PROTOCOL

Title page

Full/long title of the project

Dynamics of motivated decision-making in striatal disorders

Short title/acronym

N/A

Protocol version number and date

Protocol version number:	1.1
Protocol version date:	04/01/2024

Research reference numbers

IRAS number:	336513
Sponsor/RG number:	RG_23-163
REC reference number:	ERN_1761-Oct2023
Public registry number:	
Funder number:	

Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the CI agrees to adhere to the signed University of Birmingham's sponsorship CI declaration.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the project will be given; and that any discrepancies from the project as planned in this protocol will be explained.

Full project title:	Dynamics of motivated decision-making in striatal disorders
Protocol version number:	1.1
Protocol version date:	04/01/2024

Chief Investigator (CI)	
Name:	Matthew Broome
Date:	08/01/2024
Signature:	

Sponsor statement

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

Table of contents

Key contacts

Role/function	Contact details
Chief Investigator, secondary supervisor	Prof Matthew Broome, m.r.broome@bham.ac.uk
Primary supervisor	Dr Matthew Apps, m.a.j.apps@bham.ac.uk
PhD candidate	Dr Jamie Talbot, jxt289@student.bham.ac.uk

Project summary

Objectives:

The main objective of the research is to examine decision-making in two clinical groups; those with early psychosis (clinical high risk or first episode) and those with Parkinson's disease, to see whether apathy scores or individual descriptions of motivation symptoms correlate with specific patterns of decision-making.

Background:

Motivation problems (apathy) are common in both Parkinson's disease and psychotic disorders, such as schizophrenia (here typically referred to as negative symptoms). Both disorders are underpinned by abnormalities in dopamine signalling and medications targeting dopamine are routinely prescribed in both disorders. Although representing divergent disorders - Parkinson's disease tends to affect older individuals and predominantly causes movement problems, whereas psychosis typically presents in young adulthood and causes issues with thought and perception - impairments of motivation are common in both conditions. Much recent research has shed light on the cognitive processes and neural pathways underpinning motivated behaviour in health and disease. In both Parkinson's disease and schizophrenia, affected individuals choose to invest less effort in pursuit of goals, which appears to be correlated with negative symptom burden and/or apathy. This research aims to better understand the cognitive processes underlying apathy in individual patients, in particular how self-reported symptoms map onto performance in a decision-making task. The study in particular examines the respective influence of physical effort and monetary reward on decision-making, as well as the impact of having multiple alternatives to choose from in these decisions. A related aim is to observe specific effects of dopamine on decision-making by assessing people with Parkinson's disease in both the medicated and unmedicated state.

Procedure:

The research will aim to recruit 100 people with Parkinson's disease and 100 people with early psychosis, who will perform a novel, computer-based decision-making task incorporating choices that vary in difficulty and the number of alternatives from which to choose, and which either relate to monetary reward or physical effort. Those with Parkinson's disease will be tested in two separate sessions – once in the medicated state (having taken their usual dopaminergic medication), and once after omission of their usual dopaminergic medication. Participants will also complete a number of questionnaires probing symptoms of apathy, depression, fatigue and anhedonia. Primary data will relate to choices (accuracy, reaction time, subjective cognitive effort). Computational modelling (using well-validated evidence-accumulation models) will be fitted to behavioural data, allowing latent processes in decision-making to be examined, and correlated with questionnaire data quantifying motivation in detail. Thus certain apathy scores (or subscores relating to particular 'dimensions' of apathy) may be seen to correlate with computationally-derived parameters reflecting different aspects of decision-making. The study will also incorporate qualitative methodology in a subset of ~10 participants from both clinical groups to explore participants' subjective accounts of motivation problems in order to provide further, detailed information about individual symptoms and experiences.

Funding and support in kind

Funder(s)	Financial and non-financial support given
Wellcome Trust	Funding £15000
University of Birmingham	Sponsor

Role of sponsor and funder

The sponsor and funder have no role in project design, conduct, data analysis and interpretation, manuscript writing, or dissemination of results. Neither the sponsor nor funder controls the final decision regarding any of these aspects of the project.

Roles & responsibilities of management committees/groups & individuals

Patient & public involvement group

The study protocol has been discussed with two members of the public with Parkinson's disease, as well as a public advisor consulting on patient public involvement as part of the Midland Mental Health and Neuroscience Doctoral Training Program. The two people consulted are public representatives associated with Parkinson's UK, who helped facilitate the meetings. The study has been adapted on the basis of their feedback and suggestions. All participants will be invited to participate in further PPI, including providing comments and feedback about the study, future research direction and dissemination of study findings.

Protocol contributors

MB – Chief Investigator, project design and conduct, oversight

MAJA – Supervisor, project design and conduct, data analysis, oversight

JT – PhD candidate, project design and conduct, data collection including clinical interviews, data analysis, manuscript writing, dissemination of results

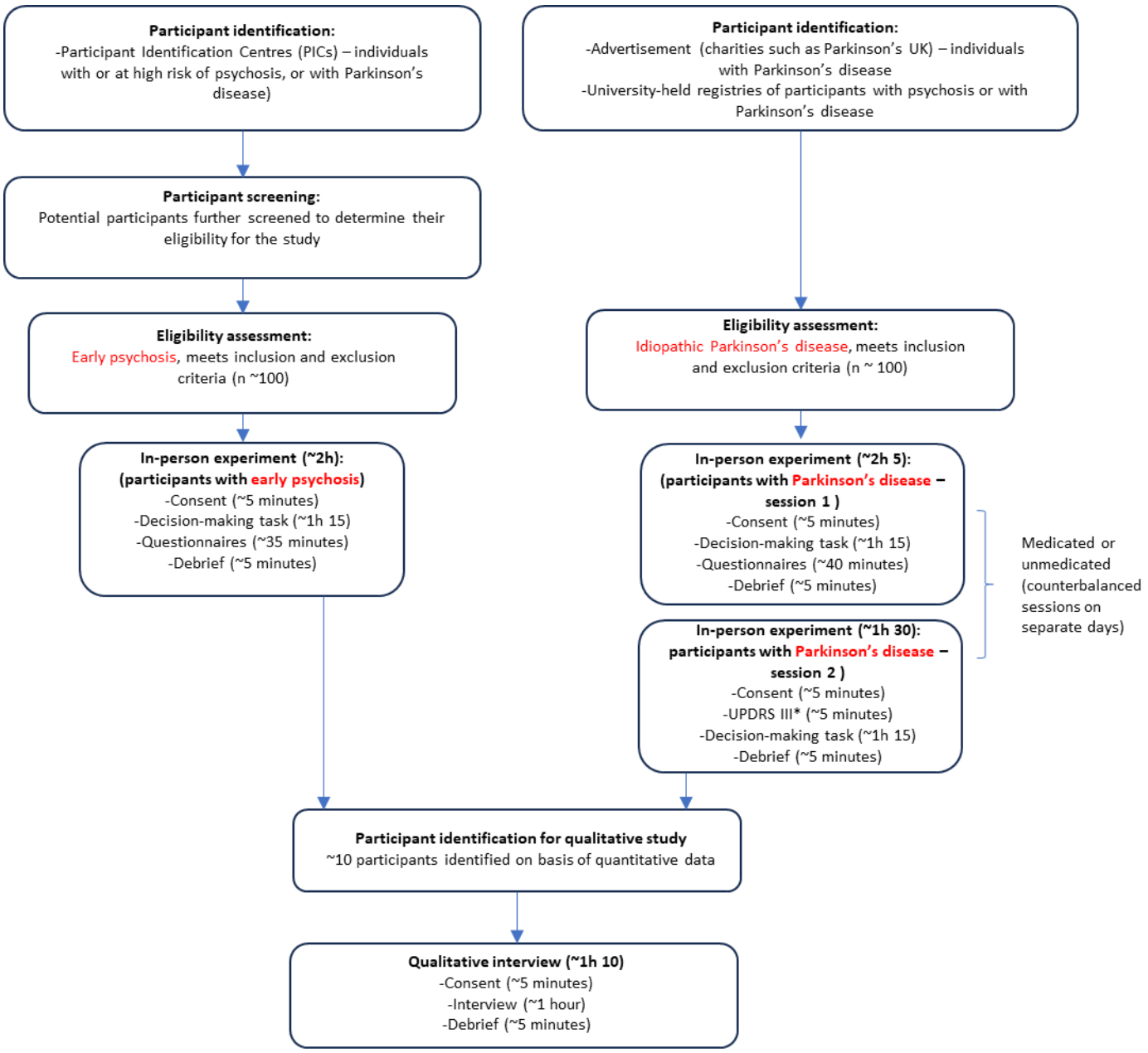
University of Birmingham – research sponsor (no role in project design, conduct, data analysis/interpretation, manuscript writing, or dissemination of results)

Wellcome Trust (Midlands Mental Health and Neuroscience Doctoral Training Program) – funder (no role in project design, conduct, data analysis/interpretation, manuscript writing, or dissemination of results)

Key words

Apathy, motivation, negative symptoms, psychosis, Parkinsons disease

Project flow chart



*UPDRS III refers to part III of Unified Parkinson's Disease Rating Scale (motor exam)

Protocol

Dynamics of motivated decision-making in striatal disorders

1. Background

Motivational impairments/apathy - often synonymous with a reduced willingness to invest effort in pursuit of goals - are seen in a variety of clinical disorders. They are common in Parkinson's disease and constitute part of the spectrum of 'negative symptoms' in schizophrenia/psychosis, a hallmark of these conditions[1]. Although Parkinson's disease and psychosis vary significantly in terms of the neuropathology, epidemiology and clinical features, striatal dysfunction and disturbances of dopamine signalling underpin both disorders and forms the basis of pharmacological treatment. For many years, researchers have postulated that apathy is not one all-encompassing entity, but can be dissociated into different component dimensions, possibly relating to different neurological structures or substrates, although conclusive evidence for this is lacking[2,3].

A popular method of examining motivation involves an experimental paradigm known as effort-based decision-making, in which participants are asked to choose whether or not to invest physical effort in order to obtain an incentive or reward. Aversion to effort is a frequent and normal observation, both in animal and human experiments, in which the objective value of a reward is discounted by the effort costs and subjects opt to forgo physical effort at the expense of reward[4,5]. This discounting can be defined mathematically by employing computational modelling to behavioural data and is seen to exhibit a concave or parabolic shape[6]. Previous studies of effort-based decision-making in both Parkinson's disease and schizophrenia have observed that individuals with these disorders experience greater amounts of effort discounting, which appears to be correlated with negative symptom burden and/or apathy[7,8]. However it remains less well-known how individual's subjective experience of motivation symptoms relates to specific underpinning cognitive processes, such as integration of information about incentives (rewards) and costs such as effort, allocating attention or cognitive resources, or comparing value between different options. The current study would therefore aim to better understand these processes by examining decision-making in two clinical groups in which motivation problems are commonly reported and which are underpinned by dysregulation of dopamine-signalling - people with Parkinson's disease and people with early phase psychosis. The study would specifically investigate how the presence of multiple alternatives can affect decision-making by means of a novel behavioural task where participants either aim to minimise physical effort or maximise a reward – thereby allowing direct comparison between these different choice outcomes. Unlike previous experiments that have largely examined the *willingness* of participants to put in effort for an incentive, this experiment would more be concerned with the *dynamics* of these choices, employing well-established computational methods to better understand latent processes in these choices. In this way it will be possible to determine things like how physical effort influence decisions, potentially correlating with higher response caution observed in those with apathy, or alternatively apathetic individuals may display lower willingness to invest attention or cognitive resources regardless of the outcome.

2. Rationale

Most existing studies of human motivation have employed binary choices – whether or not participants choose to exert a defined level of effort to receive a reward - which does not necessarily reflect real-world decision-making, where decision-making involves an evaluation of more than two options. It has been observed that the presence of distracting alternatives in multi-option decision-making tasks can affect the valuation of available options[9,10], whilst in apathy, sufferers are noted to take longer choosing between options when different alternatives exist[11]. To date, no studies have explored the effect of multiple alternatives on decision-making in people with apathy. The decisions naturally involve greater complexity and more elaborate computations, and therefore, examination of the observable effects associated with these choices (such as accuracy and reaction times) might be able to shed greater light on specific processes impaired in decision-making in individuals with apathy, both in decisions in which one's choices aim to maximise rewarding outcomes, and in effort-based decisions in which choices determine the subsequent

expenditure of physical effort. We hypothesise that people's apathy ratings from validated questionnaires or individual descriptions of apathy symptoms will map onto performance on these tasks, and may be predictive of things such as aversion to physical effort or allocation of cognitive resources/attention, which can be quantified by applying computational modelling to behavioural data using well-validated evidence-accumulation models.

3. Theoretical framework

This study aims to better understand motivation problems in those with Parkinson's disease and early psychosis (clinical high risk/first episode). We know that motivation impairments are common in these conditions, but for most individuals negative symptoms tend to be simplistically grouped into categories of 'diminished expression' and 'motivation and pleasure'. However, in reality the neuroscience of motivation is complex, with much recent research demonstrating that specific areas of the brain are important in different aspects of decision-making, such as preferentially encoding rewards vs costs[12],translating incentives onto a common scale of value[13], controlling and allocating cognitive resources/attention[14], and converting decisions to an appropriate action[15].Despite increased understanding of these processes, we remain unable to correlate someone's individual apathy symptoms with dysfunction at the level of the underlying cognitive processes such as described above.

This study builds on previous experiments using effort- and reward-based decision-making, as well as clinical reports of patients experiencing difficulty in decisions encompassing multiple alternatives. It will examine devaluation of rewards by effort (a hallmark of apathy), whilst also studying effects of multiple alternatives on decision-making. It will also aim to examine specifics effects of dopamine on decision-making, by testing Parkinson's disease patients on and off their usual dopaminergic medication in counterbalanced sessions. Modern computational techniques will be applied to the data to better understand how different parameters affect decision-making in the participants. The research will also aim to examine the subjective experience of apathy in much greater detail than most existing studies, in order to better inform the quantitative analysis.

A proof-of-concept study has already been conducted in healthy adults (under ERN 18-1800E and ERN 20-1897PA). This confirms that the experiment captures expected behaviour (slower and less accurate responding in conjunction with closer-value choices and choices involving more options), with all (n > 60) participants managing to complete the experiment without problems.

4. Research question/aims

Research question: In two clinical disorders underpinned by dopamine dysregulation in which motivation problems are common (Parkinson's disease and those with or at high risk of developing psychosis), does an individual's apathy symptoms predict performance and decision metrics in choices that involve a number of composite processes, including integration of benefits (rewards) and costs (effort), attention and cognitive control, and value comparison in the context of multiple alternative options.

4.1. Objectives

The main objective is to investigate whether different dimensions/subtypes of motivation impairments (apathy) experienced in these conditions - for example cognitive, behavioural, or emotional dimensions of apathy[16] - correlate with performance in tasks which probe different underlying cognitive processes. These include balancing benefits (rewards) and costs (effort), accurately assessing the value of options in decisions encompassing multiple alternatives, and appropriately allocating cognitive resources/control in decisions that vary in terms of choice difficulty. These experiments would extend our current understanding of motivation impairments in these groups of patients and allow us to better characterise the underlying processes affected within individual participants. A secondary objective is to examine the role of dopamine in these same processes, by testing individuals with Parkinson's disease on and off their usual dopaminergic medication in counterbalanced sessions.

4.2. Outcome

Evidence-accumulation (computational) models will be fitted to behavioural data to further understand the dynamics of decision-making. It may be that certain apathy dimensions may correlate with specific computationally-derived parameters – for instance, the behavioural activation dimension may correlate with higher thresholds in effort-based task (greater caution), while the cognitive dimension may correspond to slower drift rates or lower response thresholds. These parameters may show dissociation in effort-avoiding and reward-maximising subtasks.

5. Design and methods of data collection and data analysis

Summary

The design will be a mixed quantitative/qualitative analysis. Quantitative data will be in the form of a computer-based decision-making task and questionnaire measures, primarily of apathy and negative symptoms. Qualitative data will take the form of semi-structured interview in a subset of participants.

Design

Those with or at high risk of psychosis will perform one in-person session, while those with Parkinson's disease will complete two counterbalanced sessions - once having taken their usual dopamine-modulating medication, and once having omitted this medication the same morning. These sessions will take place on separate days within 2 weeks of one another. If participants with Parkinson's disease feel unable to omit their medication, or do not take medication for Parkinson's disease, only a single session will be arranged. Testing will take place in person at the University of Birmingham.

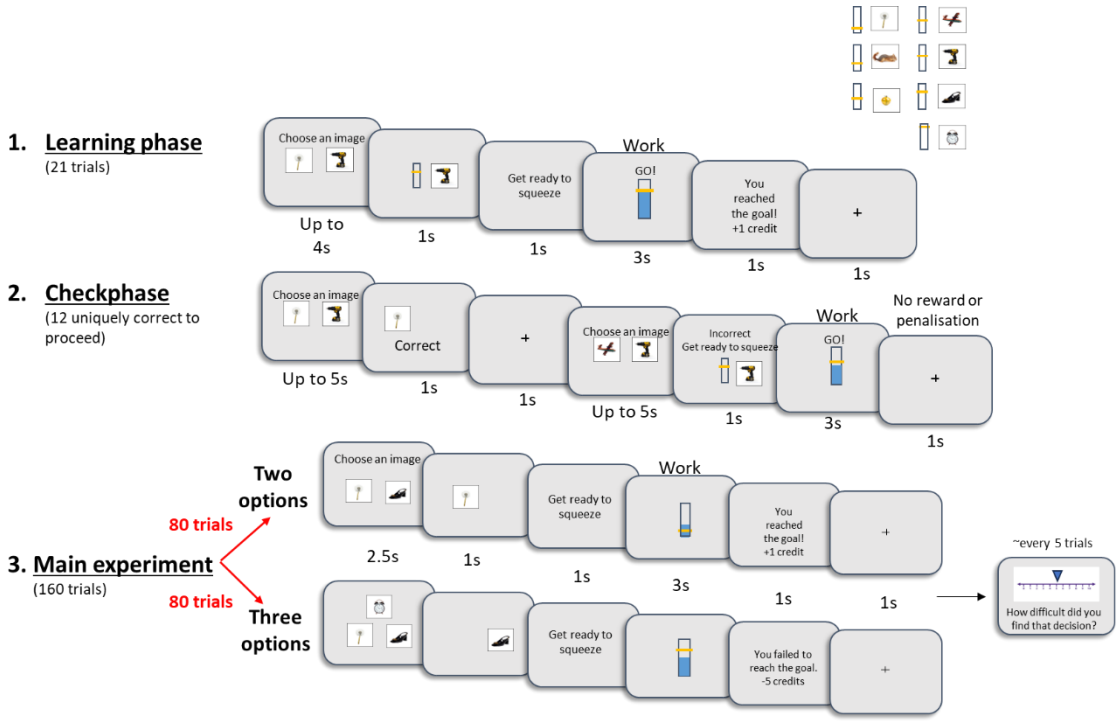
At the point of recruitment, participants will receive a unique identifier. Pseudonymisation will be performed by Dr Jamie Talbot (JT). The database linking personal data to ID numbers will be maintained by JT in a single, password-encrypted Excel file on the University server. All datafiles generated will only refer to participants with their unique ID numbers.

Participants will receive a payment of £25 for participation in a session, plus up to £10 additional payment based on their performance in the task (i.e. up to £35 for a single session).

Behavioural study and questionnaires

(estimated time 1h 30 to 2h 5, depending on clinical group/session number)

- All participants will first receive a brief explanation of the study and provide written consent (~5 minutes).
- Next all participants will complete the computerised decision-making task (~1h 15). In the task, participants will make choices using a computer keyboard, in which the outcome is either physical effort, delivered via a handheld dynamometer (SS25LA, BIOPAC Systems), or a gain or loss of reward credits (that corresponds to an additional bonus payment at the end of the experiment), requiring no physical effort. Reward and effort subsections will be counterbalanced. Data from computer-based tasks (outcomes include reaction times, choice, subjective rating of decision difficulty, force metrics) will be saved as a datafile at the end of the experiment.
- Next participants will complete a set of questionnaires (35 minutes for participants with early psychosis, 40 minutes for people with Parkinson's disease attending their first session; if people with Parkinson's disease are attending for their second session, they will only be required to complete part III of the UPDRS score (a motor exam of ~ 5 minutes duration) and digit span test. Questionnaire data will be collected using the University-approved online survey software Qualtrics or using pen and paper (any paper records will not contain personal information and will be stored in locked filing cabinets within the Centre for Human Brain Health).



The questionnaire battery to be completed by all participants includes:

-Apathy Motivation Index (~3 minutes)

-Dimensional apathy scale (~3 minutes)

-Snaith-Hamilton Pleasure Index (~ 2 minutes)

-Adapted Glasgow Content of Thought Inventory (~2 minutes)

-Patient Health-Questionnaire-8 (~2 minutes)

-Fatigue Severity Scale (~2 minutes)

-Montreal cognitive assessment (~5 minutes)

-Forward and backward digit span test (~2 minutes)

All above questionnaires are validated, with the exception of the Glasgow Content of Thoughts Inventory, which is an abbreviated version of an existing, validated questionnaire for insomnia, which has been repurposed to quantify spontaneous cognitive activity/thought.

In addition to the above questionnaires, people with Parkinson's disease attending their first session will complete the validated semi-structured interview questionnaire:

-Unified Parkinson's disease rating scale (~20 minutes)

In addition to the above questionnaires, people with early psychosis will complete the validated semi-structured interview questionnaire:

-Brief Negative Symptom Scale (BNSS) (~15 minutes)

People with Parkinson's disease attending their second session will not be required to complete the above questionnaires a second time, but will complete part III of the Unified Parkinson's disease rating scale (motor score, duration ~5 minutes) and forward and backwards digit span tests (~2 minutes).

- Participants will receive a brief debrief about the experiment in their final session and will be invited to be included in a Patient Public Involvement Steering group of research participants (~5 minutes).

Qualitative interview (~10 participants)

(estimated time 1h 10)

A subset of ~10 participants (a similar number with Parkinson's disease and psychosis) will later be invited to participate in a semi-structured interview. These participants will be chosen on the basis of their performance in the initial experiment or questionnaire scores. They will be offered a choice to conduct an interview online (Microsoft teams University of Birmingham account) or in person (School of Psychology, University of Birmingham). The interview will be structured according to the Lille Apathy Rating scale (LARS), a validated semi-structured interview for quantifying apathy according to the dimensions of behavioural activation, emotional responsivity, intellectual curiosity and self awareness. Participant responses will be followed up with follow-up questions that seek to better understand participants' lived experience of motivation problems, focusing on what participants feel and experience rather than simply which activities are impacted. Participants will be given the option to conduct interviews alongside carers or family members. Interview will be conducted by Dr JT, a specialist trainee (ST6) in neurology completing a PhD in neuroscience. Audio from these interviews will be recorded using a passcode-encrypted voice recorder. Audio recordings will not contain any personal information. JT will make a verbal note of participant's identifier code at the beginning of each recording. Interview data will be transcribed into text format by JT as soon as feasibly possible after the interview and within one week. On completion of transcription, audio recordings will be destroyed. Pseudonymised, transcribed interview data will be stored in a single, password-encrypted text file on the university server. The central identifying document linking personal data with participant ID codes will be destroyed at the end of the study period.

Data analysis:

Quantitative data will be analysed using descriptive statistics (such as mean, median), and linear mixed effect models using reaction time and accuracy as dependent variables and questionnaire scores as predictive regressors, using statistical software such as R and Python. Evidence accumulation (drift diffusion) models will be fitted to participant data (using tools such as HDM or DMC including for Bayesian model comparison), and computationally derived parameters (e.g. for drift rate, threshold) will be analysed in linear mixed effect models with questionnaire scores as regressors. Qualitative data from interview will be analysed with interpretative phenomenological analysis by JT, with support and advice by MB.

6. Project setting

All participants attending in person will conduct the experiment in testing rooms at the School of Psychology, 52 Pritchatts Road, University of Birmingham, Edgbaston, B15 2SA where MAJA has dedicated laboratories containing necessary equipment for the experiment. All testing rooms are accessible by lift. Any necessary provisions, including drinks, snacks and walking aids will be provided to participants.

7. Participant recruitment

7.1. Eligibility criteria

7.1.1. Inclusion criteria

Inclusion criteria for those with early psychosis:

-Age 18-40 (inclusive) at time of eligibility assessment (this age range has been selected in view of typical demographics, and greater chance of secondary psychosis or long-term medication effects above this age range).

-Able to understand written and spoken English

-Meets one or more criteria for Ultra High Risk for psychosis groups as assessed by the CAARMS or SIPS, SOFAS and FIGS)

-Meets criteria for early/first episode psychosis (meet ICD-10 criteria for a diagnosis of schizophrenia and related psychoses (ICD-10 code F20, F22, F25, F28, F29) and within three years of first diagnosis of psychotic disorder at the time of eligibility assessment

Inclusion criteria for those with Parkinson's disease:

-Age 18-80 (inclusive)

-Formal diagnosis of idiopathic Parkinson's disease

-Able to understand written and spoken English

-Hoehn and Yahr Parkinson's grade 1 – 4

7.1.2. Exclusion criteria

All participants:

-Lack of capacity/inability to consent.

-Significant neurological or psychiatric comorbidity other than psychosis/at risk mental state (e.g. significant mood disorder, nervous system disorders such as stroke, traumatic brain injury).

- Current or lifetime diagnosis of antisocial personality disorder, autism or other neurodevelopmental disorder.

-Significant risk to self or other people, as determined by their clinical team.

-Detained under mental health act

- History of alcohol or substance use disorder (abuse/dependence) within six months prior to eligibility assessment (nicotine and caffeine dependence are not exclusionary).

-Significant upper limb motor impairment (i.e. that would impair squeezing a handheld force-meter or clicking a mouse/button).

-Significant wrist injuries, carpal tunnel syndrome, or musculoskeletal problems that would cause discomfort in squeezing tasks.

-Bed-bound or unable to attend University for in-person study

7.2. Sampling

7.2.1. Size of sample

Around 100 participants with Parkinson's disease, and around 100 participants with or at high risk of developing psychosis will be recruited. As there are no existing studies employing the same or similar task, sample sizes have been estimated based on previous related work. A previous analysis[17] by Brysbaert and colleagues estimated that a properly powered reaction time experiment with repeated measures analysed with linear mixed effect models should have at least 1,600 observations per condition (e.g., 40 participants, 40 stimuli), which assumes an effect size between Cohen's d = 0.4 and d = 0.5. Given the experiment contains a total of four experimental conditions (two vs three options, easy vs difficult choice difficulty), 50 participants performing 160 trials would be sufficiently-powered. Another study by Saleh et al.[19] analysed reaction time data and fitted a drift diffusion model to 82 participants with cerebral small vessel disease performing an effort-based decision-making task, including those suffering with apathy. They found a significant correlation between computationally-derived parameters and apathy scores, suggesting that their study of 82 participants performing 180 trials was sufficiently powered. Accounting for a smaller number of (160) trials, 92 participants would be necessary to achieve a similarly-powered study.

For the interview-based study, an estimated sample size of ~10 individuals (~5 with Parkinson's disease and 5 with or at high risk or psychosis) should enable a diverse range of insight while balancing feasibility.

7.2.2. Sampling technique

Convenience sampling will be employed. As all participants will perform the same experiment, there is no rationale for randomisation or group allocation. For the interview-based study, judgement sampling on the basis of performance in the first experiment will guide participant selection. As the experiment principally aims to investigate motivation symptoms, participants with high levels of apathy or negative symptoms, particularly those with exaggerated distractor effects or effort-discounting on the behavioural task, will be preferentially selected for interview.

7.3. Recruitment

7.3.1. Sample identification

Participants with Parkinson's disease:

Potential participants with Parkinson's disease will be identified primarily via charities such as Parkinson's UK or University-held registries of people who have previously expressed interest in participating in research and have consented to be contacted about future research, and therefore for the most part will not rely on NHS resources for participant identification or conduct. For a number of participants, however, an NHS provider may act as a Participant Identification Centre. In this case, potential participants may be identified by their usual clinical team (consultant neurologist or geriatrician or Parkinson's disease specialist nurse, from personal knowledge of potentially eligible patients or database) and approached either in person (e.g. in a clinic) or via written correspondence (letter or email). Capacity to consent will be assessed by their clinical team. Clinicians will inform patients that members of the research team (including Chief Investigator and Primary Investigator who exist outside the direct healthcare team but have contracts with the NHS trust) will confirm eligibility (i.e. diagnosis of idiopathic Parkinson's disease, no exclusion criteria) and will be responsible for the conduct of the study. If seeing patients face-to-face, clinicians may provide some basic verbal information about the study in person (e.g. a study on motivation, duration, payment) and confirm whether they may be interested in participating. Consent to be contacted will be documented in clinical notes. If they are interested, they will either be provided with an information sheet (or link to an information sheet) or be contacted by research staff later via phone or email, who will provide a Participant Information Sheet. Otherwise, potential participants will receive a letter advertising the study and containing the Participant Information Sheet. In both cases, interested participants will be asked to contact the research team. After contacting the research team, potential participants will be provided with a short screening questionnaire to determine eligibility (Microsoft forms page under UoB account or over the telephone). If deemed eligible for the study, an experimental slot will be arranged by a member of the study team. Those people identified via non-NHS sources (e.g. charities) will receive a letter/email or see an advert about the study and will be encouraged to get in contact if interested. Respondents to the advert will receive a link to the information sheet, or will be contacted by research staff via phone or email and provided with a Participant Information Sheet. If they are interested in participating, they will then complete a short screening questionnaire, after which they may be scheduled a study slot.

Participants with or at high risk of psychosis

Potentially eligible participants with early psychosis will be identified either:

1. by members of their usual clinical team (consultant psychiatrist or Early Intervention in Psychosis Service team care coordinator - from personal knowledge of potentially eligible patients or from database search.

2. via a registry held at the Institute for Mental Health (University of Birmingham) of patients who have previously participated in clinical research (such as PIMS and PRESCIENT studies) and have agreed to be contacted about other research opportunities.

For the first group, capacity to consent will be assessed by the clinical team (consultant Psychiatrist, care co-ordinator or community psychiatric nurse). Potential participants will be approached either in person (e.g. in a clinic) or via written correspondence (letter or email). If approached in person, members of the clinical team will provide some basic verbal information about the research study and will either provide a Participant Information Sheet or seek verbal consent from participants to be contacted by a researcher who will provide a Participant Information Sheet (via post, email, or link to online information). Consent to be contacted will be documented in clinical notes. Otherwise, potentially eligible participants will be sent a study advertisement letter or email, advertising the study and containing the Participant Information sheet. Clinicians will inform them that members of the research team (including Chief Investigator and Primary Investigator who exist outside the direct healthcare team but have contracts with the NHS trust) will confirm eligibility (i.e. meets inclusion and exclusion criteria) and will be responsible for the conduct of the study. In both instances, participants will be asked to contact a member of the research team (JT - via email) if they are interested in participating in the study. Researchers will then ask participants to complete an eligibility questionnaire, either /Microsoft forms (using UoB account) or over the telephone. If eligible for the study, an experimental slot will be arranged by a member of the study team.

For the second group, researchers will contact participants directly via a study advertisement letter or email, advertising the study and containing the Participant Information sheet. Participants will be asked to contact a member of the research team (JT - via email) if they are interested in participating in the study. Researchers will then send ask participants to complete an eligibility questionnaire via, Microsoft forms (using UoB account) or over the telephone. If eligible for the study, an experimental slot will be arranged by a member of the study team.

Family/friends

It is likely that family members, friends or carers may take an active role in encouraging potential participants to participate in the research. While they will not be considered participants in the behavioural study or interview study, they may wish to be present for these sessions in a supportive capacity. Interviews will focus on individuals' personal motivation symptoms, and while it is possible that family members/carers may provide some commentary on individual patient's symptoms, only comments emanating from participants will be used in the analysis.

7.3.2. Consent

For participants identified via NHS Participant Identification Centres (PICs), potentially eligible patients will be first approached by clinical team (or, if applicable, CRN staff) working within clinical teams, either face-to-face or by a letter or email sent on behalf of the clinical team. Participants will confirm their interest by providing contact details, either via email or via a link to a Microsoft forms page (using JT's UoB account). If these individuals consent to be contacted by the research team, the research team will then take over all correspondence. If participants agree to be contacted, participants will be sent a Participant Information Sheet. They will be encouraged to contact the research team if they have any questions, and to discuss participation with their friends and families. If they express an interest in taking part, they will next complete a screening questionnaire to determine eligibility. They will complete this screening questionnaire via Microsoft forms (using JT's UoB Microsoft account), which will be linked to their unique identifier, or via telephone. This will be completed through implied consent. JT or other investigators will confirm eligibility. If eligible, an experimental slot will be arranged by a member of the study team. Full consent for the experiment will be taken by the experimenter at the beginning of this experimental session (if completing an online interview, an online consent form will be provided). Participants will have already been sent an information sheet and encouraged to ask questions prior to the session, but the key information and ethical issues will be explained verbally before participants are asked to fill the consent form. Capacity will be assessed at the time of this consent process by JT, a neurology doctor with experience in performing capacity assessments. Participants will again have the opportunity to ask questions. The same consent process will apply during any in-person

attendance (for example, during a second experimental session in people with Parkinson's disease, or for the qualitative interview in a subset of participants). For those conducting an interview online, the consent process will be identical to as that in person, although participants will complete an electronic consent form via email. They will have previously received a copy of the Participant Information Sheet via their preferred method (post, email or online copy).

Reimbursement

Participants completing the behavioural task will be reimbursed at a base rate of £25 per session, with a performance-based bonus payment of up to £10 per session. Participants participating in the interview will receive £25 for their participation. Participants will also be reimbursed for travel expenses (excluding taxi fares) including car parking if applicable.

8. Storage and analysis of human tissue

N/A

9. Safety reporting

The risk of adverse events is deemed to be low. Any accidents or injuries occurring during the study will be managed in line with University policy, with input from the Sponsor.

10. Ethical and regulatory considerations

10.1. Assessment and management of risk

See section 13.4 in the protocol for further information on risks. The following describes the main potential risks of the study:

Questionnaires:

Questionnaires enquire about or probe symptoms such as cognition, mood, fatigue and apathy and the impact on activities of daily living, which might cause a degree of emotional distress during completion but overall these risks are deemed to be low. In general, the included questionnaires do not contain highly sensitive or probing questions. The PHQ-8, which quantifies symptoms of depression, omits a question that asks about 'thoughts that you would be better off dead, or of hurting yourself in some way' posed in the longer PHQ-9 questionnaire, and therefore is less likely to raise safeguarding issues. The UPDRS (administered to participants with Parkinson's disease to assess different motor and non-motor symptoms) and BNSS (administered to participants with early psychosis to assess negative symptoms) are administered via a semi-structured interview but overall do not include highly sensitive or probing questions and are unlikely to cause distress.

Experimental tasks:

The effort-based task requires participants to squeeze a handheld force-meter on repeated occasions throughout the experiment (total 160 trials). Participants with pre-existing injuries or musculoskeletal problems will be screened for and excluded at the outset. As the experiment aims to examine decisions involving physical effort, participants are likely to experience some degree of exertion-related discomfort during the experiment. However a very large number of studies have employed these methods, including in people with Parkinsons' disease and psychosis[19,20] without significant problems or adverse events. Maximum grip force is measured at the beginning of the experiment to ensure that all work tasks are calibrated to individual participants, with no tasks exceeding 80% of the maximum calibrated force, whilst the nature of the experiment encourages participants to select lower effort options most frequently. Rest blocks are interposed every 20 trials to ensure adequate rest and recovery. If participants experience significant discomfort and indicate they wish to terminate the experiment, the experiment will be terminated immediately.

As poor performance in the tasks can lead to loss of credits (which will relate to less money being won at the end of the experiment), there is potential for upset in the event of poor performance, and/or a sense of disappointment or unfairness at the end of experiment. The experiments have been specifically designed to assess decision-making in the setting of a goal, and as such have been designed to maximise engagement and motivation. If participants appear to become overly distressed due to the experiment, researchers will pause and attempt to defuse any feelings of frustration. In the event of significant distress, the experiment will be terminated.

Delaying dopaminergic medication (participants with Parkinson's disease):

People with Parkinson's disease will perform the experimental task twice (in separate sessions), once having taken and the other having omitted their usual dopamine-modulating medication the same morning. In normal practice, levodopa (the most commonly prescribed medication for Parkinson's disease which is a chemical precursor of dopamine) is taken three or four times per day, with a duration of effect usually in the range of 3-4 hours for immediate release preparations. For this study, testing sessions will only be scheduled for the morning (commencing between 0900 and 1030), and therefore participants' medication will be delayed only by around 3-6 hours. This is unlikely to affect the timing of their medication for the rest of the day, as it is likely that the end of the testing session will coincide with participants' next scheduled dose of medication and participants will be encouraged to take the next dose as soon as possible after the session. This instruction to delay medication does not otherwise constitute any change to their usual medication regime – it will only result in a delay to a single dose. While delay of their medication will not have any long-term impact on their illness (it is a symptomatic rather than disease-modifying treatment), it may lead to temporary exacerbation of motor symptoms such as increased stiffness, slowness or tremor, resulting in greater difficulties in motor tasks such as walking and increased risk of falls. Participants will be counselled appropriately about this during the consent process with adequate provisions on the day of testing, including ensuring they are accompanied, have suitable transport arrangements (including access to free parking at the testing site), and take their medication immediately after the session.

Qualitative interview (subset of ~10 participants who have participated in the experimental session):

The qualitative study in a subset of participants aims to explore motivation symptoms in detail, and as such will encourage greater self-reflection on participants' illness, personal lives and associated disabilities, with greater potential for causing distress or upset. Interviews will be conducted sensitively, using an existing interview structure that focuses on motivation symptoms. Follow-up questions will aim to encourage participants to elaborate on particular aspects of their symptoms and will be restrictive. In the event of significant distress, participants will be given the option of pausing or terminating the interview. During the interview, it is conceivable (although highly unlikely) that sensitive information will be revealed, including participants indicating thoughts of harm to themselves or others or relating to unethical or unlawful activities. Participants will be briefed about this and the implications during the consent process. If participants express thoughts of self-harm, the interview will be terminated and participants' clinical teams will be informed immediately. If information comes to light about serious criminal activity indicating harm or potential harm to another person, the interview will be terminated immediately with further action in line with the tenets of good clinical practice (GCP), which may involve breaking confidentiality and informing the police, as well as participants' clinical teams. Researchers will be attentive to non-verbal signs of aggression and position themselves to allow a direct escape route in the event of escalation.

Handling and reporting of adverse events

No serious adverse events, resulting in harm to a participant, are anticipated during this study. In the event of any acute medical issue, a medical doctor (JT) will be present who will manage the situation accordingly. Any adverse events – including acute medical issues, harm or distress caused by an intervention – will be documented immediately after they occur and discussed with the Chief Investigator and other members of the

research team. The study will be paused in the meantime. The Chief Investigator will determine whether the adverse event constitutes a serious adverse event (SAE) and whether it is likely to be attributed to the research study. If deemed unrelated to the research, a psueodonymised record of the event, including relevant discussions with the CI, will be retained. If the event is deemed attributable to the research but not constituting a SAE, the research team will meet to discuss changes to the study protocol and carry out a further risk management plan and will consider discussion with the sponsor. In the event of an Unexpected Serious Related Event – such as a significant injury resulting from the intervention or research environment – the study will be paused and the incident will be reported to the REC and sponsor within 15 days and summarised in the Annual Progress Report to the REC.

10.2. Research ethics committee (REC) and other regulatory review & reports

Before the start of the project, a favourable opinion will be sought from a REC for the protocol, informed consent forms and other relevant documents. As the study intends to recruit some participants using NHS sites as Participant Identification Centres (PICs), HRA approval will be sought prior to the start of the project. Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement this at the site. All correspondence with the REC will be retained, and the CI will conform to the necessary responsibilities, including to produce the annual reports as required, to notify the REC and sponsor of the end of the project, to submit an annual progress report (APR) to the REC and sponsor within 30 days of the anniversary date on which the favourable opinion was given, and annually until the project is declared ended, to notify the REC and sponsor if the project is ended prematurely, including the reasons for the premature termination, and to submit a final report with the results, including any publications/abstracts, to the REC and sponsor within one year after the end of the project.

10.2.1. Regulatory review & compliance

Before enrolling participants into the project, the CI/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place and comply with the relevant guidance. For any amendment to the project, the CI or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The CI or designee will work with sites (R&D departments at NHS sites as well as the project delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the project as amended. The University of Birmingham's Clinical Research Compliance Team may carry out compliance visits to monitor adherence with applicable standards and regulations.

10.2.2. Amendments

In the event of amendments, the CI will be responsible for the decision to amend the protocol. The amendments help section in the Integrated Research Application System (IRAS) will help inform whether a review body needs to be notified, and in what capacity. The sponsor will have responsibility in deciding whether an amendment is substantial or non-substantial. For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.If an HRA and HCRW Approval central governance review is needed, participating organisation will complete local assessments and governance review, with amendments implemented or rejected. The amendment history will be tracked to identify the most recent protocol version.

10.3. Peer review

The study proposal including the study protocol has been has received independent external review by two senior researchers at the University of Oxford. The main experimental protocol, including results from a pilot in young, healthy individuals, has also been presented within the host institution to other researchers involved

in motivation research. REC review and approval will be undertaken as part of the application for HRA approval.

10.4. Patient & public involvement

The study protocol has been discussed with two members of the public with Parkinson's disease, both PPI representatives affiliated with Parkinson's UK who facilitated the meetings, as well as with a public advisor assigned to this project as part of the Midlands Mental Health and Neuroscience doctoral training program. The protocol has been adapted on the basis of their feedback and suggestions. There is a plan for further PPI involvement to enable refinement of the interview schedule for the qualitative study, after data collection has started on the experimental task. In addition to this, all study participants (as well as carers, family or other persons) will be invited to join a Patient Public Involvement Group after their participation in the experimental task. They will be encouraged to feed back on the aims and methodology of the current project, and their ideas will contribute to development of new research objectives and studies. All members will receive ongoing correspondence about the study, including dissemination of any submitted manuscripts. Information relating to closely-related research and research opportunities will also be shared with the group.

10.5. Protocol compliance

All protocol deviations will be documented in a spreadsheet and discussed with the CI and sponsor, with rectifying steps implemented wherever possible. In the event of any serious breach that affects to a significant degree the safety or physical or mental integrity of a participant, the project will be paused and a meeting urgently arranged with the Sponsor. A detailed account of any such event will be documented close to the time of occurrence. Significant deviations which are found to frequently recur will be flagged and urgently discussed with the Sponsor.

10.6. Data protection and confidentiality

Participants' identifying information will be pseudonymised at the time of enrolment. A central identifying document linking personal information to ID codes will be created as a password-encrypted Microsoft excel file, and stored in a single, password-protected file on the university server that can only be accessed by members of the research team. This file will contain participants' name only, and a sequence of 8 numbers that corresponds to the date enrolled (YYMMDD) followed by the order in which they were enrolled (e.g. 13 if 13th participant enrolled). All subsequent data collected will be stored in separate documents in which they will be identified solely by this 8-digit digit sequence. This data will be password-encrypted and stored in several locations including the university server, and an encrypted hard drive. Access to these documents will be restricted to JT, MAJA and MB. Audio data from interviews will be captured on an encrypted voice recorder and transferred to the UoB server within one week, after which it will be deleted from the recorder. The audio file will not refer to the participant by name but will state the participant's pseudonymised ID code at the beginning of the recording. The audio file will not contain any audio reference to the participant's name or other identifiable personal information. Audio files will be transcribed to password-protected pseudonymised text documents within 1 week of recording and then destroyed. Matthew Apps will be the data custodian. Screening data for ineligible patients will be destroyed promptly. Personal information will be destroyed at the end of the study period or on the request of participants. Participants will have one month to decide if they wish to withdraw from the study after participation. They may choose to retain their data, or request their data and personal information to be destroyed. Researcg data will be kept for 10 years in line with University of Birmingham policy.. Paper records will be kept in locked filing cabinets at the University of Birmingham School of Psychology.

<u>Indemnity</u>

The University has in force a Public Liability Policy and/or Clinical Trials policy which provides cover for claims for "negligent harm" and the activities here are included within that coverage.

10.7. End of study and archiving

The anticipated end of the study will be December 2026. At this point, JT will have designated responsibility for deleting files containing personal information, which will be reviewed by MAJA and MB. JT and MAJA will also be responsible for archiving the anonymised data. Researchdata will be stored for 10 years after the end of study as per UoB policy.

10.8. Access to the final dataset

JT, MAJA and MB will have access to the full dataset. Anonymised data may be shared with other researchers or used for secondary analysis at the end of the study period.

11. Dissemination policy

11.1. Dissemination policy

Data arising from the project will be owned by the University of Birmingham. On completion of the project the data will be analysed and tabulated by the research team and a final report prepared. This will be published as a preprint (on psyarvix), pending submission to an academic journal and publication as a peer-reviewed scientific paper (within 1 year of the study end date). All participating investigators will have rights to publish any of the data. The Wellcome trust need to be acknowledged within the publications although they will not review the data or have any publication rights of the data from the project. Members of the PPI steering group will be informed about the outcome of the project, both during the submission phase will receive a copy of any publication arising from the research. Participants may specifically request results from their Principal Investigator (PI) – individualised information (e.g. about individual scores or performance) will be provided as soon as feasibly possible (and within one month), whilst provisional results relating to the entire cohort may be shared after the final report have been compiled.

11.2. Authorship eligibility guidelines and any intended use of professional writers

JT will be the intended first author of any publications resulting from the research, with MAJA and/or MB being senior authors. Other individuals such as research assistants, researchers, or members of the PPI steering group who have contributed significantly to data collection, analysis or manuscript preparation will be credited accordingly.

12. References

1. Husain M, Roiser JP. Neuroscience of apathy and anhedonia: a transdiagnostic approach. Nat Rev Neurosci. 2018 Aug;19(8):470–84.

2. Levy R, Dubois B. Apathy and the Functional Anatomy of the Prefrontal Cortex–Basal Ganglia Circuits. Cerebral Cortex. 2006 Jul 1;16(7):916–28.

3. Dickson SS, Husain M. Are there distinct dimensions of apathy? The argument for reappraisal. Cortex. 2022 Apr 1;149:246–56.

4. Hull CL. Principles of behavior: an introduction to behavior theory. Oxford, England: Appleton-Century; 1943. x, 422 p. (Principles of behavior: an introduction to behavior theory).

5. Phillips PEM, Walton ME, Jhou TC. Calculating utility: preclinical evidence for cost–benefit analysis by mesolimbic dopamine. Psychopharmacology. 2007 Apr 1;191(3):483–95.

6. Klein-Flügge MC, Kennerley SW, Friston K, Bestmann S. Neural Signatures of Value Comparison in Human Cingulate Cortex during Decisions Requiring an Effort-Reward Trade-off. J Neurosci. 2016 Sep 28;36(39):10002–15.

7. Culbreth AJ, Moran EK, Barch DM. Effort-Based Decision-Making in Schizophrenia. Curr Opin Behav Sci. 2018 Aug;22:1–6.

8. Hartmann MN, Hager OM, Reimann AV, Chumbley JR, Kirschner M, Seifritz E, et al. Apathy but not diminished expression in schizophrenia is associated with discounting of monetary rewards by physical effort. Schizophr Bull. 2015 Mar;41(2):503–12.

9. Chau BKH, Kolling N, Hunt LT, Walton ME, Rushworth MFS. A neural mechanism underlying failure of optimal choice with multiple alternatives. Nat Neurosci. 2014 Mar;17(3):463–70.

10. Rushworth MFS, Kolling N, Sallet J, Mars RB. Valuation and decision-making in frontal cortex: one or many serial or parallel systems? Curr Opin Neurobiol. 2012 Dec;22(6):946–55.

11. Robert P, Lanctôt KL, Agüera-Ortiz L, Aalten P, Bremond F, Defrancesco M, et al. Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. European Psychiatry. 2018 Oct 1;54:71–6.

12. Chen Y. Neural Representation of Costs and Rewards in Decision Making. Brain Sci. 2021 Aug 20;11(8):1096.

13. Levy, D. J., & Glimcher, P. W. (2012). The root of all value: A neural common currency for choice. Current Opinion in Neurobiology, 22(6), 1027–1038.

14. Klaasen NG, Kos C, Aleman A, Opmeer EM. Apathy is related to reduced activation in cognitive control regions during set-shifting. Hum Brain Mapp. 2017 May;38(5):2722-2733.

15. Monosov IE, Haber SN, Leuthardt EC, Jezzini A. Anterior Cingulate Cortex and the Control of Dynamic Behavior in Primates. Curr Biol. 2020 Dec 7;30(23):R1442-R1454.

16. Radakovic, R., & Abrahams, S. (2018). Multidimensional apathy: Evidence from neurodegenerative disease. Current Opinion in Behavioral Sciences, 22, 42–49.

17. Brysbaert M, Stevens M. Power Analysis and Effect Size in Mixed Effects Models: A Tutorial. J Cogn. 1(1):9.

18. Saleh Y, Le Heron C, Petitet P, Veldsman M, Drew D, Plant O, Schulz U, Sen A, Rothwell PM, Manohar S, Husain M. Apathy in small vessel cerebrovascular disease is associated with deficits in effort-based decision making. Brain. 2021 May 7;144(4):1247-1262.

19. Le Heron C, Plant O, Manohar S, Ang YS, Jackson M, Lennox G, Hu MT, Husain M. Distinct effects of apathy and dopamine on effort-based decision-making in Parkinson's disease. Brain. 2018 May 1;141(5):1455-1469.

20. Hartmann MN, Hager OM, Reimann AV, Chumbley JR, Kirschner M, Seifritz E, Tobler PN, Kaiser S. Apathy but not diminished expression in schizophrenia is associated with discounting of monetary rewards by physical effort. Schizophr Bull. 2015 Mar;41(2):503-12.

13. Appendices

13.1. Appendix 1 – required documentation

Questionnaire measures:

-Apathy Motivation Index (AMI)

-Dimensional Apathy Scale (DAS)

-Fatigue Severity Scale (FSS)

-Adapted Glasgow Content of Thoughts Inventory (GTCI)

-Patient Health Quesionnaire-8 (PHQ-8)

-Snaith Hamilton Pleasure Scale (SHAPS)

-Montreal Cognitive Assessment (MOCA)

-Brief Negative Symptom Scale (BNSS)

-Unified Parkinson's Disease Rating Scale (UPDRS)

-Lille Apathy Rating Scale (LARS)

Forward and backward digit span test (~2 minutes)

13.2. Appendix 2 – schedule of procedures

	Behavioural study (session 1)	Behavioural study (session 2- PwPD only)	Qualitative study
Informed consent	X	X	X
Behavioural study	X	X	
Apathy Motivation Index (AMI)	X		
Dimensional Apathy Scale (DAS)	X		
Fatigue Severity Scale (FSS)	X		
Adapted Glasgow Content of Thoughts Inventory (GTCI)	X		
Patient Health Quesionnaire-8 (PHQ-8)	X		
Snaith Hamilton Pleasure Scale (SHAPS)	X		
Montreal Cognitive Assessment (MOCA)	X		
Forward and backward digit span test (~2 minutes)	x		
Unified Parkinson's Disease Rating Scale (UPDRS)	X (PwPD only)	X (part III only)	
Brief Negative Symptom Scale (BNSS)	X (PwPsych only)		
Lille Apathy Rating Scale (LARS)			X
Debrief	X		X

13.3. Appendix 3 – amendment history

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**

13.4.Risk Assessment Report

Trial title:	*Dynamics of motivated decision-making in striatal disorders*
Sponsor reference:	RG_23-163
IRAS number:	*336513*
REC number:	

Document control sheet

Risk assessment version:	Reason for update:
v1.1 4/1/24	

Add or delete rows as required

1. Risks to participant safety associated with intervention(s) being tests

Tick the appropriate box below to indicate project type

☐ IMP trial

☒ Non-IMP trial/clinical study

1.1. Risk category

Tick the appropriate box below to indicate trial type:

☒ **TYPE A**	☐ **TYPE B**	☐ **TYPE C**
Comparable to the risk of standard medical care	Higher than the risk of standard medical care	Markedly higher than the risk of standard medical care
Examples For CTIMPs: ☐ Trials involving medicinal products licensed in any EU Member State if: ○ they relate to the licensed range of indications, dosage and form, or ○ they involve off-label use if this off-label use is established practice and supported by sufficient published evidence and/or guidelines. For non-CTIMPs: ☐ Projects involving skin prick tests, observational measures or quality of life assessments.	**Examples** For CTIMPs: ☐ Trials involving medicinal products licensed in any EU Member State if: ○ such products are used for a new indication, ○ substantial dosage modifications are made for the licensed indication, or ○ if they are used in combinations for which interactions are suspected. ☐ Trials involving medicinal products not licensed in any EU Member State if the active substance is part of a medicinal product licensed in the EU. For non-CTIMPs: ☐ Projects involving radiotherapy dose modifications or a new combinations of non-IMP treatment (e.g. surgery and radiotherapy).	**Examples** For CTIMPs: ☐ Trial involving a medicinal product not licensed in any EU Member State. For non-CTIMPs ☐ Project involving a new surgery technique, a new radiotherapy technique or a new diagnostic technique

Justification for risk category:

Guidance

List the intervention(s) and **briefly** justify the overall risk category selected (Type A, B or C). Consider the following:

a. Phase of development
b. Study population – healthy subjects or patients?
c. Is the intervention licensed?
d. Is the intervention being used outside of its licensed indication?
e. Has the dosage regimen/route/surgical procedure/fractionation been modified? If so what are the implications of any modifications for participants?
f. What is the safety profile of the intervention(s).
   i. What are the known/anticipated safety issues? Are they all addressed within normal clinical practice (standard care)?
   ii. Anticipated risks/other effects based on pre-clinical data or knowledge of class of intervention?
   iii. Is the duration of use compatible with previous experience? Is there a potential risk of dosing errors?
   iv. May concomitant medication increase the risk i.e. interactions?
   v. Is there any published evidence – particularly for Type A trials intending to submit via the MHRA Notifications Scheme, or to support a risk category different to that indicated above?

The intervention involves withholding a single dose of a symptomatic (i.e. non-disease-modifying) medication for Parkinson's disease. This will have no adverse effects on the disease trajectory but may temporarily worsen Parkinsonian symptoms such as slowness, stiffness and tremor.

1.2. Risks related to the intervention

List below the key risks related to the intervention(s) and how these risks will be minimised. Consider all significant project-specific medical events. Examples are provided in red italic text. Add or delete rows as required.

Intervention	Body system/hazard	Mitigation/activity (including frequency)	Comments (including impact and likelihood where applicable)
Withhold single dose of dopaminergic medication (includes levodopa, dopamine agonists, monoamine oxidase inhibitors)	-Worsening of tremor -Worsening of stiffness -Worsening of slowness -Increased risk of falls	-Participants will be adequately informed of risks of withholding medication and provide informed consent. -Participants will be offered a choice of whether to withhold medication for the study. -Participants will withhold a single dose of medication and take the scheduled next dose without delay -Participants and researchers will ensure risk associated with trips and falls are mitigated. This includes ensuring participants are accompanied and have adequate transport arrangements, clarifying usual level of mobility and ensuring appropriate walking or mobility aids are provided, ensuring testing rooms are accessible by wheelchair, signposting toilets and assessing participant's needs	

		frequently, ensuring no hazards in the environment that could lead to falls.	

1.3. Other risk mitigation processes

The project will be conducted in accordance with the UoB Quality Management System that is designed to mitigate generic risks for clinical research. The table below documents other project-specific risk mitigation associated with the intervention.

Examples are provided in red italic text. Add/delete rows as required:

Mitigation/activity	**Comments**
Risk related to squeezing tasks	The effort-based task requires participants to squeeze a handheld force-meter on repeated occasions throughout the experiment (total 160 trials). Participants with pre-existing injuries or musculoskeletal problems will be screened for and excluded at the outset. Rest blocks are interposed every 20 trials to ensure adequate rest and recovery. If participants experience significant discomfort and indicate they wish to terminate the experiment, the experiment will be terminated immediately. The main researcher is a medical doctor and will manage any complications or injuries accordingly (very low risk).
Risks incurred during qualitative interview	Interviews will be conducted sensitively, using an existing interview structure that focuses on motivation symptoms. In the event of significant distress, participants will be given the option of pausing or terminating the interview. During the interview, it is conceivable (although highly unlikely) that sensitive information will be revealed, including participants indicating thoughts of harm to themselves or others or relating to unethical or unlawful activities. Participants will be briefed about this and the implications during the consent process. If participants express thoughts of self-harm, the interview will be terminated and participants' clinical teams will be informed immediately. If information comes to light about serious criminal activity indicating harm or potential harm to another person, the interview will be terminated immediately with further action in line with the tenets of good clinical practice (GCP), which may involve breaking confidentiality and informing the police, as well as participants' clinical teams.
Risk to researchers	Participants referred from clinical teams will be screened by their responsible clinicians – those deemed to be at high risk to themselves or other people will be deemed ineligible and will not be sent an invitation letter. For patients with Parkinson's disease not identified by clinical teams who refer themselves after seeing an advert, risk will not be formally screened however will be assumed to be non-significant (a reasonable judgement in this patient population). During study sessions, researchers will be attentive to non-verbal signs of aggression and position themselves to allow a direct escape route in the event of escalation.

2. Other risks associated with the design and methods of the trial

Review the protocol to identify whether or not it contains any aspects that materially increase the risks in the areas outlined below. For each hazard identified, consider the appropriate mitigation, management and optimal monitoring strategy.

Under each category are some considerations when determining risk.

Examples are provided in red italic text.

2.1. Risks to participants

Category	Risk identified?	If yes, list specific concerns	If yes, how will risks be minimised? Please specify any mitigations.	If yes, could monitoring methods help to address concerns? Please specify
Clinical procedures E.g. Do they differ from standard care? If so, what is the likelihood of severity of harm to the participant? How will this harm be managed?	☐ Yes ☐ No ☒ N/A			
Consent E.g. Is there any reason that the participants in the trial would not be able to give fully informed consent e.g. vulnerable groups, lack of capacity to consent, language difficulties? How will this be managed?	☐ Yes ☒ No ☐ N/A			

Category	Risk identified?	If yes, list specific concerns	If yes, how will risks be minimised? Please specify any mitigations.	If yes, could monitoring methods help to address concerns? Please specify
Data protection E.g. Are particularly sensitive data being collected? Are personal identifiers associated with the data? Is there a need for data to be sent outside the country? Are data protection standards equivalent to those in the UK? *Note: staff are also required to comply with all associated UoB IT policies and procedures.*	☒ Yes ☐ No ☐ N/A	The patient's full name and contact details will be collected at eligibility assessment (which is regarded as personal data in accordance with the Data Protection Act 2018 and GDPR). In addition, copies of signed Informed Consent Forms will be collected and stored with the patient's explicit consent. Audio recordings made during qualitative interviews necessarily contain personal information.	-Personal information of participants deemed ineligible will be promptly deleted. -Copies of signed Informed Consent Forms will be collected and stored in locked filing cabinets at the University of Birmingham with the patient's explicit consent. -Personal data will only be recorded on a password-encrypted central identifying document linking names to unique ID codes. All datafiles will be handled and stored in a secure environment and in accordance with GCP, Data Protection Act 2018 and GDPR. -Audio recordings will be made on a passcode-encrypted voice recorder, will not contain references to participants' names, and will be transcribed to text format within 1 week of interview.	Data protection procedures will be overseen by MAJA and MB.

Category	Risk identified?	If yes, list specific concerns	If yes, how will risks be minimised? Please specify any mitigations.	If yes, could monitoring methods help to address concerns? Please specify
Target population E.g. Phase of the disease, age range of the group, co-morbidities, prognosis of group, susceptibility to infections/complications, risk carrying intervention	☒ Yes ☐ No ☐ N/A	Participants with Parkinson's disease will be older and therefore at greater risk of comorbidities and acute medical problems.	Experimental sessions will be carried out by a medical doctor who will manage any acute medical issues appropriately. However the participant population overall does not present significant risks.	N/A; monitoring not required.

2.2. Risks to the reliability of results

Category	Risk identified?	If yes, list specific concerns	If yes, how will risks be minimised? Please specify any mitigations.	If yes, could monitoring methods help to address concerns? Please specify
Eligibility criteria E.g. Does the trial require very precise assessment of eligibility?	☐ Yes ☒ No ☐ N/A			
Are there any eligibility criteria that are not part of the clinical assessment and may need further highlighting?	☐ Yes ☒ No ☐ N/A			
Randomisation procedure E.g. Is there any possibility that the treatment allocation might be predicted prior to randomisation? Are there any aspects of the process surrounding	☐ Yes ☒ No ☐ N/A	Participants with Parkinson's disease will be randomized as to which session they perform on, and which they perform off their usual medication. There is no blinding, so participants and researchers are aware of their medicated status.		

Category	Risk identified?	If yes, list specific concerns	If yes, how will risks be minimised? Please specify any mitigations.	If yes, could monitoring methods help to address concerns? Please specify
randomisation that may cause errors to be made at site e.g. where site assigns next medication box number? Is there any possibility for randomisation not to be possible e.g. electronic systems go down?				

Category	Risk identified?	If yes, list specific concerns	If yes, how will risks be minimised? Please specify any mitigations.	If yes, could monitoring methods help to address concerns? Please specify
Intervention E.g. Is it a complex intervention/treatment regimen which might be applied incorrectly? If applicable, can process of dose escalation be easily followed?	☒ Yes ☐ No ☐ N/A	Patients with Parkinson's disease will be asked to omit their usual dopamine-based medication (levodopa, dopamine agonists or monoamine oxidase inhibitors) on the morning of testing.	Testing sessions will be scheduled for the morning (commencing between 0900 and 1030), and therefore participants' medication will be delayed only by around 3-6 hours. While omission of their medication will not have any long-term impact on their illness (it is a symptomatic rather than disease-modifying treatment), it may lead to exacerbation of motor symptoms such as difficulties in walking and increased risk of falls. Participants will be counselled appropriately about this during the consent process with adequate provisions on the day of testing, including ensuring they are accompanied, have suitable transport arrangements (including access to free parking at the testing site), and take their medication immediately after the session.	N/A
Management of intervention E.g.	☐ Yes ☒ No ☐ N/A			

Category	Risk identified?	If yes, list specific concerns	If yes, how will risks be minimised? Please specify any mitigations.	If yes, could monitoring methods help to address concerns? Please specify
Consider any IMP supply, management, storage and dispensing requirements issues and impact/likelihood of non-adherence.				
Blinding E.g. If it is required is there any risk that it could be ineffective? Does the unblinding method provide 24-hour cover with the appropriate level backup and failover processes? Is blinding to be performed by local pharmacies? Could there be any unblinding during the course of the trial?	☐ Yes ☐ No ☒ N/A			
Outcome measures (these should be defined in the grant application, ethics and the protocol) E.g. Are any key outcomes subjective, or require complex assessment?	☒ Yes ☐ No ☐ N/A	Qualitative data will be analysed using interpretative phenomenological analysis, which accepts a subjective interpretation of a person's lived experience / double hermeneutic.	Qualitative data will be analysed using a standard phenomenological approach (interpretative phenomenological analysis). Transcripts will be checked by MA and MAJA and reviewed independently.	N/A

Category	Risk identified?	If yes, list specific concerns	If yes, how will risks be minimised? Please specify any mitigations.	If yes, could monitoring methods help to address concerns? Please specify
Is there potential for standardised assessment or external verification (e.g. death certificate)?				
Sub-studies E.g. Are there any issues with sample collection, storage, transfer of materials? Obtaining consent for the sub-study? Sending data to patients?	☒ Yes ☐ No ☐ N/A	Participants are able to contact the research team if they wish to receive specific information about their assessments and results.	A standard proforma will outline results if participants request this information. It will provide their scores, information about what the test assesses, standard cut-offs if used for clinical purposes, and information about who to contact if they have concerns (e.g. NHS servies).	N/A
Follow-up E.g. Is the follow-up schedule difficult? (e.g. long and different from standard care) What is the likelihood and impact on the trial results of non-adherence?	☐ Yes ☒ No ☐ N/A			
Statistical considerations E.g. Is there any concern that the trial may have insufficient power to detect the anticipated effect of the intervention? Any other risks associated with	☒ Yes ☐ No ☐ N/A	There is a concern that there will be insufficient power to detect the anticipated effect of the intervention due to lower than anticipated patient numbers.	There should be sufficient numbers in this disease population to achieve recruitment targets. If necessary an extension to the study will be sought.	N/A; monitoring not required.

Category	Risk identified?	If yes, list specific concerns	If yes, how will risks be minimised? Please specify any mitigations.	If yes, could monitoring methods help to address concerns? Please specify
trial design/outcome measures/analysis plans?				
Data collection E.g. Is there any particular cause for concern over the data collection (e.g. volume and complexity of the data)? Potential for fraudulent data?	☐ Yes ☒ No ☐ N/A			

2.3. Other risks

Category	Risk identified?	If yes, list specific concerns	If yes, how will risks be minimised? Please specify any mitigations.	If yes, could monitoring methods help to address concerns? Please specify
Finance E.g. Availability of the appropriate resources.	☐ Yes ☒ No ☐ N/A			
Investigator sites E.g. Education and experience, existence of quality systems	☐ *Yes* ☒ No ☐ N/A			

Category	Risk identified?	If yes, list specific concerns	If yes, how will risks be minimised? Please specify any mitigations.	If yes, could monitoring methods help to address concerns? Please specify
Sponsor/coordinating centre E.g. Education and experience, existence of quality systems	☐ Yes ☒ No ☐ N/A			
Trial governance E.g. Influence upon/ interference with trial governance by a private organisation. Consider requirements placed on Trials Office by drug company if supply of drugs is provided free of charge or grants are provided.	☐ Yes ☒ No ☐ N/A			

3. Risk assessment report review

The below table indicated that this risk assessment report has been reviewed and no update was required. Review performed by chief investigator (or delegate).

Name	Signature	Date	Reason for review*
Jamie Talbot		14/3/24	

*A review may be conducted, for example, following:

- a substantial amendment to protocol or participant information sheet/informed consent form

- significant changes in trial organisation (e.g. resource allocation, governance) and/or external funding, or
- any other changes that may alter risk. See *Project Oversight & Quality Management SOP (UoB-POS-SOP-001)* for further examples.