# Brain mechanisms in clinical apathy

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# Thesis abstract

Clinical apathy is a debilitating disorder of motivation that is increasingly recognised across neurological and psychiatric disorders. Current challenges remain in understanding the underlying mechanisms of the syndrome, and the lack of licensed treatment. Some evidence has associated apathy with reduced incentivisation by reward, possibly secondary to distinct brain changes in a well defined fronto-striatal network. However, it remains unclear exactly whether the behavioural and anatomical correlates of apathy are consistent across brain disorders.

This thesis attempts to clarify these questions by considering apathy as a behavioural disorder, which can be examined using effort-based decision making tasks. Behavioural and anatomical studies were performed across several conditions, including cerebrovascular small vessel disease, schizophrenia, stroke, and healthy people. Two decision making paradigms were used, one which probes how people evaluate costs and benefits of actions, and another which characterises how motivated behaviour dynamically varies over time in the face of unexpected setbacks or uplifts.

An association between apathy, reward insensitivity, and fronto-striatal pathology was found in small vessel disease. Behavioural phenotypes of amotivation varied across conditions depending on associated factors such as level of cognitive function in schizophrenia, and concurrent depression in patients with focal stroke. Finally, dopaminergic treatment may serve as a therapeutic option for some apathetic patients with subcortical lesions.

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# 1. General Introduction

## 1.1 Apathy: definitions and general concepts

Clinical apathy is a debilitating neuropsychiatric syndrome characterised by loss of motivation (or amotivation) (Marin, 1991). It is increasingly recognised across neurological and psychiatric disorders including Alzheimer's disease (Zhao et al., 2016), cerebrovascular disease (Hollocks et al., 2015; Tay, Lisiecka-Ford, et al., 2020), major depressive disorder (Yuen et al., 2015), and schizophrenia (Yazbek et al., 2014) (**Table 1-1**). Apathy is associated with impaired functional outcomes (Boyle et al., 2003), reduced independence (Hölttä et al., 2012), and is a predictor of both dementia (Tay, Morris, et al., 2020), and all cause mortality (Eurelings, et al., 2018). Notably, it is also associated with significant caregiver distress (Kaufer et al., 1998; Thomas et al., 2001). To date, no licensed treatments for the syndrome exist, partly due to a poor understanding of its underlying mechanisms. Despite this, there is a dearth of neurocognitive models providing mechanistic accounts of the condition. Developing these can provide valuable foundations for the development of potential treatments.

Below we set out to explore the evolving definitions of apathy and the tools currently used to measure it. We suggest that these are not sufficient to provide a deep phenotypic understanding of the syndrome. Instead, we propose a neurocognitive model that aims to build a bridge between the neuroimaging changes and clinical symptoms of apathy, using well designed effort based decision making tasks. Not only can these provide more objective measures of behaviour, but they can also be used to assess efficacy and mechanisms of future treatment. While a general overview of apathy across disorders will be given, I will focus on

cerebrovascular small vessel disease (SVD), and schizophrenia – two important examples of neurological and psychiatric disorders studied in this thesis.

**Table 1-1**: Prevalence of apathy in neurological and psychiatric disease. Adapted from (Husain & Roiser, 2018).

| Disorder | Apathy prevalence (%) | References |
|---|---|---|
| **Alzheimer's disease** | 49 | (Zhao et al., 2016) |
| **Cerebrovascular small vessel disease** | 52 | (Hollocks et al., 2015) |
| **Fronto-temporal dementia** | 72 | (Chow et al., 2009) |
| **Huntington's disease** | 47 | (van Duijn et al., 2014) |
| **Major depressive disorder** | 38 | (Yuen et al., 2015) |
| **Parkinson's disease** | 40 | (den Brok et al., 2015) |
| **Schizophrenia** | 47 | (Yazbek et al., 2014) |
| **Stroke** | 36 | (Caeiro et al., 2013) |
| **Traumatic brain injury** | 61 | (Starkstein & pahissa, 2014) |
| **Vascular dementia** | 65 | (Staekenborg et al., 2010) |

### 1.1.1 Defining clinical apathy

An early definition of apathy, provided by Marin, characterised it as a primary loss of motivation, not attributable to cognitive impairment, emotional distress, or level of consciousness (Marin, 1990, 1991). Additionally, amotivation was seen to map onto multiple dimensions, including goal-directed behaviour, cognitive activity, and emotional responsiveness (Marin, 1991). Some groups have also included a social domain, concerned with amotivation in relation to social interactions (Ang et al., 2017; Dickson & Husain, 2022; Sockeel et al., 2006). Collectively, these dimensions have formed the basis of measurement tools (Ang et al., 2017; Clarke et al., 2007; Marin et al., 1991; Sockeel et al., 2006), and diagnostic criteria for clinical apathy (P. Robert et al., 2009, 2018). To date, a formal diagnosis of apathy can be made based on four criteria: (A) primary loss of motivated behaviour in relation to previous function; (B) persistent symptoms for at least four weeks across at least two dimensions (behavioural/cognitive, emotional, and social); (C) functional impairment secondary to A-B; (D) and an absence of reversible and/or acute causes including substance misuse or environmental change (P. Robert et al., 2018). One important aspect of understanding apathy is clarifying the several clinical terms used in neurology and psychiatry that may be associated with the syndrome.

### 1.1.2 Terminology and relationship with depression

Terms such as *abulia* and *akinetic mutism* have historically been used to describe amotivation syndromes of varying severity (Berrios & Grli, 1995; Bhatia & Marsden, 1994; Fisher, 1983; Marin, 1997). Abulia, derived from the Latin phrase for 'will' (*bul*) is characterised by reduced speech, motor, and emotional output (Berrios & Grli, 1995; Bhatia & Marsden, 1994; Fisher, 1983). Anatomically, it has been associated with lesions within the basal ganglia, including the caudate nucleus (Bhatia & Marsden, 1994). Its more severe

counterpart, akinetic mutism, is characterised by complete absence of spontaneous speech and movement but preserved motor responses when patients are asked questions or requested to move their limbs, and is associated with bilateral lesions within the anterior cingulate cortex (Németh et al., 1988; Yoshida et al., 1976). One recent view is that apathy, abulia, and akinetic mutism can be mapped onto a single axis of increasing severity (Spiegel et al., 2018), however this is yet to be empirically validated.

Alternatively they may reflect different choices of terminology over time and across specialties. This is relevant in schizophrenia, where amotivation is classed as a negative symptom and described using the terms *avolition* or motivational *anhedonia* (Foussias & Remington, 2010; Kirkpatrick et al., 2006; Strauss et al., 2013, 2021). Taken together, these findings suggests that there is a heterogenous number of terms and approaches that can be used to describe amotivation. These not only vary over time, but across specialty domains. In the context of this dissertation, the term clinical apathy will be used to describe people with amotivation symptoms.

Another common misconception is that apathy and depression are equivalent syndromes. This is partly driven by the DSM criteria of major depressive disorder (MDD), which includes anhedonia, which encompasses loss of interest/pleasure, as one of its possible diagnostic criteria (Battle, 2013). However it is not necessary for patients with depression to have a loss of motivation. Conversely, apathy can occur in the absence of diagnosis of MDD. This has been demonstrated in Parkinson's disease where both apathy and depression are common (Kirsch-Darrow et al., 2006, 2011). In two separate investigations, Kirsch-Darrow and colleagues demonstrated that 30-50% of patients reporting apathy do not report depressive symptoms (Kirsch-Darrow et al., 2006, 2011). This is reflected in the clinical

setting, where apathetic patients often report that while they do not feel low in mood, they just ‘can’t be bothered’ to partake in activities of daily living.

An important step in further clarifying the dissociation between these two syndromes involves conducting investigations in neurological conditions where both apathy and depression co-occur. One example is SVD, where both apathy and depression can occur in up to 50% (Hollocks et al., 2015). Notably, this condition is also characterised by microvascular damage with characteristic features on magnetic resonance imaging (MRI) (Wardlaw et al., 2019; Wardlaw et al., 2013). So one approach that can be used to dissociate apathy from associated constructs like depression in SVD may be by investigating whether they are associated with similar or diverging patterns of neural pathology on MRI (Hollocks et al., 2015; Tay, Lisiecka-Ford, et al., 2020; Tay et al., 2019). In chapters two and three, I conduct a multimodal investigation in 82 patients with SVD, including MRI analyses, to further clarify whether the behavioural and anatomical associations of apathy in SVD are similar or different to those in depression. Apathy however is not currently diagnosed using behavioural or neuroimaging markers. Instead, current practice relies on validated questionnaires. A good starting point then is to examine how these questionnaires are developed and used to understand amotivation.

### 1.1.3 Clinical measures of apathy in neurology and psychiatry

#### 1.1.3.1 Apathy questionnaires in neurological disease

Current diagnostic approaches are based on questionnaires measures designed to assess severity of apathy across its dimensions (Ang et al., 2017; Marin et al., 1991; Radakovic et al., 2017). In neurological disease the first of these was the apathy evaluation scale (AES) developed by Marin (Marin et al., 1991). This involved an 18 item questionnaire which could

be administered either by a clinician, or informant, or filled in by the patient themselves (respectively, AES-C, AES-I, and AES-S) (Marin et al., 1991). Questions reflected the tri-dimensional view of apathy presumed to affect the behavioural, cognitive, and emotional aspects of motivation (Marin, 1990; Marin et al., 1991). Respectively, these were characterised as decrements in productivity, goals, and emotional responses to success/failure .

Several subsequent questionnaires have been inspired by the AES and its framing, including the apathy scale (AS) (Starkstein et al., 1992), Apathy inventory (AI) (P. H. Robert et al., 2002), and Lille Apathy Rating Scale (LARS) (Sockeel et al., 2006). More recent measures such as the apathy motivation index (AMI) have additionally included a social dimension (Ang et al., 2017). While there is broad agreement that apathy is multidimensional, groups differ in defining what those dimensions should be. Notably, a recent review by Dickson and Husain has highlighted that empirical work has failed to consistently reproduce the classic tri-dimensional structure, with difficulties encountered especially when attempting to delineate between the behavioural and cognitive domains (Dickson & Husain, 2022). One interpretation is that the itemised questions for these two domains are too similar, or that these subtle conceptual separations do not actually exist in practice. As a result, rather than focus on the precise dimensional details of these questionnaires, I use overall scores as a primary mode of analyses over the course of my thesis.

#### 1.1.3.2 Negative symptoms, apathy, and schizophrenia

While apathy in neurological disorders is considered as an independent syndrome, in schizophrenia, it is referred to as a symptom within a wider negative syndrome. An

appreciation of this syndrome, and how apathy fits within it is important to establish prior to discussing questionnaire approaches in this condition.

Negative symptoms are a core feature of schizophrenia, observed in up to 90% of patients at first-episode psychosis (an der Heiden et al., 2016; Bleuler, 1950; Kraepelin, 1921; Mäkinen et al., 2008). They include a constellation of symptoms unified by the loss of "vital properties" such as speech, motivation, and self expression (German E. Berrios, 1985). Current classification of the negative syndrome includes five symptom domains as agreed upon by the National Institute of Mental Health (NIMH) consensus statement (Kirkpatrick et al., 2006). These are: alogia, anhedonia, avolition, asociality, and blunted affect (see **Table 1-2** for definitions).

The symptoms of avolition and anhedonia both refer to the motivation deficits in schizophrenia, and questionnaire factor analyses have shed further light on how they may contribute to the underlying structures of the negative syndrome. For example, some studies suggest that negative symptom domains aggregate into a two-factor structure where alogia and blunted affect form a 'Diminished Expression' (**EXP**) factor, while the remaining domains (anhedonia, avolition, and asociality) form a "Motivation and Pleasure" (**MAP**) factor, which can be referred to as "apathy" (See **Fig. 1-1**) (Foussias & Remington, 2010; Horan et al., 2011; Kimhy et al., 2006; Kirkpatrick et al., 2011; Kring et al., 2013; Nakaya & Ohmori, 2008). This dichotomised view of negative symptoms is reflected in the most recent version of the DSM-5 (Tandon et al., 2013).

**Table 1-2. Definitions of negative syndrome domains as defined by NIMH consensus.**

**Adapted from** (Saleh, Jarratt-Barnham, et al., 2021)

| **NIMH domain** | **Definitions based on** (Kirkpatrick et al., 2006) |
|---|---|
| **Anhedonia** | Reduced intensity and frequency of current or future pleasurable activities. |
| **Avolition** | A reduction in the initiation of and persistence in activity in relation to internally guided behaviour and experiences. |
| **Asociality** | Reduced social activity accompanied by a decreased interest in forming close relationships with others. |
| **Alogia** | A reduction in speech quantity, and spontaneous elaboration in conversation. |
| **Blunted Affect** | A decrease in outward expression of emotion including facial, vocal and expressive gestures. |

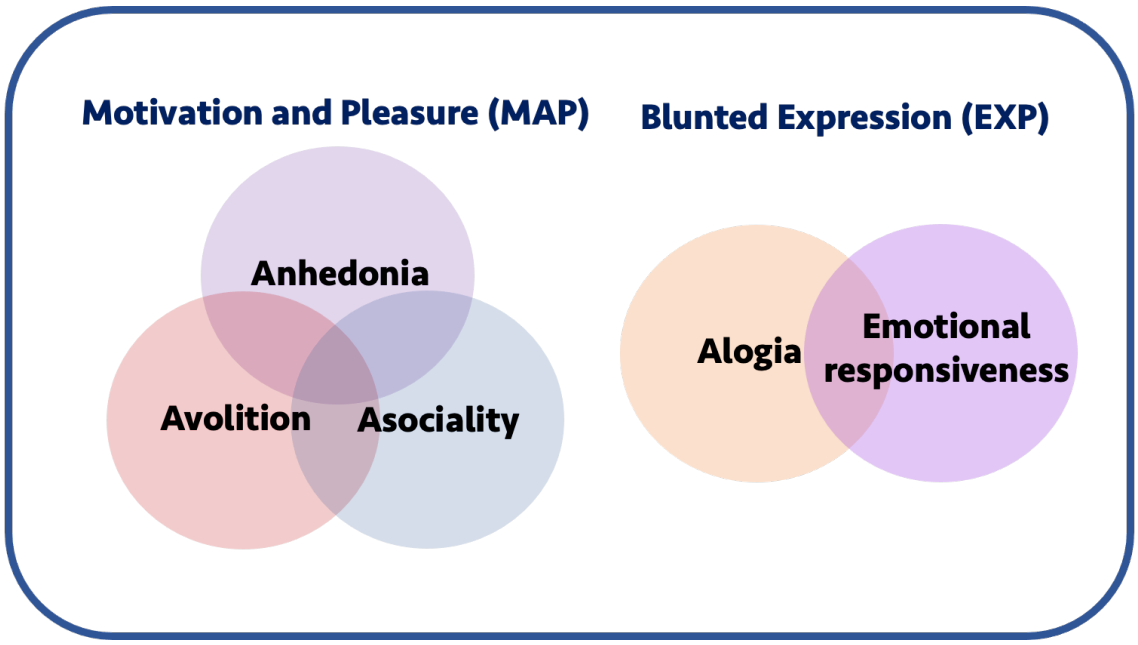



**Figure 1-1. Negative symptoms and conceptual groupings.**
Negative symptoms are often conceptually grouped into a motivation and pleasure (MAP) and blunted expression (EXP) components. The former includes anhedonia, avolition and asociality whereas the latter includes alogia and emotional responsiveness. Collectively, the motivation-pleasure symptoms are also sometimes referred to using the umbrella term "apathy". Figure reused from my review on motivation disorders (Saleh, Jarratt-Barnham, et al., 2021).

Subsequently, negative symptom questionnaires have been developed to reflect these more recent conceptualisations of negative symptoms (Kirkpatrick et al., 2011; Kumari et al., 2017; Strauss et al., 2012). These include, the brief negative symptom in schizophrenia (BNSS) questionnaire, which is clinician administered and includes detailed assessments of both avolition and anhedonia (Kirkpatrick et al., 2011). In my empirical studies of schizophrenia, I use this questionnaire when investigating negative symptoms and motivation deficits in schizophrenia. Additionally I will refer to apathy using the composite 'Motivation and pleasure' factor using validated factor structures from the literature (Strauss et al., 2012).

What is common to questionnaire measures of apathy in both neurological and psychiatric diseases is that the insights provided by them are limited. They may clarify some of the dimensional, or structural properties of the syndrome, but do not necessarily probe its

underlying mechanisms. What is needed are more granular methods that quantify deficits, possibly in relation to neural origins. One approach used to achieve this has been to objectively measure motivated goal-directed behaviour. Below I discuss the reasons for using this approach and characterise exactly what we mean by goal-directed action.

## 1.2 Apathy as a disorder of motivated, goal-directed behaviour.

### 1.2.1 From motivation to goal-directed behaviour

Historically, a major challenge in psychology has been to arrive at a unifying and general definition of motivation. In fact, in 1981 a review by Kleinginna et al collated 102 separate statements attempting to define or describe motivation (Kleinginna & Kleinginna, 1981). This included early phenomenological definitions of motivation as the "desire that precedes an act and determines it" (Kleinginna & Kleinginna, 1981). Others have defined it in terms of its underlying processes, or its intended outcomes. For instance, Ruch defined it as a neural physiological process that "impels the organism to some action or goal", whereas Geiwitz described it as the organism's tendency towards need-fulfilling and goal-seeking behaviour (Kleinginna & Kleinginna, 1981).

While I will make no attempt at a unifying theory of motivation, two observations may be taken from these characterisations. First, a commonly encountered concept across definitions of motivation is that of action towards an intended goal. In fact the word motivation derives from the Latin term *movere*, or to move. Second, while esoteric concepts such as 'desire', or 'want' are difficult to measure, the behavioural aspects of motivation as they relate to 'moving towards a goal' may offer an opportunity to assess this construct more objectively. Specifically, this would be through the investigation of goal-directed behaviour.

### 1.2.2 Pre-clinical models of goal-directed behaviour

Three key characteristics uniquely define the goal-directed behaviours that we intend to measure (de Wit & Dickinson, 2009; Dickinson & Balleine, 1994). Firstly, they are *instrumental* – which is to say they are both learned and mediated by the causal relationship between an action (e.g. go for a run) and its outcome (e.g. loose weight). Second, there must be knowledge of the contingency between action and outcome that drives this behaviour. This attempts to separate goal-directed, from *habitual* behaviours that may have been reinforced automatically without direct knowledge of the action-outcome relationship (Washburn & Thorndike, 1912). Finally, there must be a representation of goal outcome in terms of its motivational or affective value that drives behaviour (de Wit & Dickinson, 2009; Dickinson & Balleine, 1994).

One of the first examples to demonstrate that instrumental behaviour can be entrained, manipulated, and measured was by Adams and Dickinson in 1981 (Adams & Dickinson, 1981). They did this by sequentially exposing hungry rodents to either freely available feed (non-response contingent) or a reinforced alternative (response-contingent), which involved lever pressing on a variable ratio schedule in return for reward. Once the rodents had been trained to lever press for reward, a devaluation exercise followed. This involved freely pairing one of the reward options with a noxious stimulus (intraperitoneal injections of lithium chloride) and the alternative with a non-noxious control (intraperitoneal saline). The rodents were split so that in one group the noxious stimulus was coupled to the reward associated with lever pressing (paired group), whereas in the other it was coupled with the freely available reward (unpaired group). Finally, rodents underwent an extinction test, which involved exposing them to a non-dispensing lever (i.e. pressing it does not provide rewards).

In a typical extinction test, the lever pressing response should diminish over time and eventually cease, however the authors hypothesised that this response would be more pronounced in rodents in whom lever pressing was instrumentally coupled to the devalued outcome (i.e. the paired group). As expected, rodents in the paired group pressed the lever significantly less times than those in the unpaired group (Adams & Dickinson, 1981). These data demonstrated that specific aspects of instrumental motivated behaviour, in this case 'reward valuation', can be objectively measured and manipulated.

Other paradigms have since been developed to investigate the various components of motivated behaviour and how they may be altered in amotivation syndromes. These include: how benefits (i.e. reward) and costs (i.e. effort) are simultaneously evaluated when choosing between two competing options (J. D. Salamone et al., 1991); how to predict the probability of receiving future rewards (Montague et al., 1996; Schultz et al., 1997); what behaviours are characteristic of reward anticipation (Knutson et al., 2002); and how rodents respond after receiving a reward (Willner et al., 1987). Similar paradigms have been translated in humans to account for these processes in people with motivation disorders (Der-Avakian & Pizzagalli, 2018).

### 1.2.3 Effort-based decision making for rewards

An emerging framework that has been used to conceptualize the motivational aspects of apathy in people is that of effort-based decision making for rewards (EBDM) (Husain & roiser, 2018). Paradigms that assess EBDM, some translated from animal studies, have the potential to provide important insights into the phenotypes of neuropsychiatric disease by probing different phases of behaviour. These include the instrumental, consummatory and learning phases of motivated behaviour outlined in **Fig 1-2** and explained below.

When deciding whether to pursue a course action, an individual may weigh up its potential benefits (e.g., reward/avoiding punishment) against its costs (e.g., effort/risk) versus other possible actions – a process referred to as "option selection" (Husain & roiser, 2018). Alternatively, having invested some effort towards a specific goal, one may re-evaluate the merit of sustaining further effort in its pursuit. Paradigms examining these processes in patient groups can manipulate the benefits and costs of actions systematically to highlight potential deficits in effort-based decisions (Le Heron, Plant, et al., 2018; Treadway et al., 2009). Some frameworks conceptualise these processes as encompassing the "wanting" or instrumental components of motivated behaviour to seek a particular outcome (J. D. Salamone & Correa, 2012; Thomsen et al., 2015).

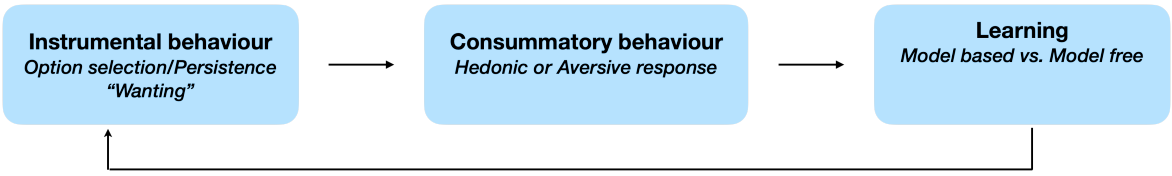



**Figure 1-2. Phases of effort-based decision making for rewards.**

Effort based decisions making can occur across three conceptual phases. Option selection includes the processes of weighing up components of decisions and behaviourally manifests as wanting. Consummatory phase refers to the interaction with a behavioural goal which may be positive or negative. Learning reflects the process of updating beliefs based on a representation of the environment that is structured (i.e. model based) or otherwise (model free). Figure based on our review on motivation disorders in (Saleh et al., 2021).

Whereas the decision making process represents the "wanting" aspect of behaviour, consummatory responses represents the interaction with a behavioural goal, which may be positive (hedonic) or negative (aversive) (J. D. Salamone & Correa, 2012; Thomsen et al., 2015). Having engaged in a behaviour with an unexpected positive/negative outcome, expectations of reward may be updated in relation to behaviour. In laboratory settings, this

can be achieved by varying the frequency of rewarding different actions. For example, one response may be rewarded 90% of time and another only 60% of the time (A. J. Culbreth et al., 2021; Hernaus et al., 2018). Over the course of an experiment, participants learn to favour one action based on the frequency of reward (or reinforcement schedule). Deficits in the learning process may impair individuals from representing the value of reward appropriately to guide future motivated behaviour to influence future decisions.

The last decade has seen a significant rise in EBDM studies in neurological and psychiatric diseases spanning several of these components of decision making (Albrecht et al., 2019; Barch et al., 2014; Chang et al., 2019, 2020; Chong et al., 2016; Cooper et al., 2019; A. J. Culbreth et al., 2021; Gold et al., 2013; le Bouc et al., 2016; Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018; Muhammed et al., 2016; Pessiglione et al., 2018). The investigations that have been performed aimed to probe cognitive mechanisms underlying behavioural deficits of clinical apathy (le Bouc et al., 2016; Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018; Muhammed et al., 2016; Pessiglione et al., 2018), as well as its associated constructs such as avolition and anhedonia (Barch et al., 2014; McCarthy et al., 2016; Treadway et al., 2009, 2015). Below I focus on the instrumental process of option selection, which forms the basis of my investigations.

### 1.2.4 Option selection: is it worth it?

Option selection tasks are designed to investigate how people weigh up the benefits and costs of initiating effortful behaviour in return for rewards (Husain & roiser, 2018). At the core of option selection is the view that decisions involve a two stage process of valuation, followed by choice (Kable & Glimcher, 2009). Several factors may influence decision making during valuation. These include the subjective evaluation of rewarding outcomes (or reward

sensitivity), the probability of receiving rewards (which may diminish or *discount* reward value), and the perception of the associated cost (or effort sensitivity) (Glimcher & Fehr, 2013). Counterbalancing both components is important in developing a comprehensive view of the valuation process and subsequent decision making. The end point of integrating these factors is the construction of an option specific *subjective value* which determines the final choice to be selected (Kable & Glimcher, 2009).

Parametric variation of variables such as reward and effort forms the basis of option selection paradigms (Bonnelle et al., 2016; Treadway et al., 2009). Reward is often represented in monetary form, while effort can be either physical (i.e. button press/squeezing a hand held device) (Bonnelle et al., 2016; Le Heron, Plant, et al., 2018; Treadway et al., 2009), or cognitive (Chang et al., 2020; McGuigan et al., 2019; Westbrook et al., 2013). The inclusion of effort is both relevant and important as it represents a critical aspect of motivation – the willingness to work for reward (J. D. Salamone & Correa, 2022). Paradigms aim to index this willingness to work by investigating their choices to pursue or reject effortful actions at varying levels of reward and effort.

#### 1.2.4.1 Option selection in neurological disease

An increasingly utilised option selection paradigm in neurological conditions is known as the 'Apple Gathering Task' (AGT, **Fig. 1-3A**) (Bonnelle et al., 2015; Chong et al., 2015). In one of its early uses, Chong et al, administered it to 26 patients Parkinson's disease (Chong et al., 2015). Participants were asked to weigh up whether to expend physical effort in return for monetary reward. Reward magnitude was represented by the number of virtual apples on a tree (one apple was worth ~ one pence) , and physical effort by the height of a yellow bar on the tree's trunk. Effort was expended by squeezing on a hand held device as a proportion of

maximum voluntary contraction (MVC). On a trial by trial basis, people were asked if an offer was 'worth the effort'. Notably, the authors used a staircase procedure to incrementally vary effort and reward in response to previous choices. For example, if a participant accepted to expend 30% of their MVC in return for five Apples, the next trial may increase the effort requirement to 50%. This was repeated until participants were equally likely to reject or accept an offer. This point, also known as the *indifference* point indexes the discounting effect of effort on different reward magnitudes and was the measure of interest in this study.

The authors demonstrated that PD patients were less willing than controls to accept offers (i.e. they had lower indifference points), but only when the rewards were low. In other words, they were less *sensitive to low rewards*. While they were interested in whether this effect was mediated by apathy, none of the patients were apathetic, as indexed by scores on the Lille Apathy Rating Scale (LARS). Subsequent option selection studies have since demonstrated that apathy in PD is associated with reduced willingness to accept offers, and specifically an *insensitivity to rewards* – that is, they accept the least offers when the rewards are low (le Bouc et al., 2016; Le Heron, Plant, et al., 2018).

More recently, Chong and colleagues have also demonstrated that PD patients with apathy are also less willing to invest cognitive effort in return for reward (McGuigan et al., 2019). Specifically, they asked 20 PD patients if they were willing to expend a low amount of cognitive effort for low reward, or a high amount for high reward. Cognitive effort was performed by participating in a rapid serial visualisation presentation (RSVP) task (McGuigan et al., 2019). This involved identifying a target letter (e.g. 'T') among a series of 24 rapidly moving streams over a 10 second trial. The number of letters (between one and six) per stream dictated trial difficulty. The authors demonstrated that the number of high

effort choices selected was inversely related to cognitive apathy, indexed by the Dimensional Apathy Scale.

These findings confirm that option selection can be used to quantifiably measure components of motivated behaviour, and that these may be demonstrably altered in apathy. A possible mechanism of apathy in PD may be that of reward insensitivity. One may ask if this pattern of behaviour is specific to apathy in PD, or common to apathy across disease states. Husain and Roiser recently proposed that apathy may be a transdiagnostic syndrome, affecting a multitude of patient groups, but caused by similar underlying processes (Husain & roiser, 2018). In neurology, most EBDM experiments have focussed on PD patients, however a recent study also administered the AGT to in 19 patients with a heritable form of cerebrovascular disease known as CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subacute Infarcts and Leukoencephalopathy) (Le Heron, Manohar, et al., 2018). The authors demonstrated that apathetic patients with CADASIL accepted significantly less offers, and were less reward sensitive than their motivated counterparts (Le Heron, Manohar, et al., 2018).

A natural question is whether these findings in CADASIL, which is rare, are also present in its non heritable form, also known as sporadic small vessel disease (sSVD). This patient group represents a valuable cohort to advance our knowledge of apathy for several reasons. First, SVD is increasingly common, occurring in up to 36% in those aged 70 or over. (Hilal et al., 2017; E. E. Smith et al., 2015). Second, apathy occurs in up to 52% of patients with sSVD (Hollocks et al., 2015). Finally, there is increasing evidence that specific white matter tract changes in sSVD are associated with apathy (Hollocks et al., 2015; Tay et al., 2019), however it is not clear whether apathy in this condition is associated with measurable deficits

in motivated behaviour, and how these may related to its brain changes (Hollocks et al., 2015). These questions are addressed in a multimodal investigation of 82 patients with sSVD in chapters two and three of my thesis which have been published here (Saleh, Le Heron, et al., 2021).

If apathy is transdiagnostic, we should also expect that deficits in option selection are also present in psychiatric diseases. For example, motivation deficits affect 47% of schizophrenia patients (Yazbek et al., 2014), however it is unclear if the behavioural deficits of amotivation in schizophrenia are like those encountered in neurological conditions. Over the last decade, an increasing number of studies have investigated how EBDM, and specifically option selection may be altered in schizophrenia, especially in relation to negative symptoms and motivation deficits. Below is a summary of the key findings of option selection experiments in schizophrenia from my review on the topic (Saleh, Jarratt-Barnham, et al., 2021).

#### 1.2.4.2 Option selection in schizophrenia

One of the earliest and most used option selection paradigms is known as the "*Effort Expenditure for Rewards Task*" (EEfRT, **Fig 1-3B**) (Treadway et al., 2009, 2015). This paradigm and its variations have been widely used to probe option selection in healthy controls and patients with psychiatric disorders including schizophrenia (Barch et al., 2014; Chang et al., 2019; Fervaha et al., 2013; Hartmann, Hager, et al., 2015; Treadway et al., 2015). In this task participants exert physical effort either by selecting to press on a key using the dominant index finger (low-effort) or the non-dominant little finger (high-effort). While the low effort condition is paired with a single fixed low reward (e.g. $1), the high effort condition can be paired with one of four possible higher reward magnitudes (e.g. $1.3-$4.3).

Additionally, the outcome probability is varied across all conditions to incorporate an element of uncertainty (25%, 50% or 88%). On a trial by trial basis, participants are offered either a low reward–low effort condition or a high reward–high effort condition with outcome probability varied (**Fig. 1-3A**).

The most consistent finding reported using this task is that schizophrenia patients paradoxically accept less offers than healthy controls when reward levels and probabilities are the *highest* (Barch et al., 2014; Fervaha et al., 2013; Gold et al., 2013; Hartmann, Hager, et al., 2015; Horan et al., 2015; McCarthy et al., 2016; Moran et al., 2017; Reddy et al., 2015; Treadway et al., 2015). Further, some studies demonstrate that this effect is most pronounced in patients with higher negative symptom severity (Cooper et al., 2019; Gold et al., 2013; Hartmann, Hager, et al., 2015), although this finding is not consistent (Barch et al., 2014; Fervaha et al., 2013; Horan et al., 2015; Moran et al., 2017). These inconsistencies might arise due to a variety of reasons which include use of different analysis approaches (Fervaha et al., 2013; Horan et al., 2015), questionnaire types (Fervaha et al., 2013; Hartmann, Hager, et al., 2015; Moran et al., 2017) or task variations (Horan et al., 2015). In those investigations where there were significant associations between performance and negative symptoms, correlations tended to be driven by the MAP components (**Fig. 1-1**) of the negative syndrome (i.e., avolition, asociality and anhedonia) and not the expressive component (i.e., alogia and blunted affect) (Barch et al., 2014; Cooper et al., 2019; Fervaha et al., 2013; Hartmann, Hager, et al., 2015).

While the EEfRT task manipulated physical effort, variations of this have investigated the effects of *cognitive* effort on decision making in schizophrenia (Chang et al., 2020; A. Culbreth et al., 2016; A. J. Culbreth et al., 2020; Felice Reddy et al., 2018; Gold et al., 2014;

Reddy et al., 2015). One example is the "N-back" working memory task, where participants are asked if a displayed letter in a rapid, serial sequence is identical to the one presented "N" steps previously (**Fig. 1-3D**) (Westbrook et al., 2013). For example, the "easy" 1-back condition involves comparing each letter to the preceding one in the sequence and reporting if it is the same or different. On the other hand, the more challenging 4-back condition requires a comparison of each letter with the one shown four steps previously. Typically, participants were given a choice between a 1-back trial at low reward ($1) or a 2-4 back trial for high reward ($2) (Chang et al., 2020; A. Culbreth et al., 2016; A. J. Culbreth et al., 2020). Critically, the value of the low-reward condition was adjusted based on the previous trial's response to arrive at an indifference point. This was used to compute a per condition subjective value as well as an overall summary measure of effort costliness known as the area under the curve (AUC). Schizophrenia patients discounted rewards more steeply than controls as a function of cognitive effort on the N-back task (Chang et al., 2020; A. Culbreth et al., 2016; A. J. Culbreth et al., 2020). This effect, as measured either by the subjective value (Chang et al., 2020; A. J. Culbreth et al., 2020) or the AUC parameters (A. Culbreth et al., 2016), was specifically associated with negative symptom severity (Chang et al., 2020; A. Culbreth et al., 2016; A. J. Culbreth et al., 2020).

However, the nature of these associations is not very clear. For example, in a recent study by Chang et al. the relationship between behaviour and negative symptoms varied depending on the outcome measure of interest (Chang et al., 2020). After taking the sum of anhedonia, asociality and avolition scores on the BNSS questionnaire, schizophrenia patients were split down the median into amotivation$^{+}$ and amotivation$^{-}$ sub-groups. When comparing the proportion of high reward-high effort responses, both amotivation$^{+}$ and amotivation$^{-}$ sub-groups accepted fewer offers compared to healthy volunteers. On the other hand, a

comparison of subjective value between groups revealed a significant decrease in this parameter in the amotivation$^{+}$ sub-group compared to controls, but there was no difference between the amotivation$^{+}$ and amotivation$^{-}$ patients. Finally, there was no association between the AUC measure and negative symptoms in this study, which contrasts with findings by other groups using very similar paradigms (A. Culbreth et al., 2016).

Taken together, these findings suggest that schizophrenia patients are impaired in the "option selection" process of motivated behaviour (**Fig. 1-3A-C**). Specifically, they forego high reward opportunities when they are coupled with high effort costs. This effect is present regardless of whether the cost is physical (EEfRT) or cognitive (N-back). Investigations utilising the EEfRT task suggest these deficits might arise due to impairments in constructing reward value (Barch et al., 2014; Gold et al., 2013; Reddy et al., 2015; Treadway et al., 2015) while N-back experiments support an additional role for cognitive effort avoidance (Chang et al., 2020; A. Culbreth et al., 2016; A. J. Culbreth et al., 2020). However the associations between these behavioural deficits and negative symptoms, including amotivation, are unclear. There are three possible reasons for this.

First, the EEfRT task and some of its variations do not vary reward and effort equally. For example, in the version of the paradigm that has been most frequently deployed, there are five reward manipulations and only two effort conditions (**Fig. 1-3A**) (Barch et al., 2014). So people accepting higher effort conditions are also accepted higher reward conditions. It is not clear whether these two components are evaluated independently or not. One way to clarify this can be by utilising task structures which parametrically and symmetrically co-vary reward and effort. Second, there is significant variation in the definitions of apathy and motivation across studies. This may contribute to the inconsistencies in the associations

between behavioural deficits in schizophrenia and questionnaire measures of apathy. One way to minimise this would be through consistent use of modern instruments like the brief negative symptom questionnaire (BNSS) and their validated factor structures for apathy (Kirkpatrick et al., 2011; Strauss et al., 2012).

Finally, Cognitive dysfunction is a well-documented core phenomenon in schizophrenia (Heinrichs & Zakzanis, 1998; Kahn & Keefe, 2013; Schaefer et al., 2013), but the association with negative symptoms is complex (Harvey et al., 2006). While questionnaire analyses reveal correlations between negative symptoms and cognitive impairment (Good et al., 2004; O'Leary et al., 2000), these associations are often modest and weakened when adjusting for confounding factors such as functional outcomes (Bowie et al., 2006; Couture et al., 2011; Heydebrand et al., 2004). In the case of EBDM, impaired cognitive function has been shown to be associated with altered decision making for rewards (Heerey et al., 2007, 2008). Notably, a recent re-analysis of several studies using the *EEfRT* task demonstrated that schizophrenia patients with difficulties in constructing value representations were characterised by greater impairments across measures of cognitive function (Cooper et al., 2019). Hence, reward sensitivity in schizophrenia is not only altered by negative symptoms but also by cognitive impairment.

These findings suggest negative symptoms and cognitive dysfunction are, at the very least, highly interdependent and might operate in tandem to regulate motivated behaviour (Robison et al., 2020). A better characterisation of this interaction at the behavioural level would be imperative in uncovering the relationship between negative symptoms, cognitive impairment and EBDM. In chapter four, we conduct an EBDM in a cohort of treatment resistant schizophrenia patients to address some of these limitations.

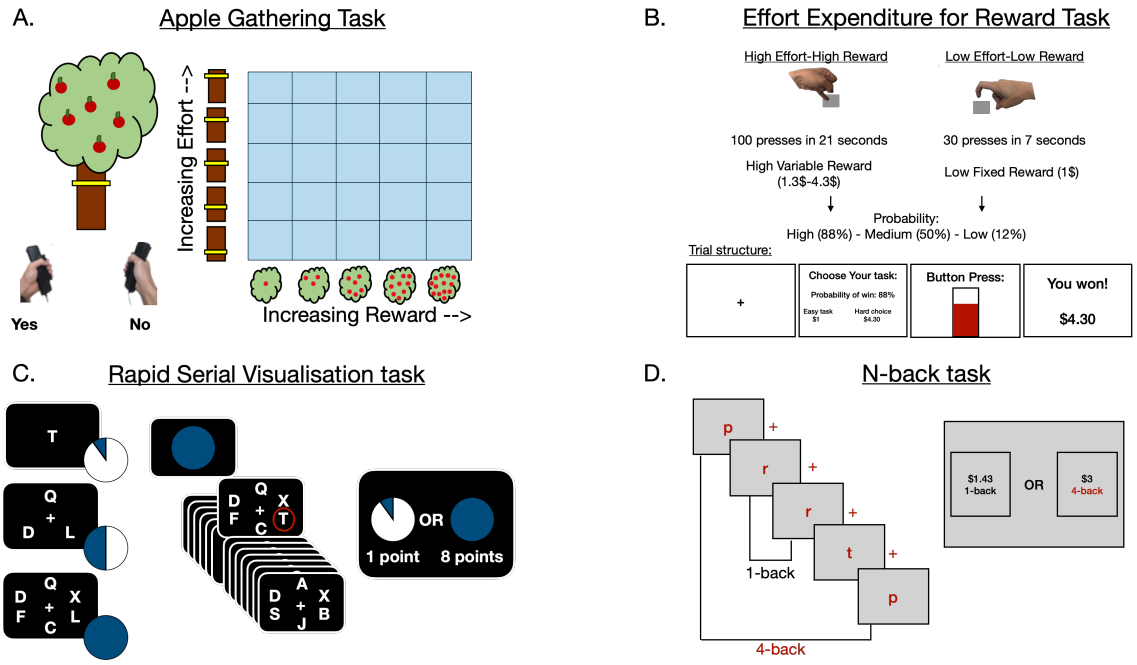



**Figure 1-3. Option selection paradigms.** A summary of physical (**A-B**) and cognitive (**C-D**) option selection tasks used to investigate apathy. (**A**)The Apple Gathering task asks participants whether they are willing to exert physical effort in return for monetary reward**.** Reward is represented by virtual apples on a tree and effort by the height of yellow bar on the tree trunk. Reward and effort are varied parametrically, creating a virtual decision space where motivated behaviour, indexed by the proportion of offers accepted, can be assessed. The Effort Expenditure for Rewards (EEfRT, **B**) is a button pressing task primarily used in schizophrenia. People are asked to choose between a high effort-high reward vs a low effort-low reward option on each trial. A difficult trial involves performing 100 presses using the non-dominant little finger, while the easy trial involves performing 21 presses using the dominant index. Rapid serial visualisation tasks (RSVP, **C**) probe cognitive effort by asking people to identify a target letter (e.g. 'T') amongst a rapidly presented stream of visual stimuli (circled in red, middle). Difficulty can be varied by altering the number of targets per stimulus (left). During each trial participants choose between a cognitive effortful option for high reward vs a cognitively easier option for low reward. Another example is the N-back paradigm (**D**) which involves asking people if letters presented in a constant stream are the same as the ones presented N letters back. For example, an easy 1-back task involves comparing each presented letter to the one before it, while a more challenging 4-back option involves comparing each letter to the one four letters prior.

### 1.2.5 Computational modelling of motivated behaviour

Analysis of option selection tasks is centred on assessing choice data (i.e. accept/reject an offer) across different experimental conditions. In other words, groups may compare the

proportion of offers accepted at different levels of reward and effort (Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018), or how many times they selected a difficult option vs. an easier one (Gold et al., 2013; Treadway et al., 2009). While these are useful in demonstrating the 'what' of behavioural differences, they are less able to account for the 'how' or 'why' aspects of behaviour. For example, PD patients completing an option selection task are less willing to exert physical effort (i.e. squeezing a hand held device) in return for rewards when they are off vs on dopaminergic (DA) treatment (le Bouc et al., 2016; Le Heron, Plant, et al., 2018). This may be due to an intrinsic loss of motivation, *insensitivity* to rewards, or a *hypersensitivity* to effort.

One approach that can help clarify which of these underlying processes is responsible is to use computational modelling tools (Husain & Roiser, 2018; le Bouc et al., 2016; Pessiglione, Vinckier, Bouret, Daunizeau, & le Bouc, 2018). These are algorithms that leverage principles of decision theory to generate predictive models of behavioural data. One example of how decision theory may frame the process of option selection is by assigning to each possible choice a subjective value (sv). This comprises a linear combination of its benefits (e.g. rewards) and costs (e.g. effort), and can be used to approximate the probability of accepting a particular choice (*p*). Mathematically sv and *p* can be represented using the following equations:

1. $sv = \alpha\text{Reward} - \beta\text{Effort}$ (amend)

2. $p = {}^{1}/_{1 + e^{-sv}}$

The symbols $\alpha$ and $\beta$ are free parameters that vary across participants and represent reward and effort sensitivities, respectively. So the process of computational modelling involves fitting this value function to each person, allowing investigators the opportunity to develop a deeper understanding of how these specific parameters may influence motivated behaviour. These tools have contributed significantly to our understanding of option selection. For example, Le Bouc and colleagues were able to use a computational modelling approach to explain why patients with PD are more willing to expend high amounts of physical effort in return for high rewards when on vs off DA treatment. Specifically they were able to demonstrate that this enhanced responsiveness to effort expenditure is driven by an increased sensitivity to reward, rather than an insensitivity to effort (Le Bouc et al., 2016). Notably, they were also able to show that changes in apathy questionnaire measures on and off DA could also be accounted for by the reward sensitivity parameter (Le Bouc et al., 2016).

More recently, Le Heron and colleagues used a similar modelling approach to demonstrate that apathetic patients with a genetic form of small vessel disease (CADASIL) are characterised by insensitivity to rewards during option selection (Le Heron, Manohar, et al., 2018). Taken together, these findings suggest that computational modelling techniques can help investigators shed valuable light on the underlying behavioural mechanisms of motivated behaviour and its possible deficits in neuropsychiatric syndromes.

While these models focus primarily on the choice behaviour, they do not account for the reaction time (RT) data. RT measures have played a key role in advancing our understanding of several psychological processes, including: attention (Saltzman & Garner, 1948), perception (Jaśkowski, 1996), arousal (Eason et al., 1969), and response inhibition (Burle et al., 2004). Critically, well validated computational models of RT data exist in tasks which

constrain choices to one of two potential options, or two alternative forced choice (2AFC) paradigms (Noorani & Carpenter, 2016; Ratcliff & Mckoon, 2008). One example is the drift diffusion model (DDM), which combines both RT and choice data to account for a variety of decision making behaviours (Bogacz et al., 2006; Ratcliff & Mckoon, 2008). These include item recognition (Ratcliff, 1978a), perceptual discrimination (P. L. Smith et al., 2014), signal detection (Ratcliff, 2002), and more recently value based decisions (Berwian et al., 2020) and reward based learning (Wiecki et al., 2013). Below I outline describe how the DDM characterises 2AFC tasks, what inherent assumptions precede its appropriate use, and whether this approach can be used in option selection tasks to advance our understanding of amotivation syndromes.

#### 1.2.5.1 Drift diffusion modelling and effort based decision making

The DDM frames two-choice decisions as a noisy process characterised by the accumulation of evidence up to a threshold, after which a decision is made (i.e. accept/reject). The model can be described by the following four terms: i) The threshold criterion, *a*, which represents the distance between the two alternative choices; ii) the bias, *z*, representing the *a priori* starting point of evidence accumulation (**Fig 1-4**). A perfectly non-biased decision would therefore have a value of $a/2$. So if $z$ is $> a/2$, then less information overall is required to reach the upper threshold (i.e. accept an offer) than is required to reach the alternative choice (i.e. reject). iii) The non decision making aspects that contribute to the reaction time including stimulus perception, encoding and motor execution. iv) The rate of evidence accumulation, or drift rate, $V$, towards $a$ (**Fig 1-4**).

One of the commonly cited applications of this modelling approach has been in perceptual decision making (Ratcliff & Mckoon, 2008), however recent work has leveraged the DDM

approach towards option selection paradigms, drawing valuable insights from several aspects of motivated behaviour (Berwian et al., 2020; Westbrook et al., 2013; Wiecki et al., 2013). For example, Westbrook and colleagues demonstrated that methylphenidate, a DA and noradrenaline reuptake inhibitor, increases willingness to exert cognitive effort in return for rewards when performing an N-back task (Westbrook et al., 2013). A DDM was then fit to the data which allowed the drift rate parameter to reflect the subjective value of offers ( as in equation 1). In other words, the rate of evidence accumulation towards accepting an offer increased with more reward and decreased with accumulating effort costs. Their model demonstrated that methylphenidate exerted its motivational effect by enhancing the effect of reward on evidence accumulation.

In another study, Berwian and colleagues used DDM to characterise effortful decisions making in patients with major depressive disorder (MDD) (Berwian et al., 2020). In a button pressing task, people were offered a choice between a high effort/high reward offer or a low effort/low reward one. The authors demonstrated that patients chose the high-effort option less frequently than healthy people (Berwian et al., 2020). Notably, this behaviour was driven by increased effort sensitivity, indexed by a parameter that measured the disincentivising effect of effort on drift rate (Berwian et al., 2020). In other words, increasing effort decreased the rate of evidence accumulation towards accepting an offer, and this effect was enhanced in patients with MDD. Taken together, these findings support the use of DDM techniques in option selection tasks, and suggest this approach can improve our mechanistic understanding of neuropsychiatric syndromes.

As a result, I have decided to use the DDM across my option selection task investigations to assess if its parameters can account for behavioural deficits in apathetic patients. This is

conducted in patients with SVD (chapter 3-4), schizophrenia (chapter 5), and fronto-striatal lesions (chapter 6).

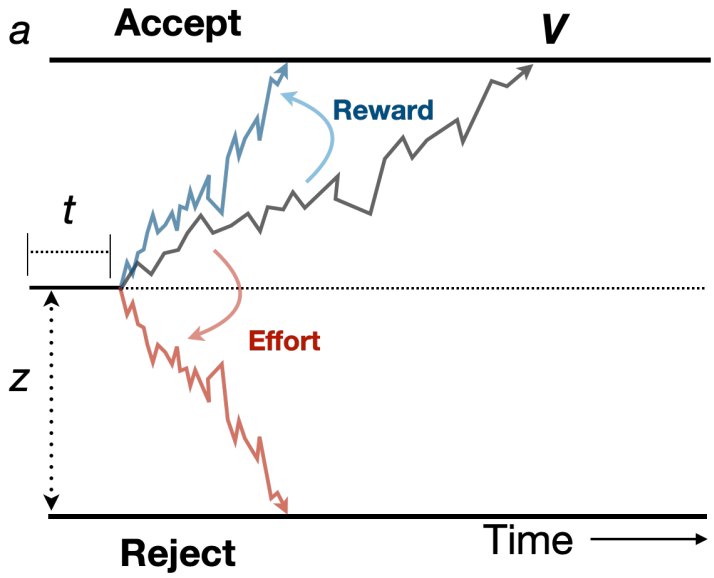



**Figure 1-4. Drift diffusion model (DDM)**. DDM combines choice and reaction time data to account for two choice forced alternative tasks, including option selection tasks. It frames a decision as a noisy process of evidence accumulation towards a threshold (*a*) after which a decision is made (e.g. Accept/Reject). The starting point of the evidence accumulation is represented by the bias term, *z*, while the average rate of evidence accumulation is referred to as the drift rate (*V*). Non-decision making components of behaviour including sensory perception and motor execution are encoded using the term, *t*. Recent adaptations of the DDM for option selection tasks have included variations of the drift rate with reward and effort. These assume that *V* increases and decreases respectively with increasing reward and effort.

### 1.2.6 Beyond action selection: modelling motivational dynamics

While option selection tasks can shed valuable light on the behavioural correlates of apathy, they provide an incomplete account of motivated behaviour. Typically, the paradigms discussed so far are concerned with the process of evaluation and terminate at the point of decision making. So while they speak to the direction of motivated behaviour (i.e. which option should I choose?) they do not speak to its intensity (i.e. how fast should I button press?), nor its dynamics (i.e. how does pressing behaviour change over time?). Some

measures of the choice behaviour can be gleaned from option selection tasks, including reaction time, however these reflect the termination of the evaluation process rather than the contents of the behaviour itself. Critically, choice behaviour is often encoded as a binary yes/no. However ecologically, motivated behaviours (e.g. hunting, gathering, grooming, mating) are both continuous and dynamic. What is missing from current EBDM tasks is a more granular view of motivated behaviour over time. Specifically, I am interested in how people sustain and vary effort while engaged in goal pursuit, especially when faced with setbacks. This is often referred to as persistence (Howard & Crayne, 2019).

Persistence and societal success have been described as "inseparably bound" (Ryans, 1938). More than 80 years on, this view endures in the modern mind. Across several studies, persistence has been associated with improved academic performance (Lufi et al., 2003), fruitful entrepreneurial ventures (Przepiorka, 2016), and successful cessation of smoking (Brandon et al., 2003). Several terms have been associated with persistence, including perseverance, tenacity, and endurance (Howard & Crayne, 2019). A popular term currently associated with it is that of "grit", which refers to the combination of perseverance and passion towards long-term goals (Duckworth et al., 2007; Jachimowicz et al., 2018; Lucas et al., 2015). Like persistence, grit been associated with several positive outcomes across professional domains (Datu, 2021; Duckworth et al., 2007). For example, questionnaire measures of grit predict: grade point averages (GPA) in undergraduate students (Duckworth et al., 2007); retention in surgical training programmes (Burkhart et al., 2014), and general psychological well being (Renshaw & Bolognino, 2016; Samson et al., 2011). One question remains as to how these constructs can be measured using behavioural paradigms.

Several behavioural investigations have attempted to measure behavioural persistence, usually as a function of time spent on difficult tasks (Lucas et al., 2015; Meindl et al., 2019; Ventura et al., 2013; Ventura & Shute, 2013) or tasks with rigged feedback (McLauchlan et al., 2019). For example, some groups have investigated how long people are willing to persist when attempting to solve a set of anagrams, some of which are unsolvable (Lucas et al., 2015; Ventura et al., 2013). Others have developed tasks that are frustrating to complete, such as the 'Mirror Tracing Frustration' task (Lucas et al., 2015). This involved asking people to trace the outline of a shape presented on a computer screen while visually reversing (or *mirroring*) the participant's movements, making it much more challenging (Lucas et al., 2015). Across paradigms, measures of persistence (Ventura et al., 2013; Ventura & Shute, 2013), or grit (Lucas et al., 2015; Styk & Klinkosz, 2020), have been associated with increased time spent on solving difficult tasks.

Only one experiment though has investigated if behavioural persistence is altered in clinical apathy (McLauchlan et al., 2019). Specifically, McLauchlan and colleagues asked 51 patients with Huntington's disease to complete a button pressing task themed around a virtual car chase where the feedback was rigged to indicate that participants' failure to catch up with their target (McLauchlan et al., 2019). They showed that questionnaire measures of apathy were associated with greater time spent on the task. While the authors interpreted these findings as suggestive of an *insensitivity to failure*, they also showed that apathy in this patient group was associated with executive dysfunction, indexed by a verbal fluency (McLauchlan et al., 2019). So it is possible that patients with apathy were not performing the task correctly, or simply perseverating.

One limitation of current tasks that try to measure persistence is that they do not provide dynamic measures of behaviour. The outcome measure across tasks is a single measure of time. What is missing is a real understanding of how motivated behaviour varies over time, especially in relation to setbacks or even uplifts in performance. Can a better understanding of behavioural persistence shed further light on motivation? And is this altered in apathy? These are questions that we aim to address in the seventh and final chapter of this thesis by developing a novel persistence task

## 1.3 Apathy as a disorder of the fronto-striatal network

### 1.3.1 The fronto-striatal network and motivated behaviour

A key component of the neuro-cognitive model that we hope to develop for clinical apathy relies on associating the symptoms and behavioural phenotypes of the syndrome to specific brain regions. Early evidence for the neural correlates of apathy come from lesion studies in patients suffering with akinetic mutism, an amotivation syndrome characterised by spontaneous lack of speech and immobility (Bhatia & Marsden, 1994; Mega & Cohenour, 1997; Németh et al., 1988; Yoshida et al., 1976). For example, Nemeth and colleagues demonstrated in a post-mortem study of four people with akinetic mutism that all displayed bilateral lesions within the anterior cingulate cortex (ACC) (Németh et al., 1988). Additionally, several case studies have associated amotivation syndromes like abulia (Bhatia & Marsden, 1994) and clinical apathy (Adam et al., 2013) with bilateral basal ganglia lesions, including the caudate nucleus and globus pallidus (Adam et al., 2013; Bhatia & Marsden, 1994). These findings suggest that amotivation syndromes may be associated with pathology within a specific network – possibly centred around the medial frontal and basal ganglia structures.

Studies in animals have played a key role in identifying the presence of such a network, typically referred to as the fronto-striatal system (**Fig. 1-5**), that plays a central role in both reward processing and motivated behaviour (Haber, 2016; Haber & Knutson, 2010; J. D. Salamone et al., 2007; J. D. Salamone & Correa, 2012). Key components include the: ventral tegmental area (VTA) within the midbrain; ventral striatum (VS) – including the nucleus accumbens (nAcc); anterior cingulate cortex (ACC); and ventromedial pre-frontal cortex (vmPFC) (Haber, 2016; Haber & Knutson, 2010). Early support for the role of this group of structures arose from self-stimulation studies in rodents (Olds & Milner, 1954). Electrodes implanted within the VTA, ACC, or septum pellucidum selectively elicited a significant increase in *learned* self-stimulation, suggesting these brain areas were associated with reward processing (Olds & Milner, 1954).

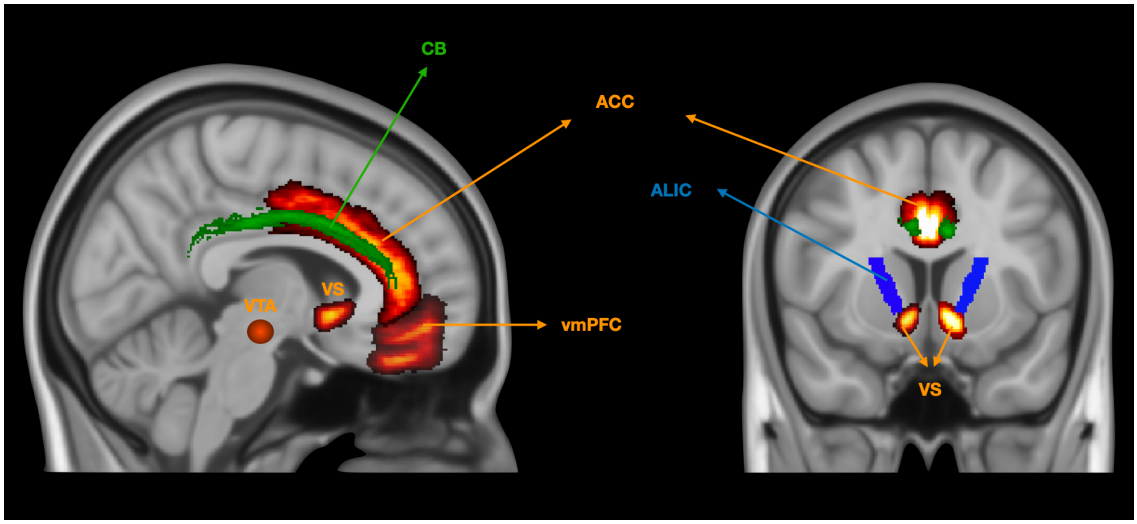



**Figure 1-5. Components of the fronto-striatal network.** This network, which is heavily implicated in regulating motivated behaviour, links the medial forebrain regions to the basal ganglia structures. Dopaminergic neurons within the ventral tegmental area (VTA) innervate the ventral striatum (VS). These project to medial forebrain regions such as the anterior cingulate cortex (ACC) and the ventromedial prefrontal cortex (vmPFC), which in turn innervates the VS, forming a fronto-striatal loop. Connecting neurons travel within specific white matter tracts including the cingulum bundle (CB) and the anterior limb of the internal

capsule (ALIC). Lesions within this fronto-striatal system, or its connecting tracts, are associated with amotivation symptoms across species.

Single cell recordings in primates have subsequently shed invaluable light onto precisely how these brain areas contribute to processing rewarding outcomes. For example, a seminal paper by Schulz in 1997 demonstrated that dopaminergic neurons within the VTA can encode the difference between expected and observed rewards, also known as the prediction error (Schultz et al., 1997). Prediction error signals play an important role in reward based learning (Schultz et al., 1997). On the other hand, OFC in primates has been associated with encoding the overall subjective value of anticipated rewards, (Padoa-Schioppa & Cai, 2011; Wallis, 2012), while the ACC has been associated with the integration of benefits (i.e. effort) and costs (i.e. effort) of decision making (Rudebeck et al., 2006). One critical question however is if lesions in this network replicate amotivation symptoms. Evidence for this can be gleaned from lesion/depletion studies within the fronto-striatal network in animals (J. D. Salamone, 1988; J. D. Salamone et al., 1991, 1994, 2001).

For example, Salamone and colleagues have demonstrated through a series of studies that inducing lesions within the VS, specifically the nACC, is associated with loss of motivated behaviour during option selection (J. D. Salamone, 1988; J. D. Salamone et al., 1991, 1994, 2001). Specifically rodents will significantly bias their choice away from a high effort – high reward option (i.e. lever press 200 times for preferred feed) to a low effort – low reward one (freely available standard feed) (J. Salamone et al., 2002; J. D. Salamone et al., 2001). Similar findings have been demonstrated using T-maze experiments, where animals must either overcome a large barrier on one side to attain a highly rewarding feed, or freely access standard feed on the other (J. D. Salamone et al., 1994). While normal rodents consistently choose to overcome the barrier in return for high reward, those with nAc lesions chose the

low reward option (J. D. Salamone et al., 1994). Similarly, lesions within the ACC and OFC of rodents have been associated with diminished willingness to expend effort and reduced time waiting for rewards, respectively (Rudebeck et al., 2006). These data support the hypothesis that lesions within individual components of the fronto-striatal network can elicit deficits in motivated behaviour. It is possible that one or more of these components are consistently affected in patients suffering with clinical apathy. One way to investigate this in humans has been through neuroimaging investigations, specifically using magnetic resonance imaging (MRI) techniques.

### 1.3.2 Neural correlates of apathy in humans

#### 1.3.2.1 Correlates of amotivation on structural MRI

Structural MRI analyses have allowed investigators to assess the thickness or volume of grey matter across the whole brain using techniques such as voxel based morphometry (VBM) (Ashburner & Friston, 2000; Mechelli et al., 2005). MRI studies have demonstrated thinning, or atrophy, of the fronto-striatal grey matter in apathetic patients across neurological and psychiatric conditions (Apostolova et al., 2007; Grool et al., 2014; Kos et al., 2016; Kostić & Filippi, 2011; Starkstein et al., 2009; Starkstein & pahissa, 2014). For example, apathy in AD (Apostolova et al., 2007), fronto-temporal dementia (FTD) (Rosen et al., 2005), and schizophrenia (Mørch-Johnsen et al., 2015) have all been associated with atrophy within the ACC and the vmPFC/OFC. On the other hand, apathy in PD has been associated with atrophy within the subcortical structures, including the caudate nucleus and the nucleus accumbens (within the ventral striatum) (Carriere et al., 2014).

Apathy is not only associated with atrophy of grey matter, but also the white matter tracts connecting the medial frontal regions to one another and to the basal ganglia (de Paepe et al., 2019; Hahn et al., 2013; J. W. Kim et al., 2011; Kostić & Filippi, 2011; Powers et al., 2014; Prange et al., 2019; Tay et al., 2019). One commonly implicated tract is the cingulum bundle (Hahn et al., 2013; J. W. Kim et al., 2011; Le Heron, Manohar, et al., 2018), which links the ACC to the OFC and to the sub-cortical structures – typically via the anterior and lateral dorsal nuclei of the thalamus (Bubb et al., 2018; Maldonado et al., 2020). Another is the anterior limb of the internal capsule (Hollocks et al., 2015; Le Heron, Manohar, et al., 2018) which carries fibres from both the ACC and OFC/vmPFC to the VS (Safadi et al., 2018a).

#### 1.3.2.2 Apathy as a disconnection syndrome

There is a view that white matter tract pathology may play a critical role in the development of amotivation syndromes. This is driven by two observations. First, while some case studies have suggested an association between specific grey matter lesions and clinical apathy (Adam et al., 2013; Németh et al., 1988), meta-analyses investigating neuroimaging correlates of apathy have demonstrated that these are inconsistent (Douven et al., 2017; van Dalen et al., 2013). For example, a pooled analysis of twelve separate studies has recently demonstrated no significant association between post-stroke apathy and any one of stroke laterality (right/left), type (haemorrhagic/ischaemic), or location (frontal/subcortical) (Douven et al., 2017). Second, some MRI studies have demonstrated associations between apathy and white matter tract abnormalities, but not grey matter changes (Agüera-Ortiz et al., 2017; Starkstein et al., 2009; Tay et al., 2019). For example, Starkstein and colleagues

showed that white matter lesion load in the frontal lobe, and not cortical atrophy, was associated with apathy in 79 patients with AD (Starkstein et al., 2009).

One condition where the role of white matter tract pathology in amotivation can be advantageously explored is that of cerebrovascular small vessel disease (SVD) (Tay, Lisiecka-Ford, et al., 2020). This common neurological disorder is characterised by white matter tract lesions of presumed vascular origin, referred to as white matter hyperintensities (WMH). While early investigations of SVD relied on WMH as the main measure of white matter tract integrity, more sensitive microstructural measures of white matter tract integrity have been developed using diffusion tensor imaging (DTI) techniques (Jones et al., 1999). DTI measures, such as fractional anisotropy (FA), measure the directionality of diffusion along white matter bundles (Jones et al., 1999). So tracts of high integrity will exhibit high anisotropy (i.e. high directionality of diffusion) while those which have been damaged, for example by WMH, will show reductions in FA (Jones et al., 1999). Notably, deficits in FA can precede changes in white matter tract integrity in otherwise normally appearing white matter (de Groot et al., 2013), suggesting that they can probe the neural correlates of apathy more sensitively than visible markers such as WMH.

DTI studies in SVD have demonstrated that apathy is consistently associated with reduced FA within the fronto-striatal white matter. These include the cingulum bundle, the internal capsule, and corpus callosum (Hollocks et al., 2015; Le Heron, Manohar, et al., 2018; Tay et al., 2019). In one recent study, Tay and colleagues demonstrated that both white matter hyperintensities and reduced FA within fronto-striatal connections were significantly associated with apathy (Tay et al., 2019). To further probe their individual contributions, a mediation analysis was conducted. This demonstrated that the association between WMH and

apathy was abolished after accounting for DTI measures. Conversely, the association between DTI measures and apathy remained after controlling for WMH (Tay et al., 2019). This suggests that disconnection within the white matter tracts characterises apathy, and DTI measures are a more sensitive measure of these deficits than visible white matter tract changes. One limitation of this study is that no experimental behavioural measures were collected, which would have allowed two further important questions to be answered. What is the behavioural phenotype of apathy in SVD, and do these correlate with the changes in FA within the fronto-striatal white matter ? We aim to answer these questions in chapters three and four of this thesis respectively.

## 1.4 Dopamine, Motivation, and the Fronto-Striatal system

DA plays a critical role in the regulation of motivated behaviour within the fronto-striatal network (J. D. Salamone, 1988; J. D. Salamone et al., 2007). Specifically, the mesolimbic pathway, which links the VTA to the nucleus accumbens has been implicated in several aspects of instrumental goal-directed action (J. D. Salamone & Correa, 2012). These include reinforcement learning (Montague et al., 1996; Schultz et al., 1997), option selection (J. D. Salamone, 1988), and action initiation (Syed et al., 2015). Notably, DA signalling within the mesolimbic pathway may occur over different timescales (Floresco et al., 2003; Grace, 1991; Niv, 2007). For example, rapid *phasic* firing of DA neurons within the VTA encodes the prediction error signal, which plays a central role in reinforcement learning and subsequent option selection (Montague et al., 1996; Schultz et al., 1997). On the other hand, slower *tonic* firing of DA neurons has been associated with overall willingness to exert effort (Beeler

et al., 2010), as well as the intensity of effortful action, indexed by its vigour or speed (Niv, 2007).

This latter effect is thought to encode the opportunity cost of wasted time, formalised as the average rate of reward lost while choosing not to engage in goal-directed action (Niv et al., 2007). Niv and colleagues proposed that manipulating opportunity cost by altering the average rate of rewards should also influence the intensity of action (Niv et al., 2007). This has been supported by work in humans demonstrating that an increase in average reward rate during effort based decision making increases decision vigour (i.e. shortens reaction times), and this effect is strengthened following treatment with L-Dopa (Beierholm et al., 2013). Taken together, these findings suggest that dopamine signalling may be critical in facilitating the *wanting* aspects of motivated behaviour, either by increasing both the willingness to work, and the intensity at which work is done (Beierholm et al., 2013; J. D. Salamone & Correa, 2012). This is supported by pre-clinical depletion studies within the fronto-striatal network.

DA depletion studies within the nucleus accumbens have demonstrated significant deficits in the willingness to exert effortful action across a range of studies (J. D. Salamone et al., 1994, 2001). This includes options selection paradigms where rodents have to choose between a high effort (i.e. more lever presses/overcome a difficult barrier) in return for a more attractive reward (i.e. higher carbohydrate feed). While they consistently demonstrate a prior preference for effortful options with higher reward outcomes, dopamine depleted rats shift their choice behaviour towards lower effort choices (J. D. Salamone et al., 1994, 2001). Conversely, rodents treated with amphetamine demonstrated an increased willingness to scale a physical barrier on one arm of a T-maze to reach a high carbohydrate feed, rather than

consume freely available low reward alternative on the other side (Bardgett et al., 2009). In healthy people, DA concentrations within the basal ganglia, specifically the caudate nucleus, can predict the baseline willingness to exert cognitive effort in return for reward while completing an N-back task (Westbrook et al., 2020). Similarly, pre-treating healthy people with a single dose of methylphenidate, which is a DA and noradrenaline agonist, significantly increases the willingness to exert effort when performing an N-back task (**Fig 1-3D**). Taken together these findings suggest that DA based therapies may represent a potential therapeutic option for patients suffering with clinical apathy. An important consideration with these findings however is that the effects of dopamine on cognitive control, and specifically working memory, is non-linear and follows and inverted 'U' shape with respect to performance (Cools & D'Esposito, 2011; Vijayraghavan et al., 2007). This should guide treatment protocols to ensure optimal amounts of dopaminergic replacement is offered.

While no clinical trials have been conducted to test this hypothesis, two case studies suggest that DA agonists such as ropinirole can clinically improve patients primarily suffering with apathy (Adam et al., 2013; Kohno et al., 2010). In both cases, patients had suffered with ischaemic strokes to prefrontal cortex and the basal ganglia, respectively (Adam et al., 2013; Kohno et al., 2010). Both patients demonstrated significant clinical improvements after treatment, associated with improvements in validated apathy questionnaires (Neuropsychiatric inventory and Apathy Inventory, respectively). Notably, in one study, the investigators conducted pre and post treatment testing using an EBDM using a saccadic eye movement paradigm. Specifically, they asked people to saccade to the left/right of a fixation cross in return for reward. Critically, only one side was rewarded at a time, and saccadic reaction time (SRT) measured as an index of *reward sensitivity*. They demonstrated that the clinical improvement experience by their patient on treatment was associated with a

significant increase in *reward sensitivity*, indexed by a significant reduction in their SRT towards the rewarded side (Adam et al., 2013).

These findings support the use of DA treatments in apathy, but offers a specific mechanism by which DA may improve apathetic symptoms. However this study only investigated one patient, and their EBDM did not include an effort component during decision making. This is critical as DA treatment may increase motivated behaviour not only by increasing sensitivity to reward, but also by reducing aversion to effort costs. To address some of these questions, we conduct a behavioural investigation of three patients with apathy on and off dopaminergic treatment (chapter six).

## 1.5 Clinical apathy as a disorder of effort-based decision making secondary to fronto-striatal disconnection

In the above sections, I have presented evidence that clinical apathy can be conceptualised as a disorder of goal-directed behaviour (defined in section 1.2.2), and that this can be experimentally measured using well designed EBDM tasks (Husain & roiser, 2018). This includes the process of option selection, which involves the process of weighing up the benefits and costs of effortful action. With the aid of computational modelling techniques, option selection paradigms can provide a deeper understanding of the behavioural mechanisms of amotivation syndromes (Pessiglione, Vinckier, Bouret, Daunizeau, & le Bouc, 2018). Anatomically, amotivation has been associated with pathology within a well defined fronto-striatal network that links the medial forebrain regions to the basal ganglia (Haber & Knutson, 2010). Advances in MRI techniques, specifically the use of diffusion

tensor imaging measures, suggest that apathy may arise due to *disconnection* within the white matter tracts that connect the medial frontal regions to the basal ganglia (Tay, Lisiecka-Ford, et al., 2020). Critically, the neurotransmitter dopamine plays a key role in the normative function of this network and may represent a possible therapeutic option for patients (Adam et al., 2013; Haber, 2014; J. D. Salamone et al., 2018).

In SVD, several studies have demonstrated that apathy is associated with white matter tract deficits , but few have investigated its underlying behavioural mechanisms (Hollocks et al., 2015; Le Heron, Manohar, et al., 2018; Tay et al., 2019). Only one study has investigated the behavioural phenotype of apathy in the genetic form of SVD known as CADASIL (Le Heron, Manohar, et al., 2018). However, the patient sample size was limited and CADASIL, being a heritable form of SVD, may not be representative of the deficits associated the more common sporadic form of the disease.

A critical step in establishing a neurocognitive model of apathy in SVD is to determine if the behavioural and neural correlates of amotivation are directly associated. To answer these questions what is needed is a multimodal investigation that combines EBDM and MRI investigations.

In schizophrenia, several studies have demonstrated behavioural deficits on option selection paradigms (Barch et al., 2014; McCarthy et al., 2016; Treadway et al., 2015). Specifically, schizophrenia patients are less sensitive to high rewards and high effort, however the individual contributions of reward and effort are not clear. Notably, the most used option selection paradigm (the EEfRT task) in schizophrenia does not parametrically vary reward and effort within its experimental structure (Treadway et al., 2015). The associations between

effortful behaviour and amotivation, which is a component of the negative syndrome, is not consistent across studies (Barch et al., 2014; Cooper et al., 2019; Gold et al., 2015; Treadway et al., 2015). This is also compounded by the lack of clarity about the contribution of cognitive impairment, which is common in the patient group, to EBDM deficits (Robison et al., 2020). Finally, it is important to establish how behavioural deficits in psychiatric conditions like schizophrenia compare to those in neurological diseases like SVD.

Dopamine plays a central role in the normative function of the fronto-striatal network, as well as the regulation of motivated behaviour (J. D. Salamone, 1988; J. D. Salamone et al., 2018). Early evidence suggest that it can be used to treat patients suffering with apathy, however these have been limited to two single patient case studies (Adam et al., 2013; Kohno et al., 2010). Only one of these have used EBDM paradigms to measure changes pre and post treatment (Adam et al., 2013), however larger scale studies are required to further clarify whether dopaminergic medications can improve motivation, as measured by performance on EBDM tasks. Finally, while option selection tasks are a valuable tool in assessing motivated behaviour, they do not measure the dynamics of motivation over time. Specifically, they do not demonstrate moment-by-moment regulation of motivated behaviour in relation to external perturbations such as setbacks or uplifts.

In summary, there is increasing evidence from that EBDM tasks are a viable approach to investigate motivated behaviour, and amotivation syndromes. Yet there are limited large scale studies in patients to verify the behavioural phenotype of apathy across neurological and psychiatric conditions. Few studies have successfully related the behavioural and neural correlate of apathy in neurological diseases. Even fewer have investigated the utility of dopaminergic therapies in apathetic patients beyond single patient case reports. I identify four

broad questions related to the use of EBDM paradigms to address some of these questions. My investigations include patients with sporadic SVD, treatment resistant schizophrenia, isolated fronto-striatal lesions, and healthy controls.

### 1.5.1 What behavioural deficits characterise apathy in neurological and psychiatric disease? Are patients reward *insensitive* or effort *hypersensitive*? Can these behavioural deficits be modelled using a drift diffusion model (DDM)?

I Investigate these questions in two separate cohorts, sporadic SVD (chapter 3) and schizophrenia (chapter 5) using a validated option selection task previously used to investigate apathy in Parkinson's disease and CADASIL (Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018). Critically we focus on modelling behaviour using Bayesian Hierarchical drift diffusion modelling (DDM), which combines both reaction time and choice behaviour (accept/reject) into a single framework. This allows us to probe exactly the underlying mechanisms of behavioural deficits, as well as compare behavioural correlates of apathy across conditions. In SVD we additionally explore whether DDM can help clarify between closely correlated constructs of apathy and depression, while in schizophrenia we use DDM to disentangle the individual contributions of negative symptoms and cognitive dysfunction.

### 1.5.2 What are the neural correlates of apathy and behavioural performance of EBDM tasks in SVD ?

In Chapter four, I investigate the neural correlates of apathy in SVD using a combination of structural and diffusion weighted MRI. Specifically, we measure grey matter atrophy using voxel-based morphometry (Ashburner & Friston, 2000), white matter lesion load using a semi-automated algorithm (BIANCA) (Sundaresan et al., 2019), and assess microstructural

measures of white matter tract integrity such as fractional anisotropy using tract based spatial statistics (Hahn et al., 2013). This allows us to test the hypothesis that apathy is a disconnection syndrome within the fronto-striatal network. Importantly, I investigate if the DDM and MRI correlates of apathy are directly related, which may support a 'brain to behaviour' neurocognitive model of apathy in SVD.

### 1.5.3 Is dopaminergic therapy a viable treatment option for apathetic patients with fronto-striatal pathology? What behavioural parameters are influenced by dopaminergic treatment during effort based decision making?

In chapter six, I investigate the use of the dopamine agonist ropinirole as a potential treatment option in three patients with apathy and fronto-striatal pathology (two with bilateral basal ganglia stroke, and one with mild SVD). We use an option selection task to determine their baseline behavioural phenotype as well as their post treatment changes in behaviour. Behaviour was modelled using DDM and individual patient analysis of parameters was conducted to establish the potential effects of dopamine on the motivated behaviour.

### 1.5.4 Can effort based decision making paradigms measure the dynamics of motivated behaviour moment-by-moment? Specifically can they measure the responses to external perturbations such as setbacks and uplifts? Are these dynamic aspects of motivation altered in apathy?

While option selection tasks are primarily used in chapters three to six, I develop a novel EBDM task in chapter seven aimed at modelling the dynamics of motivation over time. Specifically, I design a button pressing task which investigates moment by moment changes in pressing speed in response to external setbacks and uplifts. Finally, I assess if these dynamic measures of motivation are altered in one hundred healthy controls.

# 2. General Methods

## 2.1 Ethics

All clinical studies were approved by the local ethics committee. Informed written consent was obtained from all subjects and all testing was conducted in line with the declaration of Helsinki.

## 2.2 Effort-based decision making task

Chapters 3-6 involved using an effort-based decision making task known as the apple gathering task (**Fig 1-3A)** previously used to investigate apathy in both healthy participants (Bonnelle et al., 2016) and patients with neurological disease (Chong et al., 2015; Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018). This paradigm was designed in psychtoolbox (psychtoolbox.org) within MATLAB and administered on a mounted desktop.

Participants were offered monetary rewards in return for physical effort (**Fig 1-3A**). On a trial by trial basis, they were asked to consider if the reward was worth the effort on offer. They could either accept or reject the offer by gently squeezing the hand held device on the side of the preferred response (Yes / No shown on the screen). If an offer was accepted, participants had 5 seconds to squeeze in proportion to the required effort level and sustain this effort for at least 1 second. No explicit instructions related to time were given at the outset of the experiment. They were only informed that the more apples they collected, the more money they would gain in the end. Online force feedback allowed participants to visualise their proximity to the target force required. Successful effort allocation was followed by a feedback phase confirming the amount of reward secured on the trial as well as the overall reward earnings up to that point. On the other hand, a rejected offer was followed by a short pause followed by commencement to the next trial. Critically, this pause ensured that rejected

and accepted trials were matched for trial length, and less likely to bias participants to reject offers to complete the experiment faster or complete more trials in less time.

Rewards were represented by the number of virtual apples on a tree (1,3,6,9,12, or 15) and effort by the height of a yellow bar on the tree trunk (**Fig 1-3A**). Higher bar positions indicated a higher effort requirement to obtain the reward on offer on that trial. Effort was measured as force expressed by squeezing calibrated hand held dynamometers (SS25LA, BIOPAC Systems). Crucially, the force required was a percentage of each participant's own maximum voluntary contraction (10,24,38,52,66 or 80 %) established as a mean of 3 trials prior to testing, so it was 'normalized' to each individual's physical capabilities, rather than given as absolute levels of force required. To minimise fatigue, effort expenditure was equally distributed across both hands. Further, on 25% of the accepted trials, patients were exempt from squeezing and allocated the reward at no cost.

With 6 levels of reward and effort, 36 possible offer types were available. Each offer type was sampled 5 times, giving a total of 180 trials divided into 5 blocks of 36 trials. Trial order was pseudo-randomised, ensuring all patients were presented the offers in the same order. Before the experiment, each participant practiced squeezing the hand held device at each effort level and completed a full practice block with 36 trials. The extracted behavioural parameters were choice (i.e., accept or reject), reaction time and force metrics. In chapter five, a slight variation of this paradigm is used to accommodate patients with schizophrenia, who are generally more cognitively impaired than the general population. This is discussed in the specific methods section of that chapter.

## 2.3 Analyses

### 2.3.1 Raw behavioural data

Raw acceptance rates and reaction time data was compared using unpaired t-tests between groups and robust linear regressions within groups. In-depth analysis of behavioural mechanisms was conducted using a logistic regression with mixed effects for the choice data. This was conducted in MATLAB using the *fitglme* function. Trials whose reaction time (RT) was < 0.4s were discarded as being accidental, as were those with RTs > 3 times the standard deviation for each participant where they were likely to have been distracted or inattentive. For each model, the parameter estimate, F-statistic and p-value was reported. Statistical significance was inferred when p-values were < 0.05 and corrected for multiple comparisons where appropriate. Model fits were assessed using the Akaike and Bayesian information criterion (AIC/BIC).

### 2.3.2 Hierarchical drift-diffusion modelling of effort-based decision making

Performance on the effort-based decision making paradigm can be viewed as a two-alternative forced choice (2AFC) task where participants must choose between accepting or rejecting an offer. Framing the task this way enabled us to utilise well validated 2AFC modelling approaches such as drift diffusion modelling (DDM) (Bogacz et al., 2006; Ratcliff, 1978; Ratcliff & Mckoon, 2008). DDM assumes that evidence accumulates in a noisy manner until a decision boundary is reached, at which point a decision is made (i.e. reject or accept). The model is generally described by four parameters:

- The threshold, *a*, representing the distance between the two alternative decisions (i.e. Accept or reject).

- The bias, $z$, representing an a priori starting point of evidence accumulation as a function of a where a non-biased starting point = 0.5.
- The non-decision time, $t$, which represents time allocated for decision independent processes such as perception, movement initiation and execution.
- The drift rate, $V$, representing the rate of evidence accumulation.

To accommodate the structure of the experimental task, $a$, $z$ and $t$ were fixed across conditions, whereas drift rate was varied with the reward and effort in each segment of our decision space. For each subject the drift rate comprised of four subcomponent parameters:

- The average drift rate across all trials $v_0$
- The effect of reward on drift rate, or $v_r$
- The effect of effort on drift rate, or $v_e$
- The effect of the reward x effort interaction on drift rate, or $v_{r*e}$

The actual drift rate ($V_{r,e}$) for each segment within the decision space was therefore assumed to be a linear combination of reward, effort, and their interaction such that:

$$V(r,e) = v_0 + v_r r - v_e e - v_{r*e} re$$

A well validated DDM toolbox (Wiecki et al., 2013) was used to fit this model to the data (http://ski.clps.brown.edu/hddm_docs/; version 0.8.0; Python 3.6). Informative group mean priors created by Wiecki and colleagues were used (see supplementary material in (Wiecki et al., 2013)) to roughly match parameter values reported in the literature (Matzke & Wagenmakers, 2009a). Markov chain Monte Carlo methods (MCMC) generated samples

from the joint posterior distributions of all model parameters. Six MCMC chains were run , each having 10,000 samples with the first 1,000 samples discarded as "burn-ins". The model assumed a 5% fixed probability of outlier RT data. Convergence checks were conducted by visualising trace plots and computing R-hat, or Gelman Ruben, statistics across the six MCMC chains. Model fits were assessed using the deviance information criterion (DIC). Following model selection, posterior predictive checks were conducted to ensure model predictions could accurately retrieve behavioural patterns in the original data set.

Population level analysis with "subject" included as a hierarchical factor was conducted, followed by separate fits for each subject. This gave rise to whole group and per subject posterior distributions for $V$ (including its subcomponents), $z$, $a$ and $t$. Bayesian inference was used to compare the effects of reward and effort on overall drift rate across the whole group. This is reported as the posterior probability ($P_{P|D}$) of our hypothesis of interest. Additionally, for all 7 parameters, we extracted the mean of the posterior distribution per participant and assessed their relationship to clinical measures of interest such as apathy within groups.

# 3 Behavioural mechanisms of apathy in cerebrovascular small vessel disease

## 3.1 Chapter Summary

Patients with small vessel cerebrovascular disease frequently suffer from apathy, a debilitating neuropsychiatric syndrome, the underlying mechanisms of which remain to be established. Here we investigated the hypothesis that apathy is associated with disrupted decision making in effort-based decision making, and that this is dissociable from depression. Eighty two patients with MRI evidence of small vessel disease were assessed using a validated option selection paradigm. The decision making task involved accepting or rejecting monetary rewards in return for performing different levels of physical effort (hand grip force). Choice data and reaction times were integrated into a drift diffusion model which framed decisions to accept or reject offers as stochastic processes approaching a decision boundary with a particular drift rate. Overall, patients with apathy accepted significantly fewer offers on this decision making task. Notably, while apathetic patients were less responsive to low rewards, they were also significantly averse to investing in high effort. The drift rate to decision parameter was significantly associated with both apathy and altered white matter tracts, suggesting that both brain and behavioural changes in apathy are associated with this single parameter. On the other hand, depression was associated with an increase in the decision boundary, consistent with an increase in the amount of evidence required prior to making a decision. These findings demonstrate altered effort-based decision making for reward in apathy, and highlight dissociable mechanisms underlying apathy and depression in small vessel

disease. They provide clear behavioural targets for future therapeutic interventions, as well as modelling parameters that can be used to measure the effects of treatment.

## 3.2 Introduction

Small vessel disease (SVD) is a disorder of ageing which primarily affects cerebral microvessels (Van Der Flier et al., 2018; Wardlaw et al., 2019). Initially thought to be innocuous, SVD is currently considered to be the largest contributor to vascular dementia worldwide, and is typically characterised by white matter hyperintensities on magnetic resonance imaging (Pantoni, 2010; Ter Telgte et al., 2018; Wardlaw et al., 2013). Radiological and pathological features also include lacunes, sub-cortical infarcts, microbleeds, enlarged perivascular spaces and cerebral atrophy (Van Der Flier et al., 2018; Wardlaw et al., 2013). Up to 50% of people with SVD and 92% of individuals with vascular dementia suffer from apathy (Hollocks et al., 2015; Kazui et al., 2016), a syndrome associated with poor functional outcomes (Clarke et al., 2007); lower quality of life (Tierney et al., 2018); significantly increased risk of dementia (Ter Telgte et al., 2018; Wardlaw et al., 2013) as well as mortality (Eurelings et al., 2018). Despite its burden on patients and their carers (Feast et al., 2016), there are no current treatments for this condition, partly due to a poor understanding of its mechanisms.

Apathy has been conceptualised as a deficit in "motivated voluntary behaviour" - a deficit in linking motivation to the initiation of action (Le Heron et al., 2019). A novel approach to quantify motivated behaviour in patients is to examine performance on paradigms which assess effort-based decision making for rewards. These tasks, which have been translated from studies of animal models (J. D. Salamone et al., 2016; Walton et al., 2002, 2006), have played an important role in phenotyping apathetic behaviour in humans by probing different

phases of decision making (Husain & Roiser, 2018). An important component of deciding whether to take a behavioural course of action involves weighing up its perceived benefits (e.g. potential reward) , against its subjective costs, (e.g., effort required to obtain that reward). By parametrically manipulating reward and effort within an experimental task, it is possible to better characterise the behavioural changes that underly apathy (Chong et al., 2015; Chong & Husain, 2016).

A priori, at least three distinct mechanisms may contribute to apathetic behaviour. Firstly, it is possible that patients with apathy might be hypersensitive to effort, and therefore not willing to invest in behaviours that they perceive to be too physically or mentally demanding even when the reward outcome is high. Alternatively, they might be less incentivized by rewards, and only accept those few offers with the highest reward outcomes regardless of the effort requirement. Finally they may be less inclined to accept offers overall, irrespective of the associated reward or effort. A recent investigation in Parkinson's disease (PD) revealed that apathetic patients performing an effort-based decision making paradigm were less willing to exert effort in return for reward, particularly when the levels of reward were low (Le Heron, Plant, et al., 2018). Crucially, they were just as willing as non-apathetic PD patients to allocate high levels of effort when the rewards were high. Thus apathy in PD is associated with insensitivity to rewards for low magnitudes of reward, rather than hypersensitivity to effort. This has therapeutic implications because dopaminergic therapy, known to ameliorate apathy can improve reward sensitivity in PD (Drew et al., 2020; Muhammed et al., 2015). It is not clear if the same type of deficit underlies effort based decision making in SVD, or if apathetic behaviour across different diseases might be characterized by very different underlying impairments.

While reward insensitivity characterises apathy in PD, it may be that apathetic patients with SVD are hypersensitive to effort, insensitive to reward or generally less willing to initiate actions. Some evidence for reduced reward responsiveness comes from an investigation in a heritable form of SVD known as CADASIL (Le Heron, Manohar, et al., 2018). In this study, 19 patients completed an option selection task where people were asked to exert physical effort (i.e. squeezing a hand held device) in return for monetary reward. The authors demonstrated that apathetic patients with CADASIL accepted significantly less offers than their motivated counterparts, especially during low reward offers (Le Heron, Manohar, et al., 2018). This suggests that reward insensitivity may be common in both PD and CADASIL. However, this study examined a limited number of patients, and it remains an open question as to whether the findings in this rare genetic condition would translate to the much more prevalent, sporadic form of SVD that typically occurs later in life.

One important consideration to make across the EBDM studies in PD and SVD is that they have inferred many of their mechanistic insights purely based on choice behaviour (i.e. accept/reject rates) (le Bouc et al., 2016; Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018). Specifically, computational modelling algorithms were fit to the acceptance rates across conditions (i.e. reward and effort manipulations) giving rise to parameters such as *reward sensitivity* and *effort sensitivity* (Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018). However these models did not account for another important aspect of behaviour, which is reaction time (RT). RT information provides a rich source of behavioural data that has been used to account for several cognitive processes including: attention (Saltzman & Garner, 1948), perception (Jaśkowski, 1996), and response inhibition (Burle et al., 2004). One way to model both RT and choice behaviour has been using drift diffusion modelling approaches (DDM).

DDM frames decision making as a noisy process where evidence continuously accumulates towards one of two potential decision boundaries (Bogacz et al., 2006; Ratcliff & Mckoon, 2008). Historically, they have been used to model processes such as item recognition (Ratcliff, 1978) and signal detection (Ratcliff, 2002), however more recently they have been adapted to account for value based decisions (Berwian et al., 2020; Westbrook et al., 2020) and reward based learning (Wiecki et al., 2013). In one recent example, Berwian and colleagues used the DDM to model decision making of 74 patients with major depressive disorder (MDD) during an option selection paradigm (Berwian et al., 2020). They were able to adapt the DDM to accommodate the inherent experimental design of their option selection paradigm. The authors then demonstrated that patients with MDD were characterised by *hypersensitivity* to effort when compared to healthy people (Berwian et al., 2020). Taken together, these findings support the use of DDM approaches to model option selection in neuropsychiatric syndromes.

Another important question to consider when investigating the behavioural correlates of apathy is whether it is behaviourally distinct from depression. Despite their symptomatic overlap (Husain & Roiser, 2018), there is increasing evidence that these two constructs are in fact dissociable (Kirsch-Darrow et al., 2006; M. L. Levy et al., 1998; Starkstein et al., 1992, 2005, 2009; Tay, Morris, et al., 2020). For example, Kirsch-Darrow and colleagues demonstrated in 80 patients with Parkinson's disease that up to a third of patients demonstrate symptoms consistent with clinical apathy, but not depression (Kirsch-Darrow et al., 2006). More recently, Tay and colleagues showed in a large group of SVD patients that apathy, but not depression was independently associated with the future development of

dementia (Tay, Morris, et al., 2020). So can we demonstrate dissociable behavioural phenotypes of apathy and depression in SVD?

In this chapter I conducted an option selection experiment in 82 patients with SVD, which was modelled using drift diffusion modelling techniques (Wiecki et al., 2013). My aim were to answer the following question:

1. What are the behavioural changes of apathy associated with effort-based making for reward in sporadic SVD?
2. Can behavioural data in our option selection task be modelled using drift diffusion modelling?
3. Can DDM parameters accurately dissociate the behavioural phenotypes of apathy and depression in SVD?

## 3.3 Methods

### 3.3.1 Participants

We screened 104 patients with expected MRI evidence of SVD from the Oxford Vascular Study (OXVASC) and Oxford neurology clinics between January 2015 and February 2019. The OXVASC study is a population-based cohort study of patients who underwent MRI following a TIA or minor ischaemic stroke (Hurford et al., 2020; Zamboni et al., 2019). They were recruited to our study following neuroimaging and therefor a proportion were subsequently excluded if there was no evidence of SVD on their scans. Additionally, patients were recruited from three Oxford neurology clinics:

1. The memory clinic, investigating patients with cognitive complaints.
2. The TIA clinic, investigating patients with possible stroke/TIA
3. The first fit clinic, investigating patients with first possible seizure.

Clinic patients were recruited after confirmed SVD on MRI which included white matter hyperintensities (WMH) of presumed vascular origin, as defined by the STRIVE criteria (Wardlaw et al., 2013), lacunar and/or sub-cortical infarcts. Such a group of patients is likely to have heterogeneous underlying pathology, e.g. some might also have concomitant Alzheimer pathology. Therefore, we also deployed the following exclusion criteria:

Exclusion criteria included:

(1) Known diagnosis of dementia, including clinical diagnoses of Alzheimer's or vascular dementia
(2) Evidence or history suggestive of any concomitant neurodegenerative or neuroinflammatory disease other than SVD.
(3) Participants without an established diagnosis of dementia who were unable to understand and engage with the behavioural testing protocol
(4) Physical disability preventing participants squeezing a hand-held device in response to visual stimuli
(5) Cortical strokes > 1.5 cm longest dimension on MRI (slice thickness = 3mm).

Overall, twenty-two participants were excluded from the initial screening, leaving 82 participants who completed the questionnaire and behavioural decision making components of the study. Reasons for exclusion can be seen in **table 3-1** below and patient demographics in **table 3-2**.

**Table 3-1.**

| Reason for exclusion | Excluded number |
|---|---|
| **Cortical stroke on MRI** | 2 |
| **Normal neuroimaging** | 12 |
| **Unable to engage with behavioural decision making paradigm** | 7 |
| **On dopaminergic therapy** | 1 |
| **Total excluded** | 22 |

### 3.3.2 Clinical measures

Apathy was measured using the Apathy Evaluation Scale (AES), a well described instrument that has been used to characterise apathy across neurological conditions, including SVD (Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018; Marin et al., 1991) . Here we used the self-report version (AES-S). For most of the analyses reported below, the AES score was used as a continuous variable; where we compared groups with apathy and without, we used a cut off AES score of >34 to define apathy. This cut off score has been validated across neurological conditions (S. Andersson et al., 1999; Kant et al., 1998). Depression was measured using the Beck Depression Inventory (BDI) and cognitive function using the Addenbrooke's Cognitive Examination III (ACE-III). Quality of life was recorded using the CANTRIL quality of life ladder. This involves a single response to a visual scale quantifying their perceived quality of life from 1 to 10 at the time of testing (Topp et al., 2015).

### 3.3.3 Effort-based decision making

Participants completed the apple gathering task (**Fig 3-1A)**, a validated effort based decision making task described in detail in the general methods chapter (**section 2.2: Effort based decision making task).** It involved offering participants monetary rewards in return for physical effort across six counterbalanced levels of reward and effort. Parameters of interest were choice and reaction time.

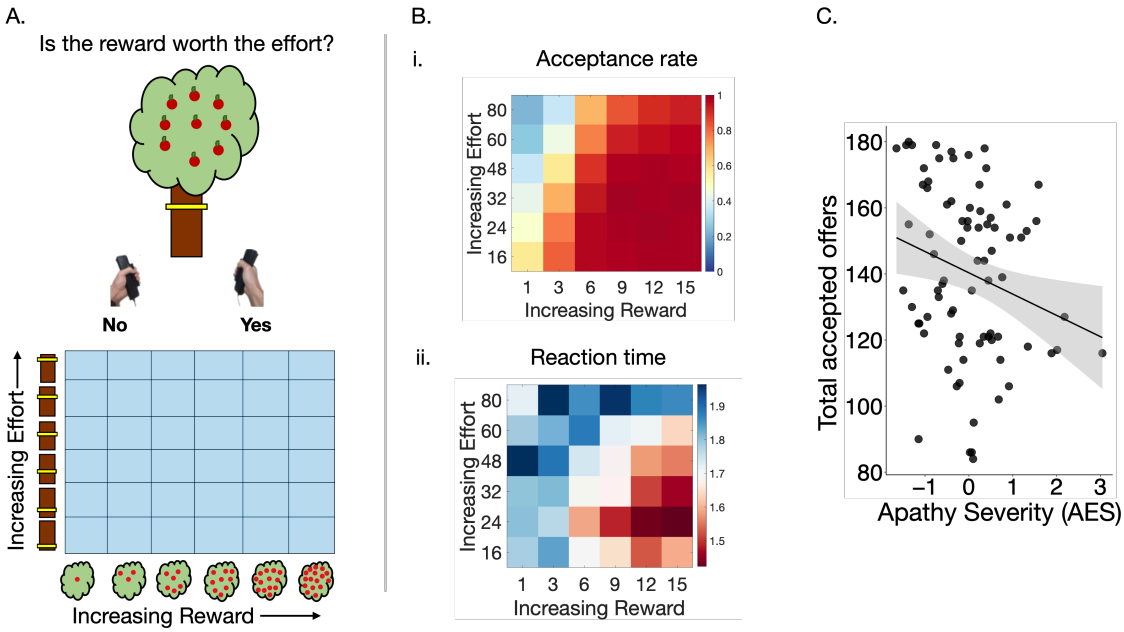



**Figure 3-1. Effort-based decision making-task and overall performance as a function of apathy. a)** On a trial by trial basis, participants were offered monetary rewards (virtual apples) in return for physical effort (height of yellow bar). By varying the amount of reward and effort, their acceptance or rejection of different reward-effort combinations could be mapped in a two-dimensional decision space of reward and effort (6x6 grid, bottom left). **b)** Acceptance rates and reaction times in each section of the decision space. Patients accepted more offers and reacted faster as rewards increased (heatmap becomes more red from left to right). Inversely they rejected more offers and reacted slower as the effort increased (heat map more blue from bottom to top). **c)** Fewer offers were accepted overall with increasing apathy severity (z scored values on x axis).

### 3.3.4 Analyses

**Clinical measures**

Associations between clinical measures of interest were using the lm_robust function in the 'estimatr' R package (https://CRAN.R-project.org/package=estimatr). This applied a weighting function to reduce the influence of outlier data and clustering methods to overcome heteroscedasticity. This approach was also used both to investigate relationships between behavioural data and clinical measures (see below).

**Behavioural data**

All primary analyses were conducted using continuous variable measures rather than clinical cut offs. This was to avoid dichotomising continuous variables (Altman & Royston, 2006; Royston et al., 2006). Where necessary, clinical cut offs were used to support primary analyses. Robust-linear regressions were used to assess the relationship between overall acceptance rate and apathy using the lm_robust function in the 'estimatr' R package (https://CRAN.R-project.org/package=estimatr). This applied a weighting function to reduce the influence of outlier data and clustering methods to overcome heteroscedasticity.

Further analysis of behavioural mechanisms was conducted using a logistic regression with mixed effects for the choice data. RT data was analysed using a similar model but with a linear rather than a logistic model. The total number of excluded trials represented only ~ 2% of trials overall. The models included a random effect of participant and fixed effects of reward, effort, and apathy status. All interactions between reward, effort and apathy were included. For each model, the parameter estimate, F-statistic and p-value was reported. Statistical significance was inferred when p-values were $< 0.05$. In all analyses, the effort penalty term was squared, in line with motor control principles which assign a quadratic

relationship between force requirements and perceived effort costs (Morel et al., 2017a; Shadmehr et al., 2016; Todorov & Jordan, 2002a).

### Hierarchical drift-diffusion modelling of effort-based decision making

Choice and reaction time data were fit using a drift diffusion model (DDM) (details in general methods section 2.3.2). Four general parameters describe this: the threshold parameter ($a$), the bias term ($z$), the non-decision time parameter ($t$), and the drift rate ($v$) which increases as people accept more offers and reduce their decision times (**Fig 3-2A**). As described in the general methods, the drift rate parameter was allowed to vary with reward and effort across each segment of our task's decision making space (**Fig 3-2**) giving rise to four further parameters: an average drift rate ($v_0$), and terms which represent the associations of drift rate with reward, effort, and their interaction (respectively, $v_r$, $v_e$, and $v_{r*e}$).

Seven different variations of our model were conducted to compare whether including all or some of these drift rate terms improved model fit. Similarly, variations of the model were run which included or excluded the bias term (**Appendix chapter three)**. Model fit was compared using the deviance information criterion (DIC), with lower values representing better model fits. Only parameters of the most parsimonious model were examined (**Model four, Appendix chapter three**). These were extracted from the model and regressed against clinical measures of interest including apathy, depression, and cognitive function using robust multiple regressions. All analyses used continuous variable measures, rather than clinical cut-offs.

Following model selection, posterior predictive checks were conducted to ensure model predictions could accurately retrieve behavioural patterns in the original data set (**Fig 3-4A**

**and C**). A detailed explanation of these model evaluation steps can be found in the 'Drift diffusion model evaluation' section in **Appendix chapter three**.

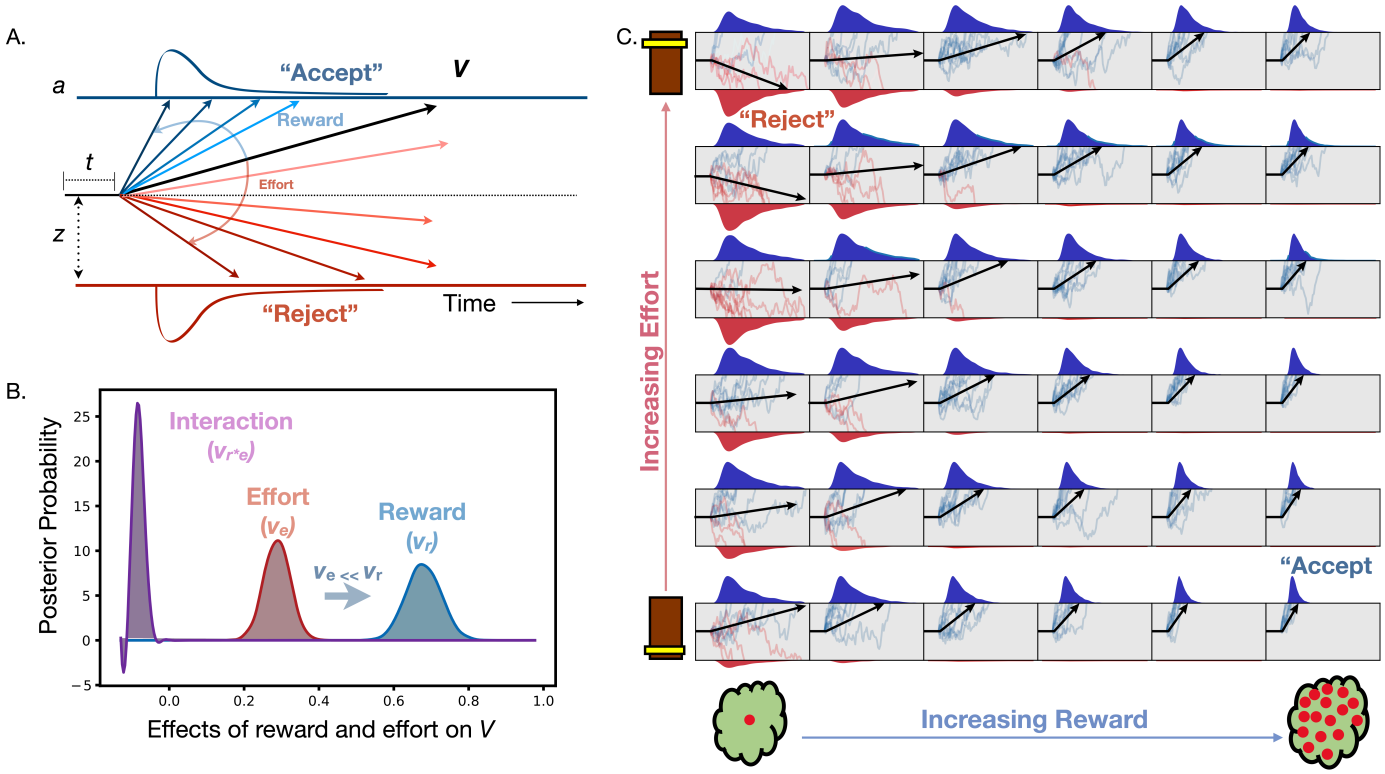



**Figure 3-2. Drift diffusion modelling (DDM) of effort-based decision making for reward. A)** Model assumes decisions to accept offers arise from a noisy process of evidence accumulation up to a decision boundary, *a,* at a drift rate, *V* and starting point of evidence accumulation termed the bias, *z*. The final term accounts for non-decision time components, *t*. **B)** Both reward and effort significantly alter drift rate but reward has a significantly greater impact than effort. **C)** Overview of how drift rate (black arrow) varies with each unique combination of reward and effort posed by our task**.** The drift rate incrementally rises with increasing reward (left to right), and falls with increasing effort (from bottom to top).

**Table 3-2. Patient Demographics**

| Measure | Patient cohort n = 82[1] |
|---|---|
| Age (years) | 68 (11) |
| Gender, female/male | 37/45 (45%/55%) |
| Apathy[a], AES, range 0-72 | 32 (8) |
| Depression, BDI, range 0-63 | 10 (7) |
| Cognition[b], ACE-III ,range 0-100 | 90 (8) |
| Quality of life, CANTRIL, range 0-10 | 7.32 (1.64) |
| Apathetic (AES > 34), Yes/No | 56/27 (67%/33%) |

[1] Statistics presented: mean (SD)

[a] Data missing for 2 participants.

[b] Data missing for 3 participants.

## 3.4 Results

### 3.4.1 Apathy but not depression reduces overall offer acceptance

The influence of apathy severity as a continuous variable on the total number of offers accepted overall was assessed using robust linear regressions. Patients with greater apathy (higher AES score) accepted fewer offers overall [F(1,79)=5.167, p=0.026, **Fig. 3-1C**]. This effect was retained after including depression, age and cognitive impairment as covariates in a multiple regression [F(1,74)=4.51, p=0.037]. By contrast, depression alone did not independently influence the total number of offers accepted [F(1,81)=0.0013, p=0.97]. Together these findings suggest an independent effect of apathy but not depression on motivated behaviour on this task. Robust regression analysis confirmed a significant positive correlation between apathy and depression [F(1,78) = 8.6, p = 0.0044], so these constructs are

clinically related but also dissociable as shown by performance on our task. Additionally both apathy and depression were independently associated with reduced quality of life in a robust multiple regression (respectively [F(1,73)=8.15, p=0.005] and [F(1,73)=10.81, p=0.002]).

### 3.4.2 Apathetic behaviour driven by altered responsiveness to reward and effort

A logistic regression with mixed effects was performed to examine how apathy severity alters decision making with varying levels of reward and effort. Two variations of this model were constructed, one using the AES as a continuous variable, and another using the clinical cut off of AES >34 (respectively Models 1 and 2 in "**Choice models**" section, **Appendix chapter three**). Model 1 provided a superior fit to the data, as measured by the Bayesian information criterion ($BIC_{M1}$=7341 and $BIC_{M2}$=7423) and was therefore deferred to where results between the two models diverged.

The results for Model 1, visualised in **Figure 3-3**, demonstrated a significant two way interaction between apathy severity and reward [t(14599)=+0.23, F(1,14599)=13.49, p=0.0002, **Fig. 3-3A**]. Patients with apathy were less responsive to low levels of reward. Additionally, a significant two way interaction was observed between apathy and effort: more apathetic patients accepted fewer offers at high effort [t(14599)=+0.24, F(1,14599)=25.58, p<0.0001, **Fig. 3-3B**]. Both these effects were observed in Model 2. Notably there was a discrepancy between the two models. Model 2, which divided patients into two groups (apathetic and motivated), showed a significant three-way interaction between reward, effort and apathy ( [t(14599)=+0.11, F(1,14599)=5.45, p=0.019]). In contrast, Model 1, which investigated apathy scores as a continuous variable, did not show such a significant three way interaction ( [t(14248)=+0.085, F(1,14248)=3.54, p=0.059]). In this case we deferred to Model 1 as this provided a significantly improved model fit and was less likely to

demonstrate false positive statistical results, which are more common when dichotomising patients into binary subgroups.

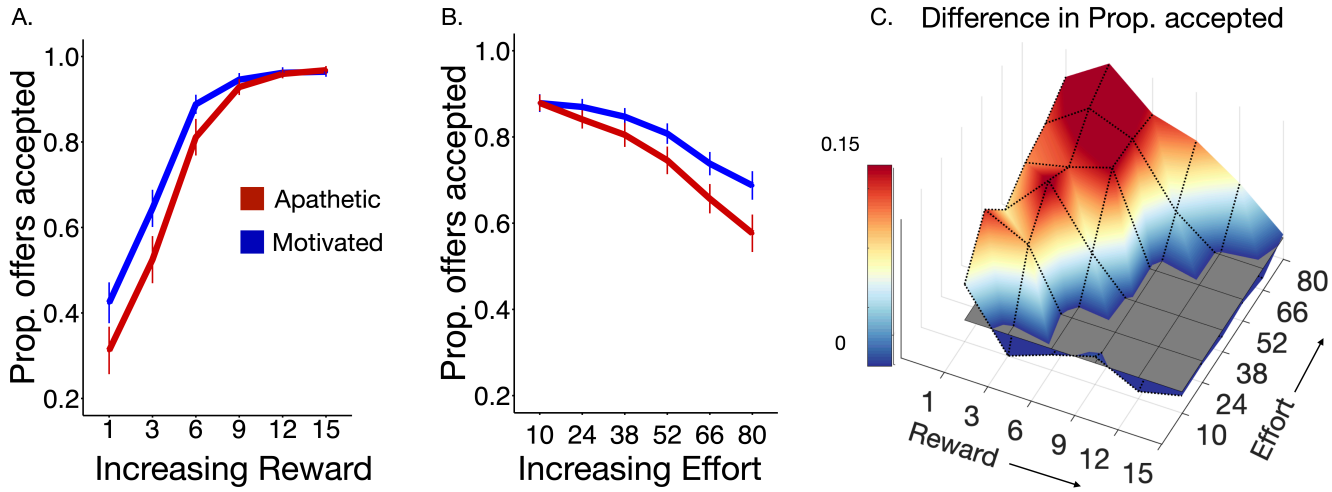



**Figure 3-3 Behavioural performance comparing apathetic vs motivated SVD patients**
**A)** Patients with apathy accepted fewer offers when the reward was low and **B)** effort was high. **C)** Difference in offers accepted between non-apathetic and apathetic individuals in reward-effort decision space. **A)** and **B)** show mean ± SE.

### 3.4.3 Apathy prolongs decision making, especially when reward is low

Two models (Models 1 and 2 in "Reaction time models" section, supplementary data) were conducted to assess the influence of apathy on reaction time data (RT) . They differed in their treatment of the effort term as squared (Model 2) or not (Model 1). The two models observed identical results, and we report Model 2 whose model fit was superior ($BIC_{M1}$=35582 and $BIC_{M2}$=34688). Overall, reward and effort were associated with significant speeding and slowing of decision making (respectively, [$F(1,14196) = 500$, $p < 0.0001$], and $F(1,14196) = 219$, $p < 0.0001$]). In the case of reward, there was an inverted U shape, where lower reward

offers generally required longer time to accept, however progressive increases in reward significantly sped up decisions to accept (**supp Fig 3-1 A)**. Inversely, lower effort offers were quicker to accept, however progressive increases in effort resulted in significant slowing of decisions to accept (**supp Fig 3-1 B)**. A main effect of apathy was demonstrated [F(1,14196)=4.55,p=0.033] as well as a significant two way interaction with reward [F(1,14196)=6.65,p=0.0099]. Patients with apathy were slower overall, and particularly less responsive to low rewards. Additionally, a significant three way interaction was noted between apathy, reward and effort [F(1,14196)=17.09,p<0.001]. There was no interaction, however, between apathy and effort [F(1,14196)=1.79,p=0.18].

Overall, this suggests that patients with apathy were more likely to reject offers and took longer to accept them, especially when the level of reward was low. Additionally, it appears that patients with apathy were also more averse to choosing the high effort option, despite this not influencing their decision speed. To better characterise the meaning of these effects, the choice and reaction time metrics were combined into a single drift diffusion model to gain further insight into these diverging responses to reward and effort. As both the tendency to accept low reward offers and the time taken to do so were altered I apathy, we anticipate that this would reflect in the drift rate, and specifically the drift rate*reward parameter.

### 3.4.4 Both speed and offer acceptance are explained by evidence accumulation model

In addition to choice, another behavioural parameter of interest was reaction time which we incorporated alongside the choice data into a single drift diffusion model to gain further insight into the behavioural mechanisms of apathy. A drift diffusion model (Ratcliff & Mckoon, 2008) was fitted to the data using Bayesian statistical methods. This approach

confers the benefit of providing probability distributions as a measure of certainty in our estimates (components shown in **Fig 3-2A**). Model comparison conducted using seven candidate models demonstrated that the best fitting model, as indexed by the lowest DIC value, was the model which varied the drift rate by reward, effort, their interaction and included a bias term (Model 4, **Supp table 3-2**). This model was used both to generate predictions of both acceptance rate and decision time, and its parameters were regressed against clinical measures of interest including apathy severity. Reward increased and effort decreased drift rate respectively (**Fig 3-2B**). A schematic representation of how the drift rate varies with reward and effort manipulations is depicted in **Fig 3-2C**. Note that the magnitude of change incurred by reward on drift rate was significantly larger than that by effort ($P_{P|D} \approx 1$). This suggests that overall reward had a larger effect on decisions than effort.

The model predictions for both acceptance rates (AR) and decision times (DT) were qualitatively very similar to the raw data (**Fig 3-4**, top panel). Notably, the model accurately predicted the pattern of increasing AR as the reward increased (**Fig 3-4A**, from blue->yellow->red) as well as the high rejection zones (**Fig 3-4A**, light blue –> dark blue) where the reward was low and/or the effort was high. Similarly, the segments of decision space with the highest decision speed (**Fig 3-4C**. in red) were also accurately predicted. Both AR and DT were derived from the drift rate, *V*, using the equations highlighted at the top of **Fig 3-4**. Our model predicted quicker reaction times at the highest levels of reward, although the maximum discrepancy between model prediction and raw RT data was 0.3 seconds (**Supp Fig 3-4C)**. It also predicted a slightly higher acceptance rate at low rewards (**Supp Fig 3-4A)**. As the raw data detected key differences between apathy and motivated people at low reward, it is possible this discrepancy may have under-estimated that model's prediction of apathetic behaviour at low reward. However, it was still accurately able to predict the key findings

demonstrated in patients with increasing apathy severity (**Supp Fig 3-5**). That is, as apathy severity increased, people accept less offers in the low reward regions of decision space, although the overall magnitude of this difference was smaller (**Supp Fig 3-6)**. To investigate how this behavioural prediction influenced the model's seven parameters, we regressed each of them against apathy and depression using robust multiple regressions.

### 3.4.5 Apathy associated with reduced evidence accumulation (drift) rate

Age was included as a covariate, as it independently decreased the baseline drift rate,$v_0$, [F(1,80) = 4.97, p = 0.028]. Crucially, apathy was associated with significantly reduced $v_0$, [F(1,76) = 4.08, p = 0.047, **Fig 3-4D**] while accounting for depression, which had no effect on drift rate [F(1,76)=0.11, p=0.73]. Additionally, apathy significantly altered the effect of reward on drift rate, $v_{r,}$ [F(1,76) = 7.47, p = 0.006, **Fig 3-4E**] but did not influence the effects of effort on drift rate, $v_{e,}$ or the reward x effort interaction with drift rate, $v_{r*e}$, (respectively [F(1,76) = 1.53, p = 0.22, **Fig 3-4F**] and [F(1,76) = 1.59, p = 0.21]). Finally, apathy was not associated with changes to the decision threshold boundary *a* [F(1,76) = 0.93, p = 0.33], nor the bias z [F(1,76)=0.15, p=0.70] .

### 3.4.6 Depression associated with increase in evidence required to make decisions

While accounting for apathy and age, depression was associated with an increase in the decision boundary, *a,* [F(1,76)= 4.74, p=0.033]. Depression was not associated with drift rate components $v_r$, $v_e$, or $v_{r*e}$ (respectively [F(1,76) = 2.62, p = 0.11], [F(1,76) = 0.066, p = 0.80] and [F(1,76) = 0.62, p = 0.43]). Finally there was no association between depression and the bias term, *z*, [F(1,76)= 2.67, p=0.098].

Taken together, this analysis demonstrates that apathy and depression have dissociable effects on DDM parameters. Namely, apathy severity reduced the rate of evidence accumulation (drift rate) towards accepting offers. Additionally, the most important criterion in driving decisions in apathy was reward magnitude. On the other hand, depression increased the amount of evidence required for making a decision, resulting in longer reaction times and less noisy decisions, likely due to increased caution when weighing up offers.

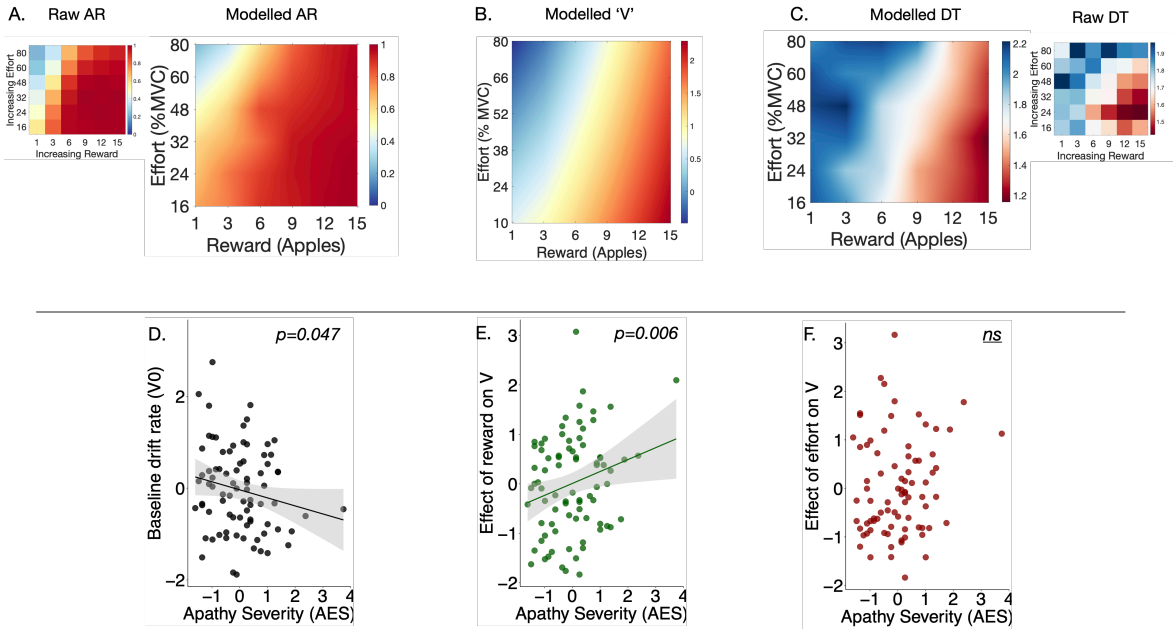



**Figure 3-4. Predicting apathetic behaviour using model parameters. Top:** Model estimates of drift rate in each sector of decision space accurately predicts the acceptance rate when compared with the raw choice data **(A).** Similarly, the model accurately predicts reaction times across different reward-effort combinations (**C**). Both AR and DT are derived from the model's theoretically predicted values, and are based on the drift rate $V_{r,e}$, whose values reflect the changes noted in both AR and DT (**B**). Apathy severity (given here as z-scores) is associated with reduced drift rate overall (**D**), and specifically altered (change) the effect of reward on drift rate (E). Apathy did not significantly influence the effect of effort on the drift rate (**F**).

## 3.5 Discussion

SVD patients with apathy accepted less monetary offers overall in an effort-based decision making task, and this effect was found to be independent of depression severity. Additionally, further behavioural analyses suggest apathy is mediated by a combination of reduced sensitivity to reward (reduced acceptance of offers and increased reaction time when accepting low reward offers) and increased aversion to high effort (reduced acceptance of offers at high efforts). Combining both choice and reaction time data into a mechanistic model of decision-making (DDM), revealed two key signatures of apathetic behaviour that were independent from depression. These were a significant reduction in the rate at which individuals accumulate evidence in favour of initiating rewarded effortful actions (decreased $v_0$), as well as an increased reliance of this drift rate on reward magnitude. Static properties of the DDM (non-decision time, initial bias, threshold) were unaffected by apathy. Importantly, these effects were dissociated from depression, which increased the overall evidence required for making decisions, represented by an increase in the decision boundary parameter.

The behavioural effects delineated here were associated with apathy, rather than arising as a general consequence of SVD severity (indexed by white matter lesion load or average FA), cognitive impairment, age and – most importantly – depression. Thus, although apathy and depression were significantly correlated on clinical measures, they diverged with respect to their association with performance on the effort-based decision making task used here, as well as in the neuroimaging findings (discussed in more detail later).

The behaviour of apathetic patients with sporadic SVD on our paradigm in some ways resembles that previously reported in both CADASIL (Le Heron, Manohar, et al., 2018) and PD (Le Heron, Plant, et al., 2018; Muhammed et al., 2015). Specifically, individuals with

apathy were less likely to accept offers whose reward outcome was low (**Fig. 3-3A**), despite engaging with high reward offers in a similar manner as their motivated counterparts. On the other hand, we also observed an increased rejection of offers by SVD apathetic participants when effort requirements were high (**Fig. 3-3B**) which has not been reported previously in CADASIL (Le Heron, Manohar, et al., 2018) or PD (Le Heron, Plant, et al., 2018; Muhammed et al., 2015). This suggests that while reward insensitivity might be a common, unifying behavioural finding in apathy across neurological conditions, there may also be some differences in effort-related decisions when comparing behaviour across patient groups. Apathy in sporadic SVD shows evidence of significant hypersensitivity to effort, as well as lack of incentivisation by low rewards.

Choice data alone is an incomplete representation of motivated behaviour as it does not include reaction time metrics. We therefore combined both into a Bayesian DDM, providing for the first time a mechanistic account of apathetic behaviour using this framework. Effort-based decisions could be described using seven core parameters. Two of these were altered in apathy while accounting for depression (**Fig 3-4**, bottom). First, the baseline drift rate ($v_0$) was reduced suggesting that evidence accumulation towards making a choice is reduced overall in apathy (**Fig 3-4D**). Second, reward was significantly more likely to alter the drift rate in apathetic patients compared to their motivated counterparts (**Fig. 3-4E**) . This can be interpreted as low reward promoting more rejection, without changing the speed or efficiency of decision-making when reward is high. Drift rate changes can be mapped on to changes in signal-to-noise ratio of information accumulation. However, our results cannot be explained solely in terms of increased *decision noise* in apathy, because crucially this would lead to differences in *both* effort and reward sensitivity. Additionally, we demonstrated this empirically by including decision noise as a covariate in an additional drift diffusion model

which demonstrated no association between apathy and decision noise (see **Appendix chapter three**). Note that it is not possible to separate global changes in decision noise from changes in threshold, in the standard DDM. Taken together, these findings suggest that while apathetic patients may be slower and less likely to exert effort overall, their willingness to exert effort is significantly influenced by how rewarding the outcome of their action is. By contrast, depression was independently associated with an increase in the threshold boundary for making decisions, demonstrating dissociable behavioural effects of apathy and depression in SVD. One criticism of this latter finding is that overall, depression scores in our patient group were low, with only 10 people displaying moderate or severe levels of depression (BDI score >19). Therefore this specific finding will need to be replicated in patient samples with higher depression severity overall.

To the best of our knowledge, this is the first time it has been shown that performance on this effort-based decision making task can be accurately and successfully modelled using DDM (Wiecki et al., 2013) and how it relates specifically to a significant reduction in the drift rate in apathy. DDM is now a well validated approach , traditionally used to model perceptual paradigms (Ratcliff & Mckoon, 2008) and more recently, value-based decisions (Mandali et al., 2019; Sugrue et al., 2005; Tajima et al., 2016). One important potential use of DDM in apathy may be to quantify treatment effects following potential therapeutic interventions, as well as to reveal their precise mechanism of action – on reward or effort sensitivity or decision threshold. A recent study demonstrated that the decision threshold parameter *a* could predict relapses in patients with depression after discontinuation of anti-depressant therapy (Berwian et al., 2020). This is notable as we were able to demonstrate a similar association between questionnaire measures of depression and the parameter *a* in our SVD cohort.

In apathy there has been some evidence suggesting a role for dopaminergic therapy as a possible treatment (Adam et al., 2013; Chong & Husain, 2016; Thobois et al., 2010, Le Bouc et al. 2016). For example, Le Bouc and colleagues demonstrated in Parkinson's disease that dopaminergic therapy is associated with both significant improvements in apathy scores as well as reward sensitivity, indexed by the peak force generated on a hand held force dynamometer in response to increasing amounts of reward (Le Bouc et al., 2016). They also investigated the effects of dopamine on the rate of the rise of force towards its peak, termed the *yank*. They were able to demonstrate that improvements in apathy scores following treatment were associated with significant increases in peak force as reward increased, but not the *yank*. On the other hand, improvements in the motor score were associated with significant improvements in *yank*, and not reward sensitivity (Le Bouc et al., 2016). Taken together this study suggested a possible behavioural mechanism by which dopaminergic treatment may improve apathy. It would be of interest to determine whether drift diffusion parameters such as $V_r$ can be used as behavioural markers of treatment response to dopaminergic therapy. Similarly, it is of interest to note whether DDM parameters are associated to dynamic force measures of motivation such as peak force or yank. One important reason this may be currently challenging to establish is due to a variation in study design in the study conducted by Le Bouc and colleagues (Le Bouc et al., 2016). Specifically, in their the experiment investigating force dynamics, participants were not told exactly how much effort they should squeeze for each level of reward, but rather they were told that they would receive a monetary reward in proportion to whatever effort level they deemed appropriate for that level of reward. This differed to our study design where each offer had a pre-specified effort requirement and people were informed that they only needed to reach that level of effort to secure the associated reward. In our case, this allowed parametric sampling of the entire decision making space in a symmetric manner, however perhaps future work can

utilise a combination of approaches to establish how these measures may relate to one another.

Nevertheless, DDM parameters may well serve as valuable behavioural markers of disease progression and treatment response. They can also be used to investigate the cognitive effects of invasive procedures such as deep brain stimulation whose targets are often implicated in effort-based decision making (Evens et al., 2015; Schlaepfer et al., 2014; Seymour et al., 2016). Combined with DDM, this task can now also be used to validate amotivated behaviour in other neurological conditions where it is common such as Alzheimer's disease (Zhao et al., 2016), Huntington's disease (Heath et al., 2019), traumatic brain injury (Kant et al., 1998; Starkstein & pahissa, 2014) and stroke (Caeiro et al., 2013).

In summary, we have demonstrated clear and distinct behavioural phenotypes of apathy in sporadic SVD that are dissociable from depression. We also demonstrate that the behavioural measures from our option selection paradigm can be fit using a DDM. Two further questions remain in order to advance our neurocognitive model of apathy in this condition. What are the neural correlates of apathy in SVD? and are they somehow related to the DDM parameters that are altered in amotivation? These questions will be addressed in the following chapter.

# 4 Neural correlates of apathy in cerebrovascular small vessel disease

## 4.1 Chapter Summary

The previous chapter characterised the behavioural correlates of apathy in SVD. Here I build on these findings by investigating its neural correlates using diffusion weighted MRI. I hypothesised that apathy, and not depression, is associated with abnormalities in the white matter network connecting brain regions that regulate motivated behaviour. Diffusion weighted MRI was completed in 67/82 of the SVD patients who had completed behavioural testing in our previous chapter. Tract-based spatial statistics were used to assess the relationship between white matter tract integrity and apathy, while accounting for depression. Significant reductions in white matter integrity were observed to be specifically related to apathy, but not to depression. These included pathways connecting the fronto-striatal brain regions previously implicated in effort-based decision making in healthy people. On the other hand, depression was not associated with any specific changes in FA after accounting for apathy. Critically, the drift rate to decision parameter, which was associated with apathy in the last chapter, was significantly associated with white matter tract integrity in the affected tracts. These findings demonstrate that apathy is associated with distinct white matter deficits within the fronto-striatal network, and that these changes are directly related to the behavioural correlates of apathy. They provide a potential neurocognitive model of apathy that links together both brain and behavioural correlates of amotivation in SVD. Notably, they also contribute to the increasingly held view that apathy and depression in SVD are dissociable constructs, that may require different treatment strategies.

## 4.2 Introduction

It is evident from functional neuroimaging studies *in healthy people* that distinct brain regions are activated while performing effort-based decision making tasks (Pessiglione, Vinckier, Bouret, Daunizeau, & Le Bouc, 2018). These are typically located within frontal and striatal regions, including the medial orbitofrontal cortex (OFC) – also referred to as ventromedial prefrontal cortex (vmPFC) – anterior cingulate cortex (ACC) and basal ganglia, including in particular the ventral striatum (VS) (Bartra et al., 2013; Bonnelle et al., 2016; Croxson et al., 2009; Kroemer et al., 2014). Within this network, different regions may contribute to specific components of decision making. For example, activation within OFC and VS correlates positively with increasing reward magnitude (Croxson et al., 2009; Kroemer et al., 2014; Schmidt et al., 2012), whereas lesions to these areas can significantly reduce responsiveness to reward (Adam et al., 2013; Manohar & Husain, 2016). On the other hand the ACC appears to compute the net subjective value of decisions by integrating reward and effort signals (Bonnelle et al., 2016; Croxson et al., 2009; Skvortsova et al., 2014). It has long been known that lesions there can result in severe forms of apathy manifest as akinetic mutism (Barris & Schuman, 1953; Németh et al., 1988). Together these findings suggests that motivated behaviour in healthy people might be regulated by a circumscribed fronto-striatal network, with deficits within this network potentially giving rise to clinical apathy.

Is apathy in SVD associated with disruption to a specific brain network? Several studies have investigated the association between motivational deficits and structural brain changes in SVD, largely focusing on white matter lesions and lacunar infarcts (Grool et al., 2013, 2014b; H. J. Kim et al., 2013; Oudega et al., 2020) . While some report a positive association between these measures and the development of apathy (Grool et al., 2013, 2014b), the findings have been inconsistent (Delrieu et al., 2015; Oudega et al., 2020). There are several

possible reasons. First, previous investigations have not consistently used the same instruments to define apathy, and a recent review highlighted the paucity of studies using validated apathy questionnaires to infer associations in neuroimaging studies (Wouts et al., 2020). Second, recruitment of SVD patients has varied considerably across investigations, from early stage non-demented patients to those with significant cognitive decline (Grool et al., 2014; H. J. Kim et al., 2013). This means that patient groups in some studies have significantly greater lesion burden than others which may alter the associations of interest. In more advanced cases of SVD, lesion load is more likely to represent general disease progression rather than highlight specific neural underpinnings of neuropsychiatric syndromes.

One way to mitigate against this is by using more sensitive diffusion weighted imaging (DWI) measures such as fractional anisotropy, which can quantify microstructural integrity in normal appearing white matter (Lawrence et al., 2013; Moonen et al., 2017; Pasi et al., 2016). These imaging indices might facilitate better detection of network deficits in patients with early stages of SVD whose overall disease burden is low. Two recent investigations have reported that apathy is associated with microstructural deficits within frontal and striatal regions (Hollocks et al., 2015; Tay et al., 2019), but neither of these studies were designed to investigate the behavioural or cognitive mechanisms underlying apathy and relate these to brain networks. Furthermore, there are concerns about how much of the effects attributed to apathy might in fact be due to depression, which is also common in SVD (Van Agtmaal et al., 2017).

While the two syndromes often co-exist, apathy is increasingly recognised as a distinct entity with its own significant clinical impacts (Ishizaki & Mimura, 2011; M. L. Levy et al., 1998; Starkstein et al., 1993). We showed in the previous chapter that despite strong questionnaire

correlations across our 82 SVD patients, apathy and depression displayed different behavioural deficits during effort-based decision making. Specifically, apathy severity was associated with a reduction in overall motivated behaviour and reduced responsiveness to reward, indexed by altered drift rate (v) and the drift rate*reward (*v*reward*) interaction respectively. On the other hand, depression severity increased the time taken make decisions, without necessarily accepting less offers, indexed by a greater threshold parameter, *a*. So there is a behavioural difference between apathy and depression in SVD, but what are the neural correlates of each construct ?

In this chapter, we addressed some of these questions by building on the previous chapter's findings. Specifically a combination of structural and diffusion weighted MRI scans was conducted within our SVD patient group to determine whether distinct neural correlates were associated with either apathy or depression. Critically, we then used the drift diffusion modelling parameters computed in chapter two to establish whether the behavioural deficits of apathy were directly related to its potential neural correlates. This is an important point as it can help us build a 'brain to behaviour' neurocognitive model of amotivation in SVD. I aimed to test the following three hypotheses:

1. Clinical apathy, indexed by questionnaire measures, is associated with distinct white matter deficits within the fronto-striatal network.
2. Apathy and depression display diverging neural correlates on diffusion weighted magnetic resonance imaging.
3. The behavioural deficits demonstrated in chapter three, specifically those generated by the DDM, are associated with white matter tract integrity within the fronto-striatal network.

## 4.3 Methods

### 4.3.1 Participants

As explained in chapter three, 104 participants with expected MRI evidence of SVD were recruited from the Oxford Vascular study, or one of three Oxford neurology clinics (**Fig 4-1**). Post screening, 82 patients completed the first part of the study, which included the questionnaire and behavioural decision making task. Of these, 67 had complete diffusion weighted neuroimaging (DWI), and 62 had both complete structural and diffusion weighted imaging (DWI). Sample size was considered adequate on the basis of previous studies using the behavioural task in patient populations which used 19 and 39 cases of CADASIL and Parkinson's disease respectively (Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018; Marin et al., 1991). A complete flow chart of the study encompassing chapters three and four can be seen in **Fig 4-1** below.

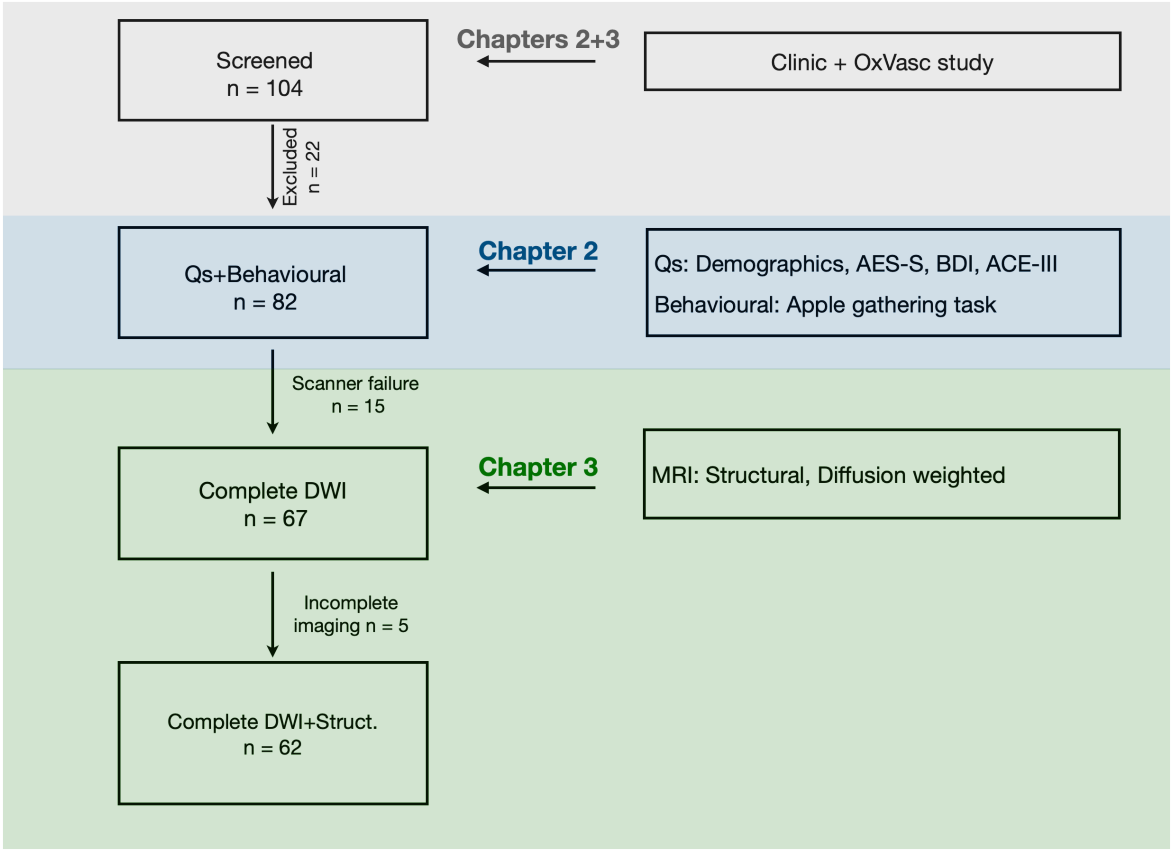


**Figure 4-1. Study flow chart.** One hundred and four patients were initially screened, 82 of which fulfilled our inclusion criteria. All patients completed a series of questionnaires to measure apathy, depression, and cognitive function. They then took part in an option selection task before undergoing a combination of structural and diffusion weighted MRI. Analysis of the behavioural and questionnaire data is discussed in chapter three, while the neuroimaging results and their associations to behaviour are discussed in chapter four. AES-S - Apathy evaluation scale (self report), BDI – Beck's depression Inventory, ACE-III – Addenbrooke's cognitive examination scale (version III), DWI – Diffusion weighted MRI.

### 4.3.2 Clinical measures

As described in the previous chapter, apathy was measured using the self-report Apathy Evaluation Scale (AES-S) (Marin et al., 1991) . Here we used the self-report version (AES-S). For all the analyses reported, the AES score was used as a continuous variable.

Depression was measured using the Beck Depression Inventory (BDI) (Li et al., 1975) and cognitive function using the Addenbrooke's Cognitive Examination III (ACE-III) (Hodges & Larner, 2016).

### 4.3.3 Neuroimaging

Images were acquired in a 3 Tesla Siemens Verio scanner at the John Radcliffe hospital, Oxford. The neuroimaging protocol included: $T_1$-weighted sequence (acquisition time [AT] 4 mins 54s, repetition time [TR] 2,000 milliseconds, echo time [TE] 1.94 milliseconds, inversion time [TI] 880 ms, flip angle 8°, voxel size 1.0 mm iso-tropic), a fluid attenuated inversion recovery, or $T_2$-FLAIR, sequence ([AT] 4 mins 32s, [TR] 9,000 milliseconds, [TE] 88 milliseconds, [TI] 2,500 milliseconds, flip angle 150°, voxel size 1.0x1.0x3.0 mm), and a diffusion weighted echo-planar (EPI) sequence ([AT] 4 mins 40 s, [TR] = 8000 ms, [TE] = 86.0 ms, voxel size = 2 mm iso-tropic, 30 scans with b-value = 1500 s/mm$^2$, b=0 s/mm$^2$).

**Structural image pre-processing and analysis**

All MRI images were initially processed and formatted into standardised brain imaging data structure (BIDS) (Gorgolewski et al., 2016).

White matter lesions were classified using a fully automated, supervised method known as BIANCA (Brain Intensity Abnormality Classification Algorithm) (Griffanti et al., 2016). For each image voxel, BIANCA assigns a probability of there being a white matter lesion of presumed vascular origin. Doing so relies on comparisons with manually segmented training data sets. In this case, we used a training data set of 18 consecutive patients from the OXVASC study who had recently experienced a transient ischaemic attach or minor stroke. This patient group, described in detail by Sundaresan and colleagues (Sundaresan et al., 2019), underwent an identical MRI scanning procedure to our patient cohort and were demographically similar to our patient group. Each scan was manually checked to ensure appropriate classification of white matter lesions by a clinician (see **Fig 4-2A and B**). Finally, total lesion load for each participant was extracted based on the number of voxels with a greater than 80 percent probability of being a lesion.

Cross validation of this method was conducted by comparing mean lesion load values based on clinician scored Fazekas grading (Fazekas et al., 1993). A one way ANOVA confirmed significant increases in lesion load when split by Fazekas score ($F(1,59)=22.92$, $p<0.0001$, **Fig. 4-2C**]. Specifically, lesion volumes in patients with Fazekas score of 3 were significantly greater than those with grade 2 or 1 respectively. This total lesion load score was subsequently used as one surrogate measure for disease severity in our analyses. Additionally, lacunar infarcts were manually checked by a qualified neurologist and included

in our analyses. These were defined based on the STRIVE criteria (Wardlaw et al., 2013) as round or ovoid subcortical, fluid filled cavities between 3-15 mm which had a white rim on FLAIR MRI.

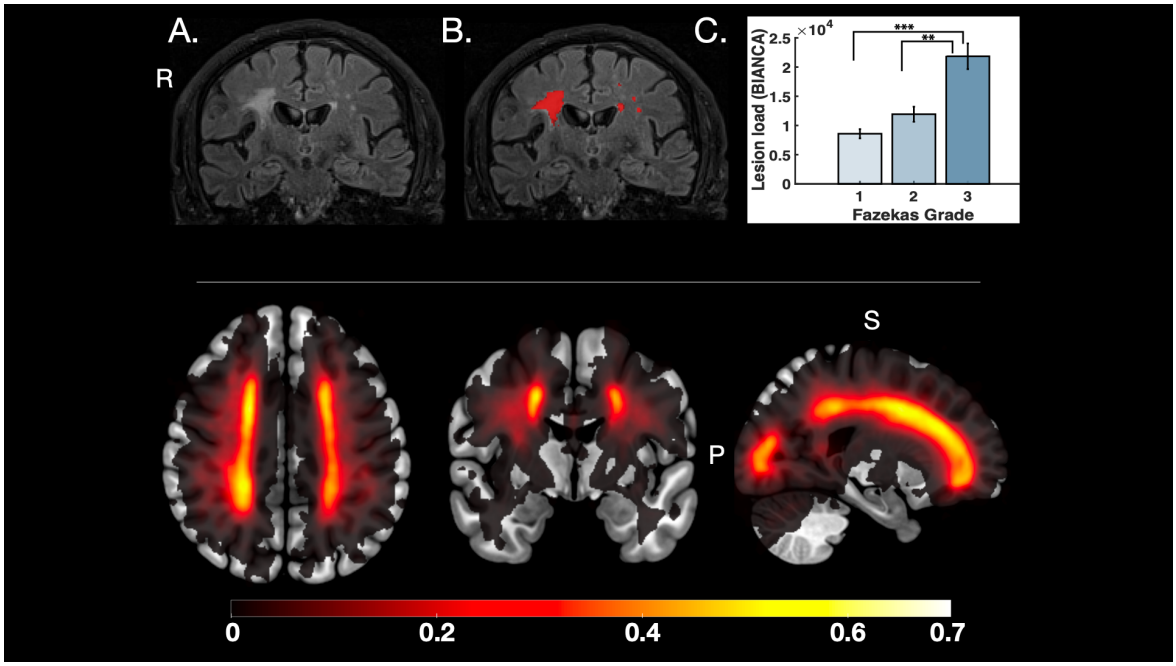



**Figure 4-2. Quantification of disease severity using white matter lesion load.** **Top:** A representative FLAIR sequence before and after applying BIANCA, an automated classification algorithm, to detect white matter lesions (respectively **a** and **b**). Lesion load was calculated by applying a threshold of 80% to minimise false positives (**b**). This measure was validated against clinician scored Fazekas gradings, and demonstrated significant increases in lesion load with higher Fazekas scores (**c**). **Bottom:** Group lesion heat map representing probability of white matter lesion presence (see colour bar) across the whole patient group. Axial, coronal and sagittal views from left to right.

**Diffusion image pre-processing and analysis**

Voxelwise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics) (S. M. Smith et al., 2006), part of FSL (S. M. Smith et al., 2004). Sixty seven FA images were created by fitting a tensor model to the raw diffusion data using FDT, and then brain-extracted using BET (S. M. Smith, 2002). All participants' FA data were then

aligned into a common space using the nonlinear registration tool FNIRT (J. L. R. Andersson et al., 2007), which uses a b-spline representation of the registration warp field (Rueckert, 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centres of all tracts common to the group. Each participant's aligned FA data was then projected onto this skeleton and the resulting data fed into voxel wise cross-participant statistics. Each subject's data was manually checked at each step and no data was excluded due to quality control issues.

The *randomise* function within FSL was used to carry out non-parametric voxel wise analyses using 5,000 permutations. A general linear model was used to investigate the positive and negative associations between apathy as a continuous measure with fractional anisotropy while controlling for depression and age. We then repeated this to assess the association with depression as a continuous measure while controlling for apathy and age. Threshold-free cluster enhancement (TFCE) was used to correct for multiple comparisons across space and corrected P-values were thresholded at $P < 0.05$ (S. M. Smith & Nichols, 2009; Winkler et al., 2014). Alongside the visible markers of SVD (see above and **Fig. 4-2**), average FA across all skeletonised tracts was used as another measure of disease severity to ensure that apathy related changes were not due to generalised disease progression. Specifically, we compared these measures to apathy and accounted for their effects when investigating the influence of apathy on specific FA tracts.

## 4.4 Results

### 4.4.1 Apathy characterised by reduced white matter integrity

Sixty seven patients were included in this analysis. Fractional anisotropy (FA) was negatively associated with apathy within several white matter tracts (**Fig. 4-3**). These included:

- anterior cingulum bilaterally
- anterior thalamic radiation within the anterior limb of the internal capsule (left)
- corpus callosum
- uncincate/inferior fronto-occipital fasciculus within the external capsule.

The association between FA in these tracts and apathy was retained after adjusting for both lesion load and the number of lacunar infarcts in a multiple regression (**Table 4-1**). Neither lesion load nor the number of lacunar infarcts was primarily associated with apathy (respectively, $F(1,59)=0.098$, $p=0.75$ and $F(1,59)=0.1$, $p=0.75$ ). No positive association between FA and apathy was observed in any tract. That is, apathy was not associated with improved white matter tract integrity. Importantly, depression was not associated with any changes in FA after accounting for apathy.

Additionally we extracted the average FA across the whole white matter tract skeleton for each subject to investigate the association between apathy and global white matter integrity. When the same covariates as in the initial analysis were included, there were no significant associations between average FA and either apathy ($F(1,63)=1.29$, $p=0.26$) or depression ($F(1,63)=0.32$, $p=0.57$). However, age was significantly associated with reductions in FA ($F(1,63)=11.20$, $p=0.0014$) confirming its generalised effect on white matter integrity. Thus the effects of apathy on white matter were not general but instead specific to those identified in **Fig 4-3**.

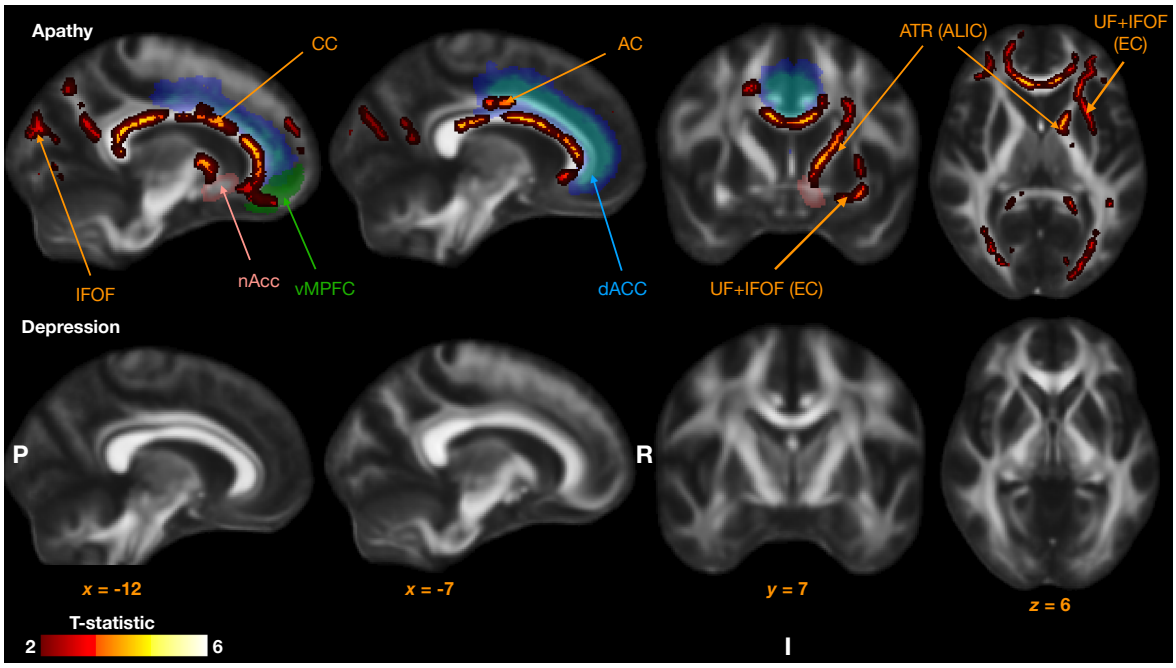



**Figure 4-3. Tracts with reduced fractional anisotropy associated with apathy.** Relevant brain regions are highlighted to demonstrate tract positions relative to the dorsal anterior cingulate cortex (dACC), vemtromedial prefrontal cortex (vMPFC) and the nucleus accumbens (nacc), all implicated in effort based decision-making studies in healthy people. Note no regions were identified to be associated with depression (bottom panel). AC = anterior cingulum; ATR = anterior thalamic radiation; ALIC=anterior limb of the internal capsule; UF = uncinate fasciculus IFOF = inferior fronto-occipital fasciculus; EC = external capsule. dACC = dorsal anterior cingulate cortex (blue). vMPFC = ventromedial pre-frontal cortex. nACC = nucleus accumbens.

| | term | estimate | std.error | statistic | p.value | outcome |
|---|---|---|---|---|---|---|
| 1 | Intercept | -0.04 | 0.14 | -0.26 | 0.80 | Apathy |
| 2 | Lesion load | -0.07 | 0.12 | -0.56 | 0.58 | Apathy |
| 3 | Lacunes (number) | 0.12 | 0.26 | 0.44 | 0.66 | Apathy |
| 4 | FA | -0.36 | 0.13 | -2.70 | 0.01 | Apathy |
| 5 | Age | -0.22 | 0.13 | -1.71 | 0.09 | Apathy |
| 6 | Depression | 0.41 | 0.12 | 3.36 | 0.00 | Apathy |

**Table 4-1. Predictors of apathy in SVD.** Multiple regression to test the hypothesis that specific associations between white matter tract integrity, indexed by FA, and apathy are not driven by predictors of general disease severity in SVD. This includes visible and non-visible markers of SVD such as white matter lesion load, the number of lacunes, and age. As demonstrated, only FA within the fronto-striatal network was associated with apathy

(highlighted in red), after controlling for depression, as well as other measures of disease severity. As previously described, depression was also associated with apathy (highlighted in red, bottom).

### 4.4.2 Drift rate is significantly associated with reductions in FA

We established in the previous chapter that apathy was associated a significant reduction in overall drift rate ($v_0$), and a significant change in reward sensitivity, indexed by the *v*reward* interaction. It might be argued that these effects relating apathy to drift rate and its components are due to general SVD disease severity rather than apathy per se. To investigate this we included white matter lesion load and global white matter integrity (average fractional anisotropy, FA) as covariates in a regression model that associated apathy with *v* and *v**reward respectively. Both the associations were retained (respectively [F(1,56)=4.12, p=0.047] and [F(1,56)=5.43, p=0.02]). Similar results were obtained if only one of white matter lesion load or global white matter integrity was used as a covariate instead of both (respectively [F(1,57)=4.51, p=0.038] and [F(1,57)=4.12, p=0.047]). So general disease severity alone does not account for the behavioural changes associated with apathy in the DDM, but what is the relationship between these behavioural parameters and the neural correlates of amotivation? More specifically, can we demonstrate a relationship between the drift rate parameter and white matter integrity within the brain network associated with apathy?

To answer this question the FA values within this network (**Fig 4-4**, top panel in orange) were extracted, together with those in two "control" white matter tract networks. These were the sensorimotor network (SMT), consisting of the corticospinal tracts and superior longitudinal fasciculi bilaterally (**Fig 4-4**, top panel in yellow) , and the auditory network, consisting of the acoustic radiations bilaterally (**Fig 4-4**, top panel in blue) (Figley et al.,

2017). There was a significant positive correlation between baseline drift rate $v_0$ and FA within the apathy network, but not the two control networks (**Fig 4-4**, bottom left), even after correcting for multiple comparison [F(1,58)=14.58, p=0.0009] indicating that integrity of those tracts is associated with higher rate of evidence accumulation to accept offers.

No significant associations were observed between FA in the apathy network and the effects of reward [F(1,58)=1.15, p=0.29] or effort [F(1,58)=0.058, p=0.81] on drift rate. There was a significant positive association between the effect of effort on drift rate and the auditory network but this did not survive correction for multiple comparison. The decision threshold and bias parameters were also not associated with FA changes (respectively [F(1,58)=1.64, p=0.20] and [F(1,58)=0.95, p=0.33]). Overall, this analysis demonstrates that significant decreases in motivated behaviour, as defined by a general reduction in baseline drift rate, are associated with white matter tract changes identified to be associated with clinical apathy in SVD. Notably, this was observed for only the overall drift rate, and not the interactions of reward and effort with drift rate. This suggests that while the overall drift rate reductions in apathy are associated with white matter integrity changes, the altered reward responsiveness in apathetic subjects may arise via secondary mechanisms.

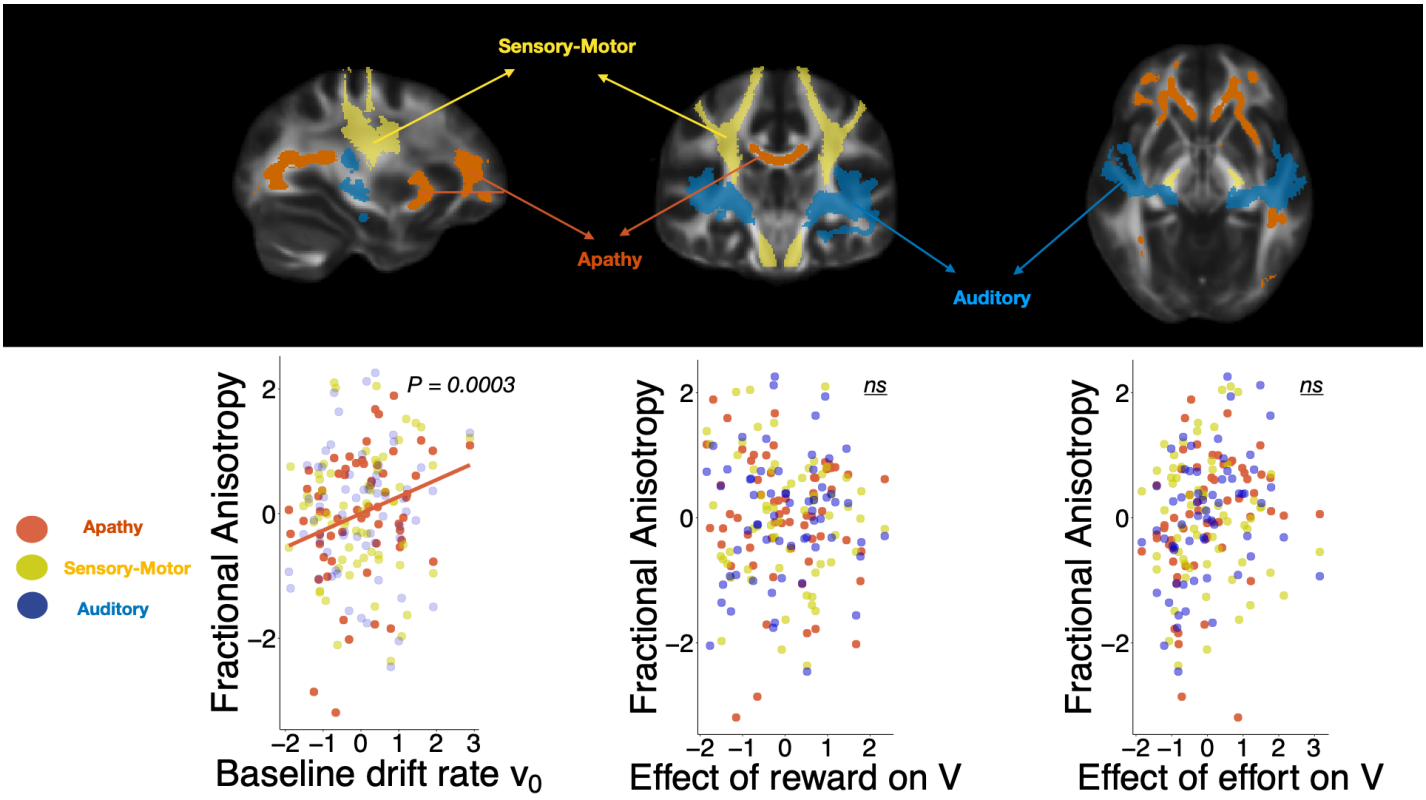



**Figure 4-4. Drift rate is associated with white matter integrity in the apathy network.** Association between drift diffusion model parameters and fractional anisotropy within the apathy network (top panel, red) and two control networks (sensory-motor, green and auditory, blue). Drift rate was significantly associated with white matter integrity within the apathy network (bottom, left) but not the control networks. These effects were not associated with the reward and effort related changes in drift rate.

## 4.5 Discussion

The findings presented here demonstrate that apathy in late-onset, sporadic SVD is characterised by distinct structural and functional correlates. Specifically, apathy severity was associated with reduced white matter tract integrity, which crucially could not be accounted for by general SVD disease severity. This included tracts within the cingulum and the anterior limb of the internal capsule which are known to connect brain regions commonly implicated in effort-based decision making such as the ACC, vmPFC and VS (Bonnelle et al.,

2016; Croxson et al., 2009; Skvortsova et al., 2014). By contrast, no significant white matter changes were associated with depression when accounting for apathy.

By using the task-derived DDM parameters from the previous chapter, we were able to directly associate the behavioural and anatomic changes in apathy. First we confirmed that the association between drift rate and apathy was not mediated by general SVD disease severity. Next, we demonstrated a significant negative correlation between drift rate to decision threshold and the brain network identified to be associated with apathy in SVD, but not two control networks. Together, these findings reveal a strong association between structural and functional changes underlying the syndrome of apathy in SVD. They also demonstrate a clear dissociation between apathy and depression in SVD at both the behavioural and anatomic levels.

**Brain networks**

Anatomically, apathy was associated with white matter tract changes in several tracts including: anterior cingulum, anterior limb of the internal capsule, corpus callosum, uncincate fasciculus, anterior thalamic radiation and inferior fronto-occipital fasciculus (**Fig 4-3**). Notably, the DDM drift parameter $v_0$, which represents the baseline rate of approaching the decision threshold (Chapter 3, **Fig. 3-2**), was also significantly associated with the changes in these tracts even after controlling for two control tracts (**Fig. 4-4**). Additionally, apathy was not associated with a global measure of white matter tract integrity, defined as the mean fractional anisotropy across all defined tracts. This suggests that the anatomical changes observed in apathy are specific to the aforementioned tracts and may be associated with overall changes in motivated behaviour as predicted by the modelling parameter $v_0$. Finally, whereas these changes were observed while accounting for depression, there were no

significant white matter associations noted for depression when accounting for apathy (**Fig. 4-3**).

The human cingulum bundle is considered to be a large-scale white matter system, carrying fibres associated with several different major white matter tracts, including those linking vmPFC, ACC and the pre-supplementary to the motor apparatus in supplementary motor and primary motor regions (Maldonado et al., 2020). It has been linked to the initiation of self- rather than externally-generated movements (Maldonado et al., 2020) and lesions involving the cingulum can result in severe forms of apathy manifest as akinetic mutism (Barris & Schuman, 1953; Németh et al., 1988). The finding of cingulum involvement in our study is largely concordant with previous reports in both genetic (Le Heron, Manohar, et al., 2018) and sporadic (Hollocks et al., 2015; Tay, Lisiecka-Ford, et al., 2020b) forms of SVD. The anterior cingulum bundle also has been previously implicated in apathy across several different neurological conditions (Hollocks et al., 2015; Le Heron, Manohar, et al., 2018; Zhang et al., 2007, 2018), as well as in healthy individuals (Bonnelle et al., 2016).

Functional imaging studies in healthy people have led to the conclusion that cortical regions linked by the cingulum play a key role in effort-based decision making for rewards. While the ACC appears to integrate reward and effort signals to compute net subjective value (Bonnelle et al., 2016; Croxson et al., 2009; Skvortsova et al., 2014), activation within vmPFC correlates positively with increasing reward magnitude (Peters & Büchel, 2010; Skvortsova et al., 2014). In the current study, only a specific portion of the bundle appeared to be associated with apathy (**Fig 4-3**, top row labelled 'AC'), in close proximity to the anterior mid-cingulate gyrus, suggesting that only alterations within the cingulum here might be sufficient to alter motivational states. This was supported by a recent study by Caruana

and colleagues who investigated the functional localisation within the cingulate cortex through intracortical stimulation of 329 subjects (Caruana et al., 2018). They observed an exclusive localisation of goal-directed behaviour to the anterior mid-cingulate region supporting our findings.

Additionally, the imaging analyses performed here identified the internal limb of the internal capsule as being associated with apathy (**Fig 4-3**, top row labelled 'ALIC'). Recent evidence has highlighted an important role of the ALIC as a conduit for tracts linking frontal brain regions (including both OFC, vmPFC and dACC) to subcortical structures including the ventral striatum, midbrain and medial thalamic nuclei (Haber & Behrens, 2014; Lehman et al., 2011; Safadi et al., 2018b).A tracing study by the Safadi and colleagues further segmented tract pathways within the ALIC into 5 distinct sub-groups based on their cortical origins, demonstrating that white matter tract deficits in distinct sub-segments within the ALIC (Safadi et al., 2018b). Unsurprisingly, the ALIC has been used as a deep brain stimulation target for several psychiatric conditions, including major depressive disorder (Bergfeld et al., 2016) and OCD (Bourne et al., 2012).

Widespread changes associated with apathy were also observed within the corpus callosum and uncinate fasciculi bilaterally (**Fig 4-3**, labelled 'CC' and 'UF' respectively). Both tracts have previously been associated with apathy in SVD (Hollocks et al., 2015; Le Heron, Manohar, et al., 2018), as well as Alzheimer's disease (Damoiseaux et al., 2009; Hahn et al., 2013). The brain regions connected by these tracts (**Fig. 4-3**, top left) encompass the medial forebrain regions such as the vmPFC and dACC, as well as subcortical structures within the basal ganglia such as the ventral striatum (Husain & Roiser, 2018; Le Heron, Apps., et al., 2018; Pessiglione, Vinckier, Bouret, Daunizeau, & Le Bouc, 2018).

**From brain to behaviour: A neurocognitive model of apathy in SVD**

That we were able to correlate these changes to our behavioural modelling parameters supports the hypothesis that apathetic behaviour arises from specific white matter tract changes within a network connecting medial frontal regions to the basal ganglia. However it is important to note that these brain changes were associated with only the baseline drift rate $v_0$ and crucially were not linked to the reward and effort sensitivities *per se* (**Fig. 4-4**). By contrast, DDM also revealed that the effects of reward on drift rate, indexed by the $v_r$ parameter, was significantly altered in apathetic compared to motivated patients. The lack of such an association with white matter structural parameters might potentially be due to lack of sensitivity of MR imaging or current analysis tools. Additionally, the overall correlation between FA and apathy was negative, making it less likely to detect a neural correlate of the positive association between apathy and reward sensitivity. An alternative explanation is that it is possible that some behavioural manifestations of apathy do not have structural correlates. For example, they might occur because of neurotransmitter changes. Regardless of the precise cause, the findings presented here suggest that white matter tract changes reduce overall goal-directed behaviour. This might in turn alter responsiveness to reward outcomes and/or effort costs, but exactly how this occurs remains to be established.

The associations between FA changes and apathy in our study were present after adjusting for lesion load and lacunar infarcts, neither of which were significantly predictive of apathy in our patient group. While some studies have demonstrated such associations between apathy and visible markers of SVD, these findings are often inconsistent (Delrieu et al., 2015; Grool et al., 2013, 2014b; Oudega et al., 2020; Yao et al., 2009). Moreover, recent findings show that diffusion weighted imaging metrics can be more sensitive than visible markers of

SVD alone in detecting white matter disruption (Auriel et al., 2014; Tay et al., 2019; Veldsman et al., 2020).

Taken together, this and the previous chapter comprise the largest study to date to combine behavioural and anatomical methods to investigate the syndrome of apathy in SVD. We also report the first application of drift diffusion modelling to a well validated paradigm which can be easily replicated in future studies. Importantly, parameters from this model were strongly associated with the anatomical changes, allowing investigators to bridge findings across behaviour, modelling and neuroimaging techniques. The findings presented here provide some support for a transdiagnostic model of apathy, across neurological disorders. While the deficits in reward related processing were largely concordant with previous studies, we also report effort aversion in apathy for the first time. Both effects may arise in apathy as a result of network disruption, in this case via white matter tract changes, within the medial frontal regions and the basal ganglia.

**Apathy and depression: anatomically and behaviourally distinct syndromes in SVD**

We provide compelling evidence that apathy and depression in SVD are behaviourally and anatomically distinct, despite displaying strong questionnaire correlations. Behaviourally, apathy was associated with a reduced motivated goal-directed action driven by an insensitivity to rewards (reduced $v$ and altered $v_r$, respectively). On the other hand, depression was associated with increased time spent deliberating on decisions, without a reduction in overall motivated behaviour (increased threshold parameter $a$). Anatomically, apathy was characterised by white matter tract deficits within the fronto-striatal network, after controlling

for depression, while depression was not associated with any changes in white matter tract integrity.

These findings support several investigations that suggest that these two syndromes are not the same. For example, a recent neuroimaging investigation by Tay investigated 331 patients with SVD using DWI techniques to compare the neural correlates of both constructs . They demonstrated that apathy, but not depression, was associated with significant white matter tract disruption – specifically connecting the anterior cingulate and the supplementary premotor cortices (Tay et al., 2019). More recently, the same group demonstrated in nearly 500 SVD patients that baseline apathy scores, but not depression were independent predictors of all-cause dementia (Tay, Morris, et al., 2020). Our results contribute further to the increasingly held view that these two constructs are not identical. Critically, we demonstrate the divergence between the them both during effort-based decision making and DWI investigations. It is important that similar studies are conducted in other conditions to establish whether these divergences are consistent across disease states, or whether this is a specific phenomenon in SVD only.

An important next step in investigating apathy is to ask whether the behavioural correlates of this syndrome are the same in psychiatric conditions. Unsurprisingly, apathy is common across psychiatric conditions, where it forms part of the negative syndrome (Strauss & Cohen, 2017). These include major depressive disorder, bipolar disorder, and schizophrenia (Strauss & Cohen, 2017). In the next chapter, I investigate whether the behavioural correlates of apathy in treatment resistant schizophrenia are similar or different to those we have encountered in SVD.

# 5 Motivational deficits in treatment resistant schizophrenia

## 5.1 Chapter Summary

Motivational deficits are a central feature of the negative syndrome in schizophrenia. They have consistently been associated with reduced willingness to expend physical effort in return for monetary rewards on effort based decision making paradigms (EBDM). Nevertheless, the mechanisms underlying such altered performance are not well characterised, and it remains unclear if they are driven purely by negative symptoms, or also in part by cognitive impairment, antipsychotic treatment, and even positive symptoms. Here we investigated the impact of all these factors using a paradigm that has not previously been used to measure EBDM in schizophrenia. Forty treatment resistant schizophrenia (TRS) patients on clozapine and matched controls *(N*=80) completed a well validated EBDM task which offers monetary rewards in return for physical effort. Choice and reaction time data was analysed using logistic regressions, as well as Bayesian hierarchical drift diffusion modelling (HDDM). Behavioural parameters were compared between groups and their association with negative symptoms, cognitive function and serum clozapine levels were assessed. Overall, TRS patients were significantly less motivated than controls. They demonstrated reduced sensitivity to increasing rewards, but were also less averse to increasing effort. Despite a positive correlation between negative symptoms and cognitive function in TRS, reward sensitivity was associated only with cognitive performance. In contrast, blunted effort aversion correlated with negative symptom severity. Clozapine levels and positive symptoms were not associated with either behavioural parameter. In TRS, both negative symptoms and cognitive dysfunction alter motivated behaviour in distinctly different ways, despite positive

associations between themselves. These findings indicate that negative symptoms and cognitive impairment are two separate factors that contribute differently to lack of motivation, and which might therefore respond differentially to individualised treatment targeting these mechanisms.

## 5.2 Introduction

Negative symptoms carry a high burden of disease in schizophrenia (Fervaha et al., 2015; Iasevoli et al., 2016; Milev et al., 2005; Rabinowitz et al., 2013; Tirupati et al., 2007), where they occur in up to 60% of patients (Correll & Schooler, 2020). In treatment resistant schizophrenia (TRS) patients suffer with disproportionately poor functional outcomes (Iasevoli et al., 2016) and disease severity is mediated primarily by these symptoms (Iasevoli et al., 2018). Despite their significant impact, there are no effective interventions for negative symptoms, and they are typically non-responsive to antipsychotic therapy (Fusar-Poli et al., 2015). Clearly, they represent an unmet therapeutic need (Kirkpatrick et al., 2006), yet their underlying mechanisms remain poorly understood.

Motivational deficits are a central feature of the negative syndrome (Strauss et al., 2013, 2019, 2021), and represent a critical treatment target in schizophrenia (Strauss et al., 2021). They include decreased goal directed behaviour (avolition), reduced socialisation (asociality), and a lack of pleasure when anticipating or engaging in activities (anhedonia) (Kirkpatrick et al., 2006). Other symptoms include minimal speech production (alogia) and blunted affect (Kirkpatrick et al., 2006). Factor analyses of questionnaire reports have often supported a two-factor structure for negative symptoms (Kimhy et al., 2006; Kring et al., 2013; Nakaya & Ohmori, 2008; Strauss et al., 2012, 2013). These consist of a motivation and pleasure factor (**MAP**) which includes avolition, anhedonia, and asociality; and a blunted self expression

factor (**EXP**), which consists of alogia and blunted affect (Kimhy et al., 2006; Kring et al., 2013; Nakaya & Ohmori, 2008; Strauss et al., 2012, 2013). While these analyses are insightful, they do not clarify exactly how motivational deficits or blunted expression contribute towards pathological behaviour. A deeper understanding of these symptoms is needed to shed light on their underlying mechanisms and lay foundations for future treatments.

One framework used to conceptualise motivated behaviour in schizophrenia is that of effort based decision making for rewards (EBDM) (A. J. Culbreth et al., 2018; Husain & Roiser, 2018). Tasks that probe people's willingness to expend effort for reward, often inspired by pre-clinical studies, investigate the behavioural mechanisms of motivational deficits by probing the different phases of decision making (Husain & Roiser, 2018). One example is the process of option selection, where participants are asked to weigh up the benefits (e.g., potential reward) and costs (e.g., effort required to obtain that reward) of a decision prior to initiating goal-directed action (Husain & Roiser, 2018; Le Heron, Apps., et al., 2018; Saleh, Jarratt-Barnham, et al., 2021). A commonly used option selection paradigm in Schizophrenia is the "Effort Expenditure for Rewards Task" (EEfRT) (Barch et al., 2014; Fervaha et al., 2013; Treadway et al., 2009, 2015), where people are asked to choose between a low reward–low effort option or a high reward–high effort one (Treadway et al., 2009). Compared to healthy controls, schizophrenia patients select significantly fewer high effort offers when the reward levels are at their highest (Barch et al., 2014; Fervaha et al., 2013; Gold et al., 2013; Moran et al., 2017; Reddy et al., 2015; Treadway et al., 2015). Some studies have found that this behavioural pattern correlates with negative symptom severity (Gold et al., 2013) or specifically amotivation (Barch et al., 2014; Cooper et al., 2019; Fervaha et al., 2013;

Hartmann, Hager, et al., 2015). Nevertheless, several important questions remain unanswered.

First, it is not entirely clear exactly why schizophrenia patients performing the EEfRT task accept fewer offers than controls when rewards are at their *highest* levels. Patients may misrepresent value because they are less responsive, or insensitive, to reward; more averse, or hypersensitive, to effort; or intrinsically unmotivated. It remains unclear which of these possibilities might best account for the behaviour observed. One critique of the EEfRT task, which relates to these issues, is that it does not simultaneously vary the amount of reward and effort within its experimental structure, often using five reward levels but only two effort levels (Barch et al., 2014). Paradigms with more symmetrical task structures might help disentangle the precise contributions of reward and effort through the extraction of behavioural parameters such as reward sensitivity, effort sensitivity and intrinsic motivation (Bonnelle et al., 2016). These measures, derived from EBDM data, have been used to characterise clinical apathy in Parkinson's (Le Heron, Plant, et al., 2018) and cerebrovascular disease (Le Heron, Manohar, et al., 2018; Saleh, Le Heron, et al., 2021), adding valuable insights into their underlying mechanisms.

Second, while schizophrenia patients frequently suffer from cognitive deficits (Heinrichs & Zakzanis, 1998; Kahn & Keefe, 2013; Schaefer et al., 2013), the relationship between cognition and negative symptoms is unclear (Harvey et al., 2006). Analyses of questionnaire data demonstrate positive associations between cognitive dysfunction and negative symptom severity (Heydebrand et al., 2004; O'Leary et al., 2000), although these have been described as modest (Heydebrand et al., 2004). Further, like negative symptoms, cognitive deficits in

schizophrenia are also associated with impaired reward based decision making (Cooper et al., 2019; Fervaha et al., 2013; Heerey et al., 2007, 2011). So what is the relationship between negative symptoms and cognitive impairment?

One view is that they may be independent constructs that share a similar aetiology (Harvey et al., 2006; Robison et al., 2020). Moreover, Robison et al. propose that synergistic interactions between cognitive deficits and negative symptoms may drive motivational impairments in schizophrenia (Robison et al., 2020). Recent re-analyses of EBDM data in schizophrenia by Cooper et al. showed that cognitive impairment and negative symptom severity might both altered motivated behaviour through independent, yet complimentary mechanisms (Cooper et al., 2019). Specifically, cognitive dysfunction was associated with the inability to incorporate information about reward. On the other hand, negative symptoms related to motivation were associated with increased effort aversion (Cooper et al., 2019). However, there were several limitations with the findings. First, the behavioural effect associated with cognitively impaired patients was unclear. Did they fail to process information about rewards in isolation or were they unable to *integrate* reward and effort cues? This was difficult to dissociate as the task did not systematically vary these two variables (Cooper et al., 2019). Second, the correlation between amotivation and effort aversion was limited to a subgroup accounting for 29% of all patients. Moreover, this group actually had higher cognitive scores, and were more able to utilise all task information systematically according to computational modelling analyses. The way that effort was processed in the other 71% of the patients, however, remains unclear.

To answer some of these questions we conducted an EBDM study in a group of 40 TRS patients on clozapine treatment which requires therapeutic monitoring through plasma

concentration measurements (Khan & Preskorn, 2005). Our aims were to answer two questions:

1. How do TRS patients behave on an EBDM task which parametrically modulates reward on offer and effort required, and has previously been used to assess motivation in neurological disorders (Bonnelle et al., 2016; Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018; Saleh, Le Heron, et al., 2021)?
2. What are the individual contributions of negative symptoms and cognitive impairment to motivated behaviour in this patient group?

## 5.3 Methods

### 5.3.1 Participants

Forty outpatients with TRS were recruited from a clozapine clinic in the Cambridgeshire and Peterborough NHS foundation Trust. Disease severity in this patient group is significantly mediated by negative symptoms (Iasevoli et al., 2018). Participants were clinically stable, with no medication dose changes in the last eight weeks. They were recruited during routine monthly blood-tests between August 2018 and March 2019. Additionally, forty healthy-age and gender-matched controls were recruited over the same time course. Inclusion and exclusion criteria can be found in (**Appendix chapter five, 'supplementary methods'**).

### 5.3.2 Clinical measures

Negative symptoms in patients were measured using the clinician administered brief negative symptom scale (BNSS) (Kirkpatrick et al., 2011). Factors derived from a previous investigation of 146 schizophrenia patients were used as the MAP (motivation and pleasure which includes avolition, anhedonia, and asociality) and EXP (self expression which

includes alogia and blunted affect) negative symptom factors for our patient group (Strauss et al., 2012). Cognitive function was quantified using both the Addenbrooke's Cognitive Examination (ACE-III) (Hodges & Larner, 2016; Hsieh et al., 2013) and the composite score of the brief assessment for cognition in schizophrenia (BACS) (Keefe et al., 2004). Depression was measured using the Calgary depression scale (CDS) (Addington et al., 1993), and positive symptoms using the positive subscale (P1-P7) of the positive and negative syndrome scale for schizophrenia (PANSS) (Kay et al., 1987). Clozapine dose, plasma clozapine levels, and Olanzapine dose equivalents for other antipsychotic medications were additionally recorded.

### 5.3.3 Effort-based decision making task

Participants completed a variation of the 'Apple Gathering' task described in the general methods section that was adapted to this specific patient group (**Fig. 5-1**). There were two key differences in this experimental design:

1. Five, instead of six, levels of reward and effort were used to shorten the experiment time giving rise to 25 possible offer types were available (5x5). Each offer was sampled five times, giving a total of 125 decisions divided into five blocks of 25 trials.
2. Participants were not required to squeeze for every single accepted choice. Instead, ten choices were randomly selected at the end of the experiment and if they had chosen "Yes", they would have to expend the appropriate amount of effort to secure the trial specific rewards. Based on the number of apples collected on these trials, they were told that they would receive a cash prize. In practice, all participants were rewarded with a fixed amount based on an hourly rate (~10 GBP/hour).

These two adaptations ensured that the experiment can be completed in less than half the time without compromising data quality. The extracted behavioural parameters were choice (i.e. accept or reject) and reaction time.

### 5.3.4 Analyses

***Clinical measures and factor analyses***

Pearson correlations were used to establish within group associations between questionnaire measures, including the factor weighted questionnaire scores. Clinical measures were subsequently used as predictors of the behavioural parameters outlined below.

***Between group behavioural comparisons***

Groupwise comparisons of accepted offers and log-transformed reaction times were conducted using two-sample t-tests. Logistic regressions with mixed effects were used for analysis of behavioural mechanisms. Three initial models were run to determine the behavioural differences between patients and controls (**Appendix chapter five, supplementary table 5-1**). These included all interactions between reward and effort and the fixed effects of patient group. Model fits were assessed using the Akaike information criterion (AIC). Statistical significance was inferred when P-values were $< 0.05$. Behavioural parameters of interest were:

1. **Intrinsic motivation** – general tendency to accept offers, represented by $\kappa$.
2. **Reward sensitivity** – responsiveness to increasing reward, represented by $\alpha$.
3. **Effort sensitivity** – aversion to increasing effort, represented by $\beta$.

4. **Reward:effort interaction** term – ability to integrate reward and effort related information, represented by γ.

These were used to model behaviour across the whole group by computing **subjective value** (*sv*) and **choice probability** (*p)* using the following equations:

3. $$sv = \kappa + \alpha\text{Reward} + \beta\text{Effort} + \gamma\text{Reward:Effort}$$

**4.** $$p = {}^{1}/_{1 + e^{-sv}}$$

Within-group logistic regressions were conducted to assess the independent effects of cognitive function, total negative symptoms, and both negative symptom subcomponents. Family-wise error rate (FWER) correction was conducted for four multiple comparisons using the Bonferroni method (Frey, 2018). Multiple regressions were conducted between behavioural parameters and negative symptom subcomponents, positive symptoms, cognitive function, depression, and clozapine levels.

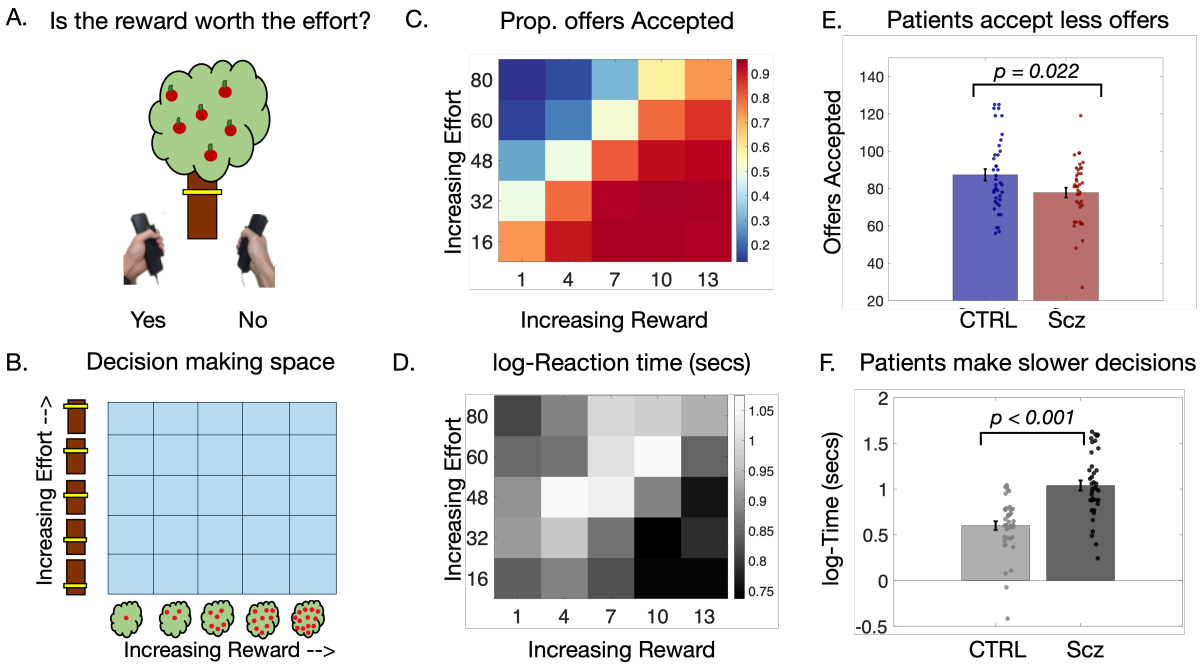



**Figure 5-1. Effort based decision making task and groupwise results**
**A** Participants completed a computer task which offered monetary rewards (virtual apples) in return for physical effort (height of the yellow bar). **B** Five different levels of reward and effort were pseudorandomised throughout the paradigm (permutations mapped on a two-dimensional decision space of reward and effort 5x5 grid). **C,D** Acceptance rates and reactions times within each segment of the decision space for all 80 participants. **C** More offers were accepted as the rewards increased (heatmap becomes more red from left to right). Inversely more offers were rejected at high effort (heatmap more blue from bottom to top). **D** Decisions were slowest (lighter colours) when the levels of reward and effort were at their intermediate levels. Otherwise, offers were accepted and rejected more quickly (darker colours) at the extreme ends of reward and effort. **E** Patients accepted fewer offers overall compared to controls. **F** They were also significantly slower across all decisions.

### Hierarchical drift-diffusion modelling of effort-based decision making

A Bayesian drift diffusion model (DDM) was fit to both the reaction time and choice data as described in the general methods section (section 2.3.2). Groupwise comparison of parameters was assessed using Bayesian inference, reported using posterior probabilities ($P_{P|D}$) of hypotheses of interest. A posterior probability of 0.95 or more was deemed significant. A full description of the model and its specifications can be found in **Appendix four ('Drift diffusion model'** section). Exploratory multiple regressions were repeated between each DDM parameter and: negative symptoms, cognitive function, depression, and clozapine level.

## 5.4 Results

### *5.4.1 Reduced responsiveness to high rewards, decreased aversion to high effort in TRS*

Patients and controls did not significantly differ in age nor gender. Overall, TRS patients were significantly more cognitively impaired as indexed by ACE-III scores ($t(77)=5.71$, $p < 0.001$, **Table 5-1**). They accepted significantly fewer offers and had prolonged reaction times in comparison to controls (respectively, $t(78)=-2.32$, $p = 0.023$ and $t(78)=+6.06$, $p < 0.001$; **Fig. 5-1E and F**). Model comparison for between group analysis was initially conducted using two different logistic regression models (**Appendix chapter five, supplementary table 5-1**). These differed in their use of either the squared effort term vs. unsquared term, and model comparison was conducted using the AIC values. This showed a superior fit of the model with the unsquared effort (AIC 5758 vs 5761, respectively). Therefore the model with unsquared fit was used to assess the effect of group on choice behaviour. This demonstrated that patients accepted significantly fewer offers overall [$F(1,9977)=7.66$, $P=0.0056$]. Additionally, there was a two way interaction between Schizophrenia*Reward and Schizophrenia*Effort (respectively, [$F(1,9977)=4.94$, $P=0.026$] and [$F(1,9977)=3.96$, $P=0.046$]. Specifically, TRS patients accepted significantly fewer offers than controls at the *highest* levels of reward (**Fig. 5-2A**). On the other hand, as effort progressively increased, they rejected proportionally fewer offers when compared to healthy controls (**Fig. 5-2B**). There was no three way interaction between patient group, reward and effort [$F(1,9977)=0.27$, $P=0.60$].

**Table 5-1. Demographics table**

| | *Control (n=40)* | *Schizophrenia (n=40)* | *p-value* |
|---|---|---|---|
| *Age* | 42.78 (12.72) | 46.35 (10.12) | 0.17 |
| *Gender (M/F)* | 39/1 | 36/4 | 0.17 |
| *ACE-III* [a] | 95.5 (5.94) | 84.6 (10.45) | ***<0.001 |
| *BNSS total* | - | 20.9 (17.25) | - |
| *Serum clozapine* [a] | - | 0.36 (0.17) | - |
| *PANSS (Positive)* | - | 12.52 (4.2) | - |
| *CDS* | - | 3.15 (3.14) | - |

Statistics are presented as mean (SD).

* implies statistical significance

Chi-squared test used to compare gender across groups

Paired t-tests used for remaining measures

a Data missing for one participant

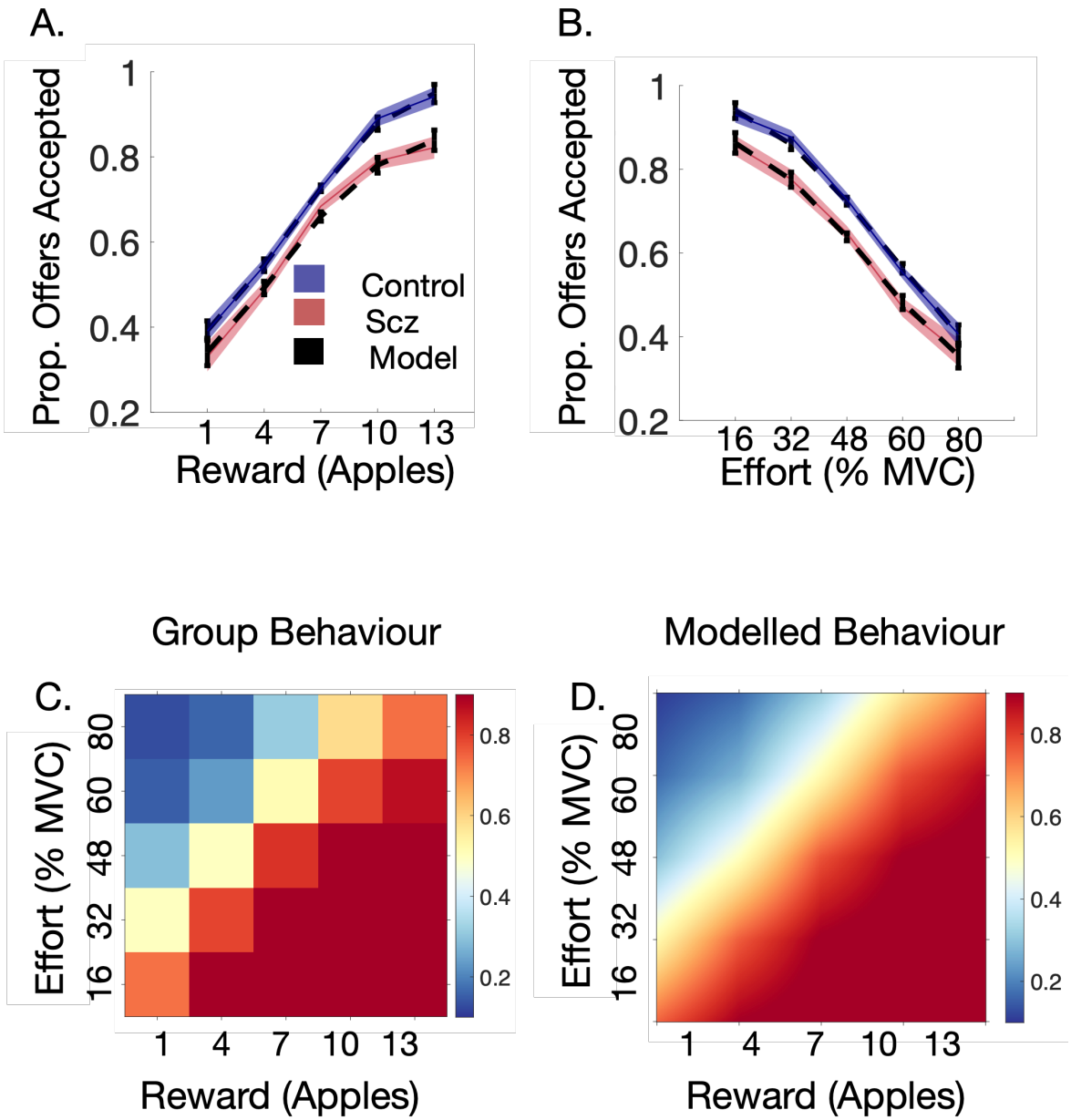



**Figure 5-2. Performance and modelling of data**
**A, B** Patients accepted fewer offers compared to healthy participants. This was especially the case at high reward and low effort. Controls were more sensitive to increasing effort than patients. An overlay of model predictions plotted in black dotted lines. **C** Raw data for all 80 participants across the entire decision making space. **D** Modelled behaviour for all participants.

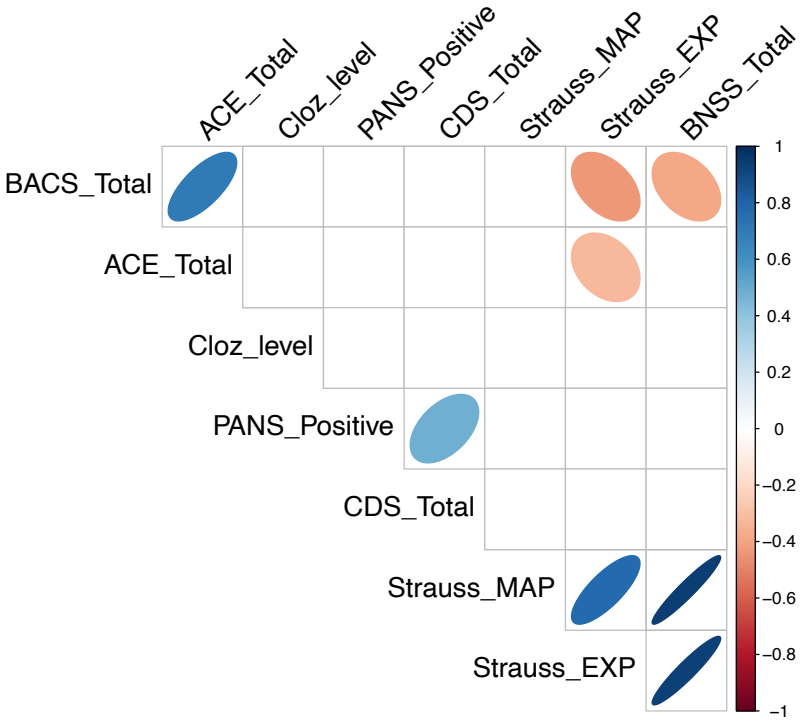
### *5.4.2 Negative symptom severity positively associated with cognitive impairment*

Pearson correlations between clinical measures within the TRS patient group are provided in **Fig. 5-3**. Total negative symptom severity (BNSS total) was significantly negatively associated with the BACS (composite score), but not the ACE-III total score (respectively,

r(38) = -0.38, p = 0.02 and r(38) = -0.28, p = 0.079). The factor weighted **MAP** and **EXP** were correlated with one another r(38) = 0.77, p <0.0001). Notably, only the **EXP** but not the **MAP** component was significantly negatively associated with both the BACS and ACE-III cognitive scores (respectively, r(38) = -0.43, p = 0.009 and r(38) = -0.32, p = 0.045). Serum clozapine was not associated with any clinical measures. Together, these findings show that in TRS, the greater the total negative symptom severity, the worse the cognitive function. Additionally, this seems to be driven by blunted expression (**EXP** factor), rather than the motivation and pleasure (**MAP**) component of negative symptoms.

**Figure 5-3. Clinical associations within schizophrenia patients.**

A visualisation of significant associations within a pairwise comparison using the corrplot function in R. Colour indicates the direction of associations so that blue and red represent



positive and negative associations respectively. Only significant correlations (i.e. $p < 0.05$) are shown. Correlation strength, as measured by Pearson's *r,* is represented by the width of the ellipses so that stronger correlations produce thinner the ellipses (**Fig 5-3**).

### *5.4.3 Relationship of behavioural parameters to cognition and negative symptoms*

We focussed on the ACE-III, instead of the BACS as the main cognitive measure of interest as it was more sensitive to behavioural measures (**Appendix four, 'Cognitive variables'**). Within group analyses showed that ***reward sensitivity*** was positively associated with the ACE-III score (**Fig. 5-4A and B**) after correcting for four multiple comparisons [$F(1,4852)=13.39$, $P=0.0008$]. Post-Hoc analysis revealed that all but the fluency sub-domains were significantly positively associated with the reward parameter (**Table 5-2**).

Table **5-**2: Association of ACE-III subdomains with reward sensitivity

| **Subdomain** | **DF** | **F-statistic** | **uncorrected P value** | **Corrected p-value** |
|---|---|---|---|---|
| **Attention** | 1,4852 | 12.29 | 0.00046 | 0.0023** |
| **Fluency** | 1,4852 | 3.29 | 0.069 | 0.34 |
| **Language** | 1,4852 | 9.72 | 0.0018 | 0.009** |
| **Visuo-Spatial** | 1,4852 | 7.02 | 0.008 | 0.04* |
| **Memory** | 1,4852 | 6.76 | 0.0094 | 0.047* |

On the other hand, ***effort sensitivity*** was negatively associated with the **EXP** but not the **MAP** component (**Fig. 5-4A**) of the negative syndrome (respectively, [$F(1,4977) = 6.6$, $P=0.036$] and [$F(1,4977) = 0.78$, $P=0.38$]). Thus, patients with little or no sensitivity to effort (blunted effort sensitivity) had the highest **EXP** scores (**Fig. 5-4C**). There was also a three

way interaction between reward*effort*EXP [F(1,4977)=6.76,*P*=0.036, after multiple comparison]. Neither parameter was associated with total negative symptom score as measured by the BNSS.

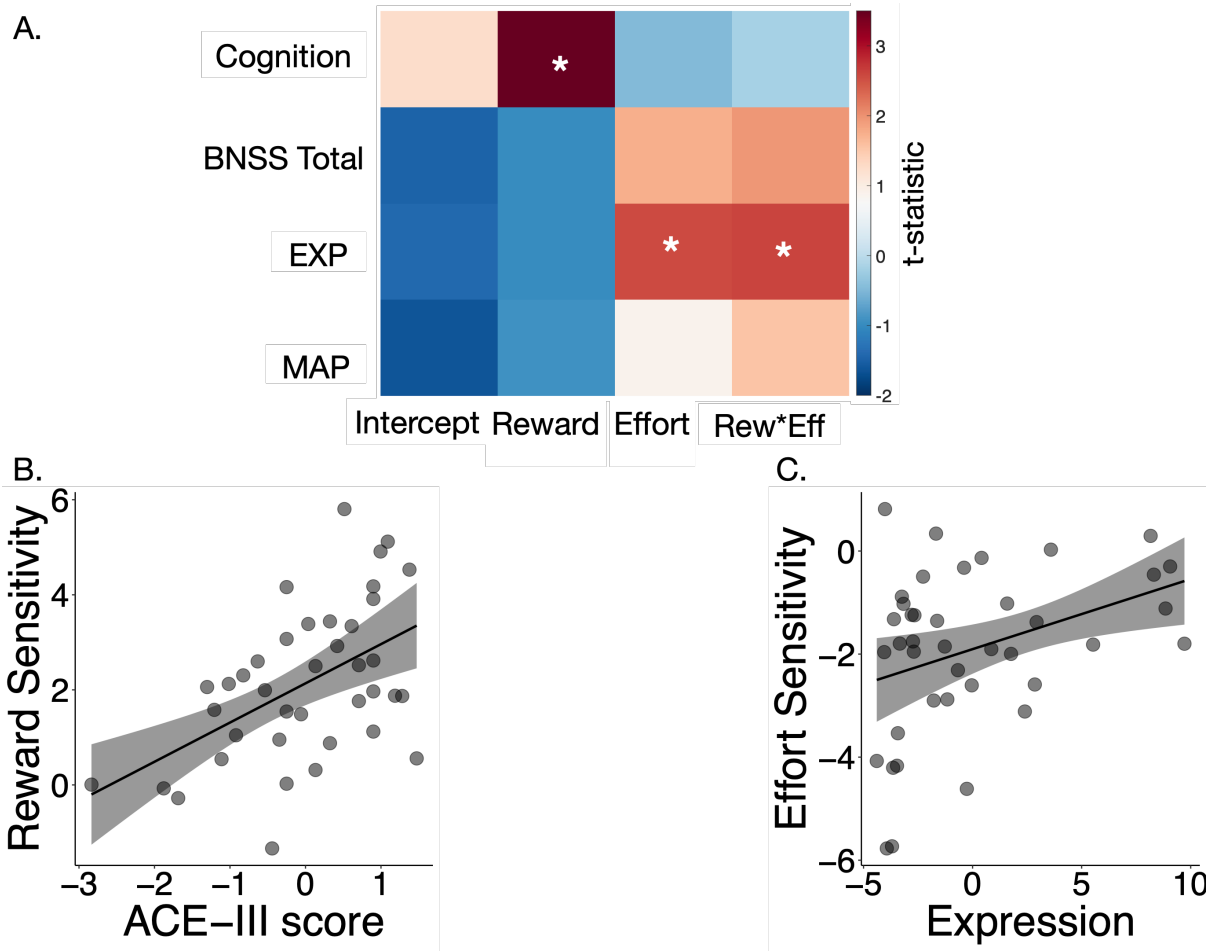



**Figure 5-4. Relationship of behavioural parameters to clinical measures.**

**A** T-statistic map showing associations between the four behavioural parameters and clinical measures of interest (respectively, along the x and y axes). **B** Robust regression demonstrating the positive association between cognitive function and reward sensitivity. **C** Association between blunted self-expression score and effort sensitivity.

Multiple regressions were conducted between behavioural parameters and the following six variables: Cognitive function (ACE-III), negative symptom factors (**EXP** and **MAP**),

depression (CDS), positive symptoms (PANS positive subscale), and clozapine level (**Appendix chapter five, supplementary table 5-3,**). ACE-III score was significantly associated with reward sensitivity ($\beta = 0.87$, $p = 0.014$ after multiple comparison). Similarly, the **EXP** negative symptom factor was associated negatively associated with effort sensitivity ($\beta = 0.28$, $p = 0.036$ after multiple comparison). These findings were replicated when additionally including olanzapine equivalents for other anti-psychotic medications. There were no significant associations between behavioural parameters and other clinical measures after correcting for multiple comparison.

Sub-group analysis was then conducted to assess if our two clinical variables (Cognitive function and **EXP**) could be used to retrieve the groupwise differences between TRS patients and controls. Four sub-groups were generated using median splits of ACE-III and **EXP** score. This gave rise to cognitively impaired; cognitively intact, high blunted expression; and low blunted expression sub-groups. Each group was compared to controls, and p values corrected for the four multiple comparisons. We did not compare the two subgroups to one another as this analysis would have been accounted for more accurately using the continuous measure within group analyses above. Cognitively impaired TRS patients, accepted fewer offers overall and were less reward sensitive than controls after correcting for four multiple comparisons (respectively, [$F(1,7356)=12.76$, $P=0.0016$] and [$F(1,7356)=11.3$, $P=0.0032$], see **Figs 5-5A-B**) . Cognitively intact TRS patients did not differ from controls across behavioural parameters (respectively, [$F(1,7613)=0.755$, $P=0.76$] and [$F(1,7613)=0.006$, $P=1$]). On the other hand, TRS patients with high **EXP** scores accepted fewer offers overall and showed blunted effort sensitivity compared to controls (respectively, [$F(1,7481)=8.1$, $P=0.018$] and [$F(1,7481)=7.15$, $P=0.0028$], **Figs 5-5C-D**). TRS patients with low **EXP** scores did not differ from controls across parameters.

Taken together, these analyses suggest that two distinct mechanisms characterise TRS patients from controls. These are reward insensitivity and blunted responsiveness to effort. Despite positive associations between cognitive dysfunction and negative symptoms within patients, each construct was distinctly associated with one of these behavioural deficits suggesting different underlying mechanisms.

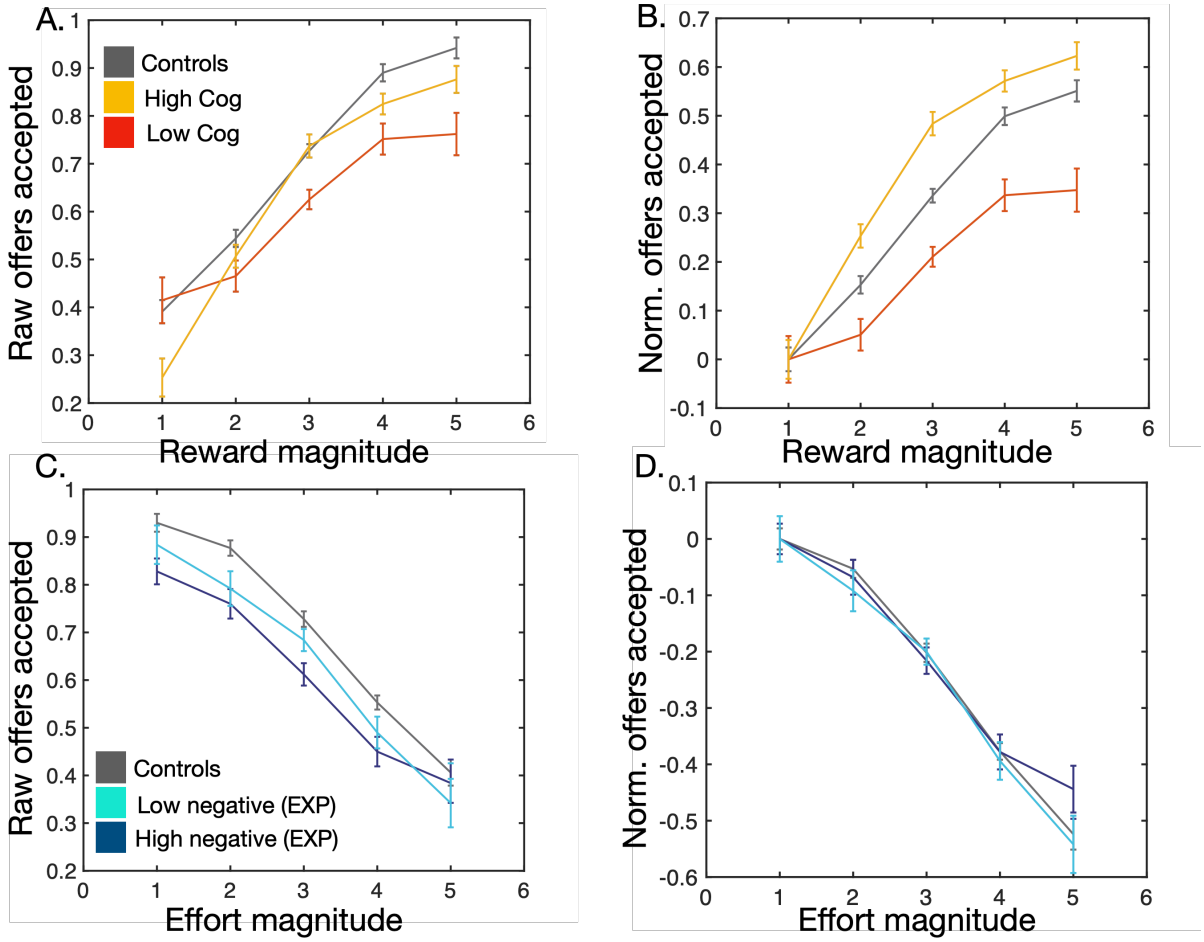



**Fig. 5-5 Subgroup analyses of patients with cognitive impairment or high negative symptom burden.** Comparison of median split TRS subgroups to controls using ACE-III (A-B) and EXP factor scores (C-D). Two plot variations are shown, one using raw offers accepted (A and C) and another using values normalised by baseline acceptance rate (B and D). **(A-B)** Cognitively impaired patients (red) accepted less offers and were less reward

sensitive compared to controls (grey). Cognitively intact patients (yellow) were not significantly different to controls. (**C-D)** Patients with high negative symptom burden (dark blue) accepted less offers than controls (C) and were less effort averse at the highest effort level (best seen in normalised figure, D).

### *5.4.4 Drift diffusion modelling*

A hierarchical DDM was fitted to the data using Bayesian statistical methods. Probability distributions were generated, providing a measure of uncertainty for each parameter estimate (**Fig. 5-6A** displays model schematic). Both reward and effort significantly affected drift rate to decision threshold such that drift rate rose with increasing reward and fell with increasing effort (**Fig. 5-6B**). Parameters were used to accurately model acceptance rate (AR) and Decision time (DT) (**Fig. 5-7**). Groupwise comparison between parameters was conducted using Bayesian hypothesis testing (**Fig. 5-8**). Overall, schizophrenia patients had significantly larger threshold ($a$) and non-decision time ($t$) values ($P_{P|D} \approx 1$ for both parameters). Conversely, they had lower overall baseline drift rates ($P_{P|D} \approx 1$). Namely, they were less likely to accept more offers as reward increased (reduced $v$*reward interaction, $P_{P|D} \approx 1$) and less likely to reject offers as effort increased ($v$*Effort interaction was closer to 0 in relation to controls, $P_{P|D} \approx 1$). There was no difference between controls and schizophrenia patients in the *v*Reward*Effort* interaction ($P_{P|D} \approx 0.13$), or bias ($z$) ($P_{P|D} \approx 0.74$). Multiple regressions between DDM parameters and clinical measures revealed similar findings (see **Appendix chapter five, table S5-4**). Specifically, ACE-III significantly positively associated with the reward parameter ($V_r$) whereas blunted expression (EXP) was negatively associated with the effort sensitivity parameter ($V_e$), although the latter association was not significant after six multiple comparisons ($p = 0.09$).

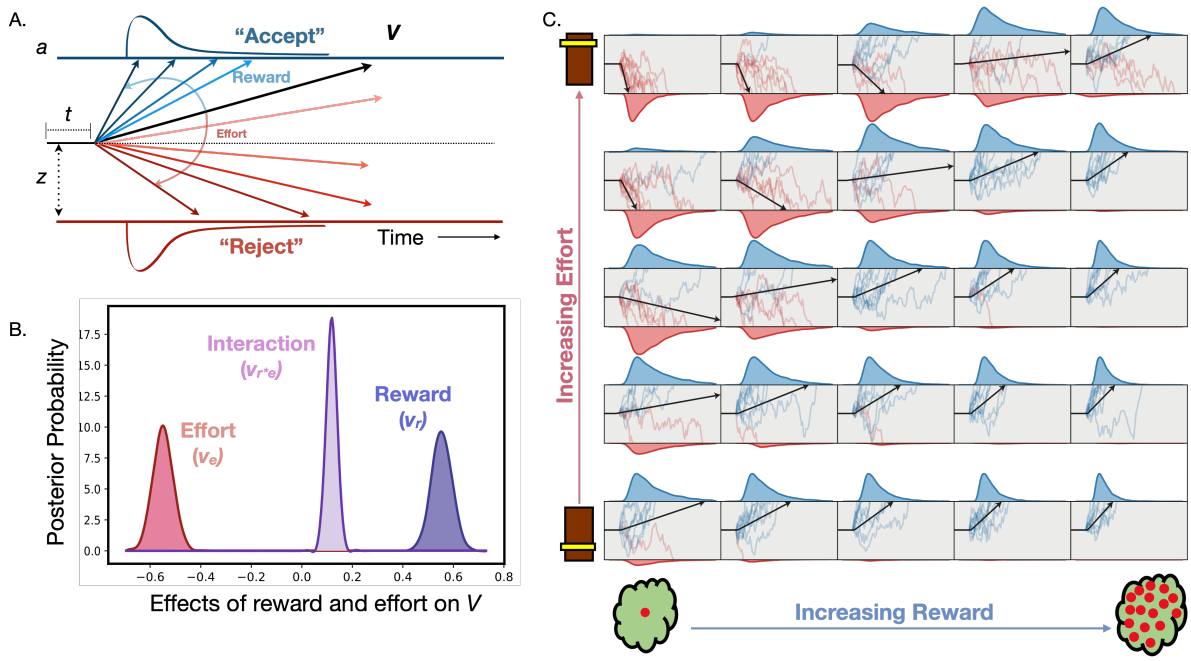



**Fig. 5-6 Drift diffusion model (DDM) of effort-based decision making for reward.** **A** Decision making is modelled as a noisy process of evidence accumulation up to a decision boundary, *a*, occurring at a drift rate, *V*, from a starting point termed the bias, *z*. Time spent in non-decision making processes is encapsulated by a non-decision term, *t*. **B** Reward and effort both significantly altered drift rate. **C** A simulation of the influence of reward (x-axis) and effort (y-axis) on drift rate (black line) within our decision space. There is an incremental rise in drift rate with increasing reward (left to right), and fall in drift rate with increasing effort (bottom to top).

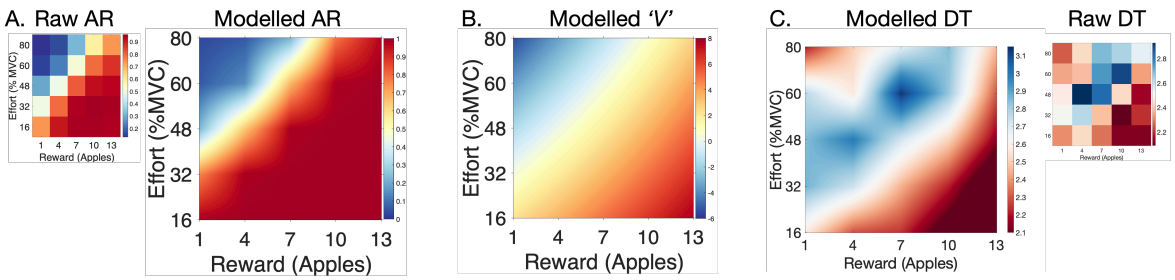



**Fig. 5-7 Prediction of behavioural changes using DDM parameters.**
Model estimates of drift rate accurately predict acceptance rate (AR) (**A**) and decision times (DT) (**C**) when compared to the raw data. Predictions for AR and DT are both derived from the actual drift rate $V_{r,e}$ which reflects increasing and decreasing drift rate values with reward and effort respectively.

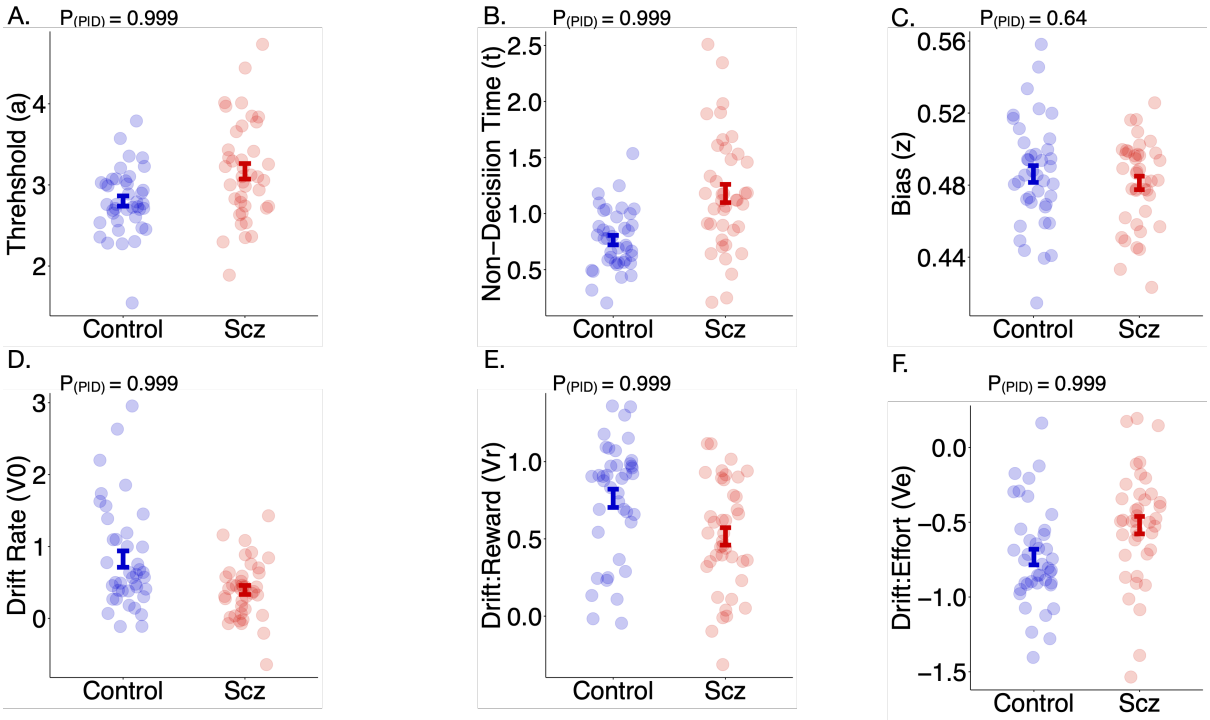



**Figure 5-8 Drift diffusion parameter estimate comparison between patients and controls.**
Drift diffusion modelling parameters, split by group and posterior distributions compared using Bayesian hypothesis testing. Visualisations are of mean + SEM. Significant probability of differences between groups is set at 0.95. Schizophrenia patients had significantly higher thresholds (**A**) and non decision times (**B**) but were not more biased towards rejecting offers (**C**). They also had lower overall drift rates (**D**) and showed impaired modulation of drift rate in response to both reward **(E)** and effort **(F).**

## 5.5 Discussion

The results presented demonstrate that patients with treatment resistant schizophrenia were less motivated than healthy controls when performing an EBDM task. This behaviour was characterised by reduced incentivisation to reward and blunted responsiveness to effort (**Fig. 5-2A and B**). Drift diffusion modelling of the choice and reaction time data (DDM) confirmed these findings while revealing the following groupwise differences. Patients needed to accumulate more evidence than healthy volunteers prior to initiating rewarded effortful decisions (increased $a$), and their rate of evidence accumulation was slower (reduced $v_0$). This parameter was less responsive to changes in both reward and effort (reduced $v_r$ and less negative $v_e$, respectively). Despite this, they did not show an indiscriminate propensity, or bias ($z$), towards rejecting offers. Within group analyses of clinical measures and behavioural parameters highlighted two further findings. First, cognitive impairment was the single best predictor of reward insensitivity (**Fig. 5-4A-B**). This was supported by both choice behaviour analysis as well as DDM, which incorporated reaction time data. Second, negative symptom severity as defined by the **EXP** factor best explained blunted responsiveness to effort (**Fig. 5-4A, and C**). While this effect was demonstrated in choice behaviour, it was not present in the DDM analysis.

Several studies have shown a reduced responsiveness to *high* values of reward across the schizophrenic disease spectrum (Barch et al., 2014; Chang et al., 2019; Gold et al., 2013; Treadway et al., 2015). This includes in first episode psychosis (Chang et al., 2019), established schizophrenia, or schizoaffective disorder (Barch et al., 2014; Gold et al., 2013; Treadway et al., 2015). Here we confirmed these findings in patients with TRS, demonstrating that there are common behavioural deficits across the schizophrenic spectrum. Additionally, we showed that TRS is characterised by blunted responsiveness to high effort,

with patients accepting significantly less offers than controls at low effort but not at high effort (**Fig. 5-2B**). A plausible interpretation of this is that they display inefficient effort allocation during EBDM. This finding is less commonly reported (Chang et al., 2019; McCarthy et al., 2016) and may be a unique characteristic of TRS patients. On the other hand, it is also possible that our task design which co-varies reward and effort across five levels is better able to detect this more subtle effect. Some EBDM paradigms in schizophrenia commonly only vary five reward values across only two effort levels (easy vs hard) (Barch et al., 2014; Treadway et al., 2015) and recent work has highlighted this as a possible limitation in understanding how reward and effort processing are individually affected in schizophrenia (Cooper et al., 2019).

Within our patient group we demonstrated that reward sensitivity was positively associated with cognitive impairment, while effort insensitivity correlated with negative symptom severity (as measured by blunted self-expression). Notably, these two constructs were significantly associated with one another on questionnaire correlation (**Fig. 5-3**). So despite their association, they were characterised by unique behavioural deficits, suggesting that they may respond to different treatment strategies.

A similar divergence in behaviour was recently characterised by Cooper and colleagues (Cooper et al., 2019), who reanalysed EEfRT task data from two previously published studies (Barch et al., 2014; Reddy et al., 2015). They were able to demonstrate that in 153 schizophrenia patients pooled across two studies individuals unable to incorporate reward related information during EBDM were characterised by cognitive impairment, even after accounting for negative symptoms. On the other hand, sub-group analysis demonstrated that some patients with motivational deficits were more effort averse (Cooper et al., 2019). Our

findings diverge from that study in that while they demonstrated an *increase* in effort aversion with increasing negative symptoms, we demonstrated the opposite effect. Further, we showed that **EXP**, and not **MAP**, was associated with these changes.

There are several possible explanations for the differences in our studies. First, Cooper et al. did not investigate associations between behavioural parameters and the **EXP** factor (Cooper et al., 2019). Rather, they investigated the **MAP** dimensions while accounting for total negative symptom scores (Cooper et al., 2019). It is not clear if the **EXP** factor would have demonstrated an association in their study. Further, the association between amotivation and increased effort sensitivity was demonstrated only in approximately one third of their patients (Cooper et al., 2019). Thirdly, as they used pooled questionnaire data from previous studies, negative symptoms were measured using three different questionnaires. Two of these, the scale for the assessment of negative symptoms (SANS) (Andreasen, 1989) and the negative component of the PANSS (Kay et al., 1987), were developed more than thirty years ago and do not reflect the current understanding of the negative syndrome (Kirkpatrick et al., 2006; Kumari et al., 2017). Nevertheless, the authors were also able to demonstrate this association in a sub-group of their patients using a 'next-generation' negative symptom questionnaire known as the Clinical Assessment Interview for Negative Symptoms (CAINS) (Cooper et al., 2019). A recent comparison between this and the BNSS questionnaire, which we used, showed that while both demonstrated good psychometric properties, there was low to moderate convergence between the two questionnaires on motivation and pleasure questions (Strauss & Gold, 2016). It is possible there for that the BNSS **MAP** factor was not able to detect this effect in our patient group.

More generally, the association between negative symptom severity and increased effort sensitivity is actually quite variable. [22–25,29,52,53,57]Indeed, several studies have failed to demonstrate this association at all (Fervaha et al., 2013; McCarthy et al., 2016; Treadway et al., 2015) whereas others have only done so using categorical, not correlational approaches (Chang et al., 2019; Gold et al., 2013). These inconsistencies are possibly due to variations in task design, analytic approaches and questionnaires used to measure negative symptoms. The association between inefficient effort allocation and negative symptoms might also be explained by these technical differences. Nevertheless, this finding has also been previously described by two studies (Chang et al., 2019; McCarthy et al., 2016). In 48 patients with Schizophrenia, McCarthy and colleagues demonstrated that blunted self expression, indexed by alogia, was associated with inappropriate allocation of high effort regardless of reward value (McCarthy et al., 2016). More recently, Chang et al. showed that this behavioural pattern was associated with increasing negative symptom severity, indexed by motivation and pleasure (Chang et al., 2019).

Taken together, our findings support the possibility that negative symptoms are not exclusively associated with increased effort aversion, but also with inefficient effort expenditure. Additionally, they suggest that the **EXP** component of the negative syndrome may also play an important role in characterising behavioural deficits in schizophrenia patients. Nevertheless, the inconsistency across studies is important to note and steps towards resolving these will play an important role in clarifying exactly what kind of behavioural deficits characterise negative symptoms in schizophrenia. Standardised questionnaires, task designs, and analytic approaches would all be useful to reduce variation between studies and improve interpretation.

To conclude, patients with TRS demonstrate significant behavioural deficits compared to controls when undergoing an EBDM task. Moreover, negative symptoms and cognitive dysfunction uniquely alter motivated behaviour in TRS, despite being positively associated with one another. This suggests that these factors contribute uniquely to motivated behaviour and may respond differentially to individually tailored therapy.

# 6 Dopaminergic agonists as a therapeutic option in clinical apathy

## 6.1 Chapter Summary:

Apathy remains an untreated condition, despite its debilitating effects on patients and their carers. Two lines of evidence suggest that clinical apathy is associated with dysfunction within dopaminergic transmission within the fronto-striatal circuit. Early case studies have supported the use of dopamine (DA) agonists to treat clinical apathy, however these have been limited in size, and only one study to date has investigated the behavioural changes incurred by dopaminergic treatment for apathy. In this chapter, I conduct a case study to investigate whether apathy can be treated using ropinirole, a dopaminergic agonist, while measuring pre and post treatment behaviour using an option selection task. Three patients are included, two with focal sub-cortical strokes, and one with cerebrovascular disease. They completed the apple gathering task (AGT), and behavioural data was modelled using drift diffusion modelling (DDM) techniques. At baseline, all three patients were significantly apathetic, as measured by the apathy evaluation scale. Behaviourally, they demonstrated a significant reduction in overall offers accepted. DDM demonstrated this was associated with a reduction in the rate of evidence accumulation, or drift rate parameter ($v$) as well as a decrease in the bias term, $z$. In two patients, reward sensitivity, indexed by the $v_r$ term, was also significantly altered and in one patient with concurrent depression effort sensitivity was heightened ($v_e$). DA treatment was associated significant clinical improvements associated with an improvement in both questionnaire and behavioural parameters. Across patients, the drift rate and bias parameters returned to similar levels as controls. In patients with altered reward and effort sensitivity, this also significantly improved. Taken together, we

demonstrate that DA agonists can represent a viable treatment option in apathy, and that the behavioural changes associated with clinical improvement can be represented by validated DDM parameters.

## 6.2 Introduction:

Clinical apathy remains an untreated condition, partly due to a poor understanding of its underlying mechanisms. When considering potential therapeutic targets, a useful starting point might be to ask whether specific brain regions, networks and their associated neurotransmitters might be associated with the syndrome. One way to investigate this has been through neuroimaging studies, including magnetic resonance imaging (MRI) structural and diffusion weighted techniques (Kos et al., 2016; Starkstein & Brockman, 2018). MRI investigations of apathy across neurological diseases have implicated a network of brain areas, and their connecting tracts, that link the medial forebrain regions to the basal ganglia (Kos et al., 2016; Le Heron, Apps., et al., 2018; Starkstein & Brockman, 2018). This *fronto-striatal* network includes: anterior cingulate cortex (ACC); ventromedial prefrontal cortex (vmPFC); ventral tegmental area (VTA); and ventral striatum (VS) which is considered to be the human homologue of the nucleus accumbens (nAC) (Kos et al., 2016; Le Heron, Apps., et al., 2018). Notably, a key neurotransmitter within this network is dopamine (DA) (Haber et al., 2000; Haber & Knutson, 2010).

Originating within the VTA of the midbrain, DA neurons project to the VS, including nAC (Haber et al., 2000; Haber & Knutson, 2010). Striatal outputs also project, via thalamus, to medial frontal regions, including the vmPFC and ACC, which in turn project back to the striatum, forming the basis of the fronto-striatal system (Haber & Knutson, 2010). Pre-clinical studies in rodents demonstrate that DA activity within this network plays a critical

role in reward processing (Cagniard, Balsam, et al., 2006; Cagniard, Beeler, et al., 2006; Montague et al., 1996; Schultz et al., 1997). For example, DA neurons within the VTA of the midbrain continually track the difference between expected and observed rewards (i.e. reward prediction errors) (Montague et al., 1996; Schultz et al., 1997), and increasing DA concentrations within nAC is associated with enhanced willingness to expend effort (i.e. press a lever) in return for rewards (Cagniard, Balsam, et al., 2006; Cagniard, Beeler, et al., 2006). So can disrupting DA transmission within the fronto-striatal network result in diminished motivation? If so, could this play a role in the pathology underlying clinical apathy?

Pre-clinical studies in rodents support this hypothesis. For example, while injections of DA stimulants into the nAC significantly increases locomotor activity in rodents, pre-administration of a DA antagonists attenuates this effect (Delfs et al., 1990). More detailed investigations have assessed the effect of DA antagonists on effort-based decision making (EBDM) paradigms (J. D. Salamone et al., 2007, 2016b; J. D. Salamone & Correa, 2012). In one example, rodents chose to select either a preferred high carbohydrate feed in return for physical effort (i.e., lever press five times), or a less appealing *chow* that was freely available (J. Salamone et al., 2002; J. D. Salamone et al., 1991). At baseline, rodents consistently chose the high effort option. However, injecting them with a DA antagonist significantly reduced the frequency of selecting this choice. Critically, their consumption of standard chow significantly increased after DA antagonist treatment, suggesting that DA manipulation specifically altered their willingness to work for reward, rather than overall feeding behaviour (Koch et al., 2000; J. Salamone et al., 2002; J. D. Salamone et al., 1991). These findings support the possibility that dysfunctional DA transmission within the fronto-striatal system

may be associated with symptoms of amotivation. A question remains as to whether these findings translate in humans.

While it is not feasible to perform invasive depletion studies in people, some insights can be gleaned by investigating diseases that target components of the fronto-striatal system. For example, in Parkinson's disease (PD) – which is characterised by degeneration of DA neurons within the SNc – up to 40% of patients suffer with clinical apathy (den Brok et al., 2015). Dopaminergic therapy remains a mainstay of treatment for its motor symptoms including tremor, rigidity, and bradykinesia (Jankovic & Aguilar, 2008). Can we infer something about the role of DA in motivated behaviour from these patients? In a study conducted by Muhammed and colleagues, 40 PD patients were investigated on and off DA treatment using pupillometry as a measure of reward sensitivity (Muhammed et al., 2016). Two key findings were demonstrated. First, PD patients with increasing apathy severity demonstrated reduced pupillary dilatation in response to rewards. In other words, they were less *reward sensitive* (Muhammed et al., 2016). Second, pupillary modulation was significantly increased in PD patients on DA when compared to off treatment. This suggested that apathy may be characterised by reward insensitivity, and that this may be modulated by DA (Muhammed et al., 2016).

In a similar study design, Le Heron and colleagues investigated PD patients on and off DA using an effort based decision making (EBDM) for reward task (Le Heron, Plant, et al., 2018). Patients were asked to weigh up whether to exert physical effort (squeezing a hand held device) in return for monetary reward. By parametrically varying the amount of rewards and effort across trials, the authors were able to highlight several findings in relation to apathy and DA. First, apathy and DA depletion were both associated with a significant

reduction in offers accepted overall (Le Heron, Plant, et al., 2018). Second the specific mechanisms by which apathy and DA altered choice behaviour were slightly different. Patients with apathy were characterised by insensitivity to low levels of reward. On the other hand, DA treated patients accepted significantly more offers at high reward and high effort, rather than low reward (Le Heron, Plant, et al., 2018).

Taken together, these studies support the role of DA for improving motivated behaviour during EBDM. However it is worth noting that the exact mechanisms by which DA increases motivated behaviour were not identical to those associated with the phenotype of apathy (Le Heron, Plant, et al., 2018). Despite this potential difference in the mechanisms associated with DA therapy and the presence of apathy, it is important to consider whether clinically apathetic patients get better on treatment. In PD there is evidence that this might be the case. For example, Thobois and colleagues demonstrated in 37 apathetic PD patients that treatment with a selective D2/D3 agonist piribedil significantly improves questionnaire measures of apathy compared to placebo (Thobois et al., 2013).

Further, two case studies on stroke patients also suggest that dopaminergic therapy can improve apathy, using the DA agonist Ropinirole (Adam et al., 2013; Kohno et al., 2010). Kohno and colleagues were able to successfully treat a patient with significant apathy following a stroke affecting prefrontal cortex (Kohno et al., 2010). They used the neuropsychiatric inventory (NPI) as an index of apathy and conducted single photon emission CT (SPECT) pre- and post-treatment to measure changes in perfusion within the brain. They demonstrated a significant clinical improvement, associated with a significant decrease in apathy score on NPI (from 12 to 3). Additionally, there was improved perfusion on treatment within the prefrontal cortex and basal ganglia on SPECT imaging. These results suggests that

there may be a clinical benefit associated with treatment. However, the investigators did not conduct any experimental behavioural testing in their patient to establish potential underlying mechanisms. Only one study to our knowledge has reported data on testing a stroke patient with apathy using experimental paradigms on and off DA treatment (Adam et al., 2013).

In that study, the authors treated a patient who had developed profound apathy following focal bilateral basal ganglia strokes (Adam et al., 2013). He was treated with the DA agonist Ropinirole, and completed two EBDM tasks that measured reward sensitivity, indexed by reaction time during saccadic eye movements (Adam et al., 2013). In one of these, he was asked to saccade to the left or right of a central fixation target as fast as he could to earn monetary rewards. However only one side was rewarded at a time, changing sides every 10-14 trials without warning . Following treatment, the investigators demonstrated a significant clinical benefit, associated with an improvement in apathy questionnaire scores. Behaviourally, the patient showed an increase in reward sensitivity, indexed by quicker reaction times towards the rewarded side (Adam et al., 2013). However, the tasks used in this investigation did not parametrically vary effort alongside reward. It is unclear therefore if the benefits incurred by treatment were purely due to improved reward sensitivity, or also affected effortful processing. DA treatment in PD patients undergoing an EBDM task has been associated with increased willingness to exert the highest amounts of effort, but only when reward is high (Le Heron, Plant, et al., 2018). This indicates that DA may influence both reward and effort processing aspects of option selection. Clarifying this, especially in the context of treatment mechanisms in apathy is therefore important.

Another reason this is of interest relates to the relationship between apathy and depression, where anhedonia may be a core feature. While these two constructs are often closely

correlated, it is unclear if they are associated with different behavioural deficits during EBDM. For example, some paradigms in anhedonia have demonstrated an increased aversion to effort (Berwian et al., 2020; Treadway et al., 2009), whereas in apathy these often show an isolated insensitivity to reward (Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018). However, late-onset sporadic small vessel cerebrovascular disease patients show in addition hypersensitivity to effort (Saleh, Le Heron, et al., 2021).

Using a paradigm where effort and reward equally co-vary, we may be able to demonstrate a behavioural divergence between these two constructs. For example, patients with isolated apathy may be insensitive to reward, while those with isolated depression may be hypersensitive to effort. Finally, patients with both symptoms may demonstrate a combination of both deficits. This would be an important contribution, especially in relation to how these behavioural changes may respond to treatment in each type of patient. For example, are patients with concurrent apathy and depression less responsive to DA treatment than those with isolated apathy?

To answer some of these questions, we conducted a case series of patients who presented to our cognitive disorders clinic with profound apathy and fronto-striatal pathology, two associated strokes and one probably related to small vessel disease. All patients were treated with ropinirole, and assessed using questionnaire measures, MRI, and a validated EBDM task.

We had three hypotheses:

1. Apathetic patients with fronto-striatal pathology are characterised by insensitivity to reward, however those with concurrent depression may also suffer with hypersensitivity to effort.
2. Ropinirole can significantly clinical improvement in apathy in these cases
3. Behaviourally, the mechanism by which ropinirole exerts its effect primarily by increasing reward sensitivity.

Our EBDM task was analysed using several approaches. First, logistic regressions were used to look at choice behaviour. Second, we analysed choice behaviour and reaction time data using a validated modelling approach known as drift diffusion modelling (DDM) with Bayesian statistical methods. This approach is particularly well suited to smaller sample sizes, and critically provides behavioural parameter distributions that are amenable to Bayesian statistical testing.

## 6.3 Methods:

### 6.3.1 Participants

Patients were recruited from the Oxford cognitive disorders clinic between November 2017 and February 2020. They were referred to our clinic specifically due to a significant loss of motivation in relation to their neurological diagnoses. A full history and clinical examination were conducted before recruitment onto our research protocol. All three reported cases involved young, previously high functioning individuals referred primarily due to a significant decrement in their levels of motivation. However, they had different aetiologies and timelines associated with their symptoms. A summary of each patient's history and

investigations can be found in the 'Clinical Summary' section below. Throughout the manuscript, patients one, two, and three will be referred to as AZ, BY, and CX respectively.

## Clinical Summary

### Patient one - AZ

AZ was a 42 year old gentleman who presented locally in 2015 with insidious behavioural change, characterised by a significant decrease in motivation and empathy limiting his activities of daily living. Having previously been a successful construction site manager, he was suspended from work after neglecting his duties, and eventually made redundant. At home he became much less involved with his family, resulting in a divorce from his wife and estrangement from his children. At the time of his first clinic appointment with us in 2017, he was residing in a brain injury rehabilitation unit where he received full time care. Nursing staff described a decline in his behaviour for at least one year. For example, he needed prompting to perform basic activities such as getting out of bed, eating meals and showering. He smoked up to 20 cigarettes a day and generally only wanted to eat junk food. He had little insight into his deterioration and felt that he was *normal*. He denied low mood, symptoms of a stroke, and had no previous medical history prior to this presentation.

There were no remarkable findings on neurological examination, and he was subsequently referred for neuroimaging. An initial MRI scan of his brain demonstrated an abnormal signal within the right thalamus consistent with a vascular event. He also underwent nuclear imaging to investigate if there was evidence of reduced cortical update consisted with fronto-temporal dementia (FTD), which can present with similar symptoms. A Fluorodeoxyglucose Positron Emission Topography (FDG-PET) scan showed no evidence of FTD, however confirmed the previously reported sub-cortical right thalamic infarct, as well as a low density

area lateral to the left head of the caudate in keeping with another vascular event (**Fig 6-1A**). In summary, this was a young, previously high functioning male with significant apathy following a presumed ischaemic vascular event affecting his basal ganglia bilaterally. The main reason for referral was to enquire about possible treatment.

**Patient two – BY**

BY is a 53 year old female executive who presented to the local accident and emergency (A&E) department in December 2017 following an acute episode of confusion during a morning run. She regularly ran up to 5 miles every morning before going to work, however returned home one morning confused and with a graze on her cheek that she could not remember the cause of. She tried to make her usual journey to work later that morning but returned home after getting lost on the tube. The following day, her colleagues noted that she was unable to complete routine tasks at work and took her to the A&E department. While her neurological examination was unremarkable, she had a CT scan which demonstrated a hyperdensity within the left basal ganglia. This prompted an MRI scan which showed evidence of haemorrhage in the basal ganglia bilaterally (**Fig 6-1B**). Examination by the stroke team noted a flat affect and a lack of concern when informed she had suffered with a stroke.

There were no physical signs of a stroke however, and her neurological examination was unremarkable. Subsequent neuropsychological assessment revealed significant decline in memory, complex reasoning and problem solving. Notably, she had a significantly elevated apathy score, indexed by the Lille Apathy Rating Scale (LARS). A collateral history from her husband revealed she had stopped running completely and was no longer working at her previous employer as it was deemed too arduous. She would spend most of her day watching

television, and had stopped engaging with hobbies such as baking which she used to enjoy. Like patient AZ, she reported no low mood, and did not give any reasons for her change in behaviour. She was subsequently referred by her neurologist to the cognitive disorders clinic to consider possible treatment options for her amotivation, which had become her dominant problem according to her husband.

**Patient three – CX**

CX is a 52 year old gentleman who was referred to us in 2019 with significant apathy and low mood over the last two years. He was previously a full time GP until 2013 when he suffered with a stroke. Although there was no evidence of this on neuroimaging, there was some evidence of small vessel disease (SVD). His medical history was additionally complicated by a diagnosis of neurosarcoidosis, and myasthenia gravis. Therefor he was on multiple treatments including infliximab, corticosteroids, and methotrexate (**Table 6-1,** medications). Unlike the first two patients, this gentleman was both apathetic and profoundly depressed. Having been an independent practitioner, he was no longer working and unable to do much more than surf the internet all day. He found this very upsetting and wanted to become more motivated. He also reported experiencing some visual hallucinations and possible REM sleep behavioural disorder. On examination he demonstrated a reduced arm swing on one side, however his examination was otherwise unremarkable. He was investigated for Parkinson's disease using a Dopamine Transporter (DAT) scan which was unremarkable, but confirmed the previously reported SVD. A repeat MRI was conducted which was unremarkable, with no evidence of abnormality, nor any evidence of previous stroke (**Fig 6-1C)**. The primary reason for referral by his GP to our clinic was to query any possible therapeutic solutions for his apathy, as this was a significant source of distress for him.

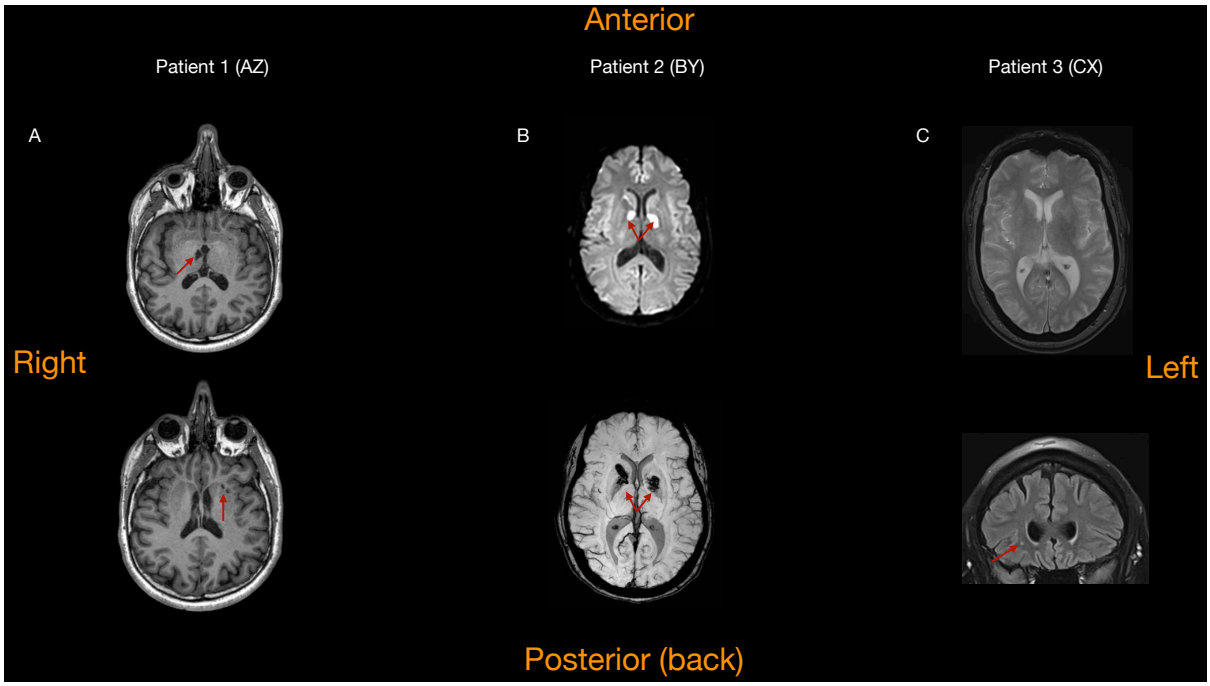



**Figure 6-1. Magnetic resonance imaging (MRI) findings**. (**A-C**) All views are axial, with exception to the bottom right coronal slice. Pathology is highlighted using red arrows. (**A**) Patient AZ had two distinct ischaemic lesions as demonstrated on T1 weighted MRI: a right thalamic infarct (top) and a presumed vascular infarct lateral to the left head of the caudate nucleus (bottom). (**B**) Patient BY's bilateral basal ganglia pathology is more distinctly visible and demonstrated on diffusion weighted MRI. This demonstrated haemorrhagic transformation in both basal ganglia, with increased extension on the left hand side, specifically affecting the caudate nucleus on that side (top). Different view of pathology using susceptibility weighted imaging demonstrates extent of restricted diffusion within the basal ganglia (bottom). (**C**) Patient CX had no significant changes in comparison to AZ and BY (top), however did show some minor cerebrovascular small vessel disease changes in the periventricular and supratentorial regions (bottom).

### 6.3.2 Treatment protocol

The dopamine agonist (DA) Ropinirole was used in all three patients and was prescribed using a standardised protocol split into two phases (**Supp Fig 6-1** for flowchart):

1. **Safety phase**: This involved a slow dose titration from 250 mcg once a day up to 2mg once daily over a thirty day period. The purpose of this was to anticipate any unwanted side effects in the early phase of treatment. Baseline testing was conducted either before or in the early part of this phase.

2. **Efficacy phase**: This involved dose escalation in 2 mg increments monthly, as tolerated, up to a maximum of 8 mg OD. This was titrated up to either one of clinical response or the maximum dose. Follow-up testing was completed at the highest tolerated dose.

Both patients and their partners/carers were counselled about side effects, specifically the risk of impulse control disorders, and advised to contact our clinic immediately in the event of any concern.

### 6.3.3 Clinical measures

Apathy was measured using the Apathy Evaluation Scale (AES), a well described instrument that has been used to characterise apathy across neurological conditions, including SVD (Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018; Marin et al., 1991). Here we used the self-report version (AES-S). In line with previous studies, a cut of > 34 was used to determine if patients were deemed clinically apathetic (S. Andersson et al., 1999; Kant et al., 1998). Depression was measured using the Beck Depression Inventory (BDI) (Li et al., 1975) and cognitive function using the Addenbrooke's Cognitive Examination III (ACE-III) (Hodges & Larner, 2016). This was done at baseline, and where possible, during follow up.

### 6.3.5 Effort-based decision making

Participants complete the Apple Gathering task (AGT), as described in the general methods (section 2.2) and in chapter three (**Fig 6-2A-B**).

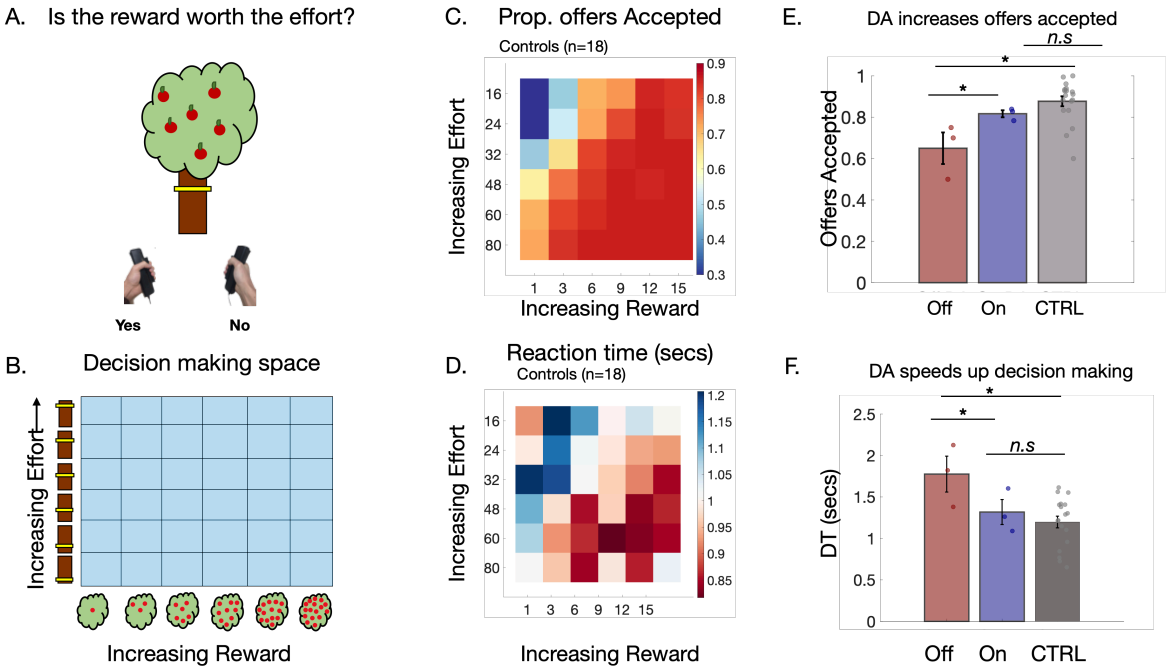



**Figure 6-2 Effort-based decision making-task and overall performance On and Off DA** (**A**) On a trial-by-trial basis, participants were asked if an offer of monetary reward (virtual apples) was worth the physical effort (height of yellow bar). (**B**) A total of 36 possible reward effort combinations were presented (6 levels of reward and effort). Acceptance and rejection rates of different offer types could be mapped in a two-dimensional decision space of reward and effort (6x6 grid, bottom). (**C-D**) Acceptance rates and reaction times in each section of the decision space for the 18 controls' data to establish normative behaviour. People accepted more offers and reacted faster as rewards increased (heat map becomes more red from left to right). Overall, they were very motivated and accepted most offers. On the other hand, they rejected more offers and reacted slower as the effort increased (heat map more blue from bottom to top). (**E**) Overall, untreated patients accepted significantly less offers than healthy controls and DA treated patients. Notably, there was no difference in offers accepted between DA treated patients and healthy people. (**F**) Similarly, untreated patients were significantly slower to make decision when compared to both controls and treated patients. That said, controls remained significantly quicker to make decisions than patients on treatment.

### 6.3.4 Analyses

**Raw behavioural data**

The primary measures of interest within the raw data were overall acceptance rate (AR), and log-transformed reaction time (RT). Overall, only 3% of all trials were excluded across all sessions.

Logistic regression with mixed effects were conducted to assess if groupwise effects in choice behaviour and reaction time varied with different permutations of reward and effort. All models included random effects of Intercept, reward, and effort and fixed effects of group. All interactions between reward, effort and apathy were included. For each model, the F-statistic and *P*-Value were reported. Statistical significance was inferred when *P*-values were $< 0.05$ and corrected for multiple comparisons where appropriate.

**Hierarchical drift-diffusion modelling of effort-based decision making.**

A Bayesian drift diffusion model (DDM) was fit to both the reaction time and choice data as described in the general methods (section 2.3.2) and in chapters three and five. Results of these model evaluation steps can be found in the 'Drift diffusion model evaluation' section of the supplementary material.

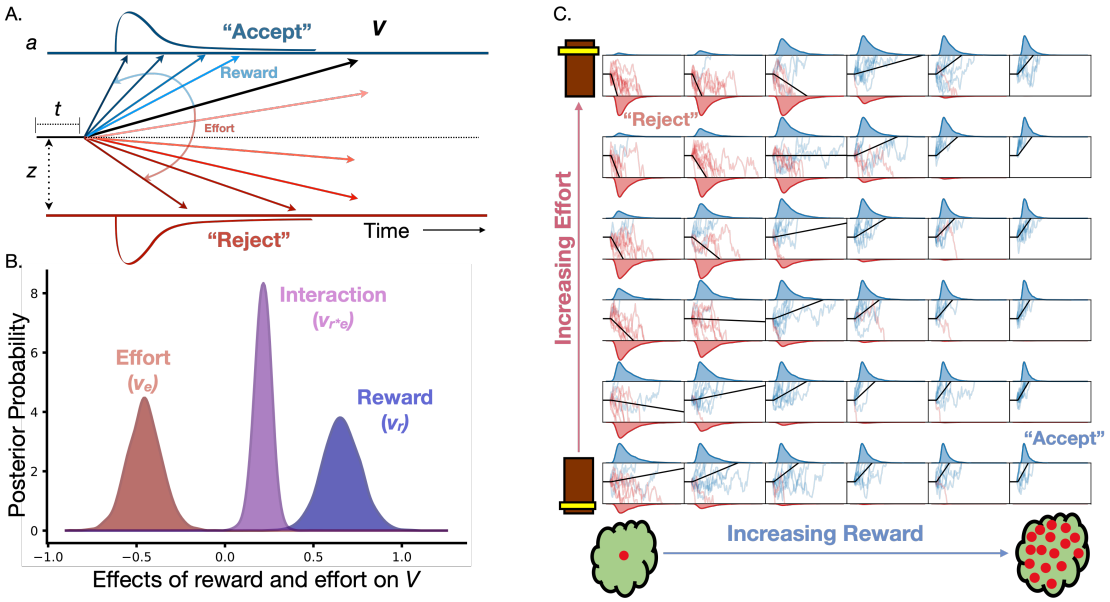



**Figure 6-3. Drift diffusion modelling (DDM) and simulation of effort-based decision making.**
(**A**) In a DDM, decisions are framed as a noisy process involving evidence accumulation towards one of two possible choices (i.e. accept/reject). Decision making is influenced by: The distance between the two decision boundaries (i.e. threshold, *a*), the rate of evidence accumulation (drift rate, *V*), the starting point of evidence accumulation (bias, *z*), and the overall time spent on non-decision making aspects of behaviour (e.g. perception, motor control). (**B**) We fit a DDM model which varied the drift rate by the different levels of reward and effort. Both reward and effort increased and decreased drift rate, respectively. (**C**). A simulation of how the drift rate (black lines) varies with each unique combination of reward and effort based on parameters extracted from a DDM fit to our patient group (averaged across all sessions). The drift rate incrementally increases with increasing reward (left to right), and diminishes with greater effort requirement (bottom to top).

## 6.4 Results

Demographics

Our patients consisted of two males and one female (mean age: 49 years). On average, untreated patients had an elevated AES score of 53.67, which was greater than our assigned cut-off score of 34 (**Table 6-1**) (S. Andersson et al., 1999). This improved on treatment, lowering to 33.67, which is just under the apathy cut off score (**Supp Fig 6-2**). Baseline cognitive scores in patients were relatively preserved, with an average ACE-III of 88.67, although this was lower than healthy controls (96.57). Depression scores, indexed by BDI

total, were relatively low in patients as well as in controls, however it was noted that patient CX had a relatively raised BDI score (19, **Supp Table 6-1**) consistent with mild-moderate depression (von Glischinski et al., 2019). All patients were able to tolerate treatment, however the final doses differed slightly. AZ was able to tolerate a dose of 8 mg OD, whereas the other two patients stopped at 6 mg. In one BY this was due to her general preference to minimise the amount of medication she took. In CX, this was due to feeling agitated and a recurrence of visual hallucinations that he had prior to treatment.

**Table 6-1.** Patient demographics and baseline testing measures.

| ***Demographics*** | ***All Px*** | ***CTRL (n=18)*** |
|---|---|---|
| ***Age*** | 49 (6.08) | 54.47 (11.18) |
| ***Gender (M/F)*** | 2/1 | 7/11 |
| ***Treatment drug*** | Ropinirole | - |
| ***Highest effective dose*** | 6-8 mg | - |
| ***Apathy Evaluation Scale (AES) - Off/On*** | 53.67(6.5)/33.67(9.71) | 30.78 (10.30) |
| ***ACE-III (Score/100)*** | 88.67 (5.68) | 96.57 (2.41) |
| ***Beck's Depression Inventory (BDI) - Off/On*** | 7.67 (10.01) | 4.52 (5.64) |

**Raw Behavioural data**

### 6.4.1 Apathetic people accepted fewer offers and respond more slowly than healthy people, and these effects are reversed following DA treatment.

Generalised logistic regression with mixed effects demonstrated that at the group level, there was a significant reduction in the total number of offers accepted in untreated patients compared to healthy people ([F(1,3658) = 4.69, p = 0.030], **Fig 6-2E**). No significant differences in reward sensitivity, effort sensitivity, or their interaction were found between the two groups (respectively, [F(1,3658) = 1.3, p = 0.25], [F(1,3658)=0.39,p=0.53], and [F(1,3658)=1.98, p = 0.16]). Notably, DA treated patients accepted a similar amount of offers compared to healthy people and were more reward sensitive (respectively, [F(1,3662)=1.04,p=0.32], and [F(1,3662)=4.33, p = 0.037], suggesting that treatment improved overall motivation, possibly due to increased reward sensitivity.

Similarly, a generalised linear regression demonstrated that patients were significantly slower to accept offers overall compared to healthy people ([F(1,3655) = 6.46, p = 0.011]. There was also a two way interaction between reaction time and reward, as well as a three way interaction between reaction time, reward, and effort (respectively, [F(1,3655) = 11.15, p = 0.0008] and [F(1,3655) = 5.41, p = 0.02]). Following DA treatment, there were no significant difference in any DT metrics between patients and healthy controls. Taken together these findings suggest that overall, apathetic people accept less offers overall and response more slowly than healthy people. Additionally, the effect of dopamine on choice may be mediated by increased reward sensitivity. I additionally conducted subject wise analysis to determine whether groupwise effects were consistent at the individual level. This was motivated by the

fact that these patients all had slightly different neural pathology, and therefore may demonstrate slightly varied behavioural phenotypes at baseline.

### 6.4.2 Apathy is characterised by insensitivity to rewards, while concurrent depression is associated with hypersensitivity to effort

Subject-wise comparison revealed two important findings. First, only CX accepted significantly less offers than controls, but not AZ or BY (respectively, [$F(1,3313)=83.75$, $p = 0.003$ after multiple comparison], [$F(1,3303)=0.53$, $p = 0.47$], and [$F(1,3314)=0.41$, $p = 0.52$] ). This suggests that the overall group effect may have driven by CX's overall low intrinsic motivation. Second, two further behavioural mechanisms were present at the individual level that were not found in the group level analysis.

Both AZ and BY showed reduced incentivisation to low levels of reward compared to healthy people, although this effect was only marginally insignificant in the former after correcting for three multiple comparisons (respectively, [$F(1,3303) = 5.19$, $p = 0.06$], [$F(1,3314)=9.9$,$p=0.0048$]). On the other hand, CX showed a significant hypersensitivity to increasing effort [$F(1,3313)=6.95$, $p = 0.024$], **Fig 6-5 A-B, and F**). Notably, CX was the only patient who reported symptoms of depression and had an elevated BDI score of 19, whereas the other two patient's scores were considered normal (0 and 10, respectively). It has been previously demonstrated that patients with major depressive disorder undergoing option selection tasks demonstrate increased sensitivity to effort (Berwian et al., 2020). As we had a sample size of three, a linear regression examining the relationship between effort sensitivity and depression/apathy would be significantly underpowered to detect an association between effort sensitivity and depression in the three patients.

In summary, our two patients who were apathetic and not depressed were insensitive to low rewards, whereas the patient who was concurrently depressed was hypersensitive to effort. Additionally, groupwise differences between patients and controls may be significantly driven by a single participant's behaviour. Therefore, within subject analyses were conducted for all subsequent investigations to ensure consistency between group level and individual findings. The next question we asked was whether ropinirole therapy was associated with a change in behavioural parameters within the patient group.

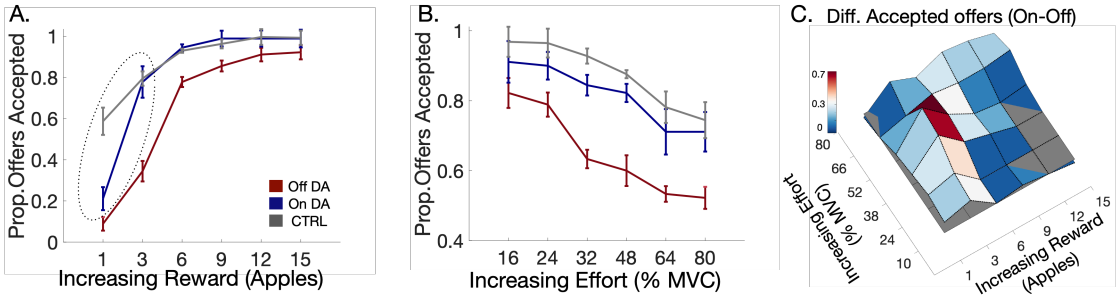



**Fig 6-4. Behavioural performance On and Off DA in relation to controls. (A-B)** Untreated patients (red) accepted significantly less offers than treated patients (blue) and controls (grey) across almost all levels of reward and effort. While treated patients accepted a statistically similar number of offers as healthy people, they were more reward sensitive. Behaviourally, this was driven by the relative increase in offers accepted from low to high rewards (**A, circled**). (**C**) Three dimensional heatmap demonstrating differences in offers accepted in patients on and off treatment. The grey grid represents the zero point (i.e. no difference). Treated patients accepted more offers across most offers with exception to low effort-high reward offers. They also accepted significantly more offers at low reward, as well as at the highest levels of effort.

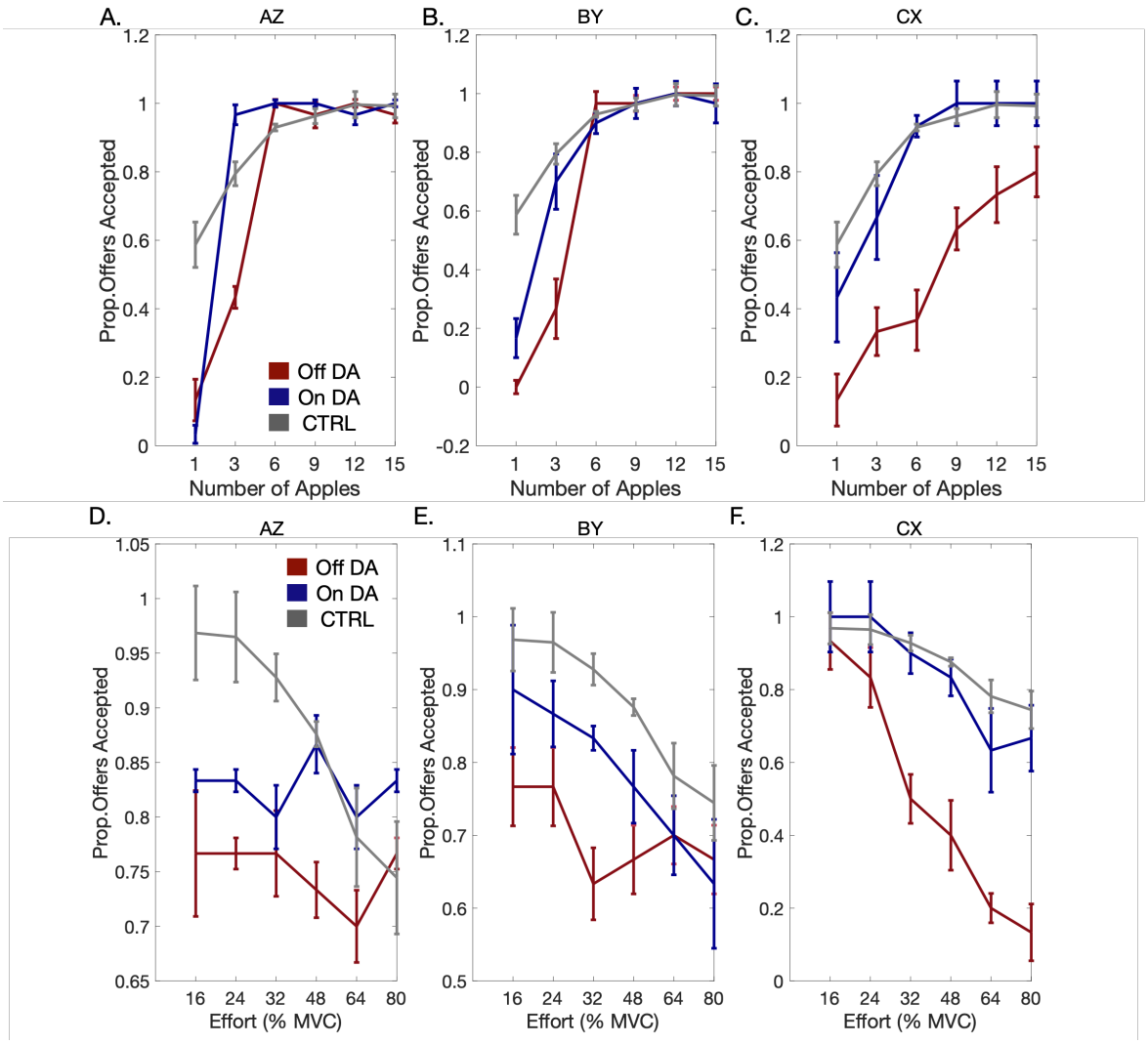



**Figure 6-5**. **Patient wise analysis of acceptance rates**. **(A-C)** Patient-wise acceptance rates with increasing levels of reward. Across patients there is a reduced number of accepted offers at the lowest reward levels. This is significant in AZ and BY, but only marginally so in patient CX **(D-F)** Acceptance rates per patient as effort levels increase. **(F)** Before treatment, only CX shows a significant decrease in offers accepted with increasing effort levels (i.e. they are more effort sensitive). Notably, this is the only patient who had a baseline BDI score consistent with clinical depression. This significantly improves following treatment.

### 6.4.3 DA agonist increases sensitivity to low levels of reward, and boosts intrinsic motivation.

Within the patient group, ropinirole treatment was associated with significant changes across all behavioural parameters. Specifically, it increased overall offers accepted, improved sensitivity to reward and reduced sensitivity to effort (respectively, [$F(1,1040) = 26.53$, $p < 0.001$], [$F(1,1040)=4.15$,$p=0.04$], and [$F(1,1040)=17.8$, $p < 0.001$], **Fig 6-4**). However as with previous analyses, within subject analysis shed further light on these mechanisms. Specifically, the most consistent findings across patients was altered sensitivity to low levels of reward, and an overall increase in offers accepted. There was a significant two-way interaction between reward and ropinirole treatment in patients AZ and BY, and a marginal effect in CX (respectively, [$F(1,332) = 6.9$, $p = 0.015$], [$F(1,347)=6.23$,$p=0.013$], and [$F(1,345)=3.56$, $p =0.06$]). An overall increase in offers accepted was also demonstrated in patients one and three, but not two (respectively, [$F(1,332) = 6.9$, $p = 0.009$], [$F(1,345)=6.45$,$p=0.01$], and [$F(1,347)=2.2$, $p =0.14$]). Despite a group level difference in effort sensitivity, this was not detected across any of the three patients individually, although a non-significant trend was present in CX (respectively, [$F(1,332) = 0.19$, $p = 0.66$], [$F(1,345)=0.036$,$p=0.84$], and [$F(1,347)=3.02$, $p =0.08$], **Fig 6-5F**). All significant effects within patients were retained after correction for three multiple comparisons.

Taken together, these findings suggest that ropinirole therapy is most likely associated with an overall increase in incentivisation to low levels of reward, and an overall increase in offers accepted. One critique of this analyses is that it may not be suited to small data samples as we have in our patient group. Another is that these logistic regressions do not account for both the choice and reaction time data collectively. To mitigate these issues we fit a drift diffusion model (DDM) using Bayesian statistical methods. This includes both reaction time and

choice data, increasing the number of sampling points for each patient. Crucially, probability distributions of each parameter estimate are produced providing a measure of certainty in our analysis.

### 6.4.4 Drift diffusion modelling.

Three HDDM models were run for: untreated patients (M1), treated patients (M2), and controls (M3). For each model, convergence was assessed using Gelman Rubin statistic across five iterations of each model. Trace plots were also generated to assess for parameter drift, and autocorrelation. Finally Posterior predictive checks To validate our model, simulated datasets were generated by sampling from our model's posterior distribution. Five hundred simulated reaction time (RT) datasets were generated using the '*hddm.utils.post_pred_gen'* function in the HDDM toolbox. These were subsequently plotted to compare visual fits of simulated and raw data.

**Untreated patients characterised by lower evidence accumulation (drift) rates and a general tendency (bias) to reject offers**

Three parameters were significantly different between untreated patients and controls (**Fig 6-6**). Baseline drift rate ($V_0$) was significantly lower in patients ($P_{P|D} \approx 0.95$), suggesting that the rate of evidence accumulation towards accepting offers was diminished. They also had a significantly lower bias parameter ($z$), indicating an increased general tendency to reject offers ($P_{P|D} \approx 0.99$). Finally, their non decision time parameter ($t$) was raised, suggesting a slowing down in non-decision making aspects of their behaviour ($P_{P|D} \approx 0.98$). At the group level, there was no significant difference in the threshold parameter ($a$) between groups ($P_{P|D} \approx 0.46$). Reward sensitivity (V*reward) was reduced in the patient group, albeit not significantly ($P_{P|D} \approx 0.81$). Finally, there was no observable difference between the two

groups in the V*effort, and V*reward*effort parameters (respectively $P_{P|D} \approx 0.81$, $P_{P|D} \approx 0.46$, and $P_{P|D} \approx 0.46$). Taken together, these data suggest that in comparison to healthy people, untreated patients were slower to accumulate evidence towards accepting an offer (lower drift rate, $v_0$), required less information to reject offers (lower bias, z), and were slower in non-decision making aspects of their behaviour ( non-decision time, $t_0$).

This analysis was repeated within each subject to establish if these parameter changes were consistent across people (**Supp. Table 6-1**). The baseline drift rate parameter ($v$) was significantly lower across all three subjects (respectively $P_{P|D} \approx 1.0$, $P_{P|D} \approx 0.99$, and $P_{P|D} \approx 1.0$), while the bias parameter was significantly reduced in patients one and two, but not three (respectively $P_{P|D} \approx 0.99$, $P_{P|D} \approx 0.99$, and $P_{P|D} \approx 0.80$). Finally, the non-decision time parameter $t$ was significantly greater in all three people compared to controls (respectively $P_{P|D} \approx 1.0$, $P_{P|D} \approx 1.0$, and $P_{P|D} \approx 1.0$). These results support the presence of a common phenotype for these apathetic patients in relation to controls. Namely, that they have a significantly lower evidence accumulation rate, tend to reject more offers, and take longer to complete non-decision components of behaviour (e.g. perception, motor execution, etc). These findings are encouraging in that they demonstrate more consistency between groupwise and individual results when compared to the choice logistic regressions. However, there were additional differences noted between the controls and individual subjects when conducting subject wise comparison. These are summarised below.

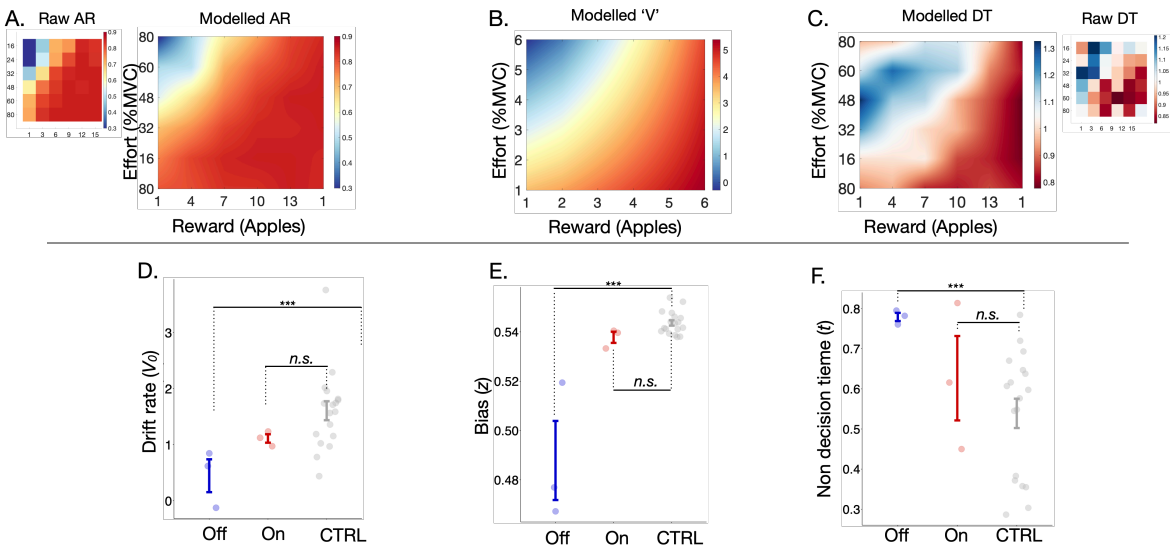



**Figure 6-6. Predictions of DA treatment using DDM parameters.**
**A-C**: Model predictions of DDM fit to the 18 control participants using theoretically predictive values. These demonstrate accurate predictions of both AR (A) and DT (C) which are also reflected in the values of the drift rate $V_{r,e}$ which increases with increasing reward and decreases with increasing effort (B) (**D-F**). Untreated patients had a significantly lower bias to accept offers ($z$), a lower baseline evidence accumulation rate ($V_0$), and generally took longer in non-decision making aspects of behaviour ($t$). All three groupwise differences were abolished following DA treatment. Comparing these parameters between On-Off patients yielded no significant differences, however within group analyses revealed notable differences in all three parameters (see **Supp table 6-2**).

**Insensitivity to low levels of reward characterises apathy**

The reward sensitivity parameter was raised in all untreated patients compared to controls, albeit only significantly in patients BY and CX, but not AZ (respectively $P_{P|D} \approx 0.76$, $P_{P|D} \approx 1.0$, and $P_{P|D} \approx 0.99$). As demonstrated by the logistic regression analysis, a raised V*reward parameter is a consequence of a greater slope between accepted offers at low vs high offers (**Fig 6-4, left)**. However, as the DDM also incorporates the reaction time alongside choice data, the V*reward parameter is a function of both how changing levels of reward change acceptance rates, as well as time taken to accept. The greater the difference in behaviour between the lowest and highest reward levels, the greater the slope, or value of the V*reward parameter. In our patient group, this is driven by lower proportion of offers accepted in the low reward vs high reward option compared to controls (**Fig 6-4**). Similarly in the reaction

time data, this is driven by significant change in reaction times across reward levels in comparison to healthy people. I have plotted the raw reaction time data so this can be appreciated (**Supp. Fig S6-3A-C**).

**Co-occurrence of apathy and depression may increase sensitivity to effort on DDM, while pure apathy is associated with effort insensitivity**

As demonstrated in the logistic regression analysis, only CX, who was both apathetic and depressed demonstrated a significant increase in effort sensitivity compared to healthy people ($P_{P|D} \approx 1.0$). Interestingly, while the logistic regression did not demonstrate any associations with effort sensitivity in AZ, and BY, DDM revealed that they were *insensitive* to effort compared to healthy people ($P_{P|D} \approx 0.99$, and $P_{P|D} \approx 0.94$). So the two patients with isolated apathy were insensitive to effort, while, the patient with both apathy and depression (CX) was hypersensitive to effort. This is an important finding for two reasons. First, it highlights a possible diverging behavioural phenotype in patients who are concurrently apathetic and depressed when compared to those with pure apathy. Second, it demonstrates the DDM measures of effort sensitivity, which incorporate RT and choice data, may be more informative than choice behaviour measures alone. Next, the effect of ropinirole treatment on the DDM parameters was investigated at both the group, and individual level.

**DA treatment increases evidence accumulation (drift) rate and/or the tendency (bias) to accept offers.**

There were no groupwise differences between patients on treatment and healthy controls that exceeded a probability threshold of 0.95 across all seven parameters. Notably, the groupwise

differences in drift rate, decision bias, and non-decision time were abolished (respectively $P_{P|D} \approx 0.93$, $P_{P|D} \approx 0.59$, and $P_{P|D} \approx 0.68$). Similarly no differences were observed in the threshold parameter (*a*), V*reward, V*effort, and V*reward*effort parameters (respectively $P_{P|D} \approx 0.73$, $P_{P|D} \approx 0.86$, $P_{P|D} \approx 0.58$, and $P_{P|D} \approx 0.47$). These findings suggest an improvement in the DDM parameters that were altered in patients prior to treatment. Specifically, ropinirole treated patients no longer displayed significantly slower accumulation rates towards accepting offers, nor were they more biased towards rejecting offers. Repeating this analysis within the patients (i.e. all patients off vs all patients on) showed some interesting findings.

We expected that treated patients would demonstrate significantly higher drift rates, increased bias to accept offers and a lower non-decision time threshold. While the changes across the three parameters were in the expected direction, none of the groupwise comparisons exceeded the threshold value of 0.95. Specifically, there was a non-significant increase in both drift rate and decision bias in treated patients, as well as a decrease in non-decision time (respectively, $P_{P|D} \approx 0.87$, $P_{P|D} \approx 0.94$, and $P_{P|D} \approx 0.87$). Similarly, there was the lack of significant groupwise effect on either reward and effort sensitivity, as demonstrated in the choice data analysis.

Per subject comparisons of parameters on and off treatment were then conducted to investigate this further. This demonstrated two important findings. First, all three patients displayed significant increases in either one of the drift rate, the bias to accept offers, or both (See **supp table 6-2** in 'Drift diffusion model results'). For example, AZ demonstrated a significant increase in both drift rate and bias, as well as a decrease in the threshold parameter (respectively, $P_{P|D} \approx 0.99$, $P_{P|D} \approx 0.95$, and $P_{P|D} \approx 1.0$). BY showed a significant increase in

bias only, and a non significant increase in drift rate (respectively, $P_{P|D} \approx 0.98$, $P_{P|D} \approx 0.75$). Finally, CX showed a significant increase in drift rate, but not the decision bias (respectively, $P_{P|D} \approx 1.0$, $P_{P|D} \approx 0.72$). Taken together, this confirms the positive effect of dopaminergic therapy on the drift rate and/or bias parameters across participants. Notably, this is observed during subject wise analysis, not group level comparison. Finally, it is clear that the precise effects of ropinirole on each patient are not identical. This is confirmed in out next analysis, investigating the effects of DA on reward and effort sensitivity were within each patient.

**DA therapy may improve apathy by restoring reward sensitivity**

At baseline, BY and CX had significantly altered reward sensitivities compared to healthy people ($P_{P|D} \approx 1.0$, and $P_{P|D} \approx 0.99$, **Fig 6-7B-C,** red vs. grey). Specifically, in both patients, the V*Reward parameter was greater, driven by the gradient of change in choice behaviour and reaction time between the low reward and high reward conditions. ropinirole treatment significantly reduced this in both patients (respectively, $P_{P|D} \approx 0.99$, and $P_{P|D} \approx 0.99$, **Fig 6-7B-C,** red vs. blue). Specifically, both patient's reward sensitivity was no longer significantly greater than healthy people as they were at baseline (respectively, $P_{P|D} \approx 0.93$, and $P_{P|D} \approx 0.88$, **Fig 6-7B-C,** red vs. grey). Interestingly, in patient AZ, whose reward sensitivity was not different to controls at baseline, there was no significant change in this parameter following treatment ($P_{P|D} \approx 0.88$, **Fig 6-7B-C**). This suggests that one possible mechanism of ropinirole treatment in apathetic patients is to restore reward sensitivity in patients with deficits in this behavioural parameter.

**DA reverses effort hypersensitivity in patient with concurrent apathy and depression.**

We reported earlier that patient CX, who suffered with both depression and apathy, was hypersensitive to effort when compared to healthy people. DA treatment in this patient

significantly reduced his sensitivity to effort (**Fig 6-7F,** red vs blue). In real terms, his V*Effort parameter, which was more negative at baseline increased towards 0. The effort sensitivity parameter estimate is negative by virtue of its aversive nature (i.e. increasing effort usually decreases effortful behaviour). There for, someone who is no longer sensitive to effort will have a V*effort parameter closer to 0. While DA ameliorated effort hypersensitivity in CX, DA had no significant effect on effort sensitivity in AZ, and BY (respectively, $P_{P|D} \approx 0.73$, and $P_{P|D} \approx 0.94$, **Fig 6-7D-E,** red vs. blue). This is intriguing, as both patients were less effort sensitive than controls at baseline. Taken together, these findings suggest two broad effects of DA treatment at the group level and two more specific mechanisms at the individual level. At the group level, DA treatment across patients increases the drift rate, as well as the bias towards accepting offers. Within individuals, ropinirole can also restore reward sensitivity in patient and reverses effort hypersensitivity.

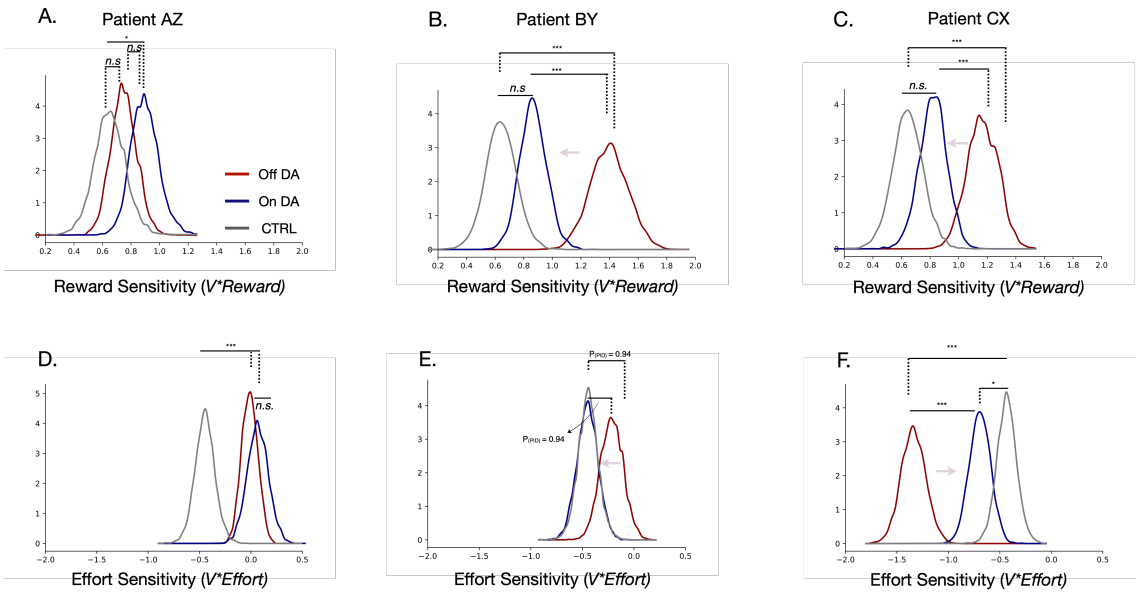



**Figure 6-7. Within subject change in reward and effort sensitivities following DA** (**A-F**) Within subject posterior distributions of reward and effort sensitivity, indexed by the *V*Reward* and *V*Effort* parameters. There was significant variation within patients' reward and effort sensitivities following treatment (**A-C, red to blue distributions**). Reward sensitivity *decreased* in patients BY and CX, but not AZ. Interestingly, both patients with changes in reward sensitivities had baseline levels that were significantly greater than controls (**B-C, red to grey**). Following treatment, reward sensitivities in these patients were

similar to controls (**A-C, blue to grey distributions**). Interestingly, AZ increased their reward sensitivity (**A, blue to grey distributions**). Effort sensitivity was significantly altered only in CX (**F, red to blue**). Their baseline levels were significantly lower than controls, and DA treatment improved this towards the levels of controls. Statistics involved Bayesian hypothesis testing which compared posterior distributions probabilistically.
* = $P_{(P|D)} > 0.95$, *** = $P_{(P|D)} > 0.99$, and $P_{(P|D)} = 0.94$ considered a marginal difference.

## 6.5 Discussion

We conducted the first case series investigating the behavioural mechanisms of apathy and the effects of ropinirole, a dopamine receptor agonist, using a well validated option selection task in a small series of patients with focal lesions. Drift diffusion modelling was used to clarify the precise behavioural mechanisms underlying apathy in these patients. Using a validated option selection paradigm, we showed that untreated patients rejected more offers than healthy controls, and responded more slowly. Logistic regression analysis of choice data highlighted two further mechanisms of apathy. First, patients with isolated apathy (AZ and BY) were less sensitive to low rewards, while one patient with concurrent apathy and depression (CX) was hypersensitive to effort. Following ropinirole, patients accepted significantly more offers and showed improved sensitivity to low rewards. DDM analysis, which combined choice analysis and RT data, further clarified possible mechanisms of both apathy and ropinirole therapy.

As a group, untreated patients demonstrated slower rates of evidence accumulation towards accepting offers (lower drift rate, *v*) compared to controls. They were also more biased towards rejecting offers (lower bias term, *z*). Finally, they generally took a longer time to complete non-decision making aspects of behaviour (higher *t*). Additionally, reward insensitivity was demonstrated in two patients, and effort hypersensitivity in one patient. DA treatment was associated with improvements in evidence accumulation rates, the bias to accept offers as well as non-decision time. It also significantly improved both reward

insensitivity and reversed effort hypersensitivity in affected patients. Together, these findings support the use of dopaminergic therapy to treat amotivation syndromes, and demonstrate the DDM parameters can be used to monitor improvements in a quantifiable manner alongside clinical assessment.

Our effort based decision making task has been used to investigate apathy in both PD and SVD (Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018; Saleh, Le Heron, et al., 2021). In both patient groups, apathy was characterised by a reduction in the number of offers accepted overall, and insensitivity to low levels of reward (Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018; Saleh, Le Heron, et al., 2021). The findings presented here are consistent with these studies, supporting the possibility of a common phenotype of apathy across neurological conditions.

Nevertheless, one patient (CX) was also significantly hypersensitive to effort at baseline when compared to controls. They were unique in two ways. First, they did not have any direct evidence of a stroke on MRI, but rather demonstrated evidence of SVD. Second, they were significantly depressed at baseline, whereas the other two patients suffered with isolated apathy. While effort hypersensitivity in apathy is less commonly reported, a recent behavioural study in 82 patients with sporadic SVD demonstrated that apathetic people with SVD not only suffer with reward insensitivity, but also demonstrate effort hypersensitivity during option selection (Saleh, Le Heron, et al., 2021). So one possibility is that patients with SVD and apathy may also demonstrate effort hypersensitivity alongside reward insensitivity. Another is that the co-morbidity of depression may have contributed to this behaviour.

In a recent study by Berwian and colleagues, an option selection paradigm was used to investigate 123 patients suffering with major depressive disorder (Berwian et al., 2020). This consisted of a button pressing task where people chose between making twenty presses for one point, or one hundred presses for a higher amount (3-7 points). Compared to healthy people, patients with MDD showed two main behavioural changes. First, they accepted a significantly lower number of high effort choices (Berwian et al., 2020). Second, they accepted even less high choice offers when the reward was low (Berwian et al., 2020). Taken together, this can be described as hypersensitivity to effort, and insensitivity to low levels of reward. This was the pattern behaviour demonstrated by patient CX across both our logistic and DDM analyses. This is a potentially valuable finding, which may allow future studies to discern between people who suffer with isolated apathy and those who suffer with concurrent apathy and depression.

DDM analysis was used to further probe the mechanisms of apathy in our untreated patients, with three potential mechanisms demonstrated. Patients had a significantly reduced drift rate, were more biased (lower $z$) towards rejecting offers, and took longer to complete non-decision making aspects of behaviour (longer $t$). Additionally, two patients were insensitive to reward and one hypersensitive to effort. While not many studies have examined the DDM associations of apathy in disease, we previously investigated this in 82 patients with SVD (Saleh, Le Heron, et al., 2021). The results showed that apathy was associated with a significantly lower drift rates ($v$) and altered reward sensitivity (Saleh, Le Heron, et al., 2021). Notably, reduced drift rate was associated with reduced white matter integrity within the fronto-striatal network (Saleh, Le Heron, et al., 2021). It is encouraging that our patients, who also suffered with fronto-striatal pathology, consistently showed reduced drift rates on

baseline testing despite the small sample size. However, two of the three patients also showed an overall reduced bias in rejecting offers which was not demonstrated in our SVD study.

The bias term indexes the starting point of evidence accumulation, and is there for closely associated to the drift rate. For example, increasing the bias to accept an offer means that the total distance required to reach the decision threshold (*a*) is shorter. In real terms this means faster RTs and quicker decisions to accept offers, which in turn influences the drift rate (*v*). Unsurprisingly, changes in the bias parameter during decision making in perceptual tasks have been associated with activation within components of the front-striatal network, including the anterior cingulate cortex (ACC) (Mulder et al., 2012). So, while it has not been demonstrated before, it is anatomically consistent that some apathetic patients with fronto-striatal pathology may be more biased towards rejecting effortful choices. DDM analyses of larger samples will be needed to confirm if this parameter is altered in apathy generally, or if it is associated with specific anatomical lesion patterns.

All our patients significantly improved clinically on ropinirole. For example, AZ was stepped down from needing full time care, and was looking for work. Patient BY returned to her hobby of running every morning and had a new full time job. Finally, patient CX was able to completely read a book for the first time in five years and returned to part time work as a governor in a care home. Our findings build on the small collection of in-human case studies investigating DA therapy as a treatment for apathy. For example, two separate groups have published single patient case studies demonstrating clinical improvements in apathy secondary to stroke following treatment with Ropinirole (Adam et al., 2013; Kohno et al., 2010). While clinical improvement is the intended end goal of treatment, understanding the mechanisms by which DA therapy improves symptoms can help us develop more targeted

therapies in the future. We hypothesised that DA therapy would improve some of the behavioural deficits demonstrated in untreated patients.

All the DDM parameters that were altered at baseline were improved by DA treatment. The evidence accumulation rate and bias to accept offers improved, whereas non-decision time was reduced. In the two patients with altered reward insensitivity, indexed by the *v*reward* parameter, this significantly decreased towards similar levels to controls. Finally, in the patient with effort hypersensitivity, indexed by the *v*effort* parameter, DA treatment was associated with a normalisation of this parameter in comparison to healthy people. Three insights can be gleaned from these findings. First, the drift rate and its components are heavily influenced by DA therapy. Second, there are within patient variations in the extent of these differences. For example, in patient AZ, the overall drift rate was altered but not the reward or effort sensitivity parameters. In BY only reward sensitivity was significantly affected, whereas in CX the drift rate, reward, and effort sensitivities changed following treatment. So why are there within-patient variations in how ropinirole alters drift rate?

Some insight may be gleaned from a recent study investigating the role of methylphenidate, a dopamine reuptake inhibitor, on option selection task in 50 healthy people. Participants were asked to complete a cognitively effortful working memory task known as the "N-back" task after taking a single dose of methylphenidate. This involved presenting letters in a serial sequence and asking participants if this letter was identical to the one presented "N" steps prior. For example, easier 1-back conditions require a comparison of each letter to the one immediately before it, where as more difficult 4-back conditions involve comparing each letter to the one presented four letter before. On a trial-by-trial basis, participants were asked if they wanted to complete an easy (i.e. 1, or 2-back) or difficult (2,3, or, 4-back) trial for a

small or large reward respectively. Notably, they also underwent Flurodopa positron emission topography ([$^{18}$F]DOPA PET) at baseline to quantify each participant's dopamine synthesis capacity within the caudate nucleus. They demonstrated two important findings. First, higher endogenous dopamine synthesis capacity at baseline was associated with increased willingness to choose cognitively effortful choices. Second, while methylphenidate also significantly increased the proportion of difficult choices, it only did so in people with low dopamine synthesis capacity at baseline.

Taken together, these findings suggest that striatal dopamine, specifically within the caudate nucleus, may influence the responsiveness of patients to DA therapy. We did not record this measure in our patients, which may serve as one limitation of this study. Another limitation is that despite being larger than single case studies, our sample size remains modest (n=3). At the time of writing, three more patients have been recruited and are currently undergoing the study protocol (**Supp Fig 6-1**). Nevertheless it is encouraging that even with such small sample sizes, we are able to detect specific differences in behaviour in both the untreated patients when compared to healthy people and within patients treated with DA.

In summary, we report the first case series in apathetic patients with fronto-striatal lesions successfully treated with the dopamine agonist Ropinirole. Using a validated effort based decision making paradigm and drift diffusion modelling analyses, we demonstrated four key findings:

1. Patients with apathy and fronto-striatal lesions are characterised by an overall reduction in drift rate (low *v*), and increased bias to reject effortful actions (low *z*).
2. At the individual level, patients with isolated apathy are insensitive to low rewards, whereas those with concurrent depression are hypersensitive to effort.

3. DA treatment significantly boosts intrinsic motivation, specifically by increasing drift rate, and the bias to accept offers.
4. Within subjects, DA treatment improves reward sensitivity, and reverses effort hypersensitivity in patients who have deficits in these parameters.

These findings offer preliminary evidence that DA therapy may offer possible therapeutic benefits to patients suffering with primary motivation loss, as well as those with concurrent depression. To build on this, larger case series will need to be conducted, ideally alongside pre-post treatment neuroimaging studies to confirm if improvements in behavioural parameters are associated with changes in neural function. Critically, this would clarify if certain types of focal lesion are more or less responsive than others, depending on its position within the fronto-striatal network.

# 7 Apathy as a deficit in motivational dynamics

## 7.1 Chapter Summary:

Option selection tasks, while valuable are unable to shed light on several important aspects of motivation. For instance, it is not clear exactly how motivated behaviour dynamically varies once initiated, and whether it is specifically modulated in response to unexpected changes in task demands. These include responding to setbacks and uplifts, which may increase or decrease task difficulty during task pursuit. Critically, are these processes altered in apathy? In this chapter, I designed a novel online paradigm to address these questions in healthy participants. This was themed around a virtual race where people had to button press as fast as possible towards a finish line to earn a reward. During goal pursuit, some trials included setbacks while others included uplifts. One hundred people completed our task, which demonstrated that setback trials significantly increased pressing speed, while uplifts slowed it down. Notably, trial-wise measures of subjective motivation predicted starting speed on subsequent trials and was influenced by the preceding trial type. For example, uplift trials significantly increased subjective motivation, which in turn invigorated pressing speed for up to seven trials later. Conversely, setback trials increased subjective fatigue, which in turn slowed down pressing speed on subsequent trials. Two behavioural deficits characterised apathy, indexed by the apathy motivation index. First, the positive association between trial-wise ratings of motivation and pressing speed was significantly reduced in apathetic people. Second, their ability to dynamically vary pressing speed in response to setbacks and uplifts was significantly blunted. These findings demonstrate that our paradigm can successfully probe motivational dynamics, which are not accounted for by many EBDM tasks. Importantly, we show that apathy may be associated with behavioural deficits within these dynamics while engaged in goal-pursuit.

## 7.2 Introduction:

The premise of the work presented in this thesis has centred on probing the components of goal-directed behaviour using well designed effort based decision making (EBDM) tasks. Previous chapters have focussed on the process of option selection, which is concerned with the valuation phase of motivated behaviour (i.e. how we weigh up costs and benefits). Investigation of this process using the Apple Gathering Task (AGT) has allowed us to shed light on apathetic behaviour across three different patient groups: small vessel disease (Saleh, Le Heron, et al., 2021), schizophrenia, and stroke. However, some important questions about motivated behaviour and apathy remain unanswered and cannot be addressed by option selection paradigms alone.

First, it is unclear how effortful action is sustained, and if it is dynamically modulated once it has been initiated during goal-directed behaviour. For example, in the AGT, participants squeeze a hand held dynamometer for up to 3 seconds to confirm their preferred choice (Bonnelle et al., 2016; Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018). While it is possible to analyse force metrics such as vigour from this data (the additional force expended beyond the trial's requirement) (Le Heron, Plant, et al., 2018), it is difficult to deduce how effort is regulated beyond action initiation due to the brevity of this part of the trial (Bonnelle et al., 2016). Similarly in the EEfRT task, people are asked to button press 30-100 times in order to complete a selected trial, however no measures of effort expenditure are recorded in real time (Treadway et al., 2009, 2015). In both paradigms, the primary outcome measure is binary (0/1 for rejected/accepted offers), and analyses focus on the total accepted offers rather than actual effortful behaviour (Bonnelle et al., 2016; Treadway et al., 2009). What is missing is a deeper understanding of how effort is initiated, sustained, and

invigorated on a moment-to-moment basis during goal-directed action. These processes usually fall under the appetitive or approach phase of motivated behaviour (Husain & Roiser, 2018) and could complement the findings that have already been established using option selection paradigms.

In terms of goal-directed behaviour, the ability to dynamically vary motivation and effortful action can play an important role in changing environments. For example, a person walking to an important meeting may encounter a road closure that unexpectedly prolongs their journey. This may prompt them to speed up to avoid arriving late. Conversely, they may be offered an unexpected lift by a friend to a nearby stop and enjoy a short walk at a leisurely pace. The first example represents a 'setback' which increases the perceived distance between current state and desired goal, while the second represents an 'uplift', which decreases this distance. In each case, a different behavioural response (respectively, speeding up or slowing down) is chosen in line with the change in task demands. Such motivational reactions may be dynamic, with immediate and sustained components. Thus one question is whether EBDM paradigms can measure these behavioural changes in real time.

Moreover, setbacks or uplifts may alter future behaviour through their imposed costs or benefits. For example, speeding up requires more effort and may increase fatigue or lead to disappointment (i.e. arriving late at a meeting). Conversely, an uplift may boost motivation, and lead to unexpected positive outcomes (i.e. praise for arriving early). So do setbacks or uplifts have longer term effects on motivation and effortful action? Below I highlight some benefits of characterising these aspects of goal-directed behaviour. Specifically, I focus on the ability to sustain and vary effort while engaged in goal pursuit, especially when faced with setbacks. This is often referred to as persistence (Howard & Crayne, 2019).

Persistence is a multidimensional construct that has been described as a defining characteristic of goal directed action (Attneave et al., 1950; Feather, 1962). A recent conceptualisation by Howard and Crayne characterises it as personal tendency to endure through hardships to achieve goals (Howard & Crayne, 2019). Like many multidimensional constructs, persistence is often associated with several similar concepts such as perseverance or 'grit' (Duckworth et al., 2007). Unsurprisingly, as far back as 1926, persistence has been associated with childhood predicted lifetime achievement (Miles, 1926). More recently, persistence and the related construct of 'grit' have been associated with higher grade point averages (GPAs) in high school students, an increased likelihood to complete military academy programmes, and long term job retention (Duckworth et al., 2007; Eskreis-Winkler et al., 2014; Owusu et al., 2020; Jachimowicz et al., 2018). Therefore, persistence may an important feature of motivated behaviour, and is associated with positive real world outcomes. But how do we measure it experimentally?

Historically, people have attempted to measure persistent behaviour by asking participants to partake in tasks which are either unsolvable, extremely difficult, or rigged (Lucas et al., 2015; McLauchlan et al., 2019; Meindl et al., 2019; Porter et al., 2020; Styk & Klinkosz, 2020; Ventura et al., 2013; Ventura & Shute, 2013; Welker & Carré, 2015). For example, Ventura and colleagues asked participants to complete 28 anagrams, twelve of which were significantly more difficult than the others (Ventura et al., 2013). Their primary outcome measure was the time spent on trials. They demonstrated that participants with high self-ratings of persistence spent significantly more time on difficult anagrams. This was confirmed by Lucas and colleagues in the first of a two part experiment (Lucas et al., 2015). In the second half they asked if persistent people actively respond differently in response to

failure. To answer this they asked participants to complete a button pressing task, themed around Russian roulette (Lucas et al., 2015). Before each trial participants had to press as many times as possible on a mouse to increase their likelihood of winning against a competitor. However the trial feedback was rigged so that participants were randomly allocated a 'win' or 'loss' unknowingly. The primary measure was number of clicks specifically following a loss trial. People with high grit scores had more mouse clicks following a loss trial, however this was not significant ($p = 0.06$) (Lucas et al., 2015).

Meindl and colleagues asked participants to complete a computerised version of the Mirror Tracing Task (Meindl et al., 2019; Snoddy, 1920). This involved tracing the outline of a shape by looking at its reflection in a mirror (i.e. movements were reversed in direction, making them very challenging). Here, investigators framed persistence as a function of 'frustration tolerance', or the ability to tolerate obstacles that impeded progress towards a goal (Meindl et al., 2019). Their primary outcome measure of 'frustration tolerance' was time spent on the tracing task instead of a passive alternative (watching videos, or playing computer games). Frustration tolerance, indexed by time spent on the task, was significantly associated with both self and teacher reported measures of grit (Meindl et al., 2019).

To our knowledge, only one study has attempted to investigate persistent behaviour in apathy (McLauchlan et al., 2019). This was conducted in a group of 51 patients with pre-symptomatic to moderately symptomatic Huntington's disease (HD). They were asked to participate in a button pressing task themed around a car race against a computer. The task was rigged so that no matter how much people pressed, the visual feedback indicated that they were losing the race. There was an option to quit whenever they liked and the primary outcome measure was the time spent on the task up to a maximum of ~ 10 minutes

(McLauchlan et al., 2019). Surprisingly, the authors showed that HD patients with apathy spent significantly longer on the task than their motivated counterparts. They concluded this meant patient with apathy were less 'sensitive' to failure. However, they also demonstrated a significant negative association between apathy and cognitive function, as measured by fluency (McLauchlan et al., 2019). Therefore, it is possible that time spent on the task was not purely due to greater persistence, but rather poor engagement with the task and its requirements. Another possible interpretation is that apathetic people have greater motivational stability, being less modulated by recent events.

While we have highlighted several approaches towards measuring persistence, none of them specifically probe how dynamic changes in task demands alter either motivation or effortful behaviour. Rather, their overarching theme is based around a single measure of time spent on difficult tasks. It is unclear exactly what spending more time on a task means. Did people get bored and simply stare at the screen? Did they suffer an impairment of sustained attention? Critically, how did they modulate their behaviour over time? To answer these questions we developed a task that measured effortful behaviour in real time while dynamically varying task demands by incorporating setbacks, and uplifts within trials. Effortful action was measured by looking at button pressing speed over time, especially in relation to moment by moment changes in the task. We made the following predictions:

1. Effortful action, indexed by pressing speed, is invigorated in response to setbacks, and diminished following an uplift.
2. Setbacks increase subjective fatigue, while uplifts boost subjective motivation.
3. Moment-by-moment levels of motivation and fatigue can alter effortful behaviour both within and across trials.

4. People suffering with apathy are less able to dynamically modulate pressing speed in response to setbacks and uplifts.

## 7.3 Methods:

### 7.3.1 Recruitment and participants

The paradigm was designed and administered online, due to COVID related restrictions at the time of development. Participants were recruited using the online recruitment platform *Prolific (https://www.prolific.co),* which has been successfully used to collect high quality experimental data online (Palan & Schitter, 2018; Peer et al., 2022). Inclusion criteria were adults aged 18-60 and exclusion criteria were participants on antidepressant therapy, or major depressive disorder. Upon recruitment, an information sheet and consent form were completed online. A series of online questions collected on *Qualtrics (https://www.qualtrics.com)* was subsequently presented. Demographics and questionnaires of interest were digitised and included in a custom designed questionnaire panel, after which participants were directed to the experimental task. This was developed in *Psychopy (https://www.psychopy.org)* and hosted on *Pavlovia (https://pavlovia.org)*. Upon completion of the study people were re-directed to the online recruitment platform and renumerated according to the time spent on the experiment and their overall performance on the behavioural paradigm. A summary of this process can be seen in **Appendix chapter seven, Figure S7-1**.

### 7.3.2 Demographics/Questionnaires

Demographics collected included: Age, gender, age at leaving full time education, highest level of educational attainment, employment status, and whether they had ever received a

diagnosis of COVID-19. In the event of COVID infection, further details were requested (date of diagnosis, and whether hospital admission was required).

Three questionnaires were administered as part of the study:

1. The Apathy Motivation Index (AMI), a validated questionnaire which assesses three different dimensions of apathy (behavioural, social and emotional) in healthy people (Ang et al., 2017).
2. The short Grit questionnaire (Grit-S), developed by Duckworth et al. as a measure of persistence/perseverance (Duckworth & Quinn, 2009).

### 7.3.3 The Persistence task

This key pressing paradigm involved racing against the clock to secure a monetary reward. On a trial-by-trial basis, participants alternately pressed the "A" or "L" key on a keyboard as fast as possible, to advance a visual progress bar from the starting point to a finish line (**Fig. 7-1A**, middle). This had to be completed within 13 seconds, otherwise no reward would be offered for that trial. Reward was represented by a "virtual dollar" on the left-hand side of the finish line, and a countdown timer was presented on the right hand side so participants were aware of the time left throughout each trial (**Fig. 7-1A**, middle). Each press corresponded to an incremental rise in the progress bar beyond the starting point. Additionally, auditory feedback was provided in the form of a tone that increased in pitch with every key press. If the finish line was reached within the trial time, an auditory "*Ca-Ching*" sound was played. Otherwise, a low pitch "bleep" signified the lack of a reward for that trial. Either outcome was followed by a feedback screen showing the reward secured on this trial ($0 or $1) and the total virtual dollars accrued up to that point (**Fig 7-1A**, right). Alongside the trial specific feedback, two rating scales were displayed for participants to rate their motivation and fatigue levels after each trial.

Task difficulty was standardised across people by incorporating three calibration trials (**Fig 7-1A**, left) where they were encouraged to press the "A" or "L" keys as many times as possible within a 13 second period. During these trials, a countdown clock demonstrated the time remaining, and a visual counter kept participants informed of their progress in the middle of the screen. After each calibration trial, a feedback screen presented their last trial's performance, and their best effort so far. They were encouraged to beat this number of presses before subsequent calibrations, to ensure a true maximum number of presses was attained. "No intervention" trials were set at 60% of maximum calibration effort (i.e. well within the maximum press rate). In other words, people had to press 0.60*maximum number of presses to secure reward on those trials. Three additional intervention types were included within the experiment structure (**Fig. 7-1B**). All interventions were randomised, and delivered at 3.3 seconds, approximately one fourth of the way into a trial. This meant that participants could not anticipate trial types and influence their pre-intervention behaviour.

1. **Setback trials**: These increased trial difficulty to approximately 80% of the maximum number of presses at calibration. This was achieved by adding on a 20% 'setback' on top of the no intervention trial requirement (60% of maximum presses during calibration). Visually, a setback was indicated by widening the distance between the moving progress bar and the finish line. Two variations of this trial type were included, one which manipulated the progress bar (i.e. set it back), and another which pushed the finish line further away.
2. **Boost trials:** These decreased trial difficulty to approximately 40% of the maximum effort at calibration. In contrast to setbacks, a 20% boost diminished the baseline difficulty of trials (from 60% of maximum). Visually, the physical distance between

progress bar and finish line was reduced either by “boosting up” the progress bar or bringing the finish line closer to it.

3. **Catch trials:** These simultaneously incorporated a progress bar manipulation alongside a finish line manipulation in the opposite direction. For example, the bar was set back by 20%, but the finish line was brought closer by the same magnitude, there for nullifying the effect of the initial manipulation. Overall, this retained the difficulty of a non-intervention trial (60% of maximum presses at calibration) while incorporating a visual stimulus. This was designed to control for the possibility that behavioural responses in intervention trials were due to the presence of visual stimuli, rather than their content.

This design yielded seven different trial types, which each occurred at a frequency of 14%. One experiment included 119 trials, 17 in each condition, in a randomly shuffled order. The inter-trial interval was self-paced and consisted of two phases. First, a feedback screen (**Fig 7-1,** top right) was presented with their trial outcome, and trial-wise motivation and fatigue ratings to be filled. Once participants were ready, they would press ‘Spacebar’ to continue onto the next trial. This prompted a trial screen which presented the reward on offer that trial (fixed at 1 virtual dollar) followed by the rest of the trial components (e.g. Finish line, Clock, and instruction to press keys to begin as in **Fig 7-1**, top middle). The intertrial interval was computed as the time taken from reward cue until first key press to initiate the trial. On average, participants took 58.16 ± 20.0 minutes to complete the task including breaks. The average time from reward cue onset to trial initiation was 0.81 ± 0.24 seconds.

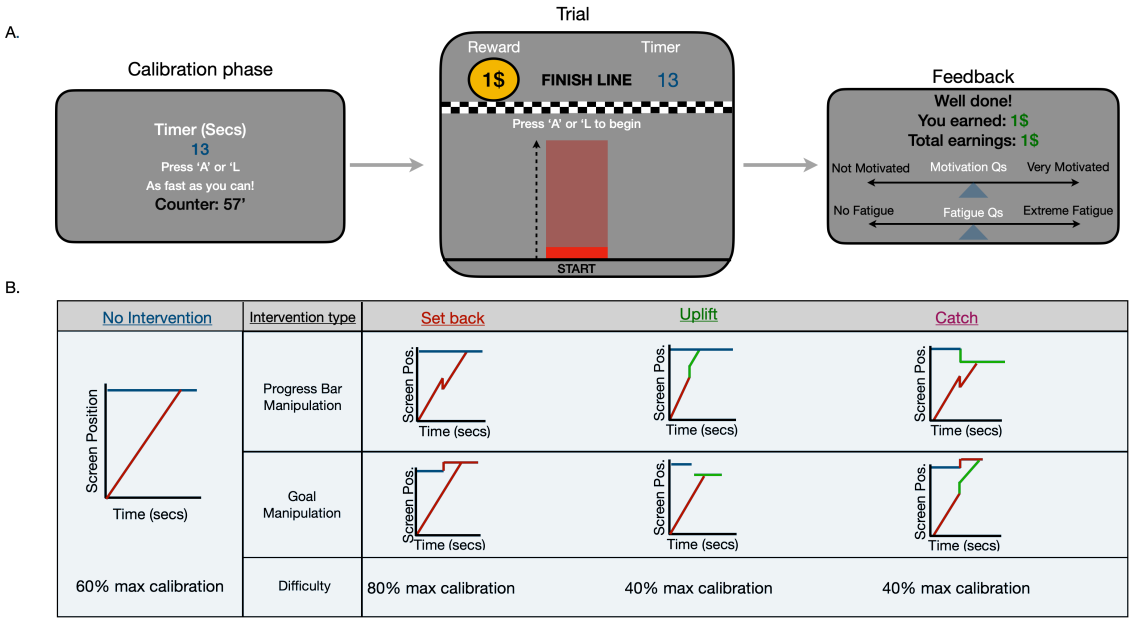



**Figure 7-1. Behavioural persistence task**. Participants were asked to press the 'A' or 'L' keys as fast they could in the setting of a virtual race (**A**, middle). Visual progress was monitored using a red bar which increased in height with each key press up to a finish line. They had to cross the finish line before the time allocated to secure a virtual reward. Upon completing the race successfully, feedback was provided with the trial and overall earnings. After each trial, people were asked to complete a subjective questionnaire on motivation and fatigue (**A**, right). Trial difficulty was calibrated based on people's maximum number of keypresses over three trials (**A,** left). Trial difficulty was subsequently computed over four conditions (**B**). Trials with no intervention required 60% of maximum effort (**B**, left**)**. Three further intervention types were randomly allocated. Setback trials increased the difficulty by either dropping the progress bar or furthering the finish line (**B**, 'Setback'). Boosts decreased difficulty by boosting the progress bar towards the finish line or bringing the finish line closer (**B**, 'Boost). Finally catch trials provided a combination of a setback and boost to provide a control condition with equal difficulty to a no intervention trial (**B**, 'Catch). All interventions were fixed in time, at three seconds into the trials.

**Data processing**:

All data processing was conducted in MATLAB using custom scripts. The main measure of interest was pressing speed. Specifically, we were interested in the change speed in response to within trial interventions. This measure was derived by taking the difference in time between each key press, and computing its reciprocal value. A smoothing function was applied to the data to average data speed across each 20 key press period. Finally, the data was linearly interpolated to obtain the instantaneous speed at100 time points so that trials could be compared. Data analysis was conducted on the interpolated data.

Three types of trial were excluded:

1. Those completed before the 3.3 seconds as the effect of an intervention could not be measured
2. Trials where the reaction time was > 800 milliseconds as this suggested a lack of engagement. As trials were self initiated, we expected reaction time to a visual stimulus to be 200-500 milliseconds, in line with the literature (Amini Vishteh et al., 2019; Jain et al., 2015).
3. Trials where participants stopped key pressing early within a trial. This was defined as trials with fewer than 30 keypresses. After accounting for all three trial types, 57 trials were excluded, equivalent to 0.47% of all trials.

### 7.3.4 Analysis

For all included trials, change of speed after intervention involved comparing the averaged speed in 1.5 second period preceding the intervention and 1.5 second following the intervention, allowing for a 500 ms lag for reaction time (**Fig 7-2A**). Key pressing speed at each interpolated timepoint was normalised by the mean of trials in the no-intervention condition, to better appreciate relative changes across conditions. A repeated measures ANOVA was used to investigate if there was a change in key pressing speed across all trial types (**Fig 7-2B**). A 3x2 ANOVA was subsequently conducted to assess if any changes in speed were due to the intervention types (setback, boost, and catch) or specific manipulations (progress bar vs finish line manipulation). In the absence of an effect of manipulation, data was averaged to include 3 main trial types (i.e. uplift, catch, and setback).

To assess the dynamics of trial-wise motivation and fatigue ratings over time, a generalised linear model with mixed effects was fit to the data. Normalised Motivation/Fatigue ratings were included as the dependent variables, and trial index as the predictor while accounting for random effects of each subject. We then asked if the preceding trial type influenced subsequent motivation/fatigue rating. To investigate this, a repeated measures ANOVA was conducted between normalised motivation/fatigue ratings and preceding trial type.

One question of interest was whether prior motivation/fatigue ratings could in turn influence starting speed on subsequent trials. Ratings and starting speeds in the pre-intervention period (i.e. 1.8-3.3 seconds) were first normalised per-subject, then a generalised linear mixed effects model was run between subjective ratings and starting speed on subsequent trials while accounting for random effects of subject (**Fig. 7-3C-D**). While this analysis established if prior motivation influenced starting speed on the subsequent trial, it did not assess whether this effect persisted in following trials. To answer this question, a generalised linear mixed effects model was fit to investigate the relationship between motivation/fatigue rating and normalised starting speed *n* trials later. For example, where n = 2, the motivation/fatigue ratings for all subjects was associated to started speed two trials later. This was repeated for *n* = 1 to 30, so a total of 30 generalised linear models were run and p-values adjusted for thirty multiple comparisons.

The beta-coefficient of each one of these models was subsequently extracted and plotted as a linear regression across subjects to visualise the relationship between ratings and starting speeds from one to thirty trials later (**Fig 7-4A and C**). Beyond the association between motivation/fatigue rating and starting speed, we also explored if subjective ratings influenced

subsequent trials beyond the starting period. To investigate this, we ran a generalised model with mixed effects between prior subjective rating and five hundred individual time points. The beta co-efficient were subsequently visualised and linear regressions used to establish if there were any significant changes in these associations over time (**Fig 7-4B and D)**. All linear models included the random effects of subject within the model.

**Questionnaire analyses:**

Pearson correlations were conducted between the AMI and Grit questionnaire scores to confirm their association. As we were interested in apathy as a construct, we split our patient groups into an Apathetic and Motivated sub-group using a median split of the AMI questionnaire. The effect of apathy on pressing speed across conditions was assessed by including apathy as a grouping variable in a repeated measures ANOVA looking at the effect of trial type (uplift, catch, and setback) on pressing speed. This was conducted using the raw data as well as data normalised by non-intervention trials. Grit was added as a continuous covariate. This analysis was also repeated using continuous measures of the AMI questionnaire.

## 7.4 Results

One hundred and one participants completed our experiment. They were 25.7 years old on average, two thirds male and half of participants were students (**Table 7-1**). Only six had a recent diagnosis of COVID 19. Overall, participants were able to complete almost all trials (99.4% completion rate of all trials).

On average, no intervention trials took approximately 8.24 seconds to complete and time taken to complete trials during conditions ranged from 6.76 seconds (uplift conditions) and 9.61 seconds (setback conditions, see **Supp table 7-1**). Reaction times, defined as the time between two consecutive key presses, were compared across the seven conditions using a RM-ANOVA for three time periods: The course of the entire trial, the pre-intervention and post intervention period. This demonstrated that while reaction times were similar over the course of the whole trial and in the pre-intervention period across the seven conditions, there was a significant difference in reaction times in the post-intervention period, suggesting a change in pressing dynamics following intervention (respectively, $[F(1,6) = 1.89, p = 0.09]$, $[F(1,6) = 0.88, p = 0.51]$, and $[F(1,6) = 5.78, p < 0.001]$, **Supp Fig 7-2**). This effect survived three multiple comparisons. This suggests that our participants altered pressing dynamics, and that this was specifically in response to an external perturbation.

**Table 7-1. Participant demographics.**

| Demographics | Whole group (n=101) |
|---|---|
| Age | 25.7(8.7) |
| Gender (M/F/Non-Binary) | 60/33/2 |
| Employment. (Student/Employed/Unemployed/Other) | 49/28/19 |
| Covid (Hospitalised) | 6 (1) |

### 7.4.1 Pressing speed decreases over the course of trials

The main measure of interest was the change in pressing speed between the post-intervention (3.8-5.3 seconds) and pre-intervention (1.8-3.3 seconds) periods (**Fig 7-2A)**. Across all experimental conditions, participants slowed down in the post-intervention period compared to early in the trial ([$t(100) = 8.8$, $p < 0.0001$], **Fig. 7-2A**). We hypothesised this effect would be variable across different trial conditions.

### 7.4.2 Setbacks invigorate, while uplifts dampen pressing speed

To ensure that any differences were not accounted for by anticipatory/learned behaviour in the pre-intervention phase, a one way ANOVA was conducted to assess if pressing speed varied across conditions in the pre-intervention phase. There was no significant effect of pressing speed in this period across trial types [$F(1,6)=0.4$, $p=0.84$].

Next, a one way ANOVA with seven levels confirmed a significant difference in the change of pressing speed after intervention across the seven trial types [$F(1,6) = 12.73$, $p < 0.001$]. Post Hoc *Holm-Bonferroni* test (adjusted for a family of 21) was conducted to compare the effect of each condition on pressing speed change (**Appendix chapter seven, Supp Table 7-2**). Setback trials resulted in significant increases in pressing speed compared to all other trial conditions (see **Fig 7-2B**, and **Supp Fig 7-4**. for per-subject visualisations). Both bar and finish line manipulations within the setback condition were significantly faster than non-intervention trials (respectively, $p < 0.001$, 95% C.I. = [0.07,0.4] and $p = 0.013$, 95% C.I. = [0.013,0.34] ) and uplift trials (respectively, $p < 0.001$, 95% C.I. = [0.15,0.48] and $p < 0.001$, 95% C.I. = [0.08,0.42]).

Compared to non-intervention trials, both uplift manipulations (bar and finish line) were non-significantly slower, although the finish line manipulation showed a non-significant trend (respectively, $p = 0.92$, 95% C.I. = [-0.08,0.24] and $p = 0.052$, 95% C.I. = [-0.012,0.32]).

Importantly, non-intervention trials did not significantly differ from catch trials ($p = 1$, 95% C.I. = [-0.11,0.22] and $p = 1$, 95% C.I. = [-0.13,0.19]). This suggested that changes in behaviour were not purely due to the simple visual stimulus but rather to the changing task demands. Based on this, data were normalised by subtracting each subject's no-intervention condition's mean trace from all their trials. This allowed for better conceptual understanding of the relative change in behaviour (**Fig 7-2C**).

One finding of note was that only the bar setback, and not the finish line setback manipulation, was significantly faster than catch trials (respectively, $p < 0.007$, 95% C.I. = [-0.035,-0.025] and $p = 0.14$, 95% C.I. = [-0.286,0.041]) . This suggested that the type of manipulation (i.e. progress bar vs. finish line) may influence pressing speed. A two-way ANOVA was conducted (3 levels of intervention type vs. two levels of manipulation) to verify this (**Fig 7-2D**). While there was a main effect of intervention, there was no significant effect of manipulation or intervention*manipulation on pressing speed (respectively, [$F(1,2)=19.85$, $p < 0.001$], [$F(1,1)=2.7$, $p = 0.18$], and [$F(1,2)=0.15$, $p=0.86$]). So while the presence of a manipulation altered pressing speed, the type of manipulation was not a key factor in altering pressing response. Thus we averaged the bar and finish line manipulations for each trial type for future analyses. A plot using this averaged and normalised data can be seen in **Figure 7-2C**.

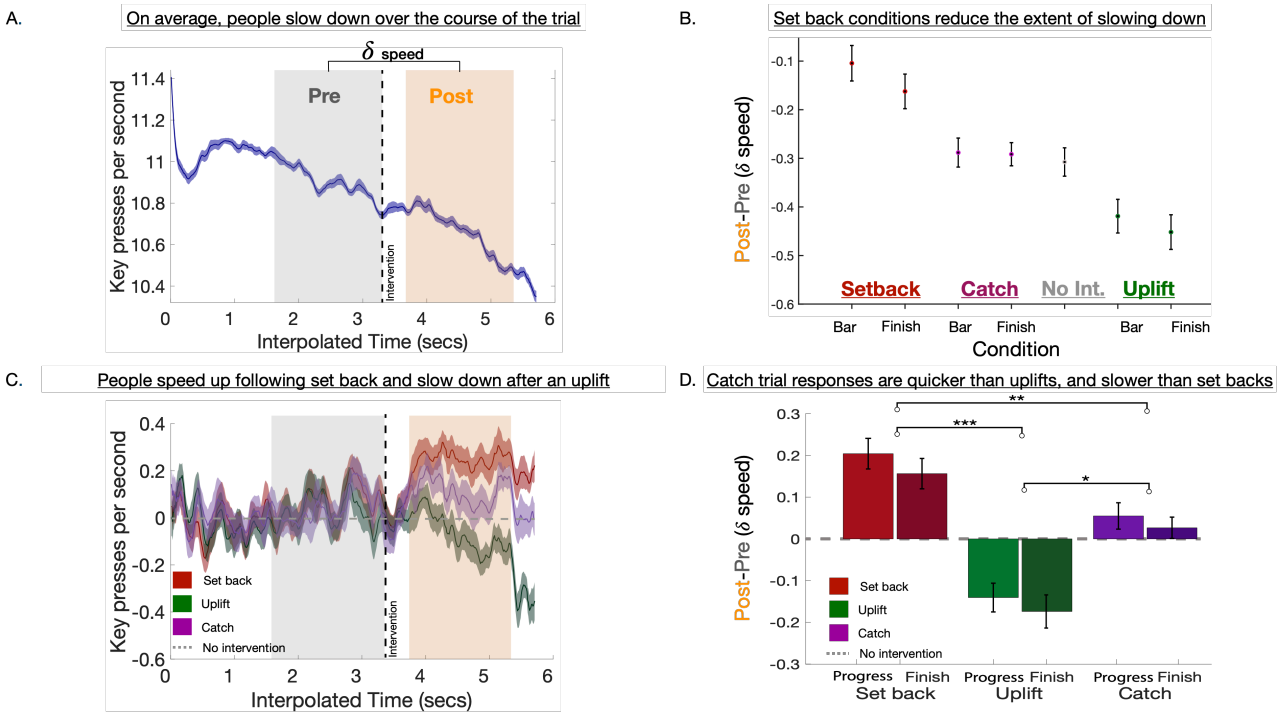



**Figure 7-2. Change in pressing speed as a measure of persistent behaviour. A.** Across all trial types, pressing speed significantly decreased in the post intervention period (highlighted orange) compared to the pre-intervention period (highlighted grey). **B.** The extent of slowing significantly varied based on condition. Whereas setback trials were associated with a relative speeding up, where as uplift trials were associated with a relative slowing down. **C.** One way of visualising effects of trial type on pressing speed is to normalise this by pressing speed on no-intervention trials (grey dotted line). The three trial types averaged across manipulation type (i.e. bar or finish line manipulation). **D.** Comparison of change in pressing speed across three trial types when normalised by no intervention trials. Setback trials associated with significant increase in pressing speed compared to uplift and catch trials. Uplift associated with significant slowing down compared to catch trials.

### 7.4.3 Uplifts increase subjective motivation and reduce fatigue, while setbacks increase subjective fatigue and reduce motivation

Across participants, subjective ratings of motivation progressively decreased over the course of the experiment, while fatigue ratings increased (respectively, [$F(1,12017) = 944$, $p < 0.0001$)] and [$F(1,12017) = 6490.8$, $p < 0.0001$)], **Supp Fig. 7-5**). Further, a one way ANOVA demonstrated a significant effect of the preceding trial type on subsequent

motivation and fatigue ratings (respectively, [F(1,2) = 7.77, p = 0.002] and [F(1,2) = 6.3, p =0.008] ). Post-hoc comparisons with Holm-bonferroni correction further clarified these effects. Specifically, uplift trials significantly increased subjective motivation ratings when compared to setback (p=0.001, 95% C.I. = [0.017,0.115]), and catch trials (p= 0.003, 95% C.I. = [0.024,0.11], **Fig. 7-3A**). Another interpretation of this is that setback and uplift trials both result in a significant decrease in subjective motivation when compared to uplift trials. There was no difference between setback and catch conditions in their effects on motivation.

On the other hand, setback trials were associated with significant increases in subjective fatigue ratings compared to catch (p = 0.012, 95% C.I. = [0.009,0.13]), and uplift trials (p=0.003, 95% C.I. = [0.022,0.14], **Fig. 7-3B**). Another interpretation would be that uplift trials incur significantly less subjective fatigue when compared to setback trials. Taken together, these findings demonstrate that both setbacks and uplifts have inverse effects on subjective levels of motivation and fatigue during effort based decision making.

### 7.4.4 Motivation and fatigue ratings predict starting speed on subsequent trials

A natural next question is if motivation or fatigue ratings can in turn predict key-pressing speed on subsequent trials. Specifically, we asked if prior motivation/fatigue ratings influenced the starting speed of subsequent trials. A generalised linear mixed effects model was run with between subjective ratings, normalised by subject, and subsequent trial starting speed while accounting for the random effects of subject. There was a significant positive association between prior motivation rating and starting speed on the next trial (**Fig 7-3C**,

[F(1,11417)=40.1, p <0.001] ). Conversely fatigue was associated with a significant decrease in starting speed (**Fig 7-3D**, [F(1,11417)=37.9, p <0.001]).

We next asked if this association persisted for more than one trial. To explore this further, we asked to what extent subjective motivation or fatigue influenced starting speed beyond the next immediate trial. In other words, what is the association between subjective motivation/fatigue on one trial, and performance several trials down the line. To answer this question, thirty generalised linear mixed effects models were conducted between the motivation/fatigue ratings on any given trial and starting speed on trials one to thirty following a rating. P-values were adjusted for 30 multiple comparisons. The positive association between subjective motivation rating and pressing speed was significant for the first seven trials, but not beyond after correcting for multiple comparison [F(1,11471)=40.1,p<0.0.001 and F(1,10830)=12.37,p=0.012 for trials one and seven, respectively]. Similarly, the negative association between fatigue rating and initial pressing speed was only significant for the first nine trials [F(1,11471)=37.8, p<0.0.001 and F(1,10635)=15,p=0.003 for trials one and nine respectively]. This suggested that the trial wise ratings of motivation and fatigue can predict starting speed up to nine trials later, but not beyond.

To visualise the relationship between trial wise rating and subsequent starting speed, the beta coefficients from all thirty models were extracted and included in a linear model alongside trial index (**Fig. 7-4A and C**). Over the course of thirty trials after a motivation/fatigue rating, the association with initial pressing speed significantly weakened. So the accelerating effect of subjective motivation on trial ‘n’ was significantly weaker on trial ‘n+30’ compared to ‘n+1’ [F(1,28) = 21.7, p <0.001]. Similarly, the decelerating effect of subjective fatigue on

trial ‘n’ was also significantly less predictive of starting speed thirty trials later than immediately after [$F(1,28) = 64.1$, $p < 0.001$].

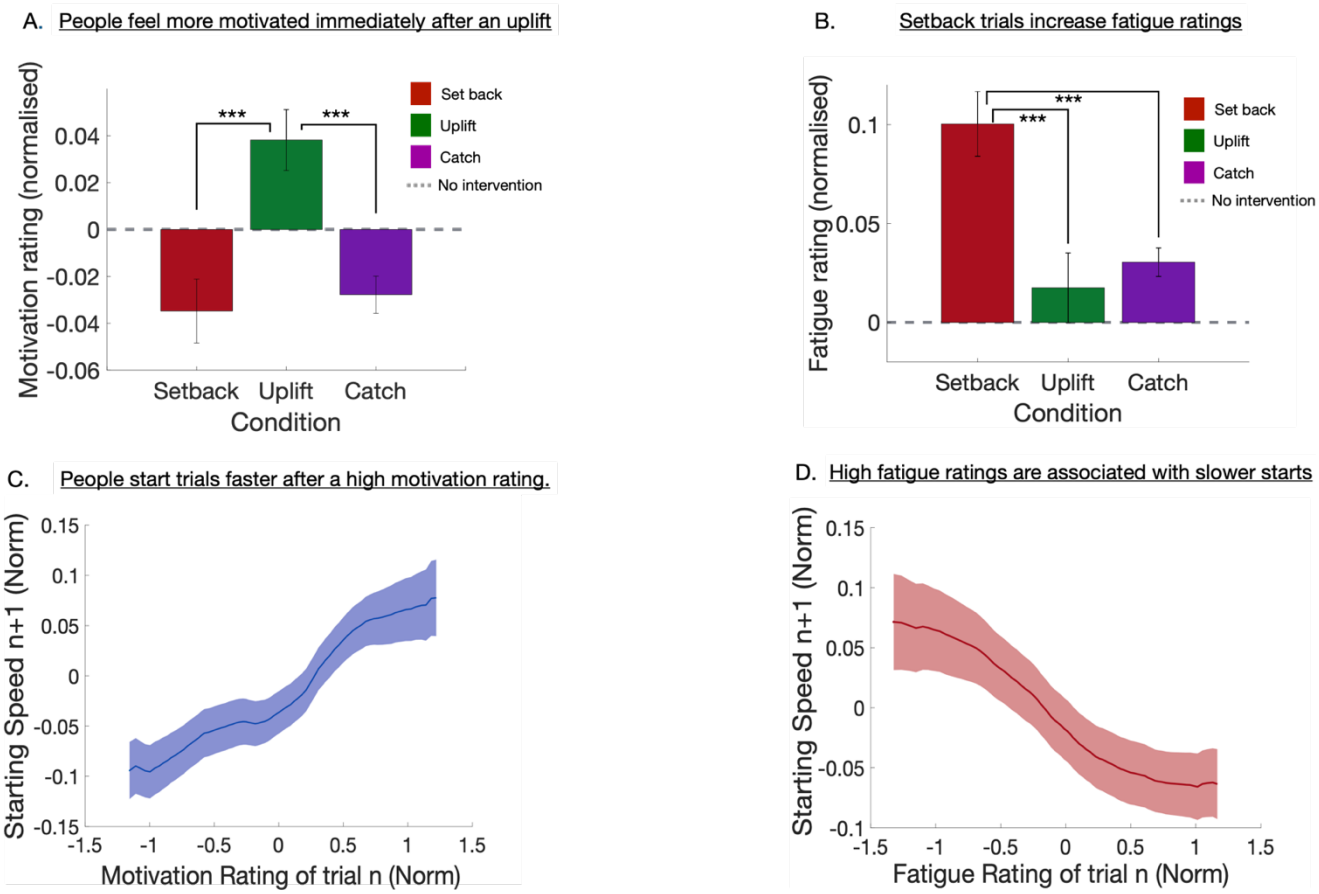



**Figure 7-3. Trial type influences subsequent ratings. A.** Subjective ratings of motivation were significantly higher following an uplift trial when compared to setback or catch trials. **B.** Fatigue ratings were significantly higher after a setback trials. **C.** Conditional plot demonstrating the association between prior motivation and subsequent trial’s starting speed. **D.** Similar plot demonstrating the inverse association between fatigue rating and subsequent starting speed.

### 7.4.5 Motivation ratings influence both starting speed and responses to perturbations

As we had established that proximity predicted the strength of the association between subjective rating and starting speed, we then asked if this association varied *within* a trial. To test this, generalised linear mixed effects models were run between motivation/fatigue ratings and pressing speed for 500 individual time points between one and five seconds within the trial. Conditional plots between beta estimates and time within trial were conducted. These

demonstrated unique dynamics of motivation and fatigue ratings over the course of a trial (**Fig. 7-4C - D**). Subjective motivation demonstrated a bimodal effect on pressing speed (**Fig 7-4C**). There was a positive association with starting speed which significantly decreased throughout the course of the trial [$F(1,498) = 267$, $p < 0.0001$]. Notably however, the association between motivation and pressing speed showed a slight upturn immediately following the intervention period (**Fig. 7-4C**, inset) [$F(1,229) = 6954$, $p < 0.0001$]. In other words, there was a second significant positive association between pressing speed and prior subjective motivation specifically after an intervention. On the other hand, fatigue ratings were associated with a progressive decrement in pressing speed over the course of the trial [$F(1,498) = 1153$, $p < 0.001$]. These effects were present even after including both motivation and fatigue in a single model. Together these data suggest that online subjective ratings of motivation and fatigue not only change in response to the trial type, but in turn are independently associated with altered effortful behavioural both across and within trials.

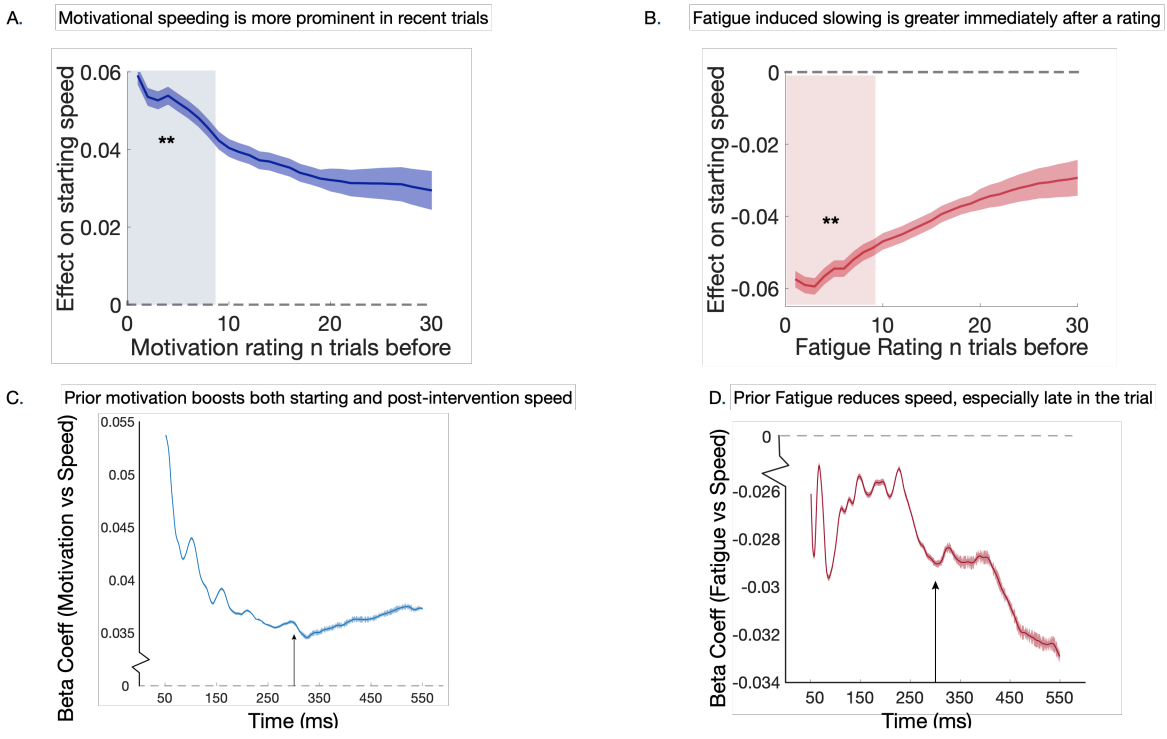


**Figure 7-4. Subjective ratings alter pressing behaviour across and within trials. A-B.** Plots displaying the strength of the association between starting speed and ratings of motivation (A) or fatigue (B) at proximity '*n*'. For example, the association at *n*=10 represents the beta-coefficient of a generalised linear model between the subjective ratings at each experimental trial and the trial speed 10 trials later. A. Prior ratings of motivation were associated with significant increases in subsequent starting speeds for up to seven trials later (or up to *n*=7, corresponding to the shaded area in figure A). **B.** Conversely, prior fatigue ratings were associated with significant decreases in starting speed for up to nine trials later (shaded area), but not beyond. **C-D**. Moment by moment associations between pre-trial motivation/fatigue and pressing speed. The y-axes are cut to demonstrate the dynamics clearly while visualising the approximate xero line. Arrows indicate the point of intervention **C.** The association between motivation on the preceding trial and pressing speed was most pronounced at the beginning of the trial, and immediately following intervention (intervention time represented by arrow)**.** The association between fatigue ratings on the preceding trial and pressing speed linearly decreased over time on trial.

### 7.4.6 Apathy severity is significantly negatively associated with Grit

Questionnaire associations demonstrated significant negative correlations between apathy and the Grit questionnaire [r(93) = -0.21, p =0.038]). This has not been demonstrated before, and suggests the construct of grit may be associated with the apathy. Next, we asked if apathetic people behaved differently to their motivated counterparts during our task. Our patient group was split into an apathetic (n=38), and a motivated (n=63) sub-group by taking a median split of the total AMI scores. Mean and standard deviation scores in both subgroups were consistent with previous validation studies of this questionnaire in healthy controls (respectively, 1.38 (0.27) and 2.09 (0.33)) (Ang et al., 2017). There was no significant difference in number of trials completed, either overall, or in the more challenging setback condition (Respectively, [t(1,99) = -0.62, p=0.53], and [t(1,99) =-0.58,p=0.56]). Similarly, there was no significant difference between overall self-ratings of motivation or fatigue between the two groups (respectively, [t(1,99) = -0.67, p=0.530], and [t(1,99) = -0.41,p=0.68]). Further, apathetic people were also not significantly slower to start a trial following reward cue onset [t(1,99) = 1.73, p=0.085].

### 7.4.7 Apathy is associated with deficits in linking motivation to vigour

A repeated measures ANOVA was conducted to investigate if apathy influenced the effect of trial type on subjective rating (**Fig 7-3A-B**). It did not alter either the motivating effect of uplift trials nor the fatigue inducing effect of setback trials (respectively, [$F(1,2)=1.058, p=0.35$ ] and [$F(1,2)=0.39, p=0.67$]). Next, using a generalised linear mixed effects model, I investigated if the association between motivation/fatigue ratings and starting speed was influenced by apathy. There was a significant interaction between apathy group (split down the median), prior motivation rating, and subsequent starting speed ([$F(1,11415)=10.51, p=0.001$],**Fig 7-5A**). Specifically, apathy significantly reduced the positive association between prior motivation rating and starting speed on subsequent trial (whole group effect **in Fig 7-3C**). This effect was also present when using apathy as a continuous variable measure [$F(1,10706)=17.5$, $p<0.001$]. Notably, it did not influence the relationship between fatigue rating and starting speed [$F(1,11415)=0.95, p=0.33$]. Taken together, this set of analyses suggests that people with apathy have a specific deficit in translating subjective motivation into effortful action, despite not differing overall in either total successful trials or in their subjective rating throughout the task. I next investigated if apathy was associated with any changes in how effort was dynamically modulated throughout the task.

### 7.4.8 Blunted responsiveness to varying task demands characterises apathy

A repeated measures ANOVA was subsequently conducted to determine if total apathy influenced change in pressing speed across the three main conditions of interest (Uplift, Catch, and Setback trials). A Greenhouse-Geisser correction was applied to account for a violation of Mauchly's test of sphericity ($p<0.001$). Overall, there was a significant effect of

condition on change in pressing speed [F(1,2)=13.1,p<0.001]. Additionally, there was a significant two way interaction between apathy and the change of pressing speed across the three conditions [**Fig. 7-5B** F(1,2)=4.2,p=0.026]. This effect was marginally significant when using continuous measures of AMI [F(1,2)=2.98,p=0.069]. Repeating this analyses using Grit showed no significant association with pressing speed [F(1,2)=1.9,p=0.16] .

Post-Hoc analysis to further clarify the association between apathy and pressing speed demonstrated two key findings. First, the overall effect of condition on pressing speed was abolished in the apathetic sub-group. In other words, apathetic patients did not regulate their pressing speed appropriately in response to the three different trial types. Second, there was a significant difference between change in pressing speed between the two groups in the Uplift trials, but not the catch or setback trials. Specifically, motivated people were able to slow down significantly more during uplift trials. Interestingly, there was no difference between the two groups for the catch and setback trials. In summary, apathetic people demonstrated blunted responsiveness to varying task demands, and this was partly driven by inappropriate speeding up during easy trials.

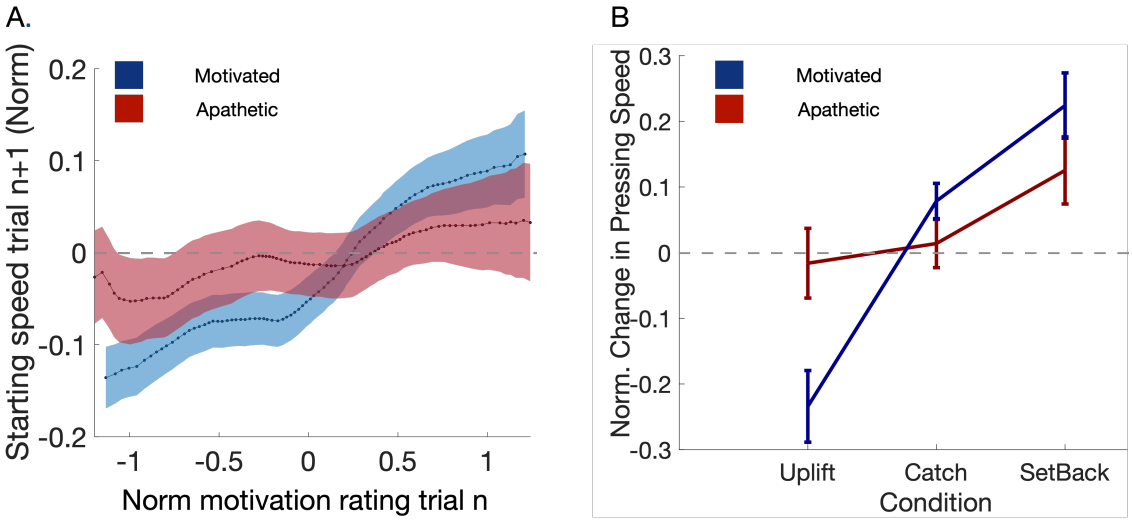



**Figure 7-5. Apathy associated with decreased behavioural flexibility**

A. Questionnaire correlations demonstrating a positive association between apathy, and anxiety/depression, and negative correlations between both with Grit. B. Conditional plot between prior rating of motivation and subsequent trial's pressing speed. Apathy significantly impaired peoples' ability to translate their subjective motivation on one trial into higher pressing speeds in the subsequent trial C. Median split groups showed that apathetic people (red) show significantly less variability in their pressing speed in response to condition. This may be driven by a lack of slowing down when trials are easier (uplift trials). This effect remained after including anxiety/depression and Grit as covariates.

## 7.5 Discussion

In this study, a new online effort based decision making task was developed to measure the dynamics of effortful behaviour in 101 healthy participants. The task involved racing to progress to a finish line, as indexed by button presses, in a limited time. Changes in pressing speed were examined while varying the effort demands dynamically (**Fig 7-1A**). Perturbations included setbacks, uplifts, and catch conditions (**Fig 7-1B**). While pressing speed naturally decreased over the course of a trial (**Fig 7-2A**), unexpected perturbations dynamically altered pressing speed. Specifically, setbacks invigorated effortful behaviour, as indexed by the change in pressing speed immediately following interventions, while uplifts dampened it (**Fig 7-2B-D**). We additionally demonstrated that people's subjective motivation ratings significantly increased after an uplift trial, with subjective fatigue ratings increasing after a setback trial (**Fig 7-3A-B**). These ratings in turn determined the pressing speed of subsequent trials (**Fig 7-3C-D and Fig 7-4A-B**). Thus the dynamics of effortful action can be altered by including well timed perturbations during goal-directed action.

Subsequently, we asked if apathy influenced these dynamics. Two key findings emerged. First, the invigorating effect of subjective motivation on starting speed (**Fig 7-3C**) was impaired in apathetic people (**Fig 7-5A**). This was despite there being no overall difference in motivation ratings between the two groups and a similar trial success rate. Thus a specific

deficit in translating motivation into effortful action characterised the apathetic people. Second, the ability to dynamically regulate pressing speed following perturbations was blunted in apathy (**Fig 7-5B**). That is, apathetic people did not vary their pressing speed in line with changing task demands as well as motivated people. We expected that this effect would be driven by an inability to invigorate behaviour during the setback trials. However, it was in fact due to their relative inability to slow down their pressing speed during uplift trials (**Fig 7-5B**). So apathetic people could not slow their pressing behaviour down when it was advantageous to do so (i.e. the trial became significantly easier to complete). There was no significant association between pressing speed and the construct of 'grit', despite being strongly negatively associated with apathy.

To our knowledge, this is one of the first tasks aiming to investigate the dynamics of effortful action over time, or persistence. Other paradigms that have examined persistence typically employ tasks which do not have the ability to continuously measure effortful behaviour, nor its dynamics (Lucas et al., 2015; McLauchlan et al., 2019; Meindl et al., 2019; Porter et al., 2020; Styk & Klinkosz, 2020; Ventura et al., 2013; Ventura & Shute, 2013). For example, people have been asked to complete a difficult set of anagrams (Lucas et al., 2015; Ventura et al., 2013), mazes (Styk & Klinkosz, 2020), or tracing tasks (Meindl et al., 2019), and time on task has been used as a surrogate of persistence. While this can be a useful measure, there are several issues with over reliance on this single statistic. First, it does not give any insight into the dynamics of behaviour, which may shed important light into the motivation process. Second, it is unclear exactly what an increase in time spent on task means. For example, Lucas and colleagues asked participants to complete a series of 37 anagrams, 16 of which were unsolvable (Lucas et al., 2015). They found that people with high Grit scores spent significantly longer on tasks, but did not necessarily solve any more anagrams than their non-

gritty colleagues (Lucas et al., 2015). Similarly, Ventura et al showed that people with high self-report measures of persistence spent more time on unsolvable anagrams, but did not solve the easy ones any faster (Ventura et al., 2013). In other words, people spent longer on tasks without much to show for it. So were they measuring a motivational construct that matters?

It might be argued that the authors were measuring inappropriate repetition of an aimless activity , or perseveration (Hotz & Helm-Estabrooks, 1995). This is further supported by the only study using a similar paradigm to investigate apathy in a group of patients with Huntington's disease (McLauchlan et al., 2019). Here they employed a button pressing task themed around a virtual car race where the feedback was rigged so that participants always failed to overtake their fellow racer (McLauchlan et al., 2019). Time on task increased both in HD patients compared to controls, and specifically in apathetic people within the HD group. Nevertheless, apathy in HD was also associated with significant cognitive impairment, as measured by verbal fluency (McLauchlan et al., 2019). The authors proposed that patients with apathy spent longer on a task because they demonstrated impaired responses to failure (McLauchlan et al., 2019). In other words, the same metric (time on task) used to represent perseverance and motivation in one set of studies (Lucas et al., 2015; Ventura et al., 2013), also represented impaired responses to failure in another (McLauchlan et al., 2019). This highlights that this measure in and of itself is not sufficiently sensitive to detect the dynamic aspects of motivation we seek to understand.

Our study was able to measure dynamics of behaviour more directly, especially following unexpected trial perturbations (e.g. setbacks). The paradigm used here was able to investigate these questions in more depth, demonstrating that setbacks invigorated pressing behaviour

while uplifts dampened it (**Fig 7-2C-D**). We also showed that these perturbations influenced subjective measures of motivation and fatigue (**Fig 7-3A-B)**, which in turn impacted pressing behaviour for subsequent trials (**Fig 7-3C-D**). This is an interesting finding as it demonstrates a possible virtuous loop between positive stimuli (e.g. uplift trial), subjective rating (e.g. increased subjective motivation) and persistent behaviour (e.g. invigoration of pressing speed on next seven trials). We explored if this relationship and the effort dynamics of behaviour in apathetic patients using the Apathy Motivation Index, a well validated apathy score (Ang et al., 2017).

There were two key findings in the apathetic group. First, the positive association between motivation rating and pressing speed was significantly impaired in apathy (**Fig 7-5A**). This was despite showing similar ratings overall compared to motivated people, as well as performing similarly throughout the task. On first consideration, this would be consistent with one view of apathy as a deficit in 'auto-activation', or the inability to self initiate while retaining relatively preserved externally guided behaviour (R. Levy & Dubois, 2006). However, participants with apathy showed similar starting reaction times to motivated people in this study. That is, on starting a new trial, their first key press following reward cue onset was not slower than their motivated counterparts. Therefore, it is not action initiation, but invigoration of action that is impaired. This is an interesting finding as it relates to several studies investigating the role of vigour in motivated behaviour (Beierholm et al., 2013; Michely et al., 2020; Niv, 2007). Specifically, vigour can be predicted by the average reward rates on task (Beierholm et al., 2013; Niv, 2007) and has been linked to dopaminergic activity within the ventral tegmental area of the midbrain (Niv, 2007; Wang et al., 2021). Therefore, one possible mechanism of apathy in healthy people may be the inability to energise behaviour appropriately once committed to goal-pursuit. That is despite reporting 'normal'

subjective motivation. Can this deficit be further understood by perturbing task demands in real time? Our second key finding supports this.

Apathetic participants were less able to dynamically vary their vigour, indexed by change in pressing speed, following trial-wise perturbations. Intriguingly, this was driven by an inability to slow down pressing speed in uplift trials, rather than an inability to invigorate pressing speed following setbacks (**Fig 7-5B**). This was unexpected. One possible explanation for this is that our setback trials represented an externally guided behaviour that apathetic people were able to appropriately respond to despite a deficit in internally guided action. However, this would not account for the significant difference in pressing speed during the uplift trials, which were also externally guided. Another possibility is that the setback trials simply were not challenging enough. While they were designed so that they were equivalent to 95% of participants' maximum number of key presses, more than 99% of trials were completed successfully. Additionally, apathetic people did not fail any more times during setback trials than their motivated counterparts. One of the important criteria in assessing constructs such as grit, or persistence, is the process of overcoming a feeling of adversity (Cheng, 2017; Duckworth et al., 2007; Duckworth & Quinn, 2009; Feather, 1962; Howard & Crayne, 2019). It is therefore feasible that participants were not challenged close enough to their physiological ceiling to uncover further behavioural deficits. Future versions of this task can be developed to focus purely on how failure and adversity interact with effortful persistence in apathetic people.

In summary, we designed a novel EBDM task that successfully measured the dynamics of effortful behaviour over time. Additionally, we demonstrated specific deficits in apathy in relation to these dynamics. First, apathetic people show a weaker association between their

subjective motivation ratings and subsequent effortful behaviour. Second, they demonstrated blunted responsiveness to dynamic changes during effortful behaviour. Moving forward, it might be useful to explore in more depth the concept of adversity and failure in a similar task where either a proportion of setback trials are insurmountable, or feedback is rigged so that people must respond to true failure.

# 8 General Discussion

Over the course of this thesis, I have attempted to demonstrate that apathy is a disorder that manifests itself through deficits in goal-directed behaviour, and is associated with dysfunction within specific brain regions and their connections. Specifically, I tested the hypothesis that amotivation is caused by pathology within a well defined fronto-striatal network, which regulates the process of option selection – that is how we weigh up the costs and benefits of decision making. I investigated this across three different patient groups: SVD (Chapter three), Schizophrenia (chapter five) and patients with bilateral basal ganglia lesions (Chapter six). The data was analysed using drift diffusion modelling to establish whether apathy was characterised by a common behavioural phenotype.

I also investigated the neural correlates of apathy in SVD (chapter four) and conducted a drug study in apathetic patients to investigate whether dopaminergic therapy can improve apathetic symptoms and motivated behaviour during option selection (chapter six). Finally, I developed a novel paradigm that aims to probe the dynamics of motivation on a moment by moment basis (chapter seven). In the following pages, I will present a brief summary of each chapter's main findings, followed by a synthesis of their clinical and scientific implications, with a view towards future research opportunities.

## 8.1 Summary of Experimental findings

### 8.1.1 Behavioural correlates of apathy in SVD

In chapter three I tested the hypothesis that apathy in 82 patients SVD is characterised by deficits in option selection, a measure of goal-directed effortful behaviour. Option selection was measured using a validated EBDM paradigm known as the apple gathering task (AGT, **Fig. 3-1A top**). Apathy severity in SVD was associated with a significant reduction in overall offers accepted on the AGT (**Fig 3-1C**). DDM analysis revealed that this was driven by a significant reduction in the drift rate parameter ($v$), which represents the rate of evidence accumulation towards accepting offers to exert effort in return for reward (**Fig 3-4D**). It was driven by an insensitivity to reward, indexed by the interaction term between drift rate and reward ($v_r$) (**Fig 3-4E**).

### 8.1.2 Neuroimaging correlates of apathy in SVD

In chapter three, I conducted an anatomic investigation of apathy in SVD using a technique known as tract-based spatial statistics (TBSS). This was used to measure white matter tract integrity, indexed by fractional anisotropy, across the whole brain. This demonstrated that Apathy severity was associated with deficits in specific white matter tracts connecting the medial forebrain regions to the basal ganglia (**Fig 4-3, top)**.

These included:

- anterior cingulum bilaterally
- anterior thalamic radiation within the anterior limb of the internal capsule (left)
- corpus callosum
- uncincate/inferior fronto-occipital fasciculus within the external capsule.

Critically, the drift rate parameter (*v*), which was associated with apathy, was also significantly associated with white matter integrity (**Fig 4-4)**, suggesting that these fronto-striatal white matter changes may have been driving the behavioural deficits in apathetic patients.

### 8.1.3 Apathy in Schizophrenia

In chapter four I investigated the behavioural correlates of amotivation in in 40 patients with treatment resistant schizophrenia (TRS) and 40 age and gender matched controls. TRS patients accepted significantly fewer offers than healthy people, and showed two behavioural patterns. They were less sensitive to increasing reward, and less averse to high effort (**Fig 5-2)**. Despite a positive correlation between negative symptom severity and cognitive function, only cognitive impairment was associated with reward insensitivity (**Fig 5-4B)**. On the other hand, blunted effort aversion was associated with overall negative symptom severity, but not directly to amotivation per se (**Fig 5-4C)**. So despite their correlation to one another, negative symptom severity and cognitive dysfunction showed two different behavioural phenotypes.

### 8.1.4 Effects of dopamine

In chapter five I conducted a drug study in three apathetic patients to investigate whether using ropinirole, which is a dopamine agonist, can improve apathetic symptoms. Two of these had suffered with bilateral basal ganglia stroke, and one had SVD (**Fig 6-1**). Patients were tested on the apple gathering task before and after being established on ropinirole, and the behavioural changes were measured using the DDM approaches established throughout the thesis so far. At baseline untreated patients accepted significantly less offers and were slower to respond to monetary offers compared to healthy controls (**Fig 6-2E-F)**. DDM

modelling confirmed that as a group, they were characterised by lower evidence accumulation towards effortful action ($v$) and were more biased towards rejecting offers overall (lower $z$ parameter). Individually, two patients showed increased reward sensitivity at baseline ($v_r$), one of which also showed increased effort sensitivity ($v_e$) (**Fig 6-6D-F)**. This latter patient had concurrent apathy and depression.

Following DA treatment, all three patients improved clinically and this was reflected in their apathy evaluation scores. Behaviourally, patients significantly increased their number of offers accepted on the AGT, and this was reflected within the DDM parameters. Specifically, both the drift rate parameter ($v$) and the bias to accept offers ($z$) increased (**Fig 6-6D-F)**. Within subject analyses additionally showed that those patients with altered reward and effort sensitivity at baseline showed significant improvements in th parameter ($v_r$) (**Fig 6-7B-C)**. Similarly, the apathetic and depressed patient who had displayed increased effort sensitivity at baseline showed a significant improvement in this parameter (**Fig 6-7F)**.

### 8.1.5 Motivational persistence and apathy

Chapter six explored whether the dynamics of motivation can be measured on a moment-by-moment basis, especially in response to setbacks during goal pursuit. This involved developing a novel persistence task which consisted of a button pressing task themed around a virtual race (**Fig 7-1A)**.

One hundred healthy participants completed this task online, and completed questionnaire measures of apathy. Across participants I showed that people could indeed dynamically change their behaviour in response to setbacks and uplifts – by speeding up and slowing down respectively (**Fig 7-2B-D)**. I also demonstrated that trial types influenced trial-by-trial

measures of subjective motivation and fatigue, which in turn predicted starting speed on the following trial. For example, uplifts were associated with a subsequent increase in subjective motivation (**Fig 7-3A)** and faster pressing speed (**Fig 7-3C)**. Conversely, setbacks were associated with an increase in subjective fatigue (**Fig 7-3A)**, and slower pressing speed (**Fig 7-3D)**. These findings supported the view that motivated behaviour is intrinsically dynamic, it adaptively responds to changes in task demands, and these demands themselves may influence future motivated behaviour.

Several important findings were also demonstrated in apathy. First, they were unable to modulate their pressing speed in response to external stimuli compared to their motivated counterparts (**Fig 7-5B)**. Second, there was a blunted association in apathetic people between subjective motivation on any given trial and that trial's vigour, indexed by pressing speed (**Fig 7-5B)**. In other words, compared to motivated people, when people said they were motivated, that was not reflected in their behaviour. This sheds light on several new ways to understand the behavioural mechanisms of apathy beyond option selection.

## 8.2 Synthesis of DDM findings across studies

### 8.2.1 A neurocognitive model for apathy across disorders

One of the differentiating aspects of this thesis is its systematic investigation of apathy in different neurological and psychiatric conditions using a single EBDM paradigm (apple gathering task) and a consistent analytic approaches (DDM) across experiments. One would hope in doing so that we can reveal some valuable insights about amotivation across diseases. So what have I learnt? A starting point may be to ask whether my investigations have revealed a common transdiagnostic behavioural phenotype of apathy across diseases.

The most consistent behavioural findings noted across groups was the association of amotivation with a reduced baseline drift rate parameter $v_0$ (**Table 8-1**). This was the case in SVD (**Fig. 3-4D**), Schizophrenia (**Fig. 5-8D),** and patients with basal ganglia lesions before treatment with a dopamine agonist (**Fig. 6-6D**). This parameter represents the average rate of evidence accumulation towards accepting an offer. Behaviourally, this reflected both a general tendency to reject offers, as well as prolonged reaction times across patient groups. In SVD, $v_0$ was the only DDM parameter associated with reduced white matter tract integrity within tracts connecting the medial forebrain bundle and the basal ganglia in SVD (**Fig 4-4**). So it is possible that a unifying mechanism of apathy across diseases can be proposed centred around this parameter. Specifically, it is that patients suffering with apathy are characterised by reduced evidence accumulation towards accepting offers during option selection, and that this is also associated with reduced white matter integrity within the fronto-striatal network.

One criticism of this latter statement is that I did not relate behavioural and neuroimaging parameters in the schizophrenia and dopamine drug study. Multimodal studies which combine option selection with neuroimaging would have to be conducted in schizophrenia and other patient groups to clarify whether drift rate decrements are consistently associated both with apathy and white matter tract deficits in the fronto-striatal network. Another criticism is that the drift rate parameter has been associated with a multitude of other cognitive processes, including working memory (Ratcliff, 1978), perceptual discrimination (P. L. Smith et al., 2014), and signal detection (Ratcliff, 2002). Similarly, reduced drift rates have been associated with other functional neurological disorder (Sadnicka et al., 2020), attention deficit hypersensitivity disorder (ADHD) (Kofler et al., 2020), sleep deprivation (Ratcliff & van Dongen, 2009), and alcohol intoxication (Van Ravenzwaaij et al., 2012). So

is the drift rate really a specific measure that can help diagnose apathy? Or does it just reflect general cognitive decline?

Lack of specificity unlikely for two reasons. First, post-hoc analyses of our data showed that the $v_0$ parameter was not significantly associated with general cognitive function (indexed by the total ACE-III score) in either SVD, or schizophrenia (respectively, [$F(1,77) = 1.46$, $p = 0.23$], and [$F(1,37) = 0.15$, $p = 0.65$]. Second, our chosen DDM allowed for the drift rate to vary by reward and effort, highlighting at least one additional specific mechanism that may be common in apathy across diseases – that of reward insensitivity, indexed by $v_r$. Insensitivity to reward during option selection was demonstrated in SVD (chapter three), treatment resistant schizophrenia (chapter five), and patients with focal lesions within the basal ganglia (chapter six). This has also been demonstrated in apathetic patients with Parkinson's disease (Le Heron, Plant, et al., 2018), basal ganglia stroke (Adam et al., 2013; Rochat et al., 2013), and CADASIL, a genetic form of SVD (Le Heron, Manohar, et al., 2018). So our findings suggest that there is indeed a distinct behavioural phenotype in apathy across diseases. Namely that people show a general tendency to accept less offers during option selection, and that this may be driven by reduced incentivisation to reward.

Anatomically, amotivation was associated with deficits within a well defined fronto-striatal network, which links the medial forebrain regions to the basal ganglia (chapter four). Specifically, we demonstrated that in SVD, white matter tract metrics within the cingulum bundle, and anterior limb of the internal capsule were significantly implicated (**Fig 4-2**). These tracts play an important role in linking the ACC and vmPFC to the VS (Safadi et al., 2018a). Notably, our neural correlates of apathy in SVD are consistent with other MRI studies in SVD (Hollocks et al., 2015; Le Heron, Manohar, et al., 2018), AD (J. W. Kim et

al., 2011; Ota et al., 2012; Starkstein et al., 2009), and schizophrenia (Bortolon et al., 2018). This suggests that clinical apathy across disorders may be characterised by fronto-striatal pathology leading to behavioural deficits during effortful decision making – specifically insensitivity to reward. While several of our findings support this view, others suggest there are some nuanced aspects of phenotyping apathy that warrant consideration.

First, we demonstrated on more than one occasion that reward sensitivity was not the only parameter altered in apathy. For example apathetic patients with SVD also showed hypersensitivity to effort when examining choice behaviour during option selection (**Fig. 3-3B**). Similarly, one of our DA treated patients who suffered with SVD also demonstrated this phenotype (**Fig. 6-5F**). On the other hand, in our schizophrenia patients negative symptom severity was associated with blunted sensitivity to effort (**Fig. 5-4C**). So it is not only reward sensitivity that is affected in option selection studies investigating apathy, but also effort sensitivity. Does that matter? And is there really a part of the brain that processes effort only, and another that processes reward?

A recent metanalysis of option selection tasks by Pessiglione et al. suggests that there are distinct brain areas within the fronto-striatal network that are selectively activated when responding to reward and effort related information (Pessiglione, Vinckier, Bouret, Daunizeau, & le Bouc, 2018). Specifically, while the VS and vmPFC were associated with reward related processing, regions including the ACC and anterior Insula where more likely to be activated when processing effort costs, or at least integrating reward and effort during decision making (Pessiglione, Vinckier, Bouret, Daunizeau, & le Bouc, 2018). One contributing factor to our detection of effort related signalling is that our task symmetrically and parametrically varied and effort and reward, whereas several option selection tasks do

not (Le Bouc et al., 2016; Treadway et al., 2009). So it is possible that altered effort sensitivity is also prominent in patients with clinical apathy and that this is increasingly detected when using tasks designed to separately investigate reward and effort processing. Alternatively, it may be that apathy in different conditions has different contributing factors. An important way to resolve these views is by ensuring large scale behavioural studies are conducted in apathetic patients using tasks which probe both reward and effort processing in a symmetric fashion.

Another important consideration is that reward insensitivity across different conditions displayed different underlying behaviours. Specifically, we showed that in SVD, reward insensitivity was driven by reduced incentivisation to low-reward offers (**Fig. 3-3A**), whereas in schizophrenia people were less sensitive to the highest levels of reward (**Fig. 5-2A**), but not the low-reward ones. Questionnaire measures of apathy were not associated with reward insensitivity as originally anticipated in schizophrenia. Rather, the best predictor of this behavioural deficit was cognitive dysfunction (**Fig. 5-4B** and **5-5A-B**). This is an important finding, as the effects of associated constructs like cognitive impairment and depression on effort-based decision making may be often ignored in behaviour studies of apathy.

When somebody is less motivated by reward during EBDM, is this because they don't feel pleasure in response to reward receipt (i.e. they are anhedonic)? Is it because they might enjoy them but don't want to put the effort (i.e. less motivated, or wanting)? or because they cannot construct reward value appropriately (i.e. cognitively impaired)? Better characterising these aspects of reward insensitivity, and motivated behaviour in general has the potential to significantly improve our understanding of what we think *apathetic behaviour* is. One conceptualisation of this, known as the 'equifinality model', has been put forward by Strauss

and colleagues in relation to reward responsiveness in psychiatric disease (Strauss & Cohen, 2017). In their model responsiveness to reward is arrived at via either a *hedonic* or *cognitive* pathway, each of which arises due to distinct underlying processes (**Fig 8-1**). Applying similar models to the behavioural study of clinical apathy might enrich our understanding of exactly how to interpret behavioural deficits in motivated behaviour. For example, they may allow us to pose challenging questions about apathy such as: if a patient is demonstrably reward insensitive on EBDM, but not on an apathy questionnaire, are they apathetic or not? If the behavioural associations of apathy are entirely accounted for by cognitive impairment, which specific cognitive deficits might be crucial.

To sum up, an important aspect of advancing the transdiagnostic hypothesis of apathy (i.e. similar phenotype across diseases) lies in clarifying which aspects of motivated behaviour we specifically seek to measure (reward vs effort processing), but also in understanding the disparate processes that may give rise to its characteristic behaviours (i.e. reward insensitivity) that we seek to identify. One way to do this is by expanding our tool box of behavioural measures so that the behavioural correlates apathy can be defined more sensitively.

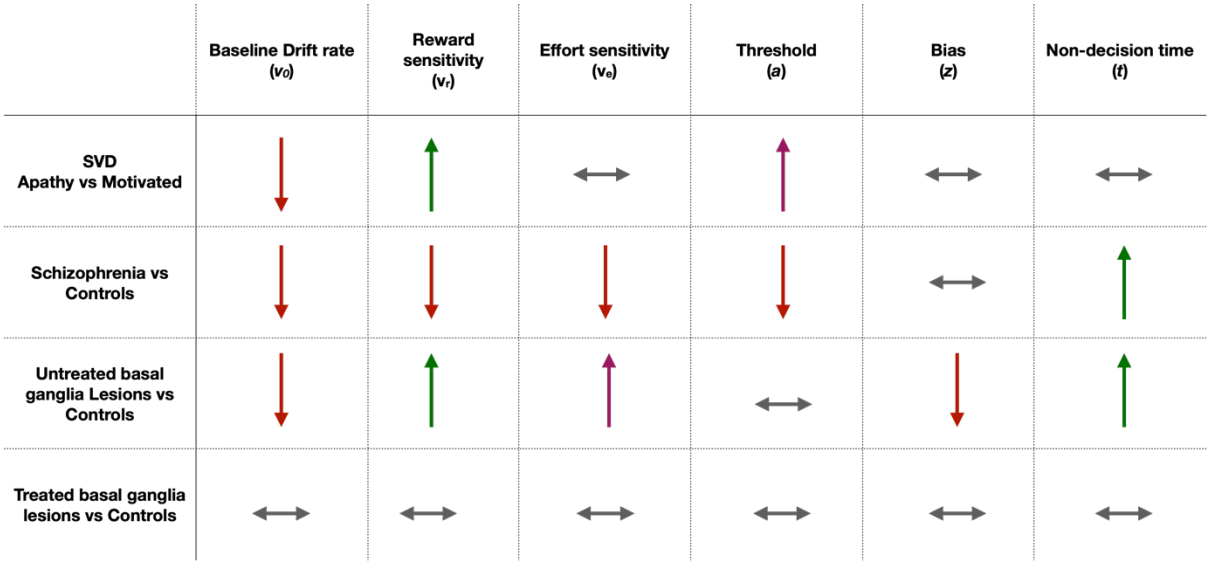



**Table 8-1.** Summary of DDM parameters across patient groups. Arrows denote how parameters in each patient group were altered in relation to a reference group. Red and green arrows denote significantly lower and higher parameter values respectively in those patient groups, while grey demonstrate no difference. The two purple arrows indicate conditional relationships depending on depression severity. For example, in SVD only depression and not apathy was associated with increased threshold, and in the basal ganglia lesion case series, the one patient with concurrent apathy and depression demonstrated increased effort sensitivity.

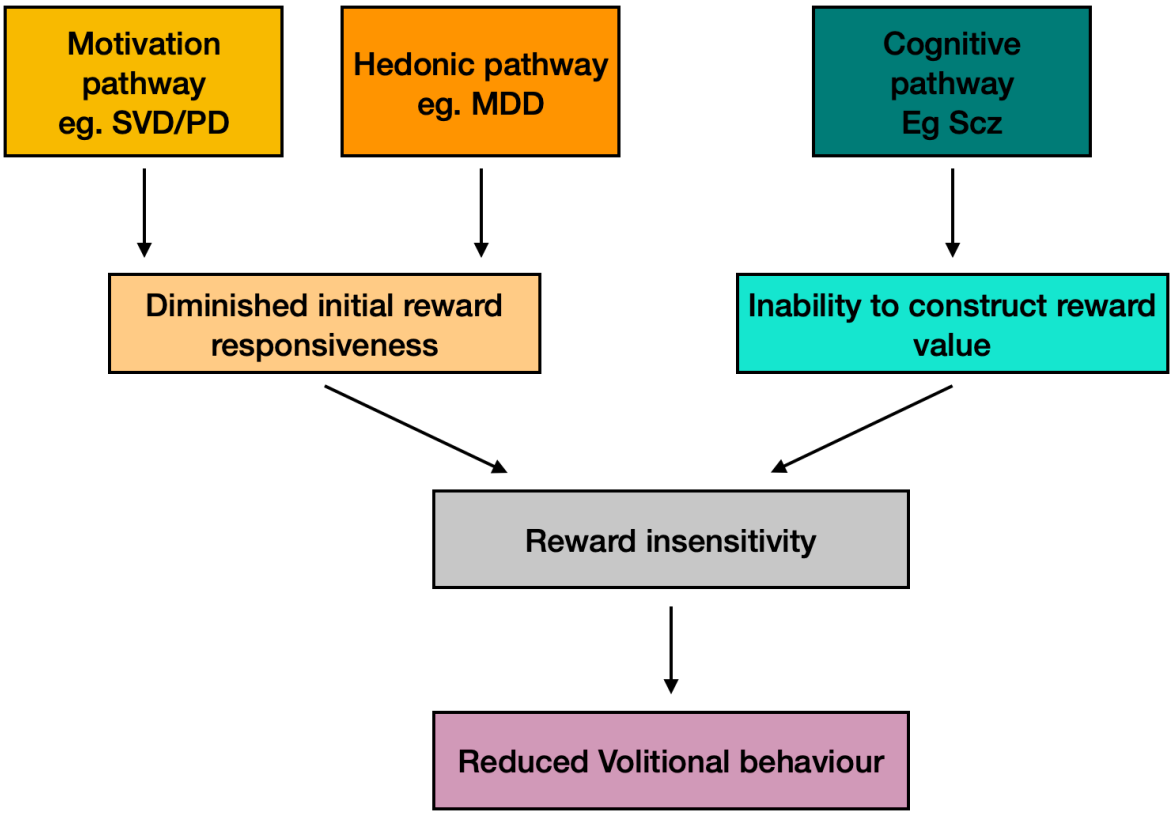



**Figure 8-1. Equifinality of reward insensitivity across diseases**. Reward insensitivity as a common end point of three potential pathways. People may display diminished responsiveness for reward due to anhedonia (reduced liking of reward), amotivation (reduced wanting of an otherwise enjoyable reward), or cognitive impairment (i.e. an inability to assign subjective value to reward). Adapted from (Strauss & Cohen, 2017). SVD – small vessel disease, PD – Parkinson's disease, MDD – Major depressive disorder, Scz – Schizophrenia.

### 8.2.2 Apathy and depression, are they the same?

In my introduction, I highlighted that a common misconception about apathy is that it is often conflated with depression, and that some evidence in PD (Kirsch-Darrow et al., 2006, 2011) and SVD(Tay, Morris, et al., 2020; Tay et al., 2019) suggests they are dissociable. The work in this thesis provides three key insights about the relationship between these two constructs. First, we showed that questionnaire measures of apathy (AES) and depression (BDI) were associated with one another, as demonstrated in our SVD study (chapter three), and basal ganglia patients (patient CX, chapter six). Nevertheless, despite correlations between questionnaire measures, apathy was both behaviourally and anatomically distinct from

depression. For example, while apathy severity in SVD was characterised by a lower evidence accumulation rate ($v_0$) and altered reward sensitivity ($v_r$), depression was associated with an increase in behavioural conservatism, indexed by a greater threshold parameter *a*. In other words, people who were depressed spent more time deliberating, and needed more information to make a decision, but ultimately were not less likely to perform effortful action than anybody else. Anatomically, apathy in SVD was associated with white matter tract deficits within the fronto-striatal network after accounting for depressive symptoms, while depression showed no associations with white matter tract deficits after accounting for apathy. This finding is consistent with neuroimaging investigations of both constructs in SVD (Tay, Morris, et al., 2020; Tay et al., 2019). Taken together, these findings support a behavioural and anatomic dissociation between the two constructs. However, one limitation of these findings is that overall depression severity in the SVD cohort was low and may have under-estimated the effects of depression during our investigation.

In our basal ganglia patient group, one of our patients (patient CX) who had concurrent apathy and depression demonstrated a unique combination of reward insensitivity and effort hypersensitivity that was not present in the other two patients. While the sample of this study was small, it did demonstrate two important potential insights. First, patients with concurrent apathy and depression can demonstrate some behavioural similarity with apathy (i.e. reward insensitivity). Second, effort hypersensitivity, indexed by $v_e$ may characterise this patient group from those with isolated apathy or depression. Moving forward, two types of investigation are needed to further clarify the relationships between both these constructs and their underlying mechanisms. First, multimodal investigations of the individual contributions of apathy and depression to behaviour/anatomy should be conducted across disease groups to clarify whether associations vary across disease. Second, these should ensure a wide enough

variance of depression and apathy severity to ensure findings represent the entire spectrum of each construct. Third, deeper phenotyping of the sub-components of depression and how each may relate to apathy can be of value. For example, depressed patients with high levels of dysphoria or low mood may have different behavioural phenotypes to those with high levels of anhedonia (loss of interest/pleasure). The latter sub-group may represent a point of overlap with apathy in terms of behavioural phenotype.

### 8.2.3 From option selection to persistence

My final empirical chapter sought to build on our conceptual understanding of apathy by developing a novel behavioural paradigm that probed the dynamics of motivation (**Fig 7-1**). Specifically I wanted to test the hypothesis that people with apathy did not appropriately regulate their response vigour, indexed by pressing speed, in response to external perturbations. These included setbacks, which made the task more difficult. I demonstrated that apathetic (healthy) people showed a diminished ability to regulate response vigour in response to task demands (**Fig 7-5B**). I also show that apathy is significantly inversely related to the psychological construct of Grit. Interestingly, grit was not itself associated with the ability to regulate behaviour, suggesting that behaviourally it may encode other aspects of motivated behaviour – for example response vigour following task failure. This version of my task ensured that even setback conditions were realistic to achieve, and participants seldom *failed* to complete a trial. However this is one aspect of apathy and grit I hope to explore in the future. Specifically, how do gritty and apathetic people respond to task failure? Can response vigour after failure represent a measure of motivational persistence ?Can this be added to the behavioural measures used to index apathetic behaviour?

Anatomically, response vigour and its dynamics during decision making have been linked to tonic dopamine signalling within the basal ganglia and prefrontal areas (Niv, 2007; Niv et al., 2007; Wang et al., 2021). Tonic DA signalling is thought to encode the average reward rate during instrumental behaviour over time (Niv, 2007). This contrasts with the more rapid phasic signalling, which encodes prediction errors and plays an important role in re-enforcement learning and processes like option selection (Montague et al., 1996; Schultz et al., 1997; Stopper et al., 2014). A recent study confirmed this in healthy people completing an EBDM task while receiving a single dose of Levodopa, which increases DA concentrations (Beierholm et al., 2013). Specifically response vigour, indexed by reaction time to a reward cue, was significantly improved on dopamine. However this investigation did not examine the dynamics of vigour over time, and did not assess how this metric changed in apathy. Moving forward, I intend to test our persistence paradigms in patients with PD on and off dopamine. PD, being a natural model of dopamine depletion within the basal ganglia, can shed more valuable insights on how apathy, and dopamine can influence motivational vigour and its dynamics in patient groups.

## 8.3 Effort-based decision making: where next?

Several other behavioural aspects of motivated behaviour have not been addressed in this thesis, but can also contribute to our understanding of clinical apathy as a syndrome. These include option generation, reinforcement learning, and patch leaving behaviour – typically referred to as foraging behaviour. I will briefly give some insight into each of these processes before exploring how they and the processes already considered in this thesis can be used to further advance our understanding of apathy.

**Option Generation**

Option generation refers to the process of creating possible choices to select from before engaging in the evaluative process of option selection. It has been examined using different approaches, including verbally describing as many potential solutions to a virtual scenario (Hartmann, Kluge, et al., 2015), or tracing as many hand drawn paths on a touch screen device (Ang et al., 2018). Option selection tasks have been shown to be significantly reduced in apathetic patients with schizophrenia (Hartmann, Kluge, et al., 2015), but not in healthy people or PD (Ang et al., 2018; Mole et al., 2022). In healthy people, apathy was associated with a significant decrease in the number options generated (Ang et al., 2018). On the other hand, apathy in PD was not associated with significant changes in option generation (Ang et al., 2018).

Anatomically, the process of generating options and creativity has been associated with pre-frontal cortical activation (Dietrich & Kanso, 2010; Kaiser et al., 2013; Stuss, 2011), supporting its potential involvement within the fronto-striatal network. However, few studies have specifically investigated whether this aspect of motivated behaviour in apathy and no investigations have attempted to relate its neural correlates to apathetic behaviour in patients. It would be especially useful to understand how these processes relate to option selection and persistence. For example, are people who are capable of generating a lot of options also less sensitive to effort? Or is the effort associated with thinking about potential goal-directed actions dissociable from the effort associated with pursuing them? Perhaps individuals who generate a lot of options are less likely to persist in goal pursuit, due to an increased awareness of alternative courses of action. Behavioural dissociations across these motivational processes might help disentangle apathy from its closely related constructs such as depression and cognitive function.

**Reinforcement learning of reward value**

Much of the focus of EBDM tasks probes the wanting aspects of motivation, however some valuable insights can also be gleaned from the "learning" aspects of behaviour. Learning follows from instrumental goal-directed behaviours like option selection and motivational persistence (**Fig 1-2**). Critically, it informs the likelihood of repeating a behaviour having assigned to it a subjective value based on its associated costs, benefits, and likelihood. A key aspect of reward based learning lies in prediction error signals, which encode the difference between an expected and observed reward (Montague et al., 1996; Schultz et al., 1997). Several canonical studies have implicated the VTA, VS (Montague et al., 1996; Schultz et al., 1997), and the ACC (Holroyd & Coles, 2008; Jocham et al., 2009) in encoding prediction error signalling in the brain. These are anatomically similar brain regions to those associated with amotivation syndromes. So is it possible that the underlying mechanism of reward insensitivity that we have demonstrated in apathy is mediated by a deficit in accurately learning about the value of reward?

Reinforcement learning paradigms have explored this specific hypothesis in patients with schizophrenia, specifically in relation to negative symptoms (A. J. Culbreth et al., 2020; Gold et al., 2008, 2012; Hernaus et al., 2018; Moran et al., 2017; Strauss et al., 2011; Yilmaz et al., 2012). In one experiment conducted by (Gold et al., 2012), participants were presented with image pairs of different landscapes and asked to choose the "correct" option. In half the trials, choosing the correct answer resulted in monetary gain (versus no gain if incorrect), and in the other half it prevented monetary loss (versus a loss if incorrect). Correct responses were reinforced at varying probabilities for each pair. After learning all possible associations,

participants were asked to choose the best option between novel combinations of the original images.

In the learning phase, schizophrenia patients with high negative symptom severity demonstrated impaired learning in the conditions rewarded with high probability (90%) when compared to controls. However, loss-avoidance learning was intact, suggesting that reward-based learning was specifically affected. Healthy participants and patients without negative symptoms incorporated the expected value of responses in their decisions more frequently than patients with high negative symptoms. Thus, schizophrenia patients appear to suffer impairments in reward-based learning due to a specific deficit in representing expected value. This impairment is specific to reward learning and not loss avoidance (Gold et al., 2012).

In Parkinson's disease, similar findings have also been demonstrated, using a reward-based paradigm based on a gambling task (Martínez-Horta et al., 2014). The authors concurrently measured neural activity in response to response outcomes using electroencephalogram (EEG). Specifically, they quantified the difference in electric activity between a positive prediction error (i.e. unexpected gain), and a negative prediction error (unexpected loss). They demonstrated that this measure of neural activity was significantly blunted in apathetic patients, suggesting their responsiveness to unexpected gains/losses was impaired.

Taken together, there is evidence that how people learn from rewards may play an important role in the behavioural phenotype of apathy. Is reward insensitivity always due to learning deficits? The findings presented in this thesis suggest otherwise. For example, We showed in SVD that apathetic people actually *will* accept the same amount of offers as motivated people if the reward on offer is high enough (**Fig 3-2A**). On the other hand, schizophrenia patients

seemed to accept fewer offers at the highest possible rewards, which is more consistent with a deficit in representing reward value (**Fig 5-2A**) – possibly secondary to cognitive impairment. One argument is that those people who arrive at reward insensitivity via the *hedonic* or *motivational* pathways, but not the *cognitive* pathway, are likely to demonstrate intact learning from rewards (**Fig 8-2**). This could offer a valuable opportunity to distinguish between different groups of patients who demonstrate apathetic behaviour due to different underlying causes.

**Mapping motivated behaviour**

Several motivational processes have been implicated in the pathophysiology of clinical apathy. This includes option generation, option selection, motivational persistence, and reward-based learning (Husain & roiser, 2018). Using a single paradigm to frame apathy, while valuable, may offer an incomplete picture of the motivational processes that are impaired in affected patients. For example, option selection may highlight reward insensitivity, but not necessarily whether this is caused by deficits in reward-based learning. Similarly, learning paradigms do not necessarily predict whether somebody will persist when engaged in goal-pursuit (at least we don't know yet). One way to address some of these challenges can be by creating representational *maps* of motivated behaviour, which combine behavioural measures across paradigms into a two dimensional space (**Fig 8-2**). These can be used to compare motivated behaviour across diseases (**Fig 8-2A**), or the effects of pharmacological treatment in apathetic patients **Fig 8-2B**.

A challenge with this approach is that testing multiple paradigms is both time and resource intensive. However, following the pandemic and its restrictions, both patients and investigators have significantly increased their use of digital platforms for behavioural

testing. For example, our persistence experiment was conducted online in 100 participants over the course of seven days, which would have been unthinkable if done in-person. This may represent a valuable opportunity to expand our testing capacities, and possibly enriching our understanding of motivated behaviours and their associations with apathy.

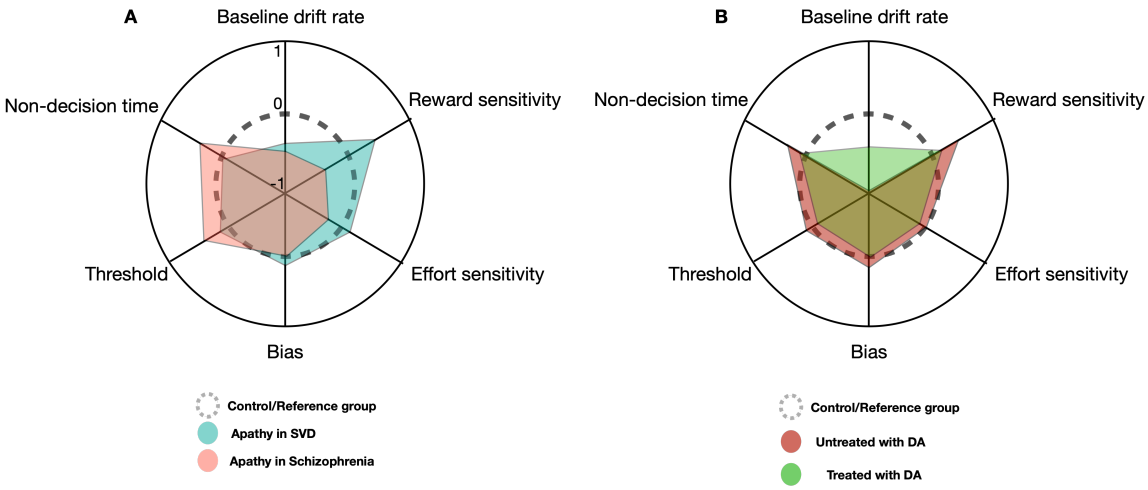



**Figure 8-2. Mapping of motivational processes.** Mapping of apathy across disease states (A) and within patients on and off treatment (B). Here I use values of six DDM parameters and compare values of these parameters across disease states in relation to healthy controls or a reference group (grey circle). **A-B)** Each radius represents an axis of values between -1 and 1 for each parameter centred on the intersection point of the grey circle with each radius. The zero point represents the control group's value for that parameter, and each patient group's parameter is then plotted relative to the control group. **A**)This can highlight the differences in behavioural phenotypes between SVD (teal) and Schizophrenia (Red), especially in terms of their difference in reward and effort sensitivity. **B)** Here patient specific cognitive mapping is being used to represent the treatment effect of DA in patients with basal ganglia lesions.

## 8.4 Treatment insights: To dopamine, or not to dopamine

In chapter six, I showed that apathetic people with fronto-striatal pathology respond clinically to treatment with the dopamine agonist, ropinirole. Although only three patients completed our protocol, we have recruited another three who will also undergo this protocol. We hope that through a case series we can further clarify whether dopaminergic medication can represent a possible therapeutic option for patients with primary amotivation syndromes.

Mechanistically, the actions of DA on motivated behaviour were described using DDM parameters. Specifically, DA primarily increased evidence accumulation towards effortful action (*v*) and patients' bias towards motivated behaviour in general (*z*). In those patients who had altered reward sensitivity at baseline, DA treatment reverted this to levels similar to those displayed by healthy controls.

The effect of DA treatment across people is clearly not uniform. For example, one patient showed increases only in drift rate, another showed the opposite effect, and in the third both parameters increased. Similarly, one patients did not display changes in reward sensitivity, however they had normal sensitivities to start with (i.e.. similar to controls). So an important future direction may be to appreciate how baseline levels of motivation influence treatment response. This can be another avenue where representational mapping plays a role in clarifying individual differences in treatment response in relation to baseline behavioural deficits. In fact it may be that DA treatment is not suited for all patients. To that effect, other neurotransmitters including noradrenaline and serotonin are also being investigated as possible treatment options in apathy.

**Noradrenaline**

Anatomically, the rationale for dopaminergic therapy stems from two lines of evidence. First, dopaminergic VTA neurons within the fronto-striatal circuit, and especially the VS, play a central role in the regulation of motivated behaviour (Haber, 2014; J. D. Salamone, 1988; J. D. Salamone & Correa, 2012). Second, dopaminergic depletion studies suggest that dysfunctional dopamine signalling is associated with amotivation symptoms (J. Salamone et al., 2002; J. D. Salamone et al., 2001, 2007; J. D. Salamone & Correa, 2012).

More recently however, there is also increasing evidence that pathology in patients suffering with apathy also includes the noradrenergic and serotonergic systems.

For example, post-mortem studies of patients with fronto-temporal dementia syndromes (FTLD), where apathy is common, demonstrate that there is evidence of pathology within the locus coeruleus (LC) (Irwin et al., 2016), which is the principal source of noradrenaline signalling within the brain (Aston-Jones & Waterhouse, 2016). In PD, neuronal degeneration within the LC precedes loss of dopaminergic neurons within the substantia nigra (SN) (Rommelfanger & Weinshenker, 2007), and in both AD and PD patients, more neuronal loss is evident within the LC than the SN (Zarow et al., 2003). Interestingly, lesion studies within the LC result in subsequent loss of DA neurons within the SN and VTA (Szot et al., 2012), suggesting the integrity of the LC is protective of upstream dopaminergic signalling.

Behaviourally, pre-clinical investigations suggest that noradrenergic signalling within the LC is associated with energisation of motivated behaviour, indexed by grip force while squeezing a hand held device (Varazzani et al., 2015). This has prompted groups to suggest the use of noradrenaline uptake inhibitors as potential therapeutic agents for the treatment of apathy and other neuropsychiatric syndromes (Gorman & Sullivan, 2000). However to date, two published clinical trials using noradrenaline reuptake inhibitors bupropion and atomoxetine showed no significant improvements in either questionnaire measures of apathy nor depression in PD (Weintraub et al., 2010) and AD (Maier et al., 2020) respectively. Interestingly, in PD patients, atomoxetine was associated with a significant increase in global cognitive impairment, suggesting the noradrenergic stimulation may improve general cognitive state (Weintraub et al., 2010). More recently, O'Callaghan and colleagues demonstrated using 7T MRI scanning of 25 patients with PD, and 14 with progressive supra

nuclear palsy (PSP), that reduced contrast within the LC was positively associated with apathy and inversely related to cognition (Ye et al., 2022). This is a very interesting findings as it implicates the LC and associated noradrenergic as a possible link between apathy and cognitive dysfunction.

Few, if any studies have investigated how noradrenergic medication may alter motivated behaviour during EBDM paradigms, although one recent study using atomoxetine in PD patients demonstrated that it may modulate people's prior beliefs about action outcomes (Hezemans et al., 2022). The authors also showed that apathetic patients with PD demonstrated reduced confidence in their beliefs about action-outcome relationships when engaged in a task where they had to predict the final position of a ball in flight on a computer screen (Hezemans et al., 2020, 2022). While this an interesting study, it needs to be conducted alongside other EBDM, to better clarify exactly whether these changes are associated with downstream behaviours such as option selection, behavioural persistence, and reinforcement learning.

**Serotonergic and cholinergic targets**

Unsurprisingly, both serotoninergic (Daw et al., 2002; Seo et al., 2008) and cholinergic neurons (Aosaki et al., 2010) can influence dopaminergic transmission within the brain, and drugs that modulate both neurotransmitter systems have been assessed in the treatment of amotivation syndromes (de Berardis et al., 2013; Devos et al., 2014; Erkinjuntti et al., 2002; Wongpakaran et al., 2007). Interestingly, several retrospective studies have demonstrated a *positive* association between selective serotonin reuptake inhibitors and apathy severity, despite an improvement in overall depression symptoms (Wongpakaran et al., 2007; Zahodne

et al., 2012). However, some groups have demonstrated that specific antagonists of the serotonergic 5HT2C receptor, such as agomelatine can significantly improve apathetic symptoms in patients with fronto-temporal dementia and AD (Callegari et al., 2016; de Berardis et al., 2013; Karaiskos et al., 2014). Mechanistically, activation of 5HT2C receptors in rodents is associated with significant decrease in striatal DA, while antagonism of these receptors increased DA concentrations (Alex et al., 2005; Fink & Göthert, 2007).

On the other hand, the acetylcholinesterase inhibitors rivastigmine and galantamine have both been associated with significant improvements in apathy in patients with PD, lewy body dementia and mixed dementia (Devos et al., 2014; Erkinjuntti et al., 2002; McKeith et al., 2000). Taken together, one can conclude that multiple neurotransmitter deficits may be associated with amotivation syndromes. While the literature often focusses on dopamine, it is clear that there are roles for other neurotransmitter based therapies in the treatment of clinical apathy. What is missing is a deeper understanding of exactly how manipulating each of these neurotransmitters specifically alters motivated behaviour. This is critically important for two reasons. First, some disease processes may selectively influence one neurotransmitter system over another, and therefore response to specific treatments more favourably. Second, it may be that the combination of two neurotransmitter modulators significantly improves outcomes while minimising side effects that can arise from incrementally increasing a single medication.

What is needed moving forward are well designed, randomised clinical trials across that combine one or more neurotransmitter modulators with pre and post treatment EBDM paradigms and MRI. Ideally, one may want to create patient specific *cognitive maps* that both

relate to neural deficits and can predict responsiveness to specific neurotransmitter replacement.

## 8.5 Closing remarks: staying motivated about apathy

Four years ago, I set out to improve my understanding of amotivation syndromes by framing them as a behavioural disorder, with distinct neural origins. I have demonstrated that clinical apathy can indeed be objectively framed as a behavioural disorder, using well designed EBDM tasks, and that these can allow us to probe the underlying mechanisms of the syndrome. Today I look ahead at the exciting possibilities that this field can contribute, not just by discovering the underlying processes of motivated behaviour, but by relieving the suffering of patients through drug trials.

The increased digitisation of EBDM paradigms means that we can conduct behavioural experiments in apathetic patients across using a greater number of paradigms, and in increasing numbers of patients. This can help us develop a broader picture of how amotivation maps onto multiple motivational and cognitive processes. In doing so we stand a much better chance of defining motivated action and the different processes by which it can go awry. Similarly, clinical trials that leverage our understanding of these processes alongside rapidly advancing neuroimaging techniques can allow us to probe whether patient specific treatment approaches can be tailored to specific neural pathology, and their accompanying behavioural deficits. I am confident that the future of clinical apathy is motivating enough to stick around for.

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## Appendix

## Appendix Chapter three

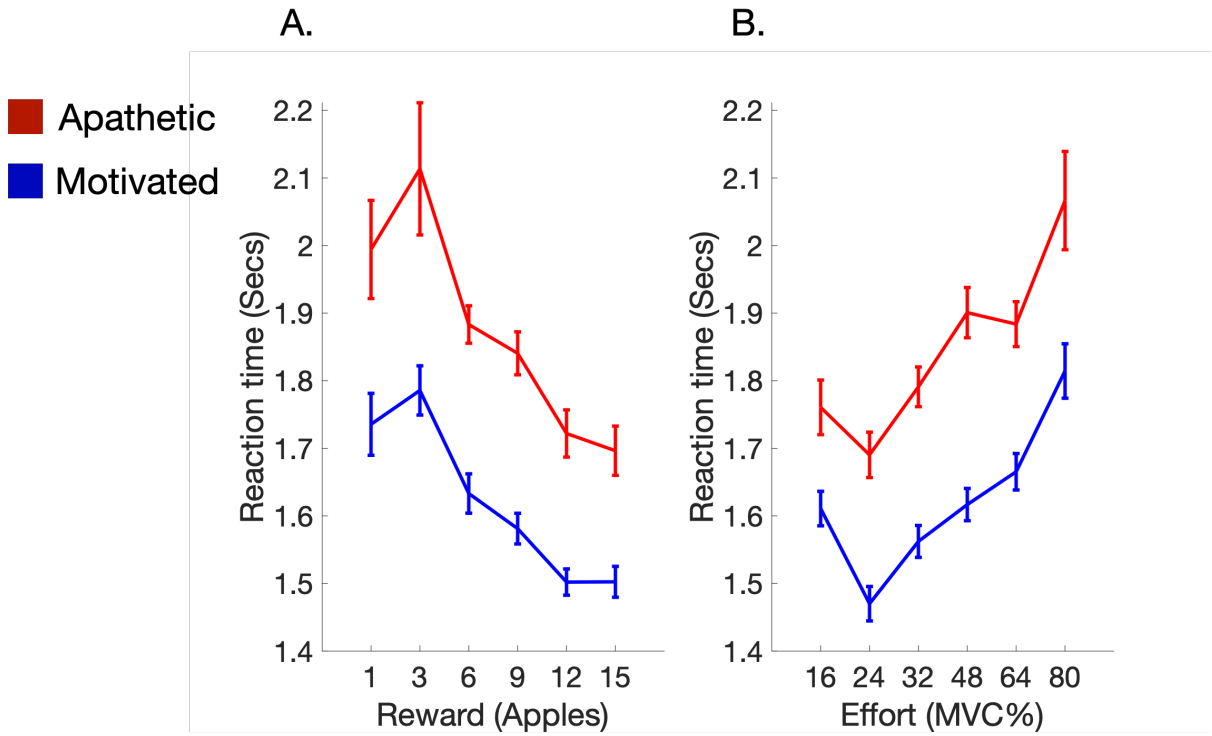
### Choice models:

Logistic regressions for raw choice data using a dichotomised cut-off using continuous variable measures as well as a cut off (AES>34) (Model 1 and 2). Key results for each model are in bold within red text boxes. Comparative BIC at the bottom of the model illustration in bold. Models with a lower BIC are favourable. "Apathy_cut" refers to the categorised group (AES>34), and "Apcont" refers to the continuous variable measure.

## Supplementary table 3-1: Choice models

| | Model 1 (continuous variable) | Model 2(cut-off) |
|---|---|---|
| (Intercept) | β = +3.37<br>SE = 0.236<br>$F_{1,14070}$ = 204.53<br>**p < 0.0001** | β = +3.44<br>SE = 0.24<br>$F_{1,14421}$ = 205.10<br>**p < 0.0001** |
| Effort | β = +1.18<br>SE = 0.0463<br>$F_{1,14070}$ = 649.10<br>**p < 0.0001** | β = +1.18<br>SE = 0.0464<br>$F_{1,14421}$ = 645.23<br>**p < 0.0001** |
| Reward | β = +2.66<br>SE = 0.0616<br>$F_{1,14070}$ = 1871.68<br>**p < 0.0001** | β = +2.71<br>SE = 0.0619<br>$F_{1,14421}$ = 1911.49<br>**p < 0.0001** |
| Reward:Effort | β = +0.224<br>SE = 0.0456<br>$F_{1,14070}$ = 24.05<br>**p < 0.0001** | β = +0.235<br>SE = 0.0456<br>$F_{1,14421}$ = 26.65<br>**p < 0.0001** |
| Apcont | β = −0.361<br>SE = 0.235<br>$F_{1,14070}$ = 2.36<br>p = 0.12 | |
| Apcont:Effort | β = +0.116<br>SE = 0.0454<br>$F_{1,14070}$ = 6.56<br>**p = 0.01** | |
| Reward:Apcont | β = +0.136<br>SE = 0.0611<br>$F_{1,14070}$ = 4.99<br>**p = 0.026** | |
| Reward:Apcont:Effort | β = +0.0869<br>SE = 0.0452<br>$F_{1,14070}$ = 3.70<br>p = 0.059 | |
| Apcut | | β = −0.207<br>SE = 0.242<br>$F_{1,14421}$ = 0.74<br>p = 0.39 |
| Apcut:Effort | | β = +0.24<br>SE = 0.0473<br>$F_{1,14421}$ = 25.73<br>**p< 0.0001** |
| Reward:Apcut | | β = +0.231<br>SE = 0.0641<br>$F_{1,14421}$ = 12.93<br>**p = 0.00032** |
| Reward:Apcut:Effort | 1 | β = +0.108<br>SE = 0.0458<br>$F_{1,14421}$ = 5.60<br>**p = 0.018** |
| Nobs | 14078 | 14429 |
| adj − $R^2$ | 0.38 | 0.33 |
| BIC | 7341.42 | 7423.69 |

**Reaction time analysis:**




**Supplementary Figure 3-1 A-B. Effects of reward and effort on reaction time**
**A.** Generally an inverted U shape was demonstrated for increasing levels of reward. Specifically, accepting lower reward offers was more time consuming, with progressive increases in reward subsequently speeding up decisions. This effect was more visible in apathetic people (red), as indexed by a significant two way interaction of apathy*reward in relation to reaction time (see supp Table 2-2 below). **B.** Low effort levels were accepted quicker while progressive increases in effort were associated with increasing reaction times. There was no significant effect of apathy on the extent of this effect.

| | Beta | $FSTAT_{(1,14196)}$ | P Value |
|---|---|---|---|
| Intercept | -0.0084 | 1.51 | 0.22 |
| Reward | -0.15 | 500.85 | **<0.00001** |
| $Effort^2$ | 0.1 | 219.25 | **<0.00001** |
| Reward*$Effort^2$ | 0.053 | 59.87 | **<0.00001** |
| Apathy | 0.015 | 4.55 | **0.033** |
| Apathy*Reward | 0.018 | 6.65 | **0.0099** |
| Apathy*Effort | -0.009 | 1.79 | 0.18 |
| Apathy*Reward*$Effort^2$ | 0.028 | 17.09 | **<0.0001** |

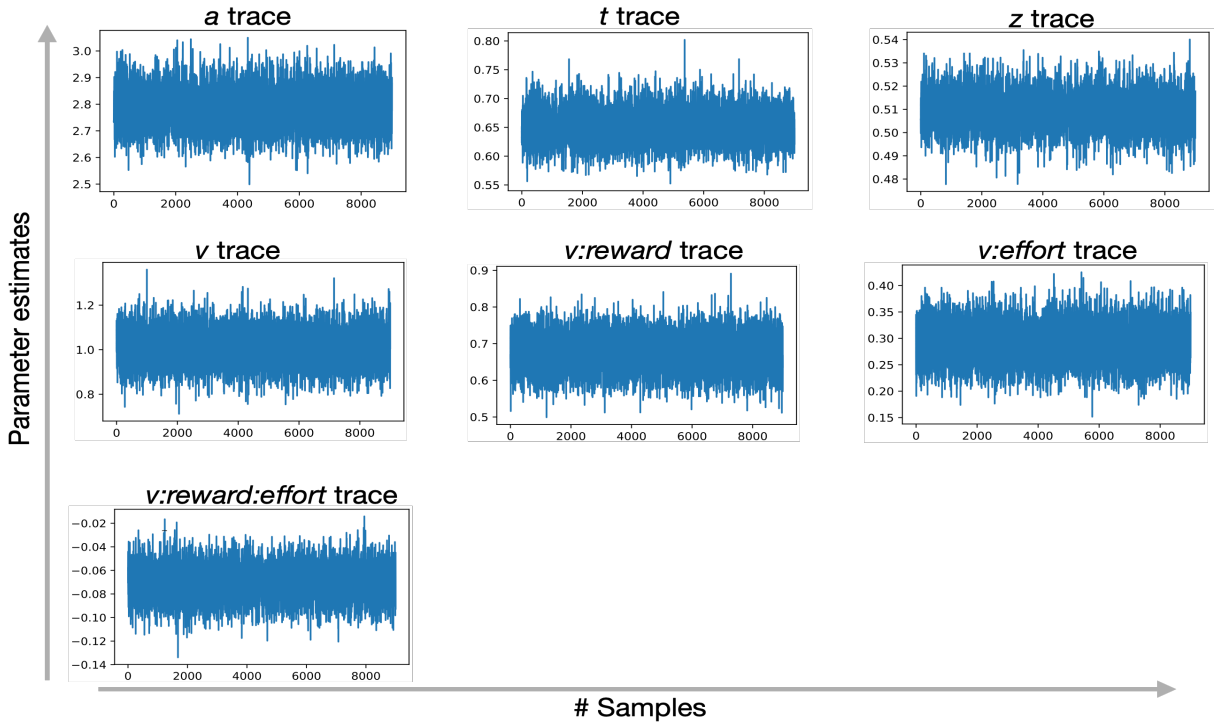
**Supplementary table 3-2:** Reaction time model. Model output looking at the association between RT and apathy in a generalised linear mixed effects model with random effects of subject and fixed effects of reward and $effort^2$.

**Drift diffusion model evaluation.**

**Model comparison and selection**:

**Assessing model convergence**:

Our DDM chains appropriately converged as demonstrated in supplementary Figure 1. This was validated across six iterations of our model using the Gelman Ruben, or R-hat statistic, which assessed model convergence between and within MCMC chains. Typically R-hat values < 1.1 imply appropriate convergence. All computed R-hat values were < 1.001, and can be seen below in table 1.




**Supplementary Figure 3-2. Model convergence trace plots.** All seven model parameters appropriately converged after 10,000 Markov chain Monte Carlo samples. The first 1,000 samples have been discarded as burn-in and are not shown here.

| Parameter | R-hat |
|---|---|
| **Threshold (a)** | 1.0000415570433712 |
| **Bias (z)** | 1.0007296051220003 |
| **Non decision time (t)** | 1.0000062930142812 |
| **Baseline Drift rate (V)** | 1.0000102057505023 |
| **V:reward** | 0.9999553245536233 |
| **V:effort** | 1.0000122137718024 |
| **V:rew:Effort** | 1.0000362395276252 |

**Supplementary Table 3-3. Gelman Ruben statistic (R-hat) across six MCMC chains.** Appropriate model convergence in our model as demonstrated by R-hat values < 1.1 across all seven model parameters.

**Model comparison:**

Model comparison was conducted comparing seven iterations of our model and the winning model was chosen based on the lowest DIC score. This equated to a full factorial model including the bias term and a drift rate which varied by: reward, effort, and the reward*effort interaction. This can be seen below as model 4 (M4).

**Supplementary table 3-2: Drift diffusion model comparison**

| **Model** | **Model description** | **Model Fit (DIC)** |
|---|---|---|
| M1 | Single drift rate term (V) with no bias term (z) | 33990 |
| M2 | Single drift rate term (V) with bias term (z) | 34003 |
| M3 | Drift rate varies with reward, effort, and interaction and no bias term | 26461 |
| **M4** | **Drift rate varies with reward, effort, and interaction + bias term** | **25882** |
| M5 | M4 with reward term removed | 32451 |
| M6 | M4 with effort term removed | 28948 |
| M7 | M4 with reward*effort interaction removed | 26201 |

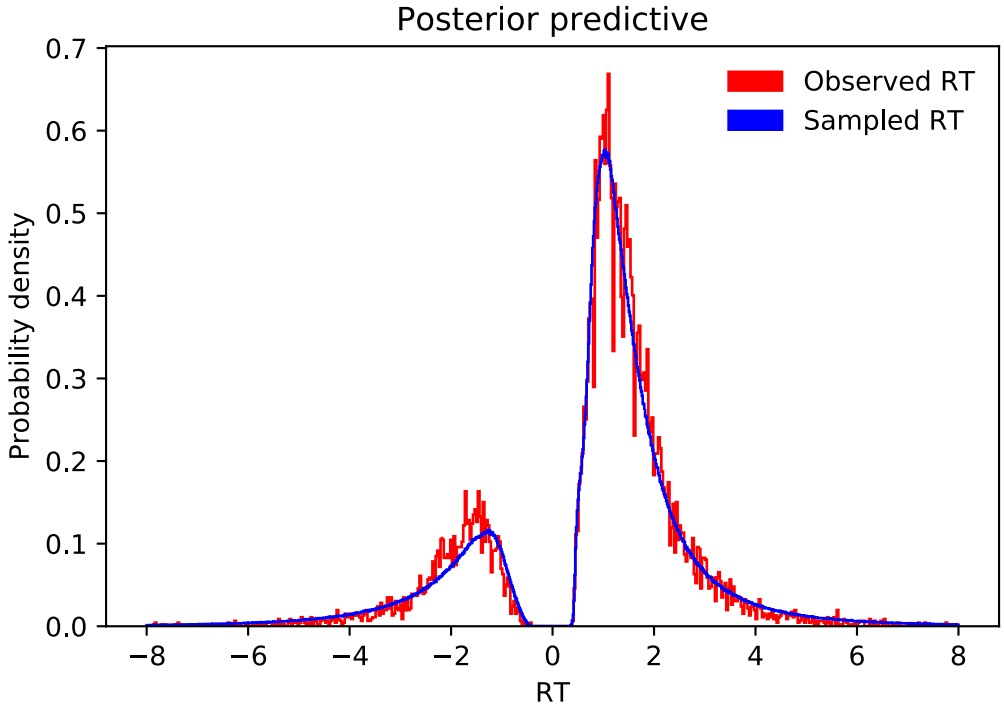
**Posterior Predictive checks:**

To validate our model, simulated datasets were generated by sampling from our model's posterior distribution. Five hundred simulated reaction time (RT) datasets were generated using the '*hddm.utils.post_pred_gen'* function in the HDDM toolbox. These were subsequently compared to the true RT data using the '*hddm.utils.post_pred_stats'* function. Output summary statistics can be seen in table 2 below. These include comparisons between the proportion of offers accepted, as well as the RT distributions for both accepted and rejected offers between the true and simulated datasets. For each quantile of the RT distribution, the simulated data was probable to lie within the 95% interval of the true RT distributions and thus deemed "Credible" (see supplementary table 2 below). A plot of the posterior probability density of the simulated data can be seen in Supplementary figure 2 and closely approximates the original data.

| STAT | OBSERVED DATA | SAMPLED DATA | STD | SEM | MSE | CREDIBLE |
|---|---|---|---|---|---|---|
| **ACCEPTED OFFERS (%)** | 0.79 | 0.79 | 0.15 | 0.00 | 0.02 | TRUE |
| **MEAN_RT ACCEPT** | 1.63 | 1.80 | 0.77 | 0.03 | 0.62 | TRUE |
| **STD_RT ACCEPT** | 0.97 | 0.95 | 0.57 | 0.00 | 0.33 | TRUE |
| **10Q_RT ACCEPT** | 0.78 | 1.02 | 0.36 | 0.06 | 0.18 | TRUE |
| **30Q_RT ACCEPT** | 1.08 | 1.24 | 0.47 | 0.02 | 0.24 | TRUE |
| **50Q_RT** | 1.39 | 1.50 | 0.61 | 0.01 | 0.38 | TRUE |

| | | | | | | |
|---|---|---|---|---|---|---|
| **ACCEPT** | | | | | | |
| **70Q_RT ACCEPT** | 1.81 | 1.92 | 0.85 | 0.01 | 0.73 | TRUE |
| **90Q_RT ACCEPT** | 2.78 | 2.92 | 1.43 | 0.02 | 2.08 | TRUE |
| **MEAN_RT REJECT** | -2.10 | -2.21 | 0.90 | 0.01 | 0.82 | TRUE |
| **STD_RT REJECT** | 1.37 | 1.16 | 0.75 | 0.05 | 0.61 | TRUE |
| **10Q_RT REJECT** | 1.08 | 1.19 | 0.42 | 0.01 | 0.19 | TRUE |
| **30Q_RT REJECT** | 1.47 | 1.49 | 0.54 | 0.00 | 0.29 | TRUE |
| **50Q_RT REJECT** | 1.78 | 1.86 | 0.72 | 0.01 | 0.52 | TRUE |
| **70Q_RT REJECT** | 2.25 | 2.41 | 1.04 | 0.03 | 1.10 | TRUE |
| **90Q_RT REJECT** | 3.37 | 3.61 | 1.79 | 0.06 | 3.27 | TRUE |

**Supplementary Table 3-3. Posterior predictive check summary.** Sampled data from our model reproduced RT data for both accepted and rejected offers that were within the 95% credible interval of the observed RT data (credible column). This was consistent across all Quantiles of the RT data. STD = Standard deviation; SEM = standard error of the mean; MSE = mean Squared error.

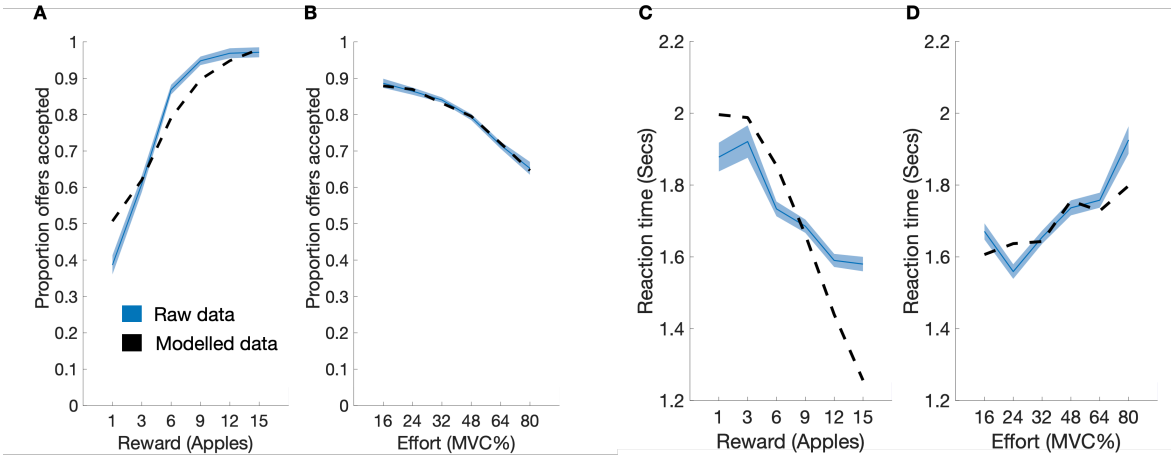



**Supplementary figure 3-3.** Posterior predictive plot for all patients**.** Probability density plot for all subjects' raw reaction time (RT) data (Red) in comparison to our model's predictions (blue). The two peaks represent the accepted trials' RT (positive x-axis values) and rejected trials' RT (negative values).

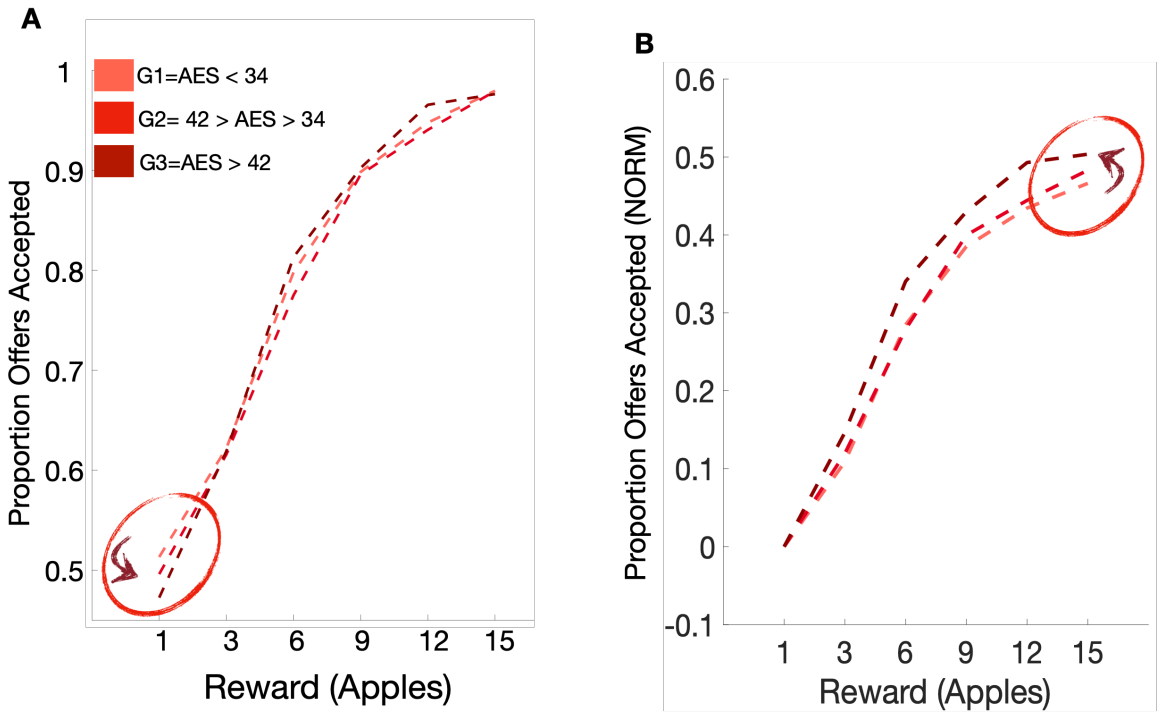
**Does apathy drive increases in decision noise during decision making?**

The drift rate is determined by the quality of information extracted from the stimulus (Ratcliff & McKoon, 2008b). One possible hypothesis for the reduced drift rate observed in apathetic patients is that apathy is associated with an increase in decision noise. To test this hypothesis, we fit a variation of our original drift diffusion model, including per-subject parameter estimates of the inter-trial variability in the drift rate *sv* – a measure of noise. The model fit was marginally improved in comparison to our original model as measured by the DIC (28116 for new model vs 28119 for original model). All original associations between

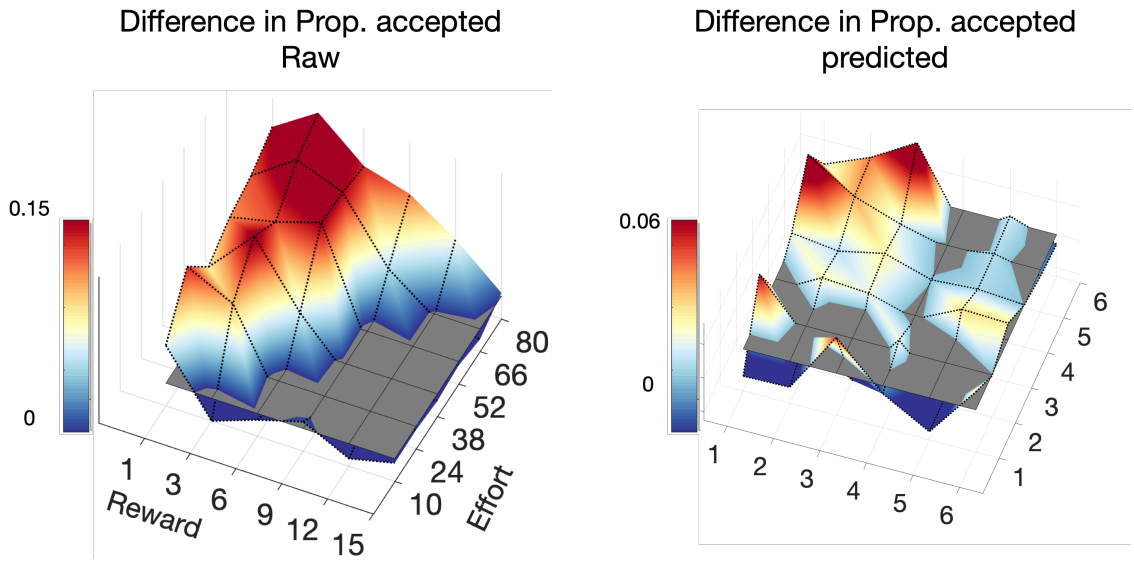
apathy, depression and the DDM parameters were retained in this model. Specifically, apathy was still negatively associated with baseline drift rate while accounting for depression and age (F(1,77)=4.28,p=0.042). Crucially, there was no association between apathy and the inter-trial variability parameter *sv* (F(1,77)=0.0089,p=0.92). This suggests that increased decision noise is an unlikely mechanistic explanation for apathetic behaviour in this patient group.




**Supplementary figure 3-4. Model predictions for AR and DT as a function of reward and effort. A-B)** Model accurately predicts behaviour in response to increasing levels of reward and effort, although at low reward the predicted accepted rates are slightly higher. **C-D)** Model predicts reaction time data relatively well for increasing level of reward and effort, however slightly over estimates this at high reward levels.




**Supplementary figure 3-5. Model predictions for Increasing apathy severity. A)** Increasing apathy severity is associated with a reduction in overall offers accepted at low reward, replicating the raw behavioural data. **B)** As a result of this behaviour, the overall slope of the reward sensitivity parameter increases, hence the positive association between apathy severity and reward sensitivity.




**Supplementary figure 3-6. Comparison of modelled and raw data across the decision space.** Modelled data accurately predicts the greatest differences to be in the low reward regions of the decision space, although one thing to note is it predicts a smaller magnitude of change when compared to raw data.

**Appendix chapter five**

## Abbreviations table

| ABBREVIATION | MEANING |
|---|---|
| ACE-III/ACE_TOTAL | Addenbrooke's cognitive examination version III /Total score |
| PANS_POSITIVE | Positive sub score of positive and negative syndrome scale for schizophrenia. |
| BACS_TOTAL | Total score for Brief Assessment of Cognition in Schizophrenia scale |
| CLOZ_LEVEL | Serum Clozapine level |
| CDS_TOTAL | Total score for Calgary depression scale |
| STRAUSS_MAP | Motivation and pleasure factor of BNSS questionnaire using factor weightings from Strauss et al |
| STRAUSS_EXP | Blunted expression factor of BNSS questionnaire using factor weightings from Strauss et al |

## Supplementary methods

### Participants

Inclusion criteria:

1. Aged between 18-65
2. Formally diagnosed with schizophrenia
3. Clinically stable on medication and an unchanged medication regime for at least 8 weeks

Exclusion criteria:

1. Participants who were unable to understand and engage with the behavioural testing protocol.
2. Physical disability preventing participants squeezing a hand-held device in response to visual stimuli.
3. Evidence of history suggestive of any concomitant neurodegenerative or neuroinflammatory disease such as Alzheimer's disease or vascular dementia.

**Logistic regression with mixed effects**

**Model comparison for between group analysis**

**Supplementary Table 5-1**. Model comparison of choice behaviour between schizophrenia and controls.

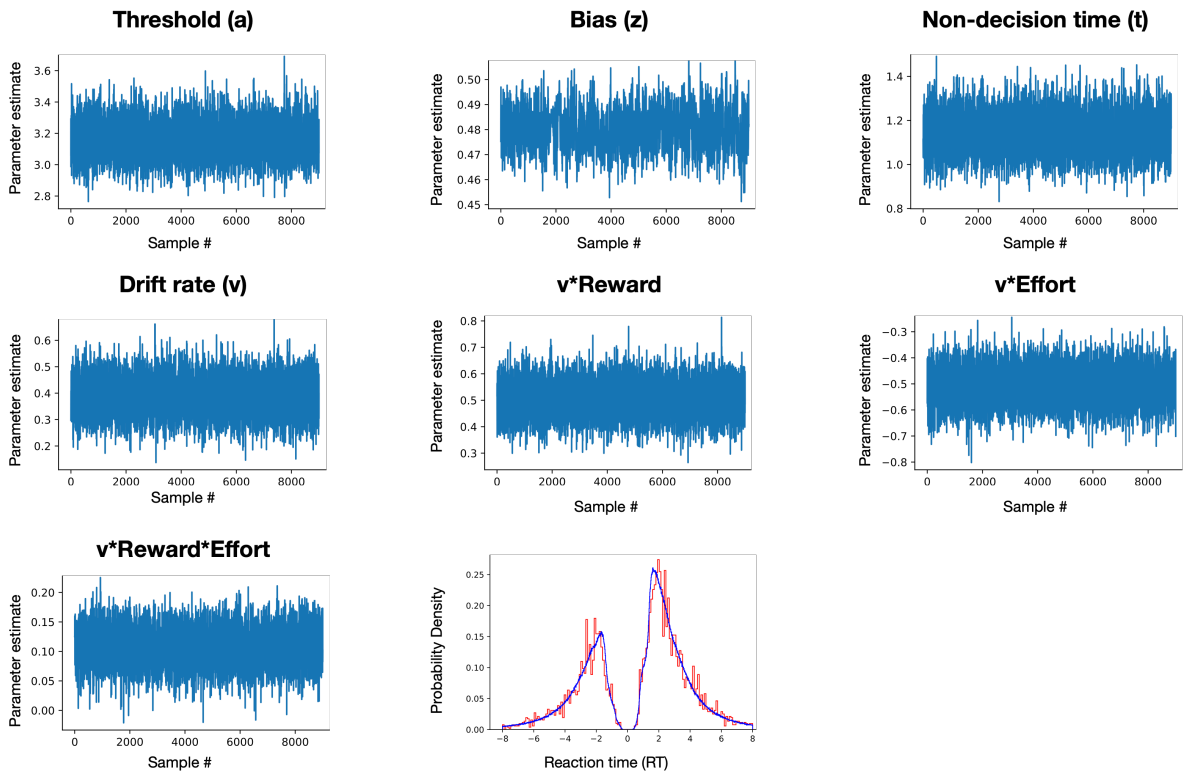
| *Model* | *Model specification* | *Random effects* | *AIC* |
|---|---|---|---|
| *1* | 'Choice ~ Reward*Effort*Group' | (Reward + Effort \| Subject) | 5758 |
| *2* | 'Choice ~ Reward*Effort$^2$*Group' | (Reward + Effort$^2$ \| Subject) | 5761 |

**Drift Diffusion Model**

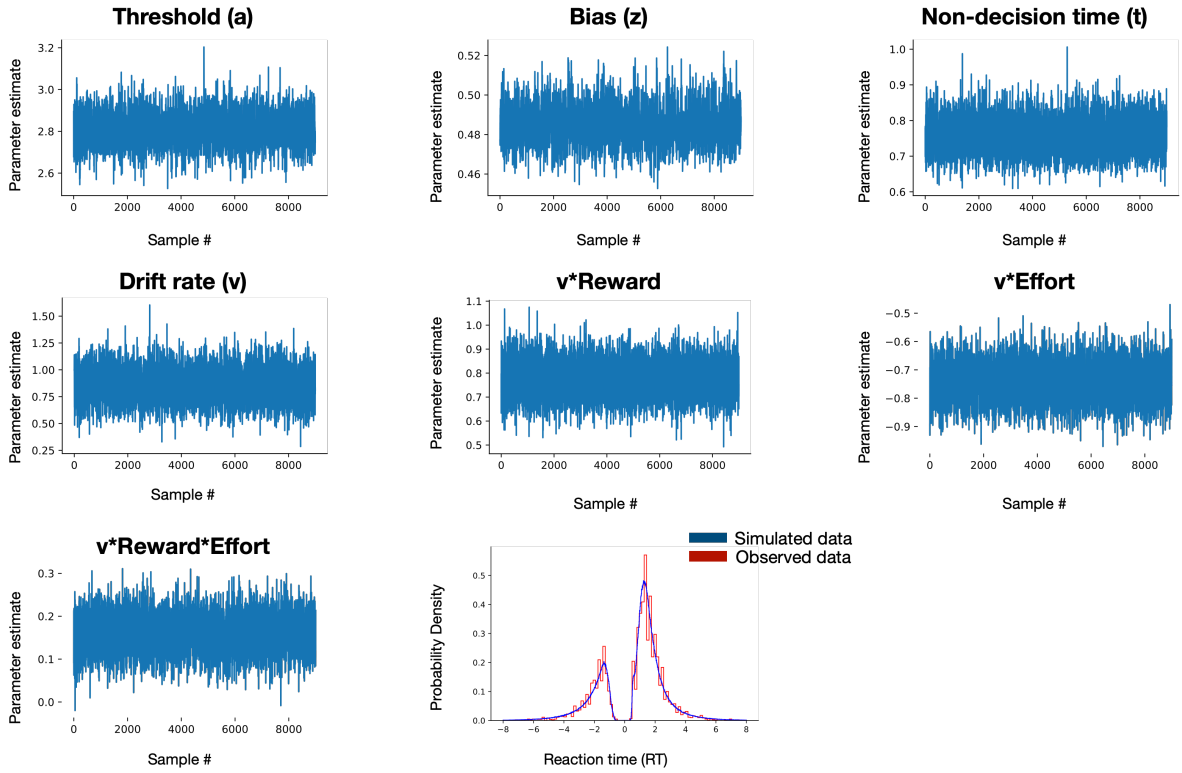
**Supplementary Table 5-2**: Gelman Ruben Statistics

| ***DDM Parameters*** | ***R-Hat M1 (SCZ)*** | ***R-Hat M2 (CTRL)*** |
|---|---|---|
| ***Drift rate (V)*** | 0.9999 | 1.0004 |
| ***V:Reward*** | 1.0000 | 1.0000 |
| ***V:Effort*** | 1.0001 | 1.0001 |
| ***V:Reward*Effort*** | 1.0000 | 1.0000 |
| ***Threshold (a)*** | 1.0005 | 1.0019 |
| ***Non-decision time (t)*** | 1.0000 | 1.0000 |
| ***Bias (z)*** | 1.0006 | 1.0006 |

**Supplementary figure 5-1**: Convergence plots and posterior predictive plots for M1



**Supplementary figure 5-2**: Convergence plots and posterior predictive plots for M2




## Cognitive variables:

Both ACE-III and BACS total scores were independently positively associated with reward sensitivity (respectively, [F(1,4852)=13.39, *P*=0.0002] and [F(1,4852)=4.481, *P*=0.035]). Including both scores in a logistic multiple regression with mixed effects retained the association between reward sensitivity and ACE-III but not BACS (respectively, [F(1,4352)=5.6, *P*=0.018] and [F(1,4352)=0.004, *P*=0.94]). Hence the ACE-III was deemed a more sensitive measure when correlating cognitive function and behavioural markers using our paradigm.

## Correlating behavioural parameters and clinical measures.

Below are multiple regressions of behavioural parameters extracted from the two analytic approaches. First the generalised models which used only the choice data. Second the DDM models which combined choice data and reaction times.

### Generalised linear mixed effects model parameters

**Supplementary Table 5-3:** Association between choice parameters and clinical measures

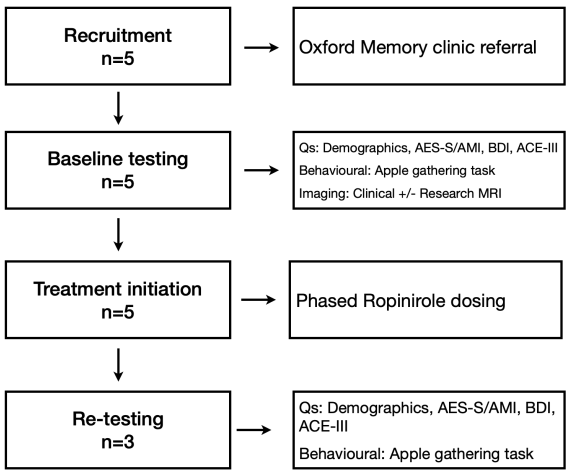
| DF(1,31) | **Intercept** | **Reward sensitivity** | **Effort sensitivity** | **Reward*Effort** |
|---|---|---|---|---|
| Cognition (ACE-III) | β = 0.24<br>t = 0.83<br>p = 0.41 | β = 0.87<br>t = 3.32<br>p = 0.002<br>p(corr) = 0.014 | β = 0.03<br>t = 0.15<br>p = 0.88 | β = 0.25<br>t = 2.07<br>p = 0.046<br>p(corr) = 0.28 |
| Depression (CDS) | β = - 0.1<br>t = -0.33<br>p = 0.74 | β = -0.1<br>t = -0.36<br>p = 0.72 | β = 0.28<br>t = 1.00<br>p = 0.32 | β = -0.08<br>t = -0.64<br>p = 0.52 |
| Clozapine level | β = -0.44<br>t = -1.6<br>p = 0.11 | β = 0.16<br>t = 0.67<br>p = 0.51 | β = -0.60<br>t = -2.56<br>p = 0.015*<br>p(corr) = 0.09 | β = 0.014<br>t = 0.12<br>p = 0.90 |
| Positive Sx (PANS positive) | β = -0.27<br>t = -0.88<br>p = 0.38 | β = -0.21<br>t = -0.75<br>p = 0.46 | β = -0.096<br>t = -0.35<br>p = 0.72 | β = -0.092<br>t = -0.70<br>p = 0.49 |
| EXP | β = 0.1<br>t = 0.98<br>p = 0.33 | β = 0.077<br>t = 0.77<br>p = 0.45 | β = 0.28<br>t = 2.94<br>p = 0.006<br>p(corr) = 0.036 | β = 0.10<br>t = 2.20<br>p = 0.035<br>p(corr) = 0.21 |
| MAP | β = -0.14<br>t = -1.37<br>p = 0.18 | β = -0.06<br>t = -0.63<br>p = 0.53 | β = -0.18<br>t = -2.00<br>p = 0.054 | β = -0.04<br>t = -0.96<br>p = 0.34 |

## Drift Diffusion model parameters

**Supplementary Table 5-4**: Association drift diffusion model parameters and clinical measures

| DF(1,31) | Threshold (a) | Decision time (t) | Bias (z) | Drift rate | Drift * Reward | Drift *Effort | Drift*Rew*Eff |
|---|---|---|---|---|---|---|---|
| **Cognition (ACE-III)** | β = -0.076<br>t = -0.69<br>p = 0.49 | β = 0.16<br>t = 1.97<br>p = 0.058 | β = -0.00012<br>t = -0.14<br>p = 0.89 | β = 0.006<br>t = 0.12<br>p = 0.90 | β = 0.15<br>t = 3.25<br>p = 0.0027<br>p(corr) = 0.016 | β = 0.036<br>t = 0.72<br>p = 0.47 | β = 0.015<br>t = 0.87<br>p = 0.39 |
| **Depression (CDS)** | β = -0.05<br>t = -0.455<br>p = 0.65 | β = -0.15<br>t = -1.7<br>p = 0.098 | β = -0.00001<br>t = -0.013<br>p = 0.98 | β = -0.036<br>t = -0.58<br>p = 0.56 | β = 0.019<br>t = 0.38<br>p = 0.71 | β = 0.051<br>t = 0.94<br>p = 0.35 | β = -0.0020<br>t = -0.14<br>p = 0.89 |
| **Clozapine level** | β = -0.49<br>t = -0.48<br>p = 0.63 | β = -0.0022<br>t = -0.029<br>p = 0.97 | β = -0.0004<br>t = -0.49<br>p = 0.63 | β = -0.051<br>t = -0.97<br>p = 0.34 | β = -0.01<br>t = -0.23<br>p = 0.81 | β = -0.085<br>t = -1.83<br>p = 0.07 | β = -0.020<br>t = -0.123<br>p = 0.23 |
| **Positive Sx (PANS positive)** | β = -0.17<br>t = -1.4<br>p = 0.17 | β = 0.06<br>t = 0.74<br>p = 0.46 | β = -0.0007<br>t = 0.82<br>p = 0.41 | β = -0.05<br>t = -0.85<br>p = 0.40 | β = 0.02<br>t = 0.42<br>p = 0.68 | β = -0.042<br>t = -0.77<br>p = 0.44 | β = -0.0026<br>t = -0.14<br>p = 0.89 |
| **EXP** | β = -0.0066<br>t = -0.15<br>p = 0.88 | β = -0.039<br>t = -1.27<br>p = 0.21 | β = -0.0002<br>t = -0.58<br>p = 0.56 | β = 0.017<br>t = 0.82<br>p = 0.42 | β = 0.025<br>t = 1.43<br>p = 0.16 | β = 0.048<br>t = 2.58<br>p = 0.015<br>p(corr) = 0.09 | β = 0.0009<br>t = 1.48<br>p = 0.14 |
| **MAP** | β = -0.045<br>t = 1.13<br>p = 0.26 | β = 0.07<br>t = 2.44<br>p = 0.02<br>p(corr) = 0.12 | β = -0.0002<br>t = -0.67<br>p = 0.50 | β = -0.033<br>t = -1.6<br>p =0.11 | β = -0.023<br>t = -1.37<br>p = 0.18 | β = 0.13<br>t = -1.56<br>p = 0.12 | β = -0.0005<br>t = -0.81<br>p = 0.43 |

## Appendix chapter six

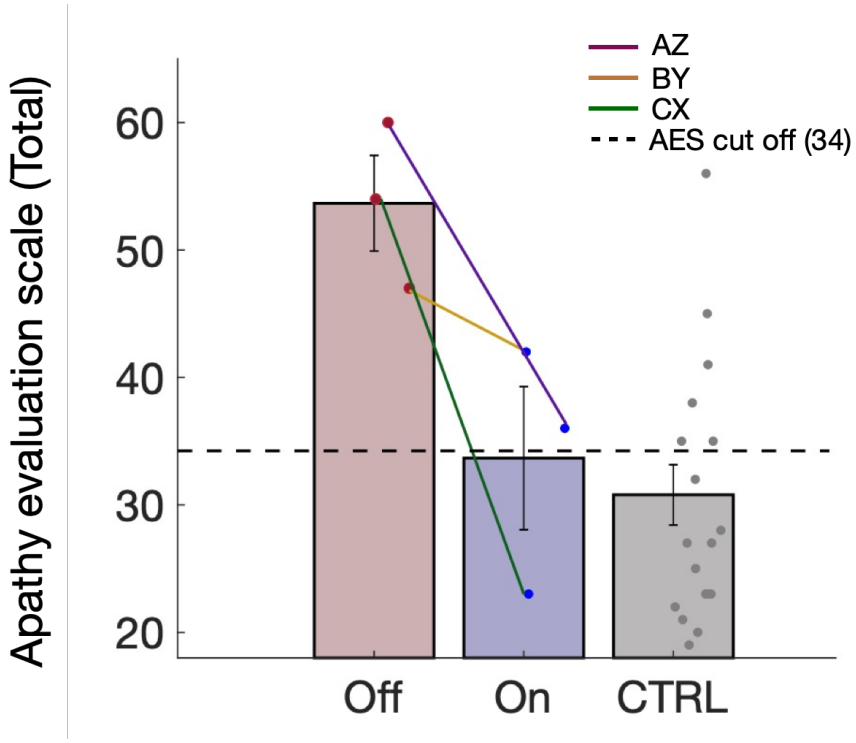



| Step | Safety Phase dosing | Time (days) |
|---|---|---|
| 1 | Ropinirole standard release 250 mcg once daily | 3 |
| 2 | Ropinirole standard release 250 mcg twice daily | 3 |
| 3 | Ropinirole standard release 250 mcg thrice daily | 14 |
| 4 | Ropinirole standard release 500 mcg thrice daily | 14 |
| 5 | Ropinirole modified release 2 mg once daily | 30 |

If tolerating treatment

| Step | Efficacy Phase dosing | Time (days) |
|---|---|---|
| 1 | Ropinirole modified release 2 mg once daily | 30 |
| 2 | Ropinirole modified release 4 mg once daily | 30 |
| 3 | Ropinirole modified release 6 mg once daily | 30 |
| 4 | Ropinirole modified release 8 mg once daily | 30 |

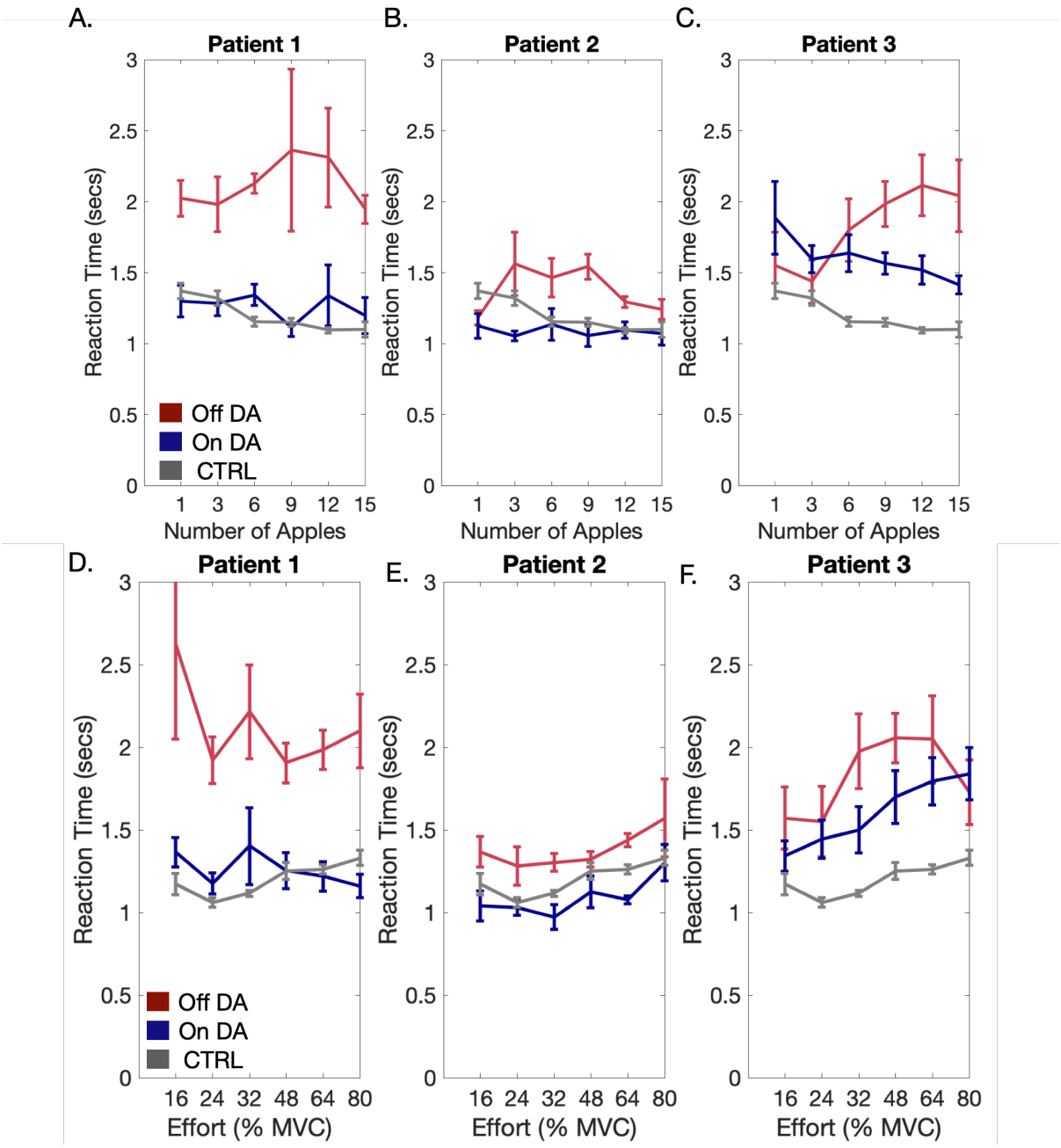
**Supplementary Figure 6-1. Study protocol**. (**Left**) Patients were recruited from the Oxford memory clinic, where they underwent baseline testing using MRI, questionnaire analysis and behavioural testing using an effort based decision making task. They then began a phased dosing regime of ropinirole (**right**) after which they were re-tested on questionnaire and behavioural measure.




**Supplementary Figure 6-2. Apathy Evaluation Scale (AES) analyses.** All three untreated patients had baseline AES scores above the clinical cut-off 34 (black dotted line). All three patients' AES scores improved following treatment, and their average AES score was < 34. Purple, yellow and green lines represent paired AES changes for patient AZ, BY, and CX respectively.

| *Demographics* | *Patient 1* | *Patient 2* | *Patient 3* | *Controls (n=18)* |
|---|---|---|---|---|
| *Age* | 42 | 53 | 52 | 54.47 (11.18) |
| *Gender (M/F)* | 1/0 | 0/1 | 1/0 | 7/11 |
| *Previous Medical history* | - Ischaemic stroke (2015) | - Haemorrhagic stroke (2019)<br>- Myectomy<br>- Post menopausal<br>- Overactive bladder | - Stroke (?Microvascular, 2013)<br>- Neurosarcoidosis<br>- Pituitary insufficiency, possible related to above<br>- Myasthenia Gravis<br>- Microvascular disease with possible cardiac and cerebrovascular effects | - |
| *Medications* | - Atorvastatin<br>- Clopidogrel<br>- Fluoxetine<br>- Omeprazole<br>- Zopiclone | - Solifenacin | - Infliximab<br>- Prednisolone<br>- Methotrexate<br>- Hydroxychloriquine<br>- Clopidogrel<br>- Atorvastatin<br>- Diltiazem<br>- Isosobide Mononitrate<br>- Ramipril<br>- Ranolazine<br>- Indapamide | - |
| *Treatment drug* | Ropinirole | Ropinirole | Ropinirole | - |
| *Highest effective dose* | 8 mg | 6 mg | 6 mg | - |
| *ACE-III (Score/100)* | 92 | 90 | 84 | 96.57 (2.41) |
| *Apathy Evaluation Scale (AES) - Off/On* | 47/42 | 54/23 | 60/36 | 30.78 (10.30) |
| *Beck's Depression Inventory (BDI) - Off/On* | 0/32 | 10/4 | 19/14 | 4.52 (5.64) |

**Supplementary table 6-1. Detailed patient wise demographics**. Patient demographics including medica history, and medications.



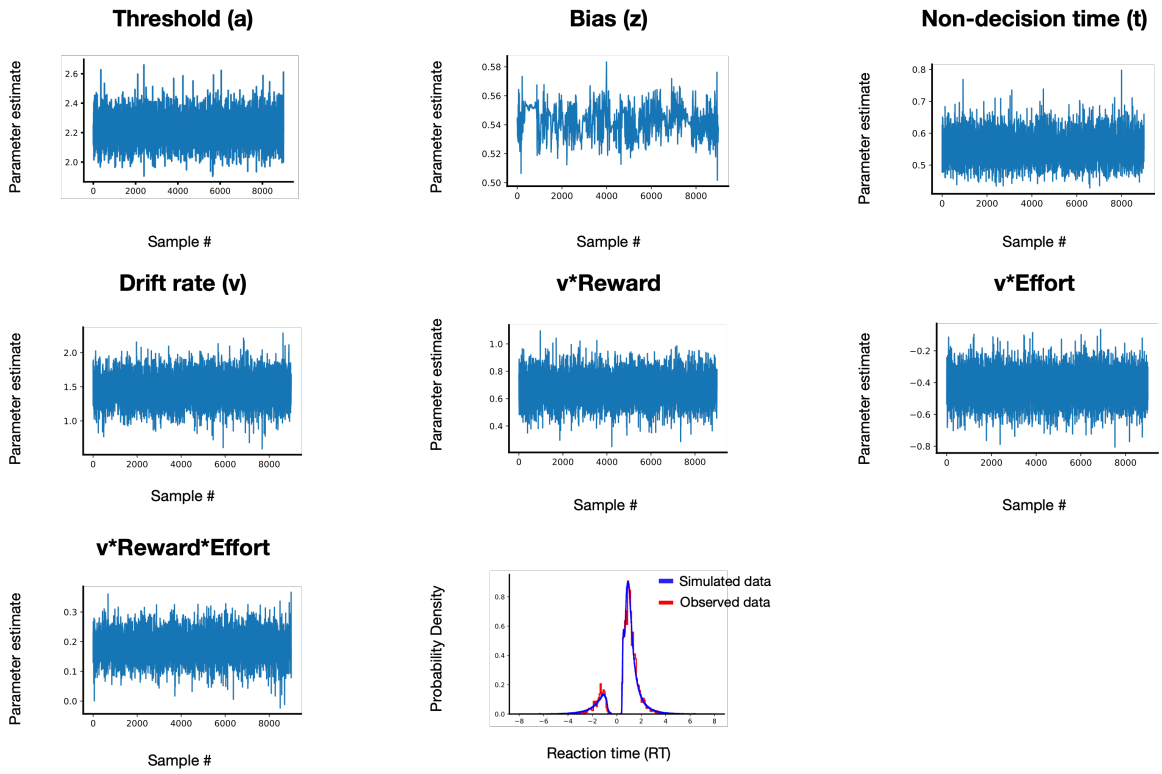

**Supplementary Figure 6-3. Patient-wise Reaction Time (RT) Data**. (**A-C**) Patient wise comparison of reaction time data with increasing levels of reward. Control data included in grey. Untreated patients (red) display generally higher RTs, and are more sensitive to changes in reward compared. This significantly improves following treatment, where their reaction times are more similar to controls. (**D-F**) Per patient comparison of RT data with increasing effort. The key finding here is that patient three (**F**), who is depressed, shows a significantly greater sensitivity to increasing effort levels compared to both controls and patients one and two. This is reflected in their DDM analyses, where reaction times are integrated.

**Drift diffusion model evaluation:**

A DDM was first fit to the whole data set. To assess model convergence, two methods were used. First, trace plots were generated across all 10,000 samples to ensure each parameter estimate converged with no significant drifts or jumps across samples within a single model (Supp Fig 4). Second, Five iterations of the DDM were run, and a Gelman Ruben statistic conducted to ensure parameter estimates between different model iterations did not diverge (Supp Table 2). The statistic of interest for this analysis is the R-hat, which represents model convergence and should be < 1.1. Across five runs, all parameter estimates displayed R-Hat values well below 1.1. This was the case for a DDM fit to the whole data set, as well as each sub-group (i.e. untreated patients, treated patients, and controls, **Supp Table 2**). Finally, the DDM parameters were used to simulate predicted reaction time (RT) data using the *posterior predict generate* function of the HDDM software. This involved generating the equivalent of 500 simulated RT datasets. This was then plotted against the observed dataset, demonstrating a good fit to the data (Supp Fig 4, bottom right).

| ***DDM Parameters*** | ***Whole Group*** | ***R-Hat M1*** | ***R-Hat M2*** | ***R-Hat M3*** |
|---|---|---|---|---|
| ***Drift rate (V)*** | 1.00002 | 1.0000 | 1.00000 | 1.0002 |
| ***V:Reward*** | 0.9999 | 0.99997 | 1.00002 | 0.9999 |
| ***V:Effort*** | 1.0000 | 0.99996 | 0.99998 | 0.9999 |
| ***V:Reward*Effort*** | 1.0002 | 1.00015 | 0.99999 | 1.0002 |
| ***Threshold (a)*** | 1.0000 | 0.99996 | 1.00004 | 1.0002 |
| ***Non-decision time (t)*** | 1.0002 | 1.00026 | 1.00001 | 1.0002 |
| ***Bias (z)*** | 1.0033 | 1.00025 | 1.00084 | 1.0071 |

**Supplementary Table 6-3. Gelman Rubin convergence tests.** Convergence tests conducted for the whole data set as well as DDM fits of untreated patients, treated patients, and controls (respectively, M1, M2, and M3). Each Gelman Rubin test is conducted on five runs of the same model. Across all three models, model convergence for all seven parameters was observed indicating stable parameter estimate generation as demonstrated by an R-hat value < 1.1.




**Supplementary Figure 6-4. Trace plots and posterior predictive checks.** These trace plots and posterior predictive checks are based on the whole group DDM including patient data on/off treatment and healthy controls. Trace plots for all seven parameters showed model convergence. Similarly, simulated RT data based on the DDM parameters displayed a good fir to the observed data (**Bottom right**).

**Drift diffusion model results:**

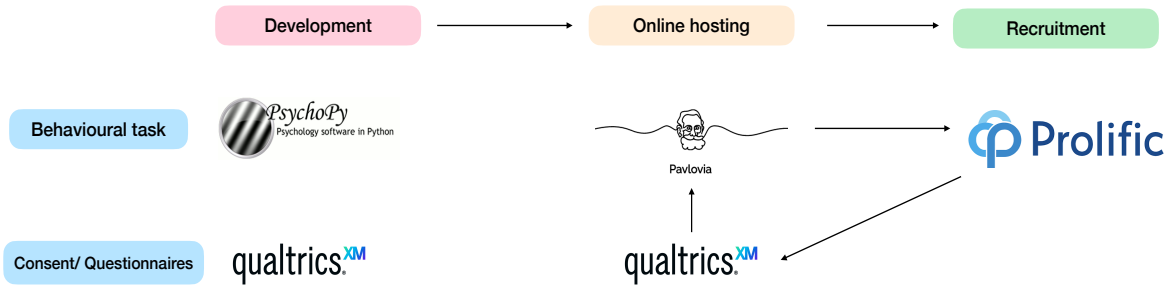
**Supplementary Table 6-3**. Effect of dopamine treatment on patients (bias model). Results demonstrating within patient effects of DA treatment across all parameters. Significant increases or decreases in parameter estimate values are shaded in green and orange respectively. Comparisons are made using Bayesian hypothesis testing between posterior distributions of parameters, and threshold for significance was set at 0.95.

| *Effect of DA Tx (Probability)* | *Patient 1* | *Patient 2* | *Patient 3* | **All Patients** |
|---|---|---|---|---|
| ***Drift rate (V)*** | ↑ (0.99) | ↑ (0.75) | ↑ (1.0) | ↑ (0.85) |
| ***V:Reward*** | ↑ (0.87) | ↓ (0.99) | ↓ (0.99) | ↓ (0.69) |
| ***V:Effort*** | ↑ (0.73) | ↑ (0.94) | ↓ (0.99) | ↓ (0.55) |
| ***V:Reward*Effort*** | ↑ (0.88) | ↑ (0.94) | ↓ (0.85) | ↓ (0.72) |
| ***Threshold (a)*** | ↓ (1.0) | ↑ (0.78) | ↓ (0.75) | ↑ (0.67) |
| ***Non-decision time (t)*** | ↓ (1.0) | ↓ (1.0) | ↑ (0.83) | ↓ (0.87) |
| ***Bias (z)*** | ↑ (0.95) | ↑ (0.98) | ↑ (0.719) | ↑ (0.94) |

**Supplementary Table 5-4.** Comparisons of patients vs controls before and after treatment. Comparisons are made using Bayesian hypothesis testing between posterior distributions 6f parameters, and threshold for significance was set at 0.95.

| *Parameter* | *P1 (Off/On vs CTRL)* | *P2 (Off/On vs CTRL)* | *P3 (Off/On vs CTRL)* | *All Px (Off/On vs CTRL)* |
|---|---|---|---|---|
| ***Drift rate (V)*** | ↓(1)/ ↓(0.98) | ↓(1)/ ↓(0.99) | ↓(1)/ --(0.94) | ↓(0.95)/ ↓(0.93) |
| ***V:Reward*** | ↑(0.76)/↑(0.95) | ↑(1)/↑(0.93) | ↑(0.99)/↑(0.88) | --/-- |
| ***V:Effort*** | ↓(1)/ ↓(1) | ↓(0.94)/ --(0.5) | ↑ (1)/ ↑ (0.96) | --/-- |
| ***V:Reward*Effort*** | ↓ (0.99)/ --(0.84) | ↓ (0.97)/ --(0.5) | --/-- | --/-- |
| ***Threshold (a)*** | ↑(0.99)/ ↓ (0.99)/ | ↓ (0.99)/ ↓ (0.94)/ | ↑ (0.97)/ -- (0.81)/ | --/-- |
| ***Non-decision time (t)*** | ↑(1)/--(0.93) | ↑(1)/0.959 | ↑(1)/ ↑(1) | ↑(1)/-- |
| ***Bias (z)*** | ↓ (0.99)/0.65 | ↓ (0.99)/0.57 | 0.79/0.554 | ↓ (0.99)/--0.59 |

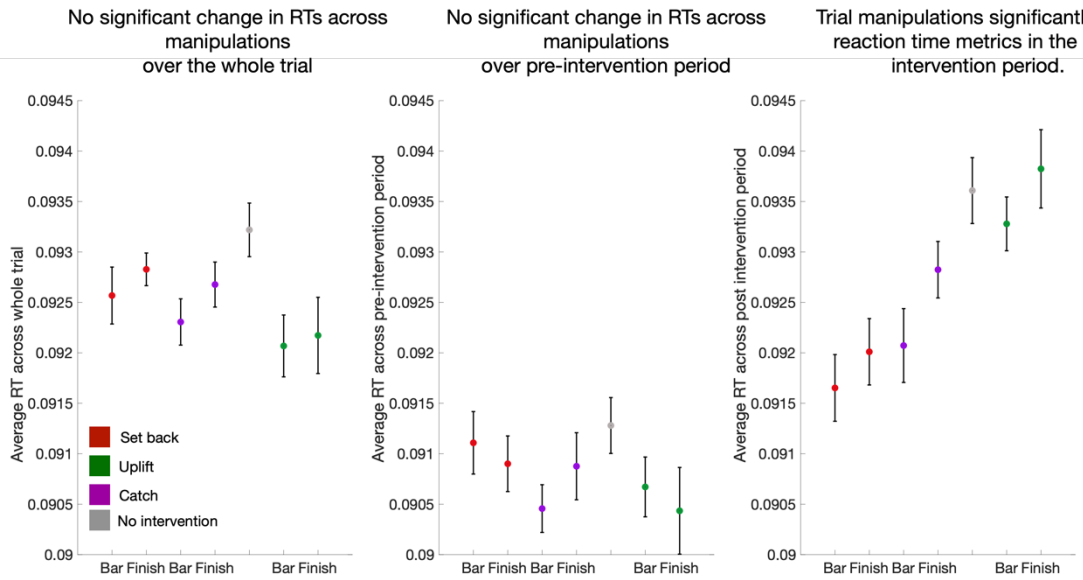
## Appendix chapter seven




**Supplementary Figure 7-1. Study workflow.** Participants were recruited on *Prolific* (top right) where they were redirected to online consent forms and questionnaires on *Qualtrics* (bottom left and centre). They were then directed to *Pavlovia* (top centre), a hosting platform for the online task that was developed on a python based software, *Psychopy* (top left).

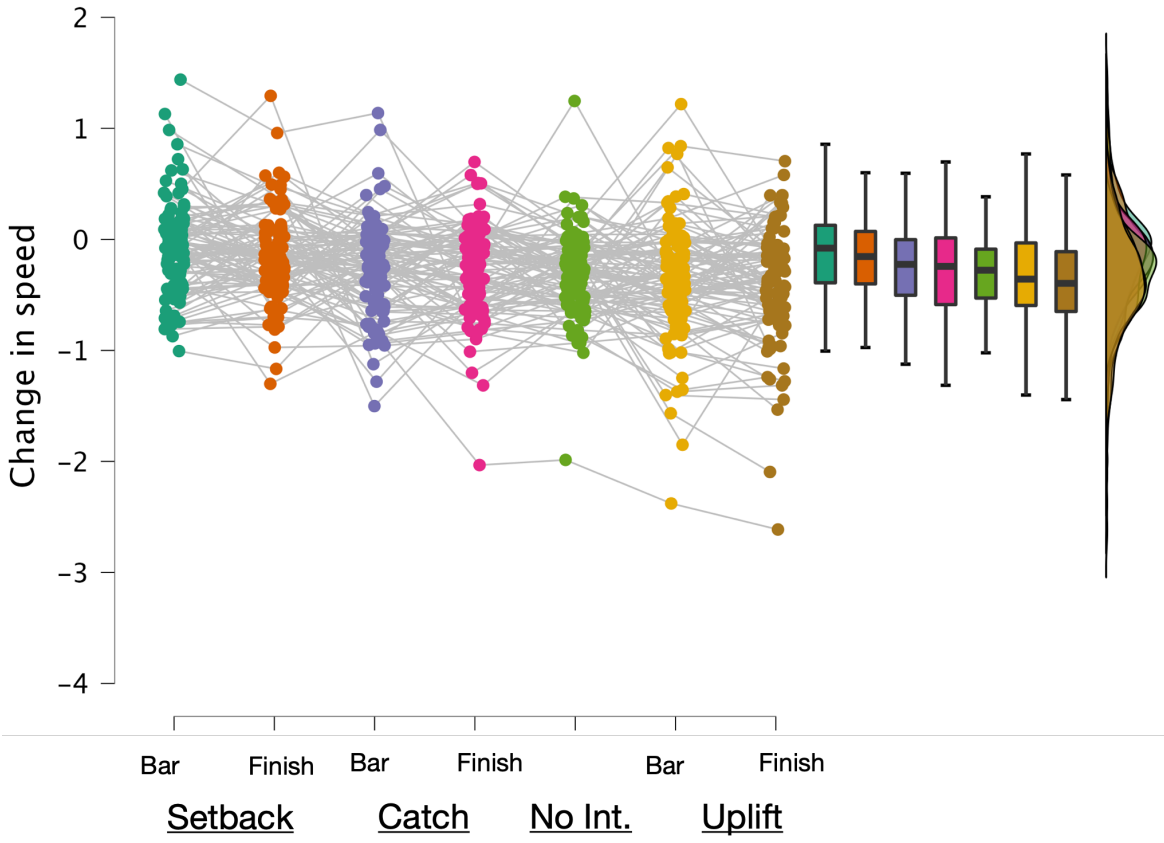
**Supplementary table 7-1. Reaction time data across trial periods.** Reaction time here is referred to as the time between consecutive key presses.

| Condition | Trial length (secs) | Overall RT (secs) | Pre-Intervention RT (secs) | Post Intervention RT (secs) |
|---|---|---|---|---|
| **Setback (Bar)** | 9.58 (0.11) | 0.0926 (0.0015) | 0.0911 (0.0017) | 0.0917 (0.0017) |
| **Setback (Line)** | 9.61 (0.13) | 0.0928 (0.0013) | 0.0909 (0.0016) | 0.0920 (0.0019) |
| **Catch (Bar)** | 8.21 (0.11) | 0.0923 (0.0015) | 0.0905 (0.0016) | 0.0921 (0.0018) |
| **Catch (Line)** | 8.230 (0.11) | 0.0927 (0.0013) | 0.0909 (0.0014) | 0.0928 (0.0014) |
| **No intervention** | 8.24 (0.13) | 0.0932 (0.0019) | 0.0913 (0.0018) | 0.0936 (0.0021) |
| **Uplift (Bar)** | 6.76 (0.09) | 0.0921 (0.0016) | 0.0907 (0.0016) | 0.0933 (0.0016) |
| **Uplift (Line)** | 6.77 (0.09) | 0.0922 (0.0017) | 0.0904 (0.0018) | 0.0938 (0.0019) |

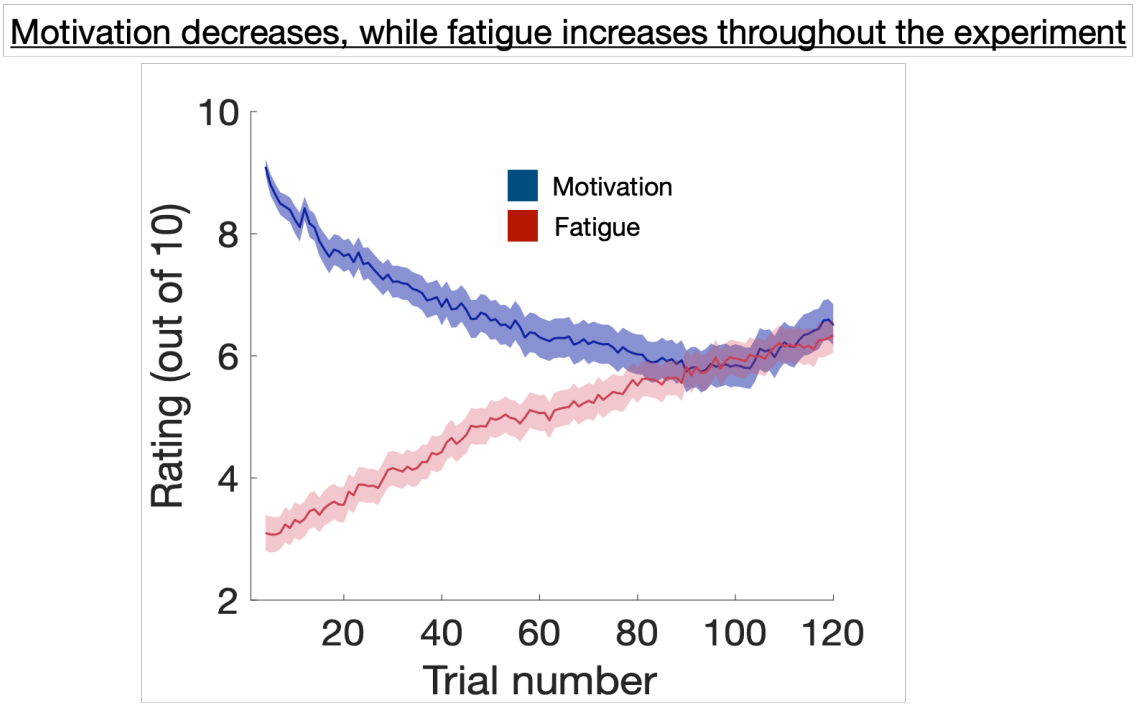



**Supplementary Figure 7-3. A-C Reaction time plots over different trial periods.**

Reaction time data over the whole trial showed no significant difference across the seven conditions. B) Similarly no difference in RT data was detected in the pre-intervention period. C) Post intervention reaction times were significantly altered. Specifically, reaction times in the setback condition were faster than in the no intervention and uplift condition. This suggests a dynamic change in pressing speed is elicited by our trial conditions.



**Supplementary Figure 7-5. Per-subject plots for trial conditions vs. pressing speed**




**Supplementary Figure 7-5. Subjective ratings of motivation and fatigue.** Across subjects, there was a significant decrease in motivation over the course of the experiment. Inversely, Fatigue levels significantly increased during time on trial.

**Supplementary table 7-2. Post Hoc analysis for effects of 7 trial conditions on pressing speed.**

| | | *Post Hoc Comparisons - Condition* | | | |
|---|---|---|---|---|---|
| | | **Mean Difference** | **SE** | **t** | **$p_{holm}$** |
| Setback (Bar) | FinFar | 0.059 | 0.052 | 1.141 | 1.000 |
| | Catch | 0.164 | 0.052 | 3.171 | **0.022** |
| | Catch2 | 0.193 | 0.052 | 3.733 | **0.003** |
| | NoInt | 0.223 | 0.052 | 4.306 | **< .001** |
| | Uplift | 0.280 | 0.052 | 5.422 | **< .001** |
| | FinClose | 0.337 | 0.052 | 6.510 | **< .001** |
| Setback (Fin) | Catch | 0.105 | 0.052 | 2.030 | 0.342 |
| | Catch2 | 0.134 | 0.052 | 2.592 | 0.108 |
| | NoInt | 0.164 | 0.052 | 3.165 | **0.022** |
| | Uplift | 0.221 | 0.052 | 4.281 | **< .001** |
| | FinClose | 0.278 | 0.052 | 5.369 | **< .001** |
| Catch (Bar) | Catch2 | 0.029 | 0.052 | 0.562 | 1.000 |
| | NoInt | 0.059 | 0.052 | 1.135 | 1.000 |
| | Uplift | 0.116 | 0.052 | 2.251 | 0.247 |
| | FinClose | 0.173 | 0.052 | 3.339 | **0.013** |
| Catch (Fin) | NoInt | 0.030 | 0.052 | 0.574 | 1.000 |
| | Uplift | 0.087 | 0.052 | 1.689 | 0.642 |
| | FinClose | 0.144 | 0.052 | 2.778 | 0.068 |
| No Int | Uplift | 0.058 | 0.052 | 1.116 | 1.000 |
| | FinClose | 0.114 | 0.052 | 2.204 | 0.251 |
| Uplift (Bar) | FinClose | 0.056 | 0.052 | 1.088 | 1.000 |

*Note. P-value adjusted for comparing a family of 21*