Research Plan – Elucidating the genetic underpinnings of the increased prevalence of Parkinson's Disease diagnosis in the autistic population.

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Background

Overarching Theory

Recent reports suggest an **increased prevalence** of **Parkinson's Disease** (PD) in **the autistic population** (ASD)[1].

This raises two interesting possibilities:

1. It may be that **autistic individuals** have a **higher genetic risk** of developing **Parkinson's**.
2. It is also possible that **behavioural similarities** between the two conditions mean that **autistic individuals** are **more likely** to reach the threshold of Parkinson's **diagnostic criteria**, even if they do not exhibit parkinsonian biological markers*

* Parkinson's **assessments** primarily relate to **motor function** and **similarities** between **autistic** and **parkinsonian movement** have been noted.

Genetic similarities

- A number of **PD risk genes** have also been **associated** with **ASD**: PARK2[2], PINK1[3], LRRK2[4].
- This insight overlooks the observation 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 establish the amount of shared genetic risk between ASD and PD.

Using GWAS data and **individual-level** genetic data, **polygenic risk scores** (PRS) can be calculated[5]:

- A single value estimate of an individual's **propensity** to a **phenotype**.
- 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.

Behavioural similarities

What do we know about movement in ASD and PD?

Similarities have been highlighted between ASD and PD movement[6]

- **Increased** *jerk* and *sub-movements* in both ASD[7, 8] and PD[9, 10]
- *Velocity* and *acceleration* – **increased** in ASD[7]**, decreased** in PD[9, 11]

What do we know about theory of mind in ASD and PD?

- Both ASD and PD show differences in mental state attribution[12, 13]

How do movements relate to theory of mind?

- **Movement kinematic similarity** between a participant and the observed individual translates to **more appropriate mental state attribution**[12]

Aims

1. Provide crucial early insight into whether the **increased prevalence** of Parkinson's diagnosis in the autistic population is attributable to **increased genetic risk**.
2. Elucidate the **genetic basis** of the **social** and **motor overlap** observed between autism and Parkinson's.

Methods

5000 individuals from the general population

Trait Measures

- ***Autistic traits*** - Autism Quotient
- ***Parkinsonian traits*** - section 2 of the Unified Parkinson's Disease Rating Scale (Part II: Motor Aspects of Experiences of Daily Living)
- ***Alexithymic traits*** - Toronto Alexithymia Scale
- ***Non-verbal reasoning*** - the Matrix Reasoning Item bank

Genetics Data

GWAS Data

ASD GWAS[14]	**PD GWAS**[15]	**Comparison GWAS**
Generated from 18,381 cases and 27,969 controls.	Generated from 37,688 cases, 18,618 UK proxy-cases who have a first degree relative with PD, and 1,417,791 controls.	ADHD[16]; Dementia with Lewy bodies (DLB)[17]; Tourette Syndrome[18]

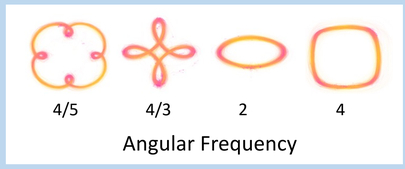
Individual-Level Data

- **Polygenic Risk Scores** will be calculated for each individual for **ASD** and **PD**.

Experimental Tasks

1. Shapes Tracing Task

- Participants will **trace shapes** on a **touchscreen device**
  - 4 blocks of 12 trials (Each block = different angular frequency shape)
  - **Movement kinematics** extracted: velocity, acceleration, jerk, sub-movements, speed-curvature gradients

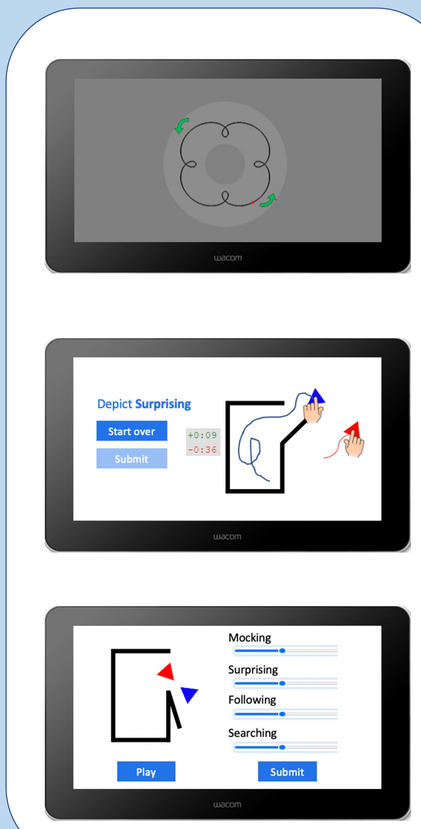


2. 'Create' Animation Task

- Participants will **create animations** for the words: mocking, surprising, following and searching
  - **Movement kinematics** extracted: velocity, acceleration, jerk, sub-movements

3. 'Narrate' Animation Task

- Participants will **rate** the extent to which **animations** depict the words: mocking, surprising, following and searching
  - 32 trials (8 per word)
  - Accuracy - calculated by **subtracting** the **mean rating** for all **non-target words** from the **rating** for the **target word**



Analysis

Genome-Wide Investigation

We will employ the **cross-trait Linkage Disequilibrium Score Regression** technique[16] to obtain a genetic correlation between ASD and PD:

- The technique accounts for linkage disequilibrium, the non-random association of variants at different positions of the genome.

Hypotheses:

→ A **small** but **significant** genetic correlation between ASD and PD
→ ASD will exhibit its strongest relationship with ADHD
→ PD will exhibit its strongest relationship with DLB

Further analyses

- Investigate **Gene Ontology** terms to identify biological processes associated with the overlap

- Employ **MAGMA** analysis to investigate biological pathways associated with the overlap

Individual-Level Investigation

Calculating PRS will allow us to assess the relationship between:

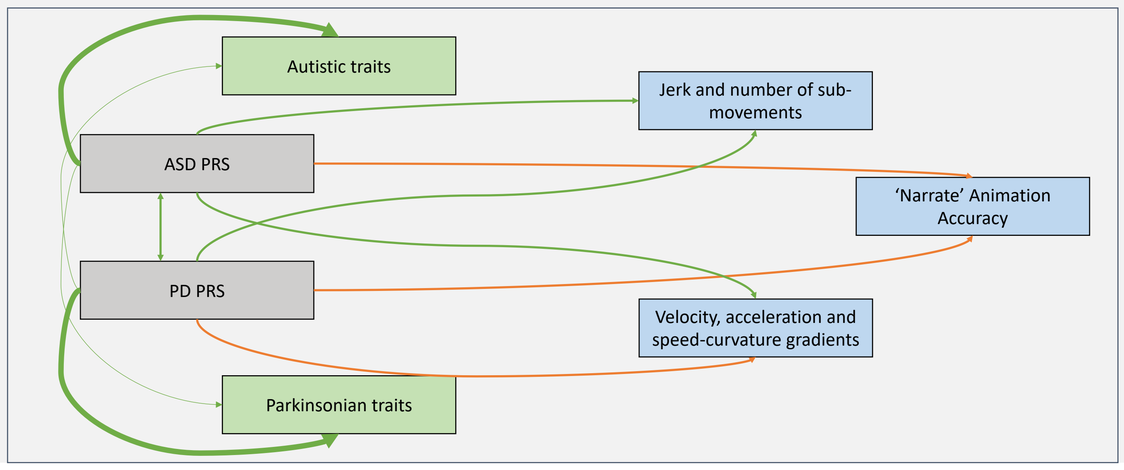
1. **ASD** and **PD PRS** within the **same individuals**
2. **ASD/PD PRS** and performance on **tasks** of motor function and social cognition

Regression analyses will be employed to assess the relative predictive strengths of autism and Parkinson's genetic profiles to the above measures of motor function, social cognition, and traits.

Hypotheses:

Positive prediction

Negative prediction



Limitations

- The **remit** of this study only extends as far as **SNPs**.
- Other genetic differences including rare genetic **de novo mutations** may contribute to shared risk for ASD and PD.
- The findings of this study are limited to genetic correlations with regards to a specific type of genetic variation, thus **a null result will not be sufficient** for concluding that ASD and PD are **not** genetically linked.

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