

# Cognitive Impairment in Parkinson's Disease

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#### Parkinson's disease and dopamine

- Neurodegenerative disease characterised by loss of dopamine neurons in the substantia nigra
- Typically defined as a motor disorder, with motor symptoms including tremor, rigidity, gait and balance problems, and bradykinesia (slowed movement)



Substantia nigra



Diminished substantia nigra as seen in Parkinson's disease





# Cognitive impairment

- Roughly 25% of newly diagnosed PD patients have some degree of cognitive impairment (prior to initiation of drug therapy)<sup>1</sup>
  - Studies show a point prevalence of mild cognitive impairment ranging from 20-65%<sup>2</sup>
- Within 20 years of diagnosis, approximately 80% will have developed Parkinson's disease dementia (PDD)<sup>3</sup>



Our research aims to better characterise the profile(s) of cognitive impairment in Parkinson's.

# Dopamine and decision-making

- Generally, when choosing between possible actions, we think about the expected outcome of each possible action, with the goal of maximising gains and minimising losses
- How do we determine the expected outcome associated with each alternative? Often, we rely on our knowledge of **past experience**
- Whether a certain choice was followed by good or bad consequences when chosen previously will influence our likelihood of repeating that choice in similar situations
- How do we encode information about whether our past actions were followed by good or bad consequences?



# Dopamine and decision-making

- Dopamine helps us encode rewarding and punishing stimuli in our environment
- Our capacity to encode **rewards** is facilitated by dopamine **bursts**
- Our capacity to encode **punishments** is facilitated by dopamine **dips**



#### **Unmedicated Parkinson's**

- Reduced dopamine availability in unmedicated Parkinson's results in:
  - *Smaller* dopamine bursts in response to rewards, *reducing* sensitivity to rewarding stimuli in the environment
  - *Larger* dopamine dips in response to punishments, *increasing* sensitivity to punishing stimuli in the environment
- Highlights that cognitive changes in Parkinson's aren't necessarily all 'deficits' – some areas of cognition can be 'enhanced'
  - Although this enhanced sensitivity to punishments might not be a good thing – could contribute to depression and anxiety in Parkinson's (observed in ~30% of patients)



# Medicated Parkinson's

- Typical drug treatments for Parkinson's include dopamine agonists, which increase dopamine availability in the brain, resulting in the opposite pattern, namely:
  - Larger dopamine bursts in response to rewards, increasing sensitivity to rewarding stimuli in the environment
  - *Smaller* dopamine dips in response to punishments, *reducing* sensitivity to punishing stimuli in the environment
- This 'enhanced' sensitivity to reward might not be a good thing being particularly sensitive to rewards – especially alongside reduced sensitivity to punishment – might contribute to impulsivity and impulse control disorders (observed in ~20-25% of patients)



The relationship between motor and cognitive function

#### Motor symptoms

- Parkinson's disease is typically described as a motor disorder
- Parkinson's is a highly heterogenous disease, resulting in diverse motor symptom profiles





# Motor subtypes

 Parkinson's patients are often assigned to one of three motor subtypes

> Tremor-Dominant

Akinetic-Rigid (PIGD) Mixed/ Indeterminate



# Motor subtype and cognitive impairment

- In one study, 42 out of 128 undemented Parkinson's patients were found to have dementia at 4 years follow-up – of these, 41 were classified as belonging to the PIGD subtype at the time of their dementia diagnosis<sup>1</sup>
- In another study, patients with mild cognitive impairment scored higher on a measure of PIGD symptoms compared to those without mild cognitive impairment<sup>2</sup>



#### Motor subtype and cognitive impairment

- It seems that Parkinson's patients belonging to the PIGD subtype are more likely to experience mild cognitive impairment and dementia
- If this is the case, we could use information collected from a patient's motor assessments to make inferences about the likelihood of mild cognitive impairment and dementia
  - For time-poor clinicians, this could be leveraged as a decision aid to help determine whether conducting comprehensive cognitive assessments is an appropriate use of time



# Our research

- We've developed a comprehensive cognitive test battery for iPad that assesses several areas of cognition (learning, memory, attention)
- Our cognitive battery will be administered alongside a series of psychiatric measures (anxiety, depression, impulsivity), an objective motor assessment battery, and genetic testing
  - This will allow us to look at the relationship between cognitive function and motor symptoms, as well as other individual differences
- Roughly 300 patients will be tested ON and OFF medication
  - This will help us to get a better idea of which changes are medication-induced
  - We will also be able to look at fluctuations in cognitive, psychiatric, and motor symptoms



# (Some) research questions

- Which assessments are best suited to identifying cognitive impairment in PD?
  - Which are best at predicting conversion to Parkinson's disease dementia?
- Are there different cognitive subtypes in PD? If so, which assessments are best at distinguishing between cognitive subtypes?
  - If so, do different cognitive subtypes have different risk and/or rate of conversion to Parkinson's disease dementia?
- Is there a relationship between cognitive subtype and motor subtype?
  - If so, in what ways might we use motor assessment tools to make predictions about an individual's current and future cognitive impairment (and vice versa)?



#### **Potential implications**

- Provide a basis to developing a comprehensive but succinct cognitive test battery that:
  - Only comprises those tasks shown to be sensitive to cognitive changes in PD
  - Is available to clinicians and researchers alike as an app, with the ability to monitor individuals' progress over time and compare scores against appropriate normative data
- Provide a basis to developing an objective, low-cost motor assessment battery that can be integrated with the cognitive testing app



#### **Potential implications**

- Developing a taxonomy of motor and cognitive subtypes (or integrated subtypes) that can be used in research and practice
  - Using subtypes to inform diagnosis, individualised treatment, and prognosis
  - Using subtypes to account for otherwise unaccounted variance in treatment response in clinical trials
  - Evaluating treatment (or prevention) programs tailored to each subtype (e.g., cognitive rehabilitation programs)



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