic features extracted from the Shapes Tracing Task, classification analyses were subsequently employed to identify whether trait questionnaires and/or kinematic features were most useful in predicting group membership. This Chapter aimed to highlight any movement similarities (and differences) between ASD and PD, with a view to comment on the veracity of the theory that older autistic individuals may exhibit parkinsonian-like movement differences which enable a more readily accessible diagnosis (or misdiagnosis) of PD. Given that individuals with PD will not be taking medication when initially obtaining a diagnosis, any confusion between autistic and parkinsonian movement in the diagnostic process would be with respect to unmedicated PD movement profiles. Consequently, participants with PD were OFF their dopaminergic medication when completing the movement task.

A pre-registration for the study can be found online at https://osf.io/dnk6j. Content from the pre-registration has been reproduced in the current Chapter. Supplementary materials for this Chapter can be found in Appendix 2. Data and analysis scripts can be found online at https://osf.io/5g7ft/?view_only=a6bde915a13d46b2ad9c61edaa351260.

3.1 Introduction

Whilst the majority of research into ASD has focused on differences in social communication, and restricted and repetitive interests (American Psychiatric Association, 2013), differences in motor function have garnered attention in recent years. A growing body of evidence has highlighted differences between autistic and non-autistic individuals in motor planning (Gowen & Hamilton, 2013; Mari et al., 2003), execution (Mari et al., 2003; Wang et al., 2015) and coordination (Lum et al., 2021). Indeed, meta-analyses have revealed significant differences between autistic and non-autistic individuals on a variety of motor tasks (Fournier et al., 2010; Wang et al., 2022). Differences are apparent at early stages of the condition, with both delayed motor development and motor function atypicalities reported in autistic children (Posar & Visconti, 2022). As such, calls have been made to include movement differences as "specifiers" to autism diagnoses (i.e., condition-relevant but non-selective symptoms used to further clarify a diagnosis; Licari et al., 2022).

Anecdotally, autistic movements have been likened to those of PD (Mari et al., 2003; Maurer & Damasio, 1982; Vilensky et al., 1981). However, similarities between autistic individuals and individuals with PD may extend further than the behavioural level. Recent reports have highlighted an increased prevalence of parkinsonism and PD diagnosis in the autistic population (Croen et al., 2015; Geurts et al., 2022; Hand et al., 2020; Mai et al., 2023; Starkstein et al., 2015). This raises two interesting possibilities: on the one hand, it is possible that autistic individuals are more likely than members of the general population to develop PD. For instance, there could be genetic overlap between ASD and PD wherein the same genes confer risk for both conditions. However, a number of studies have failed to show a significant correlation between the genes associated with ASD and PD (Ellis et al., 2020; Sey et al., 2020; Smeland et al., 2021; The Brainstorm Consortium et al., 2018). Alternatively, it

may be that autistic individuals are more likely to be diagnosed with PD because they exhibit parkinsonian-like movement differences (i.e., the misdiagnosis hypothesis). To address this, it is important to quantify the extent to which autistic and parkinsonian movement overlaps. Without a direct comparison of the groups' movement profiles, it is unclear whether overlapping movement features may contribute to this prevalent co-diagnosis. This is particularly relevant in the context of a wide body of literature using kinematic features to classify individuals into PD and non-PD groups (Al-Yousef et al., 2020; Carvajal-Castano et al., 2022; Dehghanpur Deharab & Ghaderyan, 2022; Drotár et al., 2016; Gerger & Gümüşçü, 2022; Kamble et al., 2021; Lamba et al., 2021; Netšunajev et al., 2021; Rios-Urrego et al., 2019). If autistic and parkinsonian movement is similar, autistic individuals are at risk being categorised into the PD group in classification algorithms.

Whilst no direct comparisons of autistic and parkinsonian movement have been conducted, reviewing the literature indicates potential movement similarities including jerky movements (Alberts et al., 2000; Cook et al., 2013; Edey et al., 2016) and an increased number of alternations between acceleration and deceleration (or "sub-movements"; Castiello et al., 2000; Cook et al., 2023; Flash et al., 1992; Lange et al., 2006). Nevertheless, there is also evidence of movement differences: a distinction between autistic and parkinsonian movement can be made with respect to speed. Whilst autistic individuals have been found to move with increased velocity and acceleration (Cook et al., 2013; Grace et al., 2017; Johnson et al., 2013), and with reaction times that are comparable to the general population (Ferraro, 2016), all three of these kinematic features are reduced in PD (Alberts et al., 2000; Bloxham et al., 1987; Broderick et al., 2009; Flash et al., 1992; Jankovic, 2008; Lange et al., 2006; Pullman et al., 1988; Rafal et al., 1984; Van Gemmert et al., 2003; Viviani et al., 2009). Thus,

preliminary work indicates both similarities and differences between autistic and parkinsonian movement.

The aforementioned kinematic features can be computed across a wide range of movement trajectories, as seen in Chapter 2, but certain features of movement can only be ascertained from set movements. For example, Spectral Arc Length (SPARC; Balasubramanian et al., 2012; Balasubramanian et al., 2015) is a measure of movement smoothness calculated by applying a Fourier transformation to the speed profile and taking the arc length of the resultant magnitude spectrum. For this metric to be comparable between participants, it must be calculated on identical movement trajectories, as SPARC values are higher for longer movement trajectories. Comparing SPARC to jerk can shed light upon whether differences in jerk are an epiphenomenal consequence of effects on speed, as SPARC is a speed-independent measure of movement smoothness whereas jerk is not.

An additional kinematic feature that has been overlooked, specifically in the study of PD, is speed modulation. In the general population, movement speed is modulated according to the curvature of shapes (Huh & Sejnowski, 2015), whereby individuals speed up along straight parts of a shape and slow down for corners. Additionally, this modulation differs according to the angular frequency of shapes (i.e., the number of curvature oscillation per two π of angular displacement; an ellipse has an angular frequency of 2) adhering to a spectrum of power laws, such that more gradual speed modulation is observed for higher angular frequency shapes (Cook et al., 2023; Huh & Sejnowski, 2015; Matic & Gomez-Marin, 2019; Matic & Gomez-Marin, 2020; Matic & Gomez-Marin, 2022). Speed modulation values are higher in the autistic population (Cook et al., 2023; Fourie, 2022) meaning that autistic individuals tend to "slam on the breaks" as they approach corners. Speed modulation has not been investigated in PD but, given that speed is affected by dopamine dysfunction (Alberts et

al., 2000; Broderick et al., 2009; Lange et al., 2006), it is possible that speed modulation may also be affected. Thus, speed modulation across the angular frequency spectrum may comprise a useful metric on which to compare ASD and PD populations.

At present, drawing conclusions regarding autistic and parkinsonian movement similarities requires the utilisation of findings drawn from separate studies with different experimental designs, each varying with respect to participant demographics. This is problematic because kinematic features are known to be influenced by a range of factors. For example, slower movement is seen with increasing age (Ketcham et al., 2002), lower IQ (Forti et al., 2011), and higher levels of depression and anxiety (Pijpers et al., 2005; Sachdev & Aniss, 1994) – clinical traits that are known to be elevated in ASD (Hollocks et al., 2019) and PD (Broen et al., 2016; Reijnders et al., 2008). Indeed, the movements of those with melancholic depression have been quantitatively likened to those of PD (Sachdev & Aniss, 1994). Gender differences in the motor symptoms of PD have also been reported (Miller & Cronin-Golomb, 2010). A primary objective of the current Chapter was to directly compare autistic and parkinsonian movement in a single controlled experiment, either matching or – where matching was not possible – controlling for these variables.

Whilst substantial research has employed classification algorithms to separate PD and non-PD populations (Al-Yousef et al., 2020; Carvajal-Castano et al., 2022; Dehghanpur Deharab & Ghaderyan, 2022; Drotár et al., 2016; Gerger & Gümüşçü, 2022; Kamble et al., 2021; Lamba et al., 2021; Netšunajev et al., 2021; Rios-Urrego et al., 2019), the relevance of movement differences arising from other clinical conditions (such as autism) has been overlooked. Existing algorithms do not incorporate, and thus account for, co-occurring movement conditions (though see Duque et al., 2023 for a differential diagnosis method for PD versus essential tremor). A secondary aim, therefore, was to identify whether movement

differences are useful for classifying whether someone might belong to a clinical group (here, ASD or PD) or non-clinical group (control; CTRL) and, subsequently, which clinical group they belong to. This Chapter assesses how well kinematic features can discriminate between ASD, PD and CTRL groups, and whether these predictions are helpful above and beyond common questionnaire measures of autistic and parkinsonian traits.

To summarise, the current Chapter compares the kinematic features of three groups of older adults: autistic individuals, individuals with PD and control participants. To index kinematics, participants traced set movement trajectories – shapes that have a highly predictable relationship between speed and curvature when traced by members of the general population (Huh & Sejnowski, 2015) – on a touchscreen device. Kinematic features were extracted from participants' recorded movements and a choice reaction time task was used to index reaction time. The current Chapter presents the first controlled comparison of kinematic features between these groups on a task of restricted movement, and assesses the utility of such kinematic features in predicting group membership.

3.2 Methods

3.2.1 Participants

Three groups were recruited: autistic individuals (ASD; N = 31), individuals with PD (PD; N = 32) and control participants (CTRL; N = 31). Descriptive statistics for each participant group are detailed in Table 3.1 (see Appendix 2 for ethnicity information). Participants were excluded if they had any co-occurring movement or developmental disorders. Recruitment occurred via Parkinson's UK, Autistica, the University of Birmingham Psychology Autism Research Database, the University of Birmingham Older Adults Database, or social media. All participants gave fully informed consent and received

remuneration of £10 per hour. The experimental procedure was approved by the local Research Ethics Committee (ERN_18-1800B and ERN_16-0281AP5).

3.2.2 Procedure

Participants first completed an online screening form followed by a set of questionnaires and the Matrix Reasoning Item Bank (MaRs-IB; Chierchia et al., 2019). Subsequently, participants completed two testing days. These testing days occurred at home using equipment that was posted to them. On each testing day, participants completed a reaction time task and the Shapes Tracing Task using a stylus and touch-screen device (Samsung Galaxy Tab A7; 10.40-inch touchscreen; 2000x1200 pixels). The tasks were programmed in PsychoPy and run on Pavlovia (PsychoJS platform version 2021.1.4). PD participants completed these tasks prior to taking their first dose of dopaminergic medication in the morning; this protocol achieved OFF-medication state and is standard practice in the literature (e.g., Kojovic et al., 2014; Moore et al., 2010; Whitfield et al., 2018). Performance was also recorded on a separate day ON-medication – on this day PD participants completed the task approximately one hour after taking their first dose of dopaminergic medication in the morning. It should be noted that the order of these days was counterbalanced across participants, and the current Chapter only analyses OFF-medication data. To control for practice effects, ASD and CTRL participants also completed the tasks on two separate days. Testing days were no longer than three days apart for any participant.

Online questionnaires

Following demographic questions to check eligibility (i.e., official clinical diagnosis of ASD or PD) and to facilitate group matching (e.g., age, gender), participants completed a number of questionnaires to index autistic traits (AQ, RAADS), parkinsonian traits (UPDRS

Part II), depression (PHQ) and anxiety (GAD). Questionnaires were completed on Qualtrics and presented in a random order.

Matrix Reasoning Item Bank

Participants completed the Matrix Reasoning Item Bank (MaRs-IB) on Gorilla as described in Chapter 2.

Reaction time task

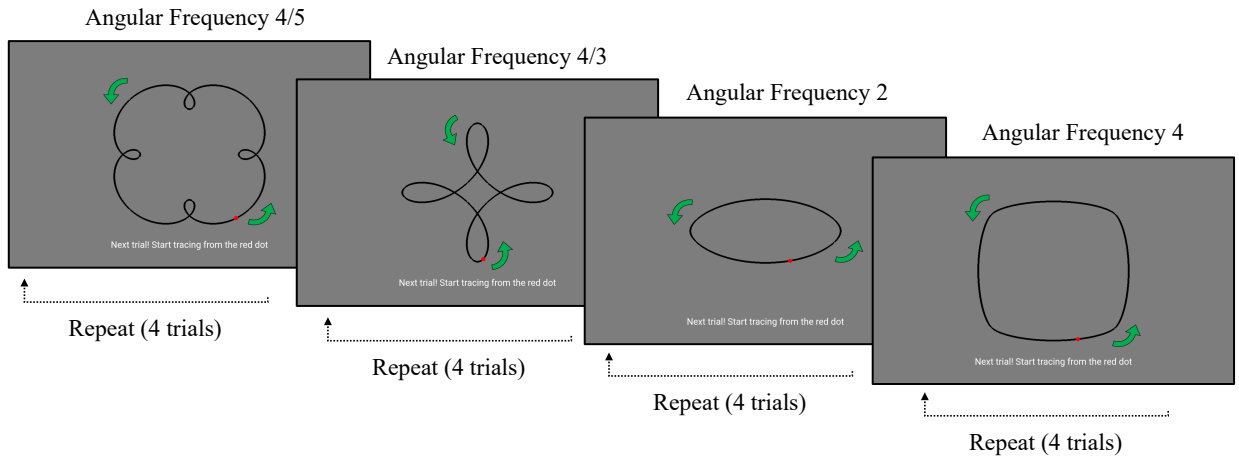
The choice reaction time task included 8 practice trials and 40 experimental trials. In each trial, participants were asked to use a stylus held in their dominant hand to press a stimulus (X) that appeared on the screen in one of four boxes as quickly as possible.

Shapes Tracing Task

In the Shapes Tracing Task, participants used a stylus and touch-screen device to trace shapes in a counter-clockwise direction for 10 full cycles per trial. They were instructed to make these movements "as fluidly as possible", using a stylus in their dominant hand. Four shapes were traced during the task (angular frequencies 4/5, 4/3, 2 and 4; Figure 3.1), with shapes not exceeding 9 cm by 9 cm on the device. Eight blocks were completed, two for each shape, in a random order. Within each block, seven attempts could be made to complete four successful trials, with trials deemed "unsuccessful" if participants lifted their stylus from the screen or deviated too far from the shape following a 5-second grace period. Thus, a maximum of eight successful trials was possible per shape. A timeout of 90 seconds was set for each trial.

Figure 3.1

The Shapes Tracing Task Trial Appearance



Note. A total of eight blocks were completed, two of each shape. During each block, four successful trials were to be completed out of a limit of seven attempts. Blocks were presented to participants in a random order.

3.2.3 Data Pre-Processing

Reaction time task

Scores for the reaction time task were calculated as the average response time (ms) across the 40 experimental trials. Outliers, defined as values further than 2 standard deviations away from the mean, were removed. It should be noted that reaction time data were *not* log transformed as this variable adhered to a normal distribution without transformation.

Shapes Tracing Task

X and y coordinates of the stylus position over time were used to calculate kinematic features for each trial. Trials with fewer than 2.5 traces of the shape were removed. The first ½ π angular displacement of each trial was discounted before data processing. Samples which did not achieve a minimal speed (200 pixels per second) within the 5-second grace period

were removed. The device had a maximum sampling rate of 60Hz but, given deviations, positional data was resampled using the spline method to achieve a consistent 60Hz.

Speed, acceleration, jerk, minimum speed, maximum speed and sub-movements were all calculated as set out in Chapter 2. Speed modulation values (also known as speed-curvature gradients; β in Equation 1) were calculated as the gradient between tangential velocity (v in Equation 1) and the current curvature of the shape being drawn (κ in Equation 1), converted to an absolute value. This followed the established filtering and regression procedure set out in Huh and Sejnowski (2015) and Cook et al. (2023). A higher speed modulation value indicated a steeper adaptation of movement speed to curvature.

$$v \propto \kappa^{-\beta}, \qquad \log(v) \propto -\beta * \log(\kappa)$$

[Equation 1]

SPARC was obtained by calculating the arc length of the magnitude spectrum arising from a Fourier transform of the speed profile. A value for each repeated identical sub-element of each shape within a trial was calculated and values were averaged to obtain a single value per trial. Finally, an error measure reflecting participants' deviations from the target shape was calculated for each trial as the absolute mean of the normal distance to the tangent of the nearest point on the shape's curve (see Madirolas et al., 2022).

Outliers of each kinematic feature were removed (defined as values further than 2 standard deviations away from the mean). To meet normality assumptions, a log transform was applied to speed, acceleration and jerk values, and a reciprocal transform to the minimum speed values. Variables were then z-scored prior to running linear mixed models.

3.2.4 Analyses

Group matching was conducted in R Studio (2022.07.2). Linear mixed models (LMMs) were conducted in MATLAB 2022A using MATLAB's *fitlme* function. Bayesian analyses and classification models were conducted in JASP (0.17.2.1). Data and analysis scripts are available online at https://osf.io/5g7ft/?view_only=a6bde915a13d46b2ad9c61edaa351260.

Group matching

To assess group differences in age, non-verbal reasoning, depression and anxiety, ANOVAs were employed in which group was a between-participant factor. Significant differences were further explored using post-hoc t-tests between groups. A chi squared analysis was run to assess group differences in gender. Any variables that were not matched between groups were included in subsequent LMMs as control variables.

Group differences

Group differences in parkinsonian traits (UPDRS) and autistic traits (RAADS and AQ) were assessed using ANOVAs in which group was a between-participant factor, with post-hoc t-tests unpacking any significant group differences.

Kinematic differences

To identify kinematic differences between groups, effects-coded LMMs were employed for each kinematic feature with group, shape, and group-shape interaction as fixed effects. Random effects were included for trial number to account for fatigue or practice effects, day of task administration to account for practice effects, and participant number to account for within-participant similarities across conditions. Group matching variables that were significantly different between groups (i.e., age, depression and anxiety) were also

included in the model, and their predictive ability on DV performance was assessed. As such, the model formula was as follows:

DV ~ Group * Shape + Age + Depression + Anxiety + (1|Day) + (1|Trial number) + (1|Participant ID)

Follow-up analyses were conducted for cases in which a main effect of group was observed, to identify which groups significantly differed on the DV. This was achieved by running the model above on subsets of the data only including data from two groups.

Interactions between group and shape were further investigated to identify on which shape the two groups significantly differed. This was achieved by running the following model on subsets of the data in which values from two groups on one shape were included:

DV ~ Group + Age + Depression + Anxiety + (1|Day) + (1|Trial number) + (1|Participant ID)

ANOVAs were conducted on the model coefficients to obtain p-values for the fixed effects.

When analysing the reaction time data, the following model was used:

DV ~ Group + Age + Depression + Anxiety + (1|Day) + (1|Participant ID)

Again, to further explore a main effect of group, the model above was rerun on subsets of the data in which data for only two groups were included.

To assess evidence for the null hypothesis in cases in which group differences in kinematic features were not found, Bayesian ANOVAs were conducted. The input values were the residuals of the DV after controlling for age, anxiety and depression. Fixed factors were group and shape (except in the case of reaction time), and random factors were participant ID, trial number (except in the case of reaction time) and day. Bayes Factors (BF_{01}) for the main effect of group are reported, with values of 3-10 and 1-3 taken as moderate and anecdotal evidence for the null hypothesis respectively (Lee & Wagenmakers, 2014).

Classification analyses

Methods of classification

To identify how well the three groups could be classified using the obtained data, the current study employed three methods of classification: K-Nearest Neighbours (KNN), Random Forest (RF), and Support Vector Machine (SVM). KNN is a method of classification in which input data are plotted in a multidimensional space. The k nearest neighbour(s) are then identified, and group membership predictions are made using the modal identity of those neighbours in close proximity. In RF classification, a set of decision trees are constructed from the input variables which each return a prediction regarding group membership; the majority vote determines the model's final prediction. RF models required multiple input variables and so are not reported for cases in which only one variable acted as the input variable. Finally, SVM is a classifier which differentiates between groups through the construction of a hyperplane. New observations are mapped onto the same space and classifications are made depending on which side of the boundary they fall. These three classification methods have been widely used alongside each other in studies of similar sample sizes classifying parkinsonian movement (Al-Yousef et al., 2020; Carvajal-Castano et

al., 2022; Dehghanpur Deharab & Ghaderyan, 2022; Drotár et al., 2016; Gerger & Gümüşçü, 2022; Kamble et al., 2021; Lamba et al., 2021; Netšunajev et al., 2021; Rios-Urrego et al., 2019). Each classification algorithm was based on 80% of the data and the test accuracy relates to the accuracy of the classification algorithm in classifying the remaining 20% of the dataset. Test accuracy is reported for each method, as well as the mean test accuracy across all three methods. The number of nearest neighbours (KNN) and decision trees (RF) were optimised for each analysis as per JASP functionality, and the SVM classifications employed a linear kernel.

Feature selection

Input variables for the analyses consisted of kinematic features (two sets: *all kinematic features* and *core kinematic features*) and questionnaire measures (three sets: *ASD*, *PD* and *ASD & PD*).

To extract *all kinematic features*, data from each participant was used to calculate a single value of each kinematic feature for each shape: residuals for all DVs were calculated after controlling for age, depression and anxiety, and an average was taken for data from the same shape across trials and days where relevant. This resulted in 37 input variables for the *all kinematic features* dataset (four shapes x nine kinematic features, plus one reaction time value per participant averaged across days).

Core kinematic features were identified using a supervised filter-based feature selection in which kinematic features were selected according to group difference significance. For each group comparison, DVs at which a significant group difference was found in the above LMM analysis ($p < .05$) were selected. For example, if a main effect of group was found for a given DV between two groups, then values for that DV on all shapes would be included in the *core kinematic features* dataset. However, if a group by shape

interaction was observed which only yielded a group difference for a particular shape, then the DV value for that specific shape was included in the *core kinematic features* dataset. When multiple groups were included in a classification model, *core kinematic features* included all DVs that significantly differed across the two sides of the classification model (i.e., for the ASD/PD versus CTRL comparison, DVs that significantly differed between ASD and CTRLs, and PD and CTRLs, were included, but not those that significantly differed between ASD and PD (as they grouped as the same class).

ASD questionnaires comprised performance on the AQ and RAADS, and the *PD questionnaire* comprised performance on the UPDRS. All three questionnaires were included in the *ASD & PD questionnaires* set. Scores used in the classification analyses were residuals after controlling for age, depression and anxiety.

Model details

First, it was investigated whether kinematic features and/or questionnaires were able to classify whether an individual belonged to a clinical or non-clinical population, and subsequently which clinical group an individual belonged to. For the former, the ASD and PD groups were coded as 1, and the CTRL group as 0, and classification was assessed for ASD/PD versus CTRLs. For the latter, analyses were run on a subset of ASD and PD participants and classification was assessed for the ASD versus PD comparison. Eleven versions of the group classification analyses were run: (1) using ASD questionnaires, (2) using the PD questionnaire, (3) using ASD & PD questionnaires, (4) using *all* kinematic features as predictors, (5) using only the *core* kinematic features as identified in the LMM analyses, (6) using ASD questionnaires and *all* kinematic features, (7) using ASD questionnaires and *core* kinematic features, (8) using the PD questionnaire and *all* kinematic features, (9) using the PD questionnaire and *core* kinematic features, (10) using ASD & PD

questionnaires and *all* kinematic features, (11) using ASD & PD questionnaires and *core* kinematic features.

Next, classification models were conducted to assess the utility of kinematic features and/or questionnaires for distinguishing ASD from CTRLs (i.e., ASD versus CTRL) and all other groups (i.e., ASD versus non-ASD (PD/CTRL)). For each of these group comparisons, eight sets of classification models were run: (1) using ASD questionnaires, (2) using ASD & PD questionnaires, (3) using *all* kinematic features, (4) using *core* kinematic features, (5) using ASD questionnaires and *all* kinematic features, (6) using ASD questionnaires and *core* kinematic features, (7) using both ASD & PD questionnaires and *all* kinematic features, and (8) using both ASD & PD questionnaires and *core* kinematic features.

Finally, it was assessed whether kinematic features and/or questionnaires could distinguish PD from CTRLs (i.e., PD versus CTRL) and all other groups (i.e., PD versus non-PD (ASD/CTRL)). Again, eight sets of classification models were run for each group comparison: (1) using the PD questionnaire, (2) using ASD & PD questionnaires, (3) using *all* kinematic features, (4) using *core* kinematic features, (5) using the PD questionnaire and *all* kinematic features, (6) using the PD questionnaire and *core* kinematic features, (7) using both ASD & PD questionnaires and *all* kinematic features, and (8) using both ASD & PD questionnaires and *core* kinematic features. Given that no significant differences in kinematic features were found between the PD and CTRL groups, no models containing core kinematic features were run for the PD versus CTRL comparison (i.e., models 4, 6 and 8 were not run).

3.2.5 Pre-Registration and Power Analysis

A pre-registration for the study can be found online at https://osf.io/dnk6j. Contrary to the pre-registration, here data is only analysed from PD participants OFF their dopaminergic

medication as opposed to both ON and OFF medication. Following discussions with collaborators post pre-registration, questionnaires were added as control variables (e.g., RAADS, PHQ and GAD). All participants also completed the UPDRS as a measure of parkinsonian traits. Additional kinematic features were calculated beyond the pre-registered parameters of speed, acceleration, jerk, sub-movements and speed modulation values (i.e., SPARC, error measure, minimum speed, maximum speed, and reaction time). Finally, classification analyses, listed as exploratory analyses in the pre-registration, are reported.

An *a priori* power analysis was calculated with G*power (Erdfelder et al., 1996) using data from a pilot study that showed that autistic adults (N = 19) moved with significantly higher jerk than non-autistic adults (N = 21) in the Shapes Tracing Task; with a Cohen's d effect size of 0.76 and 0.05 alpha level, it was determined that a minimum of 29 participants would be required in each group to achieve a power level of 0.80 for a two-tailed two-group comparison. Thus, it was ensured that each participant group had a sample size of at least 30 to ensure a power level greater than 0.80. Note that it was not possible to conduct an a priori power analysis for the exact proposed statistical analyses (i.e., linear mixed models and classification analyses) due to a lack of suitable power analysis methods and existing data (e.g., the Shapes Tracing Task has not been run in the PD population).

3.3 Results

3.3.1 Group Matching

Table 3.1 presents descriptive statistics for all groups, in addition to tests of equivalence. The three groups were matched on gender and non-verbal reasoning ability. Significant differences were found for age: whilst both clinical groups were age-matched to the CTRL group (ASD-CTRL: $t(57.36) = -1.52$, $p = .135$; PD-CTRL: $t(56.13) = 1.86$, $p =$

.068), the ASD and PD groups were not age-matched ($t(60.57) = -3.88$, $p < .001$). Groups had significantly different levels of depression: whilst there was no difference between ASD and PD groups ($t(57.40) = 0.23$, $p = .822$), the CTRL group had significantly lower levels of depression compared to both the ASD group ($t(42.26) = 4.67$, $p < .001$) and the PD group ($t(45.54) = 5.11$, $p < .001$). Groups also significantly differed with respect to anxiety: whilst the CTRL group and PD group were matched ($t(58.65) = 1.22$, $p = .227$), the ASD group had significantly higher levels of anxiety than both the CTRL group ($t(58.08) = 4.57$, $p < .001$) and the PD group ($t(55.42) = 3.64$, $p = .001$). As such, age, depression and anxiety were included in subsequent models as covariates.

Table 3.1

Descriptive Statistics and Tests of Equivalence for the Autism, Parkinson's Disease and Control Groups

	ASD	**PD**	**CTRL**	**Test of equivalence**
Gender	14 M, 16 M, 1 O	19 M, 13 F	15 M, 16 F	$X^2(4)= 3.25$, $p = .517$
Age	55.52[8.01]	63.16[7.60]	59.00[9.96]	$F(2, 91) = 6.27$, $p = .003$**
Non-verbal reasoning	0.57[0.15]	0.55[0.13]	0.58[0.16]	$F(2, 89) = 0.43$, $p = .655$
Depression	8.2[5.59]	7.87[4.56]	3.0[2.58]	$F(2, 89) = 13.26$, $p < .001$***
Anxiety	9.9[5.89]	5.1[4.39]	3.6[4.90]	$F(2, 89) = 12.86$, $p < .001$***
Years since diagnosis	4.23[2.69]	3.69[2.38]	-	-
Parkinsonian traits	3.7[3.76]	11.91[6.93]	0.94[1.69]	$F(2, 91) = 46.81$, $p < .001$***
Autistic traits (RAADS)	32.97[8.05]	10.7[9.43]	6.32[6.46]	$F(2, 89) = 97.31$, $p < .001$***
Autistic traits (AQ)	37.61[7.06]	19.19[7.72]	16.03[5.95]	$F(2, 91) = 87.19$, $p < .001$***

Note. Table contains means (M) and standard deviations (SD): M[SD]. Significant p-values in tests of equivalence indicate differences between groups. ASD = Autism Spectrum Disorder, PD = Parkinson's Disease, CTRL = Control, M = male, F = female, O = other. *** $p < .001$, ** $p < .01$ and * $p < .05$.

3.3.2 Group Differences

As expected, the PD group had significantly higher levels of PD traits, as measured via the UPDRS, than both the CTRL ($t(34.80) = 8.70$, $p < .001$) and ASD ($t(48.13) = 5.84$, $p < .001$) groups. As in Chapter 2, whilst numerically below the PD group, the ASD group also

had significantly higher levels of PD traits compared to the CTRL group ($t(41.67) = 3.79$, $p < .001$).

A further interesting result was observed when assessing autistic traits via the RAADS. Elevated autistic traits, relative to the general population, were observed in both the ASD group ($t(57.30) = 14.37$, $p < .001$) and the PD group ($t(51.13) = 2.11$, $p = .040$), though a significant difference remained between the two clinical groups ($t(56.96) = 9.91$, $p < .001$). This indicates that the levels of autistic traits in the PD group were elevated beyond that of the CTRL group but did not reach the level of the ASD group.

Whilst the same pattern of results was observed for mean scores on the AQ (see Table 3.1), the higher mean score in the PD group compared to the CTRL group was not significant ($t(58.10) = 1.82$, $p = .074$). The ASD group remained significantly above both the CTRL group ($t(58.32) = 13.01$, $p < .001$) and PD group ($t(60.81) = 9.89$; $p < .001$) in autistic traits measured on the AQ.

3.3.3 Kinematic Differences

Groups can be distinguished by kinematic features.

The ASD group significantly differed from both the PD group and CTRL group on speed modulation values. A significant interaction between group and shape was observed in the main LMM ($F(6, 4482) = 13.37$, $p < .001$). For the ASD and PD comparison, a significant interaction between group and shape ($F(3, 2655) = 15.81$, $p < .001$) was unpacked to reveal a significant difference between the two groups for speed modulation values on shape 4 ($F(1, 658) = 5.40$, $p = .020$), in which values in the ASD group were higher than those in the PD group (beta estimate = 0.229, 95% CI [0.0354, 0.423]). This result was also reflected in the ASD and CTRL comparison, in which the exploration of a significant interaction between

group and shape ($F(3, 3601) = 10.91$, $p < .001$), revealed a significant difference between groups for shape 4 ($F(1, 898) = 5.92$, $p = .015$). Here, ASD values were higher than the CTRL group (beta estimate = 0.216, 95% CI [0.042, 0.390]). A significant group by shape interaction between PD and CTRL ($F(3, 2705) = 13.86$, $p < .001$) did not yield significant group effects for any individual shape (all $p > .05$).

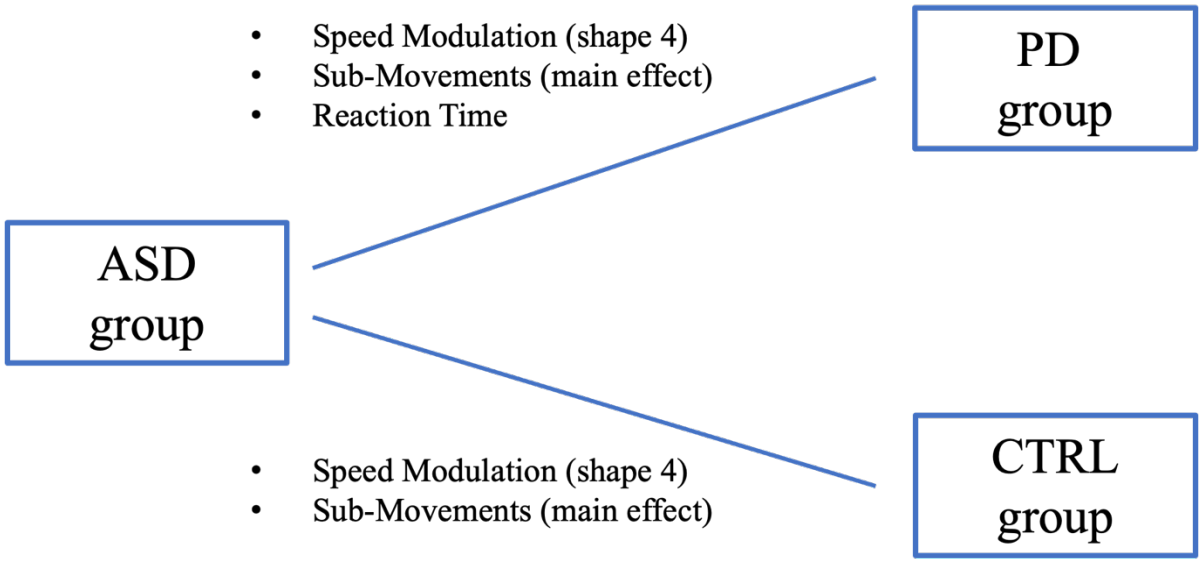
Both the PD group and CTRL group also differed from the ASD group in terms of sub-movements, whereas no differences were found between the PD group and the CTRL group. A significant interaction between group and shape was present in the main LMM ($F(6, 4450) = 3.75$, $p < .001$). When comparing ASD and PD groups, a main effect of group was observed ($F(1, 2637) = 4.46$, $p = .035$), whereby a greater number of sub-movements were used by the ASD group (beta estimate = 0.197, 95% CI [0.014, 0.379]). A significant interaction between group and shape was also observed ($F(3, 2637) = 5.55$, $p < .001$). Further analyses revealed a main effect of group for shape 4/5 ($F(1, 694) = 7.76$, $p = .005$; beta estimate = 0.151, 95% CI [0.045, 0.258]), shape 4/3 ($F(1, 680) = 5.067$, $p = .025$; beta estimate = 0.217, 95% CI [0.028, 0.405]), and shape 4 ($F(1, 662) = 6.12$, $p = .014$; beta estimate = 0.288, 95% CI [0.059, 0.517]); in each case, an increased number of sub-movements were used by the ASD group compared to the PD group. For the ASD and CTRL comparison, a main effect of group was observed ($F(1, 3544) = 4.00$, $p = .046$), with a greater number of sub-movements in the ASD group (beta estimate = 0.181, 95% CI [0.004, 0.359]). A significant group by shape interaction ($F(3, 3544) = 4.14$, $p = .006$) was unpacked to reveal a significant main effect of group for shape 4/5 ($F(1, 933) = 6.42$, $p = .011$; beta estimate = 0.127, 95% CI [0.029, 0.226]), shape 4/3 ($F(1, 905) = 4.00$, $p = .046$; beta estimate = 0.177, 95% CI [0.003, 0.350]), and shape 4 ($F(1, 898) = 5.46$, $p = .020$; beta estimate = 0.267, 95% CI [0.043, 0.491).

For the reaction time data, a main effect of group was observed in the main LMM ($F(2, 140) = 3.90$, $p = .022$). Further analyses revealed that only significant group difference in reaction time was between the PD group and ASD group ($F(1, 83) = 7.18$, $p = .009$); ASD reaction times were shorter than PD reaction times (beta estimate = -0.023, 95% CI [-0.040, -0.006]).

In sum, the ASD group significantly differed from the CTRL group in terms of speed modulation values for shape 4 and sub-movement values for all shapes (main effect). By contrast, reaction time data was able to distinguish the PD and ASD groups, as well as speed modulation values for shape 4 and sub-movement values for all shapes (main effect). These combinations of DVs were taken as *core kinematic features* in subsequent classification models for ASD versus CTRL and ASD versus PD comparisons respectively (Figure 3.2).

Figure 3.2

The Core Kinematic Features Identified for Each Group Comparison



Note. Core kinematic features were determined by a series of linear mixed models, in which a significant main effect of group led to the incorporation of that dependent variable as a core kinematic feature for that group comparison. ASD = Autism Spectrum Disorder, PD = Parkinson's Disease, CTRL = Control.

Some kinematic features are the same between groups.

No group differences were found for speed, acceleration, jerk, SPARC, or maximum and minimum speed (all main effects of group: $p > .05$). Subsequently, Bayesian ANOVAs were conducted on each of these kinematic features, with the main effect of group being the result of interest. Moderate evidence for the null hypothesis of no differences between groups, as indicated by Bayes Factors (BF_{01}) of 3-10, was found for SPARC ($BF_{01} = 5.987$) and maximum speed ($BF_{01} = 8.131$). Anecdotal evidence for the null hypothesis, as indicated by Bayes Factors (BF_{01}) of 1-3, was found for speed ($BF_{01} = 1.490$), acceleration ($BF_{01} = 2.165$), jerk ($BF_{01} = 2.671$), and minimum speed ($BF_{01} = 2.852$). BF_{01} values for the main effect of group for each group comparison are reported in Table 3.2.

Importantly, the groups did not differ with respect to the error measure ($p > .05$), thus providing evidence that any kinematic differences did not arise from significant deviations in the spatial location of the stylus tip when tracing the shapes. This was supported by moderate evidence for the null hypothesis as indicated by a BF_{01} value of 4.301.

Table 3.2

Bayes Factors for Kinematic Features with No Group Differences

	All groups	**ASD-CTRL**	**ASD-PD**	**PD-CTRL**
Maximum Speed	8.131	3.046	6.120	2.124
SPARC	5.987	6.088	2.840	1.421
Error Measure	4.301	2.451	1.861	1.361
Minimum Speed	2.852	0.792	4.652	2.751
Jerk	2.671	3.421	1.935	1.608
Acceleration	2.165	2.550	1.225	1.734
Speed	1.490	1.869	0.788	1.560

Note. Table contains BF_{01} values for the main effect of group obtained in Bayesian ANOVAs. ASD = Autism Spectrum Disorder, PD = Parkinson's Disease, CTRL = Control, SPARC = Spectral Arc Length.

As noted in the analysis above, no differences were found between the PD group and the CTRL group in terms of speed modulation, sub-movements, or reaction time (all $p > .05$).

This was supported by moderate evidence for the null hypothesis for speed modulation (BF_{01} = 4.071), and anecdotal evidence for sub-movements (BF_{01} = 1.951) and reaction time (BF_{01} = 1.709). Further to this, the lack of group difference between the ASD group and the CTRL group for reaction time ($p > .05$) was supported by moderate evidence for the null hypothesis (BF_{01} = 4.974).

Age is a predictor of kinematic features, but anxiety and depression are not.

Age significantly predicted speed modulation values ($F(1, 4482) = 6.06$, $p = .014$), whereby speed modulation values decreased as age increased (beta estimate = -0.017, 95% CI [-0.030, -0.003]. A negative prediction was also observed for sub-movements ($F(1, 4450)$ = 13.02, $p < .001$; beta estimate = -0.025, 95% CI [-0.039, -0.012]). Slower reaction times were observed as age increased ($F(1, 140) = 9.18$, $p = .003$; beta estimate = 0.002, 95% CI [0.001, 0.004]. Finally, age was also a significant negative predictor of speed ($F(1, 4450) = 13.20$, $p < .001$; beta estimate = -0.037, 95% CI [-0.056, -0.017]), acceleration ($F(1, 4464) = 8.13$, $p = .004$; beta estimate = -0.029, 95% CI [-0.049, -0.009], and jerk ($F(1, 4527) = 5.19$, $p = .023$; beta estimate = -0.023, 95% CI [-0.043, -0.003]. No significant predictions of age were observed for SPARC, error measure, minimum speed or maximum speed (all $p > .05$). Depression and anxiety did not predict any of the kinematic features (all $p > .05$).

3.3.4 Classification Analyses

Combining questionnaires and kinematic features yielded the strongest classification accuracy of clinical versus non-clinical groups.

When classifying the ASD, PD and CTRL groups into clinical (i.e., ASD and PD) and non-clinical (CTRL) groups, the mean test accuracy arising from ASD & PD questionnaires (i.e., the AQ, RAADS and UPDRS) was 0.630. This was higher than the mean test accuracy

resulting from ASD or PD questionnaires on their own (mean test accuracy = 0.556 and 0.500 respectively), and from models including all kinematic features (mean test accuracy = 0.584) and core kinematic features (mean test accuracy = 0.542). Combining questionnaires and kinematic features led to the highest test accuracy, with the strongest model comprised of core kinematic features and ASD & PD questionnaires (mean test accuracy = 0.729). Accuracy scores for all classification models are detailed in Table 3.3.

Table 3.3

Test Accuracy Scores for All Classification Models Predicting Clinical (ASD And PD) Versus Non-Clinical (CTRL) Groups

	Mean	**KNN**	**RF**	**SVM**
ASD questionnaires	0.556	0.667	0.556	0.444
PD questionnaire	0.500	0.556	-	0.444
ASD & PD questionnaires	0.630	0.667	0.667	0.556
All kinematic features	0.584	0.438	0.688	0.625
Core kinematic features	0.542	0.438	0.563	0.625
ASD questionnaires & all kinematic features	0.708	0.625	0.750	0.750
ASD questionnaires & core kinematic features	0.542	0.500	0.625	0.500
PD questionnaire & all kinematic features	0.604	0.563	0.688	0.563
PD questionnaire & core kinematic features	0.646	0.688	0.625	0.625
ASD & PD questionnaires & all kinematic features	0.688	0.625	0.750	0.688
ASD & PD questionnaires & core kinematic features	0.729	0.625	0.813	0.750

Note. KNN = K-Nearest Neighbours; RF = Random Forest; SVM = Support Vector Machine, ASD = Autism Spectrum Disorder, PD = Parkinson's Disease.

Questionnaires alone or in conjunction with kinematic features yielded the strongest accuracy for classifying ASD and PD groups.

When classifying the ASD versus PD groups, using ASD & PD questionnaires yielded a stronger mean test accuracy than using ASD or PD questionnaires alone (mean test accuracy = 0.917, 0.833 and 0.667 respectively). Using all kinematic features and core kinematic features resulted in lower classification accuracy (mean test accuracy = 0.533 versus 0.633 respectively), however some classification methods yielded a test accuracy close to that of

questionnaires (e.g., core kinematic features SVM test accuracy = 0.800). Combining ASD & PD questionnaires and core kinematic features resulted in the highest mean test accuracy of all models (mean test accuracy = 0.933). Whilst other combinations of kinematics and questionnaires yielded weaker *mean* test accuracy than questionnaires alone (see Table 3.4), some models using particular classification methods demonstrated that kinematics increased test accuracy scores when added to questionnaire-only models. For example, in the SVM models, the ASD questionnaires and all kinematic features model (test accuracy = 0.900) and the ASD questionnaires and core kinematic features model (test accuracy = 0.900) had a higher test accuracy score than ASD questionnaire alone (test accuracy = 0.833). In addition, adding core kinematic features to the PD questionnaire yielded a stronger test accuracy than the PD questionnaire alone (test accuracy = 0.900 versus 0.750 respectively). In the KNN models, the ASD questionnaires and core kinematic features model had a higher test accuracy score than ASD questionnaire alone (test accuracy = 0.900 versus 0.833 respectively). Similarly, the PD questionnaire and core kinematic features model had a higher test accuracy score than the PD questionnaire alone (test accuracy = 0.600 versus 0.583 respectively).

Table 3.4

Test Accuracy Scores for All Classification Models Predicting ASD Versus PD Groups

	Mean	**KNN**	**RF**	**SVM**
ASD questionnaires	0.833	0.833	0.833	0.833
PD questionnaire	0.667	0.583	-	0.750
ASD & PD questionnaires	0.917	0.917	0.917	0.917
All kinematic features	0.533	0.500	0.400	0.700
Core kinematic features	0.633	0.500	0.600	0.800
ASD questionnaires & all kinematic features	0.767	0.600	0.800	0.900
ASD questionnaires & core kinematic features	0.767	0.900	0.500	0.900
PD questionnaire & all kinematic features	0.500	0.400	0.500	0.600
PD questionnaire & core kinematic features	0.767	0.600	0.800	0.900
ASD & PD questionnaires & all kinematic features	0.633	0.600	0.400	0.900
ASD & PD questionnaires & core kinematic features	0.933	0.900	0.900	1.000

Note. KNN = K-Nearest Neighbours; RF = Random Forest; SVM = Support Vector Machine, ASD = Autism Spectrum Disorder, PD = Parkinson's Disease.

Questionnaires alone were generally most useful for classifying ASD and CTRL groups.

When classifying the ASD versus CTRL groups, the ASD questionnaires yielded a stronger mean test accuracy than combining ASD & PD questionnaires (mean test accuracy = 0.917 and 0.889 respectively). All kinematic features and core kinematic features yielded weaker test accuracy scores (mean test accuracy = 0.485 and 0.639 respectively). Combining kinematics and questionnaires weakened test accuracy scores compared to questionnaires alone, with classifications using *core* kinematic features yielding stronger scores than those using *all* kinematic features (see Table 3.5). One combination of questionnaires and kinematics using a specific classification method resulted in a higher test accuracy than questionnaires alone: using ASD & PD questionnaires and all kinematic features resulted in an RF test accuracy of 1.000, compared to 0.917 when using ASD & PD questionnaires alone.

Table 3.5

Test Accuracy Scores for All Classification Models Predicting ASD Versus CTRL Groups

	Mean	**KNN**	**RF**	**SVM**
ASD questionnaires	0.917	1.000	0.833	0.917
ASD & PD questionnaires	0.889	0.833	0.917	0.917
All kinematic features	0.485	0.545	0.545	0.364
Core kinematic features	0.639	0.583	0.667	0.667
ASD questionnaires & all kinematic features	0.576	0.545	0.364	0.818
ASD questionnaires & core kinematic features	0.833	0.750	0.833	0.917
ASD & PD questionnaires & all kinematic features	0.758	0.455	1.000	0.818
ASD & PD questionnaires & core kinematic features	0.861	0.833	0.833	0.917

Note. KNN = K-Nearest Neighbours; RF = Random Forest; SVM = Support Vector Machine, ASD = Autism Spectrum Disorder, PD = Parkinson's Disease.

Questionnaires alone were the more useful for classifying autistic and non-autistic individuals.

When classifying the ASD, PD and CTRL groups into ASD and non-ASD (i.e., PD and CTRL) groups, a strong mean test accuracy of 0.907 resulted when using either ASD questionnaires only or both ASD & PD questionnaires. Classifications using all kinematic

features and core kinematic features yielded substantially weaker test accuracy scores, with means of 0.605 and 0.563 respectively. Combining questionnaires and kinematics reduced mean test accuracy scores compared to questionnaires alone (see Table 3.6).

Table 3.6

Test Accuracy Scores for All Classification Models Predicting ASD Versus Non-ASD (PD And CTRL) Groups

	Mean	**KNN**	**RF**	**SVM**
ASD questionnaires	0.907	0.889	0.944	0.889
ASD & PD questionnaires	0.907	0.889	0.944	0.889
All kinematic features	0.605	0.688	0.688	0.438
Core kinematic features	0.563	0.625	0.438	0.625
ASD questionnaires & all kinematic features	0.813	0.750	0.813	0.875
ASD questionnaires & core kinematic features	0.834	0.813	0.875	0.813
ASD & PD questionnaires & all kinematic features	0.804	0.786	0.750	0.875
ASD & PD questionnaires & core kinematic features	0.792	0.813	0.813	0.750

Note. KNN = K-Nearest Neighbours; RF = Random Forest; SVM = Support Vector Machine, ASD = Autism Spectrum Disorder, PD = Parkinson's Disease.

Questionnaires yielded the strongest accuracy for classifying PD versus CTRL.

When classifying the PD versus CTRL groups, using the PD questionnaire alone yielded a stronger mean test accuracy compared to using ASD & PD questionnaires (mean test accuracy = 0.875 versus 0.833 respectively). Using all kinematic features and combining these with questionnaires yielded weak classification accuracy (see Table 3.7).

Table 3.7

Test Accuracy Scores for All Classification Models Predicting PD Versus CTRL Groups

	Mean	KNN	RF	SVM
PD questionnaire	0.875	0.833	-	0.917
ASD & PD questionnaires	0.833	0.833	0.833	0.833
All kinematic features	0.600	0.500	0.600	0.700
PD questionnaire & all kinematic features	0.633	0.600	0.700	0.600
ASD & PD questionnaires & all kinematic features	0.667	0.800	0.600	0.600

Note. KNN = K-Nearest Neighbours; RF = Random Forest; SVM = Support Vector Machine, ASD = Autism Spectrum Disorder, PD = Parkinson's Disease.

Questionnaires yielded the strongest accuracy for classifying PD versus non-PD.

When classifying the three participant groups into PD and non-PD (i.e., ASD and CTRL) groups, questionnaires (either the PD questionnaire alone or both ASD & PD questionnaires) yielded the strongest classification accuracy (mean test accuracy = 0.833 for both models). Kinematics both alone and in conjunction with questionnaires yielded weaker test accuracy scores than questionnaires alone (see Table 3.8).

Table 3.8

Test Accuracy Scores for All Classification Models Predicting PD Versus Non-PD (ASD And CTRL) Groups

	Mean	KNN	RF	SVM
PD questionnaire	0.833	0.833	-	0.833
ASD & PD questionnaires	0.833	0.778	0.778	0.944
All kinematic features	0.741	0.786	0.813	0.625
Core kinematic features	0.625	0.688	0.625	0.563
PD questionnaire & all kinematic features	0.667	0.750	0.688	0.563
PD questionnaire & core kinematic features	0.792	0.813	0.750	0.813
ASD & PD questionnaires & all kinematic features	0.667	0.750	0.750	0.500
ASD & PD questionnaires & core kinematic features	0.729	0.625	0.813	0.750

Note. KNN = K-Nearest Neighbours; RF = Random Forest; SVM = Support Vector Machine, ASD = Autism Spectrum Disorder, PD = Parkinson's Disease.

3.4 Discussion

Whilst the current Chapter revealed a range of kinematic features that did not differ between autistic individuals and individuals with PD, these features were not found to be distinct from the general population. This means that the current Chapter does not provide evidence for the proposal that ASD and PD movement differences (compared to the general population) are similar to each other, something which is required for the veracity of the misdiagnosis hypothesis. Instead, it appears that a number of kinematic features could be used to distinguish between the three groups. For example, autistic movement differed from parkinsonian movement in terms of speed modulation values, sub-movements, and reaction time. By contrast, autistic movement only differed from the general population with respect to speed modulation values and sub-movements. This is in line with extant literature highlighting steeper speed modulation values and a greater number of sub-movements in ASD (Cook et al., 2023; Fourie, 2022), and slower reaction times in PD (Bloxham et al., 1987). Thus, combinations of these kinematic features may be useful for distinguishing the three groups. It should be noted that kinematic differences between groups were not seen for all shapes in the Shapes Tracing Task; most notably, the ellipse was the *least* helpful for distinguishing groups. This is particularly important given that many drawing tasks in the literature only index elliptical or spiral movements (e.g., Dayan et al., 2012; Fourie, 2022; Kamble et al., 2021; Lamba et al., 2021; Rios-Urrego et al., 2019), with only one other study utilising other angular frequency-defined shapes (Cook et al., 2023). As such, a recommendation of this Chapter is that future studies employ a range of shapes from across the full angular frequency spectrum to observe the strongest group differences in kinematic features.

A core aim of the study was to assess the utility of kinematic measures in predicting clinical groups instead of, or in addition to, questionnaire measures; mixed results were found. Kinematic features resulted in stronger classification accuracy than questionnaires in three cases: classifying clinical versus non-clinical populations, ASD versus PD populations, and ASD versus CTRL populations. In the case of clinical versus non-clinical populations, combining kinematic features and questionnaire measures yielded the strongest classification accuracy. A classification algorithm that can distinguish between clinical and non-clinical populations is particularly important given that the current Chapter demonstrated changes to kinematic features with increasing age; thus, there is a need to distinguish movement decline arising from clinical conditions as opposed to normal ageing. The results of this classification algorithm indicate that kinematic features may be useful in conjunction with questionnaires for early screening of clinical conditions. In the case of ASD versus PD, the highest mean test accuracy arose from the classification model containing both ASD and PD questionnaires in addition to core kinematic features. Kinematics were also useful in other models which utilised particular classification methods, both alone and in conjunction with questionnaires. This indicates that, once it has been determined that an individual exhibits kinematic features that differ from normal ageing, further examination of these kinematic features can reveal which clinical group the individual belongs to. Finally, in the case of ASD versus CTRL, kinematics were only useful in conjunction with questionnaires when using specific classification methods. Overall, these cases show promise for classifying clinical groups using a variety of subjective and objective measurements. However, when classifying ASD versus non-ASD populations, PD versus non-PD populations, or PD versus CTRL, the use of kinematics in fact reduced classification accuracy. It is perhaps unsurprising that kinematics

had no utility in the latter two cases given the lack of group differences in kinematic features between PD and CTRLs in the linear mixed model analyses.

The questionnaire measures varied with respect to their utility in different classification analyses. For example, when distinguishing ASD and PD group from CTRLs (as in the clinical versus non-clinical classification), using both ASD & PD questionnaires yielded a stronger accuracy than ASD or PD questionnaires alone. This may be because the ASD and PD groups – here grouped as one class – each had elevated traits compared to CTRLs on *both* questionnaires, thus aiding classification. However, when distinguishing the ASD group from the PD and CTRLs (as the in ASD versus non-ASD comparison), test accuracy was the same regardless of whether just ASD questionnaires or both ASD and PD questionnaires were used. One possible explanation is that the addition of the PD questionnaire did not improve the accuracy of the model because both the PD and ASD groups – here grouped as separate classes – score highly on this questionnaire. The same pattern of results was seen for the PD versus non-PD comparison: the addition of the ASD questionnaire did not strengthen test accuracy scores above and beyond the PD questionnaire alone. It is interesting to note that when the CTRL group was removed and the ASD group was only compared to PD, it was useful to have both ASD & PD questionnaires in the algorithm, as opposed to just one of these questionnaires. This is perhaps because it is only in the context of CTRLs that ASD and PD appear similar on these measures, as they both have elevated traits compared to CTRLs; however, there are in fact group differences on both questionnaires which appear useful in an ASD-PD classification model. In sum, it is clear that the questionnaires that yield strongest classification accuracy depend on the group comparison made, and there is not one model that is optimal for all comparisons.

A move towards including kinematic features in screening clinical conditions has advantages over self-report measures. For example, kinematic features are not susceptible to biased or inaccurate self-report. With respect to bias, questionnaires for conditions such as autism may be limited in their utility due to social desirability bias and the camouflaging of autistic traits (Cook et al., 2021; Hull et al., 2017; Keating et al., 2024). Arm movement, specifically, may be useful given that more socially-relevant movements such as facial expressions can be altered due to camouflaging behaviours (Allely, 2019; Hull et al., 2020). With respect to inaccurate self-report, co-occurring conditions such as alexithymia, a difficulty identifying and describing one's own emotions (Bagby et al., 1994; Hickman, 2019; Nemiah et al., 1976), may lead to difficulties introspecting for the purposes of questionnaire completion (Gaigg et al., 2018; Hickman et al., 2022). This may be particularly exacerbated in autism questionnaires which often refer to thoughts and feelings regarding one's emotions. Elevated alexithymic traits have been observed in both ASD (Berthoz & Hill, 2005; Kinnaird et al., 2019) and PD (Assogna et al., 2012; Costa et al., 2010) populations and, therefore, inaccurate self-report may exist in both groups. In addition, minimally verbal individuals may struggle to complete self-report measures, which is a relevant concern as these individuals are thought to make up 25-35% of the autistic community (Rose et al., 2016). Objective measures are likely to be useful when assessing alexithymic or minimally verbal individuals. In the case of self-reported movement differences, subjective measures of symptom severity can yield inaccurate responses due to the fact that individuals may have different opinions on what movement difficulties are classed as "mild" versus "severe". In addition, clinician-based assessments are also limited by intra- and inter-rater variability, and calls for more objective movement-based analyses have been made (Guerra et al., 2023). Thus, refining objective

measures of autistic and parkinsonian traits, such as kinematic features, is important for advancing diagnosis accuracy.

The current investigation of the relationship between ASD and PD was prompted by literature evidencing increased PD diagnosis prevalence in the autistic population. The current Chapter supports these findings by showing elevated PD traits in the ASD population and, similarly, elevated ASD traits in the PD population. However, it remains unknown whether these elevated trait levels are due to similarities between the two conditions or their co-occurrence. For example, it may be that members of the ASD group with elevated PD traits may actually go on to develop PD, meaning the elevated traits could be early signs of PD rather than characteristic of ASD. As such, future studies should ensure longitudinal follow-ups to determine whether results are confounded by undiagnosed conditions. Relatedly, the PD participants are from a generation in which ASD assessments were less readily available in adolescence (Lai & Baron-Cohen, 2015); they were born between 1943 and 1975 yet autism did not appear in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III until 1980. Indeed, the ASD group, also an older adult population, only received their diagnoses a mean of 4.23 years prior to completing the study. Given this lack of diagnosis availability in adolescence, in addition to difficulties in diagnosing autism in elderly individuals with comorbid conditions (van Niekerk et al., 2011; Zagaria, 2019), it is possible that the elevated ASD traits in the PD group may actually reflect a missed ASD diagnosis. This limitation could be ameliorated in future studies by conducting thorough ASD assessments on all PD participants to ensure they are not also autistic, or recruiting non-autistic individuals with PD who underwent an ASD assessment earlier in life. Nevertheless, knowledge of potential overlapping traits between ASD and PD populations will be useful for clinicians when making assessments of both conditions. This is particularly relevant as

information regarding prevalent co-diagnosis has recently been incorporated into autism-related healthcare documentation (Haydon et al., 2021), but a note of similarities between conditions is absent.

It should be noted that the current Chapter did not find any movement differences between the PD and CTRL groups. This finding is contrary to a wide body of evidence indicating clear movement differences between these groups, particularly in terms of movement speed and reaction time (e.g., Bloxham et al., 1987; Broderick et al., 2009). One reason may be the lack of sensitivity of the apparatus used. Due to the inability to enter the lab due to the COVID-19 pandemic, data were collected remotely using touch-screen tablets, as opposed to using a more sensitive device with a higher sampling rate. Whilst this did improve the real-world applicability of the findings and enabled the assessment whether such a process would have utility in clinical settings, a degree of experimental sensitivity was lost. Thus, it may be that any existing movement differences were not able to be detected by the equipment. Indeed, bayes factors for the null group differences between PD and CTRLs only revealed anecdotal evidence, meaning it cannot be strongly concluded that kinematics were the same between groups. In combination, given that the current Chapter specifically recruited individuals with PD who were early in their diagnosis and did not have extreme tremor, it may be that only subtle differences were present between the PD and CTRL groups that could not be detected here.

Although the current Chapter *did not* find movement differences between PD and CTRL groups, differences *were* found between the PD and CTRL groups in Chapter 2, which involved an assessment of free movement as opposed to restricted movement. These patterns of data in conjunction with the experimental paradigms align with the motor motivation hypothesis (Mazzoni et al., 2007). Mazzoni and colleagues proposed that slowed movement

in PD stems from the energetic cost of movement. They state that in PD an implicit decision is made to not increase movement speed due to an imbalance in the cost/reward trade-off of the energy expenditure required to move faster. In the Animation Production Task used in Chapter 2 there is a fixed movement period of 30 seconds during which participants are able to move in any way – and at whatever speed – they choose. This means that fast movement is not incentivised; participants can move slowly and they will still progress to the next stage of the task in the same amount of time. By contrast, in the current Chapter participants completed the Shapes Tracing Task in which they were required to trace 10 rotations of the shape to complete a successful trial or face redoing the trial (participants were not aware of the trial timeout at 90 seconds). This means that if participants moved quickly they were able to complete the task in a shorter amount of time, thus fast movement is incentivised in the task used in the current Chapter. Therefore, the lack of group difference between PD and CTRL here may result from the fact that it is beneficial for the PD participants to move quickly and accurately to complete the task.

This Chapter did not support findings that autistic movement is characterised by increased speed, acceleration and jerk (e.g., Cook et al., 2013). However, as in the case of PD versus CTRL, low bayes factors were observed for the group similarities, indicating that there is not strong evidence to conclude their movements were the same. However, an interesting distinction can be made between jerk and SPARC. Bayes factors indicate that evidence for the lack of group difference between ASD and CTRL in terms of SPARC was double that of jerk. Given that SPARC is a speed-independent measure of movement smoothness, whereas jerk is not, this leads us to question whether literature showing decreased smoothness in ASD in fact results from an epiphenomenal effect on speed; in other words, a true group difference in

movement speed may cause an apparent difference in jerk due to the fact that the calculations of the two kinematic features are inherently linked.

To summarise, the current Chapter identified both similarities and differences in the kinematic features used by autistic individuals, individuals with PD, and the general population in a task of restricted movement. Whilst the three groups did not differ on a range of kinematic features (e.g., speed (average, minimum and maximum), acceleration, jerk and SPARC), points of distinction between the three groups included speed modulation values, sub-movements and reaction time. This Chapter did not provide evidence for the misdiagnosis hypothesis as there were no kinematic variables which were similar between ASD and PD but distinct from the general population. Instead, this Chapter proposes that certain kinematic features may help distinguish between the three groups. In a number of cases, kinematic features (either alone or in conjunction with questionnaire measures) yielded strong classification accuracy in models predicting the three participant groups, in particular when distinguishing clinical groups from the general population and subsequently identifying which clinical group an individual belonged to. This implies that kinematic features may be useful in the development of more selective diagnostic procedures.

Chapter 4 – Dopaminergic Manipulations Affect the Modulation and Meta-Modulation of Movement Speed: Evidence From Two Pharmacological Interventions

Chapters 2 and 3 highlighted both similarities and differences in the behavioural and cognitive presentations of ASD and PD. However, whilst similarities were apparent between the two groups, many aspects of performance were not additionally distinct from CTRLs. Chapter 3 highlighted movement differences between ASD and PD which could be useful in establishing differential diagnoses, but the biological basis of these movement differences is unclear. Understanding the mechanisms underlying similarities and differences between ASD and PD performance may elucidate the extent to which ASD and PD overlap at a biological (or neurochemical) level. Consequently, Chapter 4 investigated the role of dopamine in complex movement processes. The results of two pharmacological intervention studies are set out: Study 1 reports movement differences in individuals with PD both ON and OFF their dopaminergic medication; Study 2 reports movement differences in individuals from the general population on haloperidol (a dopamine receptor blocker, or "antagonist") and placebo. In addition, the dopamine baseline dependency of each drug effect was investigated in Study 2. As in Chapter 3, both Studies utilised the Shapes Tracing Task.

Supplementary materials for this Chapter can be found in Appendix 3. Data and analysis scripts can be found online at https://osf.io/vwu5t/?view_only=f1ce99b65142493bb313472f389c2e1f.

A pre-print of an earlier draft of this Chapter has been published on BioRxiv:

Hickman, L. J., Sowden, S. L., Fraser, D. S., Schuster, B. A., Rybicki, A. J., Galea, J. M., & Cook, J. L. (2023). Dopaminergic manipulations affect the modulation and meta-modulation of movement speed: evidence from two pharmacological interventions. *bioRxiv*, 2023-07.

The studies were designed by LJH with input from all authors. LJH and DSF programmed the tasks. LJH, SLS, BAS and AR collected the data. LJH analysed with data, with assistance from DSF and JLC. LJH wrote the manuscript, which was then edited by JLC and approved by all co-authors.

Abstract

A body of research implicates dopamine in the average speed of simple movements. However, naturalistic movements span a range of different shaped trajectories and rarely proceed at a single constant speed; instead, speed is reduced when drawing "corners" compared to "straights" (i.e., speed modulation), and the extent of this slowing down is dependent upon the global shape of the movement trajectory (i.e., speed meta-modulation) – for example whether the shape is an ellipse or a rounded square. By employing two pharmacological intervention studies – individuals with Parkinson's Disease (PD) both ON and OFF dopaminergic medication (N = 32) and members of the general population on a D2 receptor blocker (haloperidol) versus placebo (N = 43) – dopamine is implicated in speed, speed modulation and speed meta-modulation. These findings move beyond vigour models implicating dopamine in average movement speed, and towards a conceptualisation that involves the modulation of speed as a function of contextual information.

4.1 Introduction

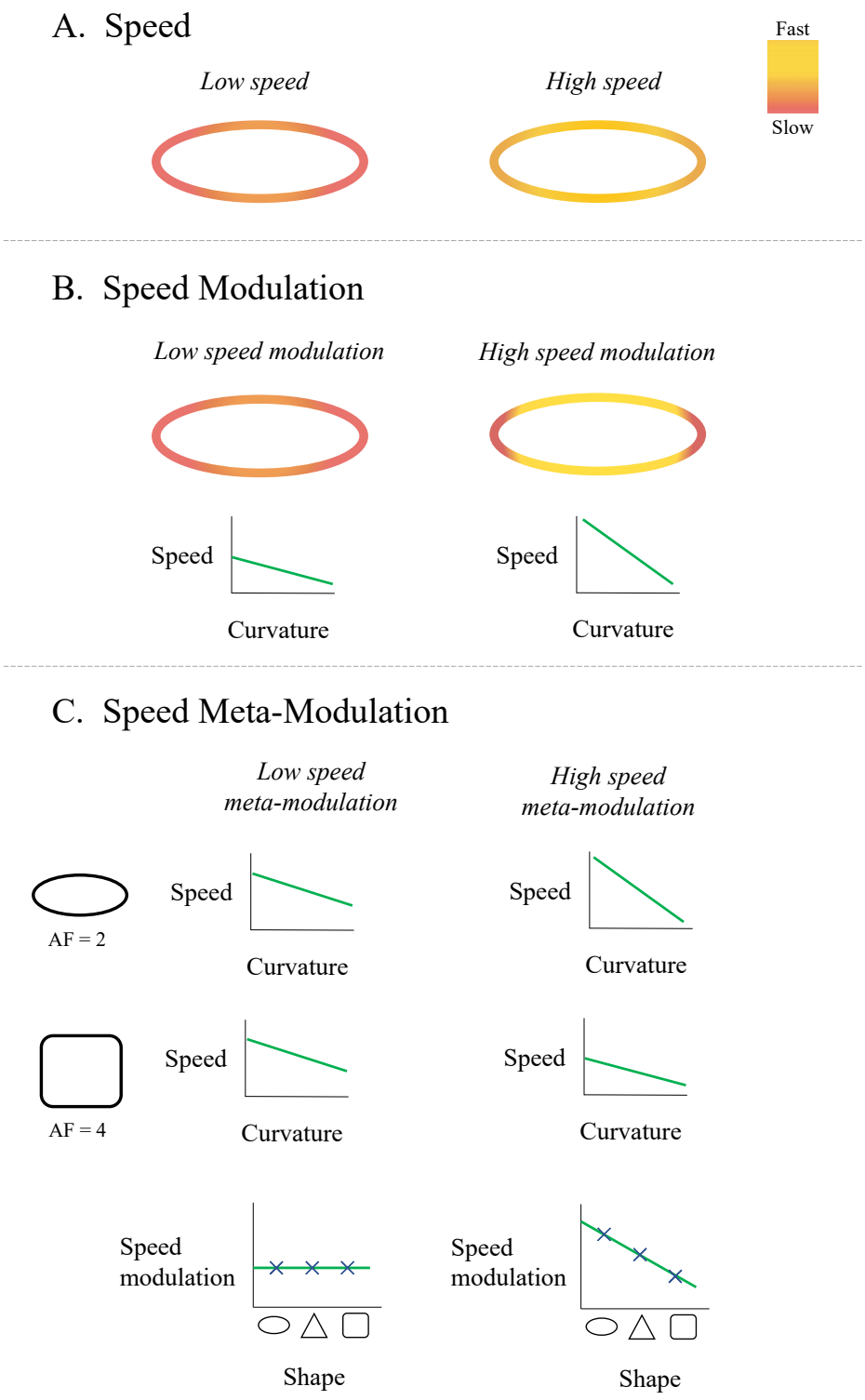
Dopamine is robustly associated with the speed, or "vigour", of movements (Alberts et al., 2000; Bartholomew et al., 2016; Broderick et al., 2009; Eichhorn et al., 1996; Lange et al., 2006; Quattrocchi et al., 2018; Rueda-Orozco & Robbe, 2015; Tomassini et al., 2016; Tucha et al., 2006). However, naturalistic fluid movements – such as the movements recorded in human handwriting, or when a rat navigates a maze – do not simply proceed at a single, constant, speed. Rather, humans and non-human animals continuously modulate speed according to the curvature of their movements, speeding up along straights and slowing down for corners (Huh & Sejnowski, 2015; Lacquaniti et al., 1983). This phenomenon of adapting movement speed to curvature is mathematically described by a set of scale-invariant power

laws (Huh & Sejnowski, 2015) and is robust across various species (Dagenais et al., 2021; James et al., 2020; Zago et al., 2018) and effectors (de'Sperati & Viviani, 1997; Hicheur et al., 2005; Lacquaniti et al., 1983; Richardson & Flash, 2002). Speed modulation of this sort is thought to be a fundamental principle of biological motion but the role of dopamine in speed modulation is unknown.

Recent advances have shown that speed can also be said to be "meta-modulated" (Huh & Sejnowski, 2015). That is, the *extent to which* one slows down for corners and speeds up for straights is dependent on the global shape of one's movement trajectory: if you were drawing a rounded square you would barely modulate your speed (i.e., your speed modulation value – or the gradient of the slope between your movement speed and current curvature – would be low), whereas speed is dramatically modulated when drawing shapes such as ellipses with fewer, and tighter, "corners" (Cook et al., 2023; Huh & Sejnowski, 2015; Matic & Gomez-Marin, 2019; Matic & Gomez-Marin, 2020; Matic & Gomez-Marin, 2022). This means that you would adapt your speed differently to a specific curvature value based on the global shape you are drawing. This observation – that the number of corners in a shape influences the degree to which one slows down for said corners and speeds up for straights – has been mathematically formalised as a spectrum of power laws (Huh & Sejnowski, 2015). If a "corner" is defined as a curvature oscillation per two π of angular displacement, then a shape with two "corners" (an ellipse) is defined as having an angular frequency of two, a shape with four corners (a rounded square) has an angular frequency of four, and so on. Speed modulation (the gradient of the slope between speed and curvature) is modulated as a function of angular frequency: the higher the angular frequency the lower the speed modulation. The distinction between speed, speed modulation and speed meta-modulation is set out in Figure 4.1.

Figure 4.1

A Depiction of Speed, Speed Modulation and Speed Meta-Modulation



Note. Ellipses are shaded to represent different movement trajectories, with red shades representing slow speeds and yellow shades representing fast speeds. (A) Movements varying

in movement speed: the ellipse on the left has been drawn slowly (red shades indicate slow speed), whereas the ellipse on the right has been drawn quickly (yellow shades indicate fast speed). (B) Movements varying in speed modulation: in the ellipse on the left there are barely any changes in speed (shades do not differ much), whereas in the ellipse on the right there is a sharp slowing down at the corners (as indicated by the stark change from yellow to red shades). These movement profiles would be depicted as low and high modulation of movement speed to curvature respectively. (C) Participants varying in speed meta-modulation: the participant depicted on the left has low speed meta-modulation (i.e., they exhibit the same relationship between speed and curvature when drawing different shapes), whereas the participant depicted on the right has high speed meta-modulation (i.e., they change their speed modulation values based on the shape).

Although fluid, naturalistic movements nearly always require both speed modulation and speed meta-modulation, little is known of the role of dopamine in either of these processes. A number of existing theories link dopamine and movement speed (Mazzoni et al., 2007; Niv et al., 2007; Shadmehr et al., 2016; Yoon et al., 2018), however they do not paint a clear picture of the relationship between dopamine, speed modulation and speed meta-modulation. The opportunity costs model, for example, proposes that (tonic) dopamine signals average reward availability, with increased dopamine signalling higher reward availability and thus enhancing the vigour of movements by increasing the opportunity cost of sloth (Niv et al., 2007). This model predicts that movements will be less vigorous under low dopamine conditions (e.g., PD OFF-medication, or under haloperidol – a dopamine antagonist). In line with this, many studies have shown less vigorous movement under low dopamine conditions, including long reaction times on button press paradigms (Beierholm et al., 2013) and slow simple reaching arm movements (Mazzoni et al., 2007; Quattrocchi et al., 2018; Tomassini et al., 2016). It is, however, unclear how this translates to more complex, naturalistic movements. Consider the example of drawing an ellipse: the opportunity cost of sloth is uniform and unrelated to curvature or global trajectory – it is no more costly to move slowly at corners versus straights. Similarly, it is no more costly to move slowly for low angular frequency (e.g., an ellipse) compared to high angular frequency (e.g., a rounded square)

shapes. Therefore, it could be argued that the opportunity costs model would predict that low dopamine conditions should result in a uniform reduction in the average speed of movement with no change to speed modulation or speed meta-modulation (i.e., no modulation as a function of curvature or global trajectory). On the other hand, one could argue that curvature and vigour are related such that straights require more vigorous movements than corners (because straight movements are executed at a higher speed; Cook et al., 2023; Huh & Sejnowski, 2015; Matic & Gomez-Marin, 2019; Matic & Gomez-Marin, 2020; Matic & Gomez-Marin, 2022), and shapes with more, and less tight, corners (high angular frequency shapes) require more vigorous movement (because they tend to be drawn faster; Cook et al., 2023). Low dopamine conditions, which reduce vigour, might disproportionately affect straights and high angular frequency shapes because the requisite movements demand more vigour. Under this interpretation, in addition to the effects on speed, the opportunity costs model predicts an effect of dopaminergic manipulation on speed modulation and speed meta-modulation.

Existing models, therefore, do not provide clear, unequivocal predictions of the effects of dopaminergic drugs, or of naturally occurring disruptions of the dopamine system (as in PD), on natural movements that include speed modulation and speed meta-modulation. The current Chapter investigates the role of dopamine in speed, speed modulation and speed meta-modulation. To do so, the Shapes Tracing Task is employed in two pharmacological intervention studies in which people with PD are studied both ON and OFF dopaminergic medication (Study 1), in addition to members of the general population on a D2 receptor blocker (haloperidol) versus placebo (Study 2).

4.2 Methods (Study 1)

4.2.1 Participants

A total of 32 people with PD were recruited, 19 male and 13 female (age range 46-78 years; mean (SD) = 63.2(7.6); see Appendix 3.1 for ethnicity information). The mean number of years since diagnosis was 3.7(2.4) and the average Unified Parkinson's Disease Rating Scale (Part II: Motor Aspects of Experiences of Daily Living; a self-report measure appropriate for assessing symptom severity; Rodríguez-Blázquez et al., 2017) was 11.91(6.93). All participants were taking a form of dopaminergic medication such as levodopa and/or dopamine agonists (see Appendix 3.2), and their dosage was calculated as the levodopa equivalent dose using an online calculator (https://www.parkinsonsmeasurement.org/toolBox/levodopaEquivalentDose.htm). Participants were recruited via Parkinson's UK, the University of Birmingham Older Adults Database or social media. All participants gave fully informed consent and received renumeration of £10 per hour. The experimental procedure was approved by the local Research Ethics Committee (ERN_18-1800B).

4.2.2 Procedure

Participants completed two testing days, one to two days apart, which followed the same protocol but differed with respect to drug administration. On one of the days, participants completed the task prior to taking their first dose of dopaminergic medication in the morning. On the other day, participants completed the task approximately 1 hour after taking their first dose of dopaminergic medication. These protocols achieved OFF-medication and ON-medication states respectively and are standard practice in the literature (Kojovic et

al., 2014; Moore et al., 2010; Whitfield et al., 2018). The orders of the OFF-medication and ON-medication days were counterbalanced across participants. Following the medication protocol, participants undertook the Shapes Tracing Task using a stylus and touch-screen device (Samsung Galaxy Tab A7; 10.40-inch touchscreen; 2000x1200 pixels). The task was programmed in PsychoPy and run on Pavlovia (PsychoJS platform version 2021.1.4).

Shapes Tracing Task

In the Shapes Tracing Task, participants traced four different shapes of varying angular frequencies (4/5, 4/3, 2, 4). The size of the shapes presented on the device did not exceed 9 cm by 9 cm. During each trial, participants were asked to trace around the shape on the screen "as fluidly as possible" in a counter-clockwise direction, using a stylus held in their dominant hand. Participants completed eight blocks, two for each shape, presented in a random order. Each trial required participants to draw 10 full cycles of the shape, and the x and y coordinates of the stylus were recorded over time. During each block, participants had a total of seven attempts to complete four successful trials. Thus, a maximum of eight successful trials per shape was set, with participants limited to completing up to 14 trials to achieve this number. If participants significantly deviated from the shape (and into a region surrounding the shape which was not displayed to participants) or removed the stylus from the touch-screen (after a 5-second grace period), the trial was not classed as "successful". Each trial had a timeout set at 90 seconds.

4.2.3 Data Pre-Processing

Shapes Tracing Task

Trials with fewer than 2.5 traces were excluded. The first samples of every trial which did not achieve a minimal speed (200 pixels per second), within the 5-second grace period,

were removed to address a discontinuity of reported position at the start of the trial. The maximum sampling rate of the tablet was 60Hz, but deviations occurred, thus positional data was resampled using the spline method to achieve a consistent 60Hz. Kinematic features were calculated for each trial of the experiment using the x and y coordinates recorded over time. Movement speed (measured in pixels per second) was calculated as the change in x and y coordinates of the stylus location over time by smoothly differentiating the raw positional data. A value per trial was taken as the average movement speed across the full trial duration, with null data discarded. Maximum and minimum speed values were calculated as the average of the top and bottom 10% of speed values obtained during each trial. Speed modulation values (also known as speed-curvature gradients; β in Equation 1) were calculated as the gradient of the relationship between tangential velocity (v in Equation 1) and the current curvature of the shape (κ in Equation 1), converted to an absolute value.

$$v \propto \kappa^{-\beta}, \qquad \log(v) \propto -\beta * \log(\kappa)$$

[Equation 1]

This followed the filtering and regression procedure set out in Huh and Sejnowski (2015) and Cook et al. (2023), whereby a smoothing differentiator was first applied, following which log velocity was regressed against log curvature using MATLAB's *regress* function to obtain speed modulation values. A higher speed modulation value indicates a steeper slope of the log speed to log curvature relationship. The first ½ π angular displacement of each trial was discounted before processing the speed modulation values. To quantify speed meta-modulation, a novel index was calculated: the gradient of the regression line between speed modulation values and an ordinal shape value (using MATLAB's *polyfit* function to a

polynomial power of 1) was taken to represent the extent to which one changes speed modulation values as a function of the shape being draw. To meet normality assumptions, a log transform was applied to the movement speed data. Outliers of each DV were removed, defined as values further than 2 standard deviations away from the mean. The data were then z-scored prior to analysis.

Data subsetting

To ensure each participant had data across the range of shapes, speed meta-modulation slopes were calculated from participants who had valid trials for at least the shapes with the highest and lowest angular frequency values (i.e., shapes 4/5 and 4 in Study 1). To keep analyses consistent, analyses on speed and speed modulation in the main text were run on subsets of the data excluding participants who did not have valid trials for these shapes. This led to the removal of one OFF-medication dataset. Analyses on all datasets for speed and speed modulation are reported in Appendix 3.3.2 and Appendix 3.5.2 respectively.

4.2.4 Analyses

All analyses were conducted in MATLAB 2022A. All mixed models were run using MATLAB's *fitlme* function. Data and analysis scripts are available online at https://osf.io/vwu5t/?view_only=f1ce99b65142493bb313472f389c2e1f.

Speed and speed modulation

To analyse the shapes tracing task data, effects-coded linear mixed models were employed for movement speed and speed modulation values with drug state and shape as fixed effects, dosage interacting with drug state, and day, trial number and participant ID as random effects.

DV ~ Drug State * Shape + Drug State:Dosage + (1|Day) + (1|Trial number) + (1|Participant ID)

This analysis was repeated for data averaged across trials (i.e., one value per participant per shape) to observe the impact on the main effect of drug.

Maximum and minimum speed values

Given the possible prediction highlighted in the Introduction that dopaminergic manipulation may disproportionately affect high speed movements, maximum and minimum speed values were analysed using the following LMM:

DV ~ Drug State * Shape + Drug State:Dosage + (1|Day) + (1|Trial number) + (1|Participant ID)

Speed meta-modulation

For speed meta-modulation, models were run using the following formula:

DV ~ Drug State + Drug State:Dosage + (1|Day) + (1|Participant ID)

ANOVAs were conducted on the model coefficients to obtain p-values for the fixed effects.

4.3 Methods (Study 2)

4.3.1 Participants

A total of 43 participants (24 male, 19 female; age range 18-42 years, mean (SD) = 26.0(6.3)) were recruited. Participants passed a health screening prior to the experimental testing days following the protocol described in Rybicki et al. (2022) and Schuster et al. (2022) which involved Body Mass Index (BMI), blood pressure and electrocardiogram QT interval checks, as well as relevant medical history. Recruitment was conducted via the School of Psychology Research Participation Scheme or social media. All participants gave fully informed consent and received renumeration of £10 per hour. The experimental procedure was approved by the local Research Ethics Committee (ERN_18_1588).

4.3.2 Procedure

Participants completed two testing days, one to four weeks apart, lasting approximately 5.5 hours each. Following an on-the-day health check involving blood pressure and blood oxygenation levels, participants were administered capsules containing either 2.5mg of haloperidol (a dopamine D2 receptor antagonist) or a placebo, in a double-blind, placebo-controlled, within-subjects design. The orders of the days for haloperidol and placebo were pseudorandomised such that half of participants received haloperidol on day 1 and half on day 2. Haloperidol dosage and administration times were in line with previous studies in the literature demonstrating behavioural and psychological effects (Bestmann et al., 2015; Frank & O'Reilly, 2006). At 1.75 hours post-tablet intake, participants completed a working memory task, followed by the shapes tracing task 4 hours post-tablet intake. Given that oral haloperidol is reported to be at its peak concentration in the blood plasma between 1.7 and 6.1

hours post-tablet intake on average (Kudo & Ishizaki, 1999), both tasks were completed within the peak range of haloperidol blood plasma concentration, ensuring that drug action was likely to occur throughout administration of the tasks. Medical symptoms, blood pressure and mood were monitored before capsule administration, three times throughout the testing day, and at the end of the testing day.

Shapes Tracing Task

The general principles of the shapes tracing task remained the same as in Study 1, with a few exceptions. Three shapes were presented to participants (4/3, 2, and 4), as opposed to four shapes (Study 1: 4/5, 4/3, 2, and 4) to allow for a greater number of trials for the included shapes. The size of the shapes presented on the device did not exceed 12 cm by 12 cm. Each shape was traced for a total of 10 trials per shape, as opposed to a maximum of eight trials in Study 1, and each trial consisted of 10 x angular frequency (i.e., 10 x 2π radians of angular displacement) curvature oscillations (in the case of the ellipse and rounded square this is 10 complete traces of the shape). Participants were asked to repeat trials if they deviated from the shape or removed their stylus from the device. Participants could repeat the trial if they felt fluidity was not achieved. The task was programmed and run using MATLAB 2014b 32-bit on a Surface Pro 4, using a touch-screen device to record participants' movements (WACOM Cintiq 22 HD drawing tablet).

Working memory task

Participants completed a visual working memory task, adapted from the Sternberg visual working memory task (Sternberg, 1969), programmed using MATLAB 2017b. The task involved 60 experimental trials across five blocks which were completed following 10 practice trials. In each trial, a fixation cross was presented in the centre of the screen (for a variable duration between 500 ms -1000 ms), followed by a list of letters (between five and

nine consonants depending on the block; 1000 ms duration) and a blue fixation cross (3000 ms duration). A single letter was then displayed (4000 ms) and participants indicated with a keyboard press whether the letter was present in the previously displayed list (1 = yes, 2 = no, 3 = unsure). Accuracy and response time were recorded for each trial.

4.3.3 Data Pre-Processing

Shapes Tracing Task

Movement speed (average, maximum and minimum values), speed modulation values and speed meta-modulation values were calculated for each trial using the x and y coordinates recorded over time, as in Study 1. To meet normality assumptions, a log transform was applied to the movement speed and speed modulation data. Outliers of each DV were removed, defined as values further than 2 standard deviations away from the mean. Again, data were z-scored prior to analysis. Three participants failed to complete both testing days, therefore two haloperidol datasets and one placebo dataset are missing from analyses.

Working memory task

As in previous studies (e.g., Rybicki et al., 2022; Schuster et al., 2022), working memory span was calculated as the percentage of correct responses across all trials. Given evidence that baseline working memory span reliably predicts individual dopamine synthesis capacity (Cools et al., 2008; Landau et al., 2009), baseline striatal dopamine synthesis capacity was estimated using the working memory span obtained under placebo. This value was used to explore any baseline dependent effects of the drug, as a body of literature reports that effects of dopaminergic drugs are modulated by striatal dopamine synthesis capacity (Frank & O'Reilly, 2006; Hofmans et al., 2020; Schuster et al., 2022). Five participants failed to complete the working memory task at baseline, thus baseline striatal dopamine synthesis

capacity could not be estimated and these participants could not be included in analyses incorporating this measure. It should be noted that the correlation between working memory span and dopamine synthesis capacity was not replicated in a recent positron emission tomography (PET) imaging study (van den Bosch et al., 2023), but this may be due to the use of a less sensitive radioligand compared to earlier studies (18F-FDOPA rather than 18F-FMT).

Data subsetting

As in Study 1, speed meta-modulation slopes were calculated for participants who had valid trials for at least the shapes with the highest and lowest angular frequency values (i.e., shapes 4/3 and 4 in Study 2), and analysis of the other two DVs was also conducted on this subset of participants. This reduced the sample size of analyses reported in the main text to 34 participants under placebo and 31 participants under haloperidol. Analyses on all datasets (N = 43) for speed and speed modulation are reported in Appendix 3.4.3 and Appendix 3.6.3 respectively.

4.3.4 Analyses

All analyses were conducted in MATLAB 2022A. All mixed models were run using MATLAB's *fitlme* function. As in Study 1, all linear mixed models were followed up with an ANOVA on the model coefficients to obtain p-values for the fixed effects. Data and analysis scripts are available online at https://osf.io/vwu5t/?view_only=f1ce99b65142493bb313472f389c2e1f.

Speed and speed modulation

To analyse the DVs speed and speed modulation, a series of effects-coded linear mixed models were employed. Reported in the main text is a mixed model that incorporated

estimated baseline striatal dopamine synthesis capacity as a fixed effect alongside drug state and shape, with day, trial number, and participant ID as random effects.

DV ~ Drug State * Shape + Drug State * Estimated Striatal Dopamine Synthesis Capacity + (1|Day) + (1|Trial number) + (1|Participant ID)

As in Study 1, this analysis was repeated for data averaged across trials (i.e., one value per participant per shape) to observe the impact on the main effect of drug.
Appendix 3 contain the results of mixed models without the incorporation of estimated baseline striatal dopamine synthesis capacity (Appendix 3.4.2 (speed) and Appendix 3.6.2 (speed modulation)).

DV ~ Drug State * Shape + (1|Day) + (1|Trial number) + (1|Participant ID)

Maximum and minimum speed values

Given the possible prediction highlighted in the Introduction that dopaminergic manipulation may disproportionately affect high speed movements, maximum and minimum speed values were analysed using the following LMM:

DV ~ Drug State * Shape + Drug State * Estimated Striatal Dopamine Synthesis Capacity + (1|Day) + (1|Trial number) + (1|Participant ID)

Speed meta-modulation

For the speed meta-modulation data, the following models were run, with (main text) and without (Appendix 3.8.1) estimated striatal dopamine synthesis capacity respectively:

DV ~ Drug State * Estimated Striatal Dopamine Synthesis Capacity + (1|Day) + (1|Participant ID)

DV ~ Drug State + (1|Day) + (1|Participant ID)

When a significant interaction between drug state and estimated striatal dopamine synthesis capacity was found, this was unpacked by assessing the relationship between estimated striatal dopamine synthesis capacity and the drug effect. For speed and speed modulation, the drug effect was calculated for each participant as the mean value of the DV under placebo minus the mean value of the DV under haloperidol. For speed meta-modulation, the drug effect was calculated as speed meta-modulation under haloperidol minus speed meta-modulation under placebo. Thus, for all DVs, positive values on the y-axis indicate reduced DV values under haloperidol. Following the drug effect calculation, a linear model was then employed with estimated striatal dopamine synthesis capacity as predictor and Drug Effect and DV. To provide evidence in favour of an inverted-U-shaped function for the relationship between baseline dopamine and the DV (Cools & D'Esposito, 2011), a negative linear relationship that cuts the x-axis would be expected when plotting the drug effect against estimated striatal dopamine synthesis capacity.

Independence of drug effects

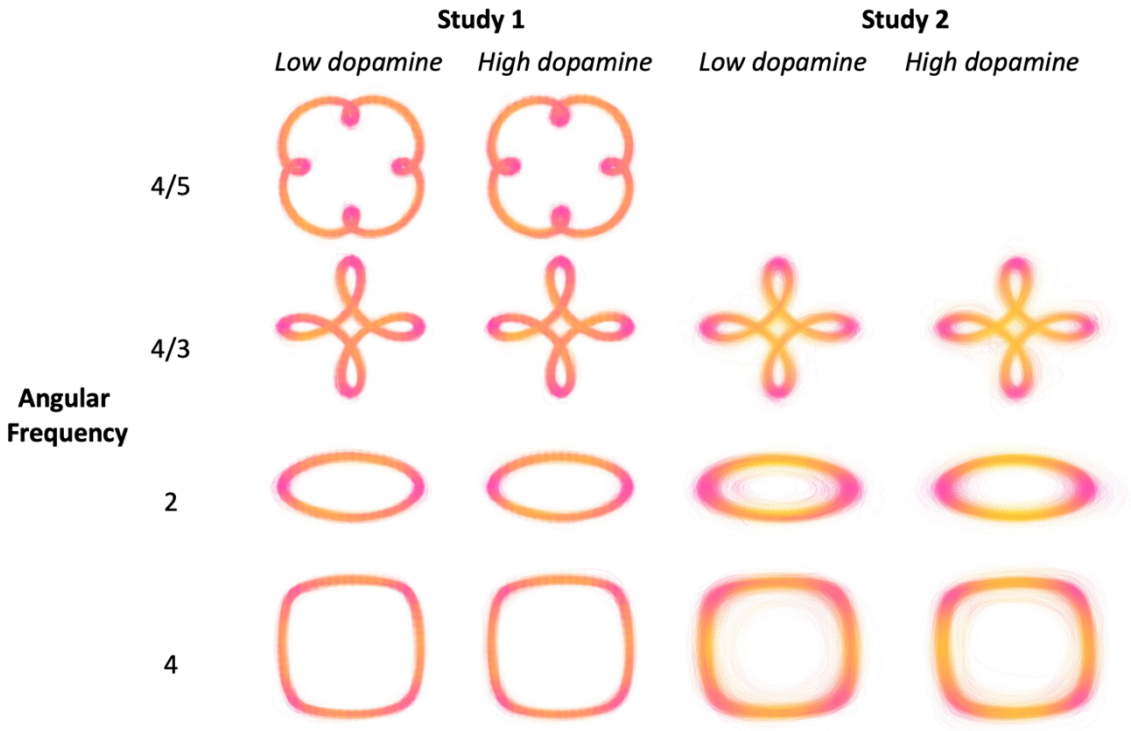
Given the presence of drug effects on all three DVs in Study 2, further exploratory analyses were implemented on this dataset to investigate whether the drug effects are independent from each other. In each case, the control variable (e.g., speed) was included in a model predicting the DV (e.g., speed modulation), from which the residuals were saved. Models also included day as a random effect, and trial as a random effect for cases in which speed or speed modulation were the DV. A mixed model testing the effect of drug was run on the resultant residuals, using the corresponding model formula that included estimated striatal dopamine synthesis capacity listed above.

4.4 Results

In both studies, participants completed the Shapes Tracing Task in which they used a stylus and touch screen device to trace a range of shapes (Figure 4.2) for 10 full cycles (where a cycle is a complete start point to start point trace of the shape) per trial. Analyses in the main text were conducted on subsets of the data in which participants had valid trials for at least the shapes with the highest and lowest angular frequency values (Study 1: 4/5 and 4; Study 2: 4/3 and 4). Supplementary analyses are detailed in Appendices 3.3-3.8 (including additional main text mixed model details, analyses on Study 2 data not accounting for estimated baseline striatal synthesis capacity, and analyses on full datasets). In the subsequent sections dopaminergic effects on speed, speed modulation and speed meta-modulation are reported, combining insight from both studies. Drug effects for speed, speed modulation and speed meta-modulation are presented in Table 4.1.

Figure 4.2

Shapes Tracing Task Raw Movement Trajectory Data



Note. Raw trajectory data for all participants under low (Study 1 = OFF Parkinson's Disease medication; Study 2 = haloperidol) and high (Study 1 = ON Parkinson's Disease medication; Study 2 = placebo) dopamine conditions in Study 1 (*left*) and Study 2 (*right*), for all trials. The colour scheme represents speed from dark pink (low speed) to yellow (high speed).

Table 4.1

Drug Effects for Speed, Speed Modulation and Speed Meta-Modulation

	β estimate	**SE**	**Lower CI**	**Upper CI**	***F* statistic**	**DoF**	***p* value**
Speed							
Study 1: PD Medication	-0.180	0.02	-0. 220	-0.139	75.22	1, 1885	< .001***
Study 2: Haloperidol	-1.120	0.17	-1.446	-0.794	45.43	1, 1600	< .001***
Speed modulation							
Study 1: PD Medication	-0.066	0.02	-0.111	-0.021	8.12	1, 1906	.004**
Study 2: Haloperidol	-1.071	0.18	-1.423	-0.719	35.68	1, 1642	< .001***
Speed meta-modulation							
Study 1: PD Medication	0.094	0.13	-0.174	0.363	0.49	1, 57	.485
Study 2: Haloperidol	0.107	0.03	0.046	0.167	12.40	1, 53	.001**

Note. SE = standard error, DoF = degrees of freedom, CI = confidence interval. *** $p < .001$, ** $p < .01$ and * $p < .05$. In each case, β estimates relate to the change from high to low dopamine conditions.

4.4.1 Movement Speed

Removal of PD medication and administration of haloperidol reduces movement speed.

PD participants OFF-medication, compared to ON-medication (Study 1; N = 32) moved more slowly. That is, a linear mixed model (LMM) including drug state, shape and dosage as fixed effects revealed a main effect of drug state on movement speed ($F(1, 1885) = 75.22$, $p < .001$; Figure 4.3) with lower speed observed OFF-medication (beta estimate = -0.180, 95% CI [-0.220, -0.139]). This significant main effect of drug remained when analysing data averaged across trials: $F(1, 238) = 12.98$, $p < .001$; beta estimate = -0.183, 95% CI [-0.284, -0.083]. There was an additional main effect of shape on movement (as is typical for shapes across the angular frequency spectrum; Cook et al., 2023): $F(3, 1885) = 139.41$, $p < .001$; Appendix 3.3.1). However, there was no interaction between drug state and shape (indicating that the effect of the drug did not vary as a function of shape and thus it cannot be the case that shapes traced with higher movement speeds were disproportionally affected by the drug), nor an interaction between drug state and dosage (all $p > .05$; Appendix 3.3.1).

Similarly, administration of the dopamine D2 receptor blocker haloperidol to members of the general population (Study 2; N=43) reduced movement speed. An LMM including drug state, shape and estimated baseline striatal synthesis capacity as fixed effects revealed a significant main effect of drug state ($F(1, 1600) = 45.43$, $p < .001$) with lower movement speed values in the haloperidol condition compared to the placebo condition (beta estimate: -1.120, 95% CI [-1.446, -0.794]). As in Study 1, the drug effect remained when analysing data averaged across trials: $F(1, 173) = 6.38$, $p = .012$; beta estimate = -1.073, 95% CI [-1.911, -0.235]. Again, a main effect of shape ($F(2, 1600) = 175.24$, $p < .001$; Appendix 3.4.1) was identified, and no interaction between drug state and shape ($p > .05$; Appendix 3.4.1), again highlighting that the drug effect was not disproportionally higher for shapes traced at higher

movement speeds. Results from both studies indicate slowed movement under low dopamine conditions.

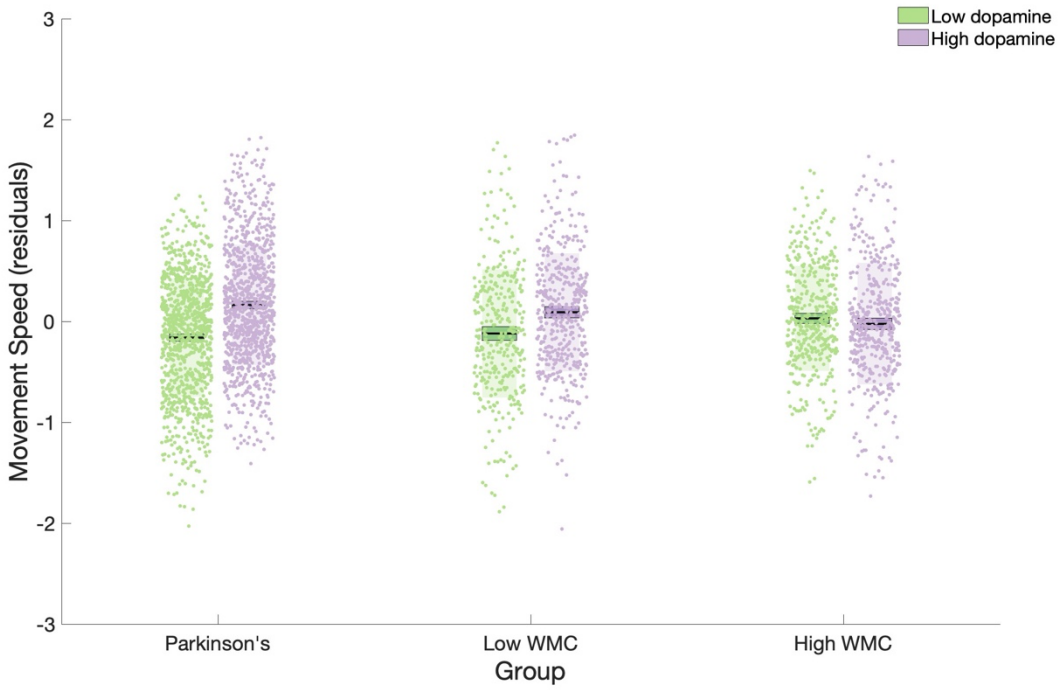
A body of literature reports that effects of dopaminergic drugs are modulated by striatal dopamine synthesis capacity (Frank & O'Reilly, 2006; Hofmans et al., 2020; Schuster et al., 2022) and that working memory capacity can serve as a proxy for this, with low working memory capacity indicating low dopamine synthesis capacity (Cools et al., 2008; Landau et al., 2009). This literature argues for an inverted-U-shaped function for the relationship between baseline dopamine and the effects of dopaminergic drugs on performance (Cools & D'Esposito, 2011). To enable the exploration of any baseline dependent effects of the drug, participants in Study 2 were asked to complete a working memory task (Sternberg, 1969) whilst under placebo. If there is an inverted-U-shaped relationship between dopamine and speed, the effect of haloperidol should be moderated by striatal dopamine synthesis capacity such that individuals with low striatal dopamine synthesis capacity move slower under haloperidol relative to placebo because their (already sub-optimally low) dopamine levels are further reduced by haloperidol. In contrast, individuals with high striatal dopamine synthesis capacity should show speeding effects of the drug because their sub-optimally high levels of dopamine are reduced by haloperidol, thus bringing them closer to the optimal level of dopamine for speedy movements. Including a proxy for striatal dopamine synthesis capacity (i.e., working memory score) as a covariate in the mixed model revealed that the main effect of drug state was indeed moderated by estimated striatal dopamine synthesis capacity ($F(1, 1600) = 42.04$, $p < .001$; Figure 4.3).

The interaction between drug state and estimated striatal dopamine synthesis capacity was unpacked by calculating the drug effect for each participant (mean speed under placebo minus mean speed under haloperidol) and plotting this against estimated baseline striatal

dopamine synthesis capacity. Results are plotted in Figure 4.4 (*top-left*). Positive values on the y-axis indicate that participants' movements were slowed by haloperidol administration, and negative values indicate that participants moved faster under haloperidol than placebo. The data revealed a negative linear relationship between drug effect and estimated striatal dopamine synthesis capacity which cut the x-axis, indicating opposing drug effects in low versus high estimated striatal dopamine synthesis capacity groups. That is, a haloperidol-induced reduction in dopamine caused participants with low estimated striatal dopamine synthesis capacity to move slower, and those with high estimated striatal dopamine synthesis capacity to move faster. These results suggest that the drug effect on speed was dependent on estimated striatal dopamine synthesis capacity.

Figure 4.3

A Graph Depicting Drug Effects on Movement Speed

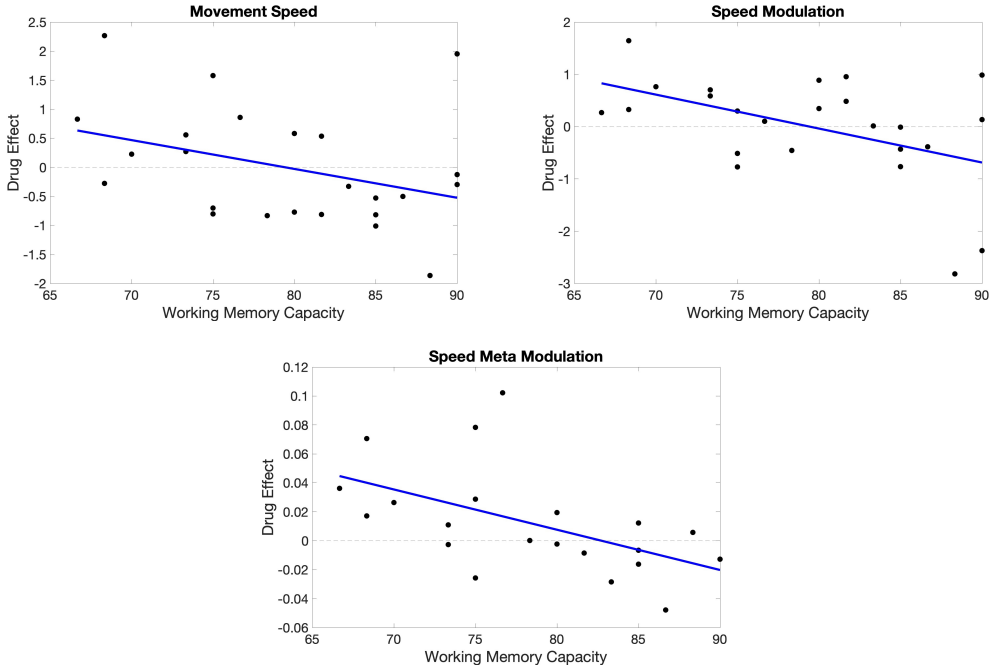


Note. Movement speed residuals plotted for low (green) and high (purple) dopamine conditions across 3 groups: individuals with Parkinson's Disease both OFF and ON their dopaminergic medication (Study 1); members of the general population with low working

memory capacity (as determined by a median split) under haloperidol or placebo (Study 2); members of the general population with high working memory capacity under haloperidol or placebo (Study 2). Residuals were calculated after controlling for dosage (Study 1) or working memory capacity (Study 2), and trial, participant number and day (Studies 1 and 2). Main effects of drug state revealed slower movement speed in low dopamine conditions, with an interaction between drug and working memory capacity (i.e., estimated striatal dopamine synthesis capacity) in Study 2 indicating opposing drug effects in the two groups. Bars = mean, box = SE, shaded region = standard deviation, trial-level values plotted, WMC = working memory capacity.

Figure 4.4

Graphs Depicting Estimated Striatal Dopamine Synthesis Capacity Dependency of Drug Effects



Note. Each graph presents the drug effect (calculated as the difference in dependent variable between low and high dopamine conditions) per participant in Study 2 plotted against the estimated striatal dopamine synthesis capacity for that participant. Graphs refer to movement speed (top-*left*), speed modulation (*top-right*) and speed meta-modulation (*bottom*) respectively. In each case, low dopamine conditions reduce performance on the dependent variable in those with low estimated striatal dopamine synthesis capacity, and increase it with high estimated striatal dopamine synthesis capacity, as indicated by a linear trend which cuts the x-axis. Blue line = line of best fit.

4.4.2 Speed Modulation

Removal of PD medication and administration of haloperidol reduces speed modulation.

To investigate effects on speed modulation, LMMs were run with speed modulation values – the gradient of the regression line between instantaneous movement speed and the curvature being drawn – as the DV. Here a main effect of drug state would comprise evidence that manipulating dopamine impacts speed modulation. An interaction between drug state and shape would be evidence of a drug effect on *speed meta-modulation*. As such, this section focuses on main effects; interactions between drug state and shape in the subsequent section.

In addition to effects on speed, removal of PD medication (Study 1) affected speed modulation. An LMM with drug state, shape and dosage as fixed effects revealed a main effect of drug state on speed modulation ($F(1, 1906) = 8.12$, $p = .004$; Figure 4.5), whereby lower speed modulation values were observed OFF-medication (beta estimate = -0.066, 95% CI [-0.111, -0.021]). The drug effect was non-significant when analysing data averaged across trials ($p > .05$). No interaction between drug state and dosage was found ($p > .05$; Appendix 3.5.1).

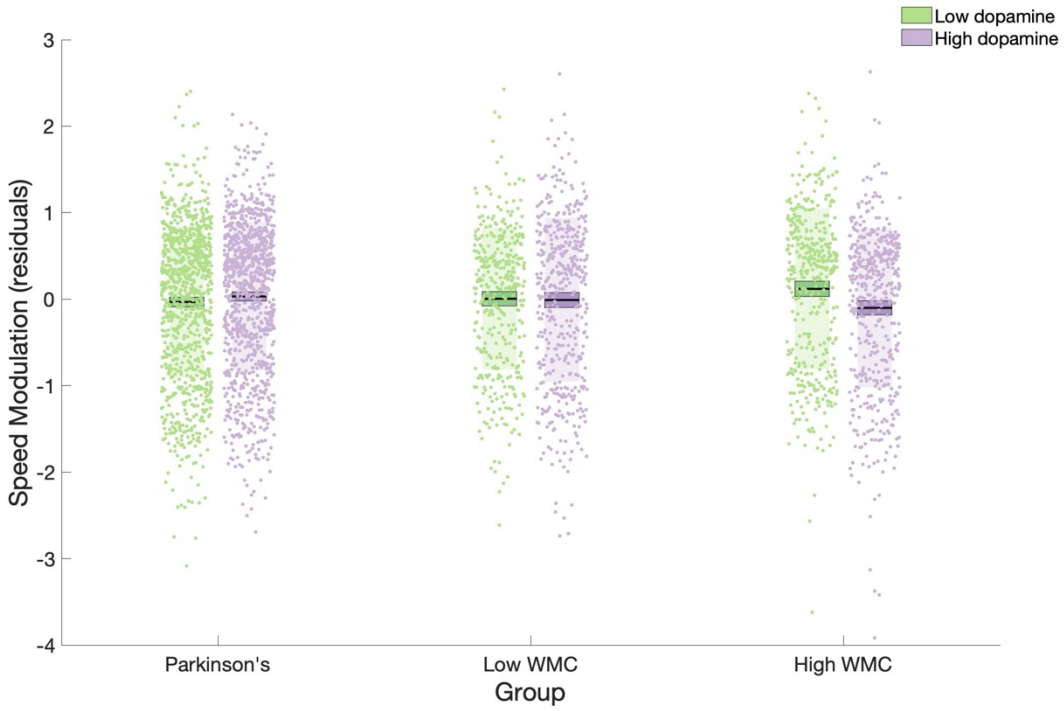
A comparable analysis with members of the general population (Study 2) revealed a parallel drug effect on speed modulation. That is, a LMM with drug state, shape and estimated baseline striatal dopamine synthesis capacity as fixed effects and speed modulation as the DV, revealed a significant main effect of drug ($F(1, 1642) = 35.68$, $p < .001$). Consistent with Study 1, speed modulation values were lower under haloperidol compared to placebo (beta estimate= -1.071, 95% CI [-1.423, -0.719]). The drug effect remained significant when analysing data averaged across trials: $F(1, 171)=11.62$, $p < .001$; beta estimate = -1.230, 95% CI [-1.942, -0.518]. The interaction between drug state and estimated striatal dopamine synthesis capacity was also significant ($F(1, 1642) = 42.85$, $p < .001$; Figure 4.5), again

illustrating the strong baseline-dependency of the effect. Figure 4.4 (*top-right*) illustrates a significant negative linear relationship between the drug effect and estimated striatal dopamine synthesis capacity ($F(1, 22) = 6.96$, $p = .015$; beta estimate = -0.065, 95% CI [-0.116, -0.014]) which again cuts the x-axis, indicating opposing drug effects in low versus high estimated striatal dopamine synthesis capacity groups. That is, a reduction in dopamine caused participants with low estimated striatal dopamine synthesis capacity to move with reduced speed modulation, and those with high estimated striatal dopamine synthesis capacity to move with increased speed modulation. Thus, as was the case for speed, the drug effect on speed modulation was dependent on estimated striatal dopamine synthesis capacity.

The Introduction highlighted that a possible prediction from the opportunity costs model is that a reduction in vigour following dopaminergic manipulation will disproportionately affect high speed movements that require more vigour. This would predict a greater effect of the drug on parts of the trajectories that are executed at higher speeds (i.e., straights relatives to corners), and may account for reductions in speed modulation values. To interrogate the data for evidence in support of this, the average of the top and bottom 10% of speed values obtained during each trial were analysed using the same LMM designs as set out previously for movement speed. For Study 1 there was no significant effect of drug state on either maximum or minimum speed values (maximum values: $F(1, 1892) = 1.03$, $p = .309$; minimum values: $F(1, 1955) = 0.00$, $p = .984$). For Study 2, whilst there was no drug effect on maximum speed values ($F(1, 1612) = 3.21$, $p = .073$), minimum speed values were significantly higher under haloperidol ($F(1, 1637) = 12.63$, $p < .001$; beta estimate = 0.801, 95% CI [0.259, 1.244]), resulting in a reduced range of speed values. Overall, neither study provided evidence that dopaminergic manipulation disproportionately affects higher speed movements.

Figure 4.5

A Graph Depicting Drug Effects on Speed Modulation



Note. Speed modulation residuals plotted for low (green) and high (purple) dopamine conditions across 3 groups: individuals with Parkinson's Disease both OFF and ON their dopaminergic medication (Study 1); members of the general population with low working memory capacity (as determined by a median split) under haloperidol or placebo (Study 2); members of the general population with high working memory under haloperidol or placebo (Study 2). Residuals were calculated after controlling for dosage (Study 1) or working memory (Study 2), and trial, participant number and day (Studies 1 and 2). Main effects of drug state revealed reduced speed modulation values in low dopamine conditions, with an interaction between drug and working memory capacity (i.e., estimated striatal dopamine synthesis capacity) in Study 2 indicating opposing drug effects in the two groups. Bars = mean, box = SE, shaded region = standard deviation, trial-level values plotted, WMC = working memory capacity.

4.4.3 Speed Meta-Modulation

Administration of haloperidol reduces speed meta-modulation, but PD medication does not.

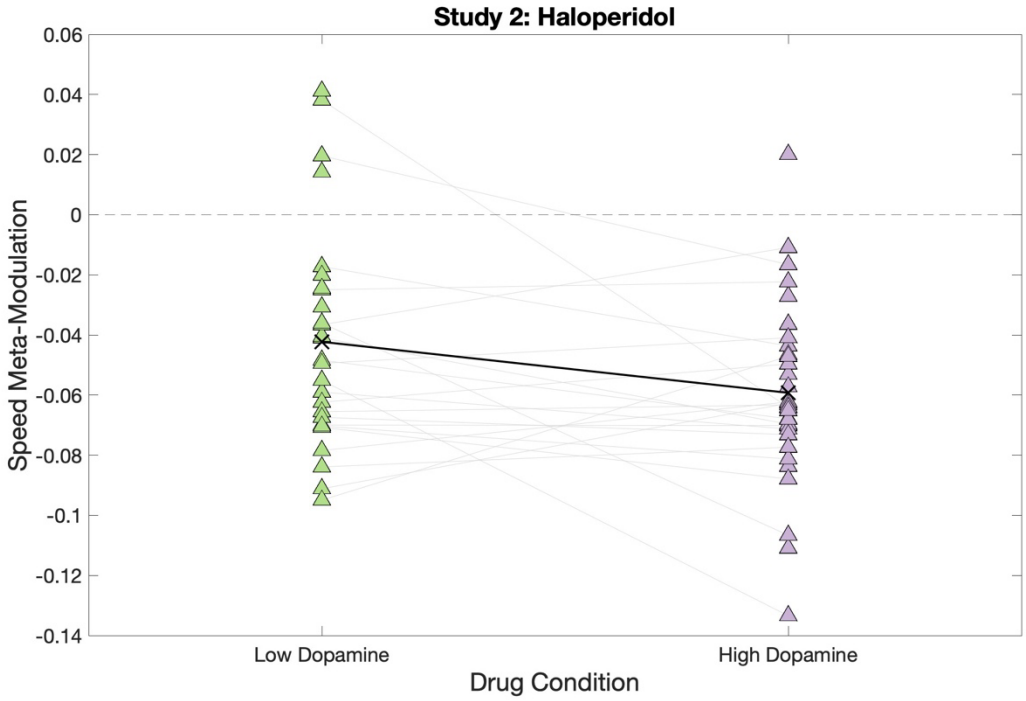
To test whether the removal of PD medication (Study 1) would reduce the meta-modulation of movement speed, a speed meta-modulation index was calculated by regressing

angular frequency against speed modulation values and calculating the gradient of the regression line. Here, a larger gradient magnitude would indicate a greater difference in speed modulation across the angular frequency spectrum. This variable was submitted to an LMM with drug state and dosage as fixed effects. There was no significant effect of drug state on speed meta-modulation, nor drug state by dosage interaction ($p > .05$; Appendix 3.7.1). This is supported by the lack of a drug state by shape interaction in the speed modulation LMM described above for Study 1 ($p > .05$; Appendix 3.7.1). As such, Study 1 did not find evidence supporting a role for dopamine in speed meta-modulation.

By contrast, in the general population (Study 2), haloperidol reduced the meta-modulation of speed ($F(1, 53) = 12.40$, $p = .001$; beta estimate = 0.107, 95% CI [0.046, 0.167], Figure 4.6), whereby speed meta-modulation gradients were flatter (i.e., had a lower magnitude or were "less negative") under haloperidol. This indicated that, under haloperidol, participants did not utilise a range of speed modulation values across the angular frequency spectrum as would be seen in appropriate speed meta-modulation. Instead, the extent to which speed was modulated as a function of curvature was similar across all shapes, thus reducing the gradient of the relationship between angular frequency shape and speed modulation value. This is supported by the presence of a drug state by shape interaction in the speed modulation LMM described above for Study 2 ($F(1, 1642) = 11.45$, $p < .001$). Therefore, Study 2 presents evidence for reduced speed meta-modulation in low dopamine conditions.

Figure 4.6

A Graph Depicting Drug Effects on Speed Meta-Modulation



Note. Speed meta-modulation values for each participant in low (haloperidol; green) versus high (placebo; purple) dopamine conditions for Study 2. A main effect of drug state was observed, revealing lower speed meta-modulation (closer to zero) in low dopamine conditions. Light grey lines represent participant data; black crosses indicate mean values for each condition.

As was the case for movement speed and speed modulation, the effect of haloperidol on speed meta-modulation was baseline dopamine dependent; a significant interaction between drug state and estimated striatal dopamine synthesis capacity ($F(1, 53) = 10.95$, $p = .002$) was observed. To aid interpretation, the relationship between the drug effect and estimated striatal dopamine synthesis capacity was plotted (Figure 4.4, *bottom*). The drug effect (y-axis) was calculated as the speed meta-modulation value under haloperidol minus the speed meta-modulation value under placebo. Note that for speed and speed modulation (Figure 4.4, *top-left* and *top-right*) the drug effect was instead calculated as placebo minus

haloperidol because more positive speed and speed modulation values indicate higher speed and greater speed modulation. Given that more positive speed meta-modulation values actually indicate *less* speed meta-modulation (i.e., flatter slopes for the negative relationship between angular frequency and speed modulation), the drug effect was calculated as haloperidol minus placebo to ensure that, in line with the other two DVs, positive values on the y-axis indicate reduced speed meta-modulation under haloperidol and negative values indicate increased speed meta-modulation. Figure 4.4 (*bottom*) demonstrates an effect consistent with the other two DVs: a significant negative linear relationship between drug effect and estimated striatal dopamine synthesis capacity ($F(1, 19) = 8.31$, $p = .010$; beta estimate = -0.003, 95% CI [-0.005, -0.001]). These data again cut the x-axis, indicating opposing drug effects whereby, a reduction in dopamine decreased speed meta-modulation for participants with low estimated striatal dopamine synthesis capacity, and increased speed meta-modulation for those with high estimated striatal dopamine synthesis capacity. As such, all three DVs exhibit drug effects that are dependent on estimated striatal dopamine synthesis capacity.

The Introduction highlighted that a possible prediction from the opportunity costs model is that a reduction in vigour following dopaminergic manipulation will disproportionately affect shapes at higher angular frequencies because these tend to be drawn at a higher speed and may therefore require more vigour. To interrogate the data for evidence in support of this, the drug state by shape interaction in the speed modulation LMM for Study 2 was further explored by running the same LMM (excluding shape) on subsets of the data for each shape. This revealed that the "flattening of the curve" between angular frequency and speed modulation (i.e., reduced speed meta-modulation) under low dopamine conditions was driven by larger drug effects for the lower angular frequency shapes than the higher angular

frequency shapes (shape 4/3: $F(1, 555) = 49.36$, $p < .001$, beta estimate= -1.794, 95% CI [-2.296, -1.292]; shape 2: $F(1, 549) = 14.78$, $p < .001$, beta estimate = -0.928, 95% CI [-1.402, -0.454]; shape 4: $F(1, 534) = 2.95$, $p = .086$, beta estimate = -0.584, 95% CI [-1.251, 0.084]). Thus, there is no evidence that dopaminergic manipulation disproportionately affected high angular frequency shapes.

4.4.4 Independent Drug Effects

Drug effects on speed, speed modulation and speed meta-modulation are independent of each other.

Given the presence of drug effects on all three DVs in Study 2, further exploratory analyses were implemented on this dataset to investigate whether the drug effects are independent of each other. A main effect of drug remained for speed after controlling for speed modulation ($F(1, 1569) = 34.40$, $p < .001$) and speed meta-modulation ($F(1,1510) = 52.23$, $p < .001$). Similarly, the effect of the drug on speed modulation persisted after controlling for speed ($F(1, 1565) = 10.36$, $p = .001$) and speed meta-modulation ($F(1, 1554) = 17.66$, $p < .001$). Finally, the main effect of drug for speed meta-modulation remained after controlling for speed ($F(1, 53) = 12.41$, $p = .001$) and speed modulation ($F(1, 53) = 18.18$, $p < .001$). These results indicate that there are separable effects of the drug on speed, speed modulation and speed meta-modulation.

4.5 Discussion

In line with the vigour literature, the results of the current Chapter showed that low dopamine conditions (removal of PD medication and administration of haloperidol relative to placebo) reduced movement speed. In addition, haloperidol independently affected speed

modulation by reducing participants' ability to modulate movement speed according to curvature. Finally, an independent effect of dopaminergic drugs on speed meta-modulation was found: haloperidol reduced participants' ability to titrate their speed modulation such that it was appropriately suited to the global trajectory (the angular frequency of the shape). This latter effect was seen in members of the general population but not for individuals with PD; it is speculated below that this may be due to the incorporation of estimated baseline striatal dopamine synthesis capacity in the general population study. Together these results implicate dopamine in average movement speed, speed modulation and speed meta-modulation, and show that dopamine's role in movement speed is broader than that which is conceptualised in current models linking dopamine and movement.

Existing models, such as the opportunity costs model, do not provide clear unequivocal predictions for the effects of dopaminergic manipulation on naturalistic movement. Nevertheless, the Introduction highlighted two *possible* predictions that can be made from the opportunity costs model. One prediction is that low dopamine conditions should be associated with speed reductions but with no effects on speed modulation and speed meta-modulation. The results presented here clearly diverge from this prediction, showing that this interpretation of the opportunity costs model does not align with empirical evidence. A second prediction is that dopaminergic manipulation will affect speed, speed modulation and speed meta-modulation because reductions in vigour will disproportionately affect high speed movements that require more vigour. More specifically, this would predict a greater effect of the drug on trajectories that are executed at higher speeds (straights vs. corners) and shapes that are executed at higher speeds (high angular frequency shapes). No evidence was found to support these predictions. That is, the data did not show that drug state disproportionately affected higher speed movements, or that drug state disproportionately

affected speed or speed modulation values for high, as opposed to low, angular frequency shapes. The results cannot, therefore, easily be conceptualised under current formulations of the opportunity costs model.

It is next considered whether the results of the current Chapter might be consistent with other popular models in the literature. Bayesian theories propose that (tonic) dopamine signals the precision with which incoming information is stored and represented (Friston et al., 2012; Galea et al., 2012; Vilares & Kording, 2017). Under high dopamine – signalling high precision – an individual is thought to be more confident in their representation of incoming sensory information compared to their prior beliefs, and thus relies more heavily on incoming sensory data. Conversely, low dopamine promotes a reliance on prior beliefs. Whilst Bayesian theories have not made *explicit* predictions about the task used, one can consider tracing as a task that requires a balance between priors and incoming evidence. One has priors, learned through previous experience, that influence our typical speed of movement (Hammerbeck et al., 2014) but as we trace around the outline of a shape we encounter changes in curvature that demand deviations from these priors. Consequently, if we assume that reduced speed modulation and meta-modulation can occur due to an overweighting of the prior (typical speed) relative to the incoming (trajectory) information, then the results presented here could be considered consistent with Bayesian theories of dopamine and movement. Bayesian theories do not, however, provide a comprehensive account of *all* of the results because they do not make clear predictions about average movement speed.

A more recent theory – the rational inattention account (Mikhael et al., 2021) – merges opportunity cost and Bayesian models by proposing that dopamine signals average reward availability and that this "pays the cognitive costs" (e.g., attention costs) of increasing precision. This is consistent with evidence that dopamine plays a role in both motivational

and cognitive control of behaviour (Cools, 2008). By merging both approaches, the rational inattention account predicts that low dopamine conditions will be associated with reductions in speed, speed modulation *and* speed meta-modulation.

Although the data can be considered consistent with the rational inattention account, this, nevertheless, leaves unanswered questions about the exact mechanisms by which dopamine affects speed modulation and speed meta-modulation. The rational inattention account argues that dopamine "pays the cognitive costs" of increasing the precision with which incoming information (e.g., trajectory information) is stored and represented but the exact nature of these "cognitive costs" are yet to be determined. Mikhael and colleagues suggest attention as a candidate cost. If this were the case, in the context of the current Chapter, the hypothesis would be that in low dopamine conditions speed modulation (and speed meta-modulation) is reduced because participants attend less to changes in trajectory curvature because of a reluctance to pay the cognitive costs of selective attention. An alternative account has been forwarded by Manohar et al. (2015) who propose that, by signalling reward, dopamine permits more aggressive error correction. Thus, in the present case, in low dopamine conditions, participants may attend to the changes in curvature but would nevertheless fail to appropriately modulate their speed due to a (presumably implicit) reluctance to pay the energetic costs of error correction. Further studies are required that specifically aim to tease apart whether, in low dopamine conditions, participants were less likely to attend to curvature changes, or whether they simply failed to adapt their movements to accommodate them.

Both Mikhael and colleagues and Manohar and colleagues suggest motivation-based mechanisms: They do not argue that dopamine changes one's *ability* to pay attentional/effort-based costs, only one's motivation to do so. Nevertheless, it is possible that dopamine plays a

role in motor ability *per se*. Dopamine has long been linked to the invigoration of movements (Bova et al., 2020; da Silva et al., 2018), is thought to play an important role in generating a range of different movement speeds (Baraduc et al., 2013), and is key in signalling the start and end points of sub-movements (Collins et al., 2016). Given the observation that distinct dopamine neurons are involved in reward signalling and self-paced movement (da Silva et al., 2018; also see Engelhard et al., 2019) it is feasible that dopaminergic manipulations directly affect participants' ability to physically modulate their actions, independent of their motivation to do so. In other words, participants may be motivated to adapt movement speed as a function of curvature/global trajectory but may be unable to do so, perhaps because they have an inadequate range of movement speeds to choose from, and/or they are unable to signal the start/end points at which the adaptation should occur.

Whilst a significant main effect of drug on speed meta-modulation was observed in Study 2 (haloperidol compared to placebo), this was not observed in Study 1 (ON versus OFF dopaminergic medication in PD). Similarly, the main effect of drug on speed modulation in Study 1 was only apparent when analysing trial-level data as opposed to data averaged across trials; thus, caution is warranted regarding the effects of dopaminergic manipulation on speed modulation in the PD sample. There are a number of possible reasons to account for these null results. First, Study 2 accounted for estimated baseline striatal dopamine synthesis capacity by including working memory (a proxy measure of synthesis capacity) in its models, resulting in larger beta estimates for the effect of drug (e.g., 0.107 compared to 0.008 for speed meta-modulation, see Appendix 3.8). To be maximally sensitive to the effect of PD medication, future studies investigating speed modulation and meta-modulation should therefore endeavour to account for baseline striatal dopamine synthesis capacity. Secondly, the two types of pharmacological intervention may differentially affect dopaminergic activity states.

PD medication is thought to primarily boost tonic dopamine (Galea et al., 2012; Guthrie et al., 2009), a slow activation of dopamine neurons associated with tracking the average reward availability in the environment (Niv et al., 2007). In addition to tonic dopamine, haloperidol is thought to additionally affect phasic dopamine (Benoit-Marand et al., 2001; Frank & O'Reilly, 2006), the firing of dopamine neurons in response to salient (often unexpected) stimuli (Schultz, 1998). Given that haloperidol induced robust effects on both speed modulation and meta-modulation whereas PD medication did not, it is possible that these variables are influenced by phasic mechanisms. Indeed, recent models have posited a role for phasic dopamine in kinematics, specifically acting as part of a "velocity control circuit" (Barter et al., 2015). A final possibility is that different results in Study 1 and 2 are due to differences in the neurotransmitter mechanisms of action of the two pharmacological interventions. Haloperidol primarily acts as a dopamine D2 receptor antagonist (Benoit-Marand et al., 2001) but can additionally affect cortical glutamate and noradrenaline function (López-Gil et al., 2007; Muller & Seeman, 1977). Given that glutamate and noradrenaline have been implicated in prefrontal mechanisms underlying the flexible adaptation of on-going behaviour in response to environmental change (Cook et al., 2019; Cools, 2016; Froböse et al., 2018; Hazy et al., 2007; Miller & Cohen, 2001; Ott & Nieder, 2019; Swart et al., 2017; van Schouwenburg et al., 2010), and that both speed modulation and meta-modulation likely rely upon such mechanisms (e.g., changing behaviour to suit the current 'environment' (i.e., curvature or trajectory shape)), haloperidol's effect on these two variables may have been amplified by its modulation of other neurotransmitter systems in the prefrontal cortex. Whilst possible, this is perhaps unlikely given haloperidol's high affinity with dopamine receptors relative to non-dopamine receptors.

The current studies quantified the effect of dopaminergic modulation across the angular frequency spectrum. Set movements were used here to obtain this insight, but these findings can be applied to more spontaneous naturalistic movement trajectories. Natural movements are made up of a wide range of trajectory shapes and these trajectories can be decomposed, using Fourier transform, into densities within different angular frequency bands. This means that the insight gained in the current study with respect to dopaminergic modulation across the angular frequency spectrum can enable the prediction of the effects of dopaminergic drugs across an extensive range of naturalistic movement trajectories. In addition, the research has practical implications for drug discovery and PD treatment. For example, future studies may build upon the current work to construct classification systems that can infer which drug an animal has taken based on their naturalistic movements (Wiltschko et al., 2020), and/or predict the effects of novel compounds (i.e., pharmacological interventions) on naturalistic movement.

To summarise, the current Chapter provides insight from two pharmacological intervention studies and implicates dopamine in movement speed, speed modulation and speed meta-modulation. Drug effects appeared to be modulated by estimated baseline striatal dopamine synthesis capacity such that an inverted-U-shaped function was observed for the relationship between dopamine levels and each DV. The involvement of dopamine in these three kinematic features extends the theoretical understanding of dopamine function beyond that which is conceptualised in current models of vigour. Instead, it appears that dopamine also plays a role in the modulation of speed as a function of contextual information. Given that speed did not appear to differ between ASD and PD groups in Chapters 2 and 3, whereas speed modulation was significantly different between the two groups (Chapter 3), the current Chapter implicates dopamine function in both areas of overlap between ASD and PD, and

points of distinction. The positive relationship between speed modulation and dopamine in the current Chapter, in conjunction with higher speed modulation values in ASD compared to PD (Chapter 3), implies hyper-dopaminergic functioning in ASD and hypo-dopaminergic functioning in PD. Thus, ASD and PD may be characterised by opposing biomarkers at the neurochemical level. The General Discussion addresses how opposing biomarkers may lead to opposing performance in some cases and similar performance in others, specifically referring to variations in the inverted-U-shaped relationships that dependent variables have with dopamine.

Chapter 5 – General Discussion

5.1 Overview of Findings

5.1.1 Autism and Parkinson's Disease Overlap

A primary goal of the thesis was to compare behavioural and cognitive traits of older autistic adults, individuals with PD and members of the general population. Chapter 2 examined movement and movement-based theory of mind ability across these three groups. No group differences were uncovered with respect to movement-based theory of mind ability; all three groups exhibited a similarly high level of accuracy, with greater accuracy for mental state inferences than non-mental state inferences. By contrast, group differences in movement were observed. Whilst many kinematic features were similar between ASD and PD, these similarities in performance were distinct from CTRLs only for jerk. Clear movement differences were found between individuals with PD and control participants where, despite being on their dopaminergic medication, individuals with PD moved in a way that was slower, had a lower maximum speed, lower acceleration and lower mean rotation than CTRLs. The ASD group did not exhibit many movement differences with either group, with their performance falling between that of PD and CTRLs. Movement cues were clearly important for theory of mind representations – significant differences were found between the type of word represented and the kinematic features contained in the animations. In sum, movement-based theory of mind ability did not differ between groups, despite group movement differences in theory of mind depictions.

In Chapter 3, kinematic features were extracted from restricted movements as opposed to free movement. Whilst many kinematic features did not significantly differ between the

three groups, the ASD group could be distinguished from both the PD and CTRL groups via speed modulation and sub-movements, with reaction time also distinguishing ASD from PD. In contrast to Chapter 2, differences between PD and CTRLs were not found. When using kinematic features and trait questionnaires to classify group membership, the addition of kinematic features resulted in stronger classification accuracy compared to trait questionnaires alone in three cases: classifying clinical versus non-clinical populations, ASD versus PD populations, and ASD versus CTRL populations. By contrast, kinematics did not improve classification accuracy for ASD versus non-ASD populations, PD versus non-PD populations, or PD versus CTRL populations. Overall, this Chapter noted distinctions between ASD and PD movement, and these kinematic features were found to be useful in the development of classification models.

5.1.2 Biological Mechanistic Insight

Chapter 4 provided clear evidence for a role of dopamine in speed, speed modulation and speed meta-modulation. In Study 1 – a comparison between individuals with PD both ON and OFF their dopaminergic medication – significant reductions in speed and speed modulation were observed under low dopamine conditions (i.e., OFF-medication). In Study 2 – a comparison between members of the general population on haloperidol (a dopamine antagonist) and placebo – the same results were found, in addition to a significant reduction in speed meta-modulation in low dopamine conditions (i.e., under haloperidol). Study 2 further allowed for an investigation of the baseline dependency of the drug effects. All three drug effects were found to be moderated by estimated striatal dopamine synthesis capacity. That is, those with low estimated striatal dopamine synthesis capacity exhibited a positive relationship between dopamine levels and performance, whereas a negative relationship was observed in

those with high estimated striatal dopamine synthesis capacity. This suggests that, for all three variables, the relationship with dopamine follows an inverted-U-shaped function. Overall, this Chapter implicated dopamine as an underlying mechanism of kinematic features that were distinct between ASD and PD, and those that appeared similar between the two groups.

5.2 Interpretation of Findings

5.2.1 Autism and Parkinson's Disease Overlap

Similarities between Autism and Parkinson's Disease

The thesis aimed to shed light upon potential similarities in the behavioural and cognitive presentations of ASD and PD. The purpose of this assessment was to understand whether it is possible that overlapping traits may contribute to the increased diagnosis of PD in the ASD population (as noted by many prevalence studies (Croen et al., 2015; Hand et al., 2020)). The Introduction highlighted that autistic individuals exhibit movement differences in domains that are used in PD diagnostic assessments. However, ASD and PD movement had not yet been directly compared. Uncovering similarities between ASD and PD but a distinction from CTRLs would support the theory that autistic and parkinsonian traits can be likened to one another. In Chapter 2, kinematic features were comparable between ASD and PD; however, there were also no differences between ASD and the CTRL group for many of these variables. However, both ASD and PD animations were found to differ from CTRLs in terms of jerk, whilst the two clinical groups did not significantly differ from each other. Thus, in this free movement task, assessment of jerk profiles would lead to ASD and PD being grouped together, separate from CTRLs. In Chapter 3, there were again a number of kinematic features that did not differ between ASD and PD (including speed, acceleration and jerk), but these variables also did not differ from CTRLs. Anecdotal-to-moderate evidence for

similarities in these variables is surprising given literature demonstrating differences in a range of kinematic features between PD and CTRLs (Alberts et al., 2000; Broderick et al., 2009; Flash et al., 1992; Lange et al., 2006; Van Gemmert et al., 2003; Viviani et al., 2009) and ASD and CTRLs (Cook et al., 2013; Edey et al., 2016; Grace et al., 2017; Johnson et al., 2013).

Chapters 2 and 3 presented a number of areas in which PD and ASD performance were comparable. However, there were not many clear distinctions between these clinical groups and the general population. With the exception of jerk, kinematic features that were similar between ASD and PD groups did not appear to differ from the general population. As such, evidence is limited in support of movement similarities between ASD and PD that may lead to an autistic individual exhibiting PD-like movements in a clinical assessment. However, it is possible ASD and PD movements may appear similar at a broad level, but these similarities do not translate to the same kinematic features being employed by both groups. Movements may appear "different" from the general population for a variety of underlying reasons. For example, one might employ a jerkier movement profile, a different number of sub-movements or an unusual level of speed modulation when moving along a trajectory, and this might be observed as a movement that is "lacking smoothness". Chapter 2 highlighted that PD differ from CTRLs in terms of speed, acceleration and jerk. In addition, Chapter 3 showed distinctions between ASD and CTRLs in terms of speed modulation and sub-movements. In a writing task, deviations from typical levels of speed, acceleration and jerk (as in PD) and deviations from typical levels of sub-movements and speed modulation (as in ASD) may make handwriting appear "less fluid" to the naked eye. Therefore, whilst kinematics may not unite performance in ASD and PD, this does not mean that similarities

cannot be observed in broader movement profiles. Indeed, existing clinical assessments focus on these broader movements as opposed to quantifying kinematics.

Turning to cognitive similarities, Chapter 2 highlighted no differences in theory of mind ability between ASD and PD. However, neither group differed from the CTRL group on task performance, meaning that performance on this task would not distinguish ASD and PD groups from the general population. The fact that all three groups exhibited comparable levels of accuracy is surprising as differences in theory of mind ability have been evidenced between both ASD and CTRLs (e.g., Abell et al., 2000) and PD and CTRLs (e.g., Orso et al., 2020). However, given that existing evidence in the PD and older autistic adult literature does not relate to movement-based theory of mind, it is possible that individuals with PD and older autistic adults may only exhibit differences from the general population in other components of theory of mind (e.g., cognitive/situational, as indexed in the Faux Pas Task). Theory of mind ability is not used in assessments of PD, meaning that these findings do not speak to the misdiagnosis hypothesis. However, it was possible that theory of mind may have been an area in which similarities could be drawn between ASD and PD in daily life, or a point at which ASD and PD could be distinguished. Similar performance on this task between all three groups suggests that movement-based theory of mind ability neither contributes to the appearance of similarities between ASD and PD, nor is a useful ability for distinguishing ASD from PD.

Differences between Autism and Parkinson's Disease

It is possible that ASD and PD movement may appear similar at a gross motor function level, but closer inspection of kinematic features may reveal points at which the groups can be distinguished. Whilst no differences were found between ASD and PD movement in the free movement task in Chapter 2, Chapter 3 shed light upon kinematic

features that can distinguish ASD and PD. In this restricted movement task, ASD and PD groups differed in terms of speed modulation, sub-movements and reaction time. Speed modulation and sub-movements did not specifically distinguish ASD from PD – instead they distinguished ASD from both PD and CTRLs, meaning that they hold utility in distinguishing ASD from not-ASD (i.e., PD or CTRL) as opposed to indicating which of the three groups an individual is likely to belong to (ASD, PD or CTRL). However, significant differences in reaction time were specific to the ASD versus PD comparison. Thus, in conjunction with one another, these tasks could distinguish both PD and CTRLs from ASD (i.e., CTRL differ from ASD in terms of speed modulation and sub-movements but *not* reaction time; PD differ from ASD in terms of speed modulation, sub-movements, *and* reaction time).

Insight into variables that differ between groups is useful for developing classification algorithms. For example, classification algorithms could be developed to distinguish ASD and PD movement in the clinic, and therefore prevent a misdiagnosis of PD in autistic individuals who exhibit movement differences that broadly look parkinsonian. Chapter 3 incorporated kinematic features into classification algorithms for a range of group comparisons, to assess whether variables obtained from movement could provide helpful insight for classifications above and beyond (or instead of) questionnaire measures. Firstly, when distinguishing clinical versus non-clinical groups (i.e., ASD/PD versus CTRL), combining questionnaires and kinematic features was found to yield the strongest classification accuracy. This indicates that movement tasks would be useful in clinical assessments to uncover whether or not an individual is displaying traits that deviate from the general population. However, this algorithm does not speak to *what* the diagnosis should be. Subsequently, when classifying ASD and PD groups, the strongest classification model included both questionnaires and kinematics. Overall, a combination of kinematic features and questionnaires appeared most

useful for determining whether an individual exhibits clinically relevant behaviour, and then subsequently identifying whether that individual should be categorised as ASD or PD. It should be noted that the models in which kinematics were useful were not always those containing only the *core kinematic features* (i.e., those that were found to significantly differ between groups). Certain classifications yielded stronger accuracy when using *all kinematic features* as opposed to *core kinematic features*. This indicates that variables that are useful for distinguishing groups cannot be ascertained by looking for significant differences alone. Variables that do not significantly differ between groups may be useful for distinguishing groups in a classification algorithm in conjunction with other variables.

A shift towards incorporating kinematic features into clinical assessments has advantages for a number of reasons. Firstly, kinematic features are objective measures and, unlike questionnaire measures, are unlikely to be susceptible to social desirability bias and camouflaging (Cook et al., 2021; Hull et al., 2017; Keating et al., 2024). In addition, questionnaire measures may not be reliable in certain populations; for example, individuals with alexithymia struggle to identify and describe their own emotions (Bagby et al., 1994; Hickman, 2019; Nemiah et al., 1976), which may lead to difficulties with self-report measures. This is particularly important given increased levels of alexithymia in both ASD and PD populations (Assogna et al., 2012; Berthoz & Hill, 2005; Costa et al., 2010; Kinnaird et al., 2019). Minimally verbal individuals may also struggle to complete questionnaires, which is highly relevant as these individuals are thought to make up 25-35% of the autistic community (Rose et al., 2016). Objective measures such as kinematic assessments may be particularly useful when studying these groups. Finally, whilst clinical assessments do currently incorporate measures of gross and fine motor function, the scoring of these tasks is

generally unspecific (e.g., “mild” versus “severe”) and subjective. Consequently, diagnosis accuracy may be improved and advanced by incorporating objective kinematic measurements.

Overall, it appears that there were more similarities between ASD and PD movement (distinguished from CTRLs) in the task of free movement (Chapter 2), whereas in a restricted movement task there were more kinematic features in which movement could be distinguished (Chapter 3). One interpretation is that restricted movement tasks are more useful than free movement tasks in differentiating between ASD and PD populations. However, an additional factor that should be considered in this interpretation is whether or not the PD participants were taking medication at the time of completing the tasks. The tasks in Chapter 2 were completed ON-medication whereas the tasks in Chapter 3 were completed OFF-medication. Thus, when addressing the question of whether ASD and PD movements are similar, the experimental design cannot tease apart whether there are more similarities in free movement compared to restricted movement, or between ASD and PD ON-medication compared to ASD and PD OFF-medication. For the sake of improving clinical assessments, it should be noted that PD movement OFF their dopaminergic medication is the most accurate representation of the parkinsonian movement that ASD groups may be confused with in the clinic. This is because when individuals with PD first present in the clinic they have not yet received any medication, meaning their movements arise from an unmedicated state. It is therefore reassuring that points of distinction between ASD and PD were found in Chapter 3, in which parkinsonian movements were quantified from PD participants OFF their medication. This implies that, through the use of kinematic features, it should be possible to successfully distinguish ASD and PD (OFF-medication) in the clinic.

5.2.2 Insight into Parkinson's Disease Functioning

In addition to comparing ASD and PD performance, the experiments in the thesis also allowed for an assessment of how performance in each condition compared to the general population. With respect to PD, Chapter 2 provided evidence in line with a reduction in vigour in PD (Alberts et al., 2000; Broderick et al., 2009; Flash et al., 1992; Jankovic, 2008; Lange et al., 2006; Van Gemmert et al., 2003; Viviani et al., 2009). Animations created by the PD group were slower, had a lower maximum speed, lower acceleration and lower mean rotation than those created by CTRLs.

The pattern of results across Chapters 2 and 3 provided evidence in line with the motor motivation hypothesis (Mazzoni et al., 2007). Chapter 2 used the Animation Production Task to index kinematic features, a task of free movement in which participants could move triangles around the screen in any way – and at whatever speed – they chose. In this task, fast movements were not incentivised as there was a fixed 30 second movement period, and moving faster would not improve task performance nor reduce the duration of the task. By contrast, Chapter 3 indexed kinematic features using the Shapes Tracing Task in which participants were required to trace 10 rotations of a given shape before proceeding to the next trial. Here, fast movement was incentivised as participants could finish each trial, and the overall experiment, in a shorter amount of time if they moved faster. It is interesting to note that kinematic differences between PD and CTRLs were only found in Chapter 2 (including slower movement speed in the PD group), and not Chapter 3. This is in line with the findings by Mazzoni et al. (2007) who stated that slowness of movement in PD is not due to an inability to move quickly, rather a lack of motivation to do so. Thus, it may be the case that PD participants were incentivised to spend the energetic cost of movement in Chapter 3 in

order to complete the task more quickly, but that in Chapter 2 there was no incentive to spend the energetic cost to move with increased speed.

It is important to additionally consider that medication state varied between Chapters 2 and 3. PD participants were ON-dopaminergic medication when completing tasks in Chapter 2, whereas they were OFF-dopaminergic medication when completing tasks in Chapter 3. Given that PD participants generally exhibit greater movement differences when OFF-medication, greater differences between PD and CTRLs would have been expected in Chapter 3 (PD OFF-medication) compared to Chapter 2 (PD-ON medication). However, this was not the case – significant differences were found between PD and CTRLs in Chapter 2 but *not* in Chapter 3. This pattern of results does not align with the expected effects of medication. Subsequently, it may be that the effect of motor motivation is stronger than that of medication, which is why differences were seen in a task of unincentivized (free) movement (despite PD participants being ON-medication) but not in a task in which fast movement was incentivised (despite PD participants being OFF-medication). Future studies could verify this by assessing PD participants on the two tasks under both medication states.

Finally, the thesis presented the first assessment of PD on a movement-based theory of mind task, the Animation Production Task. No significant differences were found between PD and CTRLs. This is contrary to existing evidence in the theory of mind literature suggesting differences between PD and CTRLs (Bodden et al., 2010; Del Prete et al., 2020; Kawamura & Koyama, 2007; Peron et al., 2009; Roca et al., 2010). However, these tasks index different components of theory of mind ability; for example, the Faux Pas Task and the Yoni Task index cognitive theory of mind (Shamay-Tsoory & Aharon-Peretz, 2007; Stone et al., 1998). Therefore, it is possible that individuals with PD exhibit differences in cognitive theory of mind but not movement-based theory of mind. Whilst differences in movement-based theory

of mind would have been expected due to movement differences in PD, it may be that a lifetime of movement experience prior to PD-onset may be sufficient to act as a "blue-print" for movement cues in mental state representation. By contrast, there is a wide body of literature suggesting loneliness and social isolation in PD (Karlsen et al., 2000; Prenger et al., 2020; Soleimani et al., 2014), and cognitive theory of mind ability may decline as experience in social situations reduces (de Sousa et al., 2018).

5.2.3 Insight into Older Autistic Adult Functioning

When comparing ASD performance to that of the general population, a number of unexpected findings were observed. For example, a wide body of literature suggests that autistic individuals move with a jerkier movement profile than non-autistic individuals (Cook et al., 2013; Grace et al., 2017). However, the current thesis provided both null evidence for this hypothesis (Chapter 3), and evidence in the opposite direction whereby autistic movements were *less* jerky than non-autistic movements (Chapter 2). To interpret these findings in the context of the wider literature, a number of factors must be considered, including the nature of the measures calculated and the participants recruited. For example, in the current thesis the measure of jerk was susceptible to influence from speed given that it was calculated as the second derivative of speed. As such, differences in jerk may be epiphenomenal of differences in speed. Numerically (but not significantly) lower speed values were observed in the ASD group compared to CTRLs, which may have led to a subsequent reduction in jerk values measured in the ASD group. Importantly, when employing a speed-independent measure of movement smoothness in Chapter 3 (SPARC), no significant differences were found between autistic and non-autistic movement. Therefore, it may be concluded that movement smoothness does not differ between ASD and CTRLs. It is relevant

to note that these studies comprise the first assessment of kinematic features in the older autistic adult population. Evidence suggesting jerky movements in autism has come from younger samples of autistic individuals (e.g., Cook et al., 2013; mean age = 41.07) or children (e.g., Grace et al., 2017; mean age = 10.58). It may be the case that jerk differences between autistic and non-autistic individuals are not present in older age, perhaps due to a change in kinematic features in the non-autistic population.

A number of differences between autistic and non-autistic movement profiles were replicated in the current thesis. For example, in Chapter 3, significantly steeper speed modulation values were observed in the older autistic participants' movements. This is in line with evidence from younger participant samples (Cook et al., 2023; Fourie, 2022). In addition, an increased number of sub-movements were employed in autistic movement profiles compared to non-autistic movement profiles, another feature of movement that has been evidenced in younger autistic samples (Cook et al., 2023). Thus, it appears that some components of autistic movement remain distinct from non-autistic movement in older age.

With respect to theory of mind ability, Chapter 2 indicated no significant differences between autistic and non-autistic performance. A number of studies have highlighted that, whilst differences in theory of mind have been observed between autistic and non-autistic individuals at younger ages, comparable performance exists between autistic and non-autistic older adults due to an ageing-related decline in the non-autistic group (Lever & Geurts, 2016a; Yarar et al., 2020). Chapter 2 appears to support this pattern of results. However, it should be noted that age significantly correlated with performance on this task, and that all groups exhibited a relatively high level of accuracy, meaning that autistic and non-autistic performance cannot be characterised as a similar *lack* of accuracy.

5.2.4 Biological Mechanistic Insight

Moving beyond behavioural and cognitive differences in ASD and PD, the current thesis also aimed to understand the biological mechanisms underpinning these abilities. This is because it may be the case that similarities between ASD and PD arise from shared biological mechanisms. The thesis investigated the role of dopamine in movement processes, given that movement differences were apparent in both ASD and PD (Chapters 2 and 3), and dopamine dysfunction has previously been implicated in both conditions (Pavăl, 2017; Rizek et al., 2016). Chapter 4 provided evidence for a role of dopamine in movement speed, speed modulation and speed meta-modulation. Whilst the exact mechanism is unknown, significant drug effects for all three features of movement is consistent with the rational inattention account of dopamine. This account states that dopamine signals average reward availability and that this "pays the cognitive costs" (e.g., attention costs) of increasing precision (Mikhael et al., 2021). Differences in speed may be accounted for by dopaminergic effects on reward signalling, whereby an increase in reward signalling in high dopamine conditions enhances the vigour of movements due to an increased opportunity cost of sloth (also in line with the opportunity costs model (Niv et al., 2007)). Differences in speed modulation and speed meta-modulation may be accounted for by subsequent effects on precision; that is, dopamine is thought to alter the weighting of priors and incoming sensory information and, as such, an overweighting of priors (e.g., typical speed) relative to incoming trajectory information (e.g., curvature or global trajectory) may alter speed modulation and speed meta-modulation (also in line with Bayesian accounts (Friston et al., 2012; Galea et al., 2012; Vilares & Kording, 2017)).

The Introduction raised the possibility that dopaminergic mechanisms may explain why ASD and PD overlap in some areas but not others. If an ability has an inverted-U-shaped

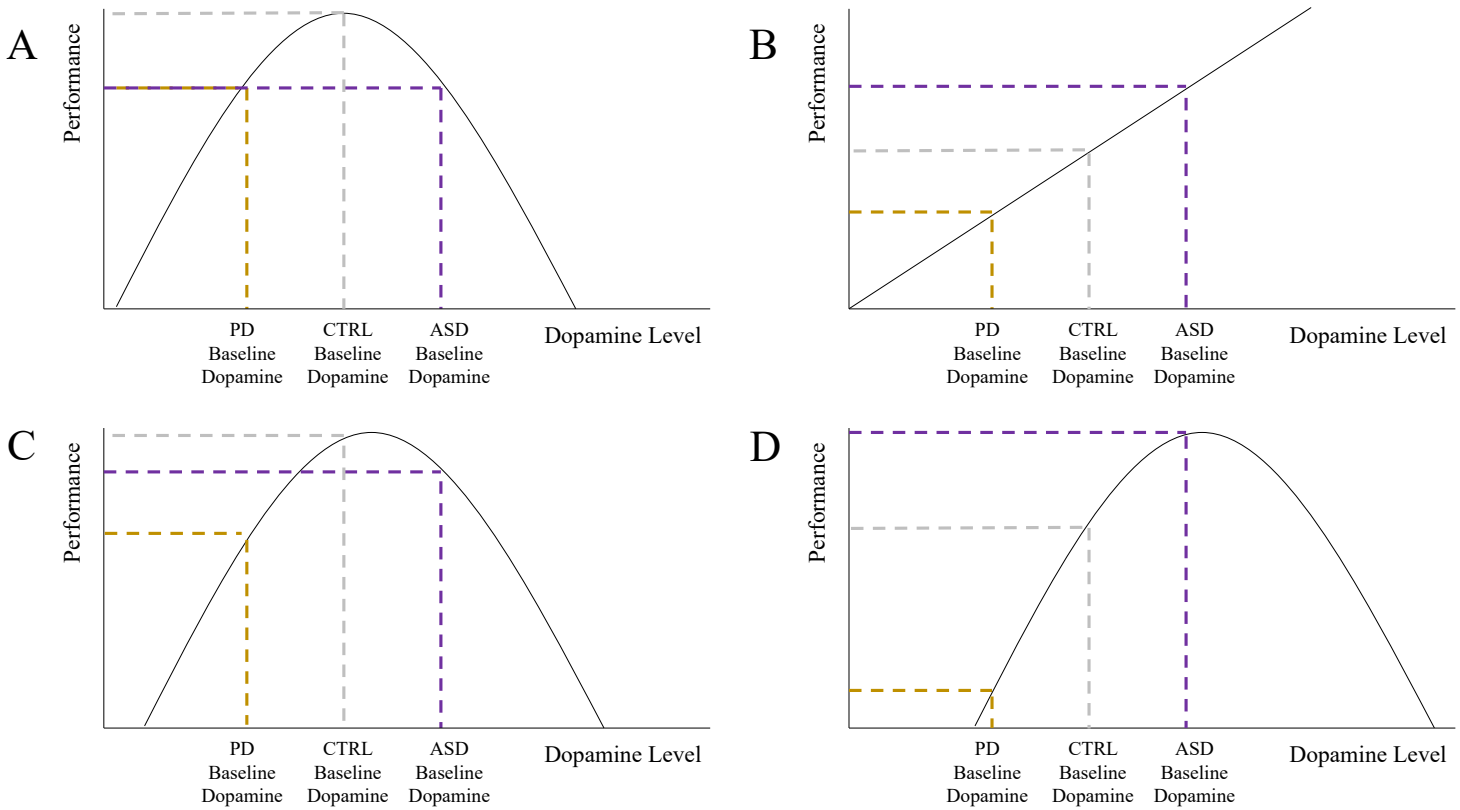
function for its relationship with dopamine, both a hyper- and hypo-dopaminergic state can result in the same behavioural performance (Figure 5.1A). By contrast, abilities with a linear relationship with dopamine would differ in hyper- and hypo-dopaminergic states (Figure 5.1B). This demonstrates that opposite biomarkers can cause similarities in some abilities and differences in others. In Chapters 2 and 3, speed modulation was found to differ between PD and ASD, whereas speed was comparable between groups. An inverted-U-shaped function would have therefore been expected for dopamine's relationship with speed but not speed modulation. However, Study 2 revealed a baseline dependency for all drug effects; for speed, speed modulation and speed meta-modulation, the relationship between dopamine levels and performance followed an inverted-U-shaped function. Whilst a linear relationship between dopamine levels and performance may initially appear to best explain the difference in speed modulation between ASD and PD, variations in the shape of an inverted-U-shaped curve may also account for this pattern of results. Comparable performance between PD and ASD arising from hypo- and hyper-dopaminergia respectively would require the two groups' baseline dopamine levels to sit at equidistant points away from optimal level on either side of the curve (Figure 5.1A). However, if the peak of the curve is closer to ASD baseline dopamine than PD baseline dopamine, ASD performance would be higher than PD performance, thus accounting for a difference in performance (Figure 5.1C). In addition, if baseline dopamine levels in PD and ASD fell on the same side of the curve's peak, this would also account for group differences in performance (Figure 5.1D).

Assuming a hypo-dopaminergic state in PD (Rizek et al., 2016) and a hyper-dopaminergic state in ASD (Presti et al., 2003), Figure 5.1A and Figure 5.1C would require CTRL performance to sit above that of PD and ASD. However, Figure 5.1B and Figure 5.1D would enable ASD performance to sit above CTRL performance. Given that speed

modulation values were higher in ASD than CTRLs (Chapter 3), and that speed modulation appears to have an inverted-U-shaped relationship with dopamine (Chapter 4), the relationship which would best reflect this is Figure 5.1D. Here, CTRL participants could have lower dopamine levels *and* lower performance than ASD, while an inverted-U-shaped function is maintained.

Figure 5.1

A Depiction of Potential Relationships Between Dopamine Levels and Performance



Note. (A) Inverted-U-shaped curve demonstrating comparable performance between ASD and PD; (B) linear relationship demonstrating different performance between ASD and PD; (C and D) inverted-U-shaped curves demonstrating different performance between ASD and PD. Black line = relationship between dopamine and performance, purple dotted line = ASD baseline dopamine and corresponding performance; dark yellow dotted line = PD baseline dopamine and corresponding performance; grey dotted line = CTRL baseline dopamine and corresponding performance. PD = Parkinson's Disease, CTRL = Control, ASD = Autism Spectrum Disorder.

The results of Chapter 4 allow inferences to be made regarding the mechanism underlying speed modulation, something which has been debated in the literature. It has previously been suggested that speed modulation has a neural mechanism (Lacquaniti et al., 1983). For example, it may be that speed modulation arises following instructions made in a motor planning process, perhaps with a view to minimising jerk (Huh & Sejnowski, 2015; Viviani & Flash, 1995). By contrast, others have posited that speed modulation is an inherent product of the constraints of musculo-skeletal joints, and thus has a biomechanical mechanism (Gribble & Ostry, 1996; Matic & Gomez-Marin, 2022; Schaal & Sternad, 2001). Given that centrally-acting dopamine agonists and antagonists employed in Chapter 4 were able to alter speed modulation levels, this aligns better with a neural mechanism for speed modulation; indeed, it is unlikely that dopaminergic manipulation caused changes to hard-wired biomechanical constraints.

5.2.5 Methodological Advancements

The current thesis employed a range of techniques to capture and assess movement and, as such, has provided novel insight into the utility of such methods for characterising group differences. For example, multiple shapes were included in the Shapes Tracing Task, characterised by angular frequencies across a wide range of the angular frequency spectrum. Chapter 3 indicated that the rounded square (angular frequency = 4) was the most useful shape for distinguishing groups. However, many movement studies in the literature utilise shapes with lower angular frequencies such as ellipses (angular frequency = 2) or spirals (angular frequency = 2/33), which may not be optimal for detecting differences (e.g., Dayan et al., 2012; Fourie, 2022; Kamble et al., 2021; Lamba et al., 2021; Rios-Urrego et al., 2019). Future studies should employ a range of shapes in movement tasks, in particular those with

higher angular frequencies, to optimise the ability to detect group differences. In addition, the use of the Shapes Tracing Task provided the first insight into speed modulation in PD, and how speed modulation differs following pharmacological intervention. Future studies may find this variable useful in characterising movement differences in other clinical conditions and pharmacological or neuroscientific investigations. Finally, whilst online versions of the Animation Perception Task have been developed (Livingston et al., 2021), this thesis presents the first development of an online version of the Animation Production Task. Given that differences between ASD, PD and CTRLs were apparent in this task, this online adaptation appears to have utility in detecting group differences.

5.3 Limitations and Future Directions

5.3.1 Autism and Parkinson's Disease Overlap

The current thesis focused primarily on movement overlap between ASD and PD due to the fact that PD diagnostic criteria relate to motor function. In addition, movement-based theory of mind was assessed due to the proposed link to movement differences. However, there are many other areas of overlap that could be examined. The Introduction notes potential similarities between ASD and PD in terms of gross motor function (e.g., postural instability, gait), emotion expression and recognition, additional components of theory of mind ability (e.g., cognitive/situational), motivation and cognitive rigidity. Assessments in these domains would help build a more detailed picture of the similarities between ASD and PD and, crucially, points at which the conditions can be distinguished. Once a greater understanding of similarities between ASD and PD is obtained, this information should be disseminated to medical professionals to ensure an awareness of the potential overlap in symptomatology

between ASD and PD. Additionally, diagnostic tools may be developed to differentiate between PD and movement differences arising from other conditions (e.g., ASD).

By assessing different abilities in conjunction with one another, it may be revealed that apparent similarities between ASD and PD in certain domains may in fact be accounted for by overlap in core cognitive features. For example, it is possible that differences in social cognition and motor function arise from a lack of motivation to engage in such processes, rather than an inability to do so (Clements et al., 2018; Contreras-Huerta et al., 2020; Damiano et al., 2012; Mazzoni et al., 2007). As noted in Chapter 4, differences in kinematic features such as speed modulation may be explained by motor mechanisms; for example, differences in movement invigoration (Bova et al., 2020; da Silva et al., 2018), the range of movement speeds generated (Baraduc et al., 2013), or the signalling the start and end points of sub-movements (Collins et al., 2016) may all affect speed modulation levels. However, differences in kinematic features may not necessarily have a motor basis; it is possible that altered speed modulation levels can be explained by a lack of attention to the movement trajectory, reduced error correction, or a lack of motivation to modulate movement speed to curvature (Manohar et al., 2015; Mazzoni et al., 2007; Mikhael et al., 2021). In addition, many motor function and social cognition tasks require efficient task switching. For example, in the Animation Tasks (Chapter 2), each trial requires switching between mental representations of different mental and non-mental state depictions. In the Shapes Tracing Task (Chapters 3 and 4), appropriate speed modulation and meta-modulation are reliant upon flexible updating of stimulus features (i.e., the shape's current curvature or global trajectory). Given that cognitive rigidity is a feature of ASD and PD (Dirnberger & Jahanshahi, 2013; Westwood et al., 2016), performance on these tasks may be affected in ASD and PD due to an inability to switch between mental representations. Future investigations should employ an

experimental design that separates motivation and task switching from motor function and social cognition, to identify the specific mechanisms affected in ASD and PD, and by dopamine function. Greater understanding of the root causes of apparent behavioural and cognitive differences in ASD and PD may lead to the development of more appropriately targeted interventions to address difficulties experienced in both conditions.

Various factors were considered in participant recruitment to ensure a well-controlled comparison between ASD and PD. Both ASD and PD participants were required to have an official clinical diagnosis, and those with other movement disorders and developmental disorders were excluded. The CTRL group was matched to the ASD and PD groups in terms of gender, non-verbal reasoning and age, and variables that could not be matched across all three groups were controlled for in analyses (e.g., age, depression, anxiety, alexithymia). To ensure specificity of ASD and PD groups, all ASD participants were required to *not* have a diagnosis of PD and vice versa. However, without a longitudinal design, it is not possible to know whether participants in the ASD group may go on to receive a diagnosis of PD. By tracking the future diagnoses of ASD participants, subsequent analyses could be conducted on participant subsets who did not receive a PD diagnosis in later life. This would ensure that results are not confounded by undiagnosed PD in the ASD group. In addition, the PD and CTRL participants come from a generation in which ASD diagnoses were not prevalent (Lai & Baron-Cohen, 2015), meaning that it may be the case that some of these participants were undiagnosed autistic individuals. If this is the case, similarities between these groups and the ASD group may be overinflated. Thus, future studies should implement an ASD diagnostic screening in PD and CTRL participants to ensure they do not meet ASD diagnostic criteria. This would increase confidence that the PD and CTRL groups do not contain any autistic participants.

Whilst this thesis presents a number of areas in which PD and ASD overlap, the evidence is not overwhelming for the misdiagnosis hypothesis. As such, it is important to consider additional factors that may account for the increased prevalence of PD diagnosis in the ASD population. To ensure a controlled assessment of ASD and PD, the current thesis excluded and therefore overlooked the involvement of other conditions. In practice, it may be the case that autistic individuals are more likely to have co-occurring movement differences that are mistaken for PD. For example, Developmental Coordination Disorder (DCD) is a condition characterised by movement differences which has a strong co-occurrence with ASD (Bhat, 2020). Future studies should quantify the involvement of co-occurring conditions in the relationship between ASD and PD. Another alternative explanation for increased PD diagnosis in ASD is that autistic individuals may have more contact with healthcare providers compared to non-autistic individuals and, consequently, they may have an increased chance of PD symptoms being detected. Overall, it is likely that increased PD diagnosis prevalence in ASD is the product of many factors including similarities between conditions at behavioural, cognitive and biological/neural levels, as well as genetic contributions and healthcare factors.

5.3.2 Future Neuroscientific Investigations

To implicate dopamine in movement processes, two pharmacological interventions were conducted (Chapter 4): PD participants ON and OFF their dopaminergic medication (Study 1), and members of the general population on haloperidol and placebo (Study 2). In addition, inferences regarding dopamine's involvement in movement processes can be made by comparing PD and CTRL performance in Chapters 2 and 3, due to the fact that PD arises from a dysfunction to the dopamine system (Rizek et al., 2016). Whilst this thesis provides novel insight into the role of dopamine in speed, speed modulation and speed meta-

modulation, conclusions cannot be made regarding precise neuroanatomical and neurophysiological actions. As such, additional neuroscientific investigations such as PET imaging may shed light upon the mechanistic action of dopamine in these movement processes. Given that PET imaging is costly and requires expertise, the current thesis incorporated a working memory task as a proxy measure of baseline striatal dopamine synthesis capacity, which has been validated using PET imaging in previous research (Cools et al., 2008; Landau et al., 2009). This enabled inferences to be made regarding variables' relationships with dopamine function. Evidence presented in Chapter 4 is consistent with inverted-U-shaped relationships between dopamine and the assessed variables (speed, speed modulation, and speed meta-modulation). However, future studies should verify these proposed inverted-U-shaped relationships by running PET imaging studies to reliably quantify baseline striatal dopamine synthesis capacity.

Whilst the majority of findings are replicated between Study 1 and Study 2, the drug effect on speed meta-modulation was only apparent in Study 2. Chapter 4 presents a number of reasons that may account for this, primarily focusing on differences in drug action between the two studies – PD medication (i.e., levodopa and dopamine agonists) versus haloperidol (dopamine antagonist). For example, haloperidol is thought to boost both tonic and phasic dopamine (Benoit-Marand et al., 2001; Frank & O'Reilly, 2006), whereas PD medication may primarily affect tonic dopamine (Galea et al., 2012; Guthrie et al., 2009). In addition, beyond dopamine D2 receptors, haloperidol can additionally affect cortical glutamate and noradrenaline function (López-Gil et al., 2007; Muller & Seeman, 1977). This suggests that speed meta-modulation may be governed by phasic dopaminergic mechanisms, or that glutamate and noradrenaline may be involved – perhaps via prefrontal mechanisms that govern flexible adaptation of on-going behaviour in response to environmental change (Cook

et al., 2019; Cools, 2016; Froböse et al., 2018; Hazy et al., 2007; Miller & Cohen, 2001; Ott & Nieder, 2019; Swart et al., 2017; van Schouwenburg et al., 2010)). However, it is important to note that these conclusions are based on the pharmacokinetic properties of the two pharmacological interventions. Thus, future work could verify these proposals by combining pharmacology with neuroimaging to identify the neural activity and brain loci associated with changes in speed meta-modulation following pharmacological interventions.

Neuroimaging techniques may additionally shed light upon the nature of dopamine function in ASD. Whilst PD is characterised by hypo-dopaminergia, current literature presents conflicting results regarding dopamine function in ASD. Models of dopamine function in this Discussion have assumed hyper-dopamine in ASD due to such findings in the motor domain (Presti et al., 2003). In. addition, the results of this thesis are consistent with hyper-dopaminergic function in ASD (i.e., increased speed modulation values in ASD compared to PD and CTRLs). Whilst the current thesis simply compares patterns of performance, more in-depth neuroscientific investigations would reveal whether similarities between ASD and PD are indeed due to dopaminergic mechanisms. As such, further investigations should employ techniques such as PET imaging in older autistic adults to confirm the nature of dopamine function in ASD.

5.3.3 Participant Diversity

The results of the current thesis are limited in terms of their generalisability to all individuals. Due to the nature of the research, only older adults were recruited in Chapters 2 and 3. Given that differences across the lifespan have been observed in movement and theory of mind (Ketcham et al., 2002; Maylor et al., 2002; Pardini & Nichelli, 2009), the findings of Chapters 2 and 3 may only apply to older individuals. By contrast, Chapter 4 recruited both

older individuals with PD (Study 1) and younger individuals from the general population (Study 2), which widens the applicability of the findings. Due to practical considerations, an opportunity sampling method was employed and therefore limitations in sample diversity should be noted. For example, whilst minimally verbal individuals make up 25-35% of the autistic population (Rose et al., 2016), these individuals were not represented in the current studies. In addition, participants were primarily White British, meaning there was little ethnic diversity in the sample. Future research should ensure the recruitment of a more diverse sample. Beyond ensuring a more representative dataset, the information could be used to strengthen analyses. Indeed, recent classification models of PD and non-PD handwriting have developed sex-specific and age-dependent models for optimal classification (Gupta et al., 2020). Thus, incorporating participant demographics into classification algorithms may lead to more accurate group classification.

5.4 General Conclusion

The current thesis presented the first empirical comparison of autistic and parkinsonian movement, as well as movement-based theory of mind. Whilst ASD and PD movement may appear similar at a gross motor function level, close inspection of kinematic features revealed points at which the groups could be distinguished. Kinematic features were found to be useful in classifying group membership alongside questionnaire measures, which is promising for ensuring the validity of diagnoses in these populations. Consequently, clinical assessments may benefit from the incorporation of kinematic assessments. In addition to similarities and differences between ASD and PD, the thesis highlighted how ASD and PD respectively differed from the general population. Movement assessments in older autistic adults are sparse and, as such, this thesis provided novel insight into kinematic differences in

the older autistic population. Movement differences were also apparent in PD, which were in line with the motor motivation hypothesis. Notably, no significant group differences were observed in terms of movement-based theory of mind, which may be due to the ages of the groups being studied (i.e., older adults) or the theory of mind component indexed (i.e., movement-based as opposed to cognitive). Turning to the biological basis of group differences in movement, this thesis evidenced a role of dopamine in speed, speed modulation and speed meta-modulation. Use of a proxy measure of baseline striatal dopamine synthesis capacity indicated that these variables had inverted-U-shaped relationships with dopamine levels. These results imply that dopaminergic mechanisms govern kinematic features that are distinct between ASD and PD, in addition to those that appear similar between groups. Results across the three Chapters are consistent with hyper-dopaminergic functioning in ASD and hypo-dopaminergic functioning in PD. This work paves the way for future neuroscientific investigations of dopaminergic mechanisms underlying movement differences in ASD and PD, to verify neural activity and brain loci associated with such differences.

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Appendix 1 – Supplementary Materials for Chapter 2

Table A1

Ethnicity Information for the Autism, Parkinson's Disease and Control Groups Recruited in Chapter 2

	ASD	PD	CTRL	Total
Ashkanazi Jewish	1	0	0	1
Asian Pakistani	0	0	5	5
White & Pakistani	0	0	1	1
White American	0	1	0	1
White British	27	30	26	83
White European	3	0	0	3
White Irish	0	1	0	1
White Other	0	1	0	1

Note. Table contains count data for each cell. ASD = Autism Spectrum Disorder; PD = Parkinson's Disease; CTRL = Control.

Appendix 2 – Supplementary Materials for Chapter 3

Table A2

Ethnicity Information for the Autism, Parkinson's Disease and Control Groups Recruited in Chapter 3

	ASD	PD	CTRL	Total
Asian Pakistani	0	0	4	4
White & Pakistani	0	0	1	1
White American	0	1	0	1
White British	28	29	26	83
White European	3	0	0	3
White Irish	0	1	0	1
White Other	0	1	0	1

Note. Table contains count data for each cell. ASD = Autism Spectrum Disorder; PD = Parkinson's Disease; CTRL = Control.

Appendix 3 – Supplementary Materials for Chapter 4

Appendix 3.1 – Ethnicity Information for Study 1 in Chapter 4

Table A3.1

Ethnicity Information for Study 1 in Chapter 4

	Study One (PD)
White American	1
White British	29
White Irish	1
White Other	1

Note. Table contains count data for each cell. PD = Parkinson's Disease.

Appendix 3.2 – Types of Medications Taken by Participants in Study 1 in Chapter 4

Table A3.2

Types of Medications Taken by Participants in Study 1 in Chapter 4

	N
Combined Totals	
Levodopa	23
Dopamine Agonists	16
MAO Inhibitors	10
Those Taking Only One Type of Medication	
Levodopa	9
Dopamine Agonists	5
MAO Inhibitors	2
Those Taking Two Types of Medications	
Levodopa & Dopamine Agonists	11
Levodopa & MAO Inhibitors	2
Dopamine Agonists & MAO Inhibitors	1
Those Taking Three Types of Medications	
Levodopa, Dopamine Agonists & MAO Inhibitors	2

Note. Combined totals refer to how many participants were taking each type of medication regardless of the other medications being taken. Subsequent rows break down participants into those taking only one type of medication, two types of medication, or all three types of medication. MAO = Monoamine oxidase.

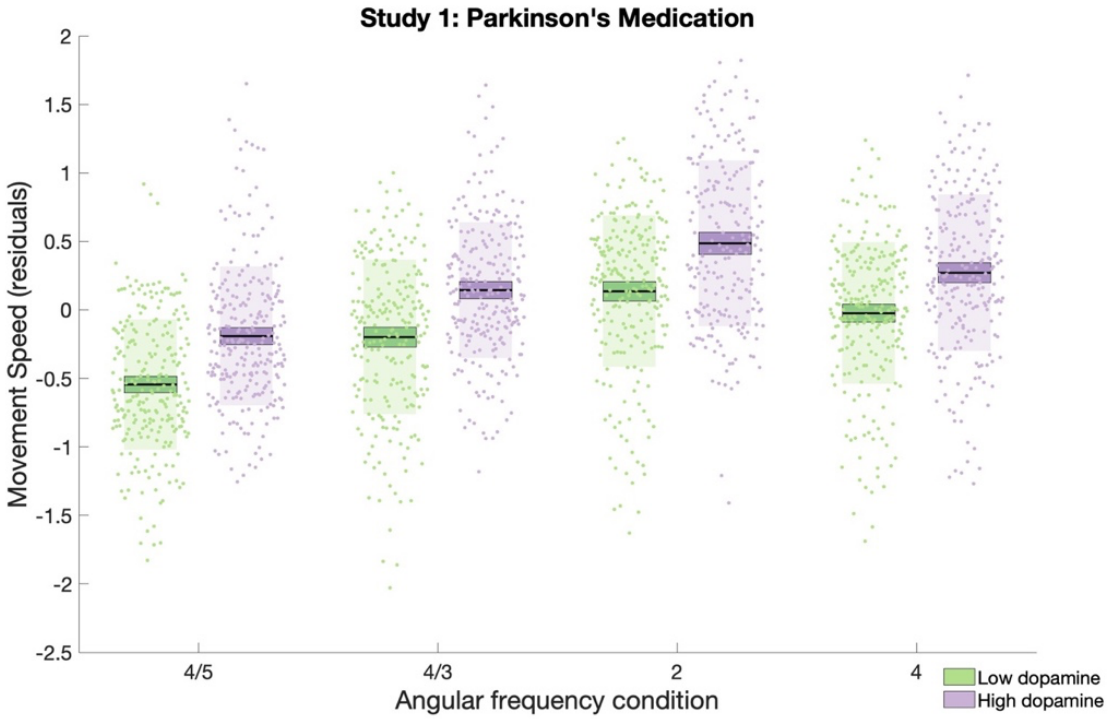
Appendix 3.3 Additional Analyses on Movement Speed in Study 1

A3.3.1 Additional Mixed Model Details

To explore the main effect of shape on movement speed, post-hoc tests were conducted on subsets of the data to compare two levels of shape. These tests revealed that the overall main effect of shape reflected lower movement speeds for lower angular frequency shapes (see Figure A3.3.1). Shape 4/5 was traced with the slowest movement speed, followed by shape 4/3 (main effect of shape between shapes 4/5 and 4/3: $F(1, 963) = 127.95$, $p < .001$), followed by shape 4 (main effect of shape between shapes 4/3 and 4: $F(1, 941) = 18.50$, $p < .001$), with shape 2 traced with the highest speed (main effect of shape between shapes 4 and 2: $F(1, 921) = 28.91$, $p < .001$). The interaction between drug state and shape was non-significant ($F(3, 1885) = 0.29$, $p = .832$) as was the interaction between drug state and dosage ($F(1, 1885) = 0.15$, $p = .699$).

Figure A3.3.1

A Graph Depicting Drug Effects on Movement Speed in Study 1



Note. Movement speed residuals plotted for low (green; Parkinson's Disease OFF-medication) and high (purple; Parkinson's Disease ON-medication) dopamine conditions for each angular frequency-defined shape. Residuals were calculated after controlling for dosage, trial, participant number and day. Bars = mean, box = SE, shaded region = standard deviation, trial-level values plotted.

A3.3.2 Analysis on All Data

Analyses reported in the main text (which were conducted on a dataset in which all participants had valid trials for at least the shapes with the highest and lowest angular frequency values) were repeated for a dataset containing all data, following the removal of outliers and a log transform. Importantly our core finding – a main effect of drug state – was observed ($F(1, 1905) = 71.79$, $p < .001$), with lower movement speeds observed OFF medication (beta estimate = -0.172, 95% CI [-0.212, -0.132]). As in our primary analysis reported in the main text, a main effect of shape was observed ($F(3, 1905) = 137.96$, $p <$

.001), with no drug by shape interaction ($F(3, 1905) = 0.33$, $p = .804$) or drug by dosage interaction ($F(1, 1905) = 0.09$, $p = .762$).

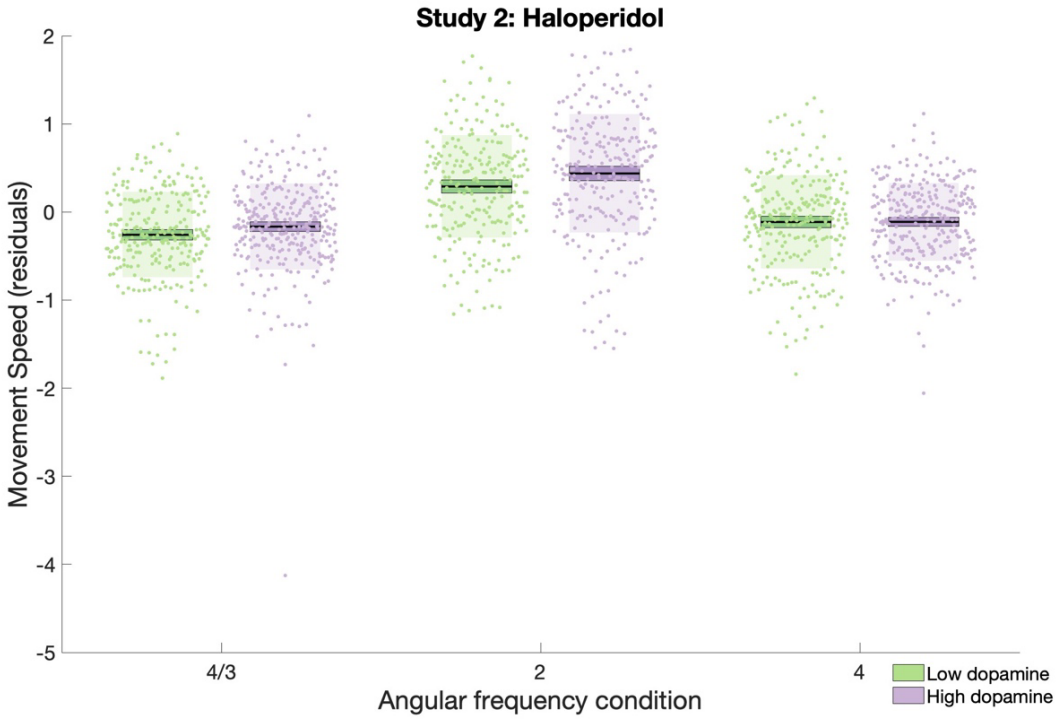
Appendix 3.4 Additional Analyses on Movement Speed in Study 2

A3.4.1 Additional Mixed Model Details

The main effect of shape on movement speed reflected lower movement speeds for lower angular frequency shapes (see Figure A3.4.1). As revealed by post-hoc tests assessing the main effect of shape between two levels of the condition, shape 4/3 was traced with the slowest movement speed, followed by shape 4 (main effect of shape between shapes 4/3 and 4: $F(1, 1111) = 15.03$, $p < .001$), with shape 2 traced with the highest speed (main effect of shape between shapes 4 and 2: $F(1, 1039) = 217.10$, $p < .001$). The interaction between drug state and shape was non-significant ($F(2, 1600) = 2.79$, $p = .062$).

Figure A3.4.1

A Graph Depicting Drug Effects on Movement Speed in Study 2



Note. Movement speed residuals plotted for low (green; haloperidol) and high (purple; placebo) dopamine conditions for each angular frequency-defined shape. Residuals were calculated after controlling for estimated striatal dopamine synthesis capacity, trial, participant number and day. Bars = mean, box = SE, shaded region = standard deviation, trial-level values plotted.

A3.4.2 Standard Model (not including estimated baseline striatal synthesis capacity)

A LMM including drug state and shape as fixed effects (but not estimated baseline striatal synthesis capacity) revealed a significant main effect of drug state ($F(1, 1700) = 10.34$, $p = .001$), with lower movement speed values in the haloperidol condition compared to the placebo condition (beta estimate: -0.049, 95% CI [-0.079, -0.019]). As in our primary analysis, we observed a significant main effect of shape ($F(2, 1700) = 157.20$, $p < .001$). Unpacking this further with post-hoc tests revealed that, as in the model above, shape 4/3 was traced with the slowest movement speed, followed by shape 4 (main effect of shape between

shapes 4/3 and 4: $F(1, 1177) = 9.96$, $p = .002$), followed by shape 2 (main effect of shape between shapes 4 and 2: $F(1, 1105) = 216.97$, $p < .001$). In addition, we observed an interaction between drug state and shape ($F(2,1700) = 4.20$, $p = .015$) in which the strongest drug effect was observed for shape 2 ($F(1, 523) = 6.04$, $p = .014$, beta estimate = -0.072, 95% CI [-0.129, -0.014]), followed by shape 4/3 ($F(1, 595) = 6.53$, $p = .011$, beta estimate = -0.050, 95% CI [-0.089, -0.012]), followed by shape 4 ($F(1, 582) = 1.57$, $p = .211$, beta estimate = -0.025, 95% CI [-0.064, 0.014]). As such, we again present no evidence that shapes typically traced at higher speeds are disproportionately affected by the drug (as shape 4/3 was traced the slowest but had the second largest drug effect).

A3.4.3 Analysis on All Data

Analysis reported in main text was repeated for a dataset containing all data, following the removal of outliers and a log transform. An LMM including drug state, shape and estimated baseline striatal synthesis capacity as fixed effects revealed a significant main effect of drug state ($F(1, 1673) = 46.73$, $p < .001$) with lower movement speed values in the haloperidol condition compared to the placebo condition (beta estimate: -1.086, 95% CI [-1.398, -0.775]). Again, a main effect of shape ($F(2, 1673) = 153.39$, $p < .001$) was identified, which reflected a pattern whereby shape 4/3 was traced the slowest, followed by shape 4 (main effect of shape between shapes 4/3 and 4: $F(1, 1163) = 12.89$, $p <.001$), followed by shape 2 (main effect of shape between shapes 4 and 2: $F(1, 1085) = 176.04$, $p < .001$). We also observed an interaction between drug state and shape ($F(2, 1673) = 3.30$, $p = .037$), whereby the largest drug effect was observed for shape 4/3 ($F(1, 586) = 52.56$, $p < .001$, beta estimate = -1.532, 95% CI [-1.946, -1.117]), followed by shape 4 ($F(1, 575) = 20.05$, $p < .001$, beta estimate = -0.941, 95% CI [-1.353, -0.528]), followed by shape 2 ($F(1, 508) = 6.73$, $p = .010$, beta estimate = -0.842, 95% CI [-1.480, -0.205]). Again, this pattern did not provide

evidence that shapes traced at higher speeds are disproportionately affected by the drug. The overall main effect of drug state was moderated by estimated striatal dopamine synthesis capacity ($F(1,1673) = 43.21$, $p < .001$), and again a negative linear relationship was found between drug effect and estimated striatal dopamine synthesis capacity which cut the x-axis ($F(1, 29) = 4.68$, $p = .039$; beta estimate = -0.051, 95% CI [-0.100, -0.003]). Thus, with the full dataset the pattern of results is the same as in our primary analysis but with the addition of a significant interaction between drug state and shape.

An LMM including drug state and shape as fixed effects (but not estimated baseline striatal synthesis capacity) revealed a significant main effect of drug state ($F(1, 1773) = 11.05$, $p = .001$), with lower movement speed values in the haloperidol condition compared to the placebo condition (beta estimate: -0.048, 95% CI [-0.076, -0.020]). We observed a significant main effect of shape ($F(2, 1773) = 137.50$, $p < .001$), with shape 4/3 traced the slowest, followed by shape 4 (main effect of shape between shapes 4/3 and 4: $F(1, 1229) = 8.18$, $p = .004$), followed by shape 2 (main effect of shape between shapes 4 and 2: $F(1, 1151) = 176.97$, $p < .001$). The interaction between drug state and shape was also significant ($F(2,1773) = 3.88$, $p = .021$), with the strongest drug effect of shape 2 ($F(1, 544) = 3.52$, $p = .061$, beta estimate = -0.055, 95% CI [-0.112, 0.003]), followed by shape 4/3 ($F(1, 622) = 7.70$, $p = .006$, beta estimate = -0.052, 95% CI [-0.088, -0.015]), followed by shape 4 ($F(1, 607) = 0.47$, $p = .493$, beta estimate = -0.013, 95% CI [-0.050, 0.024]). This pattern of results, again, does not indicate that shapes traced at faster speeds are disproportionally affected by the drug.

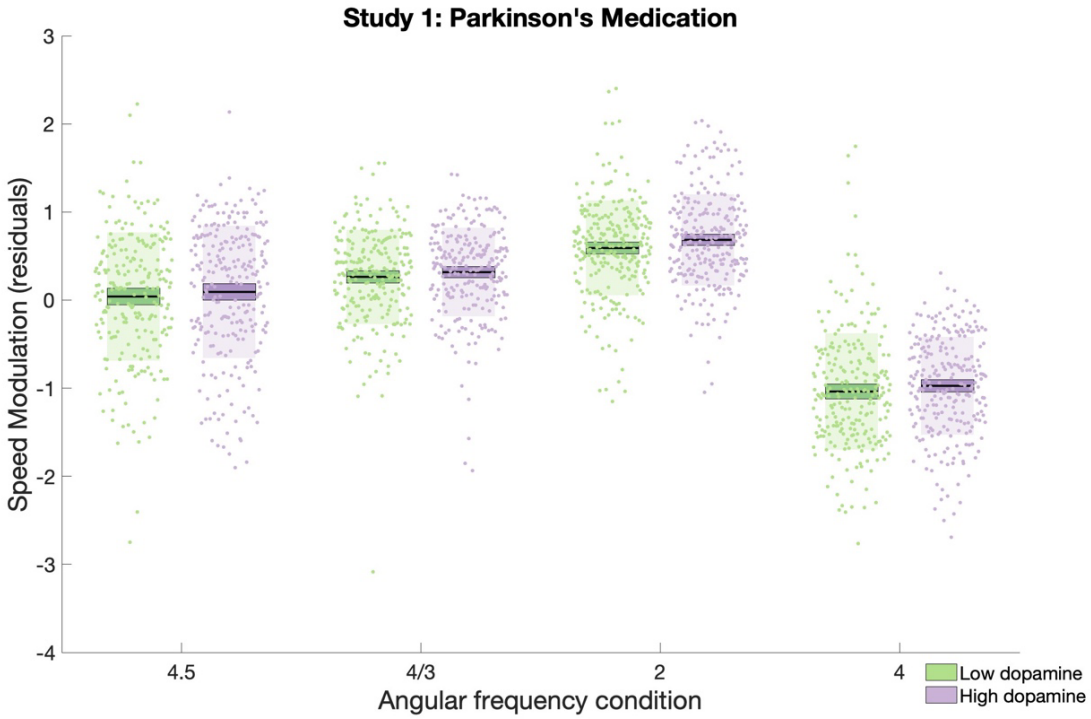
Appendix 3.5 Additional Analyses on Speed Modulation in Study 1

A3.5.1 Additional Mixed Model Details

Post-hoc tests were conducted on subsets of the data to explore the main effect of shape on speed modulation, whereby the main effect of shape for pairs of the shape condition were assessed. These analyses revealed that the main effect of shape on speed modulation ($F(3, 1906) = 676.08$, $p < .001$; see Figure A3.5.1) reflected a pattern in which shape 4 was traced with the lowest speed modulation values and shape 2 was traced with the highest, with shape 4/3 falling below shape 2 (main effect of shape between shapes 4/3 and 2: $F(1, 951) = 115.36$, $p < .001$), followed by shape 4/5 (main effect of shape between shapes 4/5 and 4/3: $F(1, 933) = 39.31$, $p < .001$; main effect of shape between shapes 4/5 and 4: $F(1, 954) = 695.78$, $p < .001$). The interaction between drug state and dosage was non-significant ($F(1, 1906) = 2.89$, $p = .089$).

Figure A3.5.1

A Graph Depicting Drug Effects on Speed-Modulation in Study 1



Note. Speed-modulation residuals plotted for low (green; Parkinson's Disease OFF-medication) and high (purple; Parkinson's Disease ON) dopamine conditions for each angular frequency-defined shape. Residuals were calculated after controlling for dosage, trial, participant number and day. Bars = mean, box = SE, shaded region = standard deviation, trial-level values plotted.

A3.5.2 Analysis on All Data

Analysis reported in the main text was repeated for a dataset containing all data, following the removal of outliers and a log transform. As in our primary analysis, a main effect of drug state was observed ($F(1, 1925) = 7.18$, $p = .007$), with lower speed modulation values observed OFF medication (beta estimate = -0.062, 95% CI [-0.107, -0.017]). Again, a main effect of shape was observed ($F(3, 1925) = 672.14$, $p < .001$), and no drug by dosage interaction ($F(1, 1925) = 2.67$, $p = .102$).

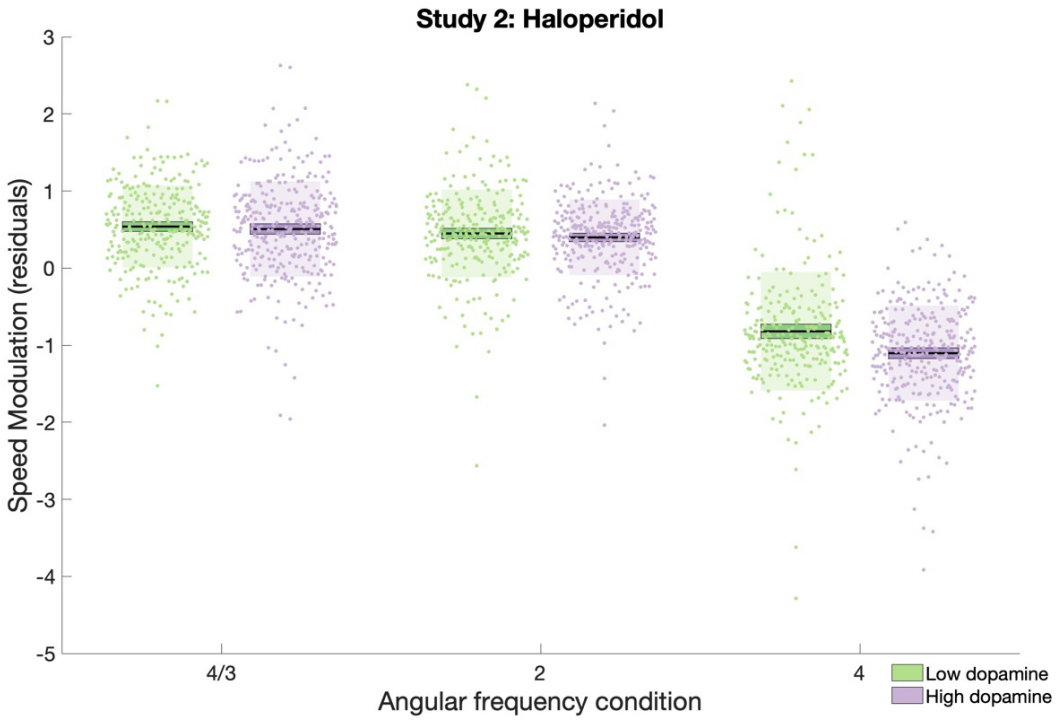
Appendix 3.6 Additional Analyses on Speed Modulation in Study 2

A3.6.1 Additional Mixed Model Details

As indicated by post-hoc analyses on subsets of the data, the main effect of shape on speed modulation ($F(2, 1642) = 1092.40$, $p < .001$; see Figure A3.6.1) reflected a pattern in which shape 4 was traced with the lowest speed modulation values and shape 4/3 was traced with the highest, with shape 2 falling between shapes 4/3 and 4 (main effect of shape between shapes 4/3 and 2: $F(1, 1106) = 8.32$, $p = .004$; main effect of shape between shapes 2 and 4: $F(1, 1085) = 1540.70$, $p < .001$).

Figure A3.6.1

A Graph Depicting Drug Effects on Speed-Modulation in Study 2



Note. Speed-modulation residuals plotted for low (green; haloperidol) and high (purple; placebo) dopamine conditions for each angular frequency-defined shape. Residuals were calculated after controlling for estimated striatal dopamine synthesis capacity, trial, participant number and day. Bars = mean, box = SE, shaded region = standard deviation, trial-level values plotted.

A3.6.2 Standard Model (not including estimated baseline striatal synthesis capacity)

A LMM including drug state and shape as fixed effects revealed a significant main effect of drug state ($F(1, 1730) = 29.85$, $p < .001$; beta estimate = 0.092, 95% CI [0.059, 0.125]). Again, a main effect of shape was observed ($F(2, 1730) = 1036.60$, $p < .001$).

A3.6.3 Analysis on All Data

Analysis reported in the main text was repeated for a dataset containing all data, following the removal of outliers and a log transform. An LMM including drug state, shape and estimated baseline striatal synthesis capacity as fixed effects revealed a significant main effect of drug state ($F(1, 1719) = 48.10$, $p < .001$) with lower speed modulation values in the haloperidol condition compared to the placebo condition (beta estimate: -1.181, 95% CI [-1.516, -0.847]). Again, a main effect of shape ($F(2, 1719) = 1127.40$, $p < .001$) was identified. The main effect of drug state was moderated by estimated striatal dopamine synthesis capacity ($F(1,1719) = 54.82$, $p <.001$), and again a negative linear relationship was found between drug effect and estimated striatal dopamine synthesis capacity which cut the x-axis ($F(1, 29) = 7.41$, $p = .011$; beta estimate = -0.062, 95% CI [-0.109, -0.016]). Thus, this analysis on the full dataset revealed the same pattern of results as in our primary analysis.

An LMM including drug state and shape as fixed effects revealed a significant main effect of drug state ($F(1, 1807) = 18.81$, $p < .001$; beta estimate = 0.069, 95% CI [0.038, 0.100]). Again, a main effect of shape was observed ($F(2, 1807) = 1065.80$, $p < .001$).

Appendix 3.7 Additional Analyses on Speed Meta-Modulation in Study 1

A3.7.1 Additional Mixed Model Details

No main effect of drug state was observed ($F(1, 57) = 0.49$, $p = .485$), nor an interaction between drug state and dosage ($F(1, 57) = 1.04$, $p = .313$). This lack of drug effect

on speed meta-modulation is supported by the lack of a drug state by shape interaction in the speed-modulation LMM for Study 1 ($F(3, 1906) = 0.30$, $p = .824$).

Appendix 3.8 Additional Analyses on Speed Meta-Modulation in Study 2

A3.8.1 Standard Model (not including estimated baseline striatal synthesis capacity)

When analysing the data without including estimated baseline striatal synthesis capacity as a predictor, the main effect of drug state on speed-meta-modulation remained. We again observed that haloperidol reduced the meta-modulation of speed ($F(1,59) = 7.93$, $p = .007$; beta estimate = 0.008 95% CI [0.002, 0.013]), with shallower meta-modulation gradients under haloperidol.